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ORIGINAL ARTICLE

Nutritional knowledge levels and food preferences of teachers

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Abstract

Nutritional knowledge includes knowing nutritional processes, major nutritional sources of foods, the relationship of diet to health and disease, and dietary recommendations. This study aimed to determine teachers' basic nutrition and nutrition-health knowledge levels, who are important opinion leaders in society, and to evaluate their food preferences. The research, a cross-sectional study, was carried out in a district in 2022. 280 teachers were included in the research. The survey form consists of 14 questions about sociodemographic information and nutritional preferences; and 32 questions on the "Nutrition Knowledge Level Scale for Adults" (NKLSA). The t-test in independent groups, Pearson Correlation and the Chi-Square test were used for statistical analysis. More than half of the teachers had a medium level of basic nutritional knowledge, nearly half had a good level of food preferences and a 52% correlation between their knowledge levels. The frequency of those with poor basic nutritional knowledge is significantly higher in men than in women. When the teachers' body mass indexes, daily water consumption, breakfast habits, number of daily meals, and skipping meals were evaluated according to information about nutrition, no significant difference was found in basic nutritional knowledge scores and food preference scores. It should be ensured that teachers have access to the right information sources about nutrition, and awareness activities should be carried out for nutrition, including students, to obtain accurate information about nutritional information and food preferences.

Keywords: Nutritional knowledge, nutrition knowledge level scale for adults, food preferences of teachers

Introduction

One of the basic conditions for the formation of a healthy society is to have individuals who have an adequate and balanced diet. Nutrition is not about filling the stomach, suppressing the feeling of hunger, or consuming the foods that one wants at that moment. A healthy diet is to maintain the body mass index within the required range by eating adequately and balanced with various types of foods, by taking all the nutrients as needed. Healthy nutrition is a lifelong process that starts in the womb and continues for the body's growth, regeneration, functioning, and prevention of chronic diseases. Sufficient and balanced nutrition is defined as an adequate intake of energy and nutrients required for the continuation of body activities and their proper use in the body [1]. If energy and nutrients cannot be taken as much as the body needs, malnutrition occurs. Some of the necessary nutrients cannot be taken into the body if healthy food choices are not made, if the variety in foods is not provided or if cooking methods are applied incorrectly. This condition is called unbalanced nutrition. Malnutrition; While it reduces the ability of people to work efficiently, plan and explore, it can negatively affect health by causing chronic diseases.

Nutritional knowledge includes knowing nutritional processes,

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major nutritional sources of foods, the relationship of diet to health and disease, and dietary recommendations. This definition may vary from person to person or from society to society [2]. Avoiding excessive fat consumption, decreasing the consumption of high-energy and fatty foods, learning healthy cooking methods, reading labels, and acquiring the habit of meal planning are the topics that can be included in the nutritional information [3]. The correct nutrition information received from parents and school will enable the child to apply this information to his/her life, make healthier food choices, to gain and maintain positive eating habits. When he becomes an adult, he will influence the people around him and ensure that positive eating habits are spread and maintained [4].

The source of the information is very important in reaching the right nutrition information. It is important where the information was obtained from, whether it is a personal opinion or newspaper article, and whether it is scientifically supported. When individually declared nutritional information is not tested with realistic experiments, its accuracy cannot be accepted. In areas such as television, newspapers and social media, some statements can be made to increase both the viewing rates and the use of a product. The important thing is to make the appropriate food selection using the right nutrition information and to make the nutrition decision [5]. Along with the developing technology, the information pollution spread by the mass media causes people to gain wrong eating habits with the wrong food selection. This information pollution, which is conveyed to society and includes wrong suggestions, causconfuses the human mind and causes incorrect eating behaviours. behaviours eating habits cause many diseases such as obesity, heart disease, diabetes and hypertension in humans [6].

Due to the lack of nutritional knowledge, some erroneous eating habits may settle in individuals and it may be difficult to get rid of these habits. Although the relationship between nutritional knowledge and behaviour is controversial, there may be more nutritional knowledge and weight loss after nutrition education. Individuals with insufficient nutritional knowledge may acquire faulty eating habits. Because nutrition directly affects healthy development, physiological needs and quality of life. Accurate information is of great importance in healthy nutrition. The first way to ensure the acquisition of the right habit in society is to provide the right information and encourage the right choices [7]. One of the main purposes of health systems is to provide people with the right behaviours that positively affect their health. The first step towards realizing this goal can be achieved with the acquisition of correct information. Current scientific studies are compiled and developed by official guidelines and a scientific committee. These guidelines are made to develop healthy nutrition recommendations for the public. These are published as brochures and booklets. If the nutritional information given is the result of a study, the study should be approved, repeated, and applicable to make healthy nutrition recommendations [5].

To protect the healing nutritional knowledge and status should be determined. In this way, nutrition education and nutrition councounsellingvices can be effectively planned and applied to society. The number of meals eaten in a day, skipped meals, reasons for skipping meals, snacking situations and psychological conditions affecting eating reflect the individual's eating habits [8]. This study aimed to determine teachers' basic nutrition and nutrition-health knowledge levels, who are important opinion leaders for the society, and to evaluate their food preferences.

Material and Methods

The research is a cross-sectional and descriptive study. The research was carried out in a district from December 2021- to January 2022. The universe of the research consisted of 984 teachers working in 40 primary schools and 18 high schools in the a district centre. Schools were selected by cluster sampling method. 95% confidence level and 0.05 margin of error, 280 teachers were included in the research. A questionnaire form as a data collection tool was used, and the data were collected through face-to-face interviews. The consent form was obtained from the participants. The survey form was created by the researchers and consists of 14 questions about sociodemographic information and nutrıtıonal preferences; and 32 questions on the 'Nutrition Knowledge Level Scale for Adults' (NKLSA). NKLSA was developed Batmaz and Güneş in 2018. The Cronbach alpha values for the basic nutrition and food preference part are 0.72 and 0.70, respectively [9]. Body mass index (BMI) was found by dividing the participants' weight by the square of their height. BMI categories defined by current World Health Organization (WHO) guidelines: underweight ($<20.0 \, kg/m^2$), normal weight ($20.0-24.9 \, kg/m^2$), overweight ($25.0-29.9 \, kg/m^2$) and obesity ($\geq 30.0 \, kg/m^2$) [10].

Statistical analysis

Descriptive data were shown as frequency, percentage, and mean/ standard deviation. It was determined that the quantitative data was distributed in a normal distribution with the Kolmogorov-Smirnov test. For quantitative data, the t-test in independent groups and Pearson Correlation were used. One-way ANOVA test was used to compare the countable data of multiple groups. The Chi-Square test was used for qualitative data. The p-value of <0.05 will be considered statistically significant.

Results

The average age of the teachers participating in the research is 36.3±7.3. 50.4% are female, and 49.6% are male. The descriptive characteristics of the teachers are given in Table 1. 49.3% of teachers are in the 30-39 age range and 46.1% have 10 to 19 working years. 77.9% of the teachers are married and 75.4% have children. 87.9% of the teachers work in primary education. The rate of smokers is 25.7%.

Information on the teachers' BMI and dietary habits are shown

in Table 2. When the teachers were evaluated according to their BMI, 47.5% were within normal limits, 5.7% were underweight, 37.9% were overweight and 8.9% were obese. The rate of overweight and obesity in males is significantly higher than that of female teachers. While 41.8% of the teachers consume between 5 and 8 glasses a day, 41.4% consume between 2 and 4 glasses a day. While the rate of those who eat breakfast regularly or frequently is 75.8%, the rate of those who eat three meals a day is 55%, the rate of those who eat two meals is 40%, and the rate of those who eat four or five meals is 5%. While 25.7% of the teachers do not skip meals, 74.3% of them can skip meals. The most frequently used sources of nutrition information are scientific publications or experts on nutrition 42.5%, internet sites 32.5%, and social media 16.4%. The rate of obtaining information from nutritionists is significantly higher in men than in women.

Table 1. Descriptive characteristics of the research group

Feature	n	%
Age group		
22-29	51	18.2
30-39	138	49.3
40-61	91	32.5
Gender		
Man	139	49.6
Woman	141	50.4
Marriage		
Not married	53	18.9
The married	218	77.9
Separated/deceased	9	3.2
Number of children*		
0	69	24.6
1-2	137	48.9
3+	74	26.4
School		
Primary education	246	87.9
High school	34	12.1
Number of working years		
1-9	111	39.6
10-19	129	46.1
20+	40	14.3
Cigarette		
Smoking	72	25.7
Not Smoking	195	69.6
Quoted smoking	13	4.6

n;number. *Single participants also answered this question. Descriptive statistics was used

Table 2. Nutritional habits of teachers and the difference in gender

Feature	n	%	Male	Female	p
BMI					
Underweight	16	5.7	1.4	9.9	
Normal	133	47.5	34.5	60.3	
Overweight	106	37.9	54.0*	22.0	0.001
Obese	25	8.9	10.1*	7.8	
Daily water consumption (number of glasses/day)					
2-4 glasses	116	41.4	46.8	36.2	
5-8 glasses	117	41.8	41.7	41.8	0.039
More than 8 glasses	47	16.8	11.5	22.0	
Breakfast habit					
Regular	169	60.4	55.4	65.2	
Usually	43	15.4	18.7	12.1	
Sometimes	41	14.6	13.7	15.6	0.207
Rarely	19	6.8	7.9	5.7	
None	8	2.9	4.3	1.4	
Number of meals per day					
2nd	112	40.0	38.1	41.8	
3	154	55.0	57.6	52.5	0.661
4-5	14	5.0	4.3	5.7	
Skipping meal					
Yes	109	38.9	36.7	41.1	
Sometimes	99	35.4	24.5	27.0	0.478
No	72	25.7	38.8	31.9	
Nutritional information resource					
Nutritionists	119	42.5	38.8*	26.2	
Websites	91	32.5	13.7	19.1	
Social media	46	16.4	11.5	5.7	0.017
TV	24	8.6	36.0	48.9	

n; number, BMI; body-mass index, TV; television. Chi-square test was used. p values <0.05 was accepted as statistically significant. * It refers to the data from which statistical significance originates.

The frequency of consumption of different types of food by the research group is shown in Table 3. Among the teachers, the rate of those who consume fruit at least 4-5 days a week is 57.5%, those who consume milk and yoghurt 67.5%, those who consume nuts 31.1%, those who consume sweets 13.6%, those who consume chocolate 12.9%, those who consume cola 1.8%, those who consume fast-food 1.1%, those who consume biscuits Those who consume /cake are 7.9%, those who consume white bread are 66.8%. Those who consume chips 2-3 times a week are 4.6%. The mean score of Basic Nutrition and Nutrition-Health knowledge is 54.9±6.3. The food Preferemeansmean score is 38.1±5.5.

Table 3. Frequency of consumption of some foods by the research group

	At least 4 days a week %	3-2 per week %	1 or less per week %
Fruit	57.5	30.7	11.8
Milk, Yoghurt	67.5	22.5	10.0
Nuts	31.1	38.9	30.0
Sweet	13.6	32.1	54.3
Chocolate	12.9	24.3	62.9
Coke	1.8	2.9	95.4
Fast Food	1.1	5.0	93.9
Biscuits, Cake	7.9	17.9	74.3
White Bread	66.8	12.5	20.7
Chips	0.0	4.6	8.9

Descriptive statistics was used

Table 5 shows teachers' basic nutrition, nutrition-health knowledge levels and food preference levels according to descriptive variables. Among male teachers, the frequency of those with poor basic nutrition and nutritional-health knowledge is significantly higher than that of female teachers. There was no significant gender difference in Food Preference. No significant difference was found in terms of basic nutrition food-health knowledge levels and food preferences according to age group, marital status, the number of children, the school worked, the number of working years and smoking status.

Teachers' basic nutrition, nutrition-health knowledge levels and food preference levels are given in Table 4. Basic nutrition and nutrient-health knowledge were moderate in 51.4% of teachers, good in 38.2%, very good in 6.1%, and poor in 4.3%. Food Preferences were good in 41.4%, moderate in 27.5%, very good in 22.9%, and poor in 8.2% of teachers.

Table 4. Teachers' Basic Nutrition Nutrition-Health Knowledge Levels and Food Preference Levels

Basic Nutrition and Nutrition-Health Knowledge Level			Level of Food Preference	
n	%		n	%
12	4.3	**Bad**	23	8.2
144	51.4	**Middle**	77	27.5
107	38.2	**Good**	116	41.4
17	6.1	**Very good**	64	22.9
280	100.0	**Total**	280	100.0

n; number. Descriptive statistics was used.

Table 5. Teachers' Basic Nutritional Nutrition-Health Knowledge Levels and Food Preference Levels According to Descriptive Variables

	n	Basic Nutrition and Nutrition-Health Knowledge Level				Level of Food Preference			
Gender		BAD	MIDDLE	GOOD	VERY GOOD	BAD	MIDDLE	GOOD	VERY GOOD
Man	139	7.9*	49.6	35.3	7.2	10.1	30.9	39.6	19.4
Woman	141	0.7	53.2	41.1	5.0	6.4	24.1	43.3	26.2
		X²=9.86	p=0.020			X²=4.00	p=0.262		
Age group									
22-29	51	3.9	52.9	35.3	7.8	11.8	17.6	41.2	29.4
30-39	138	4.3	47.1	43.5	5.1	7.2	29.0	40.6	23.2
40-61	91	4.4	57.1	31.9	6.6	7.7	30.8	42.9	18.7
		X²=3.73	p=0.714			X²=4.96	p=0.548		
Marriage									
Unmarried	53	3.8	45.3	43.4	7.5	13.2	20.8	47.2	18.9
Married	?227	4.4	52.9	37.0	5.7	7.0	29.1	40.1	23.8
		X²=1.21	p=0.750			X²=4.04	p=0.257		
Child									
No child		2.9	49.3	39.1	8.7	11.6	27.5	42.0	18.8
Having child		4.7	52.1	37.9	5.2	7.1	27.5	41.2	24.2
		X²=1.55	p=0.670			X²=1.93	p=0.588		
School									
Primary		3.7	50.8	39.8	5.7	7.7	27.6	41.5	23.2
High school		8.8	55.9	26.5	8.8	11.8	26.5	41.2	20.6
		X²=3.89	p=0.274			X²=1.55	p=0.670		
Number of working years									
<10		5.4	55.0	35.1	4.5	8.1	24.3	40.5	27.0
≥10		3.6	49.1	40.2	7.1	8.3	29.6	42.0	20.1
		X²=2.18	p=0.535			X²=2.11	p=0.511		
Cigarette									
Smoking		9.7*	48.6	37.5	4.2	15.3*	30.6	38.9	15.3
Not smoking		2.4	52.4	38.5	6.7	5.8	26.4	42.3	25.5
		X²=8.70	p=0.030			X²=8.80	p=0.032		

n; number. Chi-square test was used. p values<0.05 was accepted as statistically significant. * It refers to the data from which statistical significance originates

Table 6 shows the basic nutrition food-health knowledge score averages and food preference score averages according to the nutrition habits of the teachers. When the teachers' body mass indexes, daily water consumption, breakfast habits, number of meals, and skipping meals were evaluated according to information about nutrition, no significant difference was found in basic nutrition food-health knowledge averages and food preference averages.

Table 6. Averages of basic nutrition food-health knowledge points and food preference points according to the nutrition habits of the teachers

Feature	Basic Nutrition Nutrition-Health Knowledge Level Mean Score±SD	p	Mean Food Preference Score±SD	P
BMI				
Underweight	56.3±5.8		37.3±4.6	
Normal	55.3±6.1		38.3±5.5	
Overweight	54.6±6.7	0.337	38.4±5.5	0.385
Obese	53.1±5.9		36.4±5.9	
Daily water consumption (number of glasses/day)				
2-4 glasses	54.4±6.8		37.8±5.3	
5-8 glasses	55.1±5.9	0.525	38.4±5.2	0.691
More than 10 glasses	55.5±6.0		38.0±6.7	
Breakfast habit				
Regular/ Very often	54.8±6.2		38.3±5.2	
Sometimes	54.4±6.5	0.342	37.2±6.2	0.534
Rarely/Never	56.5±6.8		38.3±6.2	
Number of meals per day				
2nd	55.7±6.1		38.7±5.8	
3	54.1±6.2	0.055	37.6±5.1	0.166
4-5	56.8±7.8		39.4±6.7	
Skipping mail				
Yes	54.9±6.2		38.5±6.0	
Sometimes	53.9±6.4	0.292	37.7±5.7	0.622
No	55.5±6.4		37.9±4.7	
Nutritional information resource				
Nutritionists	55.1±6.5		38.6±5.5	
Websites	54.5±6.3		38.0±5.0	
Social media	54.8±8.7	0.970	36.8±5.0	0.501
Newspaper	54.9±5.7		38.0±5.8	

BMI; body-mass index. One-way ANOVA test was used. p values<0.05 was accepted as statistically significant.

The correlation between teachers' basic nutrition, nutrient-health knowledge scores and food preference scores is given in Table 7. When the teachers' basic nutrition and nutrition-health knowledge scores were evaluated in terms of age and BMI, no significant correlation was found between them. When the food preference scores of the teachers were evaluated in terms of age and BMI, no significant correlation was found between them. There is a significant 52% correlation in the same direction between the teachers' basic nutrition food-health knowledge scores and their food preferences.

Table 7. Correlation between teachers' basic nutrition food-health knowledge scores and food preference scores

r	Age	BMI	Nutrition Knowledge	Food Preference
Age	1			
BMI	0.353*	1		
Nutrition Knowledge	-0.041	-0.084	1	
Food Preference	-0.052	-0.047	0.520*	1

BMI; body-mass index. *p<0.05. Pearson correlation test were used. p values<0.05 was accepted as statistically significant

Discussion

Maintaining a healthy life is important for all segments of society. For education workers to continue their lives in a healthy way and due to the conditions and importance of their profession, they need to have a sufficient and balanced diet and set an example with these nutritional habits.

In our study, when the teachers were evaluated according to their BMI, nearly 40% were slightly obese, nearly 10% were obese, and the rate of overweight and obesity was higher in males. According to the data of the "Türkiye Household Health Survey "Risk Factors Prevalence of Non-Communicable Diseases" study conducted in 2017, the frequency of overweight individuals was 35.6% and the frequency of obese individuals was 28.8%, and obesity was found in women (35.9%) than men (21.6%). It was found to be 1.6 times more [11]. The obesity rate among the teachers participating in our study is below the Türkiye average, and differently in males, it is higher. In a study conducted in seven primary schools in the province of Uşak, the rate of obesity among primary school teachers was 3.3%, and the rate of slightly obese students was 12.0% [12]. In a study conducted in 15 different provinces, the mean BMI of primary school teachers was found to be 23.8±4.2 [13].

When their teachers are evaluated according to their water consumption, 83.2% of them consume less than two litres of water per day and there is no difference between men and women. Among them, 41.4% consume between two and four glasses of water a day. A similar result was found in a study conducted with classroom teachers, and 80% of the teachers stated that they consume 2 litres or less of water per day [14]. According to the 2019 results of the Türkiye Nutrition and Health Survey (TBSA),

daily water consumption in Türkiye is 1.6 litres on average, 1.77 litres for men and 1.42 litres for women [15]. Although the amount of daily water consumption is low in Türkiye in general, this amount was found to be lower in our study.

In our study, the rate of those who were fed two meals and stated that they skipped a meal was 40%. As a recommendation for an adequate and balanced diet, experts recommend at least three meals a day [16]. In our study, about three-quarters of the teachers stated that they had breakfast regularly or frequently, and one-fourth of them stated that they skipped breakfast. In the TBSA 2019 report, the frequency of skipping breakfast is 15%, skipping lunch is 24.7%; Men mostly skip breakfast, and women skip lunch. Among the reasons for skipping breakfast, 48.7% stated that they did not want to feel or have an appetite, 14.4% stated that they did not have a habit, and 11.2% stated that they got up late [15]. In a study conducted in Elazig, 43% reported that they ate two meals and skipped meals; 44.5% stated that they do not have a regular breakfast every day [14]. Özyazıcıoğlu et al., (2009) reported in their study that the most skipped meals of the participants were breakfast and lunch [17]. Zemzemoğlu et al., (2019) examined the determinants of the nutritional habits of health sciences students and reported that the most skipped meal by the students was lunch [18]. Similarly, Bayramoğlu et al., (2018) in a study examining the nutritional habits of female academicians, stated that the most skipped meal was lunch, and the reason for skipping a meal was not finding the opportunity [19]. If the morning meal is not made, negative effects such as dizziness, headache, weakness, tremor, and hypoglycemia may occur as a result of long-term hunger. It is known that the habit of skipping meals is common in overweight individuals, and the most skipped meal is breakfast [20].

In our study, approximately 40% of the teachers stated that the most common source of nutrition information was the opinions of experts, while 32% stated that they used websites and 16% social media. In a study conducted in Konya in 2013, it was found that consumers' preferences for mass media, through which they access nutritional information, are TV (29.1%), newspaper-magazine (25.7%), and radio (23.0%) and internet (22.1%), respectively. It has been determined that consumers follow the nutritional information from mass media on a daily and weekly basis (52.5%) and to protect their health (64.0%). It has been determined that the consumers apply the knowledge they have acquired regarding the food recipe (52.4%) and food safety (58.8%) and evaluate the nutritional information in the mass media as understandable (64.9%) and scientific (63.3%). Today, mass media have become the most widely used tool in obtaining nutritional information. In a study carried out in 15 provinces in 2004, the sources from which teachers obtain information about nutrition are newspapers with 48%, magazines with 40%, television with 39%, doctors and dietitians with 22% and 29% [13]. Today, especially the increase in the use of the Internet has surpassed broadcasting organs such as TV in accessing information. Although this situation seems to be a positive result

in terms of easy access to information, increasing information pollution and sharing non-scientific information negatively affect human health [21]. In addition, advertisements for some industrial products occupy a large place on television, the press and the internet. These advertisements create a perception on the consumer or change the existing perceptions and affect their food preferences. Changing food preferences cause society to consume a product more or less [22].

Among the teachers, the rate of those who consume fruit at least 4-5 days a week is 57.5%, those who consume milk and yoghurt 67.5%, those who consume nuts 31.1%, those who consume sweets 13.6%, those who consume chocolate 12.9%, those who consume cola 1.8%, those who consume fast-food 1.1%, those who consume biscuits Those who consume /cake are 7.9%, those who consume white bread are 66.8%. Those who consume chips 2-3 times a week are 4.6%. In the TBSA 2019 report, the rate of those consuming fruit at least 4-5 days a week is 67.9%, the rate of those consuming milk and its products is over 70%, white bread consumption is 9.5%, biscuits/crackers 24.2%, chocolate 3.3%, chips 4.0% [15]. In a study conducted in Uşak, the rate of primary school teachers consuming fast food at least 4-5 days a week was 29.3% [12]. Environmental factors, as well as genetic factors, have been reported to play a significant role in the different prevalence of chronic and allergic diseases [23,24].

In our study, more than half of the teachers had a medium level of basic nutrition, nutrition-health knowledge, and a good level of food preferences, and there was a significant 52% correlation between the two in the same direction. In studies conducted with teachers from different branches, it was stated that teachers' nutritional knowledge levels were insufficient [21]. In a study conducted in 15 different provinces, 19.1% of primary school teachers were found to have sufficient nutritional knowledge [13]. In a study conducted in Uşak, the rate of primary school teachers' correct knowledge of questions about food varies between 18.7% and 76.0% [12]. In our study, the frequency of those with good basic nutrition and nutritional-health knowledge was significantly higher among female teachers than males, but no significant difference was found in terms of gender in terms of food preference. In a study conducted with university students, no statistically significant difference was found between the nutritional knowledge levels of the students according to the gender variable [25]. In another study that measured the dietary behaviours and nutritional knowledge levels of students according to gender, it was reported that more female students had good nutrition knowledge [26]. This helps demonstrate men's disinterest in nutrition or that women are more concerned with food intake and preparation.

When the teachers were evaluated according to their body mass indexes, daily water consumption, breakfast habits, number of meals, skipping meals, and the sources of nutrition information, no significant difference was found in terms of basic nutrition food-health knowledge averages and food preference points averages. Similar to our study, in a study conducted on university

students, no significant difference was found between BMI groups in terms of nutritional knowledge scores [27]. In a study conducted with Belgian women, it was shown that education level, age and occupation type were the factors that most affected nutritional knowledge [28].

Conclusion

About half of the teachers have a normal body mass index, while one-third are slightly overweight and 10% are obese. Approximately 40% of teachers do not consume enough water and skip meals during the day. A quarter does not have a regular breakfast. About half of them are informed about nutrition from internet sites and social media. Basic nutrition, nutrition-health information and food preferences are generally sufficient but moderate. Although the food types preferred by more than half of the teachers are beneficial food groups for health, they are not sufficient. First of all, it should be ensured that the right information sources about nutrition are reached and accurate information about nutritional information and food preferences should be obtained. For this purpose, in-service training or awareness activities on nutrition can be carried out with students. Nutrition information; It is one of the important factors affecting the nutritional status and habits of individuals, families, and societies. In this respect, teachers have an important place in terms of their health, professional life and role models for students.

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ORIGINAL ARTICLE

Investigation of the relationship between emergency department applications and prognoses of geriatric patients

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Abstract

The World Health Organization (WHO) stated that the elderly population constituted 12% of the population of people over 60 years old in 2015. In the coming years, by 2030, 1 out of 6 people in the world will be 60 years or older, and this ratio will increase to 22% in 2050. In addition, it is estimated that the proportion of the elderly population will be 11.0% in 2025, 12.9% in 2030, 16.3% in 2040, 22.6% in 2060 and 25.6% in 2080. The number of admissions to the emergency services of geriatric patients, the hospital treatment process, and even the mortality and morbidity rates increase in elderly patients. In this direction, it was aimed to retrospectively analyze the data of patients over 65 who applied to a tertiary hospital emergency department and determine the factors affecting the mortality of geriatric patients. The presented study is a cross-sectional and retrospective study. All patients over the age of 65 who applied to the emergency department of Ordu University Medical Faculty Training and Research Hospital between 01 July 2022 and 31 2022 were retrospectively analyzed. Demographic features of the cases, the way they applied to the emergency room (112 Emergency Service Ambulance, others: with their own vehicle, by taxi, etc.), the last diagnosis in the emergency department (neurological, cardiovascular, respiratory, metabolic, trauma and others), treatment methods (outpatient, inpatient, intensive care), their motility and the relationship of these data with each other were examined. Between the specified dates, a total of 28459 patients over the age of 18 were admitted to the emergency department. It was determined that 10.16% (n=2894) of these patients consisted of patients over 65 years of age. The relationship between the treatment modalities and mortality according to the way the patients came to the hospital was found to be statistically significant (p<0.005). The relationship between hospitalization, treatment modalities and mortality was statistically significant according to the clinical diagnosis of the cases (p<0.005). In the presented study, it was determined that the mortality of patients who applied to the emergency department due to metabolic problems and who used the ambulance system as a referral tool was high. In fact, the prognosis of geriatric patients who apply to the emergency department for any reason, especially by using the emergency ambulance system, is worse than those who do not use the emergency ambulance system. For this reason, the use of an emergency ambulance system alone affects the prognosis negatively and it is necessary to evaluate such geriatric patients more carefully.

Keywords: Geriatrics, mortality, emergency ambulance system, prognosis, metabolic problems

Introduction

"Aging", "old age" and "senility" are concepts that are frequently used and confused in the fields of gerontology and geriatrics. "Old age", on the other hand, is defined as the dictionary meaning of being old and showing the effects of increased excess. Due to new developments in health and technology, both life expectancy and life expectancy of people have increased. It has been reported that the population aged 65 and over in Turkey is 7 million 953 thousand 555 people in 2020, and its ratio in the total population is 9.5%. In addition, it is estimated that the proportion of the elderly population will be 11.0% in 2025, 12.9% in 2030, 16.3%

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in 2040, 22.6% in 2060 and 25.6% in 2080 [1,2].

In the elderly; many physiopathological conditions can occur that negatively affect the person due to aging such as regression in physical and mental levels, decrease in the potential to establish balance, decrease in adaptation to changing environmental conditions, weakening of the immune system, delay in wound healing. For these reasons, the number of admissions to the emergency services of geriatric patients, the treatment process in the hospital and even the mortality and morbidity rates increase in elderly patients [3].

Due to the aging of the population in our country, it becomes more important to identify the problems of elderly patients and to produce solutions to increase the quality of life and reduce mortality. In this direction, it was aimed to retrospectively analyze the data of patients over 65 years of age who applied to a tertiary hospital emergency department and to determine the factors affecting the mortality of geriatric patients.

Material and Methods

The presented study is a cross-sectional and retrospective study. The emergency department, where the study was conducted, is a tertiary emergency department with approximately 180.000 patients over the age of 18 years old and approximately 10% of these patients are geriatric patients. All patients over the age of 65 who applied to the emergency department of Ordu University Medical Faculty Training and Research Hospital between 01 July 2022 and 31 August 2022 were retrospectively analyzed. Demographic features of the cases, the way they applied to the emergency room (112 Emergency Service Ambulance, others: with their own vehicle, by taxi, etc.), the last diagnosis in the emergency department (neurological, cardiovascular, respiratory, metabolic, trauma and others), treatment methods (out patient, inpatient, intensive care), their motility and the relationship of these data with each other were examined.

Inclusion criteria

All patients over the age of 65 who applied to the emergency department of Ordu University Medical Faculty Training and Research Hospital between 01 July 2022 and 31 August 2022 will be included in the study. Cases whose information could be accessed and whose information was not missing were included in the study.

Exclusion criteria

Cases younger than 65 years, Cases admitted to the emergency department as arrest, Applications other than the first application of cases with recurrent applications on the same day, Cases whose information cannot be reached or with incomplete information will be excluded from the study.

Statistical Analysis

A package program called SPSS (IBM SPSS Statistics 28) was used. Descriptive statistics for continuous variables; Mean, Standard Deviation (SD), Minimum and Maximum.

While it was expressed as values, it was expressed as numbers and percentages for categorical variables. Chi-square test was used to determine the relationship between categorical variables. Student T test was used to determine the difference between the medians of non-homogeneously distributed continuous variables. In our present study, a p value less than 0.05 was considered statistically significant.

Results

Between the specified dates, a total of 28459 patients over the age of 18 were admitted to the emergency department. It was determined that 10.16% (n=2894) of these patients consisted of patients over 65 years of age. 9 of these cases were excluded from the study because of cardiopulmonary arrest in the emergency department, 62 cases were referred to an external center and patient information could not be accessed, 212 cases were excluded due to recurrent admissions in the same day such as dressing, injection, prescribing, and 585 cases were excluded because hospital information could not be reached. The remaining 2026 cases in total were included in the study. It was determined that 43% (n=872) of the cases were male and 57% (n=1154) were female. The age range of the cases was determined as minimum 4/year, maximum 99/year, and mean age 74 ± 12/ year. When the way of admission of the cases to the hospital was examined; those arriving by 112 emergency ambulance were 26.8% (n=542), others (with their own vehicle, taxi, etc.): 73.2% (n=1484). The relationship between the forms of treatment and mortality according to the way the patients came to the hospital is shown in Table 1. According to the clinical diagnoses of the cases, the relationship between hospital admissions, treatment modalities and mortality is shown in Table 2.

Table 1. The relationship between the forms of treatment and mortality of elderly patients according to the way they came to the hospital

	Treatment			Mortality		Total	
	Out Patient	Inpatient	Intensive Care	No	Yes		P
Ambulance	277	153	112	472	70	542	<0.001
	51.10%	28.20%	20.70%	87.10%	12.90%	100.00%	
Others	1324	134	26	1457	27	1484	<0.001
	89.20%	9.00%	1.80%	98.20%	1.80%	100.00%	

Table 2. The relationship between the forms of hospital admission, treatment modalities and mortality in elderly patients according to their clinical diagnoses and forms

	Treatment			Mortality		Way_of_arrival			Total
	Out Patient	Inpatien	Intensive Care	No	Yes	Ambulanc	Others	P	
	125	56	17	182	16	110	83	<0.001	198
Neurological	63.10%	28.30%	8.60%	91.90%	8.10%	55.60%	44.40%		100.00%
	120	24	55	184	15	83	116	<0.001	199
Cardiovascula	60.30%	12.10%	27.60%	92.50%	7.50%	41.70%	58.30%		100.00%
	240	60	32	305	27	119	213	<0.001	332
Respiratory	72.30%	18.10%	9.60%	91.90%	8.10%	35.80%	64.20%		100,00%
	188	116	30	297	37	160	174	<0.001	334
Metabolic	56.30%	34.70%	9.00%	88.90%	11.10%	47.90%	52.10%		100.00%
	123	31	4	157	1	40	118	<0.001	158
Trauma	77.80%	19.60%	2.50%	99.40%	0.60%	25.30%	74.70%		100.00%
	805	0	0	804	1	30	775	<0.001	805
Others	100.00%	0.00%	0.00%	99.90%	0.10%	3.70%	96.30%		100.00%

Discussion

In line with the source information obtained, it has been reported that the admission rate of geriatric patients to the emergency department is increasing gradually in our country and in the world. It has been reported that 15% of the patients admitted to the emergency department are geriatric patients and this rate will increase over time [4]. In another source, it was reported that geriatric cases admitted to the emergency department were between 11.5% and 50% [5]. Ünsal et al. reported that this rate was 13% in their study [6]. In the present study, the rate of geriatric cases admitted to the emergency department was found to be 10.16%. As the reason for the different rates; we think that it depends on the country, city, ethnic factors, the culture of that region, the population characteristics and the equipment of the hospitals. Geriatric patients can come to the emergency department with different application tools. While some of the cases apply by their own means, some cases use the emergency ambulance system. There are studies in the literature stating that cases over the age of 65 use the emergency ambulance at different rates. In the study conducted by Ozsaker et al., they reported that 20% of geriatric patients used the emergency ambulance system [7]. In another study, they reported that 25% of them used the emergency ambulance system [8]. In another study conducted in our country, this rate was found to be 54.1%. In addition, a study reported that 76.3% of geriatric patients were discharged from the emergency department after being treated as an outpatient [7]. In different studies conducted in our country,

they reported this rate to be 78.3% and 71.4%, respectively [6,9]. In the present study, the rate of using the emergency ambulance system in geriatric cases was found to be 26.8%. In addition, it was determined that 51.1% of the cases using the emergency ambulance system were treated as outpatients, while 89.2% of the cases who came to the emergency department with other methods were treated as outpatients. In the presented study, it was determined that the patients using the emergency ambulance system had a significantly higher rate of hospitalization and intensive care admissions than the patients who came to the emergency room by other methods. Similarly, the mortality rates of the cases using the emergency ambulance system were found to be statistically significantly higher than the cases arriving by other methods. This showed that patients using ambulances in geriatric patients had worse disease status and prognosis compared to patients using other methods. In this respect, we believe that more care should be taken when evaluating geriatric patients who apply using the emergency ambulance system.

There are many factors that affect the general health status of elderly patients, the way of applying to the hospital, the way of treating, and their mortality. These include cognitive impairment, dementia, delirium, depression, polypharmacy, incontinence, malnutrition, sarcopenia, falls, gait disturbances, pressure sores, sleep disorders, fragility levels. Depending on these factors, geriatric patients develop different clinical pictures and apply to hospital emergency services. These include neurological, cardiovascular, respiratory, metabolic

(liquid-electrolyte disorders, anemia, acute kidney failure, gastrointestinal bleeding and palliative care purposes) trauma [10]. In a study conducted in our country, they reported that, in order of frequency, geriatric patients admitted to the emergency department had cardiac causes, gastrointestinal problems, and respiratory system problems [9]. Similarly, in the study of Ross et al., it was reported that geriatric patients applied to the emergency department most frequently with cardiac symptoms [11]. Ozsaker et al. reported that the most common causes were respiratory system problems, gastrointestinal system problems, cardiovascular system problems and trauma, respectively [7]. In another study, he reported the causes as neurological, oncological and cardiological causes, respectively [12,13].

In the present study, the most common causes of geriatric patients admitted to the emergency department were found to be metabolic, respiratory and cardiological problems, respectively. In addition, among the geriatric patients who applied to the emergency department, the patients with metabolic problems were admitted to the service at the highest rate. It was determined that the patients with the highest number of cardiovascular problems were admitted to the intensive care unit. While metabolic causes such as fluid-electrolyte disorders, anemia, and acute renal failure can be followed up mostly in the ward, it is thought that patients with cardiac problems (such as acute coronary syndrome, congestive heart failure and aortic dissection) are admitted to the intensive care unit because they are risky patients. It was determined that the patients with metabolic problems had the highest mortality among geriatric patients. Trauma patients had the lowest mortality rate. We believe that the prognosis worsens in geriatric patients when metabolic causes are usually accompanied by comorbid diseases and combined with physiopathological adverse changes. In addition, the low mortality in trauma patients can be attributed to the fact that most of the trauma patients in the center where the study was conducted were simple falls, presented as an outpatient and could be treated as an outpatient. In addition, it is thought that the low mortality rate of geriatric patients presenting with respiratory problems in the presented study may be due to the fact that geriatric patients were worried about covid-19 and applied to the emergency service even with all kinds of simple respiratory symptoms at the time of the study.

It was determined that the group that used the emergency ambulance the most at the time of admission to the emergency department was the patients with neurological symptoms. This may be attributed to the fact that neurological cases deteriorate both the general condition and the state of consciousness more than those who apply for other reasons, and this situation leads the relatives of the patients to go to the hospital by emergency ambulance more. It was found that the mortality of the cases who applied to the emergency department using an emergency ambulance was statistically significantly higher. For this reason, we believe that patients arriving by emergency ambulance should be evaluated more carefully. While there is no significant relationship between mortality and gender, mortality increases with age. We believe that the prognosis worsens with advancing age in individuals over 65 years of age, regardless of gender, when comorbid diseases, multiple drug use, possible malignancies are combined with physiopathological adverse changes.

Conclusion

In the present study, it was determined that the mortality of patients who applied to the emergency department due to metabolic problems and used the ambulance system as a referral tool was high. Therefore, the use of the emergency ambulance system alone affects the prognosis negatively and such geriatric patients should be evaluated more carefully.

Limitation

The most important limitation of the presented study is that it is a retrospective study, it is single-centered, and the number of cases is low.

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ORIGINAL ARTICLE

Medicine Science International Medical Journal

The impact of statin therapy in the COVID-19 patients with very high cardiovascular risk

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Abstract

Antithrombotic and anti-inflammatory impacts of statins have been studied in viral pneumonia. However, the clinical benefits of statins have not been fully explored in high-risk patients with coronavirus disease 2019 (COVID-19). Therefore, the present study assessed the effect of statin use in hospitalized COVID-19 patients with very high cardiovascular risk. Consecutive COVID-19 patients admitted from June 1 to December 31, 2020, were analysed retrospectively. Propensity score-matched analysis was used for creating a 1:1 matched cohort. COVID-19 patients with and without statin use were compared for demographic data, comorbidities, treatments, laboratory findings and in-hospital outcomes. 707 patients (56±9.3 years old; 37% female) were included. Among those, 24.6% (n=174) received statin therapy. A propensity-matched group of 342 patients (171 receiving statins and 171 not receiving statins) was demarcated. The present study demonstrated that statin use significantly reduced in-hospital mortality within 30 days (primary end-point) in univariate (OR=0.314, 95% CI: 0.195 to 0.507) and multivariable-adjusted analysis (OR=0.348, 95% CI: 0.187 to 0.648). Among hospitalized COVID-19 patients with very high cardiovascular risk, statin use was found to be significantly associated with reduced in-hospital 30-days mortality.

Keywords: COVID-19, coronavirus, high cardiovascular risk, pandemic, statin therapy

Introduction

Since the first case in 2019, the Coronavirus Disease 2019 (COVID-19) contaminated more than 260 million people. More than 5 million people died due to this disease. With newly emerging mutations, the pandemic continues to be a leading cause of mortality and morbidity worldwide.

SARS-CoV-2 mainly uses angiotensin-converting enzyme 2 (ACE2) to get into cells and triggers an intense inflammatory host response [1]. This excessive inflammatory response is known to have a negative effect in the development of acute

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respiratory distress syndrome (ARDS) [2] and in particular in the case of COVID-19. The reducing effect of anti-inflammatory drugs on the hyperinflammatory response of COVID-19 have been studied. Animal studies have indicated that inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase could modulate a number of underlying mechanisms involved in the occurrence of ARDS [3]. As an HMG-CoA reductase inhibitor, statins are postulated to be protective in the treatment of COVID-19 in consequence of their immunomodulatory properties. Early studies have demonstrated that pre- and in-hospital statin use may be associated with decreased mortality in COVID-19 patients [4].

The efficacy of statin is more prominent in patients with higher cardiovascular risk. However, its efficacy has not been examined among high-risk patients in the COVID-19 setting. Therefore, in the current retrospective study, the efficacy of statin therapy was studied among patients hospitalized for COVID-19 with very high cardiovascular risk.

Material and Methods

Study population

The patients hospitalized in the intensive care unit of Antalya due to SARS-CoV-2 infection from January 1, 2020 to December 31, 2020 were included in the study retrospectively. Among the consecutive patients hospitalized in the intensive care unit with the diagnosis of SARS-CoV-2 infection, 707 patients with very high cardiovascular risk were analyzed. This study conforms with the tenets of the Declaration of Helsinki and was approved by the ethics committee of Antalya training and research center (2021-059).

Demographic, clinical, and laboratory information of the patients were obtained from the electronic medical record system. Patients were classified according to the HeartScore high-risk countries risk chart [5]. The patients were divided into two groups as those who received and did not receive statin therapy before hospitalization The patients <40 years old were excluded from the study. Patients identified in the very high cardiovascular risk group were included in the analysis. The study population consisted of two groups: patients receiving statin therapy vs. those who did not receive statin therapy before the hospitalization. In-hospital mortality during the follow-up period was the primary outcome.

Statistical analysis

Medians with interquartile ranges or means with standard deviations for continuous variables and percentages for categorical variables were used for the presentation of summary statistics. The two-sided independent t-test and chi-squared test were used, as appropriate for the analysis of the differences in clinical and demographic characteristics and outpatient medications stratified by statin use.

With the objective of minimizing the influence of confounding by indication, a propensity-score matching was used to balance out the clinical characteristics of the two groups. In order to perform the matching, a 1:1 matching protocol without replacement was used, with a caliper width equal to 0.02 of the standard deviation of the propensity score's logit. The following variables were used for adjustment: age, sex, history of atrial fibrillation, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, cancer, chronic kidney disease, chronic obstructive pulmonary disease, smoking, and corticosteroid treatment. We performed descriptive analyses for all baseline variables in the overall cohort and the propensity-matched cohort.

To identify potential predictors of mortality, we initially performed a univariate logistic regression in the overall cohort. Covariables with p < 0.20 were selected for entry into the multivariable model, and covariables with p > 0.05 were removed from the final model. Similarly, both univariable and multivariable logistic regression was performed in the propensity-score matched cohort. All the analyses were performed with the assistance of the SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Overall, 707 patients (56±9.3 years old; 37% female) were included in the study. Hypertension (HTN; 69%), diabetes mellitus (DM; 49%), and coronary artery disease (CAD; 21%) were highly prevalent comorbidities. In addition, 46 % of patients were smokers (Table I). Within all patients, 24.6% (n=174) were chronic statin users. The patients receiving statins were younger [68.8±8.5 vs. 72.3±9.3 years, p<0.001] and we found no significant difference in sex between two groups (p = 0.37). There were significant differences between patients receiving and not receiving statins in regard of HT (86.8% vs. 62.9%), DM (66.7% vs. 43.2%), CAD (52.9% vs. 10.9%), heart failure (8.0% vs. 2.1%) (p<0.001 for all), and chronic kidney disease (9.8% vs. 5.8%) (p=0.07) respectively. Although the mean LDL value was lower in the patient group receiving statin therapy, no statistically significant difference was found between two groups (101.4±35.1 vs 105.9±53.8, p=0.31). No significant differences in chronic obstructive pulmonary disease (COPD) and atrial fibrillation were detected between the two groups (p=0.84 and 0.35 respectively). Compared to patients not on statins, those using statins were considerably more likely on ACEi (36.8% vs. 11.6%), clopidogrel (23.0% vs. 7.1%), (p<0.001 for all) and oral anticoagulant therapies (8.0% vs. 3.4 % p:0.01)

The mortality ratio in the patients included in the study was 47.5% (n:336). While the mortality ratio of the patients receiving statin therapy was 20.1% (n:35), it was found 56.5% (n:301) in the patients not receiving statin therapy (p<0.001). A total of 169 patients required mechanic ventilation. This ratio was 18.5% (n:32) in the patient group receiving statin therapy, whereas 25.7% (n:137) of the patients required mechanical ventilation in the group of patients not receiving statin therapy (p=0.054). A total of 167 patients received inotropic support therapy. This

ratio was 17.8% (n:31) in the statin treatment group, while it was found 25.5% (n:136) in the group not receiving statin therapy (p=0.038).

Propensity-matched cohort characteristics

A total of 707 patients (171 patients receiving statins, 171 patients not receiving statins) were retained using 1:1 propensity score matching. There were significant differences in terms of CAD, congestive heart failure (CHF), and ACE inhibitor medication, whereas the other demographic factors remained in

Table 1. Patient characteristics by statin use in unmatched and matched cohorts

Variable	Unmatched			Matched		
	Statin use(N=174)	No statin use(N=533)	p-value	Statin use(N=171)	No statin use(N=171)	p-value
Age	68.8±8.5	72.3±9.3	<0.001	68.8±8.5	69.0±8.5	0.84
Male	115(66.1)	332(62.3)	0.37	114(66.7)	105(61.4)	0.31
Smoking	84(48.6)	242(45.4)	0.47	83(48.5)	79(46.2)	0.66
Comorbidities						
Atrial fibrillation	5(2.9)	24(4.5)	0.35	5(2.9)	4(2.3)	0.74
Cancer	3(1.7)	33(6.2)	0.020	3(1.8)	4(2.3)	0.70
Chronic kidney disease	17(9.8)	31(5.8)	0.07	17(9.9)	9(5.3)	0.10
Chronic obstructive pulmonary disease	18(10.3)	58(10.9)	0.84	18(10.5)	12(7.0)	0.25
Congestive heart failure	14(8.0)	11(2.1)	<0.001	13(7.6)	0(0.0)	<0.001
Coronary artery disease	92(52.9)	58(10.9)	<0.001	91(53.2)	39(22.8)	<0.001
Diabetes mellitus	116(66.7)	230(43.2)	<0.001	113(66.1)	105(61.4)	0.37
Hypertension	151(86.8)	335(62.9)	<0.001	148(86.5)	140(81.9)	0.24
Medications						
ACE inhibitors	64(36.8)	62(11.6)	<0.001	64(37.4)	25(14.6)	<0.001
ARBs	34(19.5)	125(23.5)	0.28	33(19.3)	44(25.7)	0.15
Aspirin	73(42.0)	99(18.6)	<0.001	73(42.7)	52(30.4)	0.018
Clopidogrel	40(23.0)	38(7.1)	<0.001	40(23.4)	21(12.3)	0.007
Other antiplatelet agents	2(1.1)	3(0.6)	0.42	2(1.2)	3(1.8)	0.65
Oral anticoagulants	14(8.0)	18(3.4)	0.010	14(8.2)	3(1.8)	0.006
Corticosteroids	100(58.1)	314(59.0)	0.84	99(57.9)	98(57.3)	0.91
Lipid profile						
Total cholesterol	173±44.1	174.4±42.3	0.71	172.5±44.1	174.8±41.4	0.62
Low-density lipoprotein cholesterol	101.4±35.1	105.9±53.8	0.31	101.0±35.1	103.9±33.0	0.42
High-density lipoprotein cholesterol	44.9±8.4	42.5±15.5	0.05	44.8±8.4	40.8±13.0	<.001
Triglycerides	148.3±99.4	144.3±57.2	0.51	148.6±100.2	152.3±66.9	0.69
Laboratory results						
Hemoglobin	12.6±1.8	12.2±1.9	0.05	12.6±1.8	12.4±1.8	0.35
Platelet	216.4±89.8	220.9±97.9	0.59	217.2±90.3	216.5±89.1	0.95
White blood cell	8.2±3.9	8.9±5.4	0.10	8.2±3.9	8.4±4.1	0.75
Neutrophil	6.4±3.7	7.0±4.9	0.14	6.4±3.7	6.5±3.9	0.78
Lymphocyte	1.4±1.4	1.5±3.3	0.53	1.4±1.4	1.4±1.4	0.98
Neutrophil-lymphocyte ratio [median (IQR)]	4.96(3.23-7.45)	5.06(3.07–10.3)	0.43	7.3±8.0	9.0±21.1	0.11
C-reactive protein [median (IQR)]	72(25–114)	88(37-156)	0.006*	87.5±82.6	106.7±88.3	0.039
D-dimer [median (IQR)]	313(181-565)	380(211-715)	0.024*	313.0(180-555)	290(201-637)	0.042
Troponin [median (IQR)]	20.0(10.0-51.0)	17.0(9.0–36.0)	0.28	20.5±(10-51)	14(9-41)	0.17

* P with Non parametric Mann-Whitney U test
ARB: Angiotensin receptor blocker. ACE: Angiotensin converting enzyme. IQR. interquartile range

the propensity-matched cohort were similar (Table 1).

Clinical outcomes of a propensity-matched cohort

Statin use significantly reduced in-hospital mortality within 30 days (primary end point) in univariate (OR 0.314, 95% CI: 0.195 to 0.507) and multivariable-adjusted analysis (OR 0.348 95% CI: 0.187 to 0.648) (Table 2). Age, smoking, ACEI use and high CRP

Table 2. Univariable and multivariable analysis in unmatched and matched cohorts

Variable	Unmatched				Matched			
	Univariable		Multivariable		Univariable		Matched	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Statin	0.194 (0.129 to 0.292)	<0.001	0.191 (0.115 to 0.320)	<0.001	0.314 (0.195 to 0.507)	<0.001	0.348 (0.187 to 0.648)	0.001
Age (per 1 years)	1.060 (1.042 to 1.079)	<0.001	1.052 (1.027 to 1.077)	<0.001	1.056 (1.027 to 1.085)	0.001	1.082 (1.041 to 1.125)	<0.001
Smoking	1.730 (1.283 to 2.332)	<0.001	2.572 (1.747 to 3.786)	<0.001	2.115 (1.335 to 3.351)	0.001	-	-
Atrial fibrillation	0.567 (0.260 to 1.237)	0.154	-	-	0.250 (0.031 to 2.024)	0.194	—	—
Cancer	1.107 (0.566 to 2.165)	0.766	—	—	0.336 (0.040 to 2.828)	0.316	—	—
Chronic kidney disease	0.847 (0.469 to 1.528)	0.581	—	—	1.311 (0.575 to 2.991)	0.519	-	-
Chronic obstructive pulmonary disease	0.880 (0.545 to 1.419)	0.599	—	—	0.291 (0.099 to 0.854)	0.024	—	—
Congestive heart failure	0.930 (0.411 to 2.104)	0.861	—	—	0.606 (0.163 to 2.246)	0.453	-	-
Coronary artery disease	0.663 (0.459 to 0.957)	0.028	1.728 (1.022 to 2.923)	0.041	1.354 (0.853 to 2.147)	0.198	—	—
Diabetes mellitus	0.325 (0.239 to 0.442)	<0.001	0.513 (0.357 to 0.736)	<0.001	0.526 (0.331 to 0.836)	0.007	—	—
Hypertension	0.694 (0.504 to 0.955)	0.025	—	—	1.474 (0.765 to 2.839)	0.247	0.448 (0.209 to 0.960)	0.039
ACE inhibitors	0.446 (0.297 to 0.672)	<0.001	—	—	0.467 (0.265 to 0.824)	0.009	—	—
ARBs	0.978 (0.687 to 1.394)	0.903	—	—	1.325 (0.781 to 2.249)	0.297	—	—
Aspirin	0.518 (0.363 to 0.739)	<0.001	0.474 (0.305 to 0.737)	<0.001	1.190 (0.747 to 1.897)	0.464	—	—
Clopidogrel	0.582 (0.357 to 0.948)	0.029	—	—	0.833 (0.455 to 1.523)	0.552	—	—
Other antiplatelet agents	4.446 (0.494 to 39.97)	0.183	—	—	8.477 (0.937 to 76.73)	0.057	—	—
Oral anticoagulants	0.850 (0.416 to 1.737)	0.656	—	—	0.849 (0.292 to 2.471)	0.764	2.312 (1.142 to 4.684)	0.020
C-reactive protein (≥37.2)	2.480 (1.751 to 3.511)	<0.001	1.981 (1.325 to 2.961)	<0.001	3.236 (1.830 to 5.723)	<0.001		
D-dimer (≥521)	1.907 (1.374 to 2.647)	<0.001	—	—	2.133 (1.297 to 3.508)	0.003		
Troponin (≥15)	2.131 (1.572 to 2.888)	<0.0001	1.625 (1.101 to 2.398)	0.014	2.657 (1.671 to 4.226)	<0.001		

and troponin levels were the other factors related with increased rates of the primary endpoint.

Discussion

In this study of hospitalized COVID-19 patients with very high cardiovascular risk, the principal findings are: [1] use of statin therapy was common (24.6%) in the overall cohort; [2] patients receiving statin therapy was slightly younger but with a higher burden of cardiovascular morbidity including CHF, CAD, DM, and HTN; and [3] statin use reduced in-hospital mortality in both the overall cohort and the propensity score-matched cohort after multivariable adjustment.

In a recent meta-analysis of COVID-19 patients, it was revealed that while no significant reductions in intensive care unit admissions and mortality by statins were experienced, there was in fact a significant decrease in all-cause mortality in the subset of patients with cardiovascular disease [4]. However, the observed association still needs to be confirmed due to the limited number of included studies. The current study is the first to confirm the survival benefit of receiving statin therapy among hospitalized COVID-19 patients with very high CV risk.

Prior to the event of COVID-19, some studies had revealed that hospitalized pneumonia patients taking statins had a lower mortality rate in comparison to those not taking statins, and also correlation between continuous use of statins and decreased risk of mortality or intubation in patients with COPD was demonstrated [6,7]. As expected, the effects of statins on the disease were also investigated during the COVID-19 period. Several studies demonstrated favorable outcomes with statins in patients with COVID-19 [8-10]. In general, meta-analyses have also supported the efficacy of statins. Zein et al. found that in the meta-analysis of propensity score-matched cohorts with multivariable-adjusted analysis, statin decreased mortality risk in patients with COVID-19 [11]. In a meta-analysis of retrospective observational studies on hospitalized COVID-19 patients performed by Kolias et al., the authors revealed a 35% decrease in the adjusted risk of mortality with statin therapy [12]. In contrast, certain studies did not show a relation between statin use and reduced mortality, but demonstrated increased risk of severe COVID-19 infection [13]. The main reason for conflicting results between the studies and meta-analyses could be related to the cardiovascular profile of the studied patients. Given the proven benefits of statins in various and despite the mixed evidence, pursuance of statin therapy continues to be generally recommended in COVID-19 patients with increased cardiovascular risk [14].

Favorable characteristics of statins are plaque stabilization and anti-thrombotic properties [15]. It was shown in studies consisting of COVID-19 patients that there is a relation between pre-existing cardiovascular disease and worse clinical outcomes [16]. Therefore, it is possible that statin therapy confers benefit by preventing thrombotic events and myocardial injury, which are the key contributors of mortality in this population. In addition,

there is a strong evidence indicating statins' anti-inflammatory properties of statins in various clinical contexts. In this regard, patients on statin therapy were shown to have lower levels of CRP and D-dimer than those who did not receive statins. In the current study there was no significant difference in the mean LDL values of the two groups. This suggests that the beneficial effect of statin therapy is not associated with low LDL value, but may be due to its anti-inflammatory effect.

Several important limitations should be considered. First, although propensity score matching and multivariable analysis were performed, there could still be unmeasured confounding factors in this retrospective study. Especially, the difference in ACEi therapy between the two groups is confusing. It should be tested in prospective studies. Second, the duration and adherence of statin could not be verified in the study. Third, patients who received statin therapy may have undergone more intense surveillance and care due to comorbidities, which may have affected the in-hospital mortality. Finally, our sample size was relatively limited and the study method was retrospective.

Conclusion

This study has revealed that there indeed exists an association between statin use and reduced in-hospital mortality, in hospitalized COVID-19 patients presenting a very high cardiovascular risk. The results require to be validated by large-scale prospective studies.

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ORIGINAL ARTICLE

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Anticancer activity of Heat Shock Protein 70 (HSP70) Inhibitor, JG-98, against human cervical cancer HeLa and ovarian cancer SKOV-3 cells

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Abstract

Cervical and ovarian cancer are two aggressive neoplasms for women, still with high mortality and morbidity. Among the molecules and compounds that have anticancer activity, it was studied the JG-98, a heat shock protein 70 (HSP70) inhibitor. It demonstrated inhibitory effects on the growth of neoplastic cells, mediated by the induction of apoptosis, with anti-proliferation activity on neoplastic cells via the apoptotic pathway. The authors investigated the antiproliferative effects of JG-98 on human cervical cancer HeLa and ovarian cancer SKOV-3, examined by a standard XTT assay. Apoptotic effects and oxidative status were also evaluated by flow cytometry, ELISA, and total oxidant status assays in HeLa cells, respectively. The IC50 values of JG-98 in HeLa and SKOV-3 cells were recorded as 1.79 and 2.96 µM, respectively. Flow cytometry results showed that JG-98 treatment remarkably increased the proportion of apoptotic cells at IC50 concentration. The JG-98 treatment significantly increased the proteins Bax, cleaved caspase 3, cleaved PARP, and 8-oxo-dG levels, all indicators of cellular apoptosis. These findings show that JG-98 significantly decreased cell proliferation and increased apoptosis in HeLa cells, suggesting that JG-98 has a promising anti-tumor effect in cervical and ovarian cancers.

Keywords: Cervical cancer, ovarian cancer, HSP70, JG-98, HeLa cells, SKOV-3 cells, apoptosis

Introduction

Among the gynecological cancers, cervical and ovarian ones are frequent neoplasms with challenging management options, including chemotherapy modalities [1,2]. Nowadays, several types of molecules and compounds and related molecular mechanisms are leading research topics to discover novel and effective drug candidates and targets for these gynecological cancers as well as for other types of cancers [3].

Heat-shock proteins (HSP) have recently attached the scientific interest of researchers, as novel chemotherapeutic targets, since current molecular data support that HSP-70s have important roles in cancer biology with their unique functions and their interaction with other molecular pathways in cancer biology [4]. In fact, the HSPs constitute one of the main families of ATP-dependent molecular chaperones that positively affect malignant growth in many cancers through proliferation, metastasis, anti-apoptosis, and angiogenesis [1,2]. Among these HSPs, several critical roles for the HSP-70 protein in cancer initiation and progression have been demonstrated by mechanistic studies

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from cell culture and animal models [5]. This attracts attention to this protein as a promising molecule and an important target for investigating drug candidates for a variety of cancers [6].

Cancer cells need several stress-reducing survival factors, including the HSP-70 protein. The expression of HSP-70 enhances sharply during a stress response; although, at a low level, it also takes place under normal conditions [3]. Unlike normal cells, many cancer cells largely express the HSP-70 protein to resist many biological modifications, either during tumorigenesis or during cancer treatment. Therefore, the addiction of cancer cells to HSP-70 is the main reason for its suitability as a target for the development of novel chemo-therapeutic alternatives [7].

Blocking the HSP-70 expressions by the siRNA approach promotes cancer cell death, especially after dual silencing of HSC70 and HSP-70 translations. In addition, these interventions also selectively lead the malignant cells to be more susceptible to other chemotherapeutics [8]. The effects of the HSP-70 protein on malignant cells consist of (a) suppressing several steps of apoptotic pathways; (b) regulating necrosis; (c) preventing entry to the cellular senescence program; (d) negatively interacting with tumor immunity; and (e) enhancing angiogenesis and helping metastasis. Thus, the direct involvement of HSP-70 protein in various cancer types explains the phenomenon of the tight link between cancer cell survival and modulation of HSP-70 expression [7,9]. Moreover, cancer cells also intensively release HSP-70 into the extracellular microenvironment, resulting in adverse outcomes in cancer patients [4,8].

In accordance with the confirmed roles of the HSP-70 protein as a survival supporter for cancer cells, several studies revealed the major contribution of HSP-70 to the proliferation of cancer cells by enhancing their resistance to chemotherapy [10]. After the development of resistance to cisplatin, there is a significant increase in the expression of the HSP-70 protein in human ovarian cancer cells [10]. Reversing drug resistance of cancer cells leads to HSP-70 down-regulation. This biological effect may be a crucial factor in the inhibition of apoptosis by returning HSP-70 up-regulation, leading both upstream and downstream of the mitochondrial signaling molecules [11]. Hence, to increase the clinical efficacy of HSP-70 blockage, it would be beneficial to determine promising molecules, reducing the interaction of HSP-70 with other co-chaperone molecules [11]. Considering candidate molecule groups targeting the HSP-70 protein, laboratory data supported the potency of protein JG-98, an allosteric HSP-70 inhibitor, in decreasing the proliferation of cancer cells. The expression of HSP-70 protein increases in several cancers with regard to the increase in tumor grade, metastasis, and poor prognosis; in concordance with these data, the decrease in HSP-70 expression reduces cancer progress in mouse models [5].

To examine the merit of novel molecules to be a chemotherapeutic agent and the mechanisms of their effects, cell lines are vital as a first step to understanding molecular and behavioral changes, altering the proliferation and survival of cancer cells [12]. The JG-98 has an anticancer HSP-70 inhibitor effect in the HeLa human cervical cancer cell line and in the ovarian cancer SKOV-3 cell line. This significant cytotoxic effect on cancer cell lines has been mainly related to the increase in oxidative stress and apoptosis [13]. Further investigation is needed to better understand the mechanisms of action of the JG-98 protein in HeLa and SKOV-3 cells. Since HeLa cells have been detected to be more susceptible to the JG-98 protein compared to the SKOV-3 cells in the current study, mechanistic studies were performed within this cell line. In this study, the effects of the JG-98 protein, as an HSP-70 inhibitor, on the proliferation of human cervical cancer HeLa and ovarian cancer SKOV-3 cells, were evaluated.

Material and Methods

Laboratory experiments of this research were carried out between January 2021 and April 2021 at the Sivas Cumhuriyet University Faculty of Medicine Research Center. This study was approved by the Human Research Ethics Committee of the Sivas Cumhuriyet University, Sivas, Turkey (Approval number: 2021-11/56).

Cell lines and cell culture

The American Type Culture Collection (ATCC, USA) was used to obtain HeLa (CCL-2) and SKOV-3 (HTB-77) cell lines. Cells were found as standard in the modified Dulbecco Eagle environment (Sigma-Aldrich, USA). During this procedure, cells were grown in a humidified atmosphere with 5% CO_2 at 37 ˚C. When examined, the contents of the media mixture contained 10% bovine fetal serum (FBS) (Sigma-Aldrich, USA), 1% L-glutamine (Sigma-Aldrich, USA), and 1% mixed penicillin/streptomycin antibiotics (Sigma-Aldrich, USA). The JG-98 protein (Medchem, USA) was then dissolved in DMSO in DMSO. By dilution, less than 0.1% of the final DMSO content was obtained prior to the treatment of cancer cells.

Cell viability assay

A standard XTT test (Roche Diagnostic, Germany) has been used to detect the cytotoxic activity of JG-98 against HeLa and SKOV-3 cell lines. The cells were used as triplicate in 96-well cell culture plates with an adjusted density of 1×10^4 cells per well. Cells were incubated at concentrations of 0.1, 1, 2.5, 5, 10, 20 and 40 µM of JG-98 for 24 hours. In the study, viable cells were measured by adding 50 ml of XTT labeling mixture. Cells were incubated for 4 hours. Repeated absorbance measurements were obtained using an ELISA (Epoch, Biotech, United States) microplate reader at 450 nm. Cell viability was recorded in % with controls (100% viability). The IC50 values of JG-98 in HeLa and SKOV-3 cell lines were demonstrated using Graph Prism 8 software (GraphPad, United States). According to the favorable CI50 of JG-98 in HeLa cells, they have been used in ELISA and flow cytometry experiments.

Annexin V binding assay

Approximately 5×10^5 HeLa cells were seeded into 6-well plates and allowed to adhere overnight. The following day, they were grown in the presence of the JG-98 at 1 and 2.5 μM concentration and incubated for another 24 h. After trypsinization, the cells were collected and suspended in PBS containing at least 1% FBS. During these procedures, it was blended with an equal volume of Annexin V and Dead Cell reagent (Merck Milli-pore, United States) following the manufacturer's instructions. Live, dead, early apoptotic, and late cells were assessed by quantification with the Muse Cell Analyzer (Merck Millipore, United States).

Bax protein, cleaved caspase 3, BCL-2, cleaved PARP, and 8-hydroxy-deoxyguanosine expression analyses

The human Bax ELISA kit (BT Lab, catalog #E1825HU), the human cleaved caspase 3 ELISA kit (BT Lab, catalog #E6970HU), the human BCL-2 ELISA kit (BT Lab, catalog #E1832HU), and the human cleaved PARP ELISA kit (BT Lab, catalog #E6971HU), and the human 8-Hydroxy-Desoxyguanosine ELISA kit (BT Lab, catalog #E1436HU) were used to determine the levels of Bcl-2-associated X protein (Bax), cleaved caspase 3 (Asp175), BCL-2 family proteins, cleaved PARP (Asp214), and 8-hydroxy-deoxyguanosine (8-oxo-dG) levels in the JG-98-treated and untreated HeLa cells. HeLa cells were seeded in a 6-well plate and treated to JG-98 concentrations of 1 and 2.5 μM for 24 hours. JG-98 cells were collected, diluted with PBS, and destroyed by multiple freeze-thaw cycles, both treated and untreated. The levels of Bax, cleaved caspase 3, BCL-2, cleaved PARP, and 8-oxo-dG in the cell lysates were measured in the order recommended by the manufacturer. The BCA assay was used to compare the total protein contents in treated and untreated HeLa cells (Pierce Biotechnology, United States).

Measurement of Total Oxidant Status (TOS) in JG-98-treated and untreated HeLa cells

The TOS assay kit was used to determine the value of total oxidative status (TOS) in treated and untreated HeLa JG-98 cells (Rel Assay Diagnostics, Turkey). JG-98 was given to HeLa cells at doses of 1 and 2.5 μM for 24 hours, according to the manufacturer's instructions. In the case of TOS, the results were expressed in mol H_2O_2 equivalent/L [14].

Statistical analysis

Statistical analysis was performed using IBM SPSS v23 (IBM SPSS, United States). The Kruskal-Wallis ANOVA test with post hoc Dunn's test was used to examine the laboratory data, which were provided as mean standard deviation. Statistical significance was defined as a p-value lower than 0.05.

Results

First, the cytotoxic effect of the JG-98 was determined in the HeLa and the SKOV-3 cells. As seen in Figure 1, the JG-98 inhibited the growth of cancer cell lines in a concentration-dependent manner (P<0.01).

The IC50 values of JG-98 in the HeLa and the SKOV-3 cells were recorded as 1.79 and 2.96 μM, respectively, for 24 h. The JG-98 treatment also considerably impacted HeLa cell density and cell morphology (Figure 2 a, b, and c).
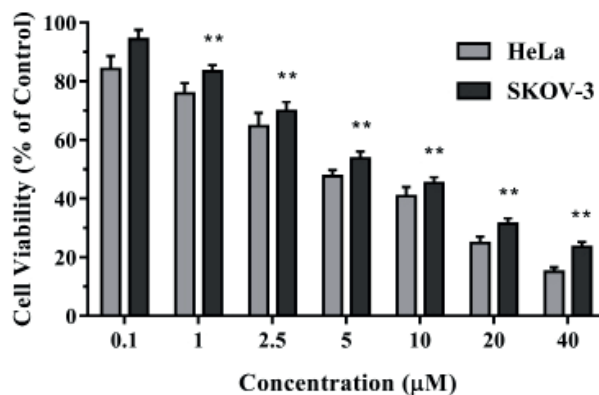
Figure 1. The effects of JG-98 on the viability of HeLa and SKOV-3 cells. JG-98 was applied to the cells for 24 h concentrations ranging from 0.1 to 40 μM. The XTT assay was used to determine the number of viable cells. When compared to untreated control, the results are expressed as a percentage of viable cells. The data represent the mean SD of two separate experiments. The differences are statistically significant when **p<0.01 compared to the control. All cell viability results for HeLa cells are significantly different from the control for 0.1, 1, 2.5, 5, 10, 20, and 40-μM concentrations (p<0.01)
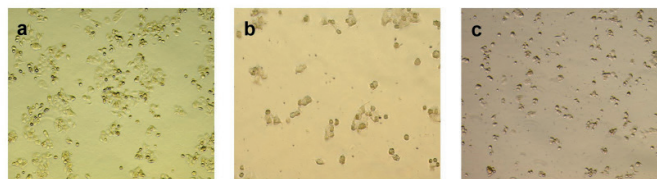
Figure 2. The effect of JG-98-treatment on HeLa cell morphology. Control cells are shown on the left (a), cells treated with 1 μM JG-98 in the middle (b), and cells treated with 2.5 μM JG-98 on the right (c)

Flow cytometry investigation of the apoptotic effects of JG-98 on HeLa cells revealed that JG-98 treatment significantly increased the proportion of apoptotic cells at IC50 concentration for 24 h compared to untreated cells (Figure 3).

The percentage of early and late apoptotic cells in the control group (3.78±0.79% and 0.91±0.11%, respectively) increased considerably to 10.61±1.35%, 13.69±0.97% and 58.33±2.45%, and 67.79%±3.11 respectively, in 1 and 2.5 μM JG-98-treated HeLa cells (P<0.01).

The effects of the JG-98 therapy on pro and anti-apoptotic protein expression in HeLa cells were also assessed using ELISA assays. The compound treatment significantly increased Bax (P<0.01), cleaved caspase 3 (P<0.05 for 1 μM and P<0.01 for 2.5 μM), cleaved PARP (P<0.01), and 8-oxo-dG (P<0.05) levels, while anti-apoptotic BCL-2 levels dropped.

The TOS assay kit analysis showed the TOS values of 2.81±0.27 in control cells and 5.62±0.51 and 7.79±0.63 in 1 and 2.5 μM JG-98-treated cells, respectively (P<0.01), as shown in Figure 5.
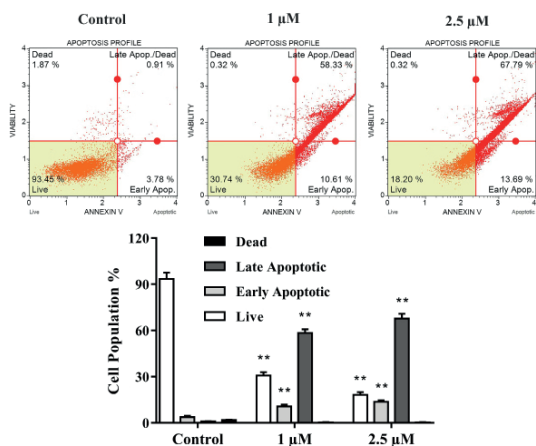
Figure 3. Annexin V staining revealed that JG-98 caused apoptosis in HeLa cells for 24 hours in a concentration-dependent manner. As detailed in the Material and Methods section, the cells were exposed to 1 and 2.5 μM JG-98, and the number of apoptotic cells was determined using the Muse cell analyzer (Merck Millipore, Billerica, USA). The percentages of early and late apoptotic cells increased significantly in cells treated with 1 and 2.5 μM JG-98. Three times each experiment was carried out. **P value <0.01 as compared to the untreated HeLa cells and the 1 or 2.5 μM JG-98-treated groups
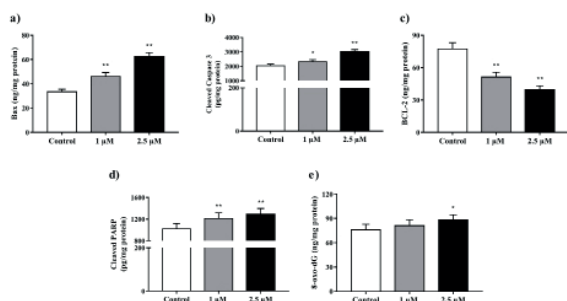
Figure 4. JG-98 treatment increased apoptosis and DNA damage in HeLa cells for 24 hours, as measured by ELISA. The levels of Bax, cleaved caspase 3, BCL-2, cleaved PARP, and 8-oxo-dG were measured using an ELISA kit after the cells were treated with JG-98 at 1 and 2.5 μM for 24 hours. The values are the mean SD of three samples of media taken from HeLa cell wells. *P value <0.05 vs. untreated HeLa cells and those treated with 1 or 2.5 μM JG-98
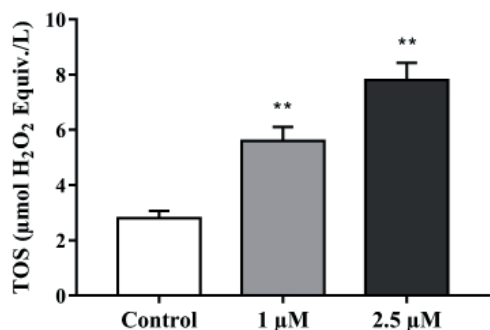
Figure 5. JG-98 treatment greatly increased the TOS of HeLa cells. The cells were treated for 24 h with 1 and 2. 5μM JG-98, and TOS was determined using a TOS assay kit. The values represent the mean SD of three samples of medium taken from wells containing HeLa cells. **P value <0.01 vs. untreated HeLa cells and 1 or 2.5 μM JG-98-treated groups

Discussion

This study screened the cytotoxic activity of the JG-98 protein in HeLa and SKOV-3 cells for the first time in the literature, showing a decreased cell viability for HeLa and SKOV-3 cells in a dose-dependent manner when treated with JG-98 for 24 hours. The authors also performed in vitro biological assays to determine the anticancer effect of the JG-98 on HeLa cells, which is the most sensitive to JG-98. Overall, the JG-98 provided an anticancer effect due to its apoptotic effects, under the influence of oxidative stress.

In cancer treatments, the development of new treatment modalities by the HSP-70s is a reliable option. The HSP-70s proteins have been reported to localize to the plasma membrane under pathophysiological states, including cancer, but apart from the corresponding normal cells [15,16]. HSP-70, which is a fundamental component of the anti-stress defense system, supports the survival of cancer cells with its interaction at key points in cellular apoptotic pathways. However, high expression of extracellular HSP-70 is indicative of a worse prognosis during the cancer process. The HSP-70 inhibition leads to anti-tumor system activation and apoptotic process in some tumors [17]. Research on HSP-70 inhibitors could provide novel drugs for physicians, to use alone and in combination, as a promising tool to develop more successful anti-cancer strategies, improve the patient's outcomes, and for long-term survival [18].

A review of related studies reveals the relationship between HSP-70 and its support for cell survival during different types of ongoing cell death, such as caspase-dependent/independent apoptosis, necrosis, autophagy, or programmed cell death [19]. Besides, cancer cells are exposed to many environmental, physiological, and pathophysiological stress conditions within the tumor microenvironment. These include high oxidative stress, limited nutrients, hypoxia, and increased expression of mutant proteins which, in combination, affect cancer cell survival [19].

Liu et al. investigated the effect of 2-Phenylethinsulfonamide (PES), a small molecular inhibitor of HSP-70, used with cisplatin to inhibit the proliferation of cervical cancer cells in vitro and tumor growth after in vivo animal models [20]. The authors showed that PES could enhance the killing effect of cisplatin on them [20]. Moreover, PES combined with cisplatin could inhibit the proliferation and development of cervical cancer cells in vitro and the transplanted tumor growth of cervical cancer cells, through the mitochondrial apoptosis pathway [20].

Garg et al. evaluated the contribution of the expression of HSP-70-2, a member of the HSP-70 chaperones protein family, to the malignant properties of cervical cancer [21]. The authors detected that HSP-70-2 is highly expressed in many cervical cancer cell lines and neoplastic tissues of cervical cancer patients, suggesting that HSP-70-2 has several significant roles in cell migration, invasion, and tumorigenesis in cervical cancer [21].

Court et al. investigated gene expression profiles during magnetic

fluid hyperthermia in ovarian cancer cells to determine cellular response and molecular targets to promote its effect in vitro and in vivo experiments [22]. The authors evaluated whether there was an up-regulation of several HSPs and the HSP-70 was found to be the most up-regulated gene. They showed that the inhibition of HSP-70 by RNA interference, as well as by PES, a novel HSP-70 inhibitor, enhanced the effect of magnetic fluid hyperthermia, both in vitro and in vivo experiments in ovarian cancer cell lines and animal models [22].

In a recent investigation on the mRNA profile in 196 patients with ovarian cancer by microarray technology, the HSP-70 (also known as hsp72 or HSPA1A protein), the single-chain type-1 glycoprotein (MIC2 or CD99), the member of the RAS oncogene family RAB3A and the POM121L9P (POM121 transmembrane nucleoporin like 9, pseudogene) were overexpressed and the combination of, at least, two overexpressed genes were found as further associated with advanced grade, chemotherapy resistance, and progressive disease [23].

The HSP-70s modulates protein homeostasis and cell survival, as a promising anti-cancer target based on expression data, knockdown studies, and the promising cytotoxic activity of first-generation inhibitors [24].

The research on a wide range of effective HSP-70 inhibitors highlighted proteins of Bcl-2 associated with the athanogene family (BAG) [25]. Of these co-chaperones, the BAG3 protein gained interest as a new anti-cancer target because this protein was selectively up-regulated in response to a stressful event in cancer cells. Moreover, its expression is accompanied by HSP-70 expressions in many cancer types. The BAG3 has also been shown to interact with HSP-70 to aid cancer development, through several molecular pathways, such as the cell cycle and suppression of oncogene-induced senescence [25].

The inhibition of HSP-70s can provide an interesting advantage when added to chemotherapy regimens, because the levels of HSP-72 are dramatically increased after exposure to other therapies, such as HSP-90 inhibitors, proteasome inhibitors, and radiation [26]. As an important side effect, HSP-90 inhibition causes a compensatory induction of HSP-70 expressions, a potent negative regulator of cell death. The HSP-70 overexpression can reduce the death of cancer cells induced by HSP-90 inhibitors and therefore reduces the effectiveness of these compounds [27]. The HSP-70 is a crucial factor for tumor cell survival and tumor growth in life. An association has been shown between high HSP-70 levels in tumors and poor prognosis for cancer patients [28]. This molecular pathway may be another opportunity for HSP-70 inhibitors to compensate for this disadvantage [28].

Our study had some limitations regarding its study design including in vitro assays without the inclusion of normal cells, although it has important findings in terms of supporting the literature, mainly associated with increased oxidative stress and apoptosis.

Since ovarian and cervical cancers also include several subtypes with very different genetic alterations and pathological features, and the Hela and the SKOV3 cannot represent all cervical or ovarian cancers, the translation of research into clinical practice could be undermined by these premises. This research could be a forerunner for other studies on other cervical or ovarian cancers.

Conclusion

The HSP-70 can promote cancer progression and facilitate tumorigenesis in all stages and the cytotoxicity as-says elucidate the cytotoxic effect of the JG-98 against the HeLa and the SKOV-3 cancer cell lines [29,30]. To this, we can add our data, in which additional in vitro assays to measure the anticancer effect of the JG-98 on HeLa cells provided the highest cytotoxic activity in all doses. The efficacy of the JG-98, as a selective agent inhibiting the in vitro proliferation of human cervical cancer HeLa cells, was remarkable. The in vitro anti-cancer activity of the JG-98 against HeLa cells was developed, at least in part, by the promotion of apoptosis and this may be a consequence of increased oxidative stress. The findings of the current study justify the performance of further in vitro cell-based and in vivo studies in cervical and ovarian cancer, to explore in more depth the potential beneficial uses of HSP-70 inhibitors.

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ORIGINAL ARTICLE

Potential cytotoxic effects of borax alone and in combination with irinotecan on YKG1 glioblastoma cell-line

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Abstract

Glioblastoma Multiforme (GBM), which is a common and primary brain tumor in adults, is an important cause of death worldwide as an aggressive and treatment-resistant cancer tumor. In this cell culture study, the apoptotic and anti-proliferative effects of borax and irinotecan at different doses, alone or in combination, were investigated in the YKG1 cell line. Cytotoxic activities were analyzed by MTT method and TUNEL staining after 24th and 48th hours of incubation with borax administered at doses of 1mg and 3mg per ml; irinotecan 50mM and 100mM. Both irinotecan and borax have been shown to induce apoptosis when used alone, and thus cause anti-proliferation. It was determined that these effects were potentiated by the combined application of the agents. In addition, it was determined that this effect in combined applications was more pronounced after 48 hours and at higher doses. In light of the data obtained, the combination of irinotecan with borax to increase the cytotoxic effect of irinotecan, which is used in many different cancer types, can be tried in further prospective studies.

Keywords: YKG1, irinotecan, borax, MTT, tunel

Introduction

Brain tumors are the third most common tumor in children and the eighth most common in adults. According to its pathogenesis, the most often brain tumor in adults is Glioblastoma Multiforme (GBM), which constitutes 35-45% of primary brain tumors. It is highly aggressive and patients with malignant glioma show unsatisfactory clinical prognosis and low survival rate [1,2]. Despite technological advances, the average survival time after diagnosis is around 12-15 months due to high invasiveness and heterogeneity. GBM treatment is very difficult because it is resistant to both radiation therapy and chemotherapy, and there is no radical solution to prevent cell growth that causes tumorigenesis. Therefore, current treatment protocols for tumors due to GBM include surgery if possible; including radiation therapy and chemotherapy [3,4]. However, regardless of applicability, combined chemotherapy is highly recommended [6,7]. One of the agents used for this purpose, irinotecan, provides Topoisomerase-I inhibition, which has a role in DNA transcription. Irinotecan diffuses across the blood-brain barrier and thus provides cytotoxic activity against brain tumors such

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as GBM. In addition, irinotecan is known to be effective against multi-drug-resistant glioblastoma cells. However, increased efficacy of irinotecan has been demonstrated when used with other chemotherapeutic agents [8–10]. Combination chemotherapy targeting the disease from different mechanisms has recently been investigated to develop more effective treatment protocols.

Borax whose chemical formula is sodium tetraborate decahydrate, is a common form of boron in nature and obtained from different natural sources [11]. It has beneficial effects in medicine such as antiseptic, antifungal, and antiviral and also anti-osteoporotic, anti-inflammatory, hypoglycemic, and anti-coagulant [12,13]. The current literature indicates that borax has antioxidant properties with its free radical scavenging activity, inhibits proliferation in tumor cells, and therefore may exhibit anticancer effects by inducing apoptosis [14–18]. The mechanism underlying the anti-proliferative activity of borax has not been elucidated. However, there are not many studies investigating the biological activity of borax, especially in terms of its cytotoxicity in cancer cells. For these reasons, borax can be evaluated as an agent that can potentiate the effect of irinotecan. In this study, we investigated the possible effects of borax for enhancing the tumoricidal effects of irinotecan at different concentrations and combinations in human glioblastoma cell lines for 24 and 48 hours.

Material and Methods

Reagents

RPMI1640 medium (R8758), FBS (F9665), Penicilin-Streptomycin (P4333), L-glutamine (G7513), and Thiazolyl Blue Tetrazolium Bromide (M2128) were purchased from Sigma (Steinheim, Germany). Irinotecan (14180) was purchased from Cayman Chemical Company (USA). Borax (S9640) was obtained from Sigma (Steinheim, Germany). A Tunel assay kit was obtained from Millipore (S7101, MA, USA).

Cell Culture

YKG1 human glioblastoma cell line (RIKEN cell bank, Tsukuba, Japan) was used for the experiment. Cells were placed into 75 cm^2 culture flasks and produced in RPMI-1640 containing L-glutamine suffixed streptomycin (100 µg/ml), penicillin (100 U/ml), 10% fetal bovine serum (FBS), and 10 mM HEPES at 37°C with 5% CO2 in a humidified cell culture incubator. The medium was replaced every 3 days. Glioblastoma cells were incubated with determined concentrations and combinations of drugs (borax, irinotecan, borax + irinotecan) for the indicated time periods (24 and 48 hours). Three separate wells were used for each dose administration. Irinotecan doses were established according to the previous study [19], and borax' doses were established according to our preliminary study [20].

Experimental design

The study was designed as follows:

Group 1: Control group (no treatment, only 0.1% DMSO was used as a solvent). *Group 2:* Borax administered groups (at concentrations of 1mg/ml, 3mg/ml). *Group 3:* Irinotecan administered groups (at concentrations of 50mM, 100mM). *Group 4:* Combination groups of borax and irinotecan, respectively (1mg/ml + 50mM; 3mg/ml + 50mM; 1 mg/ml + 100 mM; 3mg/ml + 100mM.

Cell viability assay

MTT(3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide) assay was used for detecting cell viability. MTT assay is a colorimetric survival assay based upon enzymatic degradation of the MTT formazan molecule in living cells. The purpose is to determine the percentage of surviving cells compared to the control after application. For this purpose, YKG1 cells were seeded into 96-well plates containing 100 µl cell suspensions at a concentration of 2x104 cells/ml for performing MTT. YKG1 cells were exposed to determined concentrations of borax, irinotecan, and borax + irinotecan combinations before the cytotoxicity determination and incubated for 24 and 48 hours at 37°C. DMSO was used for the control group. 20 µl MTT (5mg/ml) was added to the wells and plates were incubated again for 24 h at 37°C after 24 and 48 hours' of incubation. Then MTT dye was removed and 150 µl/well of DMSO was joined to each well and incubated for 10 min in the dark at room temperature. Finally, the plates were analyzed using a microplate spectrophotometer (Epoch, Biotek Inst., Winooski, USA) at a wavelength of 5740 nm. All experiments were performed three times, mean values were calculated and the percentage of cell viability was calculated for each group. Finally, control cell viability, not treated with components, was considered to be 100% and the viability of experimental cells was calculated as follows;

Cell viability (%) = OD treatment/OD Control x 100.

Detection of apoptosis by Tunel method

Tumor cell apoptosis was examined by the Terminal Deoxynucleotidyl Transferase dUTP Nick-end Labeling (Tunel) method. The apoptotic activity of GBM cells was defined as the apoptotic index (APOI). APOI was calculated by proportioning the non-apoptotic cells to the apoptotic cells. Tunel assay was performed with in situ apoptosis detection kit Apoptag® (Millipore, S7101) according to the manufacturer's protocol. Briefly, cells were seeded into 24-well plates and incubated for 24 and 48 hours after drug administration. Cells were taken to tubes at a density of 1x106/ml per well and centrifuged for 5 min and treated with PBS and fixed with 4% formaldehyde, and cells were centrifuged for 5 min again. Subsequently, the cells were re-suspended in 80% alcohol and taken to Poly-L-sine coated slides and permeabilized with Proteinase-K (100 µg/ml) and washed with TBS. Inactivation of endogenous peroxidase was provided with 3% H_2O_2 for 5 min. After washing with TBS, cells were incubated with Equilibration buffer at room temperature and TdT enzyme was added to the cells in a humidified chamber at 37°C for 60 min. Then stop wash buffer for 10 min and subsequently anti-digoxigenin conjugate for 30 min. were applied. Then slides

were washed with TBS and DAB was used to label the apoptotic cells. Then the slides were rinsed in water and counterstained with methyl green and after dehydrating, cleaned with xylene and mounted with Entellan (Sigma). Finally, slides were evaluated under a light microscope using an image analysis program (NIS Elements, Nikon, Japan). Apoptotic and non-apoptotic cells were counted under x40 magnification in six different areas and APOI was calculated by proportioning the non-apoptotic cells to apoptotic cells.

Statistical analyses

MTT results were subjected to one-way analysis of variance (ANOVA) using the Statistical Package for the Social Sciences (SPSS 21.0, SPSS Inc., Chicago, IL, USA) software. Differences among the groups were obtained using Tukey's test option. All data were expressed as mean ± standard error mean (SEM) in each group. Statistical significance was accepted as p<0.05.

Results

Cytotoxicity results

The results of the viability test performed in the 24th and 48th hours are shown in Table 1 and Figure 1. According to these results, the application of alone irinotecan has had an effective cytotoxic effect on glioblastoma cells. While this cytotoxic effect did not show a significant change dose-dependently in the 24th hour, it gradually increased dose-dependently in the 48th hour. According to MTT results, an evident cytotoxic effect was observed after the application of borax alone both in the 24th and 48th hours on glioblastoma cells. In the borax alone-treated groups, an increase in cytotoxicity on YKG1 cells was observed parallel to the increasing doses both in the 24th and 48th hours. Cytotoxic effect on YKG1 cells caused by borax alone was more prominent than irinotecan alone treatment. In the combination groups formed by different doses of irinotecan and borax, it was observed that the combined use of irinotecan and borax potentiated each other's cytotoxic effects to some extent in comparison to applications of irinotecan and borax alone. Cytotoxic effect was less than at lower dose combinations, it was observed to be higher at higher dose combinations. In MTT results after 24 hours, the most cytotoxic effect were observed in the combination of borax (1mg/ml) + irinotecan (50 mM) administered group. Looking at MTT results, more pronounced cytotoxicity on the YKG1 cell line was observed at the 48th hour compared to the MTT results at the 24th hour. The most cytotoxic effects were detected in combinations of borax (1mg/ml) + irinotecan (50mM), borax (1mg/ml) + irinotecan (100 mM) and borax (3mg/ml) + irinotecan (10mM). Evaluating the effectiveness of the combined use of irinotecan and borax in the 24th and 48th hours, it has been proved by the ratio of dead cells detected in the 48th hour being significantly higher than in the 24th hour.

Tunel assay results

APOI was calculated by dividing the number of non-apoptotic cells by the number of apoptotic cells. AI results of the groups

are shown in Figure 2 and images of the Tunel assay are shown in Figure 3. According to these results, the application of irinotecan alone caused a dose-dependent increase in apoptotic cell death in the glioblastoma cells both in the 24th and 48th hours. The application of borax alone was observed to enhance apoptotic cell death dose-dependently both in the 24th and 48th hours at similar values to the administration of irinotecan alone. Apoptotic cell death was observed considerably higher in the groups of irinotecan and borax administered alone at the 48th hour compared to the 24th hour and also apoptotic cell death was higher in combination groups of irinotecan and borax compared to irinotecan and borax were administered alone. As the weakest effect inducing apoptosis in combined use was observed at lower combination doses, the strongest effect was detected when borax and irinotecan were administered at the doses of borax (1mg/ml) + irinotecan (50mM), and borax (1 mg/ml) + irinotecan (100 mM) and borax (3mg/ml) + irinotecan (100 mM) both in the 24th and 48th hours.
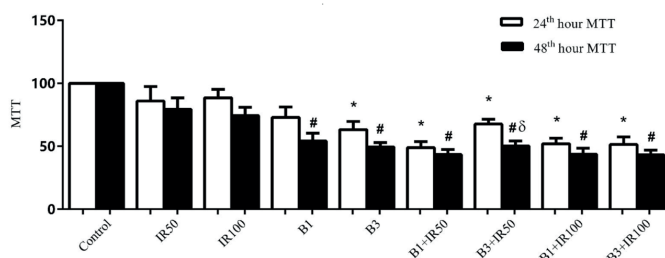
Figure 1. Cytotoxic activities of Borax (B) and Irinotecan (IR) with by MTT assays on glioblastoma YKG1 cells at 24th and 48th hours. Values are expressed as mean ± SEM. Control group (no treatment, only 0.1% DMSO was used as a solvent). Irinotecan administered groups IR50 (50mM) and IR100 (100mM); Borax administered groups B1 and B3 (at concentrations of 1 mg/ml and 3mg/ml, respectively). δ shows a significant difference from the 24th hours of each group. (p<0.05); *shows significantly difference from the 24th hours of Control (p<0.05); # shows significantly difference from the 48th hours of Control (p<0.05)
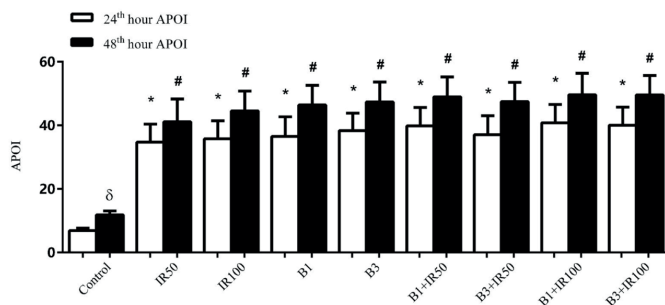
Figure 2. Apoptotic index (APOI) of Borax (B) and Irinotecan (IR) with by MTT assays on glioblastoma YKG1 cells after Tunel assay at 24th and 48th hours. Values are expressed as mean ± SEM. Control group (no treatment, only 0.1% DMSO was used as a solvent). Irinotecan administered groups IR50 (50mM) and IR100 (100mM); Borax administered groups B1 and B3 (at concentrations of 1 mg/ml and 3 mg/ml, respectively). δ shows a significant difference from the 24th hours of each group. (p<0.05); *shows significantly difference from the 24th hours of Control (p<0.05); #shows significantly difference from the 48th hours of Control (p<0.05)
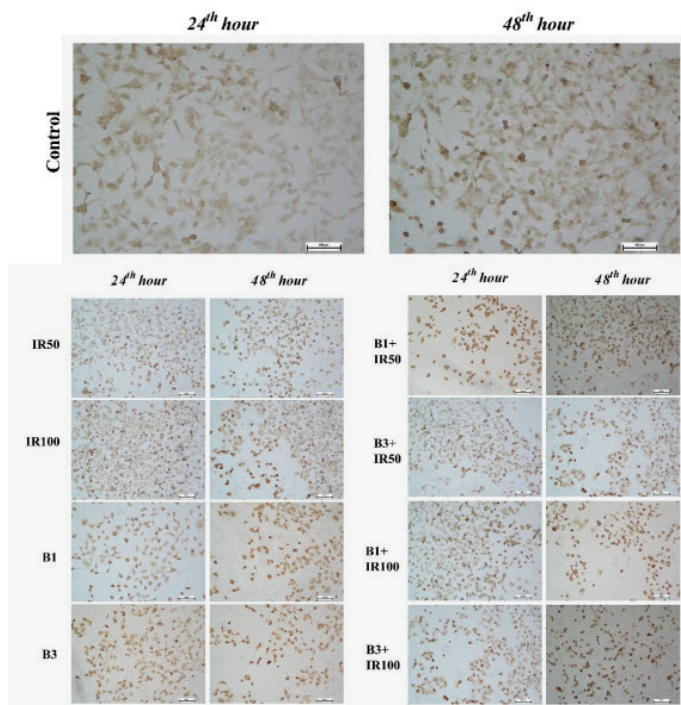
Figure 3. The immunohistochemically stained YKG1 glioblastoma cells (Tdt-TUNEL based apoptosis detection kit). The cells green in color are non-apoptotic and brown in color are apoptotic cells (×200, scale bar: 50 μm). Control group (no treatment, only 0.1% DMSO was used as a solvent). Irinotecan administered groups IR50 (50mM) and IR100 (100mM); Borax administered groups B1 and B3 (at concentrations of 1 mg/ml and 3 mg/ml, respectively)

Table 1. Effects of irinotecan and borax on YKG1 glioblastoma cells' viability after 24 and 48-hours of treatment

Groups	Cell viability (% of control)	
	24th hour	48th hour
Control	100	100
IR50	86±12	79±9.2
IR100	89±6.7	75±6.6
B1	73±8.4	54±6.3
B3	63±6.4	50±3.4
B1 + IR50	49±4.9	43±4.2
B3 + IR50	68±3.8	50±4.1
B1 + IR100	52±4.4	44±4.7
B3 + IR100	51±6	43±3.9

Values are expressed as mean ± SEM. Control group (no treatment, only 0.1% DMSO was used as a solvent). Irinotecan administered groups IR50 (50mM) and IR100 (100mM); Borax administered groups B1 and B3 (at concentrations of 1 mg/ml and 3 mg/ml, respectively)

Discussion

Brain tumors are very diverse in their biological behavior and therefore their treatments are considered a major issue in modern medicine. GBM is the most encountered primary cancer of the central nervous system in adults, characterized by uncontrolled, aggressive cell proliferation, infiltrative growth in the brain, and general resistance to conventional treatment [20,21]. Despite management improvements, the outcome of patients remains extremely poor, with a mean life expectancy of approximately 1-2 years. Different combination chemotherapies are considered to overcome this aggressive cancer. It has become clear that therapeutic improvements will likely depend on effective combination therapies targeting multiple mechanisms. More effective new agents, or novel synergic combinations, are required for GBM treatment [2,5-7]. Although temozolomide is the standard chemotherapy regimen for primary GBMs, recurrent GBMs are frequently treated with high doses of DNA topoisomerase inhibitors such as irinotecan [8,9].

Irinotecan, which inhibits Topoisomerase-I, is widely used as a second-line drug for the treatment of GBM. DNA topoisomerases are nuclear enzymes that reduce torsional stress in supercoiled DNA, allowing for selected regions of DNA to become sufficiently relaxed to permit its replication, recombination, repair, and transcription [23]. Irinotecan is broadly used in solid cancer therapy, especially in combination with other drugs [10,19]. In previous studies, topoisomerase inhibitors have demonstrated antitumor activity in human glioblastoma cell-line with multidrug resistance [24,25]. Irinotecan has the capacity to deactivate the proliferation of tumor cells by attenuating the early phase of the cell cycle, G1. At the same time, irinotecan can impede metastatic processes and induce apoptotic cell death which is primarily responsible for its anti-tumor activity [26]. SN-38 (7-Ethyl-10-hydroxycamptothecin) is a metabolite that occurs with the carboxylesterase-mediated breakdown of irinotecan and it is 100–1.000 times more potent than irinotecan. Glioma cells are capable of converting irinotecan to SN-38 by intrinsic tumor carboxylesterases [27,28].

The effects of boron on many diseases have been the subject of research in the field of health recently. The biological, medical, and environmental roles of boron have attracted considerable attention over the years. Boron is an essential element for normal growth and development which is involved in a series of important physiological functions, including membrane integrity, cell wall formation, calcium uptake, protein metabolism, nucleic acid metabolism, and translocation [11]. Furthermore, boron has extensively been used in a variety of industries, including insecticides, food preservatives, fire retardants, glass products, detergents, and reagents for chemical synthesis [14]. Because boron is preferably used in industry, its medical applications are omitted today. What impacts it may create on cancer patients has been one of the recent issues recently. The consumption of nutrients with rich boron contents such as nuts, avocados, broccoli, and raisins has been reported to decrease the risk of certain cancers. Dietary boron intake is associated with reduced some cancers risks such as prostate and lung cancers [15-18]. In addition, epidemiological, animal, and cell culture studies have identified boron compounds have anti-tumor properties as chemo-preventative agents [14]. It has been observed in a study

that when administered to the cancer cells in the culture medium, different boron products have decelerated the proliferation of cancer cells. It has been shown that boron reduces the expression of cyclin proteins (cyclin A1, B1, C, D1, and E) which are effective in the cell cycle, inhibits Ca+ release by NAD+CADPR system, and induces apoptosis [29]. In light of this information, it has been considered that boron can show beneficial effects on cancer treatment. Accordingly, in an effort to find better treatments for glioblastoma, we tested and compared single borax and irinotecan and also combined borax + irinotecan agents for their ability to enhance the standard cytotoxic drug currently used to treat glioblastoma. Current literature sources indicate the predominant activity of irinotecan on GBM. In patients with recurrent glioblastoma, irinotecan has been found to significantly improve survival when combined with Bevacizumab [30]. In the cell culture study, it was stated that irinotecan alone or in combination with alisertib showed efficacy by providing strong inhibition of O6-methylguanine DNA methyl transferase. In the study, it was determined that irinotecan showed absolute synergy with other agents [31]. Another study's data reveal that the metformin and irinotecan have the potential to decrease neurons and U-87 MG glioblastoma cell viability, in vitro; however, in vivo studies disclose that the metformin and irinotecan have the capacity to reduce tumor size in Sprague–Dawley rats [32].

The present study demonstrated that irinotecan alone demonstrated more cytotoxicity on YKG1 cell-lines at 48th hour dose-dependently, as compared to 24th hour. Borax alone also showed higher cytotoxicity in both 24th and 48th hour than irinotecan alone administration. In addition, in borax-administered groups, an increase in cytotoxicity was observed from low dose groups to high dose groups in both 24th and 48th hours. We found that both borax and irinotecan, as a single agent, effectively induced apoptosis dose-dependently at 24th and 48th hours. The combination therapy of borax and irinotecan has additive cytotoxic effects on YKG1 cells. Combined use of borax and irinotecan treatment remarkably reduced cell proliferation on YKG1 glioblastoma cells compared to single treatments of them which appears to be a consequence of increased DNA damage, resulting in apoptosis induction. Combination of borax with irinotecan enhanced anti-tumor efficacy in vitro by inducing cell death by apoptosis, to impressively increase the efficacy of irinotecan, a topoisomerase-1 inhibitor used in cancer treatment [29]. Borax showed potent synergic effects with irinotecan, and the most potent combinations were shown in combinations of borax (1 mg/ml) + irinotecan (50 mM) at 24th hour and also borax (1 mg/ml) + irinotecan (50 mM), borax (1 mg/ml) + irinotecan (100 mM) and borax (3 mg/ml) + irinotecan (100 mM) combinations had remarkably strong synergistic cytotoxic and apoptotic effects to YKG1 cells at 48th hour. The data obtained indicate that borax potentiates the cytotoxic effects of ironotecan on YKG1 glioblastoma cells.

The obtained results show that individual use of borax and irinotecan demonstrated lower cytotoxic and apoptotic effects compared to the combined use. Nevertheless, these effects were observed more than in particular at high dose usages. The obtained results showed us that supplementation appropriate doses of borax can enhance the cytotoxic and apoptotic effects of irinotecan during irinotecan chemotherapy. Our data highlight the therapeutic potential of borax used in combination with the known chemotherapy drug irinotecan and offer important insights for the development of more effective and selective therapies against GBM. However, these dosages must be supported by phase 2 study levels, before the implementation of phase 3 of a large study.

Conclusion

It was found that irinotecan and borax as a single agent inhibited the proliferation of YKG1 cells and enhanced cytotoxicity and apoptosis. The irinotecan-borax combined therapy had a synergistic effect on the antitumor efficacy of glioblastoma treatment, not only increasing tumor cell apoptosis but also significantly inhibiting tumor cell proliferation. In patients with glioblastoma, the combination of borax and irinotecan may be promising for a new anti-cancer therapy. The effect of borax on mechanisms can be better understood if new studies are performed with different timings and doses with further investigations. However, more studies are needed to prove this synergism with the borax-irinotecan combination.

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ORIGINAL ARTICLE

Magnetic resonance imaging features varying by size in giant hemangioma of the liver

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Abstract

Different definitions are used for giant liver hemangiomas. When liver hemangiomas are larger than 4 cm, they are called cavernous hemangiomas (CHs). 6cm or higher thresholds have also been suggested in the literature. Mastering the magnetic resonance imaging (MRI) features that change as the size of CHs increases can prevent misdiagnoses. The aim of the study was to compare MRI features of CHs between 4-6cm and >6cm. The contrast-enhanced abdominal MRIs in the hospital image archiving system was retrospectively examined in the last two years. A total of 52 patients (39 females, 13 males) with CHs were detected by screening. MRI features of 30 patients in Group 1 (between 4-6cm) and 22 patients in Group 2 (>6cm) were analyzed and the two groups were compared in terms of imaging features. The presence of a central cleft-like area was found to be more in Group 2 (54.5%) than in Group 1 (6.7%) (p<0.001). Internal hemorrhage was not detected in Group 1, but it was seen in 3 (13.6%) patients in group 2 (p=0.07). The multiloculation-like appearance was significantly higher in Group 2 (86.4%) than in Group 1 (23.3%) (p<0.001). Delayed diffuse enhancement was observed at a rate of 30% in Group 1 patients, while it was not seen at all in Group 2 (p=0.007). In Apparent diffusion coefficient (ADC) mapping, the incidence of the hypointense rim in the periphery of CH was significantly higher in Group 2 (90.9%) than in Group 1 (66.7%) (p=0.04). ADC value was higher in Group 1 (1.76±0.28) than Group 2 (1.55±0.24) (p=0.007).

Keywords: Giant liver hemangioma, magnetic resonance imaging, apparent diffusion coefficient

Introduction

Liver hemangiomas are defined as non-cancerous lesions. In the literature, different sizes are used for the definition of giant hemangioma (>4, >5, >8, >10cm) [1,2]. In addition, different definitions such as extremely giant, super-giant or hypergiant have been reported in previous studies. This confusion in definition regarding hemangioma size still continues today. Liver hemangiomas, which are usually asymptomatic and detected incidentally, may become symptomatic depending on the increase in their size [3]. Typically abdominal pain is seen in 23–57% of patients [4]. Abdominal ultrasonography, contrast-enhanced computed tomography and magnetic resonance imaging are used in diagnosis and follow-up. Frequent follow-up of imaging is not recommended since changes in hemangioma size are rare [5]. However, as the size increases, the imaging features may also vary. Low signal intensity on T1-weighted images (T1WI) and high signal intensity on T2-weighted images

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(T2WI) defined as "cotton wool" appearance [6]. High signal intensity on T2WI and discontinuous peripheral enhancement are known as typical findings for giant hemangiomas of the liver [7]. The enhancement kinetics of giant hemangiomas is slow [8]. Small hemangiomas usually have a homogeneous appearance. As the size increases, the homogeneity of the lesions decreases, and they have a heterogeneous appearance. Cleft-like areas of low signal intensity on T1WI and internal septa are found more frequently [9]. The magnetic resonance imaging (MRI) can identify spontaneous hemorrhages well due to providing adequate better tissue characterization [10]. A peripheral low-signal-intensity rim may be found owing to the effect of the presence of pseudocapsule [10].

The unclear definition of giant hemangiomas and varying imaging findings with the increase in size of giant hemangiomas may cause difficulties for the correct diagnosis and treatment approach. In our study, it was aimed to define magnetic resonance imaging features varying by size in giant hemangioma of the liver.

Material and Methods

This retrospective study was approved by the local ethics committee (2018/0226) and performed according to the tenets of the Declaration of Helsinki Declaration. Informed consent was obtained from each patient before the MRI examination.

Patient Population

We retrospectively reviewed sixty-one patients diagnosed with CHs and treated or followed-up in our hospital between 2016 and 2018. Contrast-enhanced abdominal MRIs performed with a 1.5 Tesla MRI device in the last two years were evaluated. Patients with a history of liver surgery, liver trauma, additional hepatic pathologies on MRI and patients with incomplete data were excluded from the study. Fifty-two patients (39 females, 13 males) with CH who met the current criteria were enrolled in the study.

Radiological Evaluation

Contrast-enhanced abdominal MRI images of all patients performed with a 1.5 Tesla (General Electric) machine were evaluated by an 8-year-experienced abdominal radiologist.

The MRI scan protocol consists of contrast and non-contrast enhanced axial T1WI (section thickness:5mm; TR/TE, 170/2 ms; field of view, 420×420mm; scan time(sn): 20;), axial and coronal T2WI (section thickness:5 mm; TR/TE, 1100/82 ms; field of view, 420×420mm; scan time(sn): 180), axial and coronal dynamic gradient echo sequence (section thickness:3 mm; TR/TE, 4/2ms; field of view, 320×192mm; scan time(sn): 30; after intravenous contrast injection(sn): 0,25,45,90,120,180), DWI (TR/TE, 1500/86ms; field of view, 420×420 mm; section thickness: 5mm; matrix, 96×160; scan time (sn): 180; b value: 0 and 800 s/mm^2).

The diagnosis of CH was made according to characteristic imaging findings on MRI, such as hyperintense relative to liver parenchyma on T2WI and peripheral nodular discontinuous enhancement in post-contrast T1W1. The size of 6 cm and over was accepted as the threshold value for the definition of giant hemangioma.

Study Design

The patients were divided into two groups based on the size of the hemangioma.Patients diagnosed with hemangiomas between 4 - 6 cm were included in Group 1, and hemangiomas of 6 cm or over were included in Group 2.

Statistical Analysis

SPSS and Microsoft Excel computer programs were used to analyze the data obtained from the study. Descriptive statistics were obtained to represent data. Categorical variables were expressed as counts or percentages and continuous variables as mean and standard deviations. The chi-square test was used to compare categorical variables.Student-T test and Mann-Whitney U test were used according to the normal and abnormal distribution of the data in continuous variables. The results were evaluated at the 95% confidence interval and $p<0.05$ significance level.

Results

The mean age of patients in Group 1 and 2 were 51±10 and 50±13 years, respectively and were similar (p=0.77). The frequency of female gender was higher in Group 2 (90.9% vs. 63.3%, respectively, p=0.02). The average size of CH was 4.5±0.4cm in Group 1 and 8±2.3cm in Group 2.
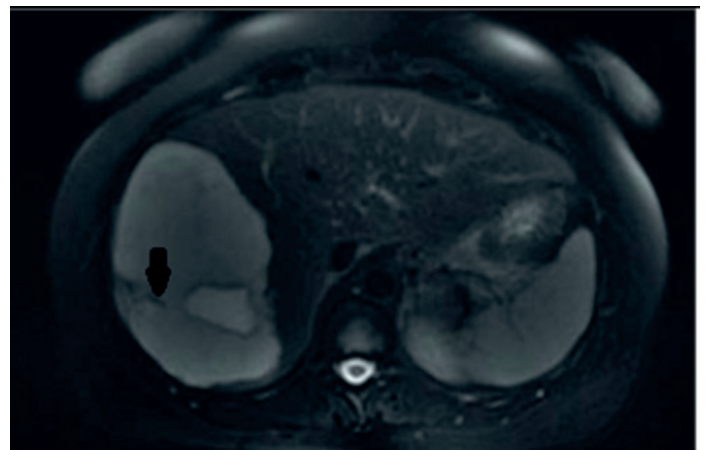
Figure 1. Central cleft(arrow) is observed in giant hemangioma on axial fat-saturated T2WI

The presence of a central cleft-like area was found to be more in Group 2 (54.5%) than in Group 1 (6.7%). (p<0.001). (Figure 1) Internal hemorrhage was not seen in group 1, but it was detected in three (13.6%) patients in group 2 (p=0.07). (Figure 2). Multiloculation-like appearance was higher in Group 2 (86.4%) than in Group 1 (23.3%) and it was statistically significant (p<0.001).(Figure 3) The incidence of concomitant hemangiomas in the liver was similar and was present in half of

the patients in both groups. Delayed diffuse enhancement was observed at a rate of 30% in Group 1, while it was not seen at all in Group 2 (p=0.007).
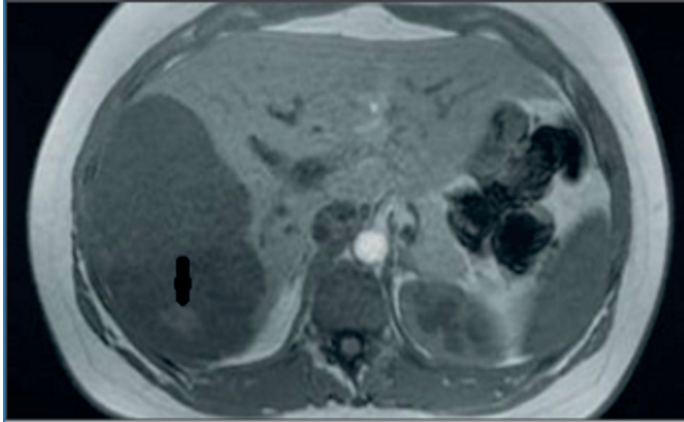
Figure 2. T1 hyperintense internal hemorrhage(arrow) is observed within the giant hemangioma
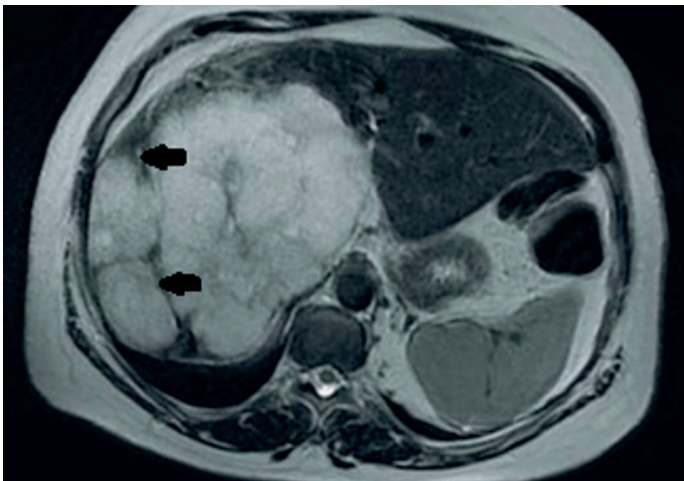
Figure 3. A giant hemangioma has a multilocular-like appearance due to internal septa and contour lobulation (arrows) on axial T2WI
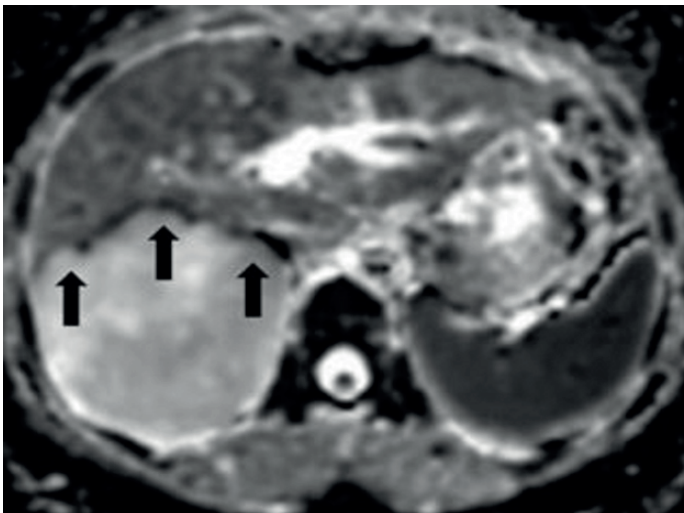
Figure 4. Axial ADC map image on MRI shows a hypointense rim (arrows) in the area where the giant hemangioma is adjacent to the liver parenchyma

In ADC mapping, the incidence of hypointense rim in the periphery of CH was higher in Group 2 (90.9%) than in Group 1 (66.7%) and it was statistically significant (p=0.04). (Figure 4) ADC value was higher in Group 1 (1.76±0.28) than in Group 2 (1.55±0.24) (p=0.007).

Discussion

The definition of giant hemangiomas varies in the literature [11]. In addition to its definition, clear lines in terms of disease management are not yet available. Furthermore, there is a lack of distinct guidelines about "when" and "how" to operate these lesions. In order to resolve of this confusion in disease management, additional information provided by imaging methods such as MRI may guide the planning of the treatment. In a review published in 2016, the need for a change in size categories for the definition of giant cavernous liver hemangiomas was emphasized. Additionally, the study reported that it would be appropriate to use 10cm as the threshold value for the definition of "giant" [12].

Depending on the increase in CH size, MRI findings change as mentioned our statistical results. Our results shows that if the CH size is >6 m, the entity of T2 hyperintense central cleft-like area, which shows the presence of necrotic-cystic patency increases with age, is seen more commonly. A multiloculation-like appearance occurs when peripheral lobulation accompanies the internal septa in CHs. As stated in the statistical results, frequent multiloculation-like appearance in group 2 might attributed to the increase in peripheral lobulation as the mass enlarged. Although it has been reported that there is no significant relationship between the size of typical hemangiomas and ADC values [12], the mean ADC value in Group 2 was lower than Group 1 in our study. Our results also revealed that peripheral hypointense rim is seen in ADC mapping and this finding is more common in Group 2. This may be due to the pressure effect of the mass.

The incidence of central cleft-like area is closely related to the size of the hemangioma. In the study of Ashida et al., the frequency of central cleft-like area was reported to be 78% in liver hemangiomas larger than 4 cm, and it was concluded that the frequency increases with increasing size [13]. In the study of Castrillon et al., in which they reported the data results of 21 patients diagnosed with liver hemangioma with a mean size of 10.4cm, the frequency of central cleft was reported as 100% [14]. In our study, this rate was found to be lower (54.5%) than the rates reported in the literature. Heterogeneity in mean hemangioma sizes in the studies also directly affects the frequency of central clefts.

Multiloculation-like appearance is another finding detected in liver hemangiomas. According to the results reported by Choi et al. [9], the frequency of this appearance increases with the increase in size in giant hemangiomas. However, according to the results of Castrillon et al. [14], internal septa was not detected in any case and multiloculation-like appearance was not reported. In our study, this rate was found to be 86.4%, which supports the

results reported by Choi et al.

In recent years, the number of studies on ADC mapping on MRI in the diagnosis of hepatic hemangiomas has increased to learn "how" to differentiate to hepatic hemangiomas from malign lesions.In a study on ADC value in the evaluation and differential diagnosis of hemangiomas, Tokgöz et al. reported that the ADC values of hepatic hemangiomas were higher than those of malignant lesions of the liver, and they also reported that the defined "cut-off" ADC value (1.800×10(-3) mm (2)/s) [15]. In another study, the ADC value in the differential diagnosis was found to be 2.30×10-3mm²/ and it was reported to have 55% sensitivity and 100% specificity [16]. In the study by Hardie et al., hepatic hemangiomas and metastatic lesions of the liver were compared and the mean ADC value of hemangiomas was found to be significantly higher than metastatic lesions [17]. Differential diagnosis for giant hemangiomas can always involve difficulties. Misdiagnosis of liver hemangioma appears to be the foremost challenge [18]. The results in the literature show that; malignant lesions are found to have lower mean ADC values than hemangiomas. However in our study, the mean ADC values of giant hemangiomas were found to be lower than those of smaller hemangiomas. The results of our study can be evaluated as a warning in terms of omitting the differential diagnosis of giant hemangiomas and possible malignant lesion. Unfortunately, the number of studies on ADC features in MRI in the evaluation of giant hemangiomas in the literature is not sufficient.We think that focusing on this subject will contribute to the literature.

We have limitations in our study and the first of which is the retrospective design of the study. Secondary, the patient population's small size seem to be a problem. Prospective studies will allow us to define magnetic resonance imaging features varying by size in giant hemangioma of the liver better.

Conclusion

When a threshold value of 6cm is accepted for the definition of giant hemangioma, late diffuse enhancement is not frequently detected. However, central cleft-like area, multiloculation-like appearance, peripheral hypointense rim on ADC map, and internal bleeding are seen more common in MRI.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This retrospective study was approved by the local ethics committee (2018/0226) and performed according to the tenets of the Declaration of Helsinki Helsinki Declaration.

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ORIGINAL ARTICLE

COVID-19 vaccination literacy, attitude and hesitation towards vaccination and vaccination status of pregnant women

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Abstract

The study aims to determine COVID-19 vaccine literacy, attitude and hesitation towards the vaccine, and vaccination status of pregnant women in a rural region. This is a cross-sectional study. It was carried out between June 7 – 7 August 2022. 209 pregnant women were included in the study. The mean score of pregnant women was found to be COVID-19 vaccine literacy 2.5±0.4, attitude 3.1±0.8, and hesitation 7.7±6.6. It was found that 12.4% of the pregnant women had COVID-19 disease in their current pregnancy, and 7.2% of them had COVID-19 disease in the first trimester. It was determined that 34.4% of the pregnancy had a single dose, 30.2% had two doses, and most of them were BioNTech vaccines. Vaccine literacy was determined to be higher in pregnant women who are working, have social security, have a higher income than their expenses and have a master's degree. Those who are married, have social security, and have a female baby have a positive attitude for vaccines. There was a positive significant relationship between COVID-19 vaccine literacy and attitude, and a negative significant relationship between COVID-19 vaccine literacy and hesitancy. It was discovered that COVID-19 vaccine literacy is moderate, vaccination rates are low, and vaccination literacy influences vaccination attitudes and hesitation.

Keywords: COVID-19, pregnant, vaccination

Introduction

Vaccination is the most widely used protective application in the world for disease prevention. The purpose of vaccination programs is to prevent avoidable infectious diseases and disease-related mortality or permanent sequelae [1,2]. Vaccine is the ability of a person to access, process, and understand fundamental health information and services to make appropriate health decision regarding vaccinations [3].

The effect of the virus on the human body in the COVID-19 epidemic, the lack of treatment for the disease, contradictory informations about vaccination studies and inconsistent information about the advantages and disadvantages of vaccines spread rapidly in the mass media, causing individuals to believe incomplete and wrong information. Therefore, this situation prevents access to accurate information about COVID-19 disease and vaccines, leading to wrong decisions about getting vaccinated and increasing vaccine hesitancy [3-6]. In addition, reasons such as concerns about safety of the vaccines developed, short and long-term side effects of the vaccines and uncertainty

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of protective effect of the vaccines, lack of information on safety of the vaccines, and the concern of the vaccine harming the fetus lead to an increase in the negative attitudes and hesitations of pregnant women [7-13]. Therefore, individuals seek information about COVID-19 disease and COVID-19 vaccine types from current and reliable sources. The attitudes of individuals about the vaccination are influenced by their opinions of the information they have obtained [12].

In researches evaluating individuals' attitude of towards COVID-19 vaccine types, it was revealed that almost all of the non-pregnant participants are willing to be vaccinated and have a positive attitude towards the vaccine. It was reported that people experiencing fear and anxiety about vaccine believe that the vaccine is effective against epidemics and are therefore willing to be vaccinated [12,14,15]. However, pregnant women constitute a risk group for pandemic infection. Because suppression of the immune system during pregnancy, they are more susceptible to pathogens and severe pneumonia. In latter stages of pregnancy, rise in diaphragm height, increase in oxygen demand, and edema of respiratory tract mucosa lower pregnant woman's tolerance to hypoxia [16]. Therefore, during pregnancy vaccination to prevent COVID-19 is essential. According to a research, after vaccination to prevent COVID-19, pregnant and non-pregnant women exhibited comparable levels of protection. In addition, it was claimed that complications such as premature birth, stillbirth, intrauterine growth retardation, and congenital anomalies do not increase following vaccination; nevertheless, further research is required on this topic [17]. Studies on COVID-19 vaccine types are still insufficient. Although the current COVID-19 vaccines have protective properties, it is stated that the attitudes towards these vaccines vary and the hesitation towards the vaccine is high in studies conducted on the pregnant population. It is reported that the perspective of the society towards vaccines and sociocultural factors have a significant effect on attitudes and hesitancy towards vaccines [11,13,18].

No research has been found examining the vaccination literacy of pregnant women, their attitudes towards the vaccine, their hesitancy, and their vaccination status against COVID-19 in the rural and conservative part of Eastern Anatolia, where fertility is high in Turkey [19]. Therefore, this research aimed to determine the vaccination literacy of pregnant women in rural region, their attitude and hesitance towards the vaccine, and their vaccination status.

Research questions

- What is the vaccination literacy of pregnant women in rural region, their attitudes and hesitations towards the vaccine, and their vaccination status?
- Is there a difference between scale mean scores according to the socio-demographic characteristics of the pregnant women in rural region?
- Is there a significant relationship between the scale and scale

sub-dimension mean scores of pregnant women in rural region?

Material and Methods

Research Type

This is a cross-sectional study. This research was carried out at Muş State Hospital Obstetrics and Gynecology Outpatient Clinic in the province of Muş between June 7–7 August, 2022.

Variables of the Study

Dependent variable: COVID-19 Vaccine Literacy Scale, Attitudes towards COVID-19 Vaccine Scale and Vaccine Hesitancy in Pandemic Scale mean scores.

Independent variable: Socio-demographic and obstetric characteristics of pregnant women.

Population and Sample

Population of research consisted of pregnant women who applied to Muş State Hospital Obstetrics and Gynecology Outpatient Clinic. Type I error 0.05, d:0.25 effect size or correlation coefficient, 80% power, GPower 3.1 program was used for the sample of the study, and the sample size was calculated. It was found that minimum of 199 people for difference analysis should be taken into the sample [20,21]. Total 209 pregnant women living participated in the study. Pregnant women included in the study were selected by simple random sampling method. Statistical significance level of the research was determined as p<0.05, with a confidence interval of 95%.

Inclusion and Exclusion Criteria of Research

Inclusion criteria; pregnant women who are literate and have no previous psychiatric history or diagnosis.

Exclusion criteria; pregnant women who do not meet the inclusion criteria.

Data Collection Process

Data were obtained through face to face interviews by researcher (A.K.) at Muş State Hospital Obstetrics and Gynecology Outpatient Clinic Obstetrics and Gynecology Outpatient Clinic between June 7 – August 7, 2022.

Data Collection Tools

Introductory Information Form, COVID-19 Vaccine Literacy Scale, Attitudes Towards COVID-19 Vaccine Scale, and Vaccine Hesitancy in Pandemics Scale were used to collect data.

Introductory Information Form

This was developed by the researchers, consists of a total of 35 questions (18 of which question sociodemographic

characteristics of pregnant women, 17 questions about the fertility characteristics) [3,4,22-24].

COVID-19 Vaccine Literacy Scale (COVID-19-VLS)

It was developed by Ishikawa et al. (2008) to examine health literacy for chronic diseases and adapted by Biasio et al. (2021) as the COVID-19 Vaccine Literacy Scale [22,25]. It was adapted to Turkish by Durmuş et al. (2021) [3]. It consists of 12 items and 2 sub-dimensions. Functional vaccine literacy is the ability of individuals to have simple reading and writing skills, to understand health education and vaccine-related materials. Communicative/Critical vaccine literacy focuses on cognitive efforts (problem solving and decision making) [22,26,27]. The scale is a 4-point Likert type. The communicative/critical dimension questions are coded as (1) Never, (2) Rarely, (3) Sometimes, (4) Often. Functional dimension expressions are reverse coded. The fact that the average of the scores obtained from the scale is close to 4 indicates that vaccine literacy is high [3,22]. Cronbach's alpha value of entire scale is 0.86, and for communicative/critical vaccine literacy and functional vaccine literacy dimensions are 0.91 and 0.86, respectively [3]. In this study, it was found 0.63 for total scale, 0.87 for communicative/critical vaccine literacy and 0.77 for functional vaccine literacy.

Attitude towards COVID-19 Vaccine Scale (ATVS-COVID-19)

It was created by Çırakoğlu (2011) to examine people's perceptions and attitudes towards the disease and their levels of anxiety and avoidance during the Swine Flu (H1N1) epidemic [28]. Scale of Attitudes towards COVID-19 Vaccine was adapted into Turkish during the COVID-19 outbreak by Geniş et al. (2020) [23]. The scale consists of 9 items and two subdimensions (positive attitude and negative attitude), it is a Likert type. High scores obtained from scale and sub-dimensions indicate that the attitude towards the vaccine is positive. Cronbach's alpha value of the scale is 0.80. This values are 0.96 and 0.78 in positive attitude and negative attitude sub-dimensions, respectively [23]. In this study, it was found 0.90 for scale, 0.92 for positive attitude and 0.81 for negative attitude.

Vaccine Hesitancy Scale in Pandemics (VHSP)

It was developed by Larson et al. (2015) and adapted for pandemics by Çapar et al. (2021) [4,24]. Scale is in five point Likert type and consists of 10 items and two subdimensions (lack of confidence and risk). It can be obtained 10-50 points from scale. High score indicates high vaccine hesitancy. Cronbach alpha is 0.90 (Çapar et al., 2021) [4]. In this study, it was found 0.83, for lack of confidence 0.82 and for risk sub-dimension 0.69.

Statistical Analysis

It was analyzed using SPSS 26.0 (IBM SPSS Statistics Version 26, SPSS Inc., Chicago, Illionus, ABD, 2019) package program. Number, percentage, mean±standard deviation, minimum and maximum values from descriptive statistics were calculated. The Kolmogorow-Smirnow test was used to evaluate the conformity of continuous variables (age, gestational week in which COVID 19 disease experienced in this pregnancy, current gestational week, first marriage age, first gestational age, number of pregnancy, number of birth, number of living children, number of stillbirth, number of low, number of curettage, number of vaginal birth, number of cesarean deliveries, husband's age, COVID-19-VLS total and subscales, ATVS-COVID-19 total and subscales, VHSP total and subscales) to normal distribution. The difference in mean scale scores according to categorical variables (age group, marital status, family type, education status, income status, mother working status, social security status, cigarette, husband's age, husband education status, husband working status, current pregnancy trimester, baby's sex, problem status in pregnancy, having COVID-19 disease during pregnancy, trimester with COVID-19 disease during pregnancy, getting the COVID-19 vaccine during pregnancy, first dose of COVID-19 vaccine during pregnancy, second dose of COVID-19 vaccine during pregnancy, opinions on the COVID-19 vaccine in pregnancy, opinions on the effects of being vaccinated for COVID-19 during pregnancy on the baby) was determined by independent sample t-test or Man Whithney U test for two independent groups, and by One Way ANOVA or Kruskal Vallis for more than two groups. Spearman correlation analysis was used to identify correlation between numerical sociodemographic-obstetric variables and COVID-19-VLS, ATVS-COVID-19, VHSP total mean scores. Statistical significance was determined as $p < 0.05$, with a confidence interval of 95%.

Ethical Considerations

Ethics committee approval were obtained from Muş Alparslan University Scientific Research and Publication Ethics Committee (Date:30.05.2022 MAUN-SRPEC-Board Decision-8/45), and institutional permission were obtained from Mus Provincial Health Directorate (Date:08.06.2022). Written informed consent was received from pregnant women.

Results

The scale score averages of the pregnant women were determined as follows: COVID-19-VLS: 2.5±0.4, COVID-19-VLS functional:2.6±0.7, COVID-19-VLS communicating and critical 2.3±0.7; ATVS-COVID-19: 3.1±0.8, ATVS-COVID-19 positive sub-dimension 3.1±1.0, ATVS-COVID-19 negative 3.1±0.8; VHSP: 27.7±6.6, VHSP lack of confidence 21.4±5.7, VHSP risk 6.3±1.7 (Tablo 1).

In terms of their sociodemographic characteristics, it was found that 39.7% of the pregnant women were between the ages of 25-29, 91.9% were married, 82.3% came from a nuclear family structure, 24.9% were secondary school graduates, 60.3% had income=expenses, 72.7%, 72% were unemployed, 72.2% had social security, 22.5% were smokers, 66% were in their third trimester and 14.8% of them had problems in their current pregnancy (Tablo 2).

Table 1. The pregnant women's mean scores of the COVID-19 Vaccine Literacy Scale, of the Attitudes towards the COVID-19 Vaccine Scale, of the Vaccine Hesitancy in Pandemics Scale and of these scales' sub-dimensions

Scales	Total Pregnancy (n=209)	
	Mean (±SD)	Min-Max (Median)
COVID-19-VLS	2.5 (±0.4)	1-3.5 (2.5)
COVID-19-VLS Functional	2.6 (±0.7)	1-4 (2.75)
COVID-19-VLS Communicating and Critical	2.3 (±0.7)	1-4 (2.25)
ATVS-COVID-19	3.1 (±0.8)	1-4.89 (3)
ATVS-COVID-19 Positive	3.1 (±1.0)	1-5 (3.25)
ATVS-COVID-19 Negative	3.1 (±0.8)	1-4 (3)
VHSP	27.7 (±6.6)	14-46 (28)
VHSP Lack of Confidence	21.4 (±5.7)	11-40 (21)
VHSP Risk	6.3 (±1.7)	2-10 (6)

COVID-19-VLS: COVID-19 Vaccine Literacy Scale; ATVS-COVID-19: Attitudes Towards the COVID-19 Vaccine Scale; VHSP: Vaccine Hesitancy Scale in Pandemics

Table 2. The pregnant women's mean scores of COVID-19 Vaccine Literacy Scale, COVID-19 Vaccine Attitudes Scale, Vaccine Hesitancy in Pandemics Scale regarding their sociodemographic and obstetric characteristics

Sociodemographic and obstetric characteristics	Total Pregnancy (n=209)	COVID-19-VLS Total		ATVS-COVID-19 Total		VHSP Total	
	% (n)	Mean (±SD)	Test/p-value	Mean (±SD)	Test/p-value	Mean(±SD)	Test/p-value
Age							
19 years and under	2.9 (6)	2.1 (0.6)	H: 8.1	2.2 (0.8)	H: 8.9	33.1 (5.9)	F: 1.8
20-24 years old	24.4 (51)	2.5 (0.4)	p:0.08	3.1 (0.8)	p:0.06	27.5 (7.1)	p:0.1
25-29 years old	39.7 (83)	2.6 (0.3)		3.2 (0.8)		27.2 (6.5)	
30-34 years old	23.4 (49)	2.4 (0.4)		3.0 (0.8)		28.9 (6.9)	
35 years and older	9.6 (20)	2.5 (0.3)		3.3 (0.6)		26.1 (5.0)	
Marital status							
Married	91.9 (192)	2.5 (0.4)	U: 1371.5	3.1 (0.8)	U: 1162.5	27.5 (6.8)	U: 1267.5
Single	8.1 (17)	2.4 (0.5)	p:0.2	2.7 (0.7)	p:0.04	:29.6 (4.8)	p:0.1
Family type							
Nuclear	82.3 (172)	2.5 (0.4)	U: 2647.5	3.1 (0.8)	U: 3094.5	27.6 (6.6)	U: 2963.5
Extended	17.7 (37)	2.4 (0.4)	p:0.1	3.1 (0.8)	p:0.7	28.3 (6.7)	p:0.5
Education status							
İlliterate	2.9 (6)	2.2 (0.4)	H: 23.3	2.8 (0.8)	H: 4.8	28.8 (5.7)	H: 4.7
Literate	5.7 (12)	2.2 (0.2)	p<0.01	2.6 (1.0)	p:0.5	29.2 (7.3)	p:0.5
Primary school	11.5 (24)	2.3 (0.3)		3.1 (0.7)		29.3 (7.0)	
Middle school	24.9 (52)	2.5 (0.3)		3.1 (0.8)		28.3 (7.2)	
High school	23.9 (50)	2.5 (0.4)		3.2 (0.9)		26.8 (6.4)	
Associate degree	13.9 (29)	2.6 (0.4)		3.2 (0.7)		27.3 (7.0)	
Bachelor degree	17.2 (36)	2.7 (0.4)		3.2 (0.7)		26.7 (5.5)	
Income status							
Income < Expense	58 (27.8)	2.4 (0.4)	H: 8.5	3.0 (0.8)	H: 3.5	28.7 (5.6)	H: 5.7
Income = Expense	60.3 (126)	2.5 (0.3)	p:0.01	3.1 (0.8)	p:0.1	27.8 (6.8)	p:0.05
Income > Expense	12.0 (25)	2.7 (0.3)		3.5 (0.9)		25.0 (7.5)	
Working status							
Yes	27.3 (57)	2.6 (0.3)	U: 3163.5	3.3 (0.8)	U: 3858.0	26.5 (6.6)	U: 3659.0
No	72.7 (152)	2.4 (0.4)	p<0.01	3.1 (0.8)	p:0.2	28.2 (6.6)	p:0.08
Social security status							
Yes	72.2 (151)	2.5 (0.4)	U: 3202.5	3.2 (0.7)	U: 3443.5	27.2 (6.4)	U:3813.5
No	27.8 (58)	2.3 (0.4)	p<0.01	2.8 (0.9)	p:0.01	29.0 (7.1)	p:0.14
Cigarette							
Yes	22.5 (47)	2.4 (0.4)	U: 3183.5	3.1 (0.7)	U: 3635.0	27.2 (6.4)	t:-0.5
No	77.5 (162)	2.5 (0.4)	p:0.08	3.1 (0.8)	p:0.6	27.9 (6.7)	p:0.5
Current pregnancy tremester							
First	9.6 (20)	2.3 (0.4)	H: 1.3	2.7 (1.0)	F: 2.9	30.9 (8.1)	H: 3.9
Second	24.4 (51)	2.5 (0.4)	p:0.5	3.1 (0.8)	p:0.2	27.1 (6.4)	p:0.1
Third	66.0 (138)	2.5 (0.4)		3.2 (0.7)		27.5 (6.4)	
Baby's sex							
Female	17.2 (36)	2.5 (0.4)	H:1.4	3.4 (0.7)	H: 11.4	29.6 (8.4)	H: 10.8
Male	34.4 (72)	2.5 (0.4)	p:0.4	3.0 (0.7)	p<0.01	25.5 (5.6)	p<0.01
Gender unknown	48.3 (101)	2.4 (0.4)		2.9 (1.0)		28.6 (6.2)	
Problem in pregnancy							
Yes	14.8 (31)	2.4 (0.4)	U: 2542.5	3.1 (0.8)	U: 2698.0	28.2 (6.4)	U: 2704.0
No	85.2 (178)	2.5 (0.4)	p:0.4	3.1 (0.8)	p:0.2	27.6 (6.7)	p:0.8

COVID-19-VLS: COVID-19 Vaccine Literacy Scale; ATVS-COVID-19: Attitudes Towards the COVID-19 Vaccine Scale; VHSP: Vaccine Hesitancy Scale in Pandemics; t: Independent Sample t test; U: Man Whitney U test; F: One Way ANOVA; H: Kruskal Wallis Test

Table 3. The pregnant women's mean scores of COVID-19 Vaccine Literacy Scale, COVID-19 Vaccine Attitudes Scale, Vaccine Hesitancy in Pandemics Scale mean scores according to their experiences, feelings and thoughts regarding COVID-19 and its vaccine in their current pregnancy

Characteristics of pregnant women's experiences with COVID-19 disease and vaccine	Total Pregnancy (n=209)	COVID-19-VLS Total		ATVS-COVID-19 Total		VHSP Total	
	% (n)	Mean (±SD)	Test/p-value	Mean (±SD)	Test/p-value	Mean(±SD)	Test/p-value
Having COVID-19 disease during pregnancy							
Yes	12.4 (26)	2.4 (0.3)	U: 2099.0	3.1 (0.8)	U: 2376.0	27.5 (6.4)	t: -0.2
No	87.6 (183)	2.5 (0.4)	p:0.3	3.1 (0.8)	p:0.9	27.7 (6.7)	p:0.8
Trimester with COVID-19 disease during pregnancy							
First	7.2 (15)	2.4 (0.2)	H: 3.3	3.0 (0.9)	H: 1.3	28.0 (7.2)	F: 0.5
Second	4.3 (9)	2.5 (0.3)	p:0.1	3.0 (0.4)	p:0.5	27.6 (4.2)	p:0.6
Third	1.0 (2)	2.7 (0.05)		3.9 (1.3)		23.0 (9.8)	
Getting the COVID-19 vaccine during pregnancy							
Yes	34.4 (72)	2.6 (0.4)	U: 4145.5	3.2 (0.7)	U: 4348.5	25.6 (5.5)	U: 3505.5
No	65.6 (137)	2.4 (0.4)	p:0.05	3.1 (0.8)	p:0.1	28.8 (6.9)	p<0.01
1st dose of COVID-19 vaccine during pregnancy	%34.4(72)						
BioNTech	24.4 (51)	2.5 (0.4)	F: 1.3	3.2 (0.6)	F: 0.05	25.7 (4.5)	H: 0.5
Sinovac	9.6 (20)	2.7 (0.3)	p: 0.2	3.2 (0.9)	p: 0.9	25.1 (7.6)	p:0.7
Turcovac	0.5 (1)	2.25		3.4		33.0	
2nd dose of COVID-19 vaccine during pregnancy	%30.2 (63)						
BioNTech	22.5 (47)	2.5 (0.4)	F: 0.7	3.2 (0.5)	F: 0.05	25.5 (4.3)	F: 0.9
Sinovac	7.2 (15)	2.6 (0.3)	p:0.4	3.2 (1.1)	p:0.9	25.0 (8.7)	p:0.4
Turcovac	0.5 (1)	2.25		3.4		33.0	
Opinions on the COVID-19 vaccine in pregnancy							
I think it's harmful, risky	35.9 (75)	2.4 (0.3)	H: 11.9	2.8 (0.8)	F: 0.05	31.0 (7.1)	F: 0.09
I am scared	5.3 (11)	2.3 (0.4)	p<0.01	3.1 (0.5)	p:0.9	29.0 (3.7)	p:0.4
I think it is protective and useful	26.8 (56)	2.6 (0.3)		3.5 (0.8)		23.9 (5.5)	
I'm not sure, I'm undecided, I don't know	32.1 (67)	2.4 (0.4)		3.2 (0.7)		27.0 (5.5)	
Opinions on the effects of being vaccinated for COVID-19 during pregnancy on the baby							
I think it will benefit	23.0 (48)	2.6 (0.4)	F: 1.5	3.6 (0.8)	F: 15.3	23.3 (5.5)	F: 22.5
I'm undecided, I don't know, I'm not sure	43.1 (90)	2.5 (0.4)	p:0.2	3.1 (0.6)	p<0.01	27.6 (5.4)	p<0.01
I think it will hurt	34.0 (71)	2.5 (0.4)		2.8 (0.8)		30.9 (7.1)	

COVID-19-VLS: COVID-19 Vaccine Literacy Scale; ATVS-COVID-19: Attitudes Towards the COVID-19 Vaccine Scale; VHSP: Vaccine Hesitancy Scale in Pandemics; t: Independent Sample t test; U: Man Whitney U test; F: One Way ANOVA; H: Kruskal Wallis Test

There was a significant difference between the mean scores of COVID-19-VLS based on education (H:23.3, p-value<0.01), income (H:8.5, p-value:0.01), employment (U:3163.5, p-value<0.01) and social security (U:3202.5, p-value<0.01) status of the pregnant women. It was discovered that pregnant women with a master's degree, whose income is higher than their expenses, who are working and who have social security, have higher COVID-19 vaccine literacy (Tablo 2).

A significant difference was found between pregnant women's mean scores of ATVS-COVID-19 according to their marital status (U:1262.5, p-value:0.04), social security status (U: 3443.5, p-value:0.01), and gender of their babies (H:11.4, p-value<0.01). It was determined that those who are married, have social security and have a female baby have positive attitude towards the COVID-19 vaccine (Tablo 2).

A significant difference was determined between the mean VHSP scores of the pregnant women according to the sex of their babies (H:10.8, p-value<0.01), and those with a female baby had higher hesitation (Tablo 2).

It was found that 12.4% of the pregnant women had COVID-19 disease in their current pregnancy, 7.2% had COVID-19 disease in the first trimester, 34.4% had COVID-19 vaccine in this pregnancy, and 24.4% had the first dose of BioNTech vaccine. 30.2% of the pregnant women were vaccinated two doses of COVID-19 vaccine and 22.5% received BioNTech vaccine. It was revealed that 35.9% of the pregnant women think that the COVID-19 vaccine during pregnancy is harmful and risky,

and 23.0% think that the COVID-19 vaccine during pregnancy benefits the baby (Tablo 3).

A significant difference was found between the mean scores of COVID-19-VLS according to the opinions of pregnant women regarding COVID-19 vaccine (H:11.9, p-value<0.01), and those who thought that the vaccine was protective and beneficial during pregnancy had higher COVID-19 vaccine literacy (Tablo 3).

A significant difference was determined between the mean scores of ATVS-COVID-19 according to the opinions of pregnant women regarding the effects of being vaccinated against COVID-19 on baby (F:15.3, p-value<0.01), and it was revealed that those who thought that the vaccine would benefit during pregnancy showed more positive attitudes (Tablo 3).

A significant difference was determined between the mean VHSP

scores according to vaccination status (U:3505.5, p-value<0.01). Those who do not have the COVID-19 vaccine in this pregnancy were found to be more hesitant about the vaccine. There was a significant difference between the VHSP mean scores of pregnant women based on their thoughts on the effects of being vaccinated against the baby (F:22.5, p-value<0.01). It was revealed that those who think that getting COVID-19 vaccine during pregnancy will harm the baby have more hesitation towards the vaccine (Tablo 3).

A moderately significant correlation was determined between the mean scores of COVID-19-VHLS and average score of ATVS-COVID-19, ATVS-COVID-19 positive, and ATVS-COVID-19 negative, respectively (r: 0.30, r: 0.27, r: 0.24, p-value<0.01). Accordingly, as COVID-19 vaccine literacy of pregnant women increases, there is an increase in positive and negative attitude towards vaccine (Tablo 4).

Table 4. The correlation between the pregnant women's mean scores of the COVID-19 Vaccine Literacy Scale, the Attitudes towards the COVID-19 Vaccine Scale, the Vaccine Hesitancy in Pandemics Scale and their sub-dimensions

Sociodemographic and obstetric characteristics	SCALES								
	1	2	3	4	5	6	7	8	9
1. COVID-19-VLS Total	1								
2. COVID-19-VLS Functional	r:0.84 p<0.01	1							
3. COVID-19-VLS Communicating and Critical	**r:0.08** p:0.20	**r:-0.40** p<0.01	1						
4. ATVS-COVID-19 Total	r:0.30 p<0.01	r:0.32 p<0.01	r:-0.09 p:0.17	1					
5. ATVS-COVID-19 Positive	**r:0.27** p<0.01	**r:0.30** p<0.01	**r:-0.09** p:0.17	**r:0.89** p<0.01	1				
6. ATVS-COVID-19 Negative	r:0.24 p<0.01	r:0.25 p<0.01	r:-0.07 p:0.27	r:0.86 p<0.01	r:0.57 p<0.01	1			
7. VHSP Total	r:-0.28 p<0.01	r:-0.29 p<0.01	r:0.12 p:0.07	r:-0.70 p<0.01	r:-0.74 p<0.01	r:-0.51 p<0.01	1		
8. VHSP Lack of Confidence	r:-0.25 p<0.01	r:-0.27 p<0.01	r:0.14 p:0.04	r:-0.68 p<0.01	r:-0.75 p<0.01	r:-0.46 p<0.01	r:0.97 p<0.01	1	
9. VHSP Risk	r:-0.26 p<0.01	r:-0.24 p<0.01	r:0.02 p:0.72	r:-0.52 p<0.01	r:-0.45 p<0.01	r:-0.48 p<0.01	r:0.60 p<0.01	r:0.44 p<0.01	1

COVID-19-VLS: COVID-19 Vaccine Literacy Scale; ATVS-COVID-19: Attitudes Towards the COVID-19 Vaccine Scale; VHSP: Vaccine Hesitancy Scale in Pandemics; r: Spearman's rho Coefficient

A moderately significant negative correlation was determined between pregnant women's mean scores of COVID-19-VHLS and their mean scores of VHSP, VHSP lack of confidence, and VHSP risk, respectively (r:-0.28, r:-0.25, r:-0.26, p-value<0.01). This shows that as COVID-19 vaccine literacy of pregnant women increases, mistrust, risk perception and hesitations towards the vaccine decrease (Tablo 4).

A moderately correlation was determined between mean COVID-19-VLS functional scores of pregnant women and their mean scores of ATVS-COVID-19 (r: 0.32, p-value<0.01). Accordingly, as functional COVID-19 vaccine literacy of pregnant women

increases, their positive attitudes towards vaccine increase. A moderate correlation was determined between COVID-19-VLS functional and VHSP mean scores of pregnant women (r:-0.29, p-value<0.01). Accordingly, as functional COVID-19 vaccine literacy of pregnant women increases, their hesitations towards vaccine decrease (Tablo 4).

A highly correlation was found between ATVS-COVID-19 mean scores of pregnant women and their VHSP, VHSP lack of confidence and VHSP risk means scores, respectively (r: -0.70, r: -0.68, r: -0.52, p-value<0.01) (Tablo 4). Accordingly, as positive attitudes of pregnant women towards COVID-19 vaccine

increase, their fear, risk perception, and hesitation towards the vaccination diminish.

In this pregnancy of pregnant women, a positive correlation was determined between their COVID-19 vaccine literacy and their gestational age at which they had COVID-19 disease (r:0.44,

p-value:0.02), their age at first marriage (r: 0.18, p-value<0.01), their age at first pregnancy (r: 0.2, p-value<0.01), total number of their births (r:0.22, p-value<0.01). A negative significant correlation was determined between COVID-19 vaccine literacy and the number of pregnancies, living children, stillbirths, vaginal births (Tablo 5).

Table 5. The correlation between the numerical sociodemographic and obstetric characteristics of pregnant women and their mean scores of the COVID-19 Vaccine Literacy Scale, the Attitudes towards the COVID-19 Vaccine Scale, and the Vaccine Hesitancy in Pandemics Scale

Sociodemographic and obstetric characteristics	Total Pregnancy (n=209) Mean (±SD)	COVID-19-VLS Total		TVS-COVID-19 Total		VHSP Total	
Age	27.6 (±5.2)	r:-0.03	p:0.6	r:0.05	p:0.4	r:-0.03	p:0.6
Gestational week in which COVID 19 disease experienced in this pregnancy	12.8 (±8.2)	r:0.44	p:0.02	r:0.23	p:0.2	r:-0.14	p:0.4
Current gestational week	27.6 (±9.1)	r:0.02	p:0.77	r:0.04	p:0.4	r:0.02	p:0.6
First marriage age	22.2 (±3.3)	r:0.18	p<0.01	r:0.07	p:0.2	r:-0.03	p:0.6
First gestational age	23.2 (±3.7)	r:0.2	p<0.01	r:0.08	p:0.2	r:-0.09	p:0.1
Number of pregnancy	2.4 (±1.5)	r:-0.2	p<0.01	r:-0.04	p:0.5	r:0.02	p:0.7
Number of birth	1.2 (±1.3)	r:0.22	p<0.01	r:-0.04	p:0.5	r:0.03	p:0.6
Number of living children	1.1 (±1.2)	r:-0.2	p<0.01	r:-0.02	p:0.7	r:0.02	p:0.7
Number of stillbirth	0.04 (±0.2)	r:-0.15	p:0.02	r:0.002	p:0.9	r:-0.02	p:0.7
Number of low	0.1 (±0.5)	r:0.02	p:0.7	r:-0.06	p:0.3	r:-0.007	p:0.9
Number of curettage	0.1 (±0.4)	r:-0.04	p:0.5	r:0.04	p:0.5	r:-0.05	p:0.4
Number of vaginal birth	0.9 (±1.1)	r:-0.22	p<0.01	r:-0.1	p:0.14	r:0.05	p:0.4
Number of cesarean deliveries	0.2 (±0.5)	r:-0.09	p:0.1	r:0.09	p:0.15	r:-0.03	p:0.6

COVID-19-VLS: COVID-19 Vaccine Literacy Scale; ATVS-COVID-19: Attitudes Towards the COVID-19 Vaccine Scale; VHSP: Vaccine Hesitancy Scale in Pandemics; r: Spearman's rho Coefficient

Discussion

All available information and research on COVID-19 vaccines have revealed positive findings. However, the concepts of COVID-19 vaccination, vaccine literacy, attitudes towards vaccines and hesitancy are issues that need to be addressed seriously in pregnant women. The findings of the study conducted for this purpose were discussed.

In a study conducted in Ethiopia, rate of acceptance of COVID-19 vaccine by pregnant women was found 40.08%. It was stated that approximately 81.8% of the pregnant women had information about the vaccine and 37.9% of them got this information from health workers [29]. In a study conducted on vulnerable groups such as pregnant and lactating women with 1249 participants, it was determined that 41.8% of participants had limited information about suitability of vaccines [10]. A study conducted in Thailand reported that 60.8% of pregnant women accepted vaccine, and more than half (55.8%) of pregnant women who accepted vaccine preferred in second trimester. Fear of vaccine harming the baby, side effects, and distrust of vaccine efficacy were the most common reasons for rejection [30]. In a metaanalysis reported overall rate of pregnant women vaccinated

against COVID-19 as 27.5%. It was also stated that advanced age, race, ethnicity, trust in COVID-19 vaccine types and fear of COVID-19 during pregnancy are among the factors affecting vaccine acceptance [31]. A study in both pregnant and lactating women revealed that majority of pregnant women (85.6%) were in third trimester and 97.2% of them were not vaccinated during pregnancy. The study stated that 13.3% of pregnant women refused to be vaccinated despite doctor's advice. It also reported that as the education level of pregnant women increased, rejection of vaccine increased, 56.8% of the pregnant women refused to be vaccinated despite the vaccination recommendation, and 28.4% of them had commitments to the vaccine [32]. A study conducted in USA stated that pregnant women living in the countryside had a lower vaccination rate than pregnant women living in the center [18]. A study of 885 pregnant women reported that the functional (2.9) and communicative-critical vaccination literacy (3.3) of pregnant women for COVID-19 were above average [22]. In this study, it was found that COVID-19 vaccine literacy (2.5), functional vaccine literacy (2.6), and communicative-critical vaccine literacy (2.3) of pregnant women living in rural area were moderate. It was determined that as age, education and income level for COVID-19 increase, vaccine literacy,

especially functional vaccine literacy, increases. This study showed that vaccine literacy is higher in pregnant women who are working, have social security, do not smoke and think that the vaccine is protective and beneficial. In addition, it was found that vaccine literacy increased as first marriage age, first pregnancy age, total number of births and gestational age with COVID-19 disease increased. It was determined that as the total number of pregnancies, living children, stillbirths, vaginal births and age of spouse increased, vaccination literacy decreased. While this findings support results of previous studies, it shows that COVID-19 vaccine literacy of pregnant women living in rural area is significantly affected by their current obstetric characteristics. Muş province, which is a rural area and located in Eastern Anatolia, is one of the provinces with the highest fertility rate (TFR: 2.7). Individuals living in the region are mostly conservative and adhere to religious beliefs. It is the most underdeveloped province in the country that migrates to the west in the region [19,33]. This shows that women living in the region, especially pregnant women, should be evaluated carefully during pandemic process. Therefore, it is thought that these findings will make an important contribution to the literature.

The sociocultural characteristics of the society in which the pregnant women live and the level of vaccination literacy significantly affect their attitudes towards vaccination. A study stated that 79.6% of participants had a negative attitude towards COVID-19 vaccine, 96.8% were worried about the vaccine, and 84.1% were willing to be vaccinated in the future [34]. Another study reported that 36% of pregnant women had a negative attitude towards getting vaccinated during pregnancy and their concerns about safety of their babies were at the forefront. It was also stated that the probability of vaccination of pregnant women increased as age, education level, income level and gestational week increased [35]. In Saudi Arabia iı was reported that 68% of pregnant women were willing to be vaccinated, and that COVID-19 vaccine rejection increased in non-working and low-educational pregnant women [36]. In another study was reported that COVID-19 vaccine effectiveness was 90% showed that 52.0% of pregnant women and 73.4% of non-pregnant women were willing to be vaccinated and had a positive attitude towards vaccine. In addition, the study noted that among the most important indicator of vaccine acceptance are safety or efficacy, concern about COVID-19 [11]. A study conducted in Turkey revealed that 50.8% of participants did not want to be vaccinated in pregnancy, and 3.8% of pregnant women changed their views positively after giving information about vaccine studies. In addition, it was stated that 37% of pregnant women would refuse to be vaccinated even if the safety of the vaccine was proven [37]. The fact that there was no research that evaluated COVID-19 vaccine attitude of pregnant women in pregnancy with a scale shows importance of this research. This study determined that mean attitude score of participants towards COVID-19 was 3.1 and pregnant women had a moderately positive attitude towards vaccine. It was revealed that attitude of pregnant women who are married, whose spouse is between the ages of 31-35, who have

social security, whose baby is a girl, and who think that getting COVID-19 vaccine during pregnancy will benefit baby, have a positive attitude towards vaccine. It was determined that as age and income level increased, positive attitude towards vaccination increased. In addition, it was observed that 34.4% of the pregnant women had a single dose, 30.2% had two doses, and the majority of these vaccines were BioNTech vaccine. The findings support the results of previous study and show that pregnant women living in rural areas have positive attitude towards vaccine.

Level of hesitation towards COVID-19 vaccines in pregnant women is higher due to possible effects of vaccine on baby and pregnant woman. A meta-analysis study reported that rate of vaccine hesitancy in pregnant women was 49%. In terms of time factor in studies conducted since the beginning of the pandemic, vaccine hesitancy was found to be 58.0% in studies conducted in 2020, 38.1% in studies conducted in the first six months of 2021, and 42.0% in studies conducted in the second six months of 2021. These rates show that there is a moderate level of hesitation about vaccination in pregnant women [38]. It was stated in a study conducted in the USA that only 35.7% of pregnant women accepted to be vaccinated, 57.4% had only one dose vaccine during their pregnancy, and hesitancy of COVID-19 vaccination is high in pregnant women who live in big cities and have high education and income levels [39]. A meta-analysis study stated that the rate of vaccinated pregnant women was 27.5%, and advanced age, ethnicity, race, and confidence in COVID-19 vaccines were among the factors affecting vaccine acceptance during pregnancy [31]. A study conducted in Japan reported the COVID-19 vaccination rate of pregnant women as 13.4% and the vaccination hesitancy rate as 50.9%. The main reasons for hesitation included factors such as adverse reactions, adverse effects on the fetus and concerns about breastfeeding, and lack of confidence in government [8]. A multicenter study stated that 52.0% of pregnant women would agree to receive the COVID-19 vaccine during their pregnancy if they believed that the vaccine would be 90% effective. It was reported that the rate of vaccination acceptance of pregnant women varies between 28.8-84.4% according to the countries, while the acceptance level is above 80% in India and Mexico, it is below 45% in the USA, Australia and Russia [11]. A study conducted in Turkey stated that 28.5% of pregnant women refused to be vaccinated, and those with low education level (33.3%) and those who did not work in any job (47.1%) stated that vaccination rejection was higher [40]. This study measured the mean score of the vaccine hesitancy scale for COVID-19 as 27.7, the lack of confidence in the vaccine as 21.4, and the risk perception as 6.3. According to this result, it can be claimed that pregnant women have hesitations above the average. It was determined that vaccination hesitancy is higher in pregnant women whose baby is a girl, who did not have vaccine in this pregnancy and who think that vaccine will harm baby. The findings support previous study results. However, it shows that although pregnant women living in rural areas have a positive attitude towards vaccine, their hesitation is at a high level. Despite the high level of hesitation,

it was found that 34.4% of pregnant women had vaccine in this pregnancy, 34.4% had a single dose, 30.2% had two doses, and most of the vaccines were BioNTech vaccine. This shows that pregnant women are highly vaccinated and they prefer to have the BioNTech vaccine.

It is stated that as COVID-19 vaccine literacy increases, positive attitude increases and hesitation decreases [22]. This study determined that as functional and critical vaccine literacy for COVID-19 increases in pregnant women, positive attitude towards vaccine increases. As positive attitude towards vaccine increased, lack of confidence and risk perception and hesitation decreased. Research findings support the results of the study.

Limitations

The research findings cannot be generalized to the population since the research was conducted only in Muş State Hospital Obstetrics and Gynecology Polyclinic.

Conclusion

This study determined that COVID-19 vaccine literacy of pregnant women affected their attitudes and hesitations towards vaccination, and accordingly, that their vaccination rates were low. It also revealed that COVID-19 vaccine literacy was affected by their obstetric characteristics. According to the study, reasons such as lack of evidence-based findings regarding effect of COVID-19 vaccines on mother and baby during pregnancy, the uncertainty of long-term effects of vaccine, lack of confidence in existing data, and health policies applied resulted in both high hesitations of pregnant women and low vaccination rates. Healthcare professionals should support pregnant women in their antenatal care and monitoring with evidence-based information about indications, contraindications and side effects of COVID-19 vaccine.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Ethics committee approval and institutional permission were obtained from Muş Alparslan University Scientific Research and Publication Ethics Committee (Date:30.05.2022 MAUN-SRPEC-Board Decision-8/45).

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ORIGINAL ARTICLE

Complicated and suppurative skin soft tissue infections: our four-year cases

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Abstract

Skin and soft tissue infections (SSTIs) are common community and hospital-acquired infections and rarely result in severe morbidity and mortality. It is not always possible to obtain cultures and isolate the causative agent in these patients, primarily treated with empirical antibiotics. In this retrospective cross-sectional study, 57 patients with complicated SSTI followed between 2018 and 2022 with purulent and necrotizing characteristics or growth in blood cultures were included. Thirty-eight patients (66.7%) were male, and 39 (68.4) had diabetes. In 43 (75.5%) patients, the infection was in the lower extremity and gluteal region. Gram-positive agents were detected in 35 patients (61.4%), Gram-negative agents were found in 13 patients (22.8%), and Gram-positive and Gram-negative mixed growth was detected in 1 patient (1.8%), and no causative agent could be produced in 8 (14%) patients. Of the 21 *Staphylococcus aureus* produced, 4 (19%) were methicillin-resistant (MRSA). Growth was detected in blood cultures in three patients (5.3%), and all were streptococcal bacteria. It was observed that 31 patients (54.4%) required hospitalization for treatment, and 29 (50.8%) required surgical intervention such as drainage, aspiration, debridement, or amputation. Three patients (5.3%) died, and four (7%) underwent amputation. There was no significant difference between diabetic and non-diabetic patients regarding factors and mortality–morbidity. In the logistic regression analysis, none of the variables of gender, type of causative agent, presence of diabetes, and site of infection significantly affected severe morbidity and mortality. Since it was detected at a low rate in our cases, it can be said that MRSA and *P.aeruginosa* do not need to be considered in every patient for the initial empirical treatment, Gram-negative rods can be taken into account, especially in diabetics, and broad-spectrum and combined antibiotics are not needed in the vast majority of patients. Microbiological follow-up and sensitivity studies at regional and global scales will need to continue to guide empirical treatments in SSTIs.

Keywords: Infectious skin disease, soft tissue, bacteria, abscess

Introduction

Skin and soft tissue infections (SSTIs) are among the most common diseases among community-acquired infections. It can occur in a broad clinical spectrum, from simple forms that do not require systemic treatment and recover only with topical antibiotic therapy to necrotizing forms that threaten life and extremities and cause sepsis. It usually occurs when the skin's protective mechanisms are impaired following trauma, inflammation, maceration due to excessive moisture, decreased tissue perfusion, or other factors that disrupt the stratum corneum.

It is not necessary to take a culture in uncomplicated SSTI where outpatient treatment is sufficient and does not require parenteral therapy. Cultures are necessary in complicated cases involving deep structures, treatment failure, and drainage-requiring situations. The sensitivity of blood culture is low. If the patient has a purulent discharge, it is appropriate to use this pus for culture. Deep tissue samples in necrotizing infections and purulent fluids aspirated or drained in subcutaneous abscesses

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should be used for culture and stained microscopic examinations. If there is a non-purulent clinical picture such as cellulitis and erysipelas, tissue biopsy or skin aspiration and blood culture should be used for culture [1]. Using unsuitable superficial swab samples for culture may result in the evaluation of colonizing bacteria or flora elements as agents. In non-purulent SSTI, skin biopsies and skin aspirations for microbiological examination are not practical and are not used much in the clinic. Treatments are mainly organized empirically. This study aimed to review the results of the microbiological examination in groups with a chance of detecting the causative agent, evaluate their susceptibility to shed light on empirical treatments, and compare them with the literature.

Material and Methods

In this study, which is a cross-sectional retrospective study, patients with community-acquired infections who were followed up in the outpatient clinic or hospitalized in the service-intensive care unit between August 2018 and August 2022 were determined by file scanning following the inclusion and exclusion criteria. The patients were evaluated in age, gender, mechanism of infection, site of infection, presence of diabetes, need for spontaneous drainage or surgery, culture results, treatments given, and outcome (amputation, exitus, recovery).

Patients 18 years of age or older who had community-acquired necrotizing or suppurative skin and appendage infections, pus or deep tissue biopsy for culture, or had pathogen growth in blood culture were included in the study. Patients with foreign body infections, cellulitis, erysipelas, and lymphangitis patients without abscess and purulation or with no growth in blood culture, patients under 18 years of age, HIV-positive patients, and hospital-acquired infections were excluded from the study.

Ethics Committee Approval: Permission was obtained from the local ethics committee of Ordu University Faculty of Medicine (Date: 05.08.2022, No: 2022/196).

Statistical Analysis

Statistical Package for Social Sciences (IBM SPSS for Mac) version 26 and Jamovi software version 2.2.3 were used for statistical analysis. Chi-square analysis and Fisher's exact test were used to compare categorical variables. Univariate and multivariate binominal logistic regression analyzes were performed for the effects of gender, site of infection, agents, and presence of diabetes on mortality and severe morbidity. $P<0.05$ was accepted as the statistical significance level.

Results

A total of 57 patients, 38 (66.7%) male and 19 (33.3%) female were included in the study. The median age was 58 (range: 27-90). Thirty-nine patients (68.4%) had diabetes.

In 43 (75.5%) of the patients, the infection was in the lower extremity and gluteal region, and its distribution was as follows;

foot 21 (36.8%), tibial region 11 (19.3%), gluteal region 5 (8.8%), femoral region 5 (8.8%), knee 1 (1.8%). Infection focus was found in the upper extremity in 6 patients (10.5%), the torso in 4 patients (7%), and in the head and neck region in 4 patients (7%). Nine patients (15.7%) had a history of significant trauma causing infection. It was observed that 7 (12.3%) of them were in the lower extremities.

As a result of the cultures taken, the agent could not be produced in 8 patients (14%). The causative agent was isolated in blood, pus, or tissue cultures in 49 patients, with three (5.3%) in blood cultures. Gram-positive agents were detected in 35 patients (61.4%), Gram-negative agents were found in 13 patients (22.8%), and Gram-positive and Gram-negative mixed growth was detected in 1 patient (1.8%). Of the 21 *Staphylococcus aureus* produced, 4 (19%) were methicillin-resistant (MRSA).

Although Gram-negative growth was detected at a rate of 28.2% (11/39) in diabetic patients and 11.1% (2/18) in non-diabetic patients, this difference was not statistically significant (P= 0.318). The distribution of the agents is shown in Table 1. Bacteria isolated from blood cultures were *Streptococcus pneumoniae, Streptococcus pyogenes, and Streptococcus disgalactiae.*

Table 1. Distribution of pathogens

PATHOGEN	N (%)
Gram-positive	**35 (%61.4)**
Staphylococci	**18 (%31.6)**
MSSA	15 (%26.3)
MRSA	3 (%5.3)
Streptococci	**11 (%19.2)**
Streptococcus spp.	4 (%7)
S.pyogenes	3 (%5.3)
S. agalactia	1 (%1.8)
S.disgalactiae	1 (%1.8)
S. pneumoniae	1 (%1.8)
S. intermedius	1 (%1.8)
Enterococcus faecalis	**2 (%3.5)**
Corynebacterium striatum	**1 (%1.8)**
Gram-positive polymicrobial	**3 (%5.3)**
MSSA + Streptococcus	2 (%3.5)
MRSA + Enterococcus	1 (%1.8)
Gram-negative	**13 (%22.8)**
E.coli	5 (%8.8)
ESBL (-)	4 (%7)
ESBL (+)	1(1.8)
P.aeruginosa	2 (%3.5)
Proteus	**2 (%3.5)**
P.vulgaris	1 (1.8)
P.mirabilis	1 (1.8)
Gram-negative polymicrobial	**3 (%5.3)**
E.coli + Morganella	1 (%1.8)
Serratia + Morganella	1 (%1.8)
Alcaligenes faecalis + Providencia spp.	1 (%1.8)
Citrobacter freundii	**1 (%1.8)**
Mixed Gram-positive + Gram-negative	**1 (%1.8)**
No growth	8 (%14)
Total	**57 (%100)**

Surgical intervention such as drainage, aspiration, debridement, or amputation was required in 29 patients (50.8%). Adequous

spontaneous purulent drainage occurred in 22 (38.6%) of them, which did not require additional surgical intervention. It was observed that 31 patients (54.4%) required hospitalization for their treatment, and 26 patients (45.6%) were followed up and treated on an outpatient basis. The follow-up results of the patients are shown in Table 2.

Table 2. Follow-up and treatment results of the patients

Result	N	%
Death	3	5.3
Amputation[1]	4	7
Partial recovery[2]	2	3.5
Recovery	48	84.2

[1]All-foot amputation [2]Chronic ulcerated lesions on the leg

Although severe morbidity and mortality (amputation and death) were observed at a rate of 15.4% (6/39) in patients with diabetes and 5.6% (1/18) in non-diabetic patients, this difference was not statistically significant (P=0.280). In the binominal logistic regression analysis (Cox & Snell R^2=0.125, Nagelkerke R^2= 0.238, Hosmer and Lemeshow test P=0.924), none of the variables of diabetes, site of infection, type of causative agent and gender had a significant effect on severe morbidity and mortality.

Discussion

There is not enough data on the frequency of SSTIs in our country. A study conducted in the United States found that the incidence reached 3.3 million, with an increase of 40% in 2012 compared to 2000, and the cost reached 13.8 billion dollars, with a threefold increase [2]. In another study conducted in the USA, 471550 SSTI attacks of 376262 individuals were examined in the three years between 2009 and 2011, and the annual incidence was calculated as 496 for 10000 individuals [3].

Various classifications have been made for SSTI according to the depth of inflammation in the affected skin, the clinical picture it causes, the surface area involved, the pathogenic microorganism, and the mechanism of infection [4]. Infectious Diseases Society of America (IDSA) updated the skin and soft tissue infections guideline in 2014, divided the SSTI into purulent and non-purulent, mild, moderate, and severe in severity, and necrotizing and non-necrotizing in terms of tissue necrosis [5]. The U.S. Food and Drug Administration proposed a new classification and terminology describing complicated skin and soft tissue infections in 2013. acute bacterial skin and skin structure infections (ABSSSI) The guideline defined ABSSSI as cellulitis/erysipelas, wound infection, and cutaneous abscess with a minimum surface area of 75 cm^2, and did not include less serious skin infections such as impetigo and minor cutaneous abscess, as well as infections from animal or human bites, necrotizing fasciitis, diabetic foot infection, decubitus ulcer infection, infections requiring more complex treatment regimens such as myonecrosis and ecthyma gangrenosum in the definition [6].

In our study, Gram-positive bacteria were found to be the causative agent in the majority (61.4%) of purulent and complicated skin and soft tissue infections, and *S.aureus* was the causative agent in more than half of them. The share of *S.aureus* among the total causative agents was 36.8%, and the share among Gr-positive bacteria was 60%. Four (19%) of 21 *S.aureus* strains produced from clinical isolates were found to be methicillin-resistant. Gram-negative bacteria were isolated in 22.8% of the patients. More than one agent was isolated in seven patients (12.2%). In purulent and non-purulent SSTIs, Gram-positive bacteria, mainly *S.aureus* and streptococci, are the causative agents [7] . In a study conducted in the United States between 2009 and 2011, 471550 SSTIs were examined, and it was observed that only 23% of them could be cultured, and the pathogen was produced in 54% of the cultures. It was determined that 81% of the growing bacteria were S.aureus, and 46% were MRSA. In this study by Ray et al., Gram-negative agents were 14%, beta-hemolytic streptococci 10%, polymicrobial growth 6%, and blood culture growth 14% [3]. In our study, the causative agent was obtained from blood cultures only in 5% of the patients.

In another study in which 11705 hospitalized patients with a diagnosis of SSTI were evaluated, it was observed that half of the patients were obese, 30.9% had diabetes, and 56% were not cultured. It was determined that 63.9% of the bacteria produced were Gram-positive, 11.9% were Gram-negative, and 24.2% were mixed growth [8]. Although the share of Gram-negative bacteria in SSTIs is generally less than Gram-positive bacteria, there is an increase in this rate all over the world. Risk factors for developing SSTI with multidrug-resistant and pan-resistant Gram-negative bacteria include diabetes, burns, pressure sores, neutropenia, immunosuppression, previous antibiotic use, hospitalization, and long-term residence in a healthcare facility. Unfortunately, Gram-negative and mixed-infection SSTI with multi-drug resistance have a worse prognosis [9]. Gram-negative and mixed polymicrobial growths may be encountered in SSTIs, mostly in complicated and healthcare-associated infections, and may pose a risk for inappropriate initial antibiotic therapy. Risk factors for developing complicated SSTI with mixed polymicrobial and Gram-negative bacteria were the presence of comorbidities such as surgical site infections, intensive care, nursing home stay, diabetes mellitus, cirrhosis, and intravenous–subcutaneous drug use [10,11].

Since it is more difficult to take culture in SSTIs than in other clinical conditions and the rate of agent detection in the samples is low, clinicians mostly turn to empirical treatments. Taking culture is even more difficult in cellulite and erysipelas because there is no pus to aspirate and when there is a diffuse inflammation of the skin itself. In these clinical pictures, blood culture positivity is detected only at a rate of 5% or less. In the aspiration of inflamed skin, growth is detected in only 5-40% of the cases, while this rate remains in 20-30% of skin biopsy cultures. In light of these data, the microbiological etiology of most SSTIs is unclear [5]. In the study of Zervos et al., in which they examined 1096 SSTI patients requiring hospitalization between 2005 and 2008, the rate of Gram-negative factors, including those in polymicrobial

growth, was 19.4%, *S.aureus* 66.4% and streptococcal species 26.1%. This study found that approximately half of the patients had healthcare-associated SSTIs, and 74.8% of *S.aureus* were methicillin-resistant [12].

In the SENTRY program, in which the antimicrobial susceptibility of 191460 *S.aureus* isolates obtained between 1997 and 2016 from 427 centers from 45 countries was evaluated, 40.3% of the total isolates were found to be MRSA. This study found methicillin resistance in 41% of *S.aureus* isolated from SSTIs. The highest rates of MRSA were found in nosocomial isolates, urinary tract infections, patients with hospital-acquired pneumonia, and those over 80 years of age. Geographically, variability was found between continents and regions, and the rate of MRSA was 26.8% in European isolates, while it was 47% in North America [13]. Methicillin resistance in S.aureus, which we found at 19% in our study, was consistent with European data and was found to be relatively low due to the inclusion of community-acquired infections in the study.

In the study conducted by Parlak et al. in our country, in which 163 SSTI cases were included, growth was found in the culture at a rate of 63%; Gram-negative bacteria were isolated from only 7.8% of the patients with growth. In the study in which *S.aureus* was found at a rate of 65% and S.pyogenes at a rate of 9.7% in the produced agents, methicillin resistance was found to be 25.4% in *S.aureus* [14]. In the study of Turhanoğlu et al., the bacteria produced in 693 wound cultures and their susceptibility were evaluated in 5 years; Gram-positive bacteria were found to be 52% (88% of them were staphylococci), Gram-negative bacteria were found to be 42.9%. The share of *S.aureus* in all growths was 19%, and methicillin resistance was 35.8% [15]. The fact that this study included all wound cultures and hospital-acquired infections may explain the higher rates of non-*S.aureus* staphylococci, Gram-negative rods, and MRSA than our data.

The cause of death of SSTIs is usually sepsis due to necrotizing infections. There is not much data on the overall mortality rate in SSTIs. A study evaluating 275 million hospitalizations between 2005 and 2011 in the USA found that the primary diagnosis was SSTI in 1.8% of hospital admissions, and diabetes was the most common comorbidity. In the study of Kaye et al., the overall mortality was 0.45%, and it was observed that it decreased from 0.49% to %0.41 from 2005 to 2011 [16] In a study in which 115 patients with necrotizing fasciitis (NF) were examined, the mortality was 20.9%, and the most common comorbidities were cirrhosis (47%) and diabetes mellitus (39%) [17]. In another study in which 88 patients with NF were evaluated, it was observed that the rate of concomitant diabetes was 70.8%, mortality was 21.3%, and amputation had to be performed in 22.5% [18].

In an NF series of 44 cases from our country, it was reported that 52% of the patients had diabetes, 27% polymicrobial growth, 9% S.aureus, 9% Streptococcus spp, 6.8% P.aeruginosa were found in cultures, and mortality was 25% [19]. In a series of 14 cases, it was reported that 71% of the patients had diabetes, and 14.3%

died [20]. In our study, three deaths (5.3%) and four amputations (7%) were detected, and our study did not include only necrotizing infections, making it difficult to compare with the literature. In all cases that resulted in death, the causative agent was *streptococcus (S. pneumoniae, S. disgalactiae, S. pyogenes)*, and effective and broad-spectrum antibiotic treatments were started early in all of them. Thirty-nine (68.4%) of our cases had diabetes. Although the Gram-negative growth rate and severe morbidity-mortality rate were found to be higher in diabetic patients, these differences were not statistically significant. In the logistic regression analysis, diabetes was not a risk factor for death and severe morbidity (amputation). It is known that diabetes mellitus is a frequent comorbidity that accompanies infectious diseases and adversely affects the prognosis. It is more common and severe in diabetic patients than non-diabetic patients and is the leading cause of hospitalizations in SSTI [21].

In a study of 10063 people followed for seven years in Denmark, the risk of pneumonia (adjusted hazard ratio [aHR] 1.75, 95% confidence interval [CI] 1.23–2.48) was increased in diabetic patients compared to patients without urinary tract infection (aHR 3.03, 95% CI 2.04–4.49) and skin infection (aHR 2.43, 95% CI 1.49–3.95). At baseline, each 1 mmol/l increase in plasma glucose was associated with a 6-10% relative risk increase for pneumonia, urinary tract infection, and skin infection after adjusting for other possible confounding agents. In patients hospitalized for urinary tract infections, people with diabetes were found to have a higher risk of death 28 days after admission (HR 3.90, 95% CI 1.20-12.66) compared to non-diabetic patients [22]. In the study of Lipsky et al., 3030 hospitalized, culture-positive, diabetic patients were examined in 4 years in the USA, and it was determined that 1.4% of the patients died. It was observed that 73.2% of the cases had foot infection, 26.8% had non-foot SSTI, approximately half of the cases had polymicrobial growth, and Gram-negative monomicrobial growth was only in 6.8%. Those with non-foot infections were more seriously ill than those with foot infections, and mortality was two times higher than those with foot infections. Severe disease at the time of admission, non-foot infection site, polymicrobial growth containing P.aeruginosa, and Gram-negative growth were associated with mortality [23].

The limitations of our study are that the data were obtained retrospectively, limited to the information in the electronic database, and possible data losses. This study only covers some SSTIs. Only purulent, complicated infections in which tissue samples could be cultured and growth in blood culture were included in the study. It does not reflect infections such as cellulitis, erysipelas, impetigo, ecthyma. Therefore, although there were mild uncomplicated cases in our study, mortality and morbidity rates were higher than the general SSTI rates but lower than those of complicated conditions such as NF. In some patients, antibiotic treatment was started before the culture was taken, resulting in no growth in the culture. Only routine aerobic cultures were studied; anaerobic cultures could not be done.

The exclusion of hospital-acquired infections and surgical site infections makes the microbiological results more meaningful in terms of the microbiology of community-acquired SSTIs. Necrotizing and purulent SSTIs are less common among SSTIs treated as outpatients and inpatients. Some clinicians initiate empirical antibiotic therapy without needing culture, even if drainage and aspiration are performed in typical cases. Time passes from the onset of the infection to abscess and suppuration, during which the patient is started on antibiotics. Early antibiotic treatment prevents complications and progression to an abscess and prevents microbiological identification even if suppuration develops. The rate of detection of growth in blood culture in hospitalized patients is low. For these reasons, although cellulitis, erysipelas, and SSTI secondary to trauma are common, the number of patients who met the inclusion criteria remained limited even over four years. Culture facilities should be forced in all community and hospital-acquired SSTIs; blood cultures in patients with fever, aspirated or drained pus cultures in suppurative infections, and intraoperative tissue cultures should not be neglected and should be obtained before antibiotics if possible. Studies reflecting the SSTI microbiology, antibiotic resistance, and susceptibility of agents need to continue on a regional and global scale. Thus, it can be possible to determine the differences in the agents and resistance profiles caused by the patient characteristics changing due to immunosuppression treatments, chemotherapies, frequent foreign body use, increasing age, and chronic diseases. These studies will guide empirical treatments initiated in emergencies when cultures cannot be obtained, or results are awaited.

Conclusion

As a result, our study provided an up-to-date overview of the microbiological characteristics of rarer varieties of SSTIs with community-based data from our region. Although our data contain different data and rates specific to the study design, they are generally compatible with the literature of the world and our country. It can be said that it is not necessary to consider MRSA and P.aeruginosa in every patient for the initial empirical treatment because it was detected at a low rate in our cases, Gram-negative rods can be taken into account, especially in diabetics, and broad-spectrum and combined antibiotics are not needed in the vast majority of patients. It is seen that the severity of the clinical picture, the development of sepsis, and the occurrence of surgical indication are responsible rather than resistant bacteria and inappropriate antibiotic treatments in patients who died and underwent amputation.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical approval
Permission was obtained from the local ethics committee of Ordu University Faculty of Medicine (Date: 05.08.2022, No: 2022/196).

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ORIGINAL ARTICLE

Comparison of lymph node metastasis rates in breast cancer molecular subtypes; A retrospective clinical study

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Abstract

Breast cancer is the most common cancer in women. Axillary lymph node metastasis in breast cancer is the most important determinant of long-term prognosis, but isn't an independent risk factor for overall survival. Invasive breast cancer is divided into molecular subtypes according to the presence of estrogen, progesterone and Her2 receptors: these subtypes can guide systemic therapy. Our aim in the study is to compare the axillary lymph node metastasis rates statistically in breast cancer subtypes. Patients treated for breast cancer were retrospectively evaluated in Group1(LuminalA-likeERand/orPR+,Her2 -), Group2 (LuminalB-likeER and/or PR+,Her2-), Group3 (Her2+,ER and/or PR+), Group4 (Her2+,ER and/or PR-) and Group5 (Her2-,ER and PR-) analyzed for tumor type, pathological stage, lymph node metastasis.208 patients were included in the study, and the mean age of the patients was 57.3±12.8. Although the age distribution of the groups was similar, no significant difference was found between the groups in terms of menopausal status. While the lymph node distribution was highly proliferative in Group 2. Demonstrating metastasis organotropisms in the effect of molecular subtypes of breast cancer is necessary to understand tumor mechanisms. ER and PR positive tumors usually metastasize to bones, while Her2+ or triple-negative breast cancers usually tend to metastasize to the visceral system, including the central nervous system. As with distant metastasis habits, lymph node metastasis rates of molecular subtypes of breast cancer can also vary. Being aware of these metastasis possibilities is also helpful in understanding the clinical behavior of the disease. It is important to know the molecular subtypes and susceptibility of lymphatic metastases as well as trying to avoid unnecessary complications of axillary dissection using the sentinel lymph node sampling technique.

Keywords: Breast cancer, molecular subtypes, luminal, er status, pr status, Her2 status

Introduction

Breast cancer is the most common cancer in women and one of the three most seen cancers together with lung and colon cancer worldwide [1]. There are numerous publications in the literature on prognosis, overall survival, early-stage diagnosis, and various subjects about breast cancer due to having seen enormously. To date, axillary nodal involvement at diagnosis has been considered the most critical determinant of long-term prognosis of breast cancer patients. Although other clinicopathologic characteristics have also become increasingly evident in determining the long-term outcome of breast cancer patients [2]. However, it has been reported that axillary node involvement is not an independent factor for overall survival (OS) [3]. It remains important to

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perform nodal staging in breast cancer in order to provide prognostic information and to stratify patients according to their risk for recurrence and mortality.

Currently, at least ten different molecular subtypes have been determined via gene copy number and expression analyses [4]. An immunohistochemical study of the primary tumor classifies invasive breast cancer into subtypes based on the presence of estrogen receptors (ER) and progesterone receptors (PR). Early breast cancer's systemic therapy could be guided by molecular subtypes. According to the St Gallen consensus main subtypes are Luminal A-like, luminal B-like, human epidermal growth factor receptor 2 (HER2), and basal-like [5,6].

Our aim is to compare the lymph node metastasis rates in breast cancer subtypes statistically.

Material and Methods

After taking ethics committee approval numbered 46418926, dated 26/05/2022 from Gulhane Training and Research Hospital, the retrospectively designed clinical study was conducted with 208 women diagnosed and treated with the breast cancer in Gulhane Training and Research Hospital and Diskapi Research and Training Hospital general surgery clinics between 2014 to 2019. The inclusion criteria used for this study were women diagnosed and treated with invasive breast cancer and older than 18 age. The exclusion criteria were unknown hormone receptor (HR) status, missing surgical or pathologic information, the pathology with ductal carcinoma in situ or benign pathologies. Patients were then divided into five groups: Group 1-Luminal A-like subtype [ER or PR positive, or both, HER2 negative, low proliferation (pN0-1)]; Group 2- Luminal B-like subtype [ER or PR positive, or both, HER2 negative, high proliferation (pN2-3)]; Group 3- Luminal (HER2 positive and ER or PR positive, or both); Group 4- HER2 subtype, non-luminal (HER2 positive and ER and PR negative); Group 5-Basal-like subtype (HER2 negative and ER and PR negative; triple-negative breast cancer) [7].

Variables

Information obtained and analysed from the Gulhane Training and Research and Diskapi Research and Training hospitals data bases included patient age at diagnosis, pathological grade of the disease, tumor type, status of lymph node metatstasis rate, type of the used surgery (either breast-conserving, mastectomy, or none); clinicopathologic features included AJCC clinical nodal (N) designation, HER2 receptor status, ER status, and PR status. All data were enrolled and analysed statistically.

Statistical Analysis

While the mean ± standard deviation, median (minimum, maximum) descriptive statistics are given for the numerical variable examined in the study; Number (n) and percentage (%) were given for categorical variables. One-way analysis of variance (ANOVA) was used to compare ages in the groups.

Pearson chi-square test was used to compare categorical variables in groups. Statistical analyzes were performed in IBM SPSS Statistics for Windows, Version 21.0 (2012 Armonk, NY: IBM Corp). Statistical significance level was accepted as $p<0.05$.

Results

The mean age of 208 female patients was 57.3±12.8 (median =57.5; min=23; max=92) years. There were a total of 197 patients aged 40 years and over. The age distribution was similar in the groups (x^2=6.321; p=0.176). The percentages of patients for ≥40 years in the groups were 96.9% (n=94) at Group 1, 91.7% (n=33) at Group 2, 88.9% (n=40) at Group 3, 100.0% (n=13) at Group 4 and 100.0 (n=17) at Group 5, respectively (Table 1).

While 150 (72.1%) of the patients were postmenopausal, 58 female (27.9%) patients were either premenopausal or perimenopausal. A statistically significant difference was determined in groups in terms of menopause status (x^2=19.261; p=0.014). As a result of the binary comparisons; the postmenopausal ratio obtained for group 3 was 53.3% (n=24) significantly lower than those determined for Group 4 and Group 5, while it was similar to Group 1 and Group 2 [Table 1].

Lymph node distribution is significantly different in at least one of the groups (x^2=139.454; p<0.001). High proliferative (pN2 and pN3) rate in Group 2, low proliferative (pN0 and PN1) rate in Group 4 is 100.0%.

The distribution varies in pathological stages in groups (p<0.001). The observation rates of each phase in the groups and the results of the binary comparison are given in Table 1. Tumor type and surgical type distributions are similar in groups (p>0.05).

The lymph node metastasis rates according to the patients' ages, menopause status, and tumor types are given in Table 2 both for groups and in general. There are no patients with age <40 years in Group 4 and 5. The age of all 13 patients in group 4 is ≥40 years and low proliferative. The low proliferative rate of 17 patients aged ≥40 years in Group 5 is 76.5% (n=2).

Discussion

It is known that breast cancer has the direct transition from the primary tumor to the systemic circulation in the systemic metastasis pathway, and in addition, lymph node metastasis may also occur coincidentally [8]. The presence of lymphovascular invasion can be demonstrated with the use of immunohistochemistry via presenting lymphatic endothelial cell marker and in case of invasion, the risk of SLNB positivity and systemic metastasis is significantly higher due to the inclusion of the tumor into the systemic circulation [9].

Demonstrating metastasis organotropisms in the effect of molecular subtypes of breast cancer is necessary to understand tumor mechanism. While ER and PR-positive tumors usually metastasize to bones, HER2-positive or

Table 1. Distribution of multiple variables in groups (n (%))

	Total(n=208)	Group1(n=97)	Group2(n=36)	Group3(n=45)	Group4(n=13)	Group5(n=17)	F, x^2;p
Age (year)							
Mean±SD	57.3±12.8	59.0±13.4	54.8±12.2	53.6±13.1	61.3±10.3	60.1±8.7	2.231;
Median (min; max)	57.5(23-92)	59(23-92)	55.5(26-76)	51(33-88)	58(49-78)	61(46-74)	0.067
Age group							
< 40 year	11(5.3)	3(3.1)	3(8.3)	5(11.1)	0(0.0)	0(0.0)	6.321;
≥ 40 year	197(94.7)	94(96.9)	33(91.7)	40(88.9)	13(100.0)	17(100.0)	0.176
Status of Menopaus							
Premenopausal	50(24.0)	21(21.6)	11(30.6)	17(37.8)	0(0.0)	1(5.9)	19.261;
Perimenopausal	8(3.8)	3(3.1)	1(2.7)	4(8.9)	0(0.0)	0(0.0)	0.014
Postmenopausal	150(72.1)	73(75.3)[a,b]	24(66.7)[a,b]	24(53.3)[b]	13(100.0)[a]	16(94.1)[a]	
Lymph Node							
Low proliferative	151(72.6)	97(100.0)[a]	0(0.0)[b]	28(62.2)[c]	13(100.0)[a,c]	13(76.5)[c]	139.454;
High proliferative	57(27.4)	0(0.0)	36(100.0)	17(37.8)	0(0.0)	4(23.5)	<0.001
Pathological Grade							
1a	26(12.5)	18(18.6)[a,b]	0(0.0)b	4(8.9)[a,b]	3(23.1)[a]	1(5.9)[a,b]	
1b	2(1.0)	2(2.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	
2a	80(38.5)	44(45.4)[a]	2(5.6)b	16(35.6)[a]	9(69.2)[a]	9(52.9)[a]	120.625;
2b	39(18.8)	28(28.9)[a]	2(5.6)b	5(11.1)[a,b]	1(7.7)[a,b]	3(17.6)[a,b]	<0.001*
3a	29(13.9)	5(5.2)[a]	16(44.4)b	6(13.3)[a]	0(0.0)[a]	2(11.8)[a,b]	
3c	27(13.0)	0(0.0)[a]	15(41.7)b	10(22.2)[b]	0(0.0)[a,b]	2(11.8)[b]	
4	5(13.0)	0(0.0)[a]	1(2.8)a,b	4(8.9)[b]	0(0.0)[a,b]	0(0.0)[a,b]	
Type of Tumor							
Invasive ductal	183(88.0)	83(85.6)	34(94.4)	42(93.3)	12(92.3)	12(70.6)	
Invasive lobular	5(2.4)	4(4.1)	0(0.0)	1(2.2)	0(0.0)	0(0.0)	15.887;
Mikst	2(1.0)	2(2.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.190*
Diğer	18(8.7)	8(8.2)	2(5.6)	2(4.4)	1(7.7)	5(29.4)	
Type of Surgery							
MRM+RM	197(94.7)	90(92.8)	34(94.4)	43(95.6)	13(100.0)	17(100.0)	2.464;
BCS	11(5.3)	7(7.2)	2(5.6)	2(4.4)	0(0.0)	0(0.0)	0.651

Meant±SD : Mean±Standart Deviation, F: ANOVA test,x^2: Pearson Ki kare test / *Monte Carlo Ki kare test. a, b, c: There is a diffirence between the two groups shown with the same letter(adjusted p value<0.05)

Table 2. Distribution of lymph nodes in groups in terms of age, status of menapaus, type of tumor (n(%))

Age	Lymph node	Total(n=208)	Group1(n=97)	Group2(n=36)	Group3(n=45)	Group4(n=13)	Group5(n=17)
< 40 year	Low proliferative (pN0-pN1)	6(54.5)	3(100.0)	0(0.0)	3(60.0)	-	-
	High proliferative (pN2-pN3)	5(45.5)	0(0.0)	3(100.0)	2(40.0)	-	-
≥ 40 year	Low proliferative (pN0-pN1)	145(73.6)	94(100.0)	0(0.0)	25(62.5)	13(100.0)	13(76.5)
	High proliferative (pN2-pN3)	52(26.4)	0(0.0)	33(100.0)	15(37.5)	0(0.0)	4(23.5)
Status of Menopaus							
Premenopausa	Low proliferative (pN0-pN1)	33(66.0)	21(100.0)	0(0.0)	11(64.7)	-	1(100.0)
	High proliferative (pN2-pN3)	17(34.0)	0(0.0)	11(100.0)	6(35.3)	-	0(0.0)
Perimenopausal	Low proliferative (pN0-pN1)	5(62.5)	3(100.0)	0(0.0)	2(50.0)	-	-
	High proliferative (pN2-pN3)	3(37.5)	0(0.0)	1(100.0)	2(50.0)	-	-
Postmenopausal	Low proliferative (pN0-pN1)	113(75.3)	73(100.0)	0(0.0)	15(62.5)	13(100.0)	12(75.0)
	High proliferative (pN2-pN3)	37(24.7)	0(0.0)	24(100.0)	9(37.5)	0(0.0)	4(25.0)
Type of Tumor							
Invasive ductal	Low proliferative (pN0-pN1)	130(71.0)	83(100.0)	0(0.0)	25(59.5)	12(100.0)	10(83.3)
	High proliferative (pN2-pN3)	53(29.0)	0(0.0)	34(100.0)	17(40.5)	0(0.0)	2(16.7)
Invasive lobuler	Low proliferative (pN0-pN1)	5(100.0)	4(100.0)	-	1(100.0)	-	-
	High proliferative (pN2-pN3)	-	-	-	-	-	-
Mixt	Low proliferative (pN0-pN1)	2(100.0)	2(100.0)	-	-	-	-
	High proliferative (pN2-pN3)	-	-	-	-	-	-
The others*	Low proliferative (pN0-pN1)	14(77.8)	8(100.0)	0(0.0)	2(100.0)	1(100.0)	3(60.0)
	High proliferative (pN2-pN3)	4(22.2)	0(0.0)	2(100.0)	0(0.0)	0(0.0)	2(40.0)

* Medullar Carsinom, Invasive Carsinom which is differantiated as Neuroendocrinal Tumor, Recurrent Invasive Carsinom, Metastatic, Musinous Carsinom, Metaplastic Carsinom

triple-negative breast cancers usually tend to have visceral metastasis, including the central nervous system [10].

The difference in metastasis tendency may affect the frequency of visceral metastasis or bone metastasis even in ER-positive and PR-positive breast cancers due to the change in receptor expression [11]. Once Luminal A and B subtypes were compared with HER2 subtypes and Triple Negative Breast Cancer (TNBC), it was shown that they were significantly associated primarily with bone metastasis and especially with isolated bone metastasis in Luminal A subtypes [10]. Hepatic metastasis was observed more frequently in HER2 subtypes, while lung metastases were found less frequently in Luminal A and B subtypes [10]. No statistically significant difference was found in terms of distant organ metastasis in luminal A and B subtypes [12].

Similar to distant metastasis habits, the lymph node metastasis rates of molecular subtypes of breast cancer may also change. Awaring the metastasis possibilities in question is also useful in understanding the clinical behavior of the disease. It is important to know molecular subtypes and lymphatic metastasis susceptibility, as well as trying to avoid complications of unnecessary axillary dissection using the SLNB sampling technique. Thanks to the regular and predictable structure of the lymphatic system, finding the first regional lymph node to be reached by lymphatic drainage and the fact that this sentinel lymph node acts as an effective filter for tumor cells provides the clinical success of the technique. In addition, this technique provides protection of a significant group of patients from seroma, lymphedema, and nerve damage secondary to trauma that may develop due to axillary dissection [13,14]. While the axillary region involvement and staging of

the patient are provided with SLNB, it is important to remember that the pathological diagnosis of the patient is metaplastic and its molecular subtype is important in axillary lymph node involvement and disease behavior [15]. The behavioral patterns of the molecular subtypes of the disease are valuable in the effective use of the SLNB technique and in determining the approach to the axilla.

When we investigate the stereoid hormone and HER2 status of breast cancer, nearly 80% of breast cancers are ER-positive and also in 55-65% of them are detected in PR expression. When the distribution of molecular subtypes of 3,198 breast cancer patients is examined by Zhu et al; 2,089 were found as luminal A (65.3%), 608 were luminal B (19.0%), 208 were HER2 overexpression (6.5%) and 293 were basal-like subtype (9.2%) [16]. Additionally, in one of the large series with 2260 patients, Luminal A was 61.1%, Luminal B 16.1%, HER2 enriched 8.6%, and Basal-like 14.2% [17]. In another series of 1134 patients, 116 (10.2%) were ER / PR (+), HER2 (+), 781 (68.9%) were ER / PR (+) and HER2 (-), 85 (7.5%) were ER / PR (-), HER2 (+), and the remaining 152 (13.4 %) were classified as triple negative [18]. Demircioglu et al; in their analysis of 469 patients, they reported Luminal A 231 (49.3%), Luminal B 104 (22.2%), HER2 (+) 62 (13.2%) and Basal-like 72 (15.3%) [19]. In the current study, when evaluated together with the last classification, these rates are Luminal A-like subtype: 97 (46.6%), Luminal B-like subtype: 36 (17.3%), Luminal HER2: 45 (21.6%), Non-luminal HER2: 13 (6.25%), and Basal-like subtype was found to be 17 (8.17%).

When these molecular subtypes are evaluated in terms of prognosis, Luminal A group, which is the largest group, is known as the group that responds well to treatment and has a good prognosis with its effect on hormonotherapy. Luminal B group is known for its high Ki67 level and/or HER2+, with its aggressive features and higher grade compared to Luminal A group. The HER2 +group is a molecular subtype that tends to grow and spread rapidly and has a poor prognosis compared to the hormone + groups. In the HER2 + positive subgroup, with anti-HER2 therapies combined with adjuvant chemotherapies, up to 40 % pathological complete response can be achieved, but the natural course of the disease is aggressive compared to hormone positive groups. The Triple Negative group is the most aggressive subtype compared to the other groups and has a worse prognosis.

When the groups were evaluated in terms of lymph node metastases and frequency; Si et al. in 814 disease series, Luminal HER2 (+) group was defined as the group with the highest rate of lymph node positivity (49.0%), while the other subgroup rates were: Luminal HER2(-) (46.8%); HER2 (+) (44.4%); Luminal A (36.5%); TNBC (34.7%), and statistical significance could not be presented between molecular subtypes and lymph node positivity. Similar to the relationship between stage and proliferation and lymph node metastasis in our series, Si et al were able to detect a relationship between tumor size increase and

lymph node metastasis rate [20]. Falck et al. evaluated molecular subtypes on lymph node metastases, they described lymph node metastases showing molecular subtypes different from the main tumor and emphasized that it was aggressive type synchronous lymph node metastasis that could be useful in treatment planning [21]. In our series, when the frequency of lymph node metastasis was evaluated according to molecular subtypes, this rate was low proliferative (pN1) in the Luminal A-like subtype as 61 % while lymph node metastasis rate was high in the Luminal B-like subtype group (pN2, pN3) as 100%. In the luminal HER2 subtype group, the lymph node metastasis rate was 53.3% and in the non luminal HER2 subtype group, the lymph node metastasis rate was only around 23.1%. Finally, the rate of lymph node metastasis in the Basal-like subtype group was 52.9%. In determining the subtype, if we put aside the creation of this group because the Luminal A group has a small amount of metastasis due to its nature, in the Non luminal HER2 Subtype group, very few lymph node metastases were detected. The benefit of neoadjuvant therapy in patients with HER-2-overexpressing tumor is also based on the behavioral patterns of these subtypes [22]. It is thought that the low lymph node metastasis frequency of ER negative and HER2 negative tumors, but the high rate of distant metastasis, and the relationship between the frequency of axillary metastasis in HER2 positive tumors and the tumor size and the frequency of distant metastasis will become clear as biological behaviors are understood [23].

Conclusion

The whole presentation varies among molecular subtypes, and this information is particularly useful in clarifying the subgroups from which neoadjuvant therapy will be selected. The current study evaluates the fact that nodal staging in breast cancer projects the prognosis and evaluates the probability of recurrence and mortality and moreover separates the cases into higher and lower risk groups in the light of the literature. The results obtained in our study showed that breast cancer subtyping applied according to metastasis to lymph nodes, HER2 and hormone status correlated with the literature.

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ORIGINAL ARTICLE

Investigation of the frequency of left ventricular hypertrophy in hypertensive patients by the hospital anxiety and depression scale

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Abstract

The development of left ventricular hypertrophy (LVH) in patients with hypertension increases the frequency of ventricular arrhythmias and sudden death. It is known that psychiatric conditions such as anxiety and depression are associated with hypertension (HT) and other cardiovascular diseases. HT patients were assessed using the Hospital Anxiety and Depression Scale (HADS). Sociodemographic and laboratory data of the patients were recorded. LVH was seen in 34 of 103 patients, and LVH was not seen in 69 patients. The mean age was 47.8 years in the group with LVH and 49.5 in the group with non-LVH. According to the results of our study, there was no significant difference between the LVH group and the Non-LVH group in terms of age, gender, BMI, smoking, loneliness status, and EF. The most striking result of our study was that the HADS score was significantly higher in the group with LVH than in the group with Non-LVH (p<0.001). The glucose level was significantly higher in the group with LVH than in the group with non-LVH (p<0.001). Patients should be aware of adverse cardiac outcomes according to their anxiety level, and precautions should be taken while performing mental health interventions and treatments. In order to better explain the causes and pathophysiology that may lead to LVH in anxiety disorders and depression, more comprehensive and molecular-level investigations are required.

Keywords: Hypertension, anxiety, depression

Introduction

Hypertension (HT) is a prevalent disease that poses a considerable risk of cardiovascular death, coronary heart disease, and stroke. Left ventricular hypertrophy (LVH) may increase the risk of ventricular arrhythmias and sudden cardiac death due to HT [1]. The importance of mental and social factors in cardiovascular diseases has received extensive attention over the years. Given that anxiety generates symptoms and reactions that can increase blood pressure, potential relationships between anxiety and HT are being investigated [2].

It is thought that anxiety disorders seen in patients with HT could possibly be the determinant of the development of HT [3]. Earlier studies have shown that anxiety is related to nighttime and early morning HT and impaired circadian rhythm [4,5]. Elevated left ventricular mass index has been observed more frequently in some HT patients with anxiety disorders [6]. The effect of anxiety on the pathogenesis and LVH of HT is not entirely clear. Anxiety can cause high blood pressure and LVH by changing the basal autonomic nervous system and stress state [7-10].

In this study, we evaluated the level of anxiety evaluated by the hospital anxiety depression scale (HADS) in stage 1 HT (systolic 140-159 mmHg diastolic 90-99 mmHg) patients diagnosed with

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ambulatory electrocardiographic (Holter) monitoring according to the diagnostic criteria of the International Society of HT (ISH) global HT practice guidelines [11]. We investigated the rates of LVH echocardiographically, thus showing that LVH is more common in patients with high levels of anxiety and depression. We aim to reduce cardiac mortality and morbidity with early treatment of these diseases by keeping these diseases at the forefront of the clinic.

Material and Methods

Study design

This study is cross-sectional and descriptive. This study was endorsed by Local Ethics Committee (Decision Date: 25/20/2022, Meeting Number: 7, Decision Number: 2022/7-56). Signed informed consent was gathered from the participants for this study. The study was executed in compliance with the Declaration of Helsinki. In this study, a total of 145 patients, who were admitted to the Cardiology outpatient clinic between March 2022 and November 2022, were monitored with Holter monitoring and were in the stage 1 hypertension class according to the ISH global HT practice guidelines, were scanned from the hospital archive records, and 103 of these patients were included in the study. The HADS scale was applied to these patients. Turkish reliability and validity study of the form was published by Aydemir et al. [12]. According to HADS, 0-7 was defined as normal, 8-10 as borderline anxiety, and 11 and above was defined as anxiety.

Echocardiographic examination was performed by two cardiologists. Transthoracic echocardiographic examinations (GE Vivid 7 or Vivid E9, GE Vingmed, Horten, Norway; ALOKA Prosound F75, Tokyo, Japan) were performed with a 3-6 MHz phase transducer in all cases. Standard two-dimensional echocardiography with Doppler examination was performed and measurements were obtained according to the guidelines of the American Society of Echocardiography. Left ventricular mass was measured by echocardiography and left ventricular mass index (LVMI) was calculated. LVH was defined as LVMI >115 g/m2 in men and >95 g/m² in women. Left ventricular systolic functions were recorded in the echocardiography reports of the patients. Among the patients screened in the archive, patients with secondary conditions that could lead to LVH were excluded from the study (e.g., aortic stenosis, chronic renal failure, aortic coarctation, myocarditis, severe heart valve insufficiency, aortic and mitral valve insufficiency, hypertrophic cardiomyopathy, severe coronary artery disease, those with severe valvular insufficiency, those with heart failure with ejection fraction (EF)<40, and athletes as cardiac hypertrophy may occur). The included patients were evaluated according to their LVH echocardiography report notes and were recorded as present (LVH+) or absent (LVH-). Sociodemographic data, duration of HT, smoking status, loneliness status, biochemistry, hemogram parameters, systolic echocardiographic functions, LVH presence, and body mass index (BMI) were documented. We compared the patients grouped according to HADS score according to the presence of LVH.

Statistical analysis

All data analysis was accomplished on the Mac version of SPSS version 26.0. Number (n) and percentage (%) were used for nominal data. Continuous data with a normal distribution were shown as mean±standard deviation (M±SD). Among the continuous data, those that did not fit the normal distribution were shown with the median (minimum-maximum). Nominal data were compared with the chi-square test. Continuous data with normal distribution were compared with the independent samples t-test and those not with the Mann-Whitney U test.

Results

In our study, LVH was seen in 34 of 103 patients, and LVH was not present in 69 patients. The comparison of sociodemographic and clinical features of the LVH group and the non-LVH group is shown in Table 1. The mean age was 47.8 years in the group with LVH and 49.5 in the group with non-LVH. According to the results of our study, there was no significant difference between the LVH group and the Non-LVH group in terms of age, gender, BMI, smoking, duration of HT, loneliness status, and EF. The most striking result of our study was that the HADS score was significantly higher in the group with LVH than in the group with Non-LVH ($p<0.001$). The average HADS score was 10 in the group with LVH, and the average HADS score was 6 in the non-LVH group. The comparison of the laboratory parameters of the LVH group and the non-LVH group is shown in Table 2. There was no significant difference between the groups regarding hemoglobin, albumin, leukocytes, platelets, AST, ALT, creatinine, sodium, potassium, and the lipid panel. However, the mean fasting blood glucose value in the group with LVH was found to be 132 mg/dl. The glucose level was significantly higher in the group with LVH than in the group with non-LVH ($p<0.001$).

Table 1. Comparison of Sociodemographic Features and Echocardiographic Parameters of Patients with HT According to LVH

	LVH(n=34) M±SD or n (%) or Median (Min-Max)	Non-LVH(n=69) M±SD or n (%) or Median (Min-Max)	P
Age	47.88±8.93	49.52±9.26	0.395[1]
Gender			0.236[2]
Female	19 (55.9)	30 (43.5)	
Male	15 (44.1)	39 (56.5)	
Smoking	11 (32.4)	26 (37.7)	0.596[2]
BMI, kg/m²	27 (18-37)	25 (20-36)	0.128[3]
HADS	10 (3-14)	6 (2-9)	<0.001[3]
Duration of HT, years	6.24±2.34	7.21±3.44	0.366[1]
Loneliness	6 (17.6)	6 (8.7)	0.183[2]
LVEF, %	55 (45-60)	55 (40-55)	0.185[3]
DM	11 (17.5)	8 (20)	0.846[2]

HT, hypertension; LVH, left ventricular hypertrophy; BMI, body mass index; HADS, Hospital anxiety and depression scale; LVEF, left ventricular ejection fraction; DM, diabetes mellitus. [1]Independent t test was used. [2]Chi-square test was used. [3]Mann-Whitney U test was used. p<0.05 was accepted as statistically significant

Table 2. Comparison of Laboratory Parameters of Patients with HT According to LVH

	LVH(n=34) M±SD or Median (Min-Max)	Non-LVH(n=69) M±SD or Median (Min-Max)	P
Hemoglobin, mg/dL	12.8 (9.5-17.2)	13.6 (11.1-17.2)	0.386[2]
Albumin, mg/dL	3.8 (2.8-4.6)	3.8 (2.7-4.4)	0.189[2]
WBC, 10³/µL	6.42 (3.13-9.66)	6.52 (3.53-12.42)	0.241[2]
Platelet, 10³/µL	236.65±99.57	245.05±105.77	0.700[1]
Glucose, mg/dL	132 (68-452)	102 (53-220)	<0.001[2]
ALT, IU/L	15 (9-29)	13 (9-35)	0.800[2]
AST, IU/L	19.5 (11-44)	20 (11-44)	0.565[2]
Creatinine, mg/dL	0.8 (0.4-1.3)	0.86 (0.4-1.5)	0.189[2]
Na, mEq/L	138 (125-147)	138 (128-148)	0.543[2]
K, mEq/L	3.7 (3.2-4.5)	3.7 (3.2-4.5)	0.348[2]
LDL-C, mg/dL	120 (63-185)	105 (54-190)	0.175[2]
HDL-C, mg/dL	34 (21-65)	35 (24-75)	0.608[2]

HT, hypertension; LVH, left ventricular hypertrophy; ALT, alanine transaminase; AST, aspartate transaminase; Na, sodium; K, potassium; WBC, white blood cell; LDL-C, low-density cholesterol; HDL-C, high-density cholesterol. [1]Independent t test was used. [2]Mann-Whitney U test was used. p <0.05 was accepted as statistically significant

The comparison of males and females is shown in Table 3. Accordingly, there was no difference in sociodemographic and clinical parameters between males and females.

Table 3. Comparison of Sociodemographic Features and Echocardiographic Parameters of Patients with HT According to Gender

	Female (n=49) M±SD or n (%) or Median (Min-Max)	Male (n=54) M±SD or n (%) or Median (Min-Max)	P
Age	47.84±9.26	50.02±9.01	0.228[1]
Smoking	18 (36.7)	19 (35.2)	0.870[2]
BMI, kg/m²	25 (18-37)	26 (20-36)	0.900[3]
HADS	7 (2-12)	7 (3-14)	0.352[3]
Loneliness	6 (12.2)	6 (11.1)	0.858[2]
LVH	19 (38.8)	15 (27.8)	0.236[3]

HT, hypertension; BMI, body mass index; HADS, Hospital anxiety and depression scale; LVH, left ventricular hypertrophy. [1]Independent t test was used. [2]Chi-square test was used. [3]Mann-Whitney U test was used. p<0.05 was accepted as statistically significant.

The comparison of those with and without HADS scores above 7 is shown in Table 4. Accordingly, BMI was significantly higher in patients with HADS score above 7 (p=0.048). LVH was more common in patients with HADS scores above 7 (p<0.001).

Table 4. Comparison of Sociodemographic Features and Echocardiographic Parameters of Patients with HT According to HADS Score

	HADS Score ≥7 (n=63) M±SD or n (%) or Median (Min-Max)	HADS Score >7(n=40) M±SD or n (%) or Median (Min-Max)	P
Age	49.11±9.16	48.78±9.23	0.8571
Gender			0.4252
Female	28 (44.4)	21 (52.5)	
Male	35 (55.6)	19 (47.5)	
Smoking	23 (36.5)	14 (35)	0.8762
BMI, kg/m²	25 (20-36)	27 (18-37)	0.0483
LVH	16 (25.4)	18 (45)	<0.0012
Loneliness	6 (9.5)	6 (15)	0.3992

HT, hypertension; HADS, Hospital anxiety and depression scale; BMI, body mass index; LVH, left ventricular hypertrophy. 1Independent t test was used. 2Chi-square test was used. 3Mann-Whitney U test was used. p<0.05 was accepted as statistically significant

Discussion

The main result of our study is that LVH is more likely to occur in patients with HT who have a higher level of anxiety according to the HADS score. The present study is the first one in the field to examine the degree of anxiety and LVH with approved psychometric scales. The results align with studies on anxiety and HT.

There is a complex relationship between physical well-being and mental health. Anxiety and depression are proven to have various implications for physical functions. Since the autonomic nervous system regulates the cardiovascular system, emotional states can profoundly affect the cardiovascular system, including blood pressure [13].

Many researchers have studied psychological factors that may lead to HT [14]. Rutledge and Hogan found that people who experience psychological stress develop HT at a rate of 8% more often than those who experience minimal stress [3]. Myocardial hypertrophy and decreased diastolic dysfunction are frequently found in patients with HT. This result indicates the relationship between anxiety and myocardial hypertrophy in patients with HT. HT is also a significant risk factor for the development of cardiovascular disease. Considering that anxiety triggers responses and symptoms that can increase blood pressure, scientists have begun to explore its possible connection.

Various surveys around the world investigate the relationship between anxiety disorders and HT, and conflicting results have been obtained [15]. In a research focusing exclusively on men in

Hong Kong, anxiety was associated with HT, but depression was not associated with HT [13]. In a study conducted in the USA, the relationship of HT with generalized anxiety disorder, major depressive disorder, and comorbid conditions was determined [16]. In a study conducted with a group of Danish patients with anxiety, a higher rate of HT was found in the anxious group compared to the general Danish population [17]. On the other hand, Wei et al. found that 12% of patients with HT had anxiety symptoms [2].

Conversely, Hildrum et al. reported an inverse relationship between high anxiety and HT in their cross-sectional and prospective study. In a study conducted on adult men in New York, Friedman et al. investigated the relationship between multiple psychological diseases and HT. They found no difference between regular or slightly elevated HT [18,19].

However, exactly how anxiety causes LVH is not clear. In 2014, De Gui Kong et al. investigated the relationship between anxiety disorder and plasma adrenomedullin and LVH and found that plasma adrenomedullin level was higher in those with anxiety. Adrenomedullin is a biologically active peptide regulated by normal body fluids and electrolytes. In addition, this molecule plays a role in heart and kidney functions, vascular cell proliferation, and cardiac remodeling. Therefore, this molecule is thought to play a role in the pathophysiology of LVH, as shown in a previous study [20].

A study by Ma LL et al. in 2008 showed that the 24-hour circadian rhythm is disrupted in anxiety disorder and HT. It was found that the systolic pressure drop that usually occurs at night in these patients disappeared by 84% and was not observed in diastolic pressure by more than 33%. High blood pressure at night can lead to increased cardiovascular load and peripheral vascular resistance, myocardial cell volume, and an increase in the synthesis of myocardial fibrous proteins and LVH [5]. As another reason, in a study by Esler et al. in 2000, it was thought that anxiety disorders cause dysfunction in the autonomic nervous system, especially by activating the sympathetic system in the chronic process, causing an increase in catecholamine release and, as a result, an increase in plasma adrenomedullin levels with deterioration of myocardial fibroblast secretion compensation [21].

In 2022, Ling Zhu et al. found an association between anxiety with increased LVH and transmural repolarization distribution. In their subgroup analysis, they found that anxiety was more common in males and that anxiety in males was associated with LVH. They attributed this to biological stress response differences. In another study, male salivary cortisol levels were found to be higher than that of females during psychological stress [22].

In this study, there was no significant difference between the genders regarding LVH. However, since there are studies in the literature in which LVH is seen more frequently in males than in females, it has given contradictory results with the literature. In addition, we could not find any difference between the sexes regarding HADS score, smoking status, BMI, and loneliness status, regardless of LVH.

The present study has several limitations. First of all, in the study of a single center, a single scale was used instead of serial scales for anxiety-depression scoring. Since our study's small sample size makes it challenging to generalize the results. It is not clear whether LVH is seen as secondary to the inflammatory process in diabetes since the glucose ratios in the patient group in the LVH group are significantly higher than in the Non-LVH group. It is known that diabetes also causes LVH. However, it is yet to be known whether the laboratory fasting glucose level obtained from the archive records of the patients was taken at the total 8-hour fasting or postprandial time, so this difference was thought to be insignificant. Therefore, there is a need for studies with larger samples in which non-diabetic patients are selected in terms of study design. One of the limitations of our study is that some laboratory findings, such as thyroid function tests, which are necessary for secondary causes that may affect the results in terms of LVH, were not performed.

Conclusion

In conclusion, we detected LVH more frequently in HT patients with high anxiety levels. In addition, although the duration of the disease was similar, HADS scores were found to be significantly higher in the group with LVH. Therefore, patients should be aware of adverse cardiac outcomes according to their anxiety level, and precautions should be taken while performing mental health interventions and treatments. In order to better explain the causes and pathophysiology that may lead to LVH in anxiety disorders and depression, more comprehensive and molecular-level investigations are required.

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ORIGINAL ARTICLE

Therapeutic effects of transcranial direct current stimulation on ketamine-induced schizophrenia-like behaviors and oxidative stress

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Abstract

Schizophrenia is a serious neuropsychiatric disorder that affects 1% of the world's population. It plays an important role in psychiatric symptoms, including major depression and schizophrenia. However, it is also known that one of the main reasons underlying the pathogenesis of schizophrenia is oxidative stress. Transcranial direct current stimulation (tDCS) has recently been a promising method for modifying neuronal membrane stimulation, cognition, and behavioral function. Our aim in this study is to explore the effects of 0.5 mA anodal tDCS stimulation on schizophrenia-like behaviors and oxidative stress in a ketamine-induced schizophrenia model. 30 male Balb/C mice were divided into 3 groups as control, schizophrenia, and schizophrenia+tDCS. The schizophrenia model was created by administering 25mg/kg/day ketamine for 7 days. tDCS treatment was performed by giving 0.5 mA anodal tDCS stimulation for 7 days. On day 14 of the experiment, SCZ-like behaviors were assessed using a novel object recognition test (NOR), open field test (OF), and tail suspension test (TST), and also oxidative stress in hippocampus and prefrontal tissues was estimated. Results showed that locomotor activity, depressive and anxiety-like behaviors of the schizophrenia group increased significantly compared to the control group and decreased after tDCS stimulation (p<0.05). In addition, it was investigated that tDCS stimulation also significantly increased learning that decreased after schizophrenia (p<0.05). All together, it was observed that the total antioxidant capacity of the schizophrenia group decreased while the total oxidant capacity of the schizophrenia group rose in the prefrontal cortex and hippocampus tissues compared to the control group (p<0.05). Otherwise, 0.5 mA anodal tDCS stimulation increased the total antioxidant capacity of the schizophrenia+tDCS group compared to the schizophrenia group, while it decreased total oxidant capacity (p<0.05). Based on our results displayed that 0.5 mA anodal tDCS stimulation for 30 minutes for 7 days reduced schizophrenia-like behaviors and oxidative stress by modulation of N-methyl-D-aspartic acid (NMDA) receptors in the glutamatergic pathway in a ketamine-induced, NMDA antagonist, schizophrenia model.

Keywords: tDCS, schizophrenia, oxidative stress

Introduction

Schizophrenia is a serious and persistent, overwhelming neuropsychiatric disorder that affects 1% of the world's population. Schizophrenia is identified by three groups of symptoms: positive (eg, hyperactivity, hallucinations), negative (eg, flattening of emotion, aversion) and cognitive (eg, learning and memory impairments, impaired executive functions) symptoms [1]. Schizophrenia is a multifaceted disease that usually begins before the age of 25, disrupts interpersonal and occupational functioning, and has a chronic course. The most obvious symptoms of schizophrenia are; delusions, hallucinations, disorganized speech and behavior, inappropriate affect, cognitive deficits, and impairments in psychosocial

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functioning [2]. The results of radiological imaging and the detection of functional and structural disorders in brains of people with schizophrenia suggested that a neurodegenerative process that leads to progressive loss of neuron functions continues during disease. When the etiology of schizophrenia is examined, there is evidence that it is a hereditary disease, although the exact cause has not yet been determined [3]. Genetic, environmental factors, neurotransmitters, hormones, urban life, migration, trauma, substance use and nutrition are also effective in the formation of schizophrenia [4]. When the effects of neurotransmitters are examined, it is stated that the decrease in glutamate receptors causes exacerbation of psychotic symptoms, excessive dopamine production causes the formation of positive symptoms, deterioration in serotonin causes cognitive problems such as memory, and the increase in gamma aminobutyric acid A receptor (GABA-A) concentration causes sleep disturbance [5,6]. Psychosis is a psychiatric disorder with symptoms such as delusions, hallucinations, alogy, disgust, bad taste, and memory deficit [7]. Ketamine, an N-methyl-D-aspartic acid (NMDA) receptor antagonist, is preferred in rodents to induce psychosis leading to various behavioral changes seen in some psychotic patients [7]. Studies have shown that there is a link between psychosis and hypofunction of NMDA receptors [8 9]. NMDA receptor antagonists act through modulation of the neurotransmitter system in the different regions of brain, particularly GABAergic, glutamatergic, cholinergic, serotonergic and dopaminergic, which are essential in the development of psychosis [10,11]. Increased GABA release is controlled by inhibition of dopaminergic neurotransmission by NMDA receptors responsible for abnormal dopaminergic activity [12]. It is effective in the psychosis of dopaminergic dysfunction in the frontal cortex and limbic system [13]. Hyperdopaminergic and hypodopaminergic transmissions, reduction of GABAergic inhibitory neurons, hypofunctionality of NMDA glutamatergic receptors in subcortical and cortical brain regions play a vital role in pathophysiology of schizophrenia [14]. In addition, chronic administration of NMDAR antagonist causes oxidative stress and neuroinflammation in animals [15]. Chronic administration of NMDAR antagonists has been found to cause several behavioral changes, including stereotyped behaviors, hyperlocomotor activity on the actophotometer, increased immobility time in depression test, and reduced latency deceleration in learning test. These changes show cognitive symptoms of psychosis [9]. Schizophrenia, a serious mental illness identified by misinterpretation of reality, affecting more than 50 million people worldwide; It is a biological disorder that occurs in brain and causes deterioration in brain structure and function [16]. Oxidative stress causes damage to brain and its gray matter, causing difficulties in people's daily functioning [16]. While oxidative stress increases in patients with acute schizophrenia, antioxidant activity decreases [17]. Oxidative stress is the result of abnormal redox in which free radical reactive oxygen species (ROS) overrun antioxidant capacity at cellular levels. However, oxidative stress, sudden rise in toxicity and cellular metabolism,

or changed antioxidant gene expression may also be the result of decreased antioxidant defense system and/or dietary antioxidants [18]. Brain is particularly susceptible to oxidative stress as it is highly susceptible to degradation and relatively low levels of antioxidant enzymes, with high oxidative metabolic activity and oxygen consumption [19]. Although normal levels of ROS are necessary in physiological conditions, excess levels of ROS can cause detrimental effects on important macromolecules such as proteins, DNA, lipids [20]. This overgrowth of ROS can affect DNA, cause mutations and alter gene expression [21]. Reactive oxygen species can also reasen peroxidative harmful to lipids, damaging the cell membrane and membranes of cellular organelles. Abnormally increased ROS levels may provide to etiology of schizophrenia via the oxidative stress pathway (Figure 1) [22]. Since schizophrenia is a chronic disease that affects every aspect of life, the aim of treatment is; to reduce or eliminate the symptoms of the disease, to rise quality of life of patient and to reduce the complications of the disease as much as possible [23]. The most effective treatment; it is a multidisciplinary approach that includes medication, psychotherapy, and sociotherapy [24]. Haloperidol is a typical antipsychotic drug that improves symptoms of psychosis and has extra-pyramidal side effects [9]. Olanzapine, on the other hand, is an atypical antipsychotic drug that is beneficial in positive, negative, depressive or cognitive symptoms of psychosis, as well as having some side effects (e.g. weight gain and diabetes) [7]. Unfortunately, despite the effectiveness of antipsychotic drugs, it is limited due to partial side effects and risk of psychotic relapse [25]. Because of these side effects, researchers are looking for alternative methods in the treatment of neuropsychiatric diseases.
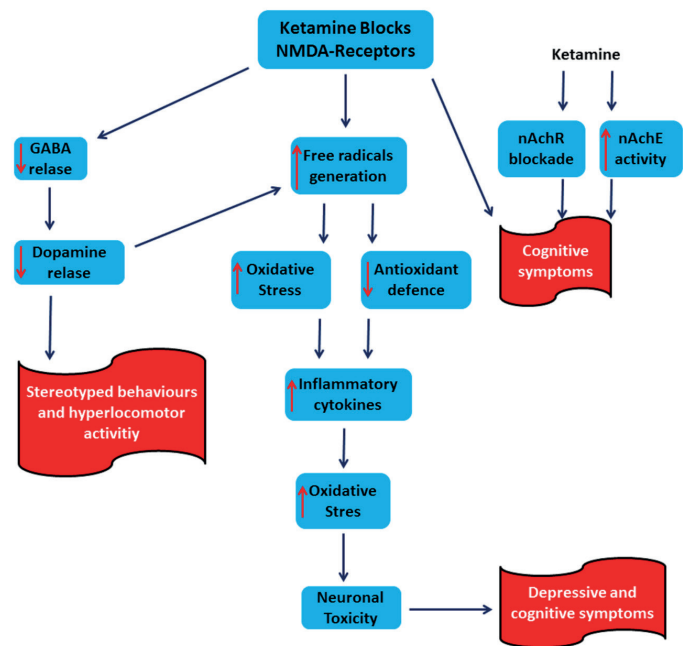
Figure 1. Ketamine-induced schizophrenia model and its molecular damage mechanism [7]

In recent years, transcranial direct current stimulation (tDCS) neuromodulation therapies have been applied in the treatment of psychological diseases such as schizophrenia [26]. tDCS is a non-invasive method of brain stimulation that can alter the excitability of neuronal activity in the cerebral cortex [26]. The neuromodulatory effects of tDCS have been demonstrated as a therapeutic effect in rat models of focal epilepsy, memory, Parkinson's disease, depression, and stroke [26,27]. tDCS exerts its effect through the activation of Na+-Ca²+ dependent ion channels and changes over NMDA receptor activity [26]. tDCS is inexpensive and easy to use, but has almost no adverse side effects [26,28]. In studies conducted with tDCS, mild itching, transient headache, weakness, nausea were observed in the applied area in some people after tDCS treatment, and no other significant side effects were observed, and neuronal damage was not reported in safety studies [26]. The current passing through the brain tissue produces increased or decreased excitable effects in the cortical region [26]. Excitability is determined by the intensity of the current and the polarity with anodal excitation or cathodal excitation [26]. While anodal stimulation depolarizes the soma of pyramidal cells with an excitatory effect, cathodal stimulation produces a hyperpolarized response with an inhibitory effect (Figure 2.) [26].
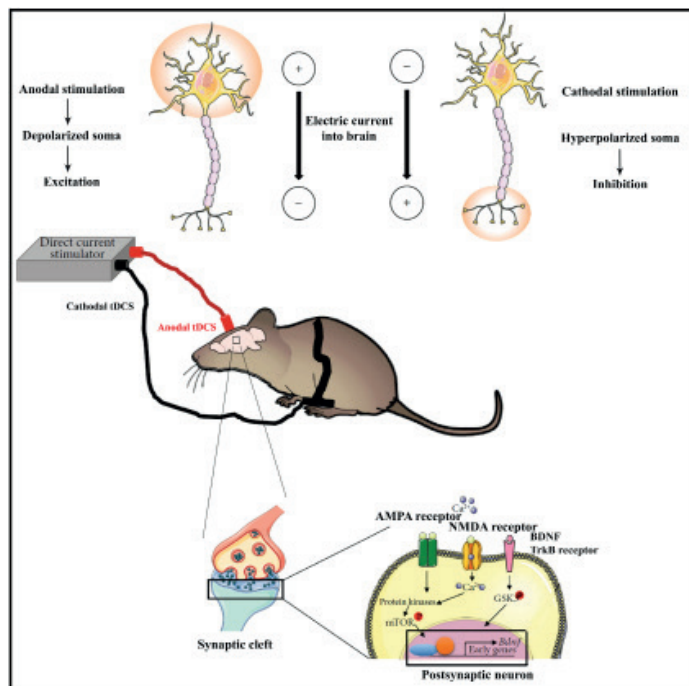
Figure 2. Schematic representation of tDCS. While A-tDCS increases excitability by acting on the neuronal membrane potential by depolarizing, C-tDCS decreases excitability by affecting hyperpolarization. A-tDCS depolarizes the presynaptic neuronal membrane and glutamate, and glutamate binds to AMPA and NMDA receptors. Adapted from Cavaleiro et al. [29].

Depending on the stimulus type, the tDCS method modulates the stimulus causing anodal tDCS depolarization and cathodal tDCS hyperpolarization in structures such as cortico-striatal and thalamocortical [26]. In our study, it was aimed to investigate the therapeutic effects of tDCS stimulation on the oxidative stress pathway in mice with schizophrenia model.

Material and Methods

This study was performed in Erciyes University Experimental Animals Unit. Mice obtained from Erciyes University Experimental Animals Application and Research Center with the approval of Erciyes University Animal Experiments Local Ethics Committee (Decision No 22/253) were used in the study.

Experimental Groups and Protocol

Experiments were carried out by dividing Balb/C male mice, 2 months old, weighing 25-30 g, into 3 groups:

1. Control Group: 1.0mL/kg/day saline was administered i.p. during 7 days (n=10),

2. Schizophrenia Group: Induced by ketamine i.p. 25mg/kg/day during 7 days (n=10),

3. Schizophrenia+tDCS Group: Ketamine-induced schizophrenic mice received 0.5 mA tDCS stimulation for 30 min during 7 days after schizophrenia was induced (n=10) (Figure 3).
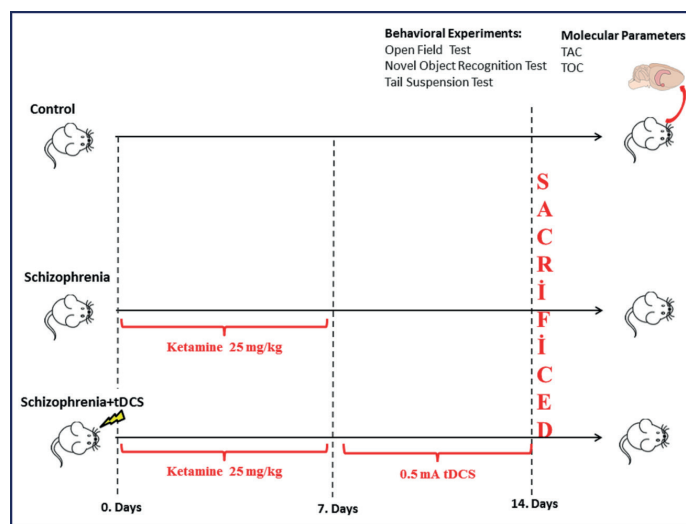
Figure 3. Experimental schedule

Schizophrenia Model

The ketamine-induced schizophrenia model induced by ketamine dissolved in saline administered i.p. 25 mg/kg/day during 7 days [30].

tDCS Application

For tDCS application, Animal DCS Stimulator (model 2100) device with temporal resolution of 1 min was used [27]. In our study, mice in the schizophrenia+tDCS group were fed 30 minutes a day for 7 days starting from the 7th day of the experiment. 0.5mA anodal tDCS was applied. During the tDCS

application, a superficial disc electrode was used, the maximum current intensity was ±1000µA, and the current resolution was set as 0.01mA.

Behavioral Experiments

Open Field (OF) Test

Locomotor activity measured in OF test. OF experiments were performed in a square-shaped apparatus with a 40x40cm base, with a black matte base. The area was divided into 16 equal small circles of 10cm². At the beginning of the experiment, the mice were left in the middle of this area one by one and their movements were examined for 3 minutes. For each mouse, the total distance (cm) and the velocity (cm/s) measured [27].

Novel Object Recognition Test (NOR)

The Novel Object Recognition Test (NOR) test is particularly effective in measuring attention or short-term memory studies and has three stages: habituation, training and retention. During the practice phase, the mice will be placed in the center of the 40 cm high, 40x40 cm arrangement and allowed to wander for 5 minutes without any objects in the environment. During the training phase, the mice will be released from the center to the field and given 5 minutes to examine the two objects placed in the environment. In the recall phase, one of the objects will be replaced with a novel object and the behavior of the mice will be recorded for 5 minutes. Mice are expected to spend more time examining the novel object in this process [31]. In the NOR test, the discrimination index and the time spent in the novel object (sec) values will be analyzed. Discrimination Index = ((Time Spent at Novel Object-Time Spent at Old Object)/Total Time)*100.

Tail Suspension Test (TST)

In Tail Suspension Test (TST), each mouse will be placed approximately 1 cm from the tip of the tail and hung 30 cm above the floor using adhesive tape. In the last 4 minutes of 6 minutes, the total time of inactivity, which can be defined as a restless suspension without any strain, shall be recorded. Mice that climb on their tails during tests will be excluded from the experiments [32].

Biochemical Method

Determination of Total Antioxidant Capacity

TAC in tissues was evaluated using the OxiSelect™ TAC Assay kit. This method is based on the principle that the hydroxyl radical, a potent radical formed by the Fenton reaction, reacts with a colorless substrate, o-dianisidine, to form a bright yellow-brown colored dianisyl radical. The addition of hydroxyl radical to the supernatants initiates oxidative reactions and this reaction is suppressed by antioxidants and color change is prevented. In this process, the effective measurement of "Total Antioxidative Capacity" in the tissue has been achieved.

Determination of Total Oxidant Capacity

Determination of TOC in tissues was measured using the OxiSelect™ ROS/RNS Assay Kit. In this method, the oxidative reaction is accelerated by adding a catalyst to the oxidants in the sample. After a short time, the oxidation reaction was allowed to proceed with the prepared dichlorodihydrofluorescein probe. The tissues were fluorometrically measured against a hydrogen peroxide or 7'-dichlorodihydrofluorescein standard. The free radical content of oxidant molecules present in the sample was determined by comparison with a predetermined 7'-dichlorodihydrofluorescein or hydrogen peroxide standard curve.

Statistical Analysis

Statistical analysis of the results was performed using SPSS 20.0 software. The results were given as mean±standard error (SEM) and statistical significance was accepted as $p < 0.05$. OF, NOR and TST datas were evaluated with one-way analysis of variance (ANOVA) and Tukey test was used as posthoc test.

Results

Behavioral experiments of the groups were measured in locomotor activity in the OF, learning in NOR and depression in TST (Figure 4). The total distance and velocity in OF in schizophrenia group was significantly rised compared with that in control group ($p < 0.05$) (Figure 4.A and Figure 4.B). After tDCS application, a significant reduce was observed in locomotor activities of schizophrenia+tDCS group compared to schizophrenia group ($p < 0.05$) (Figure 4.A and Figure 4.B). The short-term memory experiments of groups reduce evaluated in NOR test (Figure 4.C). While it was observed that there was a significant reduce in learning of schizophrenia group compared to control group ($p < 0.05$), there was a significant increase in schizophrenia+tDCS group compared to schizophrenia group ($p < 0.05$). Depression behaviors of experimental groups were evaluated in TST (Figure 4.D). It was determined that there was a significant increase in immobility time of schizophrenia group compared to control group ($p < 0.001$), while a significant decrease was found in schizophrenia+tDCS group compared to schizophrenia group ($p < 0.05$).

In the hippocampus and frontal cortex tissues, a significant reduce was observed in total antioxidant capacity of schizophrenia group compared to control group ($p < 0.05$) (Figure 5.A and Figure 5.B), while a significant rise was observed in TOC ($p < 0.05$) (Figure 5.C and Figure 5.D). After tDCS stimulation, there was a significant rise on TAC of hippocampus and prefrontal cortex tissues of schizophrenia+tDCS group compared to schizophrenia group ($p < 0.05$) (Figure 5.A and Figure 5.B). In addition, a significant reduce was found in TOC of hippocampus and prefrontal cortex tissues of schizophrenia+tDCS group compared to schizophrenia group ($p < 0.05$) (Figure 5.C and Figure 5.D).
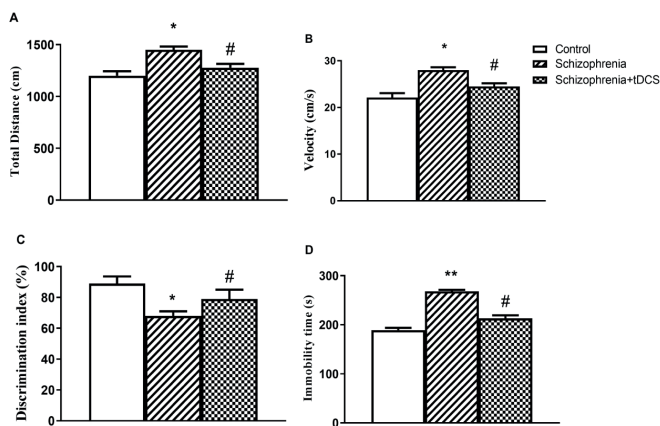
Figure 4. Behavioral test results of experimental groups. A) Total distance (cm) in OF, B) Velocity (cm/s) in OF, C) Discrimination index in NOR, DI) Immobility time in TST . (n=10, for each group; * p<0.05, ** p<0.001 shows the difference compared to the control group, # p<0.05 shows the difference compared to the schizophrenia group, one-way ANOVA test, followed by Tukey post hoc test). All data are presented as means ± s.e.m
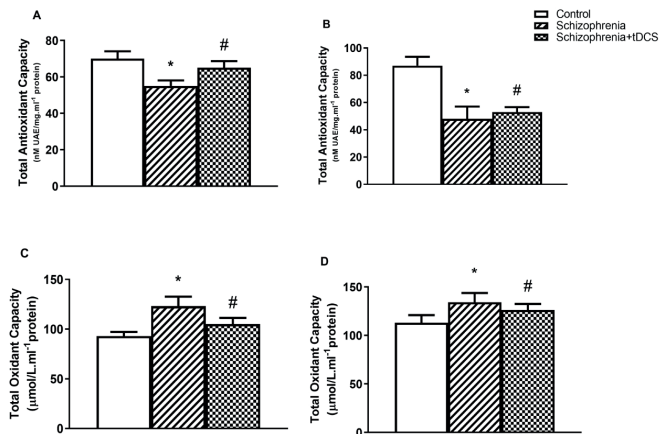
Figure 5. Oxidative stress results. A) Total antioxidant capacisity levels in hippocampus tissue, B) Total antioxidant capacisity levels in prefrontal cortex tissue, C) Total oxidant capacisity levels in hippocampus tissue, D) Total oxidant capacisity levels in prefrontal cortex tissue (n=10, for each group; * p<0.05 shows the difference compared to the control group, # p<0.05 shows the difference compared to the schizophrenia group, one-way ANOVA test, followed by Tukey post hoc test). All data are presented as means ± s.e.m

Discussion

Schizophrenia is a psychiatric disease in which psychotic symptoms such as hallucinations and cognitive disorders are also seen, although it affects approximately 1% of the world's population [14]. Although the underlying cause of schizophrenia is still unclear, it is thought to result from dysregulation of neurochemicals such as dopamine, serotonin, and glutamate [14]. Although typical antipsychotic and conventional atypical antipsychotic drugs such as dopamine D2 receptor antagonist, serotonin 5-HT2A antagonist are used in the treatment of schizophrenia, these drugs are not effective in all symptoms of schizophrenia and have serious side effects. On the other hand,

since the treatment of schizophrenia with antipsychotic drugs also causes oxidative stress, therapeutic and protective agents with less side effects are needed. tDCS is a non-invasive method of brain stimulation that can alter excitability of neuronal activity in cerebral cortex [26]. tDCS is inexpensive and easy to use, but has almost no adverse side effects [28]. The neuromodulatory effects of tDCS have been skowed as a therapeutic effect in rat models of focal epilepsy, memory, depression, and stroke [26]. tDCS exerts its effect through the activation of Na+-Ca²+ dependent ion channels and changes over NMDA receptor activity [26]. While anodal stimulation depolarizes the soma of pyramidal cells with an excitatory effect, cathodal stimulation produces a hyperpolarized response with an inhibitory effect. Anodal tDCS exerts its effects by modulation of both GABAergic (short-range intracortical inhibition) and glutaminergic (intracortical facilitation) synapses, whereas cathodal tDCS exerts its effects only by modulation of glutaminergic synapse [26].

This article investigated the effect of tDCS treatment to ameliorate ketamine-induced SCZ-like behavior in mice and oxidative stress factors. Our findings showed that tDCS contributed to the following outcomes: 1) reduction in ketamine-induced depressive and anxiety-like behaviors, 2) reduction in ketamine-induced memory deficits, and 3) oxidant system decreased and antioxidant defense system improved in prefrontal cortex and hippocampus of mice. Ketamine-induced schizophrenia model is widely used to experimentally mimic schizophrenia symptoms. Similarly, du Bois et al. (2009) reported that administration of NMDA antagonist caused anxiety and depressive behaviors in mice and also increased NMDA receptor in the hippocampus [33]. In our results, it was observed that locomotor activity increased, learning was impaired, and anxiety-depression-like behaviors increased in ketamine-induced schizophrenia model. In OF test, in which locomotor activity was evaluated, it was determined that schizophrenia group mice had an increase in locomotor activity parameters, distance and velocity, compared to control group. In addition, in NOR test, it was observed that the learning of the schizophrenia group was impaired, and there was an increase in depression behaviors according to the results of TST. These results are consistent with other studies in the literature [33-35]. It was observed that 0.5 mA anodal tDCS treatment, which we applied for 7 days, reduced locomotor activity and depression-like behaviors and learning disability caused by ketamine-induced schizophrenia. Smith et al. (2020) reported that tDCS stimulation applied to schizophrenic patients for 2 weeks increased cognitive functions and neuroplasticity [36]. Adam et al. (2021) also reported that 2mA 20-minute anodal tDCS stimulation in 24 schizophrenia patients caused significant changes in plasticity [37]. Moghaddam et al. (2021), in their study on a ketamine-induced schizophrenia model, reported that they found similar results to our study, and that they reduced the increased locomotor activity and depression-like behaviors after schizophrenia with antioxidant curcumin treatment [34]. They also reported that curcumin treatment increased antioxidant capacity and decreased oxidant capacity.

Oxidative stress, which occurs as a result of imbalance between ROS production activities and antioxidant defense mechanism, plays a vital role in pathophysiology of schizophrenia [14]. Akosman et al. (2021) reported that schizophrenia decreased total antioxidant capacity and increased total oxidant capacity in MK-801-induced schizophrenia mouse model [35]. Similar to the studies of Akosman et al. (2021), Mogheddam et al. (2021) reported that the total antioxidant capacity increased and the total oxidant capacity decreased in their study [34]. In our study, it was observed that ketamine-induced schizophrenia decreased the total antioxidant capacity and increased the total oxydant capacity. It was determined that the tDCS treatment we applied in our study increased the decreased total antioxidant capacity and decreased the increased total oxidant capacity. In some experimental studies, it was reported that antioxidant treatments after schizophrenia significantly increased the total antioxidant capacity and decreased the total oxidant capacity [14,34,35]. In addition, it has been stated that schizophrenia will increase oxidative stress via the glutamatergic pathway and may have an effect on NMDA and dopamine receptors. NMDARs in different brain regions play a vital role in anxiety and depression as well as learning and memory. NDMA blockade by ketamine lowers dopamine levels predominantly in prefrontal cortex, resulting in cognitive symptoms [38]. In this context, other studies have appered that rise in free radicals during SCZ may be associated with severity of symptoms [39]. In our results, it was determined that oxidative stress rised in hippocampus and prefrontal regions. In fact, oxidative stress can also affect neurotransmitter and cause behavioral disorders such as learning and memory. According to our results and results of previous studies, ketamine-induced schizophrenia leads to changes in locomotor activity, memory impairment and depression-like behavior. In addition, it causes an increase in oxidative stress over total antioxidant and oxidant balance. In our study, although it can be said that tDCS stimulation may have a therapeutic effect on behavioral changes and oxidative stress caused by schizophrenia, more molecular studies are needed.

Conclusion

In summary, this article shed light on the fact that tDCS stimulation has a potent therapeutic effect against ketamine-induced SCZ-like behavior and oxidative damage in mice. Therefore, tDCS therapy can be considered a promising formulation for prevention and treatment of SCZ, which needs further research.

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ORIGINAL ARTICLE

Pregnancy-related carpal tunnel syndrome; non-invasive early diagnosis and postpartum evaluation

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Abstract

The diagnosis of pregnancy-related carpal tunnel syndrome (PRCTS) was made with noninvasive methods and evaluated the effect of PRCTS on quality of life, its treatment and prognosis. Third-trimester pregnant women between the ages of 18-45 and diagnosed with PRCTS were included. For diagnosis; the presence of pain, positive motor and sensory tests, Carpal Tunnel Symptoms Scale-6 (CTS-6), and Boston Carpal Tunnel Questionnaire (BCTQ) were evaluated. The criteria used to determine improvement were the regression of complaints and symptoms based on a VAS score of 0 and a CTS-6 score of less than 5. According to these criteria, patients whose complaints regressed in the postpartum eighth week were called group A, whose complaints regressed in the postpartum sixth month were called group B, and women who still did not meet the criteria were called group C. The study included 102 wrists of 94 women. When the type of delivery, gestational age at birth, gravida, and parity were compared according to the continuity of complaints and symptoms, no differences were found. When the first trimester body mass index (BMI) measurements were compared between groups A and B, it was observed that group B had higher first trimester BMI values; this difference was statistically significant. The mean age was 29.2 years in group A, was 32.6 years in group B and the difference was significant. Conclusions: We recommend that pregnant women over 30 years old with a high BMI should be screened for PRCTS using non-invasive diagnostic tools, CTS-6, and VAS.

Keywords: Carpal tunnel syndrome, CTS-6, BCTQ, VAS, diagnosis, pregnancy

Introduction

It has been suggested that women are more prone to carpal tunnel syndrome (CTS) due to morphology [1,2]. In 1957, pregnancy-related CTS (PRCTS) was directly defined in two cases, and it was noted that the symptoms increased, especially in the advanced weeks of pregnancy [3]. Studies examining the prevalence of PRCTS (7–62%) report a range of rates because they use different methods for diagnosis [4-11].

Various factors, such as an increase in body mass index (BMI), hormones (relaxin), fluid redistribution, and maternal age, are involved in the etiology of PRCTS [4-7]. In terms of prognosis, although it has been reported that PRCTS generally regresses completely spontaneously or with conservative treatment methods after birth, residual symptoms and neurophysiological findings that require surgical decompression up to a year after birth have also been reported [3,4,6,8-13]. Considering that CTS is seen more often in women and most women get pregnant more than once in their lives, it would be valuable to perform PRCTS screening during antenatal pregnancy follow-ups when there are risk factors such as advanced maternal age and increased BMI [2,5,7].

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Objectives

In this study, the diagnosis of PRCTS in the third trimester was made with noninvasive methods, and these women were followed up with conservative treatment. In addition, the effect of PRCTS on quality of life, its prognosis, and the need for surgical treatment were evaluated.

Material and Methods

This was a prospective study. A pre-study power analysis based on previous data determined a sample size of at least 89 pregnant to reach the desired power of >0.8. The prevalence of CTS was the primary outcome measure for proportional power analysis [4,9,14].

Third trimester pregnant women between the ages of 18-45 and diagnosed with CTS were included in the study. The following were the exclusion criteria: previously diagnosed with CTS with a treatment history, conditions considered to be secondary causes of CTS, women who did not breastfeed for the first six months or stopped breastfeeding, and women who had a stillbirth. Certain professions (such as tailor, hairdresser, musician, secretary, dishwasher, cook, ironer, and dry cleaner) that require repetitive or strong wrist effort were not included in the study. The study included one hundred and two wrists of 94 women (bilateral in eight) diagnosed with CTS who fulfilled the inclusion criteria by completing their follow-ups. The pregnant who agreed to participate in the study were screened for CTS by an obstetrician and diagnosed by an orthopedic and traumatology specialist.

Diagnosis and evaluation criteria

Age, gestational age at birth, gravida, parity, BMI, and delivery type were evaluated and recorded. The criteria for diagnosis were the presence of pain, positive sensory and motor tests [grip, palmar-key-tip pinch, Semmes-Weinstein Monofilament Test (SWMT)], Carpal Tunnel Symptoms Scale-6 (CTS-6), and Boston Carpal Tunnel Questionnaire (BCTQ) [15-17]. Electrodiagnostic tests (EMG) was requested to further examine women whose symptoms and complaints did not resolve during postpartum follow-up.

Pain was evaluated with a Visual analog scale (VAS). Weakness, numbness, nocturnal numbness, thenar atrophy, and Tinel's and Phalen's tests were evaluated with the CTS-6 evaluation tool modified by Graham [16]. The CTS-6 is a scale that evaluates six essential criteria based on history, symptoms, and physical examination findings over 26 points. According to the CTS-6 scoring results, it is possible to diagnose CTS with a probability of >12=0.80 and a probability of >5=0.25. The BCTQ, on the other hand, was used as a questionnaire evaluating the severity of symptoms and functional status [17]. Handgrip strength was evaluated using a hand dynamometer (Jamar, Model SH 5001, Saehan Corporation, Masan, South Korea) in kilograms. The grip strength (key, tip, palmar) of the thumb, second, and third fingers was evaluated with a pinchmeter (Lafayette Instrument

Company Inc., Lafayette, IN, USA) in kilograms. Sensory function was evaluated using the SWMT separately in the first three fingers [18].

Outcome measures

Evaluations of women in the third trimester were called measurement I, and postpartum evaluations at the eighth week were called measurement II. The women whose complaints and symptoms continued in measurement II were called for follow-up again at the sixth month, and this evaluation was named measurement III. Sensory and motor tests, BMI, VAS, CTS-6, and BCTQ were evaluated all measurement. In addition, BMI was evaluated in the first trimester. The criteria used to determine improvement were the regression of complaints and symptoms based on a VAS score of 0 and a CTS-6 score of less than 5. According to these criteria, the women whose complaints regressed in measurement II were called group A, and those who regressed in measurement III were called group B. As a result of measurement III, EMG was applied to women who still did not meet the regression criteria (group C). Finally, all women were called by telephone at 12 months postpartum, their complaints and symptoms were reexamined, and the study was terminated.

Treatment

Pregnant who were diagnosed in the third trimester were given training on movements, sleep position, and activity modification to decrease symptoms and complaints. Tendon and nerve gliding exercises and neutral volar wrist splints were recommended in combination. Splint therapy was used all day (removal recommended only during exercising and hand washing). Patients were asked to do 5–10 repetitions of each exercise five times a day until measurement II to decrease symptoms. At the end of measurement II, the same treatment modalities were given for the patients whose complaints and symptoms continued until measurement III. Patients with clinically significant findings based on EMG were operated on after being offered surgical decompression of the median nerve. Continuation of conservative treatment modalities was recommended for patients who did not choose to be operated on.

Statistical analysis

The data obtained were evaluated using the SPSS version 23.0 (IBM Corp., Armonk, NY, USA) software program. The Kolmogorov-Smirnov test was used to evaluate the distribution of the data. Normally distributed data were presented as mean ± SD; non-normally distributed data were presented as median (IQR). Student's t-test was used to compare normally distributed data, and the Mann-Whitney U test was used to compare non-normally distributed data. Normally distributed data were evaluated with the paired sample t-test for dependent groups, and data that were not normally distributed were evaluated with the Wilcoxon test. The chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton test were used to evaluate categorical variables. A p-value

of <0.05 was considered statistically significant for all tests.

Results

The mean age was 30.6 years old (range: 19–44). The dominant hand was right in 85.3% of the women. The average gestational week was 38.5 weeks (range: 32–41). The delivery method was spontaneous vaginal delivery in 42.2% of the pregnant and cesarean section in 57.8%. Gravida and parity averages were 2 (range: 1–5) and 1 (range: 0–3), respectively. Forty-one pregnancies were primiparous and 53 pregnancies were multiparous. In terms of occupational distribution, almost two-thirds (66%) were housewives, while the others were civil servants, lawyers, nurses, teachers, sales personel, cleaners, and agricultural workers

At measurement II, the complaints and symptoms of 59 women (60 wrists) had regressed (group A). Thirty-five women (42 wrists) were evaluated at measurement III, and the complaints and symptoms of 23 women (27 wrists) had regressed (group B). While 12 women (15 wrists) underwent EMG due to their ongoing complaints and symptoms (group C). However, the evaluation criteria and life scales had improved, and the diagnosis of CTS was confirmed in all of them. Mild CTS was determined in six wrists, moderate in eight wrists, and severe in one wrist. Surgical decompression was recommended to 12 (14.6%) women (group C), as there were clinically significant electrophysiological changes. Four women (five wrists: three mild/two moderate) chose to for go surgical treatment. The symptoms and complaints of the eight women who underwent surgical treatment regressed, and no additional perioperative or postoperative complications were detected. Ninety women did not have any additional complaints or symptoms at 12 months postpartum. The complaints and symptoms of four women (five wrists) who were not operated on persisted. Four women were not followed to the end of the study; two women did not attend follow-ups because they did not accept surgical treatment, and two women moved to another city.

In Table 1, the first and second measurements of all women, and in Table 2, women with ongoing complaints, were compared. There was a significant improvement in all measurements in all parameters except group C (p<0.001). When the type of delivery, gestational age at birth, gravida, and parity were compared according to the continuity of complaints and symptoms, no statistically significant differences were found (p=0.593, p=0.089, p=0.770, and p=0.273, respectively). Although it was not statistically significant, the symptoms and complaints regressed earlier in primiparous (p=0.153). When the first trimester BMI (23.8±3.3) measurements (at the beginning of the pregnancy follow-ups) were compared between group A and B, it was observed that group B had higher first trimester BMI values; this difference was statistically significant (p=0.030). In addition, although it was not statistically significant, it was determined that the symptoms and complaints of women with higher BMI values in the first and second measurements continued longer (p=0.071,

p=0.086, respectively). The mean age of group A was 29.2 years, group B was 32.6 years; this difference was statistically significant (p=0.01). The mean age of group C was 36.7 years.

Table 1. Comparison between the measurements I and II

	Measurement I (n=94)	Measurement II (n=94)	p
BMI (kg/m²)	28.0 ± 3.8	27.0 ± 4.0	< 0.001
VAS*	3 (1-5)	0 (0-2)	< 0.001
CTS-6	14.6 ± 2.2	3.8 ± 4.6	< 0.001
BCTQ	39.6 ± 8.1	26.2 ± 9.5	< 0.001
Grip (kg)	24.2 ± 4.0	26.1 ± 4.5	< 0.001
Palmar Pinch (kg)	5.6 ± 1.2	5.8 ± 1.1	< 0.001
Key Pinch (kg)	4.4 ± 1.0	4.6 ± 1.0	< 0.001
Tip Pinch (kg)	3.4 ± 0.9	3.6 ± 0.9	< 0.001
SWMT*	2.83 (2.44-3.22)	2.36 (2.36-2.44)	< 0.001

Values presented as mean ± SD *Values presented as median (IQR) BCTQ: Boston Carpal Tunnel Questionnaire, BMI: body mass index, CTS-6: Carpal Tunnel Symptoms Scale-6, kg: Kilograms, m: Meters, SWMT: Semmes-Weinstein Monofilament Test, VAS: Visual analog scale

Table 2. Comparison between all measurements of group B

	Measurement I (n=42)	Measurement II (n=42)	Measurement III (n=42)	p**
BMI (kg/m²)	28.7±4.5	27.8±4.7	25.6±4.1	<0.001
VAS*	5(4-6)	2(1-3)	1(0-3)	<0.001
CTS-6	15.4±2.6	7.2±5.2	3.8±6.0	<0.001
BCTQ	44.8±8.0	33.3±11.1	21.4±16.4	<0.001
Grip (kg)	22.0±4.3	23.4±5.3	24.9±6.3	<0.001
Palmar Pinch (kg)	5.0±1.5	5.4±1.5	6.1±1.7	<0.001
Key Pinch (kg)	4.0±1.2	4.2±1.2	4.7±1.4	<0.001
Tip Pinch (kg)	3.0±1.0	3.2±1.0	3.4±1.2	<0.001
SWMT *	2.83(2.44-3.84)	2.44(2.36-3.22)	2.36(1.65-2.44)	<0.001

Values presented as mean ± SD *Values presented as median (IQR) **Statistical significance between the second and third measurements was evaluated. BCTQ: Boston Carpal Tunnel Questionnaire, BMI: body mass index, CTS-6: Carpal Tunnel Symptoms Scale-6, kg: Kilograms, m: Meters, SWMT: Semmes-Weinstein Monofilament Test, VAS: Visual analog scale

Table 3 provides comparisons of all the measurements of the women whose complaints did not resolve who were offered surgery (group C). When considering the motor strength of the group C, there was no significant improvement, except for palmar pinch and no statistically significant difference was found including handgrip (p<0.001) (Table 2) . In the measurements made with the SWMT test, the thumb showed the most sensitive evaluator size, followed by the second, and finally the third finger (thumb > index > middle).

Table 3. Comparison of group C for all measurements

	Measurement I (n=15)	Measurement II (n=15)	Measurement III (n=15)	p**
BMI (kg/m²)	30.5±3.4	30.1±3.7	27.0±3.0	<0.001
VAS*	7(5-8)	4(3-7)	4(2-7)	0.581
CTS-6	17.3±2.7	13.0±4.9	9.4±7.2	0.010
BCTQ	50.6±8.1	43.8±12.6	39.5±15.2	0.023
Grip (kg)	18.1±2.8	17.8±4.2	17.9±4.4	0.781
Palmar Pinch (kg)	3.6±1.2	4.1±1.6	4.4±1.4	0.250
Key Pinch (kg)	2.9±1.1	3.3±1.3	3.3±1.2	0.206
Tip Pinch (kg)	2.1±0.7	2.4±1.0	2.2±1.0	0.257
Thumb SWMT*	3.84(3.61-4.08)	3.61(3.22-4.08)	2.83(2.44-3.61)	0.007
SWMT*	3.84(3.61-4.08)	3.22(3.22-4.08)	2.83(2.36-3.22)	0.003

Values presented as mean ± SD *Values presented as median (IQR) **Statistical significance between the second and third measurements was evaluated. BCTQ: Boston Carpal Tunnel Questionnaire, BMI: body mass index, CTS-6: Carpal Tunnel Symptoms Scale-6, Kg: Kilograms, m: Meters, SWMT: Semmes-Weinstein Monofilament Test, VAS: Visual analog scale.

Discussion

It has been reported that the severity of PRCTS symptoms may increase in the last trimester; these symptoms can range from pain, numbness, weakness to sleep disorders and depression [11]. Voitk et al. found that only 46% of symptomatic pregnant consulted a doctor for hand symptoms, and only 35% of these women received treatment [19]. It is thought that the most important reason for this is that pregnant doesn't disclose their symptoms, or physicians do not question these women about their symptoms.

Since the electrodiagnostic changes that diagnose CTS may be physiological during pregnancy, the importance of determining the optimum diagnostic test in pregnant women has emerged. Electrophysiological tests may result in false-positivity at a higher rate than other diagnostic tools. It may also lead to an increase in the rates of false estimation and, accordingly, unnecessary treatment [20]. Especially in a sensitive population such as pregnant women, using non-invasive diagnostic methods based on clinical evaluations instead of EMG is less expensive [4,6,8,11,13,15,21]. When a patient clinically shows signs of CTS but there are no positive findings on EMG, it is still possible for this patient to be offered treatment for CTS and to benefit from surgical decompression [21]. Conversely, when a clinically asymptomatic volunteer is diagnosed with CTS electrodiagnostically, it will be much more difficult for this volunteer to accept treatment methods because they have no clinical complaints or symptoms [10,12,15].

We think that the CTS-6 test, in which symptoms, complaints, and clinical examination can be evaluated together, is the most useful non-invasive scale for making a diagnosis. Another

criterion we used to determine improvement in PRCTS was a CTS-6 score of less than 5. The correlation between the pretest probability established with the CTS-6 and the posttest probability calculated from the EMG results is very high [16]. As a result of the third measurement, when EMG was applied to the wrists of women whose complaints still had not resolved according to our improvement criteria, our CTS diagnosis was confirmed to be 100% compatible with the EMG. Like the CTS-6, the use of the BCTQ has been shown to offer similar sensitivity, specificity, and positive predictive value to EMG [17]. Meems et al. [11] reported that the BCTQ was compatible with the symptoms and gave even higher scores in the advancing weeks of pregnancy, especially in the third trimester. In our study, we used the BCTQ scale to better compare the severity of symptoms and the dysfunction assessed by the CTS-6 in follow-ups. Our BCTQ results were similar to the literature. It was observed that while they were high at the time of diagnosis, they decreased significantly in the second measurement at the end of the puerperium [11,14]. In the present study, the mean VAS for pain at the time of diagnosis was 3.2. At the sixth month postpartum, the VAS score was 0 for all women except those who were offered surgery. The absence of pain was a criterion for recovery in this study.

The SWMT cut-off value has been defined as 2.83 size monofilament for diagnosing CTS by many authors [18,22]. It has even been reported that the SWMT and the 3.22 size can be a valuable quantitative method to detect moderate and severe CTS [23]. Our study evaluated the first three fingers separately, including size 4.31, which is accepted as the final evaluation size for the SWMT and diminished protective sensation. The median of the first measurement was the 2.83 size monofilament, which is compatible with the literature [18,22]. In particular, in the 15 wrists for which surgery was recommended, the median of the first measurement was the size of the 3.84. This value is accepted as the size at which diminished protective sense begins to be identified. The thumb was determined as the 3.84 size median for the SWMT in the first measurement, and the diminished protective sense due to PRCTS in the third trimester was determined as that size. It has been suggested that for the diagnosis and evaluation of CTS (EMG or SWMT), the thumb is the most sensitive finger. With the SWMT, the sense of the thumb and the total sense of the entire hand correlate with each other, and it has been suggested that testing only the thumb can be used instead of testing the other fingers in the median nerve sensory test [18,24]. In our study, the order of the sensory difference between the SWMT and the fingers was the same (thumb > index > middle). There was a correlation between the SWMT and the thumb and third finger total sense in all measurements, especially in patients recommended for surgery.

It has been reported that primiparity is a risk factor for CTS in the puerperal period [6,25-27]. In other studies, it was stated that there was no relationship between parity and CTS [10,11]. Another study reported that there might be a relationship between increased parity and PRCTS [7]. Although our study showed no

statistically significant difference in terms of parity, it showed that symptoms and complaints in primiparous pregnancies regressed earlier after pregnancy. It has been reported that advanced maternal age is a risk factor for CTS detected during pregnancy and the puerperium [7,25-27]. In our study, women whose symptoms and complaints resolved early were under 30 years of age, while the average age of the women who resolved late was 32.6 years. The mean age of the women who were offered surgical decompression was 36.7 years, which is even higher.

Studies have shown that BMI is an independent risk factor for PRCTS as well as the rest of the population [2,5,7]. It has even been reported that higher weight gains during pregnancy compared to pre-pregnancy are associated with a lower probability of recovery from PRCTS during follow-up [5,12,13]. Our study revealed that women whose complaints persisted had higher first trimester BMI values. Although it was not statistically significant, the symptoms and complaints of the women with higher BMI values persisted longer in the measurements made at the end of the third trimester and puerperium. Other studies have indicated that breastfeeding is especially a significant risk factor for CTS during the puerperium, and complaints and symptoms improve after breastfeeding is stopped [25,26]. Other studies have determined that certain working conditions and people working in jobs that require repetitive hand movements are at higher risk for CTS [2,28]. Therefore, our study excluded women who had jobs that require repetitive or strong wrist effort and women who did not breastfeed, considering that these risk factors may affect the results.

Since many other studies are retrospective and focus on diagnosis with scans made with national data, sufficient information has not been presented in terms of treatment [6,7,10,11,14]. In our study, immediately after the diagnosis was made, the women were educated about sleep position and activity modification. This education was combined with treatment using tendon and nerve gliding exercises and neutral volar wrist splints [29]. Splinting in the neutral position decreases the pressure on the median nerve by increasing the carpal tunnel volume [13,29,30]. All-day use of neutral splints has been found to cause regression in CTS symptoms, improvement in functional status, and improvement in sensory and motor latencies on EMG [29, 30]. In the treatment of CTS, exercise with a neutral wrist splint reduces pain and provides a significant increase in grip and pinch strength, even if it is used for a short time, such as four to six weeks [30]. In our study, with conservative treatment modalities, complaints and symptoms completely resolved in 59% of the women at the postpartum second month and in 86.4% of the women at the sixth month. However, if symptoms persist or worsen despite conservative therapy, surgical treatment should be recommended [13,15]. In our study, 14.6% of the women were offered surgery, and surgical decompression was performed for the 9.8% who accepted it. In other studies in the literature, this rate was found to be 5.1–15–16.3% [6,8,13].

The strengths of this study are that it was prospective, and repeated measurements were made during pregnancy, the puerperium, and later. Despite the broad exclusion criteria, we still had a sufficiently large sample size to be directly diagnosed with CTS. However, it was impossible to fully determine the prevalence of CTS during pregnancy because all pregnant could not be screened, and some pregnant chose not to participate in the study. Another limitation is that there was no control group. Because healthy pregnant without a diagnosis of CTS will not show clinical signs and symptoms, clinical evaluation scales and tests can not be used.

Conclusions

This study supports that pregnant women over 30 years old with a high BMI be screened for PRCTS using non-invasive diagnostic tools (thumb SWMT), CTS-6, and VAS scales. Thus, by taking early precautions with conservative treatment methods, it will be possible to prevent additional costs to the health system by improving the mother's health, whose provides care during pregnancy and postpartum follow-up.

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ORIGINAL ARTICLE

Comparison of the effects of 3 different anti-VEGF drugs on cornea thickness, lens thickness and anterior chamber depth: Case-Control Study

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Abstract

To compare the long-term effects of 3 different anti-VEGF molecules on the lens, cornea and anterior chamber in phakic patients who have received consecutive intravitreal injections. 157 patients who did not have corneal pathology but were treated with 1.25mg/0.05ml intravitreal bevacizumab, 0.5mg/0.5ml ranibizumab or 2mg/0.05ml aflibercept injections due to diabetic macular edema were retrospectively analyzed in our clinic. Patients who received three consecutive monthly injections were included to the study. Corneal thickness, lens thickness and anterior chamber depth measurements which were taken before the injections, 1 month after the first injection, 1 month after the second injection, and 1 month after the third injection were used in the study. There was no statistical difference between the bevacizumab, ranibizumab, aflibercept and control group in terms of preoperative specifications such as number of patients, gender and age average. A statistically significant difference was found between the 4 anterior chamber depth measurements in the control group, Ranibizumab drug group, and Bevacizumab and Aflibercept drug groups ($p < 0.001$, $p = 0.026$; $p = 0.07$, $p < 0.001$, respectively). Anterior chamber depth of the Ranibizumab and Bevacizumab patients decreased in the first month and increased in the second and third months. However, anterior chamber depth of the Aflibercept patients increased over time. As a result of our study; we concluded that three different anti- VEGF drug molecules have an effect on the anterior camera.

Keywords: Bevacizumab, aflibercept, ranibizumab, anterior chamber

Introduction

Bevacizumab, Ranibizumab and Aflibercept are being used in the treatment of diseases such as diabetic macular edema, retinal vein occlusion and senile macular degeneration. Bevacizumab, which is a monoclonal antibody, can bind to all forms of VEGF-A. It is a molecule which is used to inhibit various neovascularization and shown to be beneficial in the previous studies. Ranibizumab is a high-affinity antibody particle which is formed by the recombinant DNA technology and can inhibit all biologically active isoforms and active proteolytic components of VEGF 10.

Aflibercept, which can bond to VEGF-B and placental growth factor 1-2 with high affinity can also bond with all isoforms of VEGF-A. Fc field serves as a receptor trap for all VEGF-A isoforms [1-5].

Although retinal neovascularization is the most common indicative use of anti-VEGF agents, previous studies show that they also have an effect on iris, lens and corneal neovascularization or that agents have toxic effect [2.6-9]. This makes us consider that these structures also carry receptors on them.

In our study, we aimed to compare the long-term effect of 3

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different anti-VEGF molecules on lens, cornea and anterior chamber of phakic patients who received three consecutive dose injections on monthly basis.

Material and Methods

Our study covers the retrospective analysis of total of 157 patients who have been diagnosed with diabetic macular edema (DME) in our eye clinic during the period of January 2021 to December 2021. 35 patients were given ranibizumab as intravitreal injection (IVR), 42 patients were given bevacizumab as intravitreal injection (IVB), 44 patients were given aflibercept as intravitreal injection (IVA) and 36 patients remained in the control group. Patients with refractive surgery history, corneal dystrophies, contact lens history as well as patients who have undergone cornea, lens or anterior chamber surgery during the study period and patients whose treatment cannot be completed after first or second injections were not included to the study. Local ethics committee approval (Düzce University Ethics Committee for Clinical Studies 2022-70) was granted for the study. Furthermore, informed consent forms were signed and submitted by each patient according to the Helsinki declaration.

4 separate groups were created, namely patients taking intravitreal bevacizumab (Altuzan, Roche), intravitreal ranibizumab (Lucentis, Novartis), aflibercept (Eylea; Bayer) throughout their DME treatment and the control group. The non-injected eyes of the patients taking intravitreal injection under DME treatment were used for the control group.

A detailed medical record was taken from all patients. Ophthalmologic examination of the patients was done by means of best visual acuity (Snellen chart), intraocular pressure measurement with Goldman applanation tonometry, anterior and posterior segment analysis with biomicroscope , noncontact indirect fundus examination of dilated pupil with of 90 D lens, central macular thickness measurement (OCT) and only patients diagnosed with DME through FFA and treated with intravitreal injection are included to the study. Phakic cases who received three consecutive dose injections on monthly basis have been included to the study. There was one-month interval between the injections and patients were selected among the ones with no previous treatment. Central cornea thickness (CCT), anterior chamber depth (ACD), lens thickness (LT) measurements that were made before the injection, one month after the first injection, one month after the second injection and one month after the third injection were used. Ultrasonic pachymetry device, Echoscan US 500 system (Nidek Co. Ltd., Aichi, Japan), which is considered to be the golden standard method, was used for the measurements.

Intravitreal injections were done in sterile surgery rooms. Before the process, topical anesthetic eye drop Alcaine (Proparacaine, Alcon) was applied to the eye subject to injection. The patient than was placed on the surgery table where the periorbital region was washed with 10% povidone iodine (Isosol, Merkez) and a drape was placed followed by similarly washing the surface of the eye to be injected after opening the eye lid with the help of blepharostat. 0.05 ml agent of bevacizumab, ranibizumab or aflibercept is applied as intravitreal injection. 27 Gauge injection wass used during the process where the injection was done from the inferior temporal segment side, at a measured distance of 3.5 - 4 mm from limbus. Patients with no signs of complications were called in for controls after one month. CCT, ACD and LT measurements were done during the control period. Above mentioned procedures were applied to the second and third injections as well, followed by the same control steps 1 month after each injection.

All measurements were carried out by the same experienced ophthalmologist. Since all measurements were done by the same person, the data were admitted as the mean of measurements taken after the 3 injections in order to avoid any bias.

In all 3 groups, CCT, ACD and LT values of the patients, pre-injection and post-injection values as well as values after all three injections were compared both within themselves and with the control group.

The data received throughout the study were analyzed by the SPSS 25.0 version software. Distribution of the data were shown by descriptive analysis parameters (mean, standard deviation, minimum, maximum, frequency and percentage). The coherence of the data with the normal distribution was analyzed by Kolmogorov-Smirnov test. Analysis of variance, ANOVA was employed for the purpose of determining the effect of drug applications on CCT, ACD and LT. Mann Whitney U Test was used for the mean comparison of two independent groups whereas Kruskal Wallis H Test was used for the mean comparison of more than two independent groups. Spearman's Correlation Test was employed for the relation between two constant variables. Furthermore, in cases where Mauchly's sphericity assumption was violated and epsilon value was higher than 0.75 ($\varepsilon > 0.750$), then Huynh-Feldt correction was used but if the epsilon value was less than 0.75 ($\varepsilon < 0.75$), then Greenhouse-Geisser correction was used to correct the violation.

Results

The demographic specifications of the patients are shown in the table (Table 1). A total of 157 patients participated to the study where 22.9% is the control group, 22.2% is the Ranibizumab group, 26.8% is the Bevacizumab group and 28.1% is the Aflibercept group. A statistically significant difference was found between the groups in terms of age (p=0.003). There was no statistically significant difference between the groups in terms of gender distribution. (p=0.556).

Throughout the study, the changes in the cornea thickness over time due to drug application are compared and the results are analyzed in table (Table 2). Based on these results there is no statistically significant difference between the means of the cornea thickness measurements of the control group or injection

applied groups that are done before the application as well as in the first, second and third months of the injection (p>0.05). Based on the results of simple main effect analysis over time, there is no statistically significant difference between the 4 cornea thickness measurements of the control group, Ranibizumab drug group, Bevacizumab drug group and Aflibercept drug group (p>0.05).

The changes in the lens thickness over time due to drug applications are compared in the study and the results are analyzed in the table (Table 3). Based on these results there is no statistically significant difference between the lens thickness of the control

group or injection applied groups before the application nor in the first, second and third months after the application (p>0.05). Lens thickness of patients with no drug application and Aflibercept application tend to decrease over time. However, statistically significant difference was determined among the 4 lens thickness measurements of the Ranibizumab ad Bevacizumab drug groups (p<0.001, p=0.026, p=0.07, p<0.001 respectively). Anterior chamber depth of Ranibizumab and Bevacizumab groups have decreased in the first month but increased in the second and third months. However, anterior chamber depth of Aflibercept applied group has increased over time.

Table 1. Demographic Information Distribution of the Participating Patients

| | Gender | n | % | X² | p | Age | | F | p |
						X ± SS	Min - Max		
Control	Male	16	10.2			70.6±8.7	57-85		
	Female	20	12.7						
Ranibizumad	Male	12	7.6			64.6±7.1	55-82		
	Female	23	14.6	2.030	0.566			4.819	0.003
Bevacizumab	Male	21	13.4			65.5±6.9	50-79		
	Female	21	13.4						
Aflibercept	Male	18	11.5			64.3+9.2	52-86		
	Female	26	16.6						
Total		157	100						

SD: Standard Deviation

Table 2. Comparison of Drug Application and Change in the Cornea Thickness Over Time

| Time | | Control Group | Ranibizumab | Bevacizumab | Aflibercept | F | P |
		X ± SS	X ± SS	X ± SS	X ± SS		
Cornea Thickness (μm)	0.Month	555.33±32.1	547.11±48.4	551.71±55.9	544.36±38.4	1.183	0.318
	1.Month	554.86±35.8	546.11±46.7	564.17±45.0	547.73±37.7	1.172	0.323
	2.Month	555.42±31.0	546.66±46.9	563.60±46.4	547.68±37.2	1.502	0.216
	3.Month	555.75±30.9	553.51±46.5	564.88±44.6	547.48±36.8	1.033	0.380
F		1.002	1.008	1.010	1.767		
p		0.324	0.323	0.321	0.190		

SD: Standard Deviation, μm: micrometer, statistically significant p value is taken as p<0.05 p value at the end of the table shows the inter-group changes and the p value underneath the table show the within-group changes

Table 3. Comparison of Drug Application and Change in the Lens Thickness Over Time

| Time | | Control Group | Ranibizumab | Bevacizumab | Aflibercept | F | P |
		X ± SS	X ± SS	X ± SS	X ± SS		
Lens Thickness (mm)	0.Month	4.24±0.8	4.37±0.7	4.50±0.7	4.29±0.7	0.959	0.414
	1.Month	4.23±0.8	4.36±0.7	4.56±0.7	4.23±0.7	1.840	0.142
	2.Month	4.21±0.8	4.34±0.7	4.48±0.7	4.21±0.7	1.310	0.273
	3.Month	4.11±0.8	4.29±0.7	4.44±0.7	4.13±0.7	1.716	0.166
F		4.035	2.720	1.762	4.825		
P		0.044	0.098	0.190	0.014		

SD: Standard Deviation, mm: milimeter, statistically significant p value is taken as p<0.05 p value at the end of the table shows the inter-group changes and the p value underneath the table show the within-group changes

Table 4. Comparison of Drug Application and Change in the Anterior Chamber Depth Over Time

Time		Control Group	Ranibizumab	Bevacizumab	Aflibercept	F	P
		X ± SS	X ± SS	X ± SS	X ± SS		
Anterior Chamber Depth (mm)	0.Month	2.92±0.6	3.02±0.5	3.04±0.4	2.91±0.6	0.705	0.551
	1.Month	3.15±0.4	3.01±0.6	2.94±0.6	3.03±0.5	0.979	0.405
	2.Month	3.19±0.5	3.09±0.5	3.05±0.5	3.15±0.5	0.621	0.603
	3.Month	3.15±0.4	3.21±0.5	3.17±0.5	3.17±0.5	0.091	0.965
F		13.646	3.985	5.296	16.398		
P		0.000	0.026	0.007	0.000		

SD: Standard Deviation, mm: milimeter, statistically significant p value is taken as p<0.05 p value at the end of the table shows the inter-group changes and the p value underneath the table show the within-group changes

Discussion

Intravitreal injections have been an important part of DME treatment in the recent 50 years. Hypoxia, hyperglycemia and inflammation play main role in DME formation but since VEGF is the main mediator that causes all these, the above mentioned 3 anti-VEGF agents used in the topical treatment during the disease pathogenesis provide both functional and anatomic improvement of the patients. Frequency of the intravitreal injection use rapidly elevates due to success in treatments and continuing resilience on individual based DME's however, increased amount of applied intravitreal injections bring along complications as well. These complications may end up with results such as conjunctival hemorrhage, increase in IOP, endophthalmitis and even complications that may lead to blindness [10-11].

Related studies have accelerated after reports of toxic reactions associated to cornea which seemed like a distant target for intravitreal injections [9]. In their study with 43 patients subject to 2.5 mg/0.1 ml intravitreal Bevacizumab, Güler et al. evaluated the post-injection results of the 3rd day, 15th day and 1 month. They found out that there was no statistically significant difference among these measurements in terms of CCT [12]. Herrorors et al., in their study with 26 patients with senile macular degeneration, evaluated the effects of applied IVR on cornea after 6 months. Ultimately, they did not find any statistically significant difference in terms of CCT [13]. Perez-Rico et al. found out that there was no statistically significant difference in terms of CCT after 6 months evaluation of 52 patients with IVR application [14]. In their study with 44 patients of IVA application, Muto et al. evaluated the first, third and sixth months and determined that there was no statistically significant difference in the 6-month results of CCT [15]. Arslan et al. found out no statistically significant difference in CCT evaluation of the 2 intravitreal injections in their study [16]. There was no previous study covering all 3 different anti-VEGF agents in the literature. Similar to previous literature, we did not find any statistically significant difference in the cornea thickness in our study either.

We did not find any previous literature related to the lens which is the closest neighbor after intravitreal injections are applied to vitreous. In their study of 37 patients with intravitreal dexamethasone implantation, Anayol et al. found out that the lens thickness increased in 3 months but there was no statistically significant difference [17]. Likewise, there was no statistically significant difference among the 4 groups in our study.

Although a decrease in ACD due to elevated vitreous pressure after intravitreal injection is expected, there is no sufficient data on the long-term effects. In their study of 46 patients with IVB application, Alkin et al. evaluated the effects in 5 minutes, 1 hour and 3 hours. They found statistically significant increase in ACD in terms of short-term effect [18]. In their study covering 3 different anti-VEGF comparison, Arslan et al. found a decrease in the anterior chamber depth after 2 intravitreal injection and suggested that the difference is statistically significant [16]. In our study, anterior chamber depth of the patients subject to Ranibizumab and Bevacizumab application decreased in the first month and increased in the second and third month. However, anterior chamber depth of the patients subject to Aflibercept application increased over time. As a result of literature review, no study was found that covered the comparison of different anti-VEGF molecules. We believe that the observed difference might be related to relatively low group counts.

We had a few limiting factors in our study. First one was to run the study in a single center. Second was not measuring the axial length and intraocular pressure values. Third was not using non-contact method in pachymetry measurements. The strength of our study, on the other hand, was being among the first studies in literature to evaluate 3 different anti-VEGF molecules in terms of anterior segment parameters.

Conclusion

The number of intravitreal injections keep increasing and complications related to this situation are also expected to increase. In our study, we compared the most commonly used 3 different anti-VEGF molecules. As a result of our study; we concluded that 3 different anti-VEGF molecules did not have an effect on CCT and LT but have a decreasing effect on ACD. We believe that repeating this study with a higher number of patients and on multi-centered basis would generate more reliable results

thus enabling us to have a better understanding of the medication.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Düzce University Ethics Committee for Clinical Studies 2022-70.

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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Internal fixation of acute scaphoid proximal pole & waist fractures using the dorsal mini open technique without bone grafting

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Abstract

The navicular bone of the hand is the most frequently fractured bone among the carpal bones, and if not treated well, it may result in nonunion. Dorsal, volar open, or percutaneous approaches can be used in surgical treatment. We aimed to evaluate the results of internal fixation of scaphoid fractures with the dorsal mini-open technique. Patients with acute proximal and waist fractures who have been treated with cannulated compression screws with a dorsal mini open approach without grafting between 2015 and 2020 were included. Functional outcomes were analyzed with the DASH questionnaire and MAYO wrist performance scores and compared with the contralateral wrists. The mean age of the patients was 35.6 ±10.8 years (range 20-55), seven were proximal, and 13 were waist fractures. The mean time to surgery was 16±7.3 days (range 5-30) and the mean follow-up time was 47.5±20.2 weeks (range 20-84). The mean DASH score at the last follow-up was 5.9±3.3 points (range 2.5-11.7), and the Mayo wrist performance score was 96.8±5.2 points (range 85-100). In one proximal pole fracture, cracking occurred on the cartilage surface at the screw insertion site but consolidated without any additional intervention. The mean time to union was 8.5±1.2 weeks (range 7-11). Waist region fractures consolidated faster than proximal pole fractures (p=0.002). No significant difference was found between the fracture site and mid-term functional results. Complications like proximal cartilage fractures during the embedding of the screw head or prominence of the screw head can be avoided with the dorsal mini-open technique which is a safe and effective method.

Keywords: Acute scaphoid fractures, dorsal, mini open, limited incision, bone graft, extensor pollicis longus

Introduction

The navicular bone of the hand is the most frequently fractured bone among the carpal bones, with a rate of 50% to 70%, and it usually occurs as a result of falling on the open hand in radial deviation [1]. Difficulties may be experienced in diagnosing with direct X-ray at the first application, and if not treated well, it may result in nonunion [2,3]. It has been shown that if the time elapsed between the treatment of the fracture and the day the fracture occurred is more than four weeks, the rate of nonunion increases by 40% [4]. The fact that 80% of its surface is covered with cartilage, the vascular entrances are in the non-articular region on the dorsal and volar sides, and especially the proximal region is fed with retrograde blood flow are the main causes of nonunion that occurs after waist or proximal pole fractures [1,5].

Long-term plaster treatment is generally accepted for waist region fractures without displacement. However, despite proper casting, nonunion can be seen in the waist and proximal fractures [2]. In addition, studies have been published recently showing that

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surgical treatment prevents both financial loss and limitation of movement compared to long-term casting, even in non-displaced waist and proximal region fractures [6–8].

Dorsal, volar percutaneous, or open approaches can be used in surgical treatment. In the dorsal percutaneous approach, the extensor tendons, especially the extensor pollicis longus (EPL) tendon are at risk [9]. We hypothesized that with the dorsal mini open technique, we should minimize the risk of tendon injuries and the entrance point on the proximal pole can be visualized and protected while inserting screw. There are few studies on the treatment of acute fractures using the dorsal mini-open technique [10–12]. Only one of them have used ligament sparing technique [11], and our study will be the next study which aimed to evaluate the results of internal fixation of the scaphoid fractures with the dorsal mini-open ligament sparing technique.

Material and Method

Approval for this retrospective cohort study was obtained from the local ethics committee of our hospital (Decision No: 125 Date:01.07.2020) and informed consent was obtained from the patients. Patients who underwent surgery for scaphoid fractures between 2015 and 2020 were examined. Of these, patients with proximal and waist fractures who have been treated with cannulated compression screws with a dorsal mini open approach without bone grafting were included in the study. Functional outcomes were analyzed with the DASH (Disabilities of the Arm, Shoulder, and Hand) questionnaire and MAYO wrist performance scores and compared with the contralateral wrists [13,14]. Wrist movements were measured with a goniometer and recorded. Grip strength was measured with a Jamar (Jamar, Clifton, NJ) dynamometer and was calculated with 10% correction in non-dominant hands [15]. Since the comparisons were made with the intact hand, bilateral cases or patients with any previous wrist movement limitation were excluded from the study. Fractures older than six weeks were not included in the study because the study was planned on newly formed fractures.

Surgical technique

While the patient was lying in the supine position under regional block anesthesia with a pneumatic tourniquet on the upper arm, a hand table was used to work on. A longitudinal 1.5cm incision was made just distal and ulnar to the lister tubercle from the dorsum of the wrist directing the third metacarpal. Only the distal part of the EPL tendon sheath was opened, and the tendon was protected on the radial side. The joint capsule was opened longitudinally on the same line as the incision, and the scapholunate joint was made visible. The fracture line was not opened and the scaphoid bone was not explored completely. Only the proximal pole of the scaphoid bone was seen, and the entry point of the headless cannulated screw was determined by flexing the wrist to 60 degrees. Then, the guide wire was advanced by controlling it on the fluoroscopy device (Figure 1). As putting the wrist in a neutral position to see the anteroposterior wrist X-ray would bend the guide wires, the elbow was flexed to make the wrist parallel

to the ground (Figure 2). This way radiographs were obtained at anteroposterior, lateral, and 30 degrees pronation, and the central location of the guide wire was confirmed. A second wire was used to prevent rotation. Before drilling, screw length was measured with equal-sized K-wires, and a screw 4mm shorter than the measured one was used. Osteosynthesis was achieved with mini headless cannulated compression screws (HCCS, TSTOrthopedics, Turkey) in waist region fractures and micro headless screws in proximal fractures. Grafting was not applied. After pulling the guide wires and controlling the movement, the capsule and EPL sheath were closed with absorbable sutures, and the subcutaneous tissue and skin were closed. A short arm splint was made, sutures were removed two weeks later. A removable wrist splint was given for waist fractures after two weeks. For proximal fractures, the duration of the short arm splint was extended to one month. Joint range of motion exercises was started while the splint was removed. Patients were called for follow-up at 15-day intervals after surgery.

Figure 1. Screw insertion site can be seen after flexing the wrist to 60 degrees

Figure 2. Elbow was flexed to make the wrist parallel to the fluoroscopy device

Statistical analysis

The normal distribution of the data was analyzed with the Shapiro-Wilk test using the SPSS 25.0 (SPSS Inc, IBM, Chicago, IL) program. A T-test was used to compare the postoperative range of motion with the intact side. The Mann-Whitney U Test was used to compare the union times with the fracture site. The p-value for the significant difference was accepted as <0.05.

Results

Twenty of 25 patients, 16 male and four female, could be reached. Seven fractures were in the proximal scaphoid region, and 13 were in the waist region. The demographic data can be found in Table 1. The mean time to union was found to be 8.5±1.2 weeks (range 7-11) and there was a statistically significant difference between the proximal and waist region fractures regarding the time to union (p=0.002, Table 2). No complications such as guide wire breaking, neuropraxia, hypertrophic scar, infection, tendon rupture, and nonunion were encountered. In one proximal pole fracture, cracking occurred on the cartilage surface near the screw insertion site while the headless screw was fully embedded into the bone. However, no statistically significant difference was found between the fracture site and mid-term functional scores.

Table 1. Demographic Data

	Mean	Standard Deviation	Minimum	Maximum
Age "Years"	35.65	10.840	20	55
Time from fracture to surgery "Days"	15.95	7.097	5	30
Follow-up time "weeks"	47.55	20.242	20	84
Final DASH score	5.875	3.3312	2.5	11.7
Final Mayo wrist score	96.75	5.200	85	100
Final Extension	64.70	4.566	55	73
Opposite side Final Extension	71.50	2.838	68	78
Final Flexion	77.05	4.019	70	85
Opposite side Final Flexion	79.20	3.847	72	85
Grip Strength	38.25	5.730	28	47
Opposite side Grip Strength	38.05	4.751	27	44

Table 2. Comparison of fracture consolidation time according to fracture location

Fracture localization	Mean Time to consolidation "weeks"	Std. Deviation	Significance p
Proximal	9.57	1.27242	0.001802
Waist	7.92	.75955	

Discussion

In this study we showed that there is no need to open the fourth and second dorsal extensor compartments to explore the scapholunate area with the dorsal mini open technique. Also, complications like screw prominence or entry site fracture can be avoided while protecting dorsal ligaments and tendons.

An uncontroversial area in the treatment of acute scaphoid fractures is the necessity of surgical treatment of proximal pole fractures [16–19]. Nonunion problems are frequently encountered in scaphoid proximal region fractures.Vascularity is thought to be related to this situation. For this reason, Megerle et al. reported that they performed intra-operative bleeding control in the surgical treatment of proximal pole non-unions. They have applied vascularized grafts to those without bleeding, and conventional bone grafts where they could detect bleeding [20]. In non-displaced acute fractures, it was advocated that surgical fixation without using grafts and without bleeding control is sufficient [16,21,22]. In proximal region fractures, unlike the waist region, standard 4 mm cannulated compression screws are not recommended due to the small area to be inserted, as there is a risk of fragmentation of the proximal pole [16]. In our study, all acute proximal region scaphoid fractures were surgically treated, and fixation was performed with 2.5 mm micro headless cannulated compression screws without using grafts.

The surgical treatment of acute waist fractures is controversial [23]. The indication for surgery is usually decided by evaluating the initial displacement and stability of the fracture. While fragmentation of the fracture, an intra-scaphoid angle of more than 35 degrees on the lateral radiograph, and perilunate injury indicates that the fracture is not stable, there are different opinions regarding the amount of displacement [1,11,12,16]. Classically, the presence of a 1mm gap is considered unstable. At the same time, Clementson et al. have classified it as "minimal" if the amount of displacement is less than 0.5mm,

moderate if the amount of displacement is between 0.5 and 1.5mm, and advanced if the amount of slippage is ≥1.5mm [1,10,11,16]. While they recommended surgical treatment for those with severe displacement and conservative treatment for those with minimal displacement, they reported that fractures of the waist region with moderate displacement could be treated conservatively. However, casting may be required for up to 10 weeks [16]. And even with slight displacement, the presence of a separate cortical fragment on the radial side of the scaphoid bone or the accompanying rupture of the scapho-lunate ligament is still considered unstable [24,25]. The relative surgical indication is mentioned in young active patients and patients unsuitable for long-term cast treatment, as surgery may shorten the time to return to work [7,11,26]. In our study, scaphoid waist region fractures with a displacement of 0.5mm or more were fixed by using the dorsal mini-open technique with 3.3 mm mini headless cannulated compression screws without opening the fracture line.

It has been reported that computed tomography (CT) scan should be used in preoperative planning to determine the amount of displacement and to evaluate the stability [1,27]. On the other hand, Müller et al. recommended CT scan to evaluate postoperative screw placement and to diagnose nonunion [28]. The study of Herbert and Filan showed that there might be no symptoms after stable fixation without any sign of union on direct radiographs [19]. In an examination conducted for the treatment of nonunion cases, Tada et al. divided the fracture line into three types as; linear, cystic and sclerotic or displaced type, and they reported that CT examination is required for this distinction [22]. They emphasized that graft should be used if there is a cyst or sclerosis in the CT examination. In our study, all patients had a CT scan for preoperative planning, and as the study was conducted on acute fractures no cyst or sclerosis was detected. Since union findings were detected in the direct radiographs in the postoperative follow-ups, examination with CT scan was not required after the operation.

Dorsal and volar, percutaneous or open approaches can be used in the surgical treatment of acute scaphoid fractures [1,29]. The route to be chosen is also related to the localization of the fracture and the surgeon's preference [26]. While the dorsal approach is preferred in proximal fractures, there is no consensus in waist fractures [10]. In the dorsal open approach, the blood supply to the scaphoid bone is disturbed, while in the volar approach, the scaphotrapezoid joint may be damaged. In addition, for the screw to be inserted into the center of scaphoid bone, it might pass through the trapezium in the volar approach, and tendon ruptures may be encountered when it is applied entirely closed in the dorsal approach [9,10,12].

Martus et al. reported in 2005 that tendon damage could be prevented with a limited dorsal approach [10]. According to this technique, with a 3 cm dorsal incision, the third, fourth and second extensor compartments are opened starting from the distal of Lister's tubercle, and the capsule is opened in an inverted T shape to explore the proximal scaphoid. They have investigated 18 acute waist fractures with less than two weeks between injury and surgery, which has displacement of less than 1 mm with no ligament injury, and they have found union within eight weeks in 17 patients and did not encounter any significant complications [12]. They did not report the nonunion case as a significant complication because of the short follow-up period and the continuation of the treatment for that patient. The mean DASH score was found to be 6.12 in their follow-ups. Our study was also planned on acute fractures but also included proximal region fractures. It is similar to the study of Martus et al. as union was detected in 20 patients, and the mean DASH score was 5.9.

Dodds et al. described the dorsal mini-open technique with ligament-sparing arthrotomy and presented their comparative study with the percutaneous dorsal approach [11]. They reported that they used a 1.5 cm incision in this study, which included patients with a displacement of 1 mm or more, and patients who needed early movement. They explained the technique as opening only the distal of the third compartment and radial side of the fourth compartment and then opening the capsule longitudinally to reach the proximal scaphoid. They observed minor complications that did not make a statistically significant difference in both groups, but functional results were not evaluated in their study. They recommended using the ligament-sparing surgical technique because they found it safe [11]. On the other hand, our study is similar to that of Dodds et al. in terms of incomplete opening of the EPL tendon sheath and incision size. We did not open the fourth compartment and functional scores were also evaluated in our study.

In the study by Bushnell et al., in which a closed dorsal percutaneous approach was used as described by Slade et al., they reported that the complications of percutaneous techniques are higher than expected [9,30]. In this study of 24 patients involving only waist region fractures, the time between trauma and surgical intervention extended up to 10 weeks. The significant complications they encountered were one nonunion, three screw irritation, and one proximal region fracture in the postoperative period. We think that the irritation due to the incomplete embedding of the screw head in the proximal scaphoid and the damage caused by drilling in the radio-scaphoid joint can be prevented with the mini-incision used in our study.

In our study, one major complication was observed in a patient with a proximal pole fracture. Cracking was observed in the cartilage area at the edge of the screw during tightening, immediately after the screw was embedded. The compression was stopped as soon as it was observed. Since the entry point of the screw was visible, fragmentation of the proximal region was prevented, and as stable fixation was ensured, the screw was not changed, or loosened. After a one-month standard splint period, movements were initiated, and no additional intervention was required for this patient. The pre-operative and post-operative

images of this patient can be seen in figures below (Figure 3).
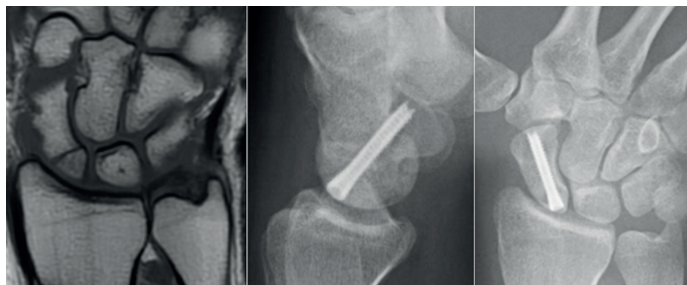
Figure 3. Images of one patient's pre-operative and 3 months after operation

In both studies using the dorsal mini-open technique, only waist fractures were examined, and therefore, the time between the union and fracture location was not investigated [11,12]. Severo et al. used the volar technique in 24 waist fractures and the dorsal percutaneous technique in 4 proximal region fractures [8]. Failure was detected in one dorsally approached fracture, since the head of the screw was not embedded in the bone. In our study, such a complication was not encountered since this region was visualized while the screw was placed. The same study reported that the waist region fractures consolidated earlier than the proximal region, which is consistent with our study.

There are some limitations of our study. First limitation is; it was arranged retrospectively and as a result the data was collected from the records of the patients and therefore, we couldn't perform a comparison between the pre- and post-operative functional outcomes. Also, no comparison with an alternative treatment method was made in the current study. Another limitation is, the union times were not evaluated with CT scan but it is not a routine recommendation. Finally, the sample size of cases was relatively small.

Conclusion

With the dorsal mini-open technique, the screw insertion site can be visualized between the third and fourth dorsal compartments without complete opening of these compartments. As a result, complications such as proximal cartilage fractures during the embedding of the screw head or irritation because of a prominent screw head can be avoided. The dorsal mini-open technique is safe and effective for proximal and waist region scaphoid fractures.

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ORIGINAL ARTICLE

The affecting factors and prevalence rate of sick building syndrome in healthcare workers

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Abstract

Sick building syndrome (SBS) is defined as symptoms that occur while living or working in a certain building but disappear after moving away from the environment. In this study, we aimed to determine the effects of indoor air pollutants on the health of employees, the prevalence of SBS in healthcare workers at the university hospital, its relationship with environmental and personal factors and the respiratory system. A questionnaire was applied to 951 healthcare workers who agreed to participate in the study. Having at least one general, one mucosal and one skin symptom every week in the last 3 months was accepted as SBS. Temperature, CO and CO_2 levels and relative humidity were measured in different areas of the hospital. The prevalence of SBS was 62.1%. There was a statistically significant relationship between SBS and having a chronic disease (p<0.0001), continuous drug use (p=0.005) and the evaluation of the environment as warm (p=0.042). Having a chronic disease (OR=0.426; 95% CI, 0.228–0.797), the environment often being too warm (OR 0.218; 95% CI, 0.084–0.567) or occasionally too bright (OR=0.300; 95% CI, 0.158–0571) and diagnosed by a doctor due to symptoms (OR=3.209; 95% CI, 1.529–6.731) was found to be significant in forward variable selection method and binary logistic regression analysis. In our study, a relationship was found between physical factors such as temperature, humidity and CO_2 level of the environment and personal factors such as stress, chronic disease and SBS. SBS can be prevented by control at the source as well as by administrative and engineering interventions among the employees.

Keywords: Sick building syndrome, hospital, healthcare worker, indoor air pollution

Introduction

In industrialised countries, people spend over 90% of their lives in closed environments and more than half of the employees spend their time in office environments [1]. Sick building syndrome (SBS) is defined as a building occupant manifests at least one symptom of SBS, the onset of two or more symptoms at least twice, and rapid resolution of symptoms following moving away from the workstation or building [2]. Itching, dry skin or eye, nasal congestion or discharge, congestion in the sinus, dry or itchy throat, cough, stiffness of the chest, dyspnea, wheezing, increase in asthma symptoms, fatigue, difficulty in concentrating, headache, dizziness, myalgia and smell or taste disturbances are common indications [3]. Indoor air pollutants can be

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classified as toxic or irritant chemicals, allergens and infectious agents and include carbon monoxide (CO), tobacco smoke and cleaning agents [3]. Passive cigarette smoke, smoke and other allergens, volatile organic compounds, particulate matter and gases, cleaning or personal care products and combustion products resulting from cooking or heating are important indoor air pollutants [3]. Viruses, fungi and rarely bacteria are cited as infectious agents [3]. Common cold and flu viruses are the routine infectious agents, but the coronavirus has been the most common infectious agent in recent years [3]. Tuberculosis is very common among healthcare workers, and an infectious agent that is rarely considered is legionella [3]. Physical factors affecting indoor climatic conditions are temperature, humidity, airflow velocity, lighting and noise. To ensure good environmental quality, the temperature should be in the range of 19°C–23°C, relative humidity should be 40%–60% and airflow velocity should be 0.1 m/sec according to American Society of Heating, Refrigerating, and Air Conditioning Engineers (ASHR AE) [4].

Studies on SBS are increasing in the world. As a result of these studies, it has been determined that the symptoms in people may occur in relation to the buildings they work or live in. Although there are studies on indoor air pollution and its effects in Turkey, there is not much research to determine SBS and its health effects.

In this study, we aimed to determine the prevalence of SBS in healthcare workers in a university hospital, its relationship with environmental and personal factors and its effects on the respiratory system. This investigation was necessary because indoor air pollutants have an important effect on the health of employees and indirectly on productivity.

Material and Methods

The university hospital has 16 floors and a total bed capacity of 1.368, including 301 intensive care beds and 39 operating theatres. The outside of the building is heat insulated and has high reflective windows and a barrier curtain wall. There is no window that opens towards the outside. Heating in all indoor areas and hygienic air conditioning in operating rooms (cooling and ventilation air handling units) are provided by air conditioners consisting of cooling groups and aspirators. The operating room, intensive care units, infectious diseases department and radiology department receive 100% fresh air (outside air), and other departements receive mixed air (50% inside and 50% outside air). No carpets are used in areas where the floor is covered with polyvinyl chloride, and wet floors are covered with ceramics. Water, 1/10 diluted bleach and detergent are used for cleaning the building, and a mopping system is used for floor cleaning. This is a cross-sectional study. This study had been carried out between 2011-2012 and data were collected between September 2010 and May 2011. Sixty-two questions were posed to determine the socio-demographic data of the individuals and the symptoms, and some characteristics related to SBS. Having at least one general, one mucosal and one skin symptom every week in the last 3 months was defined as SBS [2].

A questionnaire was applied to 951 (38%) of the 2500 people working in the university hospital who agreed to participate in the study.

People who were determined to have rhinitis, pharyngitis, sinusitis and asthma were evaluated for the presence of SBS. General symptoms: Weakness of vision, shortness of breath, feeling of tightness in the chest, flushing, sleepiness, tiredness, abdominal pain, nausea, vomiting, fatigue, restlessness, headache, dizziness, difficulty sleeping at night and generalized muscle and joint pain. Mucosal symptoms: Burning–stinging eyes, tearing, redness, dry throat, dry cough, wheezing, sore throat-tenderness, cracked lips, excessive thirst, runny nose-bleeding, nasal congestion, unpleasant smell sensation and unpleasant taste sensation. Dermal symptoms: Dry skin, redness and itching. The survey was conducted using the translated version of the questionnaire about SBS of London Hazards Center, Interchanges Studios [5] and adapted to Turkish by Efeoğlu (2006) [6].

A hand-held Fluke 975 AirmeterTM Tester, a five-sensor internal-type air quality diagnostic device, was used in the evaluation. Temperature, dew point and wet bulb temperature were measured in Celsius (C) or Fahrenheit (F); relative humidity (% RH), CO levels in parts per million (ppm) and carbon dioxide (CO_2) levels in ppm were also estimated. Pulse oximetry was used to measure peripheral blood oxygen saturation and heart rate [7,8]. Carbon monoxide (CO), CO_2 and relative humidity were measured in 36 areas in total, including one operating room, 7 intensive care units, 11 services, 10 outpatient clinics and 7 other places (kitchen, warehouse, air conditioning room, etc.). Room temperature level: normal 20–24ºC, relative humidity level: normal 30%–50%, CO level: lower limit value according to ASHRAE 62-2004 - 9 ppm as normal, CO2 level: ≤700 ppm accepted as normal [3].

Statistical Analysis

The data were calculated using the SPSS 17.0 statistics programme. The compliance of the variables in the study to the normal distribution was examined using the Kolmogorov–Smirnov test. For the definition of numerical variables, the median value, the smallest and the largest range of values were used. Categorical variables were defined as numbers and percentages. The Mann–Whitney U test was used for comparisons between two groups in terms of numerical variables. In terms of categorical variables, Pearson's Chi-square and Fisher's exact tests were used. Factors affecting SBS were evaluated using the forward variable selection method and binary logistic regression analysis. For indoor space measurements, those suitable for normal distribution were compared with one-way analysis of variance and those not suitable for normal distribution were compared with the Kruskal–Wallis H test. Levene test was used for the homogeneity control of variances. When the one-way analysis of variance result was important, multiple comparisons were made by the Türkiye's Test, and when the result of the Kruskal–Wallis H test was significant, multiple comparisons were made by the

Conover Test. Forward variable selection method and binary logistic regression analysis was used to assess relationship between SBS patients and other independent variables. A value of p < 0.05 was considered statistically significant. Clinical ethics committee approval was obtained from the university hospital ethics committee (Protocol number: 2010/48). Informed Consent was taken from the participants.

Results

Participants' characteristics

A questionnaire was applied to 951 healthcare workers (38%) in the university hospital who agreed to participate in the study. The median age of the participants was 30 years (19–65). Regarding the gender distribution of the participants, there were 515 (54.2%) men and 436 (45.8%) women. When their marital status was examined, 631 (66.4%) were married, 306 (32.2%) were single, 11 (1.2%) were in the 'others' group and 3 (0.3%) did not state their marital status. When the education level of the participants was evaluated, it was determined that two (0.2%) were illiterate, 7 (0.7%) were primary school graduates, 280 (29.4%) were high school graduates and 555 (58.4%) were university graduates. While 61% (n=578) of the participants stated that they did not smoke, 39% (n=370) were smokers. The average daily smoking load was determined as 10 cigarettes/day (1–40/day), while the mean duration of smoking was 12 years. When the distribution of tasks of the participants was assessed, the number of faculty members was 25 (2.6%), the number of research assistants was 99 (10.4%), the number of specialist doctors was 8 (0.8%), the total number of physicians was 132 (13.8%), the number of nurses was 286 (30.1%), the number of assistant health personnel was 120 (12.6%), the number of cleaning personnel was 142 (14.9%), the number of security personnel was 53 (5.6%), the number of administrative (office) personnel was 108 (11.4%), the number of the technical staff was 54 (5.7%) and the number of the kitchen staff was 52 (5.5%). The median of the total working time of the participants in the previous indoor working places and the hospital building was 6 (1–38) years. The employees were divided into three groups according to the duration of work: <5 years, 5–10 years and ≥10 years. The proportion of those working for ≤5 years was 38% (361), those working for 5–10 years was 26.3% (n=250) and those working ≥10 years was 35% (n=333). When the daily working hours in the closed environment were examined, the median working time was found to be 8 (1–40) hours, the proportion of those working ≤8 hours were 62% (n=590) and those working >8 hours were 37.5% (n=354). The relationship between the demographic data of the employees, working conditions and the presence of SBS is given in Table 1.

Furthermore, 186 individuals (19.5%) who participated in the questionnaire were found to have a chronic disease, and the most common chronic diseases were hypertension, thyroid dysfunction, and asthma. It was noted that 11.7% (n=112) of the participants were using a drug continuously. It was further observed that 14.7% (n=140) of the participants had a previous diagnosis of allergic rhinitis, 16.7% (n=159) had a diagnosis of

chronic pharyngitis and 3% (n=29) had a diagnosis of asthma. Besides, 18 (32.1%) of the 29 employees with a diagnosis of asthma stated that they were diagnosed with the disease before starting to work in this building, while only 11 (37.9%) were diagnosed after starting to work in the building. Moreover, 8 (27.6%) of the patients diagnosed with asthma stated that the severity of the condition increased in the hospital, and 13 (44.8%) stated that the severity did not change. At the time of the study, active tuberculosis was found in two people working in the chest diseases clinic.

Table 1. Relationship between employees' demographic data, working conditions and sick building syndrome

Features		SBS N(%)	p*
Gender	Female	334(56.5)	0.061
	Male	257(24)	
Marital status	Married	387(40.8)	0.737
	Single	196(20.7)	
Education Status	No	1(0.1)	0.024
	Primary education	62(6.5)	
	High school	178(18.7)	
	University	349(62.3)	
Job	Teaching asistant	15(1.6)	0.105
	Research assistant	65(6.8)	
	Specialist	5(0.5)	
	Nurse	174(18.3)	
	Technical personnel	37(3.9)	
	Assistant health personnel	83(8.7)	
	Cleaning staff	79(8.3)	
	Administrative staff	71(7.5)	
	Security	38(49)	
	Kitchen staff	24(2.5)	
Smoking	Yes	235(24.8)	0.493
	No	353(37.2)	
Stress	No	11(1.9)	< 0.0001
	Less	67(11.3)	
	Medium	211(35.7)	
	Much	156(26.4)	
	Too much	146(24.7)	
Use of computer	Yes	321(54.7)	0.293
	No	266(45.3)	
Noise level	No	49(8.3)	0.625
	Less	129(21.9)	
	Medium	286(48.6)	
	Much	125(21.2)	
Chronic illness	Yes	79(8.3)	0.293
	No	512(53.8)	
Drug use	Yes	56(5.9)	0.005
	No	534(56.3)	
Total working time	≤25	97(16.4)	0.896
	25-30	205(34.7)	
	≥ 31-40	202(34.2)	
	≥ 41	86(14.6)	
Daily working time	≤5 yıl	295(50.4)	0.286
	5-10 yıl	159(27.2)	
	≥10 yıl	131(22.4)	
	≤8 hour/day	369(62.8)	0.835

* Pearson chi-square and Fisher's exact chi-square ** p <0.05 value is statistically significant SBS: Sick Building Syndrome

Table 2. Workers' symptoms every week during their work in the hospital for the last 3 months

Symptoms	No N(%)	Rarely Once a week N(%)	Often At least 2-4 times a week N(%)	Continuous 5 times a week N(%)	Symptoms decrease or disappear away from work? No N(%)	Yes N(%)	Symptoms relieved on days away from work or on holidays No N(%)	Yes N(%)	%
Burning eyes	448(47.6)	238(25.3)	199(21.1)	56(6)	84(17.1)	408(82.9)	104(21.2)	385(78.6)	52.4
Watery eyes	500(53.2)	223(23.7)	170(18.1)	47(5)	84(19.5)	347(80.5)	102(23.8)	325(75.9)	46.8
Redness in the eyes	562(59.5)	177(18.7)	160(16.9)	46(4.9)	65(17.4)	309(82.6)	79(21.4)	290(78.6)	40.5
Dry throat	440(46.4)	210(22.1)	192(20.3)	106(11.2)	84(16.9)	412(82.9)	95(19.3)	397(80.7)	53.6
Cough	609(64.4)	181(19.1)	111(11.7)	45(4.8)	97(29.3)	234(70.7)	106(32.3)	222(67.7)	35.6
Wheezing	762(80.5)	111(11.7)	49(5.2)	25(2.6)	71(39.7)	108(60.3)	80(44.4)	100(55.6)	19.5
Sore throat-tenderness	599(63.3)	206(21.8)	103(10.9)	39(4)	115(34)	223(66)	125(37.1)	121(62.)	36.8
Cracked lips	527(55.6)	198(20.9)	146(15.4)	77(8.1)	140(34.1)	271(65.9)	154(37.7)	255(62.3)	44.4
Runny nose	606(63.9)	197(20.8)	105(11.1)	40(4.2)	161(48.2)	173(51.8)	17(52)	159(48)	36.1
Nose bleeding	878(92.7)	48(5.1)	16(1.7)	5(0.5)	30(42.9)	40(57.1)	30(42.9)	40(57.1)	7.3
Stuffy nose	562(59.5)	206(21.8)	120(12.7)	57(6)	99(26.6)	273(73.4)	109(29.4)	262(70.6)	40.6
Unpleasant smell sensation	594(62.7)	174(19.9)	119(13.6)	60(6.8)	49(14.2)	295(85.8)	63(18.5)	278(81.5)	37.2
Unpleasant taste sensation	599(63.3)	216(22.8)	92(9.7)	40(4.2)	158(46.9)	179(53.1)	169(50.6)	164(49.1)	36.8
Poor vision	704(74.4)	142(15)	69(7.3)	31(3.3)	108(46.8)	123(53.2)	112(48.9)	117(51.1)	25.6
Shortness of breath	757(79.9)	125(13.2)	45(4.8)	20(2.1)	65(35.5)	118(64.5)	111(50.2)	110(49.8)	20.1
Chest tightness	715(75.5)	173(18.3)	46(4.8)	13(1.4)	103(46.2)	120(53.8)	111(50.2)	110(49.8)	24.6
Flushes	675(71.3)	160(16.9)	82(8.7)	30(3.1)	94(35.9)	168(64.1)	105(40.2)	156(59.8)	28.7
Sleepiness	532(56.2)	228(24.1)	125(13.2)	61(6.5)	90(22.3)	313(77.7)	99(24.9)	299(75.1)	43.8
Fatigue-exhaustion	312(32.9)	219(23.1)	255(26.9)	163(17.1)	156(25)	468(75)	166(26.8)	453(73.2)	67.1
Stomachache	780(82.3)	111(11.7)	38(4)	19(2)	63(38.4)	101(61.6)	70(42.9)	93(57.1)	17.8
Nausea	757(79.9)	119(12.5)	47(5)	25(2.6)	75(40.3)	111(59.7)	82(44.3)	103(55.7)	20.1
Vomiting	889(93.8)	40(4.2)	8(0.8)	11(1.2)	21(34.4)	40(65.6)	25(41.7)	35(58.3)	6.2
Uneasiness	565(59.6)	209(22)	107(11.3)	67(7.1)	81(21.8)	290(78)	95(25.7)	274(74.3)	40.4
Headache	384(40.5)	298(31.4)	193(20.4)	73(7.7)	94(17)	458(83)	102(18.6)	446(81.4)	59.5
Dizziness	750(79.3)	118(12.5)	57(6)	21(2.2)	55(28.5)	138(71.5)	62(32)	132(68)	20.8
Muscle-Joint Pain	486(51.2)	202(21.3)	159(16.8)	102(10.7)	144(32.1)	305(67.9)	155(34.9)	289(65.1)	48.8
Dry skin	574(60.5)	135(14.3)	130(13.7)	109(11.5)	92(25.3)	272(74.7)	104(28.7)	258(71.3)	39.4
Skin rash	765(81)	94(9.9)	52(5.5)	34(3.6)	37(21)	139(79)	45(26.2)	127(73.8)	19.1
Itching	684(72.2)	140(14.7)	69(7.3)	55(5.8)	71(27.3)	189(72.7)	75(29.1)	183(70.9)	27.9

Table 3. Logistic regression analysis of factors affecting sick building syndrome

Features	B	Standard deviation	OR (95% CI)	p*
Chronic illness	-0.854	0.319	0.426 (0.228- 0.797)	0.008
Diagnosing by symptoms	-1.203	0.328	0.300 (0.158-0.571)	0.000
Working environment is too hot	-1.523	0.487	0.218 (0.084- 0.567)	0.002
Working environment is occasionally too bright	1.166	0.378	3.209 (1.529- 6.731)	0.002

* p<0.05 value is statistically significant OR: Odds ratio SBS: Sick Building Syndrome

In the study, 244 (25.7%) of the 951 people were excluded from the study in terms of SBS as they had at least one of the previous diagnoses of asthma, chronic pharyngitis and chronic rhinitis. The remaining 707 people with at least one symptom of each of the general, mucosal and skin symptoms were considered to have SBS. SBS was detected in 62.1% (n=591) of the participants who did not have any previous disease.

Workers symptoms

Employees' symptoms were questioned every week during their work in the hospital for the past 3 months, and 505 people answered this questionnaire. The most common SBS symptoms were fatigue-exhaustion (67.1%) and headache (59.5%) and the high rate of mucosal symptoms such as burning and stinging in the eyes (52.4%), dry throat (53.6%), cracked lips (44.4%) and nasal obstruction (40.6%). The numbers and percentages of the symptoms each week during the study are given in Table 2.

Environmental conditions

When the stress level in the working environment was evaluated, the number of participants who stated that there was no stress was 28 (3%), while 99 people (10.7%) rated it as low, 344 people (37.3%) rated it as moderate, 247 people (26%) rated it as high and 204 people (22%) rated it as too high. The rate of those working with computers was 510 (53.9%), and the rate of those who did not use a computer was 436 (46.1%). When the hours of computer use were examined, the average duration of computer use was found to be 4 hours (1–12 hours). When the noise level in the environment was evaluated, 75 people (7.9%) stated it as noiseless, 198 people (20.9%) found the working environment less noisy, 474 people (50.1%) found the environment to be moderately noisy and 200 people (21.1%) considered the environment too noisy.

As a result of the 36 evaluations, it was found that the limit value of CO_2 in 69.4% (n = 25) of the working environments was above the limit value of 700 ppm. When the limit value of CO was taken as 9 ppm, the limit value was not exceeded in any of the working environments. When the room temperature was checked, 77.7% of the values were not within the normal limits of 20–24ºC. Only the air conditioning room and kitchen storage had working environments <20ºC, and in 72.2% of the working environments, the ambient temperature was found to be >24ºC. In 22.2% of the evaluated working environments, the relative humidity level was within the normal limits. The relative humidity level in 77.8% of the working environments was below the limit value of 30%.

Relationship between SBS and parameters

The median peripheral blood oxygen saturation value of those with SBS was 97.2 (92–99), while the median saturation value of those without SBS was 97.3 (91–99). The relationship between peripheral blood oxygen values and SBS was not statistically significant (p=0.213). The relationship between having SBS and often considering the working environment to be too warm was found to be statistically significant (p=0.042). The relationship between the presence of SBS and evaluating the environment as dry, damp, dim, very cold and low air intake was not found to be statistically significant (p=0.422, 0.289, 0.223, 0.226, 0.223).

When assessing whether the participants had SBS using forward variable selection method and binary logistic regression analysis, the presence of chronic disease (OR=0.426; 95% CI, 0.228–0.797), the environment often being too warm (OR=0.218; 95% CI, 0.084–0.567) or occasionally very bright (OR=0.300; 95% CI, 0.158–0.571) and the fact that they diagnosed a doctor because of their symptoms (OR=3.209; 95% CI, 1.529–6.731) were found to be impressive factors. The fit of the logistic regression model was checked with the Hosmer–Lemeshow test (Table 3).

Discussion

Our study evaluated the prevalence of SBS symptoms among healthcare workers. Many studies have found that SBS symptoms are more common in women than in men [9-10]. And these studies revealed that women have more health-seeking behavior than men when it comes to perceiving and reporting health problems [9-12]. On the other hand, in a study conducted by Dhungana et al. in Nepal, no difference was found between the genders13. Although SBS was seen more frequently among women in our study, no statistically significant difference was found. The differences found might also be due to an actual gender difference in the physical work environment or the rate of male participants (54.2. %) was high.

Although the exact prevalence of SBS is not known owing to the lack of definitive diagnostic tests, it was found in a study conducted in Singapore in 1998 that 19.6% of the participants had SBS symptoms. In the study carried out in Ankara, Turkey, the rate of SBS was determined as 31.9%, it was determined that 60% of the symptoms occurred due to environmental factors in the workplace [2,14]. Furthermore, it was noted that 60% of the problems arising from air quality were related to ventilation, and in a meta-analysis, it was found that SBS symptoms were higher in buildings with artificial ventilation than in those with natural ventilation [15-7].Our study is more specific because it investigated the SBS rate in the hospital building, and the rate was found to be 62.1%. According to many investigations, the reason for the high rate may be that the ventilation is artificially made, the air conditioning system is old, the age of the building is >15 years, frequent renovations are made, and the fact that physical factors such as temperature, humidity and CO_2 ratios inside the building differ significantly from their normal values.

In many similar studies conducted in Egypt, Kenya and Singapore, the most common symptom was evaluated as fatigue [2,18,19]. We found that the most common SBS symptoms were fatigue-exhaustion (67.1%) and headache (59.5%) and were

evaluated in accordance with the literature.

The indirect indicator that indoor ventilation is sufficient is the CO_2 level. CO_2 does not directly cause symptoms, but it is considered as a parameter of insufficient ventilation 20. As a result of 36 evaluations made in our study, CO_2 levels in 69.4% of the working environments were found to be above the limit value. With the use of a CO_2 controlled ventilation system, lowering the elevated CO_2 level will increase the perceived air quality and reduce headache and fatigue symptoms. In a study conducted by Wargocki et al., it was shown that CO_2 is associated with reduced work performance and health effects in offices [21,22]. High CO_2 level is associated with high SBS symptoms and can be considered as an indicator of insufficient ventilation.

In a study of healthcare workers in Slovenia showed that the most frequent risk factors for SBS to be poor air quality, an inappropriate level of relative humidity, and inappropriate room temperature [23]. Additionally, when the ambient relative humidity and temperature are inappropriate, it increases the frequency of irritative symptoms of SBS such as dry eyes, skin and upper airway manifestations [11,14,24]. We found that the relative humidity level in 77.8% of the environments was below the limit value of 30%, and in 72.2% of the environments, it was found to be >24°C and occasionally very bright. In our study, the high rate of mucosal symptoms such as burning and stinging in the eyes (52.4%), dry throat (53.6%), cracked lips (44.4%) and nasal obstruction (40.6%) can be explained by the low humidity, high ambient temperature, and the bright environment.

Work stress is among the reasons that cause SBS. High job expectations, low job control and low support from colleagues exacerbate the symptoms [11,12]. In a study conducted in Vietnam, SBS symptoms were found to be higher in nurses, and in our study, when hospital workers were examined according to their duties, the stress levels of nurses were found to be higher than other occupational groups (62%). Moreover, the relationship between stress levels and SBS was found to be statistically significant, which is in line with the literature [25].

According to the WHO report published in 2009, 2.7% of the global disease burden occurs due to indoor air pollution and it is seen at a higher rate in infants, the elderly and those with chronic diseases [26]. In our study, it is significant that the affected individuals consult a doctor and get a diagnosis due to the presence of chronic diseases and symptoms, which is consistent with the literature.

The presence of atopy and asthma increases the incidence of SBS. More than 20% of asthma in adults is from exacerbated asthma at work [21,27]. In our study, 27.6% of the participants with asthma stated that their complaints were worsened during work in the hospital building. In addition, active tuberculosis was detected in two people working in the chest diseases clinic during the study period. Tuberculosis outbreaks have been reported in the literature, especially among healthcare workers [3]. When the

professional groups were evaluated according to the clinics they worked in, it was found that doctors, nurses and assistant staff working in chest clinics were 6.97, 7.86 and 7.70 times more at risk, respectively, when compared with their colleagues working in other clinics [28]. It is important that our study was performed before the pandemic because we think that COVID-19 would highly affect the SBS data.

Our study is an important investigation conducted with a high number of participants in Turkey. The work examined the frequency of SBS in healthcare workers and the factors affecting it and demonstrated the relationship between SBS and buildings without natural ventilation. The limitation of the research is that the causal relationship could not be fully established since it is a cross-sectional study, and environmental factors, such as noise and illumination, and stress level measurements were based on personal statements and could have caused bias, and it is a single-centred study, it could not be generalized.

Conclusion

SBS has emerged as an occupational disease with an increasing momentum among the office workers worldwide [14,29]. Depending on this situation, it causes a decrease in work performance and productivity and increases absenteeism [2,30]. This problem can be alleviated or eliminated by administrative and engineering practices and control at the source.

For this reason, studies involving the frequency of SBS among healthcare workers in Turkey, its relationship with environmental and personal factors and its effects on the respiratory system are very important. In our study, a relationship was found between SBS and physical factors such as temperature, humidity and CO_2 and personal factors such as stress and chronic disease. Therefore, there is a need for more studies in which environmental measurements are made and control studies are added after taking personal, administrative and engineering measures in areas where deficiencies are detected.

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ORIGINAL ARTICLE

Investigation of hemogram and biochemistry parameters in non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is primarily characterized by the buildup of triglycerides in the hepatocytes. The present study sought to compare the hemogram and biochemistry parameters of patients with different grades of hepatic steatosis (HS) detected in abdominal ultrasonography (USG) examinations with the healthy control group. Patients who sought treatment at the internal medicine outpatient clinic for various causes and underwent abdominal USG were included in the study. According to USG results, participants were subdivided into four groups based on their HS grade 0-1-2-3. The mean age and gender distributions of the groups were not statistically different (p=0.306 and p=0.457, respectively). There was no statistical difference between the groups in terms of smoking status (p=0.344). It was determined that the prevalence of obesity, DM and HT increased as the HS grade increased (p<0.001, p=0.015, p<0.001). Mean platelet volume (MPV), atherogenic index of plasma (AIP), and fasting triglyceride levels were significantly different between the groups (p=0.012, p=0.008, and p=0.003, accordingly). Uric acid, uric acid albumin ratio (UAR), and AIP values and HS grade were positively and significantly correlated (p=0.036 r=0.276, p=0.024 r=0.294, and p=0.013 r=0.308, accordingly). When we considered HS grade as the dependent variable, the UAR value predicted HS grade positively and significantly according to linear regression analysis (p=0.008, Beta=0.387). According to the ROC curve analysis, UAR was found to be the most significant in the diagnosis of NAFLD (sensitivity 67%, specificity 64%, cut-off value:1.05). From a practical point of view, healthcare professionals need to be alerted that patients with co-existing hyperuricemia and elevated AIP are at greater risk of progressing to hepatic steatosis and, as a result, cardiovascular diseases. Additionally, our study confirms the need for more extensive longitudinal studies to understand the processes contributing to the relationship between UAR, AIP, and NAFLD. UAR value can be used as an easily accessible marker that can be used to show fatty liver. Future studies can examine the influence of reducing uric acid levels on the fatty liver.

Keywords: Non-alcoholic fatty liver disease, hepatic steatosis, uric acid, albumin, atherogenic index of plasma

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a health issue that has increased in importance and frequency with increased living standards in recent years. NAFLD is primarily characterized by the buildup of triglycerides in the hepatocytes. Although fatty liver usually follows a mild course, it can sometimes progress and lead to fibrosis and cirrhosis of the liver. While the pathological appearance is strikingly similar to liver damage caused by alcohol consumption, patients with NAFLD do not have heavy

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alcohol consumption [1].

The true prevalence of NAFLD is unknown, but it is thought to be the most prevalent liver disease in both industrialized and developing nations. Its incidence in various societies in the world varies between 10–24%. NAFLD is a condition characterized by a low-grade inflammatory reaction in the fatty tissue of the liver parenchyma, together with pathological fat accumulation and insulin resistance. Therefore, insulin resistance is closely related to oxidative stress and endothelial dysfunction markers [2].

It is thought that phosphorylation of fructose used as a sweetener by fructokinase induces triglyceride synthesis by triggering purine degradation and, in this way, causes the development of NAFLD. The entry of AMP, produced through the activation of AMP deaminase, into the purine degradation pathway leads to the formation of uric acid mitochondrial oxidants. These oxidants disrupt the Krebs cycle and lead to citrate accumulation and fatty acid synthesis by activating the ATP citrate lyase enzyme [3].

The present study sought to compare the hemogram and biochemistry parameters of patients with different grades of hepatic steatosis (HS) detected in abdominal ultrasonography (USG) examinations with the healthy control group.

Materials and Methods

Study Design

The present study is a retrospective study. In this study, participants applied to the hospital between 01.03.2022 and 01.09.2022. The method of this study was confirmed by the university's ethics committee (IRB Number:2022/7-47). The study was undertaken in accordance with the Declaration of Helsinki. Patients who sought treatment at the internal medicine outpatient clinic for various causes and underwent abdominal USG were included in the study. The control group was comprised of people who had abdominal USG for abdominal pain, weight loss, anorexia, and indigestion but without hepatosteatosis or any pathology. Those with regular alcohol consumption were not included in the study. According to abdominal USG results, participants were subdivided into four groups based on their HS grade 0-1-2-3. The body-mass index (BMI) of the participants was calculated by dividing their weight by the square of their height (kg/m²). The smoking status of the participants, comorbid diseases such as obesity, diabetes mellitus (DM) and hypertension (HT) were recorded. Groups were selected similar in age and gender. Care was taken to ensure that the number of patients in the groups was close to each other.

Laboratory Examination

Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), monocyte lymphocyte ratio (MLR), uric acid albumin ratio (UAR), monocyte high-density lipoprotein cholesterol (HDL-C) ratio (MHR), atherogenic index of plasma (AIP) were analyzed. AIP was calculated by taking the logarithm of the triglyceride ratio to HDL-C [4].

Ultrasonographic Examination

Radiologist with 5-year experience performed abdominal USG. According to the literature, normal liver echo on USG is considered HS grade 0. A diffuse and mild increase in liver parenchyma echo on USG is referred to as HS grade 1. HS grade 2 is defined as the inability to see the portal vein and diaphragm margins clearly as well as a moderate increase in liver parenchyma echo in USG. In USG, HS grade 3 is defined as only limited or no detection of the portal vein, diaphragm, and the posterior side of the right lobe of the liver and the presence of liver parenchyma as fine echoes [5].

Statistical Analysis

All analyzes were conducted using SPSS Mac Version 26.0. Categorical data were shown as numbers and percentages, and continuous data were reported as mean ± standard deviation or median (minimum: maximum). The normality of continuous data was verified with the Kolmogorov-Smirnov test. A one-way ANOVA test was employed for multiple comparisons of normally distributed data, and a student-t-test was used for pairwise comparisons. The Tukey test was used for post hoc analysis in a one-way ANOVA. The Kruskal-Wallis test was employed for multiple comparisons of non-normally distributed data, and the Mann-Whitney U test was applied for pairwise comparisons. Receiver operating characteristic (ROC) analysis was used for determination of sensitivity and specificity of lab parameters on diagnosing NAFLD. p<0.05 was evaluated as statistically significant.

Results

Mean age and gender distribution of the groups: HS grade 0 (42.45±7.95) (F:12, M:8), grade 1 (44.80±8.30) (F:10, M:10), grade 2 (47.35±5.74) (F:14, M:6), and grade 3 (43.86±10.54) (F:10, M:10). The mean age and gender distributions of the groups were not significantly different (p=0.306 and p=0.457, respectively). There was a significant difference between the groups in terms of BMI (p=0.022). There was no statistical difference between the groups in terms of smoking status (p=0.344). It was determined that the prevalence of obesity, DM and HT increased as the HS grade increased (p<0.001, p=0.015, p<0.001). According to the Kruskal Wallis test, MPV, AIP, and fasting triglyceride levels were significantly different between the groups (p=0.012, p=0.008, and p=0.003, respectively). NLR, PLR, MLR, AIP, and UAR did not differ between the groups (p=0.515, p=0.372, p=0.287, p=0.990, p=0.116). According to Pearson correlation analysis, uric acid, UAR, and AIP values and HS grade were positively and significantly correlated (p=0.036 r=0.276, p=0.024 r=0.294, and p=0.013 r=0.308, accordingly). When we considered HS grade as the dependent variable, the UAR value predicted HS grade positively and significantly according to linear regression analysis (p=0.008, Beta=0.387). According to the ROC curve analysis, UAR was found to be the most significant in the diagnosis of NAFLD (sensitivity 67%, specificity 64%, cut-off value:1.05).

Table 1. Comparison of Sociodemographic Features and Electrocardiographic Parameters of Patients with Hepatic Steatosis and Healthy Controls

	HC (n=20) M±SD or n (%)	HS G1 (n=20) M±SD or n (%)	HS G2 (n=20) M±SD or n (%)	HS G3 (n=21) M±SD or n (%)	P
Age	42.45±7.97	44.80±8.30	47.35±5.74	43.86±10.54	0.306[1]
Gender					0.457[2]
Female	12 (60)	10 (50)	14 (70)	10 (47.6)	
Male	8 (40)	10 (50)	6 (30)	11 (52.4)	
BMI (kg/m²)	26.24±4.66[a]	28.7±5.62[b]	29.8±5.44[b]	33.95±6.2[c]	0.022[1]
Smoking	6 (30)	7 (35)	5 (20)	6 (28.6)	0.344[2]
Obesity	1 (5)	3 (15)	7 (35)	12 (57)	<0.001[2]
DM	1 (5)	2 (10)	3 (15)	6 (28.6)	0.015[2]
HT	1 (5)	2 (10)	6 (30)	10 (47.7)	<0.001[2]

HC, healthy controls; HS, hepatic steatosis; G, grade; BMI, body-mass index; DM, diabetes mellitus; HT, hypertension [1]One-way ANOVA test was used. [2]Chi-square test was used. p<0.05 was accepted as statistically significant

Table 2. Comparison of Laboratory and Inflamatory Parameters of Patients with Hepatic Steatosis and Healthy Controls

	HC (n=20) M±SD or n (%)	HS G1 (n=20) M±SD or n (%)	HS G2 (n=20) M±SD or n (%)	HS G3 (n=21) M±SD or n (%)	P
Albumin, mg/dl	4.10 (2.60:4.90)	4.10 (3.40:4.50)	4.10 (3.70:4.70)	4.10 (3.50:4.60)	0.858[2]
Uric acid, mg/dl	4.09±1.33	4.44±0.89	4.71±1.24	5.30±1.05	0.054[1]
Glucose, mg/dl	97 (74:169)	98 (78:205)	106 (71:204)	107 (84:246)	0.125[2]
Neutrophil, 10⁶/µL	5.07±1.32	4.43±1.47	4.27±1.49	4.87±2.66	0.496[1]
Lymphocyte, 10³/µL	2.38±0.59	2.17±0.55	2.55±0.60	2.66±0.78	0.093[1]
Platelet, 10³/µL	259.42±82.37	256.90±63.35	270.30±64.62	258.33±64.22	0.924[1]
Monocyte, 10³/µL	0.57 (0.30:1.13)	0.52 (0.36:0.96)	0.51 (0.27:1.20)	0.56 (0.30:1.04)	0.571[2]
MPV, fL	8.26[a] (6.34:10.40)	8.92[b] (7.41:11.60)	8.51[a,b] (7.74:12.20)	8.26a (7.07:10.30)	0.012[2]
Fasting Triglyceride, mg/dL	94[a] (30:321)	149b,c (81:632)	132[b] (70:335)	178[c] (89:293)	0.003[2]
Total-C, mg/dL	173 (122:336)	182 (138:225)	197.5 (143:265)	178 (127:253)	0.100[2]
LDL-C, mg/dL	100.69±39.68	108.56±22.49	123.61±34.70	98.82±32.08	0.117[1]
HDL-C, mg/dL	47 (28:99)	43 (26:59)	41.5 (30:61)	43 (35:59)	0.737[2]
NLR	2.24±0.77	2.07±0.63	1.86±1.20	1.88±0.93	0.515[1]
PLR	115.35±53.54	123.35±39.59	109.76±26.94	102.14±33.46	0.372[1]
MLR	0.25 (0.15:0.51)	0.25 (0.15:0.36)	0.19 (0.10:0.44)	0.19 (0.10:0.48)	0.287[2]
MHR	0.01 (0.01:0.02)	0.01 (0.01:0.03)	0.01 (0.01:0.03)	0.01 (0.01:0.02)	0.990[2]
AIP	0.26±0.35[a]	0.59±0.30[b]	0.49±0.24[a,b]	0.60±0.19[b]	0.005[1]
UAR	1.04±0.40	1.10±0.23	1.13±0.31	1.32±0.26	0.116[1]

HC, healthy controls; HS, hepatic steatosis; G, grade; MPV, mean platelet volume; Total-C, total cholesterol; LDL-C, low-density cholesterol; HDL-C, high-density cholesterol; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; MLR, monocyte lymphocyte ratio; MHR, monocyte HDL-C ratio; AIP, atherogenic index of plasma; UAR, uric acid albumin ratio. [1]One-way ANOVA test was used. [2]Kruskall-Wallis test was used. Student's t test was used for pairwise comparisons in normally distributed data, and Mann-Whitney U test was used in non-normally distributed data. p <0.05 was accepted as statistically significant.

Table 3. Correlation Analyzes of Hepatic Steatosis Grade with Laboratory Parameters

	Hepatic Steatosis Grade
Albumin	r=0.82
	p=0.476
Uric acid	r=.276
	p=0.036
UAR	r=0.294
	p=0.024
AIP	r=0.308
	p=0.013
Fasting Triglyceride	r=0.185
	p=0.141
MPV	r=-0.027
	p=0.813

UAR, uric acid albumin ratio; AIP, atherogenic index of plasma; MPV, mean platelet volume. Pearson corelation analyzes was used. $p<0.05$ was accepted as statically significance

Table 4. Linear Regression Analyzes of Hepatic Steatosis Grade

	B	Std. Error	Beta	t	P	95 % CI Lower	Upper
Constant	0.896	1.211		0.740	0.463	-1.536	3.327
AIP	0.170	0.562	0.046	0.302	0.764	-0.959	1.298
UAR	0.387	0.478	0.376	2.624	0.008	0.294	2.213
MPV	0.027	0.125	0.031	0.219	0.828	-0.223	0.278

AIP, atherogenic index of plasma; UAR, uric acid albumin ratio; MPV, mean platelet volume. Linear regression analyses was used. $p<0.05$ was accepted as statically significance. ($F_{(3,50)}=6.133$, Adjusted $R^2=.432$ and $p<0.001$)
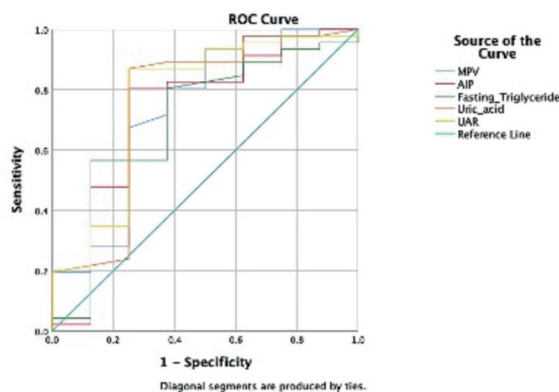
Figure 1. alt bilgi yazınız

Table 5. ROC Curve Analyzes of Lab Parameters

Variable	Area	p
MPV	0.736	0.034
AIP	0.731	0.038
Fasting Triglyceride	0.701	0.072
Uric Acid	0.755	0.022
UAR	0.768	0.016

Discussion

Serum albumin is the most prominent and abundant protein in the blood and plays a number of essential metabolic roles. The elevated inflammatory process is accompanied by decreased production and increased degradation of serum albumin. Low serum albumin levels may boost blood viscosity and lead to endothelial dysfunction [6]. Moreover, serum albumin is an essential inhibitor of platelet activity and aggregation and an effective modulator of platelet-driven coronary stenosis [7].

Uric acid is produced during purine metabolism, and its high levels increase the risk of atherosclerosis and determine the prognosis of coronary artery disease. Uric acid is one of the mediators of vascular disease, endothelial dysfunction, and inflammation. It has been shown that hyperuricemia is associated with coronary atherosclerosis with a high plaque-loaded risk [8]. Epidemiological evidence has shown that hyperuricemia and cardiovascular diseases are associated. It has been established that increased uric acid levels are an independent predictor of cardiovascular disease and cardiovascular mortality. However, the causal mechanisms linking high uric acid levels to cardiovascular disease are still unclear. Uric acid tends to crystallize and generate monosodium urate crystals in several tissues and initiates regional immune activity. The atherosclerotic plaque comprises substantial concentrations of uric acid, and elevated levels of uric

acid promote thrombus formation. In addition, uric acid can lead to oxidative stress and cause inflammation, vasoconstriction, and endothelial dysfunction [9].

A number of investigations have concluded that low serum albumin levels are connected to the existence of coronary artery disease and an elevated risk of overall mortality. There is also considerable proof that low serum albumin concentrations can lead to the formation and worsening of atherosclerosis. In coronary artery disease, hypoalbuminemia plays a part in the pathogenesis by resulting in a decrease in anti-inflammatory, antioxidant, and anti-thrombotic activities [10].

However, uric acid and serum albumin could not be included in any risk profile. First, uric acid levels are affected by renal excretion, consumption of various nutrients, and uric acid cell metabolism. In addition, abnormally high uric acid levels are usually related to gout, insulin resistance, diabetes, metabolic syndrome, hypertension, and chronic kidney disease. Serum albumin synthesis is promoted by: amino acid uptake, insulin, and low colloid osmotic pressure. The components that reduce albumin production are increased colloid osmotic pressure, inflammation, nutritional deficiency, diabetes, liver disease, and infections [11].

NAFLD has emerged as the foremost liver disease globally, caused by lipid metabolism disorders and insulin resistance. AIP, an estimated lipid measurement, is a new indicator for insulin resistance [12]. However, the association between plasma atherogenic index and NAFLD was uncertain, and scientific literature examining the relationship between AIP and NAFLD were scarce. The first study about this matter investigated the relationship between AIP and NAFLD in 538 obese participants. They showed that the risk of NAFLD increased 4.37 times in the high plasma atherogenic index group [13]. In 2014, Akbaş et al. found AIP to be higher in those with high uric acid levels, and they found that AIP is an independent predictor of hyperuricemia in diabetic patients [14]. Xie et al. investigated the association between AIP and NAFLD and showed that the risk of NAFLD increased as AIP increased, especially in women and young people [15]. In 2020, Dong et al. investigated the diagnostic value of AIP in demonstrating NAFLD in normal weight people and confirmed that AIP is a distinct risk marker in demonstrating NAFLD [16].

Many researchers have reported that elevated serum uric acid concentration is potential risk factor for cardiovascular diseases. The significant relationship between serum uric acid and dyslipidemia as aspects of metabolic syndrome has been examined in various studies. Many reasons have been suggested to elucidate the relation between hyperuricemia and cardiovascular disease risk factors. Reduced renal clearance of uric acid or higher proximal tubular reabsorption resulting from insulin resistance, elevated leptin concentrations, and excessive fructose intake commonly connected with obesity have been suggested to be potential reasons for this heightened cardiovascular disease risk [17].

It has been reported in the literature that HDL-C is decreased in the population with high uric acid. Some studies have suggested that hypertriglyceridemia reduces the renal excretion of uric acid. In addition, the heritability of high uric acid and atherosclerosis in twins supports that the underlying pathogenic mechanisms are related [18]. Previous studies have shown that uric acid induces lipid synthesis in hepatocytes. It is emphasized that uric acid may predict the risk of hypertension, type 2 diabetes mellitus, and cardiovascular disease [19].

The present study has a number of limitations. Firstly, this study is inconclusive due to its retrospective methodology. The retrospective data acquisition process may miss certain variables. Second, because it covers only one hospital, it may not reflect the entire population. Lastly, our study's retrospective design prevents us from detecting causality.

Conclusions

From a practical point of view, health care professionals need to be alert that patients with co-existing hyperuricemia and elevated AIP are at elevated risk of progressing to hepatic steatosis and, as a result, cardiovascular diseases. Additionally, our study confirms the need for more extensive longitudinal studies to understand the processes contributing to the relationship between UAR, AIP, and NAFLD. UAR value can be used as an easily accessible marker that can be used to show fatty liver. In future studies, the influence of reducing uric acid levels on the fatty liver can be examined.

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ORIGINAL ARTICLE

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The relationship between mental well-being and healthy lifestyle behaviors of seasonal agricultural worker women

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Abstract

The study was conducted to examine the relationship between the mental well-being of Seasonal Agricultural Worker (SAW) women and their Healthy Lifestyle Behaviors (HLBs). The study utilizes the descriptive research design. The study was conducted between November 2020 and December 2020 in Turkey, in a Family Health Center-supervised region, where SAW women were concentrated. The sample includes 355 women. The Personal Information Form, Warwick–Edinburgh Mental Well-Being Scale (WEMWBS), and Healthy Lifestyle Behaviors Scale II (HLBS II) were used to collect data. Descriptive statistics (number, percentage, mean), independent samples t-test, Mann Whitney U test, one-way analysis of variance, Kruskal Wallis analysis, Pearson Correlation Test, and Simple Linear Regression Analysis were also used in the analyses of the data. There was a positive, strong, and significant correlation between mental well-being and HLBs of SAW women. There was a significant difference between the WEMWBS total mean scores of SAW women according to their economic status and family type. There was a significant difference between the total mean score of the HLBS II according to income level and family type of SAW women (p<0.05). As a result, it has been determined that there is a relationship between the HLBs of SAW women and their mental well-being. It may be recommended to organize training programs and provide mobile health services to enhance HLBs and increase the mental well-being levels of SAW women.

Introduction

Seasonal agricultural workers (SAWs), an integral part of agricultural production, constitute 450 million of the 1.1 billion agricultural workforces worldwide [1]. Nevertheless, SAWs cannot take advantage of various opportunities, including housing, health, and education available throughout the world [2]. They experience setbacks in accessing healthcare services due to the challenges posed by the working conditions. Therefore, their mental well-being and healthy lifestyle behaviors (HLBs) can be adversely affected.

According to the World Health Organization (2004), mental health is "a state of well-being in which the individual realizes his or her abilities, can cope with the normal stresses of life, can work productively and fruitfully, and can make a contribution to his or her community" [3]. In the literature, it has been reported that individuals with high levels of mental well-being have better

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psychological and physical health and higher quality of life [4, 5]. It has also been suggested that such individuals are more creative, have better relationships, is more productive in their working environment, and live longer [6]. Therefore, mental well-being is an important factor at the individual, environmental, and social levels [7,8]. Furthermore, SAW, defined as the heart of sustainable agricultural production, is an important target group concerned with acquiring HLBs [9]. SAW women not only work in the agricultural fields but also fulfill their responsibilities as mothers and wives. They may experience problems in adopting HLBs due to the burden of their responsibilities. In addition, the psychological and physical health of SAW women is adversely affected by the current COVID-19 pandemic combined with their difficult working conditions and responsibilities.

Xu et al. presented a significant relationship between mental well-being with psychological symptoms and depression [10]. However, the authors could not find relevant studies investigating the relationship between mental well-being and HLBs of SAW women. Therefore, in the present study, we aimed to investigate the relationship between the mental well-being and HLBs of SAW women.

Materials and Methods

Permissions required for conducting the study were obtained from the Clinical Research Ethics Committee of Harran University (dated 27.01.2020, session numbered 02, and decision numbered 02,27), the relevant institution, and the individuals who participated in the study.

Procedure

The study utilizes the descriptive research design. It was conducted between November 2020 and December 2020 in Turkey, in a Family Health Center-supervised region, where SAW women were concentrated. The study population included 4.623 women over the age of 18 years, living in a Family Health Center supervised region in Turkey. The convenience sampling method was used to collect data from the determined population. The sample included 355 women. SAW women were visited in their houses. Data from the study was collected by the researchers through face-to-face interviews under necessary precautions regarding the pandemic (mask, distance, and hygiene).

The Personal Information Form, Warwick–Edinburgh mental well-being scale (WEMWBS), and Healthy Lifestyle Behaviors Scale II (HLBS II) were used to collect data.

Personal Information Form: The form consists of 14 questions on sociodemographic characteristics and seasonal agricultural work [9,10].

Warwick–Edinburgh Mental Well-Being Scale (WEMWBS): The scale was developed by Tennant et al., to measure the mental well-being of individuals living in the United Kingdom [7]. The validity and reliability study of WEMWBS in Turkey was performed by Keldal [8]. The WEMWBS includes 14 items

and addresses individuals' positive mental health, including psychological and subjective well-being. The scale is in the form of a 5-point Likert-type. A minimum of 14 and a maximum of 70 points can be taken from the scale. The scores associated with available responses are as follows: 1 =strongly disagree, 2= disagree, 3 =somewhat agree, 4 =agree, and 5 =completely agree. All the items included in the scale were positive. Reliability studies of the scale were performed with individuals aged 16 or more years. Accordingly, Cronbach's Alpha coefficient of the scale was 0.89. The test-retest reliability of the scale was performed on 124 individuals. The correlation coefficient was 0.83 as the tests were applied at a one-week time interval [8]. In the present study, Cronbach's alpha coefficient of the scale was 0.88.

Healthy Lifestyle Behaviors Scale II (HLBS II): The scale was developed by Walker et al. in 1987 and amended in 1996 [11]. Turkish validity and reliability study was conducted by Bahar et al. [12]. The scale, which is comprised of a total of 52 items and 6 subscales, investigates the HLBs of individuals. The subscales can be listed as nutrition (6 items), health responsibility (10 items), physical activity (5 items), interpersonal relationships (7 items), spiritual development (13 items), and stress management (7 items). All the items included in the scale are positive. The total score from the scale was referred to as the HLBs score. The available responses and associated points in the 4-point Likert-type scale are as follows: 1 =never, 2= sometimes, 3 =often, and 4 = regularly. The minimum and maximum scores are 52 and 208, respectively. Cronbach's alpha value was calculated as 0.94 [12]. In the present study, Cronbach's alpha coefficient of the scale was 0.91.

The Statistical Package for the Social Sciences software was used in the analysis of the data. Descriptive statistics (number, percentage, mean), independent samples t-test, Mann Whitney U test, one-way analysis of variance, Kruskal Wallis Analysis, Pearson Correlation test and Simple Linear Regression Analysis were also used in the analyses of the data. The Normality hypothesis was analyzed by the Kolmogorov–Smirnov test. The p-value of <0.05 was considered significant for the analyses.

Results

Among SAW women participating in the present study, 27.9% of them were illiterate, 72.9% of them were married, 58.4% of them had moderate economic levels, 56.3% of them had nuclear families, 69.7% of them had children, 64.9% of them worked as SAWs for ≥6 years, and the mean age was 33.13±11.95. 89% of women did not engage in regular exercises, 24.7% of them smoked, 61.4% of them had moderate perceptions towards their health, 56.8% of them reported that they could access health services during work, and 45.3% of them did not have any health insurance (Table 1). There was a positive, strong, and significant correlation between mental well-being and HLBs of SAW women (Table 2). There was a significant difference between the WEMWBS total mean score of SAW women according to their

economic levels and family types (p<0.05) (Table 3). There was a significant difference between the mean scores of the HLBS II according to income levels and family types of SAW women (p<0.05) (Table 4). According to the results of the posthoc Tukey test, the presence of low-income levels and nuclear families accounted for the significant differences among SAW women. To identify the effects of the mental well-being of the participants on

their HLBs, a simple linear regression analysis was conducted, and it was found that the regression model was statistically significant (F: 368.752, p: 0.000). The R^2 value representing the proportion of the variance for the predicted variable explained by the predictor variable in the regression model was calculated as 0.498. In this regard, mental well-being explained 49% of the total variance in the HLBs (R2: 0.498) (Table 5).

Table 1. The distribution of descriptive characteristics of seasonal agricultural worker (SAW) women

Characteristics		n	%
Education Status	Illiterate	104	27.9
	literate	85	22.8
	Primary School	59	15.8
	Middle School	56	15.0
	High School and Above	69	18.5
Marital Status	Married	272	72.9
	Single	101	27.1
Economic Status	Good	30	8.0
	Middle	218	58.4
	Bad	125	33.5
Health Insurance	Yes	204	54.7
	No	169	45.3
Family Type	Nuclear family	210	56.3
	Extended family	150	40.2
	Broken family	13	3.5
Having a Child	Yes	260	69.7
	No	113	30.3
Worked as a Seasonal Agricultural Worker	1-3 year	59	15.8
	4-6 year	72	19.3
	6 years and older	242	64.9
Exercising Regularly	Yes	41	11.0
	No	332	89.0
Smoking	Yes	92	24.7
	No	281	75.3
Perception of Health	Good	100	26.8
	Middle	229	61.4
	Bad	44	11.8
Access to Health Care	Yes	212	56.8
	No	161	43.2
Age	Min-Max	Mean	SD
	11-69	33.13	11.95

Table 2. The correlation between the seasonal agricultural worker (SAW) women's healthy lifestyle behaviors and the mean scores from the mental well-being scale

	Healthy Lifestyle Behaviors Scale	Mental Well-Being Scale
Min-Max	70.00-164.00	22.00-70.00
Mean-SD	117.87 ± 18.06	49.52 ± 9.67
r	0.706	
P	0.000	

Table 3. The comparison of mental well-being status of seasonal agricultural worker (SAW) women by socio-demographical characteristics

Socio-Demographical Characteristics		Mental Well-Being Scale				
		n	Mean	SD	Test	p
Education Status	Illiterate	104	48.68	9.96		
	literate	85	50.40	8.12		
	Primary School	59	49.30	9.30	F=0.397	0.811
	Middle School	56	49.87	11.21		
	High School and Above	69	49.63	10.10		
Marital Status	Married	272	50.09	9.22		
	Single	101	48.00	10.68	t=1.866	0.063
Economic Status	Good	30	54.03	7.28		
	Middle	218	51.37	9.00	F=21.722	0.001
	Bad	125	45.23	9.83		
Family Type	Nuclear family	210	50.82	9.24		
	Extended family	150	48.07	9.89	F=4.935	0.008
	Broken family	13	45.30	11.01		
Having a Child	Yes	260	50.00	9.43		
	No	113	48.42	10.16	t=1.455	0.147
Worked as a Seasonal Agricultural Worker	1-3 year	59	50.47	9.85		
	4-6 year	72	50.87	9.63	F=1.500	0.224

Table 4. The comparison of healthy lifestyle behaviors by socio-demographical features of seasonal agricultural worker women

Socio-Demographical Characteristics		n	Health Responsibility		Nutrition		Spiritual Development		Interpersonal relationships		Stress Management		Physical Activity		Total Point	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Education Status	Illiterate	104	18.91	4.51	22.27	4.39	23.54	5.19	25.47	5.16	16.47	3.51	9.74	2.44	116.42	18.06
	literate	85	19.88	4.51	22.14	3.39	23.77	4.45	26.10	4.32	16.71	3.61	9.67	2.48	118.29	15.43
	Primary School	59	19.33	4.52	21.22	4.67	23.10	5.27	24.27	5.28	16.03	3.42	11.45	4.24	116.37	18.20
	Middle School	56	19.62	4.94	20.82	4.76	24.69	5.95	25.73	4.92	17.01	3.35	11.33	3.79	118.23	18.27
	High School and Above	69	20.13	4.73	19.88	4.72	24.21	5.71	24.84	5.84	17.53	3.74	13.21	4.10	120.56	20.74
Statistical Variable			p=0.460 F=0.907		p=0.003 F=4.032		p=0.507 F=0.829		p=0.237 F=1.388		p=0.151 F=1.692		p=0.001 KW=48.870		p=0.615 F=0.667	
Marital Status	Married	272	19.84	4.70	22.11	4.22	23.92	5.05	25.76	4.99	16.69	3.51	10.50	3.35	118.63	17.83
	Single	101	18.70	4.29	19.53	4.43	23.56	5.81	24.23	5.29	16.84	3.69	11.89	3.99	115.83	18.59
Statistical Value			p=0.034 t=2.125		p=0.001 t=5.178		p=0.560 t=0.584		p=0.010 t=2.574		p=0.731 t=0.345		p=0.001 Z=-3.553		p=0.182 t=1.336	
Economic Status	Good	30	20.43	4.57	23.06	3.83	25.30	4.06	27.00	4.04	16.90	3.55	11.56	4.46	124.26	17.22
	Middle	218	20.23	4.72	21.79	4.48	24.33	5.31	25.94	5.30	17.17	3.42	11.00	3.63	120.49	18.35
	Bad	125	18.08	4.10	20.36	4.24	22.57	5.23	23.92	4.70	15.93	3.68	10.50	3.25	111.79	16.14
Statistical Value			p=0.001 F=9.646		p=0.001 F=6.650		p=0.003 F=5.883		p=0.001 F=8.195		p=0.008 F=4.948		p=0.308 KW=2.355		p=0.001 F=11.914	
Family Type	Nuclear family	210	20.15	4.79	21.97	4.24	24.68	5.20	26.29	5.14	17.30	3.66	10.89	3.79	121.04	18.52
	Extended family	150	19.10	4.07	20.91	4.50	22.88	4.97	24.34	4.72	16.12	3.29	10.98	3.37	114.36	16.80
	Broken family	13	14.38	4.11	18.23	4.67	20.76	6.80	21.61	5.59	14.69	3.01	9.38	1.66	107.30	13.28
Statistical Value			p=0.001 F=11.200		p=0.002 F=6.180		p=0.001 F=7.637		p=0.001 F=10.430		p=0.001 F=7.314		p=0.264 KW=2.665		p=0.001 F=8.647	
Having a Child	Yes	260	19.70	4.67	22.16	4.26	23.92	5.08	25.71	4.89	16.65	3.50	10.43	3.27	118.37	18.01
	No	113	19.15	4.49	19.70	4.32	23.59	5.67	24.50	5.52	16.92	3.68	11.91	4.04	116.73	18.18
Statistical Value			p=0.292 t=1.055		p=0.001 t=5.080		p=0.574 t=0.562		p=0.036 t=2.110		p=0.513 t=0.655		p=0.001 Z=-3.709		p=0.420 t=0.807	
Worked as a Seasonal Agricultural Worker	1-3 Year	59	20.93	6.03	21.22	4.83	24.69	5.26	25.28	5.83	16.86	3.46	12.18	4.24	121.18	23.29
	4-6 year	72	20.38	4.29	21.01	4.29	24.37	5.22	26.73	5.38	17.13	3.61	11.19	3.93	120.77	16.51
	6 years and Above	242	18.93	4.20	21.58	4.37	23.45	5.26	24.95	4.78	16.58	3.56	10.46	3.21	116.21	16.87
Statistical Value			p=0.002 F=6.106		p=0.587 F=0.533		p=0.164 F=1.818		p=0.034 F=3.427		p=0.492 F=0.712		p=0.006 KW=10.369		p=0.052 F=2.980	

Table 4. The results of the regression analysis conducted to find out the effect of seasonal agricultural worker women's Mental Well-Being on their Healthy Lifestyle Behaviors perceptions.

Predictor variable		B	Std. Dev.	ß	t	p	R	R²	F	Model p
Healthy Lifestyle Behaviors	Constant	52.580	3.465		15.176	0.000	0.706	0.498	368.752	0.000
	Mental Well-Being	1.313	0.069	0.706	19.203	0.000				

Discussion

The present study aims to investigate the relationship between mental well-being and HLBs of SAW women in a province located in southeastern Turkey. To the best of our knowledge, this is the first study to investigate the relationship between mental well-being and HLBs of SAW women. Therefore, the results of the study are discussed considering previous studies with different samples.

In the present study, a positive correlation is determined between HLBs and the mental well-being of SAW women. Mental well-being explains 49% of the total variance in HLBs, and it provides benefits to both physical [13] and mental health [14, 15]. Furthermore, other studies in the literature have suggested that individuals are required to maintain HLBs, and HLBs preserve and improve the well-being of individuals [16,17]. Similarly, other studies have reported that healthy lifestyle interventions positively influence mental well-being [18,19]. A study on adolescents has suggested that HLBs are associated with improved mental health outcomes [20]. Studies on individuals with heart failure and coronary artery disease have found that there is a relationship between feelings of hopelessness [21] and unhappiness [22] and HLBs. A study on university employees has presented that individuals with an active lifestyle sustain higher levels of mental well-being [23]. Another study on university employees has found that physical activity is associated with mental well-being [24]. Therefore, the results of the present study are consistent with the literature.

The current study has demonstrated that the WEMWBS total mean score of SAW women with good income levels is higher than those with moderate or low levels of income. In addition, there is a statistically significant difference between the WEMWBS total mean scores of SAW women according to their levels of income. Similar to the results of this study, a study conducted with nurses has found that the WEMWBS total mean scores of the nurses with good income levels are higher than those with moderate or low levels of income [25]. Similarly, in a study conducted in the United Kingdom, it has been found that there is a statistically significant difference between the income levels of the general population and the total mean scores from the WEMWBS [26]. In a study conducted with caregivers, it has been presented that the mental well-being of individuals who stated that their income levels are moderate, unlike this study, is better [27]. SAW women work both in the agricultural field and at home/tent. However, they are not paid for their labor; rather, they are merely considered a labor force. There is no gain in economic terms; therefore, the health status of those women can be negatively affected. Hence, the results have shown that the WEMWBS total mean score of SAW women with better economic levels is higher than that of women with moderate or low economic status.

Additionally, the WEMWBS total mean score of SAW women with nuclear families is higher compared to women with extended families because the likelihood of support for each member of the family also increases in nuclear families. In the literature, it has been reported that adequate social support is associated with the mental health of individuals [28, 29]. The fact that family members interact with each other during their spare time may account for the higher WEMWBS total mean score of SAW women with nuclear families. Furthermore, the fact that living in a tent in an agricultural field setting is more difficult for larger families could be associated with better mental well-being experienced in a nuclear family.

Moreover, the WEMWBS total mean score of SAW women who have worked as SAWs for ≥6 years is lower than those who have worked for <6 years. Individuals might have a perception of the burden regarding the responsibilities of working as SAWs. This might also have affected the mental well-being of SAW women.

In the present study, it has been found that the HLBS II total means a score of SAW women with high school or higher is greater. Nevertheless, there is no statistically significant difference between the HLBS II total mean scores according to educational levels. A study on migrant women has demonstrated that women with undergraduate degrees have a higher HLBS II total mean score (30). A similar study has found no statistically significant difference between the HLBS II total mean scores according to the participants' educational levels [30]. Unlike the results of this study, in a study on young SAWs, the HLBS II total mean scores of participants who graduated from primary school are higher [9]. Education, as one of the most essential requirements of modern society, is a prerequisite for a productive and better life. Therefore, the higher HLBS II total mean score of SAW women with an educational level of high school or higher is essential for the indicated level of awareness regarding the HLBs.

The present study has found that The HLBS II total means score significantly increases with higher income levels. Demir and Arıöz have presented similar results in their study (30). In another study on women, those with very good and good income levels have higher HLBS II total mean scores compared to other

income groups [31]. A higher income may facilitate access to health-promoting behaviors. Therefore, it is an expected result that the HLBS II total mean score increases as the income levels of SAW women increases.

Furthermore, the present study has shown that the HLBS II total means a score of SAW women with nuclear families is higher than women with extended and broken families. In another study, it has been presented that the HLBS II total means the score of women with nuclear families is higher compared to that of women with extended families [30]. SAW women assume fewer responsibilities in nuclear families than in extended families. Therefore, the likelihood of demonstrating HLBs would increase because such women would have more time to spare for themselves.

The current study has revealed that the higher number of working years of SAW women is associated with lower total mean scores in the HLBS II's subscales of health responsibility, interpersonal relationships, and physical activity. This can be explained by the fact that SAW women assume further responsibilities as their working years increase; therefore, they could not spare adequate time for interpersonal relationships and physical activities. In addition, the pandemic might also have contributed to the decrease in interpersonal relations.

Conclusion

There was a positive, high-level, and significant correlation between the mental well-being and HLBs of SAW women.

Therefore, some recommendations can be made considering the results of the present study:

- It would be beneficial to organize training programs to improve the HLBs of SAW women and increase their mental well-being levels and provide mobile healthcare services that would allow the implementation of the aforementioned programs in the working environments.
- It would be useful to develop mobile applications to facilitate access to the aforementioned educational content or programs.
- It would be advantageous to conduct studies involving larger samples of health behaviors and factors affecting the health behaviors of SAW women.
- It would be useful to perform qualitative studies to investigate the factors that prevent the achievement of HLBs and negatively affect the mental well-being of SAW women.

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ORIGINAL ARTICLE

Cervical cancer risk levels among women aged 30-65 and factors affecting compliance with the national cervical cancer screening standards

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Abstract

Screening programs for early detection of cervical cancer are extremely important for better prognosis and long-term survival. This study was conducted to determine cervical cancer (CC) risk levels among women aged between 30-65 and the factors affecting having an HPV/Pap smear test that complies with national CC screening standards. A total of 1407 women in the 30-65 age group participated in this cross-sectional study. No sample selection procedure was conducted, and 1407 women who voluntarily agreed to participate in the study were included in the study group. Data were collected between January 2019 and March 2020. The questionnaire used in the study consisted of questions about women's sociodemographic characteristics, lifestyles, CC early diagnosis and screening behaviors, and the CC risk calculation model. Pearson chi-square test, chi-square test for trend, and logistic regression analysis were used in the study. The statistical significance level was accepted as p< 0.05. In the study, 58.9% of the women reported that they had a test within one to three years, 67.5% of those who did not have the test stated they did not know that it was necessary, and 46.2% stated that they neglected it. The CC risk level of 83.6% of women was "below average". The rate of having an HPV/PS test following the national CC screening standards was significantly higher in women who were in the 50-59 age group, smoked, had a childbirth experience, or did not regularly use a condom during sexual intercourse (p<0.05). As the calculated CC risk level increased, testing behaviors decreased statistically significantly (p<0.01). The time of the last screening test was more than five years in those with a calculated CC risk level of ≥average (p<0.01). The CC risk level of the women in the study was below average. There was a significant relationship between HPV/PS testing behavior and age, smoking, having a childbirth experience, and condom use.

Keywords: Cervical cancer, risk factors, pap smear test

Introduction

Cervical cancer (CC) is an important public health problem that ranks fourth place in women worldwide, can be detected at an early stage through screening tests, and has a potential for recovery [1]. In 2020, cervical cancer accounted for 3.1% of all cancers globally, and 8.2% of cancer-related deaths were due to CC [2]. Women who are in the 40-49 age group, live in developing countries where there is inadequate screening and treatment, and has Human immunodeficiency virus (HIV) infection are most affected by cervical cancer [3,4]. CC ranks ninth among cancer types seen in women in Turkey. Its incidence is 7.6 per 100.000 after the age of 40 and 11.7 per 100,000 between the ages of 50-55 in Turkey [5]. Risk factors for cervical cancer are listed as

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follows: Human Papilloma Virus (HPV) infection, other sexually transmitted infections, first sexual intercourse at an early age (before the age of 16), multiple sexual partners, smoking, dietary habits (low consumption of fruits and vegetables), high fertility rate, low socioeconomic level, poor hygiene conditions, especially the use of birth control pills for more than 5 years, suppression of the immune system, not having regular pap smear (PS) tests, not treating those with abnormal pap smear test results [5,6]. High-risk HPV infection causes cervical cancer. There are two high-risk HPV types associated with cervical cancer in many countries and in Turkey. These are HPV types 16 and 18. Especially HPV-16 alone accounts for 60% of cervical cancers [7]. CC, which can be diagnosed and prevented at an early stage with screening tests, is the most important genital cancer type. The 5-year survival of women with cervical cancer diagnosed at an early stage is 92% [8]. PS test is an appropriate screening method for early diagnosis of cervical cancer and reduction of mortality [9]. The incidence of CC in women who have regular PS tests or HPV tests is very low [10]. CC screening programs are 60% or higher in developed countries [11,12] and below 20% in developing and underdeveloped countries [13,14]. The rate of those who have never had a CC screening in Turkey is 72.6% among women aged over 15 and 66.1% among married women aged over 40 [15,16]. Women who are aged 30-65 have been screened for cervical cancer with HPV or smear test every 5 years since 2014. Women who have had a PS test in the last five years are considered to have complied with the national cervical cancer screening standards [17]. The incidence of cervical cancer has been significantly reduced in developed countries thanks to the use of PS testing [18]. However, the incidence of cancer is gradually increasing in developing countries such as Turkey. This increase reveals the need for the effective implementation of cancer screening programs [19]. For this reason, it is extremely important to increase social awareness, identify CC-related risks, and develop appropriate strategies for prevention and treatment [20].

Women's knowledge, attitudes, and behaviors about cancer are very important in the prevention of cervical cancer [21]. It has been found that the incidence of cervical cancer has decreased in most societies where screening is known and adopted [22]. Although cervical cancer is well-known and inexpensive screening methods are available, it is among the causes of death from cancer in most low- and middle-income countries [23]. This study was conducted to determine the CC risk levels of women aged between 30 and 65 and the factors affecting having an HPV/ Pap smear test that complies with the national CC screening standards.

Materials and Methods

Participants

This is a cross-sectional study. The population of the research consisted of the 30-65 age group mothers and relatives of students from Dokuz Eylül University Health Services Vocational Higher School (student health technicians). Before the study data were collected, students were informed about the purpose and method of the research. The students who volunteered to collect data were given education by the researchers on the implementation of the questionnaire, cancer disease, CC risk factors, prevention from cervical cancer, early diagnosis of CC, and screening. The data of the study were collected by the students who received education through the face-to-face method. Data were collected through a one-time face-to-face interview. The students applied the questionnaire to their mothers, family members, and relatives. No sample selection procedure was implemented for the research. Of the family members and relatives of the students who volunteered to collect data in the project following the research method and participated in the education provided, those who agreed to participate voluntarily were included in the study. Women who did not agree to respond to the questionnaire and those with any cancer diagnosis were excluded from the study. We provided the participants with information that "the Cancer Early Diagnosis and Education Centers (KETEM) in our country work as separate units within state hospitals and conduct screening programs in cervical cancer, without charge, at the community level." The CC early diagnosis and screening brochures of the KETEM were distributed to the women taking the questionnaire by student health technicians. The student health technicians came from various regions of Turkey and families with different socioeconomic and cultural characteristics. Therefore, we think that the mothers and relatives of the students forming the sample are an important group in terms of having the general characteristics of the female population in Turkey.

The written permission of the Dokuz Eylul University Non-Interventional Research Ethics Committee was obtained for this study (September 27, 2018, 2018/23-02). Before the study data were collected, the purpose of the study was explained to the participants by the interviewer students, and the participants were informed that they were free to participate in the research and that the data would be kept confidential within the scope of the research, and their informed consent was obtained. The data of the study were collected between January 2019 and March 2020. The study was conducted following the Declaration of Helsinki.

Measurements and Definitions

The data were collected with a questionnaire created by the researchers following a review of the literature. The questionnaire included questions about women's sociodemographic characteristics, lifestyles, CC early diagnosis and screening behaviors, and CC risk levels. The CC risk calculation model developed by the Siteman Cancer Center of Washington University School of Medicine was used to determine the CC risk levels (https://siteman.wustl.edu/prevention/ydr/). The model questioned women's age, cancer history, history of hysterectomy, HPV vaccination, smoking history (age of starting smoking, the number of cigarettes smoked per day, how long ago did they stop smoking if they already stopped it), the number of male sexual partners, the age of first sexual intercourse, the status of using a

condom in each sexual intercourse, history of childbirth, history of sexually transmitted infections, history of HPV infection, and the status of having PS test or PS + HPV test in the last 3-5 years (Have you had a PS test or PS + HPV test within the last 3 - 5 years?). According to the information given, the CC risk level of women was evaluated as Low, Below Average, Average, Above Average, and High. The questions asked in the risk calculation model were added to the questionnaire form of the research.

Variables of the study

The dependent variable of the study is the status of having an HPV or HPV+ PS test every 5 years by every woman in the 30-65 age group according to the National Cervical Cancer Screening Program Standards. The independent variables are women's age, level of education, marital and employment status, chronic diseases, family history of cancer, history of sexually transmitted diseases, condom use, smoking, fertility characteristics, and calculated CC risk level.

Data analysis

The statistical analysis of the data was performed on the SPSS 24.0 statistical software package. Continuous variables were presented as mean scores and standard deviations, and grouped data were presented as numbers and percentage distributions. The conformity of the variables with normal distribution was tested with the Kolmogorov-Smirnov test, and it was determined that the data showed a normal distribution. Pearson chi-square test, chi-square test for trend, and logistic regression analysis were used in the analysis of the data. The logistic regression analysis was established with age, employment status, the status of smoking, history of childbirth, regular use of a condom during sexual intercourse, and calculated CC risk level variables to examine the factors affecting the behavior of women who complied with the National Cervical Cancer Screening Program Standards for having HPV or HPV+ PS tests. The statistical significance level was accepted as $p<0.05$. The risk of women who had below average and low calculated CC risk levels in the regression analysis was grouped as "low", and those with average or high risk were grouped as "≥average".

Results

A total of 1407 women participated in this study. The mean age of the women was 49.4±8.3 (Min=33, Max=65). Of the participants in our study, 56.9% stated that they had an HPV/PS smear test, 19.9% of those who had the test stated that they had it in the past year, and 58.9% within one to three years. Of those who did not have the test, 67.5% stated that they did not know that it was necessary, and 46.2% stated that they neglected it (Table 1).

Table 2 shows women's characteristics associated with CC risk factors. Accordingly, 22.3% of the women were smokers, 95.1% had a single sexual partner throughout their life, 96.3% had their first sexual intercourse experience at 16 and over, 45.2% had three or more births, and 21.7% stated that they had a family history of cancer (Table 2).

Table 1. The behavior of participants to have cervical cancer screening test and reasons for not having it

HPV/PAP smear test	n	%
Yes	801	56.9
No	606	43.1
Recent Pap smear status (801)		
In the past year	159	19.9
Between 1-3 years	472	58.9
Between 4-5 years	82	10.2
More than 5 years	88	11.0
Reasons for not having the test *		
Who do not know that it is necessary	395	67.5
Negligent	270	46.2
Afraid of smearing	41	7.0
Ashamed of having a smear	53	9.1
Fear of cervical cancer	13	2.2
Not knowing where to test	11	1.9

*Participants marked more than one option

Table 2. Characteristics of the participants associated with cervical cancer risk factors (n=1407)

Features	n	%
Smoking status		
Smoker	314	22.3
Quit smoking	97	6.9
Nonsmoker	996	70.8
History of hysterectomy		
Yes	89	6.3
No	1318	93.7
How many male sexual partners have you had in your lifetime?		
1	1338	95.1
2	64	4.5
3	5	0.4
Age at first sexual intercourse		
<16	51	3.7
≥16	1356	96.3
Birth		
Giving Birth	1317	93.6
Not giving birth	90	6.4
Number of live births (n=1317)		
1 Birth	191	13.6
2 Birth	490	34.8
≥3 Birth	636	45.2
Chronic disease history		
Yes	447	31.8
No	960	68.2
Family history of cancer		
Yes	306	21.7
No	1101	78.3

When the CC risk level of the women participating in our study was calculated, it was found that the risk level of 7.4% was "low", 83.6% was "below average", 6.1% was "average", and 2.9% was "above average". Table 3 shows women's compliance

behavior with the national CC screening standards according to their sociodemographic and individual characteristics and the calculated CC risk levels. The rate of HPV/PS testing behavior following the national CC screening standards was significantly higher in women who were in the 50-59 age group, smoked, and did not regularly use a condom during sexual intercourse (p<0.05). As the calculated CC risk level increased, testing behavior decreased statistically significantly (p<0.01) (Table 3).

Table 3. Women's compliance behavior with the national CC screening standards according to their sociodemographic and individual characteristics and the calculated CC risk levels (n=1407)

Features	National Cervical Cancer Screening Standard				p
	Compliance		Non-compliance		
	(n=713)	%	(n=694)	%	
Age					
30-39	80	46.2	93	53.8	
40-49	231	50.7	225	49.3	0.001*
50-59	355	55.0	290	45.0	
60-65	47	35.3	86	64.7	
Educational status					
Primary school and below	390	49.1	405	50.9	
Middle-High School	223	51.5	210	48.5	0.237*
University	100	55.9	79	44.1	
Marital status					
Married	585	51.4	554	48.6	0.289*
Single	128	47.8	140	52.2	
Employment status					
Worker	256	54.4	215	45.6	0.050*
Not working	457	48.8	479	51.2	
Cigaret					
Smoker	190	60.5	124	39.5	0.001*
Non-smoker-quit	523	47.8	570	52.2	
Childbirth					
Having given birth	684	51.9	633	48.1	0.001*
Not having given birth	29	32.2	61	67.8	
Regular condom during sexual intercourse					
No	612	51.9	567	48.1	0.037*
Yes	101	44.3	127	55.7	
History of sexually transmitted disease					
Yes	21	65.6	11	34.4	0.087*
No	692	50.3	683	49.7	
Chronic disease history					
Yes	230	51.5	217	48.5	0.690*
No	483	50.3	477	49.7	
Calculated risk of cervical cancer					
Low	74	71.2	30	28.8	
Below the middle	615	52.3	561	47.7	0.001‡
Middle	12	14.0	74	86.0	
Above the middle	12	29.3	29	70.7	

* Pearson χ², ‡ Slope χ²

A logistic regression model was set to do a multivariate examination of the factors affecting women's having a screening test following the national CC screening standards. Women's age, employment status, smoking habits, childbirth experience, regular use of condoms during sexual intercourse, and the calculated CC risk level were examined together in the model. It was determined that having had a PS test increased 1.83 times (95%CI=1.20-2.78) in the 40-49 age group and 2.10 times (95%CI=1.41-3.12) in the 50-59 age group compared to the 60-65 age group. The behavior of having a CC screening test was 7.42 times higher (95%CI=4.75-11.59) in smokers than in non-smokers, 4.01 (95%CI=2.36-6.81) times higher in those who had given birth than in those who had never given birth, 1.72 times higher (95%CI=1.25-2.37) in those who did not regularly use a condom during sexual intercourse than in those who did, and 31.49 times higher (95%CI=16.97-58.42) in those with a low calculated CC risk level than in those with ≥average CC risk level (Table 4). The time of the last screening test among those who had a calculated CC risk level of ≥average was more than five years (p<0.01, not shown in tables).

Table 4. Factors associated with the behavior of women to comply with the cervical cancer screening standard *

Variables		Crude OR (%95 GA)	Adjusted OR *** (%95 GA)	p
Age	30-39	1.57 (0.98-2.51)	1.62 (0.97-2.69)	0.060
	40-49	1.87 (1.26-2.81)†	1.83 (1.20-2.78)	0.005
	50-59	2.23 (1.52-3.31)†	2.10 (1.41-3.12)	<0.001
	60-65**	1.00	1.00	-
Employment status	Worker	1.28 (0.99-1.55)	1.22 (0.95-1.56)	0.108
	Not working**	1.00	1.00	-
Cigaret	Smoker	1.66 (1.29-2.15)†	7.42 (4.75-11.59)	<0.001††
	Non-smoker**	1.00	1.00	-
Childbirth	Having given birth	2.27 (1.44-3.62)†	4.01 (2.36-6.81)	<0.001††
	Not having given birth**	1.00	1.00	
Regular condom during sexual intercourse	No	1.35 (1.02-1.80)†	1.72 (1.25-2.37)	0.001††
	Yes**	1.00	1.00	-
Estimated risk of CC	Low	4.99 (3.19-8.04)†	31.49 (16.97-58.42)	<0.001††
	≥Middle **	1.00	1.00	-

* A model was created with age, marital status, smoking, risk perception, and estimated cervical cancer risk level. †İstatistically significant (p<0.001)** Reference value*** It has been adjusted according to the variables included in the model

Discussion

It is known that the successful implementation of cervical cancer screening programs is effective in reducing cervical

cancer [24]. Despite this, women still die from CC. Therefore, it is extremely important to identify the risks associated with CC, raise awareness about CC, develop appropriate strategies for prevention and treatment, and know the attitudes of women toward the diagnosis of cervical cancer and the factors affecting these attitudes [20,24]. The findings of this study, which was conducted to examine the factors affecting the CC risk levels of women and having an HPV/PS test following the national CC screening standards, were discussed in light of the literature.

In our study, more than half of the women were found to have had an HPV/PS test and they had the test within 1-3 years. Studies have shown varying rates of HPV/PS testing. In studies with results similar to ours, more than half of women had had their PS test [15,25,26]. According to the results of the studies conducted in different groups and regions in Turkey, the rate of women's participation in cervical cancer screening varies between 29% and 51.3% [11,25,26] Contrary to these results, the rate of women who have a PS test in some studies is low [27,28]. The fact that more than half of the women in our study had a PS test is an important finding in terms of early diagnosis. Women who had a Pap smear test in the last five years were considered to have met the national cervical cancer screening standards. In our study, it was determined that more than half of the women had their PS test, but that the frequency of the tests was not right. We think that this situation should be taken into account in the education programs about PS tests planned for women.

According to some studies, the low level of women's knowledge and negligence are among the barriers to having a PS test [15,27,29]. In our study, the majority of those who did not have the test stated that they did not know that it was necessary to have the test and that they neglected it. In a study, it was determined that more than half of the women had never had a PS test, they did not know that the frequency of having the test was once in five years and that they did not have the PS test mostly out of negligence and unawareness [30]. The most important determinant of the rate of women's having a PS test is the level of their knowledge and awareness of this issue. Women's unawareness of the risk factors and the PS test deprives them of the prevention, early diagnosis, and treatment methods for cervical cancer [10]. Our study results suggest that most women do not have a PS test because they do not have enough knowledge of it. Increasing the education and knowledge level of women about PS testing will increase the applicability of screening tests and help them make the right decisions about their own health.

It has been reported that cervical cancer most frequently affects young women aged between 35 and 50, with the average age at diagnosis being 49 [31]. In our study, the mean age of women was 49.4±8.3 years, and PS testing was more common in the 50-59 age group. Studies have shown that advancing age increases the likelihood of women engaging in health protection behavior [10,25,32]. According to these results, it was determined that the women in our study were in the risky age group for CC, and it was

thought that their knowledge, attitudes, and behaviors regarding CC were important in terms of early diagnosis and treatment.

It has been reported that the likelihood of developing cervical cancer is higher in women who smoke, and smoking is a risk factor for HPV [33]. In our study, the behavior of having a CC screening test was higher in smokers than in non-smokers. Similar to our study results, a study indicated that the rate of having a PS test among smokers was high [34]. Community health centers and family health centers in Turkey conduct education programs for smoking cessation and cancer screening (Ministry of Health). Women who smoke may have a higher awareness of the risk of CC. According to these results, it was thought that smokers took the risk into account and had a PS test.

Some studies in the literature have shown that giving birth and giving four or more births are effective in participation in cervical cancer screening [35]. In our study, the screening test was more common in women who had given birth than in those who had never given birth. Similar to the results of our study, Çankaya found the number of children affected by having a PS test [36]. In another study, a significant relationship was found between women's participation in cervical cancer screening and the number of births. In line with these results, it was thought that women with children presented to health institutions more often and that they were informed about cervical cancer screening and therefore their awareness increased.

It was determined that the CC risk level of the women participating in our study was mostly below average. The majority of the women in the study had a single sexual partner and the age of first marriage was above 16, which affected the risk level to be below average. The time of the last screening test in women with a calculated CC risk level of ≥average was more than five years. It was determined that the behavior of having a screening test was higher in women whose calculated CC risk level was low than in those with a CC risk level of ≥average. In a study, it was found that women living in areas with a high risk of CC were more prone to cancer screening tests [37]. In our study, women with a low CC risk level complied with the national cervical cancer screening standards more than those with average and high-risk levels. Compliance with the national cervical cancer screening standards increased significantly as the risk of CC decreased. This result shows that women do not have enough knowledge of CC and its risks.

Limitations and strengths of the research

The results of the study are limited to the data obtained from the women participating in the study; therefore, they cannot be generalized. Recalling may have played a role in some quantitative data since data were collected retrospectively by using a questionnaire, but this limitation is a random error and cannot be considered a bias. It is thought that providing education after the implementation of the questionnaires contributed to the elimination of women's lack of knowledge.

Conclusion

In our study, it was determined that PS testing was more common in the 50-59 age group, more than half of the women had a PS test, but most of the women who had the test did not have it at the right frequency. In our study, the majority of those who did not have the test stated that they did not know that it was necessary and therefore neglected it. The behavior of having an HPV/PS test following the national CC screening standards was significantly higher in women who were in the 50-59 age group, smoked, gave birth, and did not regularly use a condom during sexual intercourse. It was determined that the CC risk level of women was mostly below average, and the screening test behavior was higher in those with low CC risk levels. Awareness of the importance of Pap smear screening tests in the early diagnosis of cervical cancer is important for public health and especially women's health. Accordingly, all women, especially those in the risk group, should be made aware of CC, risk factors, prevention, and early diagnosis. Moreover, women should be provided with education on screening programs, and CC prevention programs should be increased.

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ORIGINAL ARTICLE

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Evaluation of the diagnosis of helicobacter pylori from stomach biopsy samples by staining methods

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Abstract

In this study, it was aimed to retrospectively investigate the presence of *H. pylori* with Modified Giemsa and Hematoxylin & Eosin in gastric antrum biopsy samples of patients who applied to Ordu University hospital with dyspeptic complaints. Also, cross-sections were stained with Giemsa, Wright's eosin methylene blue and modified Giemsa dyes to compare their effectiveness in diagnosis. The population of the study consisted of 2679 gastric biopsy samples sent to the pathology laboratory between 2014 and 2018. Gastric biopsy samples were screened, and samples stained with Hematoxylin & Eosin, Giemsa and Periodic Acid Schift (PAS) were re-examined for *H. pylori* In the microscopic examination, the samples were also evaluated in terms of intestinal metaplasia, activation and atrophy. In the study, 37 negative, 31 mildly positive, 31 moderately positive and 31 severely positive samples were randomly selected, in addition to routine staining methods. Selected samples were re-sectioned, stained with Giemsa and Wright's eosin dye, and Mayg Grunwald-Giemsa (MGG) dye, Giemsa and Wright's eosin methods were compared. A total of 2679 patients, 49.15% male and 50.85% female, were included in the study. The mean age of patients aged 17-93 was 50.42±15.32. *H. pylori* positivity was found to be 46.8% in the study. It was determined in the study that there was a significant association between *H. pylori* severity and inflammation (p<0.01). The increase in *H. pylori* severity also increased the incidence of activation positivity. The ratio of atrophic patients (56.4%) was higher in patients with severe *H. pylori* positivity (43.6%). Conclusion: It was observed that the incidence of the bacterium was high in Ordu province, and it was suggested that the public should be informed about the transmission and prevention ways of *H. pylori* . Moreover, since similar results were obtained with the staining methods applied in the study, it was concluded that Giemsa and Wright's eosin dyes can be used because they are easy and cheap to diagnose.

Keywords: *H. pylori* stomach, antrum biopsy, Ordu

Introduction

H. pylori can cause acute gastritis and chronic gastritis in the gastric mucosa. Bacteria, which can sometimes be asymptomatic, colonize the apical membrane of the surface epithelial cells. The local humoral immune response occurring is not sufficient for the elimination of this microorganism, therefore, the bacteria has been accepted as a pathogen in the stomach [1,2].

The National Institute of Health of United States of America has also specified H. pylori among the causes of peptic ulcer and emphasized the necessity of both its treatment and control.

Again, the International Agency for Research on Cancer (IARC) has reported that *H. pylori* is a carcinogen in humans [3].

H. pylori exhibits host and tissue tropism and is primarily localized in the antrum region of the stomach in humans. It can subsequently colonize the corpus region and all regions with gastric cell metaplasia [1].

It was reported that the bacterium infected 50% of the world's population, and the incidence of infection in developing countries reached 70-90%, while this rate was between 25-50% in developed countries. It was indicated that the prevalence of *H. pylori* in Turkey was between 45% and 100%, with an average of 85% [4,5].

C13 urea breath tests, stool culture, serological method, stool antigen test can be listed as noninvasive tests in the diagnosis of *H. pylori*, and also polymerase chain reaction (PCR) from stool can be used. Invasive methods are histopathological evaluation, gastric biopsy sample culture, rapid urease test and molecular methods [6,7].

In the literature, no research on the epidemiology of *H. pylori* performed in Ordu province was found. In this study, it was aimed to retrospectively investigate the presence of *H. pylori* with Modified Giemsa and Hematoxylin & Eosin in gastric antrum biopsy samples of patients who applied to Ordu University with dyspeptic complaints. Moreover, cross-sections were stained with Giemsa, Wright's Eosin Methylene Blue and Modified Giemsa dyes in parallel in order to compare the effectiveness in diagnosis.

Materials and Methods

Study population

Approval was obtained from Ordu University Clinical Research Ethics Committee before starting the study (2019/60). The population of the study consisted of 2679 gastric biopsy samples sent to the pathology laboratory between 2014 and 2018.

In the study, 37 negative, 31 mildly positive, 31 moderately positive and 31 severely positive samples were randomly selected, except for routine staining methods. Selected samples were re-sectioned, stained with Giemsa and Wright's eosin dye, and Mayg Grunwald-Giemsa (MGG) dye, Giemsa and Wright's eosin methods were compared.

Examination of the samples

In the microscopic examination, the samples were also evaluated in terms of intestinal metaplasia, activation and atrophy. After negative and positive evaluations were made, the positives were grouped as mild, moderate, and severe according to the Sidney classification (8). In addition to routine staining methods, 37 negative, 31 mildly positive, 31 moderately positive and 31 intensely positive samples were examined under the light

microscope with 100x objective lens, and the results were compared.

Data analysis

Categorical variables were presented as frequency values and continuous variables were presented as mean ± standard deviation. Normal distribution control of the data was performed with Kolmogorov-Smirnov test and homogeneity control of group variances was realized with Levene test. Afterwards, comparisons of two independent groups in continuous variables were conducted with the t-test. Two-way chi-square test was used to determine the association between categorical variables. Comparison of the frequencies in *H. pylori* positive patients was performed with one-way chi-square test. In chi-square tests, if the expected frequencies were ≥5, Pearson's chi-square value was calculated, and when <5, the likelihood ratio was calculated with chi-square value, and the significance level (α) was considered as 5%. Statistical calculations were realized with SPSS v26 (IBM Inc., Chicago, IL, USA) package program.

Results

A total of 2679 patients, 49.15% male and 50.85% female, were included in the study, and *H. pylori* positivity was detected in 1255 (46.84%) patients. *H. pylori,* atrophy, intestinal metaplasia, inflammation and activation (increased neutrophil count) were given in Figures 1 and 2.
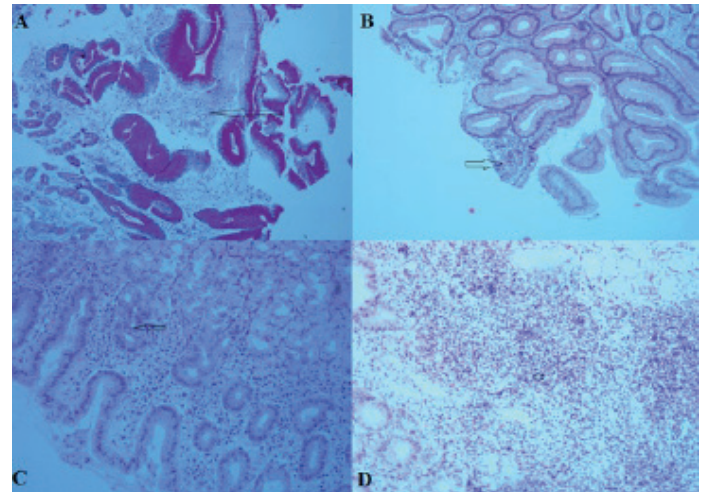
Figure 1. A: Atrophy in gastric biopsy sample stained with PAS-Alcian Blue (100X), B: Intestinal metaplasia in gastric biopsy sample stained with PAS-Alcian Blue (100X), C: Activation in gastric biopsy sample stained with H&E (200X), D: Inflammation in gastric biopsy specimen stained with H&E (200X)

The mean age of patients aged 17-93 was 50.42±15.32. In the study, which was performed by retrospective analysis of patient records of biopsy samples admitted to Department of Medical Pathology laboratory between 2014 and 2018, the descriptive statistical values of the ages of *H. pylori* positive and negative patients were given in Table 1.
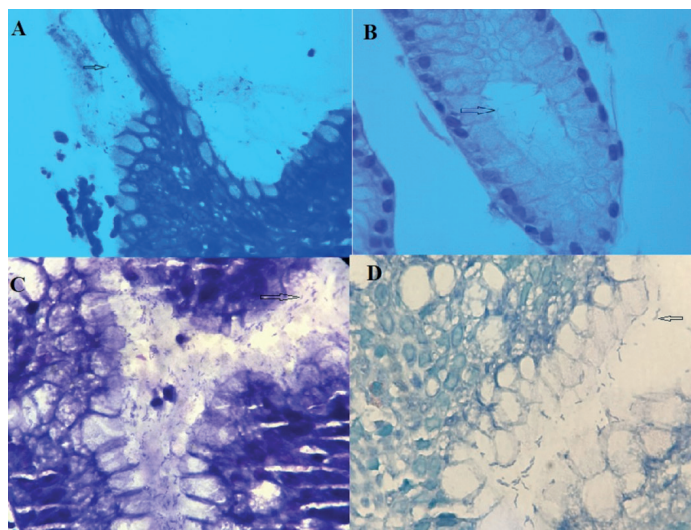
Figure 2: A: *H. pylori* in gastric biopsy sample stained with MGG dye (1000X), B: *H. pylori* in gastric biopsy sample stained with H&E stain (1000X), C: H. pylori in gastric biopsy sample stained with Giemsa stain (1000X), D: *H. pylori* in gastric biopsy specimen stained with Wright's eosin dye (1000X)

Table 1. Descriptive statistical values and comparison results of patients' ages

H. pylori	n	Mean±Std. Deviation	Minimum	Maximum	p
Negative	1424	51.90±15.41	17	93	<0.001
Positive	1255	48.75±15.04	17	86	
Total	2679	50.42±15.32	17	93	

As a result of comparison with Student's t-test, the mean age of *H. pylori* positive patients (48.75±15.04) was found to be statistically significantly lower than the mean age of *H. pylori* negative patients (51.90±15.41) (p<0.001).

The association between *H. pylori* positivity and gender by years was examined with a two-way chi-square test and the results were given in Table 2.

Table 2. Distribution of patients according to years and gender in terms of *H. pylori* positivity

Year		H. pylori				p
		Negative		Positive		
		n	%	n	%	
2014	Female	97	56.7	194	64.2	0.107
	Male	74	43.3	108	35.8	
2015	Female	300	58.1	198	55.9	0.518
	Male	216	41.9	156	44.1	
2016	Female	135	57.9	145	61.2	0.474
	Male	98	42.1	92	38.8	
2017	Female	130	67.7	74	61.2	0.236
	Male	62	32.3	47	38.8	
2018	Female	201	64.4	136	56.4	0.056
	Male	111	35.6	105	43.6	
p				0.568		

According to the table, *H. pylori* positivity was found in 508 (18.9%) male and 747 (27.8%) female patients. Chi-square test performed separately in all the years examined showed that *H. pylori* positive or negative status did not differ according to gender (p>0.05). The chi-square test performed considering all patients between 2014 and 2018, without any difference in years, also confirmed that *H. pylori* positivity did not differ according to gender (p>0.05).

The distribution of patients according to months and years in terms of *H. pylori* positivity was given in Table 3.

As a result of the two-way chi-square tests performed in the study, it was observed that *H. pylori* positivity in 2014 (p<0.001) and 2015 (p<0.05) showed significant changes according to months. In 2016, 2017 and 2018, *H. pylori* positivity did not differ significantly according to months (p>0.05). As a result of the chi-square test performed considering all patients between 2014 and 2018, without any difference in years, it was detected that there was a significant association between *H. pylori* positivity and months (p<0.001). In March, April and May, the ratio of positive patients was higher than the ratio of negative patients. In the light of these findings, it can be said that *H. pylori* positivity increases in spring.

The distribution of disease severity according to the presence of inflammation, intestinal metaplasia, atrophy and activation in *H. pylori* positive patients was given in Table 4.

In the study, a significant correlation was detected between *H. pylori* severity and inflammation as a result of the two-way chi-square test (p<0.01). In patients with severe *H. pylori*, the ratio of patients without inflammation increased as the disease severity decreased while inflammation was observed in all patients (100%). The association between the positivity of intestinal metaplasia and the severity of *H. pylori* was found to be statistically significant (p<0.01). The increase in the severity of *H. pylori* caused a mild decrease in the incidence of intestinal metaplasia. Activation positivity also showed a significant correlation with *H. pylori* severity (p<0.001). The increase in *H. pylori* severity increased the incidence of activation positivity. While the rate of patients with mild and moderate *H. pylori* positivity was higher than those without atrophy, the rate of patients with severe *H. pylori* positivity (56.4%) was higher than the rate of patients without atrophy (43.6%). However, the two-way chi-square test showed that there was no significant association between atrophy positivity and *H. pylori* severity (p>0.05).

The comparison of intestinal metaplasia types with *H. pylori* positivity was given in Table 5.

According to the table, a significant correlation was found between inflammation, atrophy, activation severity and intestinal metaplasia types and the positivity of the bacteria (p<0.001). *H. pylori* positivity was detected more in type 1 patients. Bacterial positivity was observed to be higher in moderate inflammation. Bacterial positivity was found to be higher in mild atrophy and activation.

Table 3. The distribution of patients according to months and years in terms of *H. pylori* positivity

		2014		2015		2016		2017		2018		Total		p
		n	%	n	%	n	%	n	%	n	%	n	%	
January	Negative	8	30.8	58	62.4	22	56.4	17	53.1	31	81.6	136	9.6	
	Positive	18	69.2	35	37.6	17	43.6	15	46.9	7	18.4	92	7.3	
February	Negative	2	25.0	61	64.2	74	47.7	13	76.5	26	61.9	176	12.4	
	Positive	6	75.0	34	35.8	81	52.3	4	23.5	16	38.1	141	11.2	
March	Negative	4	15.4	53	52.5	71	55.5	0	0.0	14	48.3	142	10.0	
	Positive	22	84.6	48	47.5	57	44.5	0	0.0	15	51.7	142	11.3	
April	Negative	11	16.7	56	66.7	1	16.7	8	40.0	23	57.5	99	7.0	
	Positive	55	83.3	28	33.3	5	83.3	12	60.0	17	42.5	117	9.3	
May	Negative	6	8.7	36	52.2	21	44.7	23	56.1	23	59.0	109	7.7	
	Positive	63	91.3	33	47.8	26	55.3	18	43.9	16	41.0	156	12.4	
June	Negative	0	0.0	51	63.7	11	50.0	13	65.0	56	54.9	131	9.2	
	Positive	0	0.0	29	36.3	11	50.0	7	35.0	46	45.1	93	7.4	<0.001
July	Negative	0	0.0	22	53.7	10	45.5	22	71.0	46	52.3	100	7.0	
	Positive	0	0.0	19	46.3	12	54.5	9	29.0	42	47.7	82	6.5	
August	Negative	12	30.8	26	52.0	7	63.6	11	61.1	1	100.0	57	4.0	
	Positive	27	69.2	24	48.0	4	36.4	7	38.9	0	0.0	62	4.9	
September	Negative	19	39.6	51	76.1	0	0.0	10	41.7	21	67.7	101	7.1	
	Positive	29	60.4	16	23.9	0	0.0	14	58.3	10	32.3	69	5.5	
October	Negative	23	59.0	28	56.0	5	29.4	30	71.4	13	50.0	99	7.0	
	Positive	16	41.0	22	44.0	12	70.6	12	28.6	13	50.0	75	6.0	
November	Negative	39	58.2	40	50.6	2	50.0	31	67.4	16	45.7	128	9.0	
	Positive	28	41.8	39	49.4	2	50.0	15	32.6	19	54.3	103	8.2	
December	Negative	47	55.3	34	55.7	9	47.4	14	63.6	42	51.2	146	10.3	
	Positive	38	44.7	27	44.3	10	52.6	8	36.4	40	48.8	123	9.8	

Table 4. The distribution of disease severity according to the presence of inflammation, intestinal metaplasia, atrophy and activation in H. pylori positive patients

		H. pylori severity						p
		Mild		Moderate		Severe		
		n	%	n	%	n	%	
Inflammation	Negative	19	3.5	6	1.3	0	0.0	**0.002****
	Positive	527	96.5	439	98.7	264	100.0	
Intestinal metaplasia	Negative	332	60.8	319	71.7	170	64.4	0.002**
	Positive	214	39.2	126	28.3	94	35.6	
Atrophy	Negative	278	50.9	226	50.8	115	43.6	0.108
	Positive	268	49.1	219	49.2	149	56.4	
Activation	Negative	143	26.2	58	13.0	14	5.3	<0.001
	Positive	403	73.8	387	87.0	250	94.7	

** p<0.01

Table 5. The distribution of *H. pylori* positivity according to intestinal metaplasia types

		H. pylori severity						p
		Negative		Positive		Total		
		n	%	n	%	n	%	
Metaplasia	Negative	1280	90.0	821	65.4	2101	78.5	
	Type 1	112	7.9	294	23.4	406	15.2	
	Type 2	22	1.5	112	8.9	134	5.0	
	Type 3	9	0.6	28	2.2	37	1.4	
Inflammation	Negative	798	56.0	25	2.0	823	30.7	
	Mild	426	29.9	396	31.6	822	30.7	
	Moderate	140	9.8	449	35.8	589	22.0	
	Severe	60	4.2	385	30.7	445	16.6	<0.001
Atrophy	Negative	1341	94.2	619	49.3	1960	73.2	
	Mild	78	5.5	501	39.9	579	21.6	
	Moderate	5	0.4	115	9.2	120	4.5	
	Severe	0	0.0	20	1.6	20	0.7	
Activation	Negative	1249	87.7	215	17.1	1464	54.6	
	Mild	132	9.3	460	36.7	592	22.1	
	Moderate	32	2.2	417	33.2	449	16.8	
	Severe	11	0.8	163	13.0	174	6.5	

n: number, %: percentage

Discussion

It has been reported that there may be a risk of developing functional changes and gastritis in the stomach of almost all patients, peptic ulcer in 15-20%, ulcer complications in 2-12%, gastric cancer in 1-3%, primary gastric lymphoma in 0.1%, and less frequently functional dyspepsia in *H. pylori* infection (9). Again, it has been stated that *H. pylori* may localize in the antrum first and cause chronic active gastritis, followed by atrophic gastritis, intestinal metaplasia, dysplasia, and gastric cancer (10-12). The patients were evaluated in terms of intestinal metaplasia, atrophy, inflammation and activation for their status and follow-up. In addition, Giemsa and Wright's eosin dyes, which were used in the study, were found to be as effective as the routinely used MGG method in the diagnosis of bacteria. These data can be interpreted as Giemsa and Wright's eosin dyes can also be used in routine diagnosis. Moreover, it was thought that the use of a single dye in both dyeing methods was cheaper and more applicable in practice.

In the present study, the mean age of *H. pylori* positive patients (48.75±15.04) was statistically significantly lower than the mean age of *H. pylori* negative patients (51.90±15.41) (p<0.001). Again, *H. pylori* positivity was found to be 46.5% in 35 and younger age group, 48.9% in the 36-45 age range, 53.4 in the 46-54 age range, and 58.2% in the 55 and older age group (Table 4.9). Accordingly, it was determined that *H. pylori* positivity

increased with age (p<0.001). Similarly, Chalise et al. (13) and Erdoğan et al. (14) reported that it increased with age. Again, Korkmaz et al. (15) reported that *H. pylori* positivity may increase with increasing age. Çıkman et al. (16) noted in their study that the prevalence of *H. pylori* increased in parallel with age. Tarhane et al. (17) also found *H. pylori* positivity to be higher in individuals aged 25-44 (p<0.05) and attributed this to the fact that these age groups were active working age and had a high causative exposure. However, Uyanıkoğlu et al. (18) expressed that they could not find a significant association between age and bacterial positivity. This difference may be due to the population of the study, the study area and the method. Moreover, as age progresses, the localization and colonization of bacteria may be easier. Again, it was found in the study that inflammation, intestinal metaplasia and activation of gastric mucosa caused by *H. pylori* positivity increased significantly with age (p<0.001). Although there was an increase in percentage in the presence of atrophy, no significant association was found (p>0.05). This can be explained by the fact that age facilitates the localization of bacteria and can cause more serious damage to the stomach.

In the study, *H. pylori* positivity was observed in 508 (18.9%) male and 747 (27.8%) female patients. When the association between gender and *H. pylori* was evaluated, the chi-square test performed separately in all the years examined showed that *H. pylori* positive or negative status did not differ according to

gender (p>0.05). The chi-square test performed considering all patients between 2014 and 2018, without any difference in years, also confirmed that *H. pylori* positivity did not differ according to gender (p>0.05). In similar studies, Uyanıkoğlu et al. (18) reported that the incidence of bacteria did not differ between genders. Again, Erdogan et al. (14) did not find a significant assocaition between gender and bacterial positivity. However, Çıkman et al. (16) observed positivity to be significantly higher in women in the experimental group consisting of children and adults. This difference may be due to diet, study group, study area and method.

According to epidemiological studies conducted in Turkey and in the world, Gisbert and Calvet (19) found bacteria positivity in 81.2% of 16080 patients with duodenal ulcers in 1999-2008. There are many studies on the prevalence of *H. pylori* in Turkey. In a retrospective study conducted by Salih et al. (20) in Istanbul, they applied rapid urease test on 4471 patients who had upper GIS endoscopy between 1999-2003 and reported the frequency of *H. pylori* as 62.7%. Umit et al. (21) included 4714 patients who underwent upper GIS endoscopy in the Thrace region between 2003 and 2007 and investigated the presence of *H. pylori* with the rapid urease test. In different studies conducted with children, the prevalence was found to be 80% in Bangladeshi children and 16% in 695 school children in Sweden (22,23). In Turkey, Gökşen et al. found *H. pylori* antigen positivity to be 17.8% in stool samples of children with chronic abdominal pain (24).

According to the literature, it was reported that bacteria positivity was found 48.8% of celiac patients, 85.4% of control patients in the study of Kahramanoğlu Aksoy et al. (25), 53.8% of 52 patients in the study of Topal et al. (11), in 66.7% of the patients in Adıyaman in the study of Aygün et al. (26) and 43% in Siverek region in the study of Tosun and Çakır (27). Korkmaz et al. (15) observed 49.5% of *H. pylori* positivity in 2189 patients in Ankara with the urea breath test. Again, Uyanıkoğlu et al. (28) reported positivity in 71% of 1298 patients who had antrum biopsy. Cikman et al. (16) searched for antigen in 8402 stool samples in Van between January 2006 and December 2010. Of the samples, 4304 were children and 4098 were adults, and the positivity rate was 20.7% in children and 25.5% in adults. Researchers found 23% positivity in total. Again, Tarhane et al. (17) collected samples from 195 patients in Kars by endoscopy and evaluated them for helicobacteria *(H. pylori, H. felis and H. heilmannii)*. Researchers observed that 163 (83.58%) of 195 samples were positive with May-Grunwald-Giemsa. Erdogan et al. (14) performed C14 urea breath test on 252 patients and reported positivity in 62.7% women and 66.3% men. Konakçı et al (9) detected the positivity of bacteria in 50.5% of 218 patients in Bursa. Mete et al (29) stated a positivity rate of 73.7% in Tekirdag region. Kurtulus et al. (30) found *H. pylori* in 69.5% of 262 patients in Antalya. In the presented study, 2679 gastric biopsy samples were examined between 2014 and 2018 and bacterial positivity was detected in 46.84%. The result obtained was found to be similar to the results of some studies (10,31).

The difference in the rates obtained in the studies may be due to the study method, the patient, the region where the biopsy was taken, and the socio-economic level of the region where the study was conducted.

"Triple therapy" is recommended in the treatment of *H. pylori* infection, and treatment with a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole are generally preferred. Researchers have reported that there is an association between acute neuropsychiatric symptoms and antibiotics, as a result of examining patients with chronic *H. pylori* infection and receiving antibiotic treatment (32). Again, chronic *H. pylori* infection or proton pump inhibitor drugs taken continuously for this reason cause vitamin B12 absorption defect, resulting in an increase in blood homocysteine levels and consequently an increase in clinical findings of dementia, pseudodementia, a tendency to ischemic stroke, and neurological diseases such as subacute combined degeneration. It has a clinical aggravating effect in Parkinson's disease by reducing the absorption of L.dopa taken orally with both food and drugs. 1-methyl-4-phenyl-1,2,36-tetrahydropyridine, a by-product of *H. pylori* infection (MPTP), has a degenerative effect on the substantia nigra and may contribute to Parkinson's disease by causing a decrease in dopamine levels (33). In this context, it was thought that patients should be treated after diagnosis and controlled in terms of neuropsychiatric symptoms in this process.

It was determined that there was a significant assocaition between the colonization status of the bacteria and inflammation in patients with positive *H. pylori* (p<0.01). In patients with severe *H. pylori* infection, inflammation was observed in all patients (100%), while the rates of patients without inflammation increased as the disease severity decreased. The association between intestinal metaplasia positivity and *H. pylori* density was also statistically significant (p<0.01). An increase of 50.7% in intestinal metaplasia was detected in bacterial positivity. A significant correlation was also found with activation positivity and *H. pylori* severity (p<0.001). The increase in the severity of *H. pylori* infection increased the incidence of activation positivity. While the rate of patients with mild and moderate *H. pylori* positivity was higher than those without atrophy, the rate of patients with severe *H. pylori* positivity (56.4%) was higher than the rate of patients without atrophy (43.6%). As a result of the chi-square test performed considering all patients, without any difference in years, a significant association was found between *H. pylori* positivity and months (p<0.001). In March, April and May, the rate of positive patients was higher than the rate of negative patients. In the light of these findings, it can be said that *H. pylori* positivity increases in spring.

Conclusion

In the study Giemsa and Wright's eosin dyes were found to be as effective as MGG. Accordingly, it has been presented that Giemsa and Wright's eosin dyes can also be used in routine

diagnosis. Moreover, a significant association was found between atrophy, inflammation, intestinal metaplasia and activation and bacterial positivity in presented study. In this context, it has been concluded that these parameters are important in the follow-up of the patients, and the old samples should be evaluated in parallel during the follow-up periods. It has been considered that information studies should be carried out about the transmission and protection ways of *H. pylori*, infection may be easier due to the increased incidence of bacteria in the spring season and the region receives a lot of rains in those seasons, and it has been suggested that measures for protection should be increased in these months.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

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ORIGINAL ARTICLE

COVID-19-Related life-threatening complications: pneumothorax, pneumo mediastinum and subcutaneous emphysema

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Abstract

Complications of COVID-19-related pneumothorax, subcutaneous emphysema, and pneumomediastinum are frequently observed in moderate and severe pneumonia cases. The aim of this study is to determine the incidence and potential risk factors of life-threatening complications such as pneumothorax, pneumo-mediastinum, and subcutaneous emphysema that develop in patients received in the tertiary ICUs of our hospital, which serves as a pandemic hospital and to analyze their relationship with mortality. Patients' demographic characteristics, comorbid diseases, length of hospital stay, day and duration of thoracic tube placement, discharge status, and hospitalization laboratory findings were recorded, and the relationship of these parameters with mortality due to pneumothorax, subcutaneous emphysema, and pneumomediastinum were investigated. Of these patients, 33 had pneumothorax, 12 had pneumomediastinum, and 28 had subcutaneous emphysema. Male and female patients were equally represented, and mortality rates were similar. While the rate of pneumothorax in the study patients was 2.21 %, the rate of all life-threatening sequelae such as pneumothorax, pneumomediastinum, and subcutaneous emphysema was 4.7 %, with a high mortality rate (90 %) in 70 patients with these complications. Patients diagnosed with COVID-19 pneumonia should be constantly monitored for life-threatening complications such as pneumothorax, pneumomediastinum, and subcutaneous emphysema during their long-term follow-up.

Keywords: *Covid-19, pneumothorax, pneumomediastinum, subcutaneous emphysema, intensive care unit*

Introduction

The new coronavirus, which was first detected in Wuhan, China in December 2019 and identified as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), continued to increase worldwide, and it led to the declaration of the COVID-19 pandemic on March 11, 2020 [1].

To ensure adequate oxygenation in patients admitted to the intensive care unit (ICU) due to coronavirus disease, non-invasive or invasive mechanical ventilation support is used. Therefore, pneumothorax is common in these patients [2]. Complications of COVID-19-related pneumothorax (PNX), pneumomediastinum (PM), and subcutaneous emphysema (SCE) are frequently observed in moderate and severe pneumonia cases [3]. In the etiology of PNX, PM and SCE developing based on COVID-19, alveolar destruction and spontaneous alveolar rupture caused

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by destructive damage in the lung parenchyma, as well as alveolar damage and rupture due to positive pressure air given by respiratory support devices have been demonstrated [2,4]. In the literature, PNX, PM and SCE complications due to alveolar damage caused by COVID-19 pneumonia have been included in the form of case reports [5-8]. These studies include either combining multicenter cases or single-center case reports [9]. In COVID-19 pneumonia patients followed in ICU, PNX, PM, and SCE are more common complications, unlike the definitions made in the initial stages of the pandemic [10]. The aim of this study is to determine the incidence and potential risk factors of life-threatening complications such as pneumothorax, pneumo-mediastinum, and subcutaneous emphysema that develop in patients hospitalized in the tertiary ICU of our hospital, which serves as a pandemic hospital, and to analyze their relationship with mortality.

Materials and Methods

Our retrospective cross-sectional study was carried out in accordance with the Declaration of Helsinki and the Strobe Checklist after the approval of the X University Faculty of Medicine Clinical Research Ethics Committee dated 30.12.2021 and numbered 2021/119. The written informed consent form was not obtained due to the retrospective type of study. We were able to attain vast patient potential and experience since our hospital functioned actively as a pandemic hospital. The files of 1490 patients over the age of 18 who were diagnosed with COVID -19 and hospitalized in our hospital's 3rd Stage intensive care units between March 2020 and April 2022 were scanned for the study. The diagnosis of all patients was confirmed in laboratory and radiologically. Patients who had pneumothorax, pneumomediastinum, or subcutaneous emphysema without a COVID-19 diagnosis were not included in the study.

Data on the patients included in the study were obtained from patient files and the hospital's automation system. Patients' demographic characteristics (age, gender), comorbid diseases, length of hospital stay, day and duration of thoracic tube placement, discharge status, and laboratory findings on admission to the intensive care unit (CRP, WBC, lactate, CK, D-dimer) were recorded, and the relationship of these parameters with mortality due to pneumothorax, pneumomediastinum, and subcutaneous emphysema was examined. No data could be reached regarding smoking.

Statistical Analysis

Data analysis was done with SPSS (Statistical Program in Social Sciences) 21 package program. Shapiro Wilk Test was used to determine whether the data were fit for normal distribution. The level of significance was taken as $p < 0.05$. Non-parametric test methods were used when the variables did not have a normal distribution ($p > 0.05$). Chi-square analysis was performed in the analysis of categorical data. Pairwise group comparisons were made through Mann-Whitney U test.

Results

The study included 70 patients (33 of 70 patients had pneumothorax, 12 had pneumo-mediastinum, and 28 had subcutaneous emphysema) who were diagnosed with COVID-19 pneumonia and had complications such as PNX, PM, and SCE while being followed up on and treated in the ICU. Both pneumothorax and pneumomediastinum were observed in two of these patients. Additionally, 1 patient had pneumothorax and subcutaneous emphysema. Of the 70 patients included in the study, 90% died. In the study, the mean age of the patients who died was 65.65±12.57, while the mean age of the survivors was 50.43±23.29, with similar mortality rates. Non-survivors (31-94) were older than those discharged (19-89) and the mortality rate by gender was slightly higher in females however, no significant difference was found between demographic data and mortality ($p > 0.05$) (Table1).

The most common comorbidities in our intensive care unit patients were heart diseases, respiratory issues, and diabetes. When the relationship of comorbid diseases with mortality was evaluated, the presence of comorbid disease was associated with increased mortality in these patient groups ($p < 0.05$) (Table2).

In our study, in accordance with the literature, PNX developed in 2.21% of the patients followed up in the ICU. In addition, the rate of development of complications such as PNX, PM and SCE related to COVID-19 was higher in our patients followed up in the ICU (4.7%), and the effects of these complications on mortality were similar ($p > 0.05$) (Table 3).

Invasive mechanical ventilation (IMV) support was also provided to 66 (94.3%) of 70 patients. 63 (95.4%) patients who underwent IMV support died. 33 patients developed pneumothorax, 23 patients subcutaneous emphysema, and 10 patients pneumomediastinum. There were only 4 patients who underwent NIV. The solely complication was subcutaneous emphysema. 4 (5.7%) patients who did not undergo IMV were discharged. It was observed that the mortality rate was higher in patients who were provided with IMV support. This was statistically significant ($p = 0.001$).

When the patients who underwent tube thoracostomy were examined, we observed that tube thoracostomy was applied to 18 of 20 right pneumothorax cases and 7 of 8 left pneumothorax cases. Tube thoracostomy was administered to 5 cases with bilaterally due to bilateral pneumothorax. In addition, 2 patients who underwent tube thoracostomy had both pneumothorax and pneumomediastinum. Finally, tube thoracostomy was performed in 5 patients with accompanying subcutaneous emphysema.

It was observed that the length of hospital stay, ICU stay (days) and the day of insertion of the thoracic tube did not affect the mortality rate in all patients. This was also not significant ($p > 0.05$). When the effect of laboratory values on mortality is evaluated, it was observed that high levels of CRP (C-reaktif protein) was associated with increased mortality ($p < 0.05$) (Table 4).

Table 1. Comparison of groups by age and gender

Groups		Nonsurvivors		Survivors		p values
		n	%	n	%	
Gender	Female	33	52.4	2	28.6	0.225
	Male	30	47.6	5	71.4	
Groups		Mean±SD		Median (Minimum-Maximum)		p values
Age (years)	Nonsurvivors	65.65 ± 12.57		65 (31-94)		0.054
	Survivors	50.43 ± 23.29		46 (19-89)		

Chi-squareTest value (χ2), SD; standard deviation, Mann Whitney test, p<0.05

Table 2. Comparison of comorbid diseases and mortality

Groups	n / %	Groups		Total	p Values
		Nonsurvivors	Survivors		
Cardiac diseases No	n	23	6	29	**0.011***
	%	36.5%	85.7%	41.4%	
Yes	n	40	1	41	
	%	63.5%	14.3%	58.6%	
Respiratory diseases No	n	43	7	50	0.025*
	%	68.3%	100.0%	71.4%	
Yes	n	20	0	20	
	%	31.7%	0.0%	28.6%	
Other comorbid diseases No	n	47	7	54	0.049*
	%	74.6%	100.0%	77.1%	
Yes	n	16	0	16	
	%	25.4%	0.0%	22.9%	
Diabetes Mellitus No	n	29	6	35	0.037*
	%	46.0%	85.7%	50.0%	
Yes	n	34	1	35	
	%	54.0%	14.3%	50.0%	

Chi-squareTest value (χ2), *p<0.05

Table 3. Relationship between type of complications and mortality

Groups	n / %	Groups		Groups	p Values
		Nonsurvivors	Survivors		
Pneumothorax No	n	34	3	37	0.416
	%	54.0%	42.9%	52.9%	
Right	n	18	2	20	
	%	28.6%	28.6%	28.6%	
Left	n	7	1	8	
	%	11.1%	14.3%	11.4%	
Bilateral	n	4	1	5	
	%	6.3%	14.3%	7.1%	
Pneumomediastinum No	n	54	4	58	0.088
	%	85.7%	57.1%	82.9%	
Yes	n	9	3	12	
	%	14.3%	42.9%	17.1%	
Subcutaneous emphysema No	n	36	6	42	0.119
	%	57.1%	85.7%	60.0%	
Yes	n	27	1	28	
	%	42.9%	14.3%	40.0%	

Chi-squareTest value (x2), *p<0.05

Table 4. Analysis of variables in terms of mortality

	Nonsurvivors			Survivors			
	Mean±SD	Minimum	Maximum	Mean±SD	Minimum	Maximum	p Values
Day of thorax tube insertion	7.25±13.32	1.00	85.00	8.57±14.71	1.00	37.00	0.885
Number of days of hospital stay	22.51±13.57	3.00	88.00	27.00±22.92	6.00	57.00	0.875
Number of days of stay in intensive care	20.02±13.03	2.00	86.00	21.71±20.10	4.00	53.00	0.652
	11.94±7.65	0.77	33.77	5.12±5.60	1.52	17.19	0.015
WBC (10^3/µL)	14.60±6.72	4.08	39.19	11.28±5.43	5.00	22.29	0.147
Lactate (mmol/L)	2.86±2.59	0.90	18.00	3.49±3.46	1.10	11.00	0.875
D-dimer (mg/dL)	4.39±7.57	0.01	31.80	1.11±1.33	0.12	3.99	0.111

	Yes, No (n,%)		Nonsurvivors	Survivors	Total	p Values
Endotracheal intubation	Yes	n, %	63 (100%)	3 (42.9%)	66 (94.3)	0.001*
	No	n, %	0 (0.0%)	4 (57.1%)	4 (5.7%)	

Mann Whitney test, * Chi-square Test, p<0.05

Discussion

COVID-19 disease can progress from asymptomatic illness to severe respiratory failure and even death. In retrospective studies on COVID-19 patients, it has been shown that PNX may occur in 1-2% of hospitalized patients, and 1% of patients who died from infection [10-12]. In our study, in accordance with the literature, PNX developed in 2.21% of the patients followed up in the ICU. The development of PNX has been documented in the literature to be a significant prognostic marker in COVID-19 positive patients, and in one study, 86.3 % of patients with pneumothorax were lost [2]. According to the literature, the presence of PNX in patients with COVID-19 disease causes a considerable increase in the risk of mortality, as demonstrated in our study. In addition, the rate of development of complications such as PNX, PM and SCE related to COVID-19 was higher in our patients followed up in the ICU (4.7%). In one study, the rate of PNX/SCE development was defined as 9.6% [10]. Many studies have demonstrated that these problems increase mortality [13,14]. In our study, 70 patients with these problems also had a high mortality rate (90%). In studies conducted, individuals with life-threatening complications such as PNX, PM, and SCE had similar 28-day survival rates [9]. The fact that the mortality rates were similar in our analysis and no significant difference was found validates the conclusions of this large patient series study.

The number of male and female patients in our study was equal, and the mortality rates were similar, but there are publications in which males had a more severe clinical course [9]. In a multicenter trial conducted in England, PNX and PM found in patients under 70 years of age did not alter COVID-19-related survival; however, PNX and PM seen in patients over 70 years of age were demonstrated to be more fatal [9].

In the present study, the mean age of the patients who died (65.65±12.57) was higher than the mean age of the survivors (50.43±23.29), and patients over the age of 65 were more likely to die from PNX and PM.

In a study, the most common comorbid diseases were found to be hypertension, obesity, and diabetes [15,16]. Similarly, pulmonary problems, heart diseases, and diabetes were the most common comorbidities in our ICU patients. The effects of these diseases, which are known to increase mortality, on survival were similar.

NIV and IMV are utilized as a part of treatment in intensive care patients when adequate tissue oxygenation cannot be achieved despite oxygen support. As a result, PNX, PM, and SCE may develop in patients, exacerbating the current scenario. The reduced survival rates observed in IMV patients were consistent with our findings [15,17].

While moderate episodes may heal spontaneously with watchful monitoring, oxygen support, and analgesia, alveolar damage and alveolar rupture can occur more easily in individuals with severe respiratory failure, such as our patients, and frequently necessitate chest tube drainage [10]. At the same time, high PEEP and CPAP applied to this patient group may also cause of PNX development. Tube thoracostomy was performed by a thoracic surgeon in our PNX cases with severe respiratory failure. It has been shown in studies that when PNX develops, tube thoracostomy is an adequate treatment option in most cases [18]. In a study of 124 cases, right pneumothorax was found in 82 (66.1%) patients (2). In our study, right pneumothorax developed more frequently (60.6%). In line with the literature, right pneumothorax developed more commonly in our study, and tube thoracostomy was performed on all patients with an indication. Furthermore, since there is a risk of aerosol in such applications, practitioners should use protective equipment and

take precautions to limit this risk [13]. However, as the already reduced lung capacity in COVID-19 patients is further reduced in the presence of PNX, it is more fatal, and tube thoracostomy in the intensive care unit did not impact mortality, despite being used in our COVID-19 patients with PNX.

The first laboratory results at admission revealed that most patients had normal WBC with a drop in lymphocyte and eosinophil counts in a study that examined the clinical aspects of 140 patients with a mean age of 57 years [19]. Dynamic changes in biomarker levels can help predict the course, prognosis, and outcome of the disease [20]. Serial follow-up tests (starting at >3 days) revealed a further decline in eosinophil and lymphocyte counts, which were positively correlated with disease severity, and high D-dimer, CRP, and procalcitonin levels were associated with a severe disease course [19]. In another study, it was found that high WBC levels checked in the early period had a substantial effect on prognosis, although no statistically significant association exists between CRP and WBC levels and mortality [2]. In our study, WBC levels were within normal ranges in laboratory findings obtained at the time of admission to the intensive care unit, and we believe that high CRP level are associated with the severity of COVID-19 pneumonia.

Limitations

Only COVID-19-positive patients admitted to ICU were included in the study. Suspected but undiagnosed cases were excluded from the study. The study was conducted in a single center and retrospectively.

Conclusion

PNX, PM, and SCE cases have been reported, in addition to many other clinical pictures mentioned in the literature during the COVID-19 infection process. These studies appear in the form of multicentre case reports or single-centre case reports. With 70 patients, our study is one of the most comprehensive ever conducted in a single centre. We believe that patients with COVID-19 pneumonia should be closely monitored in terms of these life-threatening complications in intensive care follow-ups, and that more comprehensive studies on prognostic factors in this regard should be conducted.

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ORIGINAL ARTICLE

Non-alcoholic fatty liver disease and sleep quality: a single center cross-sectional survey study

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Abstract

Sleep-wake disorders are probably a part of Nonalcoholic Fatty Liver Disease (NAFLD) etiology. This study aimed to evaluate the relationship between NAFLD and the Pittsburgh Sleep Quality Index (PSQI) components. Sleep quality was assessed by the PSQI, which comprised seven components. Participants diagnosed with hepatic steatosis using ultrasonographic imaging and healthy volunteers were given the questionnaire. The percentage of subjects with poor sleep quality was noticeably higher in the NAFLD patients than in the non-NAFLD control group (OR: 4.58, 95% CI: 2.67-7.85) (p<0.001). Compared to the control group, the NAFLD group reported shorter sleep duration (p=0.044), a longer sleep onset delay (p<0.001), worse subjective sleep quality (p<0.001), a higher percentage of subjects with sleep disturbances (p<0.001), a higher percentage of subjects using hypnotic drugs (p=0.009), and a higher percentage of subjects with daytime dysfunction (p<0.001). When the subjects were split into two groups based on gender, global PSQI sleep quality and subjective sleep quality were significantly worse in both genders with NAFLD than in the non-NAFLD group (p<0.001). The sleep onset delay of the NAFLD group was substantially longer in males (p=0.002) and females (p<0.001) compared to controls. Sleep disturbances were significantly higher in both sexes with NAFLD compared to controls (p<0.001). The rate of those with daytime dysfunction in the NAFLD group was considerably higher in both genders compared to the non-NAFLD group (p=0.001). Only among the male patients in the NAFLD group the prevalence of hypnotic drug use was substantially greater (p=0.033) than in the non-NAFLD group. Poor sleep was associated with NAFLD in both genders.

Keywords: Nonalcoholic fatty liver disease, sleep quality, sleep disturbance, sleep onset delay, sleep duration, daytime dysfunction

Introduction

With an estimated 32.4% global prevalence, the most common chronic liver disease is a non-alcoholic fatty liver disease (NAFLD) [1]. NAFLD has extrahepatic consequences like cardiovascular disease, extrahepatic cancers, and hepatic complications like cirrhosis and hepatocellular carcinoma [2]. Despite liver biopsy being the best technique for assessing NAFLD, it is rarely used due to the cost and risk of complications. The diagnosis is mainly based on radiological imaging after excluding other liver diseases [3]. Unhealthy diets and sedentary lifestyles are blamed for the pathogenesis of NAFLD [4].

However, sleep disturbance has received less attention in the etiology of NAFLD than diet or physical exercise. Sleep-wake disruption is believed to contribute to the pathophysiology of NAFLD [5]. Short sleep duration and obstructive sleep apnea (OSA) have been identified as NAFLD-related factors [6,7].

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Sleep disruption has been shown to increase the body mass index (BMI) by causing a decrease in leptin and an increase in ghrelin, which are hormones that affect the appetite center [8]. OSA is associated with developing NAFLD regardless of obesity or other common risk factors. Oxidative stress from tissue hypoxia induced by sleep disruption can cause inflammation, mitochondrial malfunction, and sympathetic nervous system hyperactivity. Hepatic steatosis, fibrosis, insulin resistance, and atherosclerosis have all been linked to intermittent hypoxia [9]. As a result, lifestyle diseases can be avoided by early detection and treatment of sleep disorders.

Studies on the relationship between NAFLD and sleep quality are limited in other countries [10–13]. Furthermore, no study could be found on this subject in our country. The effect of sleep duration and quality on NAFLD may also differ according to gender [11,13,14]. The Pittsburgh Sleep Quality Index (PSQI) is a well-known and often-used tool for evaluating sleep quality, which is composed of seven different components; sleep quality, sleep onset delay, sleep duration, sleep disturbance, habitual sleep effectiveness, usage of hypnotic drugs, and daytime dysfunction [15]. The links between each PSQI component and NAFLD are not fully realized. This study aimed to evaluate the relationship between NAFLD and PSQI components.

Material and Methods

Patients

This study was carried out in the gastroenterology and internal medicine clinics of Zonguldak Bulent Ecevit University Hospital between 1 May and 15 August 2022. Patients without chronic liver disease and with fatty liver on ultrasonographic imaging were included in the study as the NAFLD group. Those under 18 years of age, those with viral hepatitis, autoimmune or metabolic liver disease, alcohol consumption (any amount), and a history of malignancy were excluded from the study. Volunteers without hepatic steatosis in the ultrasonographic imaging who applied for check-ups were included in the control group (non-NAFLD group).

A face-to-face PSQI questionnaire of 18 questions was administered to the participants. In addition, liver ultrasonography results, demographic characteristics (gender, age, comorbidities, BMI, smoking habits, daily exercise habits, AST (Aspartate Aminotransferase), ALT (Alanine transaminase), GGT (Gamma-glutamyl transferase) and PLT (platelet counts) results were recorded. According to these parameters FIB-4 index was calculated.

Measurements

According to a widely accepted guideline [16], ultrasonography was used to determine NAFLD. In addition, the degree of hepatic steatosis was recorded as mild, moderate, and severe ultrasonographically [17]. The formula used to determine the FIB-4 score was as follows: FIB-4 score = [(age x AST) / (PLT x $\sqrt{ALT}$)]. Regular physical exercise was defined as the exercise

performed for at least 40 minutes at least three days a week.

Subjective sleep quality, sleep onset delay, sleep duration, sleep disturbance, habitual sleep effectiveness, usage of hypnotic drugs, and daytime dysfunction were the seven components of the PSQI Scale, which consisted of 18 self-administered items. In scoring the PSQI, seven component scores are derived, each scored 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score. A global score of greater than five was used to identify people who had poor sleep quality. Subjective sleep quality, component 1 (0 indicates extremely good, 1 indicates quite good, 2 indicates quite bad, and 3 indicates extremely bad). Sleep onset delay, component 2 was described as the total of the scores of the duration needed each night to get to sleep (0 for the first 15 minutes, 1 for the next 16 to 30 minutes, 2 for the next 31 to 60 minutes, and 3 for longer than 60 minutes.) and the likelihood of failing to fall asleep in 30-minute period (0 represents not in the previous month, 1 represents a maximum of once weekly, 2 represents a maximum of twice weekly, and 3 represents a minimum of three weekly occurrences). Sleep duration, component 3; (0 for longer than seven hours, 1 for six to seven hours, 2 for five to six hours, and 3 for less than five hours). Habitual sleep effectiveness, component 4 was described as the ratio of sleeping to lying in bed (0 represents more than 85%, 1 represents 75%–84%, 2 represents 64%–74%, and 3 represents less than 65%). Sleep disturbance, component 5, was described as having difficulty sleeping for different reasons (0 represents not in the previous month, 1 represents a maximum of once weekly, 2 represents a maximum of twice weekly, and 3 represents a minimum of three weekly occurrences). Usage of hypnotic drugs, component 6; (0 represents not in the previous month, 1 represents a maximum of once weekly, 2 represents a maximum of twice weekly, and 3 represents a minimum of three weekly occurrences). Daytime dysfunction, component 7 was described as the total of the scores of unable to maintain staying awake when driving, eating, or participating in social activities (0 represents not in the previous month, 1 represents a maximum of once weekly, 2 represents a maximum of twice weekly, and 3 represents a minimum of three weekly occurrences) and having difficulty maintaining sufficient eagerness to complete tasks (0 represents no problem, 1 represents only minor problem, 2 represents a moderate problem, 3 represents serious problem).

Statistical analysis

The statistical analysis was performed using SPSS (Statistical Package for Social Sciences), version 22. Data were presented as numbers (%), means ±standard deviations. Comparing categorical data was performed using the Chi-square test. The Shapiro-Wilk and Kolmogorov-Smirnov tests were employed to determine whether continuous variables had a normal distribution. Mann-Whitney U test was utilized to compare continuous variables with non-normal distribution. Logistic regression analysis was used to assess the association between NAFLD and sleep quality and control for any confounding variables. A p-value of less than 0.05 was used to demonstrate statistical significance.

Ethics

The present study was approved by the non-invasive clinical research ethics committee of the Zonguldak Bulent Ecevit University Faculty of Medicine (Protocol No: 2022/08, Approval date: 20/04/2022). The study protocol adheres to the 1964 Declaration of Helsinki's ethical criteria.

Results

Demographic characteristics of participants

This study included 228 patients with NAFLD and 136 participants without NAFLD as a control group. Patients with NAFLD were older and more obese than the control group, respectively (p<0.001) (p<0.001). ALT, AST, GGT levels, and FIB4 scores were higher in the NAFLD group than in the control group, respectively (p<0.001), (p<0.001), (p<0.001), (p<0.001). The proportion of patients who exercised regularly and had diabetes mellitus (DM) and hypertension (HT) was higher in the NAFLD group, respectively (p=0.036) (p<0.001) (p<0.001)

(Table 1).

Sleep quality of participants

The PSQI global score of NAFLD patients was noticeably higher than the control group (p<0.001). Multivariate logistic regression analysis revealed that patients in the NAFLD group had considerably higher odds of having a PSQI score of 5 or above (poor sleep quality) than the patients in the control group (OR: 4.58, 95% CI: 2.67-7.85), (p<0.001) (Table 2).

Compared to the control group, the NAFLD group reported shorter sleep duration (p=0.044), a longer sleep onset delay (p<0.001), worse subjective sleep quality (p<0.001), a higher percentage of subjects with sleep disturbances (composed of components such as waking up early at night, going to the toilet, having difficulty breathing, snoring, having bad dreams, and feeling extremely hot or cold) (p<0.001), a higher percentage of subjects using hypnotic drugs (p=0.009), and a higher percentage of subjects with daytime dysfunction (p<0.001) (Table 3).

Table 1. Demographic characteristics of participants

		NAFLD Group (n=228)	Non-NAFLD Group (n=136)	p-value
Gender	Male, n (%)	108 (47.4%)	64 (47.1%)	
	Female, n (%)	120 (52.6%)	72 (52.9%)	0.954
Age, years ± SD		48±13.4	37.3±14.9	<0.001
BMI (kg/m²) ± SD		30±5.7	24.8±4.45	<0.001
Exercise, n (%)		54 (23.7%)	46 (33.8%)	0.036
Smoking n (%)		64 (28.1%)	46 (33.8%)	0.248
DM, n (%)		76 (33.3%)	8 (5.9%)	<0.001
HT, n (%)		62 (27.2%)	6 (4.4%)	<0.001
ALT (IU/l) ± SD		31.18±27.6	16.59±8.23	<0.001
AST (IU/l) ± SD		24.65±11.43	17.99±5.65	<0.001
GGT (IU/l) ± SD		46.31±56.18	16.85±9.1	<0.001
FIB-4 ± SD		1.01±0.77	0.74±0.56	<0.001

NAFLD: Non-Alcoholic Fatty Liver Disease, BMI: Body-Mass Index, DM: Diabetes Mellitus, HT: Hypertension, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: Gamma Glutamyl Transferase, FIB-4: Fibrosis 4-Score

Table 2. Multivariate logistic regression analysis of risk factors for NAFLD

	p-value	OR	95% CI	
Age	0.059	1.020	0.999	1.041
Gender	0.718	1.105	0.642	1.902
BMI	<0.001	1.150	1.091	1.213
Exercise	0.215	0.695	0.391	1.236
DM	0.005	3.598	1.478	8.759
HT	0.016	3.973	1.290	12.240
Sleep Quality	<0.001	4.586	2.676	7.859

BMI: Body-Mass Index, DM: Diabetes Mellitus, HT: Hypertension, NAFLD: Non-Alcoholic Fatty Liver Disease, OR: Odds Ratio, CI: Confidence Interval

Table 3. Sleep quality of participants according to the PSQI components

	NAFLD Group	Non-NAFLD Group	p-value
Subjective sleep quality	1.46±0.76	0.79±0.56	<0.001
Sleep latency	1.24±0.98	0.6±0.79	<0.001
Sleep duration	0.78±1.05	0.47±0.68	0.044
Habitual sleep efficiency	0.38±0.88	0.19±0.58	0.071
Sleep disturbance	1.55±0.68	1.0±0.46	<0.001
Using hypnotic drugs	0.24±0.74	0.07±0.43	0.009
Daytime dysfunction	1.18±1.12	0.56±0.78	<0.001
Global PSQI score	6.89±3.64	3.72±2.49	<0.001
Sleep Quality			
Well	64 (28%)	90 (76.2%)	<0.001
Poor	164 (72%)	46 (33.8%)	

NAFLD: Non-Alcoholic Fatty Liver Disease PSQI: Pittsburgh Sleep Quality Index

When the subjects were split into two groups based on gender, global PSQI sleep quality was significantly worse in patients with NAFLD for males (p<0.001) and females (p<0.001). Subjective sleep quality in both men (p<0.001) and women (p<0.001) was worse in the NAFLD group compared to controls. The sleep onset delay of the NAFLD group was substantially longer in males (p=0.002) and females (p<0.001) compared to controls. Sleep disturbances were considerably higher in both men (p<0.001) and women (p<0.001) with NAFLD compared to controls. Only among the male patients in the NAFLD group, the prevalence of hypnotic drug use was substantially greater (p=0.033) than in controls. The proportion of subjects with daytime dysfunction in men (p=0.001) and women (p=0.001) in the NAFLD group was substantially higher than in the controls (Table 4).

Table 4. Sleep quality of participants according to the gender

MALE	NAFLD Group (n=108)	Non-NAFLD Group (n=64)	p-value
Subjective sleep quality	1.57±0.74	0.91±0.53	<0.001
Sleep latency	1.22±0.92	0.78±0.83	0.002
Sleep duration	0.89±1.11	0.53±0.8	0.07
Habitual sleep efficiency	0.5±1	0.22±0.55	0.125
Sleep disturbance	1.54±0.63	0.97±0.47	<0.001
Using hypnotic drugs	0.26±0.75	0.06±0.35	0.033
Daytime dysfunction	1.13±1.08	0.53±0.67	<0.001
Global PSQI score	7.19±3.57	4±2.17	<0.001
FEMALE	NAFLD Group (n=120)	Non-NAFLD Group (n=72)	p-value
Subjective sleep quality	1.37±0.78	0.69±0.57	<0.001
Sleep latency	1.25±1.03	0.44±0.73	<0.001
Sleep duration	0.68±1	0.42±0.55	0.325
Habitual sleep efficiency	0.27±0.75	0.17±0.61	0.295
Sleep disturbance	1.57±0.72	1.03±0.44	<0.001
Using hypnotic drugs	0.22±0.74	0.08±0.5	0.131
Daytime dysfunction	1.16±1.23	0.58±0.87	<0.001
Global PSQI score	6.62±3.7	3.47±2.51	<0.001

NAFLD: Non-Alcoholic Fatty Liver Disease PSQI: Pittsburgh Sleep Quality Index

There was no significant difference in sleep quality between patients with mild, moderate, and severe hepatosteatosis (p=0.279).

Discussion

The mechanism for the relationship between sleep quality and NAFLD is unclear. The present study showed that NAFLD patients had worse global sleep quality than the non-NAFLD group. Also, patients with NAFLD were four and a half times more likely to have poor sleep quality than those without. However, the rate of patients with DM, HT, and obesity, which are components of metabolic syndrome, was higher in the NAFLD group. The increase in appetite seen in people with poor sleep quality [8] may increase body mass and consequently

comorbidities such as DM and HT. PSQI subcomponents such as subjective sleep quality, sleep duration, sleep onset delay, sleep disturbance, usage of hypnotic drugs, and daytime dysfunction were also observed to be worse in the NAFLD group. These findings were in line with Kim et al.'s [13] and Chou et al.'s [10] results. However, not all components of the PSQI were evaluated in their studies. In the present study, although habitual sleep efficiency was worse in the NAFLD group, statistical significance could not be reached because the NAFLD group spent less time in bed and slept for a shorter time. A Japanese study [11] demonstrated that daytime dysfunction and the usage of hypnotic drugs were related to NAFLD. According to the PSQI subcomponents of that study, only the use of hypnotic medications was linked to NAFLD in both genders. When the NAFLD group in our cohort was subdivided by gender, statistical significance for hypnotic drug use in females could not be reached since the usage of hypnotic drugs in females was likely also higher in the control subjects. This could explain the high rate of hypnotic medication use in this population, as NAFLD patients may use more pharmacotherapy to treat their sleeping problems. Still, it has been emphasized that there is not enough evidence to show that pharmacotherapy improves sleep quality or duration in patients with poor sleep quality [18]. The short sleep duration at night can cause daytime sleepiness and dysfunction throughout the day. In the present study, patients with NAFLD had a greater rate of shorter sleep duration and daytime dysfunction. In a comparison study by Bernsmeier et al. [12] with healthy controls, it was emphasized that daytime sleepiness in NAFLD was correlated with disease severity. Since the body's energy consumption is higher when awake than when sleeping, the increased risk of NAFLD in those with poor-quality sleep and short sleep duration may be related to not consuming enough energy due to problems such as napping the next day.

However, the level of sonographic hepatic steatosis and sleep quality were not associated with the present study. In accordance with the findings of this study, poor sleep quality was associated with both moderate and severe NAFLD in the study by Chou et al. [10] conducted on the Taiwanese population.

Sleep has modulatory effects on hypothalamic-pituitary-adrenal (HPA) axis activity. While the onset of sleep had an inhibitory effect on cortisol secretion, bursts of cortisol secretion were detected during awakening. Sleep deprivation and poor sleep quality cause activation of the HPA axis. HPA hyperactivity is associated with metabolic disorders, and the relationship between sleeping problems and the incidence of obesity and diabetes has been demonstrated [19]. Furthermore, it has been proven that low-quality sleep and high plasma orexin-A concentrations interact to cause changes in body mass index [20]. Adipokines are proteins produced by adipose tissue and have roles in sleep physiology and sleep disorders; conversely, sleep disturbance may affect adipokine functions, possibly contributing to metabolic disorders [21]. Changes in sleep duration or quality are associated with changes in ghrelin or leptin, which affect appetite regulation [22]. The NAFLD group had a higher mean BMI and a greater prevalence of diabetic patients than the control group in our dataset. In patients with DM, poor glycemic control has been demonstrated to be independently related to poor sleep quality [23]. Also, in this study, the rate of HT patients was higher in NAFLD patients than in the non-NAFLD group. It has been established that HT and insomnia are related [24]. In our results, besides sleep disturbance, as in previous studies [25,26], high BMI, DM, and HT were shown as independent risk factors for NAFLD.

In the present study, ALT, AST, GGT levels, and FIB4 scores were also higher in the NAFLD group besides DM and HT. This finding suggests that the patient group included steatohepatitis and fibrosis beyond simple liver steatosis. Additionally, this study found that patients with NAFLD exercised more frequently than those in the non-NAFLD control subjects. This result may be related to the fact that exercise has been recommended as a treatment regimen for this patient population. Although obesity and insulin resistance have been proven to be primary causes of NAFLD [25,26], the results of this study showed that NAFLD and global sleep quality were related after confounding factors such as BMI and DM were removed.

According to our knowledge, this is the first study investigating NAFLD-sleep quality and its subcomponents in our country. However, this study has some limitations. The single-center design and relatively limited sample size were its main limitations. In addition, the fact that it is a survey study with subjective answers requires that objective methods verify the relationships between NAFLD and sleep quality. The brands and dosages of hypnotic drugs used by the patients were not evaluated. Finally, the non-NAFLD group was younger, which may have affected these results.

Conclusion

Poor sleep was associated with NAFLD in both genders. Compared to the non-NAFLD group, the NAFLD group reported shorter sleep duration, a longer sleep onset delay, worse subjective sleep quality, a higher percentage of subjects with sleep disturbances, a higher percentage of subjects using hypnotic drugs, and a higher percentage of subjects with daytime dysfunction.

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ORIGINAL ARTICLE

Effects of age, gender and modifiable risk factors on low back pain

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Abstract

Low back pain increases with age and causes a burden of serious socio-economic adverse outcomes. Gender, age, vitamin D insufficiency, and obesity are some of the factors that are considered accountable for the etiology of low back pain, however, conflicting results are present in the literature regarding their effects on low back pain. In this study, we aimed to evaluate the effect of pain duration, pain intensity, gender, and preventable risk factors including vitamin D and body mass index (BMI), on low back pain. File registration data of 274 patients (211 females, 63 males) were included in this retrospective study. Age, gender, pain intensity, BMI, and vitamin D levels were recorded. Patients aged 60 and over were considered as the geriatric group. We observed that higher Visual Analogue Scale (VAS) scores were significantly associated with increased BMI (p=0.007) and advanced age (p=0.049). Duration of pain was positively correlated with, age (p<0.001) and BMI (p=0.02). There was no significant relation between VAS scores and vitamin D levels. The duration of the disease was longer in women than men (p=0.038), but no significant difference was observed for VAS scores between genders. When the study group was divided into geriatric and non-geriatric groups, disease duration was higher in the geriatric group (p<0.001), but no significant difference was observed between VAS scores. BMI, which is among the modifiable risk factors, is closely related to low back pain. The increase in both BMI and VAS scores, especially with advancing age, indicates that overweight older individuals are at high risk for low back pain.

Keywords: Low back pain, gender, age, body mass index, vitamin D

Introduction

Low back pain is the most common musculoskeletal pathology that negatively affects a person's daily life, can cause loss of labor, and many biopsychosocial factors are blamed in its etiology. Its annual estimated prevalence is accepted as 15-45% and it is considered to be among the most common diseases in the future [1]. The World Health Organization has defined low back pain in the elderly as a major disabling condition [2].

When the risk factors associated with low back pain in all age groups are evaluated, conflicting results cause confusion. Vitamin D and body mass index (BMI) are two of these factors.

Vitamin D (25-hydroxyvitamin D (25 (OH)D) is a fat-soluble vitamin, of which approximately 90% is synthesized from the skin after exposure to sunlight and 10% is taken from the diet. Vitamin D, that insufficiency is accepted as a modifiable risk factor, is effective on many systems such as musculoskeletal, neuropsychiatry, gastrointestinal, cardiovascular and immunological systems. Vitamin D deficiency is a common health problem in the geriatric population due to decreased

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sun exposure and cutaneous synthesis, increased obesity, and comorbidities. In addition, the result of deficiency of vitamin D on the development of sarcopenia and on pain severity was well-established [3,4] A meta-analysis showed that vitamin D insufficiency was associated with low back pain in young women [5] In another meta-analysis, vitamin D supplementation was not associated with improvement of low back pain [6].

One of the other modifiable risk factor for low back pain is BMI. In recent years, conditions such as the pandemic process and electronic device addiction have resulted an increase in the sedentary life and weight gain. This situation has become more pronounced especially in the geriatric population. Moreover, it has been shown in many studies that this weight gain is a risk factor for low back pain and chronic pain [7].

The studies that evaluated the relationship between gender and low back pain, the prevalence of low back pain was found to be higher in women even after including the confounders such as age range, socioeconomic status, daily living habits, smoking and comorbidities. [8].

In the light of all these data, when the increased lifespan and the increase in the geriatric population are take into account, the role of vitamin D and BMI in low back pain get more importance. The purpose of the study is to evaluate the relation between pain severity, assessed with VAS (Visual Analogue Scale) and pain duration, pain intensity, gender and preventable risk factors, including vitamin D and BMI, in patients with chronic low back pain.

Material and Method

The study was approved by the Sivas Cumhuriyet University Clinical Research Ethics Committee (22.06.2022-06/13). This is a retrospective study that was conducted from January 2021 to December 2021. The files of 274 patients aged between 18 and 90 who applied to the physical medicine and rehabilitation polyclinic of the university hospital due to low back pain were included. Patients aged 60 and over were registered as the geriatric group. Patients with a history of inflammatory disease, trauma, compression fracture, malignancy, and patients receiving vitamin D replacement therapy for low back pain in the medical records were excluded from the study. The patients' height, weight, 25 (OH)D levels, pain duration and pain severity scores, evaluated by VAS, in the current database were recorded.

VAS scale is used both in the diagnosis of pain and determine the severity of pain, it is stated by marking the value according to the severity of the patient's pain on a 10 cm ruler (0=complete painlessness, 10= the most severe pain). The starting point is "0" or "No pain" and the ending point is "10" or "Unbearable pain". Pain severity was classified as 1-4 mild, 5-6 moderate, and 7 and above severe according to VAS scores [9]

The ranges of vitamin D levels were defined as normal (30 to 100 ng/ml), insufficient (20 to 30ng/ml), deficient (<20ng/ml), and toxic (higher than 100ng/ml) [7].

The BMI was calculated using the formula: weight in kilograms (kg) divided by height in meters squared (m²). According to BMI, the number of underweight (<18.5kg/m²), healthy weight (18.5-24.9kg/m²), overweight (25-29.9kg/m²), obese (30-39.9kg/m²) and morbidly obese (≥40kg/m²) patients were classified. [10]. The study protocol was approved by the local ethics committee.

Statistical analysis

Data normality was assessed with the Shapiro Wilks test, histograms, and q-q plots. The Student's t test and Mann Whitnay U test were used to compare the differences between continuous variables. Correlations among the variables including VAS scores, BMI, 25(OH)D levels, disease duration and age were analyzed by using Pearson or Spearman correlation analysis. $p<0.05$ was considered as statistically significant. Analyses were conducted using SPSS version 22.

Results

The registry data of 274 patients (211 females, 63 males) were included in the study, since 30 patients out of the 350 evaluated patients had minor or major trauma, 41 had inflammatory low back pain and 5 patients had malignancy. Nearly half of the of the patients (42.7%) were in geriatric population, aged 60 years and over. Mean age was 55.4±13.9 (geriatric group 68.31±7.02, non-geriatric group 45.85±9.40). According to BMI the majority of the patients were overweight and obese. Pain intensity reflected by the VAS score was mostly moderate to severe. The disease duration was approximately 24 months in most of the patients More than half of the patients had vitamin D insufficiency. Classification percentages of patients dermografik information, VAS scores, BMI values and vitamin D levels are given in Table 1.

Table 1. Frequency range of Pain and Modifiable Risk Factors in Patients with Low Back Pain

Classification of Pain Severity and Modifiable Risk Factors in Patients with Low Back Pain				
VAS classification	Mild 19 (6.9%)	Moderate 102 (32.7%)	Severe 153 (55.8%)		
BMI (kg/m²) classification	Thin 2 (0.7%)	Normal 49 (17.9%)	Overweight 110 (40.1%)	Obese 96 (35.0%)	Morbidly obese 17 (6.2%)
25(OH)D (ng/ml) levels	Normal 39 (14.2%)	İnsufficient 82 (29.9%)	Deficite 153 (55.8%)		

VAS; visual analogue scale, BMI; body mass index, 25(OH)D; 25-hydroxyvitamin D

According to the correlation analysis, VAS scores were significantly associated with increased BMI (p=0.007) and advanced age (p=0.049). The positive correlation between VAS and BMI continued after adjusting for age (r=0.128, p=0.035). Duration of pain was positively correlated with, age (p<0.001) and BMI (p=0.02). There was a negative correlation between vitamin D levels and VAS scores, but not statistically significant. BMI and vitamin D levels were also negatively correlated, but not statistically significant. There was no statistically significant correlation between increasing age and vitamin D levels. Correlation analysis results are given in Table 2.

When the gender differences in the etiology of low back pain were evaluated, the duration of low back pain in women was significantly longer than men (p=0.038). BMI values were significantly higher in women (p<0.001). However, no significant difference was found regarding pain severity and vitamin D levels among genders (Table 3).

When the data of patients was compared according to age groups as geriatric and non-geriatric, no statistically significant difference was found between the groups for 25(OH) D levels and pain intensity. Disease duration and BMI values were higher in the geriatric group compared to the non-geriatric group (both p<0.001). Table 4 shows the statistical data of geriatric and non-geriatric groups.

Table 2. Correlation analysis between age, disease duration, VAS scores, BMI and 25(OH)D levels

	Age	Disease duration (month)	VAS	BMI (kg/m²)	25(OH)D (ng/ml)
Age	r: 1	r: .489 p: .000*	r: .119 p: .049*	r: .401 p: .000*	r: .009 p: .887
Disease duration (month)		r: 1	r: .101 p: .095	r: .182 p: .002*	r: -.071 p: .242
VAS			r: 1	r: .164 p: .007*	r: -.002 p: .980
BMI (kg/m²)				r: 1	r: -.061 p: .311
25(OH)D (ng/ml)					r: 1

*p<0.05 is significant, VAS; visual analogue scale, BMI; body mass index, 25(OH)D; 25-hydroxyvitamin D

Table 3. Evaluation of pain intensity, duration and risk factors for both genders

	Total N:274	Women N:211	Men N=63	p
Disease duration (month)	24.0(38.0)	24.00 (48.00)	24.00 (24.00)	.038*
VAS (score)	6.87±1.67	7.00 (2.00)	6.00(3.00)	.130
BMI (kg/m²)	29.8±5.83	30.36 (7.29)	25.80 (3.75)	.000*
25(OH)D (ng/ml)	18.3(13.10)	18.20 (14.10)	19.50 (11.20)	.337

Data were presented as median (interquartil range) *p<0.05 is significant VAS; visual analogue scale, BMI; body mass index, 25(OH)D; 25-hydroxyvitamin D

Table 4. Comparison of data in geriatric and non-geriatric patient groups

	Geriatric groups N:117	Non-geriatrik groups N:157	p
Disease duration (month)	48.00 (42.00)	12.00 (23.00)	.000*
VAS (score)	7.07± 1.74	6.73± 1.74	.094
BMI (kg/m²)	32.11± 6.01	28.08± 5.05	.000*
25(OH)D (ng/ml)	20.00 (15.60)	17.60 (13.05)	.191

Data were presented as median (interquartil range) or mean±standart deviation. *p<0.05 is significant VAS; visual analogue scale, BMI; body mass index, 25(OH)D; 25-hydroxyvitamin D

Discussion

In this study, we observed that higher VAS scores were associated with increased BMI and advanced age. The positive correlation between VAS score and BMI persisted even after adjusting for age. No significant difference was observed between VAS scores and vitamin D levels. When comparing the genders, the duration of disease was longer in women, but no significant difference was observed between VAS scores in both genders. When the study group was divided into geriatric and non-geriatric groups according to age, disease duration was higher in the geriatric group, but no significant difference was observed between VAS scores.

There are many risk factors that can cause chronic low back pain. Two of these factors are vitamin D insufficiency and obesity,

which are considered modifiable. Age and gender are among the other defined risk factors. With advancing age, an increase in the incidence of low back pain is observed, along with loss of labor, increase in health care costs, and negative effects on activities of daily living. In a review evaluating chronic low back pain, the prevalence was found to be 3-4 times higher in individuals over 50 years of age compared to the 18-30 age group, and it was observed that in accordance with our study pain was more prevalent among women and patients with low sociocultural level [11].

An increase in the incidence of low back pain with obesity has been shown in many studies [12]. In particular, BMI values of 30 and above are a risk factor for the development of low back pain and the chronicity of pain. The limitation of movement caused by obesity has been shown to induce low back pain [13]. In the study of Bazargan et al., which included 905 patients over 55 years of age, ethnicity, lifestyle, and secondary health problems were evaluated in chronic low back pain as well as BMI and they found a positive correlation between low back pain and increased BMI values [14]. In another study, which evaluated the prevalence of chronic low back pain, in the form of telephone interviews between 1992 and 2006, and compared with data including age, gender, ethnicity, BMI and a significant increase was observed in the prevalence of low back pain, especially in women, in 2006, and BMI was the potential reason for this increase [15]. In another study involving patients over 18 years of age, physical activity, educational status, ethnicity, and BMI were evaluated, and an increase in BMI was found to be associated with an increase in low back pain [16]. In our study, the increase in BMI and the increase in VAS severity were correlated and statistically significant, which supports the literature.

Vitamin D insufficiency is frequently encountered in clinical practice and many factors are blamed for its etiology. The need for vitamin D for healthy musculoskeletal anatomy has been proven and its insufficiency is known to worsen chronic non-specific musculoskeletal pain [17]. Back pain is one of them. Ghai et al. found statistically significant increase in functional capacity and decrease in VAS severity in patients with vitamin D insufficiency and back pain in the follow-ups after vitamin replacement therapy [18]. Contrary to these findings in the literature, Thorneby et al., in the study of 44 chronic low back pain and 44 control groups, vitamin D levels were examined and it is one of the rare studies that did not find a statistically significant difference [19]. One of the factors blamed in the etiology of vitamin D insufficiency is overweight. Vitamin D was found to be 20% decreased in overweight individuals than in normal-weight individuals, and the prevalence of insufficiency was reported to be between 40-80% [20,21]. Dadkhah et al. found a significant relationship between low back pain and vitamin D insufficiency in a study including 298 volunteers with 148 low back pain. In the same study, BMI and mean age were found to be higher in the group with low back pain [22]. In another study, in which only women were included, the relationship between obesity and vitamin

D insufficiency was evaluated, and volunteers were divided into obese, morbidly obese, and control groups, and vitamin insufficiency was found to be statistically substantially lower in morbidly obese compared to normal-weights [23]. In our study, an inverse relationship was observed between BMI and vitamin D levels, but this difference was not statistically significant. This is one of the rare studies that did not find a statistically significant difference between VAS severity and vitamin D. It may be due to the very low vitamin D levels of the patients.

There are many studies on the high prevalence of low back pain in females, and this has been attributed to pregnancy, child care, and daily workload [24]. Age, gender, pain severity and psychological factors were evaluated in the cross-sectional study of Liu et al. with 2052 participants. Pain severity and age and gender differed, but they emphasized that the effect of psychological factors on this difference was very important [25]. In another study involving 22,511 volunteers over the age of 18, neck pain and migraine were evaluated in addition to low back pain, and a higher prevalence was reported in women. Advanced age and immobilization have been emphasized as associated factors in low back and neck pain [26]. In our study, a large proportion of the study population was female. Disease duration and BMI were significantly higher compared to men. However, pain severity and vitamin D levels were not significant different among genders.

The incidence of low back pain increases with increasing age, accompanied by increased degenerative changes and limitation of activity [27]. In a study that included epidemiological data by forming age ranges, they reported that low back pain was more severe in olders than in patients under 65 years of age [28]. In a 7-year follow-up study of 277 patients aged 70 years, the prevalence of chronic low back pain increased with age, but a slight decrease in pain intensity and frequency was observed [29]. In another study evaluating low back pain in the geriatric male patients, low back pain severity was associated with increased BMI [30]. Contrary to our findings, Wettstein et al. found a negative correlation, but not statistically significant, between age and pain intensity in a heterogeneous group of 228 low back pain patients [31]. In our study the BMI values were significantly higher in older age groups. However, pain intensity was not differed with increasing age. We attribute this to the high mean age of the non-geriatric patient group and the high severity of pain in the evaluated patient population.

The limitations of our study are that it was planned as a single-center, retrospective sudy. Psychological and environmental factors were not evaluated in patients while evaluating low back pain. In addition results of imaging methods were not included in the study, there was not a control group, and study population represented relatively a small sample size.

Conclusion

It has been shown that the frequency of low back pain increases with age, but the question of the different results regarding the

type and severity of pain, and the effect of concomitant vitamin D insufficiency on pain severity has still not been fully answered. In our study, no effect of vitamin D insufficiency on pain severity was found, but more than half of the study population was vitamin D insufficient. The effect of higher BMI values on low back pain as a modifiable risk factor has been shown once again. Contrary to what is expected in the female gender, the finding that the severity of pain is similar to that of the men is a remarkable finding. In addition, contrary to expectations, there was no difference in pain severity in the geriatric population. The close relationship of pain severity with advanced age and increasing BMI indicates that obese elderly individuals are at high risk for low bak pain. With the support of further prospective studies, preventive health policies should be developed for this modifiable risk factors.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was approved by Sivas Cumhuriyet University Faculty of Medicine Ethics Committee local ethics committee (Number: 2022-06/13, Date: 22.06.2022) and this study was conducted in accordance with the Declaration of Helsinki.

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ORIGINAL ARTICLE

Vascular effects of gestational diabetes can be recognized by carotid intima-media thickness: a prospective case-control study

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Abstract

Gestational diabetes mellitus (GDM) is a systemic disease that has poor maternal and fetal health outcomes. Patients who are diagnosed with GDM are more likely to encounter cardiovascular system diseases during pregnancy and after birth. Carotid intima-media thickness (CIMT) is used as an early indicator of diseases such as coronary artery disease. This study aims to define the effects of hyperglycemia at an early term using CIMT, maternal and fetal doppler flows in patients diagnosed with GDM. The study included 132 pregnant women who had reached the 24th gestational week. (GDM group n=65, Control group n=67) Comparisons were performed between women with similar demographic characteristics who received a 100-gr oral glucose test (OGT) and GDM diagnosis and who did not. The participants' routine hemograms and biochemical tests were done during OGT. Fetal biometrics, amniotic fluid index, uterine artery doppler flow, and bilateral CIMT measurements were performed during the obstetric examinations. Gravida, para, and live birth rates of the GDM group participants were higher than those of the control group (p=0.003, 0.002, 0.002 respectively). The amniotic fluid index was found to be higher in the GDM group (p<0.001). Fasting glucose values and platelet counts were higher in the GDM group (p=0.031 and p<0.001). Other laboratory data demonstrated no statistically meaningful differences between the groups (p>0.05). When the doppler measurements were compared, umbilical artery pulsatility index values were discovered to be similar between the groups (p=0.509). While the right uterine artery (UtA) pulsatility index was higher in the GDM group (p<0.001), no statistically significant differences were found between the groups in terms of the left UtA pulsatility index (p=0.485). Right and left CIMTs were higher in the GDM group (p=0.001, p<0.001, p<0.001 respectively). While in the GDM group there was a positive correlation between the thrombocyte level and uterine artery resistance (r=0.336, p=0.006; r=0.397, p=0.044 respectively), no similar correlations were found in the control group. This study found that GDM patients had inflammation, increased resistance in uterine artery flow, and increased CIMT. It has been shown, there is a correlation between CIMT and glucose levels and between thrombocytosis and UtA resistance in GDM patients. Uterine artery doppler data and CIMT measurements could be used as an indicator of systemic inflammation and cardiovascular disease in patients with GDM.

Keywords: Cardiovascular disease, carotid intima-media, gestational diabetes

Introduction

The definition of gestational diabetes mellitus (GDM) is any degree of glucose intolerance with onset or first recognition during pregnancy [1]. Since diabetes screening is rarely done in women at reproductive age, it is sometimes difficult to diagnose hyperglycemia emerging in pregnancy as gestational diabetes mellitus. The ratio of complicated pregnancies with any kind of diabetes was reported at 7%, and approximately 87% of these pregnancies were proven to be GDM [2]. The

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prevalence of gestational diabetes in society varies depending on the characteristic of the population and the criteria used for diagnosis. The prevalence of GDM ranges between 9% and 26% [3]. After giving birth, females diagnosed with GDM were found to experience a decrease in insulin sensitivity, atherogenic lipid profile and increased Carotid intima-media thickness (CIMT) and cardiovascular risks [4-6].

Coronary artery disease (CAD) is a crucial reason for death worldwide, and hypertension, diabetes, smoking, and lipid profile disorders are listed as important risk factors. Coronary angiography is the golden classic diagnosis method of CAD [7]. This invasive method brings along some risks. CAD happens as a result of the atherosclerotic process, and CIMT, a non-invasive and easily applicable marker, is used for the diagnosis of atherosclerosis [8]. A study that investigated CIMT and inter-adventitial thickness (IAT) of healthy pregnant women found that CIMT and IAT increased with the progression of the gestational week, and even if IAT returned to its previous condition after birth, CIMT could return to its previous thickness after 2.7 years [9]. Although CIMT was reported to increase in patients with GDM history, it cannot return to normal in postpartum 2.7 years like CIMT physiologically increasing in pregnancy [10]. This condition could decrease the reliability of CIMT as a reliable marker in pregnancy for CAD. Evaluation of uterine artery (UtA) blood flow of healthy pregnant and pregnant women diagnosed with GDM together with CIMT may increase the reliability of CIMT. Thus, individuals at risk for atherosclerotic diseases can be detected by CIMT measured during pregnancy.

Materials and Method

The study was conducted with pregnant women who were followed up in the Cardiovascular Surgery and Obstetric Clinic at the Medical Faculty Hospital of Amasya University between 2020 and 2021. Before starting the study, ethics committee approval was obtained from the non-interventional ethics committee of Amasya University, dated 05.12.2019 and numbered 51. The investigation, which was created as a case-control study, contained healthy pregnant females in the third trimester who had a body mass index of below 25 and who accepted GDM screening. Of all the women who were followed up in the clinic, those aged 40 and over; had diabetes, previous gestational diabetes, or preeclamptic findings; were hypertensive or diagnosed with any kind of cardiovascular diseases; used oral anticoagulant or heparin-derivatives; diagnosed with autoimmune diseases and had lipid profile disorder were excluded.

The week of pregnancy of the patients was decided by examining similar studies that had been done before. And pregnant women who completed their 24th gestational week were included in the study. Pregnant women with a gestational week between 24 and 28 who wanted to have the screening test initially received a 50gr oral glucose challenge test (OGCT). Those who had high OGCT were administered a 100gr oral glucose test following

the appropriate fasting duration and diet. While fasting blood of patients was analyzed during both tests, routine hemogram (Sysmex XN 1000) and biochemical tests were also analyzed (Beckman Coulter AU 5800). Measurements included obstetric fetal biometrics, fetal-uterine doppler flows (fetal uterine doppler Mindray DC-7), and in the same session CIMT (Philips innosight diagnostic ultrasound system) of pregnant women in the 25th to 28th gestational weeks. The clinician who performed ultrasound measurements was blind to GDM status of patients and experienced in obstetric sonography and vascular sonogram methods. All sonographic measurements were performed by the same clinician. Fetal biometric measurements included biparietal diameter, femur length, and abdominal circumference [11]. The gestational weeks of the participants were determined according to crown-rump length (CRL) and gestational age was not defined by the last menstrual period. Four quadrants of amniotic pocket measurement were utilized during the analysis of amniotic fluid volume [12]. During the obstetric sonography, umbilical artery flow was analyzed distant from the placenta and umbilicus, and umbilical artery pulsatility index values were recorded [13]. Pregnant women's bilateral UtA doppler measurements were performed abdominally from the iliac artery division, and the pulsatility indices were recorded [14]. Maternal bilateral CIMT was measured and recorded when all the obstetric and maternal doppler measurements were performed. CIMT was measured from the common carotid artery, 5 mm proximal to the carotid bifurcation.

All statistical analyses were conducted with SPSS 15.0 for Windows (SPSS, IBM Inc., Chicago, IL, USA). As the sample size analysis, the Cohen effect size was decided using prior studies in the existing literature [15]. For the two-side minimum 90% power hypothesis, 0.05 margin of error, and 0.7 effect size, a minimum of 36 participants were needed for the control and study groups respectively. The conformity of the variables to the normal distribution examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov Smirnov/Shapiro Wilk tests). Descriptive analyzes performed using the mean and standard deviations for normally distributed variables, and median minimum and maximum values for non-normally distributed variables. Since Neutrophil Count, Lymphocyte, neutrophil-lymphocyte ratio (NLR), Blood Urine Nitrogen, Aspartate Aminotransferase and Alanine Aminotransferase variables showed normal distribution, these parameters analyzed using the student t-test. Statistical analyzes of other variables performed using the man Whitney u test, as they did not show normal distribution.

The correlation analysis between the doppler values and other analysis parameters was conducted by the Spearman correlation test. A P-value of 0.05 was thought statistically significant.

Results

The study included 132 pregnant women, 67 in the control group

and 65 in the GDM group. The demographic characteristics of the groups are presented in Table 1. The participants' age and body mass index were similar to each other (p>0.05). Obstetric history demonstrated statistically significant differences. The participants in the GDM group had higher gravida, parita, and live birth rates in comparison to the control group (p=0.003, 0.002, 0.002 respectively). The amniotic fluid index was found to be higher in the GDM group (p<0.001). The baseline hemogram and biochemical parameters of the groups were compared (Table 2). Among these parameters, fasting glucose values and platelet counts were found to be higher in the GDM group (p=0.031 and p<0.001). The groups indicated no statistically important differences in terms of other laboratory data (p>0.05). Pulsatility indices of the umbilical artery and UtA doppler measurements were compared between the groups (Table 3). There were no significant differences between umbilical artery pulsatility index values (p=0.509). While the right UtA pulsatility index was higher in the GDM group (p<0.001), there was no statistically significant difference between the left UtA pulsatility indices (p=0.485). Maternal CIMT were compared between the groups. Maximum (max), minimum (min), and average (aav) values of the right and left CIMT were higher in the GDM group in comparison to the control group (p=0.001, p<0.001, p<0.001 respectively). Correlation analysis of the Carotid artery measurements with other parameters was performed separately in the control and GDM groups (Table 4 and Table 5). The control group demonstrated no significant correlational relationships between the gestational week and Carotid artery measurements (p>0.05), In the control group, except for left CIMT measurement (p<0.05), all the other glucose levels and right and left CIMT indicated a statistically significant, positive correlation (p>0.05) (Table 4).

As for the GDM group, glucose levels indicated a statistically significant, positive correlation only between the right CIMT max and left CIMT min measurements (r=0.269, p=0.030; r= 0.332, p= 0.007 respectively) (Table 5). In the control group, there was no statistically significant correlation between umbilical artery pulsatility index values and CIMT measurements (p>0.05). In the GDM group, there was a statistically significant, positive correlation between the umbilical artery pulsatility index values and left CIMT min and aav measurements (r=0.274, p=0.027; r=0.258, p=0.038 respectively). In the control group, a significant, positive correlation was found between the right UtA pulsatility index and right CIMT max ve aav values (r=0.379, p=0.002; r=0.296, p=0.015 respectively). None of the CIMT measurements of the left UtA pulsatility index indicated a significant correlation relationship in the control group (p>0.05). In the GDM group, significant correlation values were found with both right and left UtA pulsatility values of right CIMT max measurement (r=0.298, p=0.016; r=0.381, p=0.002 respectively). The GDM group demonstrated no significant correlation relationship between other CIMT measurement values and UtA pulsatility indices (p>0.05). Since there was a difference in platelet counts between the groups; Correlation analysis was performed between Doppler findings, CIMT measurements and platelet counts. There was a statistically meaningful, positive correlation between both right UtA and left UtA pulsatility index and platelet count in the GDM group (r=0.336, p=0.006; r=0.397, p=0.044 respectively). Bilateral CIMT measurements and umbilical artery pulsatility index were not significantly correlated with platelet counts in the GDM group (p>0.05). In the control group, none of the doppler measurements and CIMT measurements indicated a significant correlation relationship with the platelet count values (p>0.05).

Table 1. Demographic Characteristics and Fetal Biometrics of the Groups

	Control Group (n=67) (Median. min-max)	Gestational Diabetes Group (n=65) (Median. min-max)	P value
Age (Year)	28.0 (18.0-38.0)	27.0 (22.0-39.00)	0.223
Body Mass Index (kg/m2)	22.5 (20.2-24.00)	21.9 (19.5-24.4)	0.103
Gravida	1.0 (1-3.0)	1.0 (1-4.0)	0.003
Para	0 (0-1.0)	0 (0-2..0)	0.002
Live Pregnancy Count	0 (0-1.0)	0 (0-2.00)	0.002
Abortus	0 (0-1.0)	0.00 (0-1.0)	0.105
Gestational Week (Femur Length)	26.0 (24.0-37.0)	28.0 (24.0-32.0)	0.006
Amniotic Fluid Index	91.0 (55.0-170.0)	125.0 (69.0-202.0)	<0.001
Fetal Heart Rate	89.0 (65.0-108.0)	90.0 (73.0-105.0)	0.398
Maternal Heart Rate	140.0 (120.0-154.0)	135.0 (128.0-151.0)	0.014

Table 2. Laboratory Results of Groups

	Control Group (n=67) (Mean±Std) (Median. min-max)	Gestational Diabetes Group (n=65)(Mean±Std) (Median. min-max)	P-value
Hemoglobin (g/dl)	11.6 (8.9-14.2)	11.7 (9.1-13.3)	0.412
Platelet Count(109/L)	203.0 (149.0-288.0)	223.0 (155.0-297.00)	0.031
Neutrophil Count (109/L)	4.2±1.1	4.4±1.2	0.410
Lymphocyte (109/L)	1.8±0.2	1.9±0.1	0.114
NLR	2.4±0.8	2.4±0.6	0.774
PLR	115.2 (90-196.3)	110.7 (81.5-174.5)	0.533
Glucose (mg/dl)	78 (65.0-99.0)	89.0 (70.0-117.0)	<0.001
Blood Urine Nitrogen (mg/dl)	15.4±3.4	16.1±2.9	0.858
Creatinine (mg/dl)	0.6 (0.4-0.9)	0.8 (0.4-1.0)	0.101
Aspartate Aminotransferase (U/L)	21.7±6.2	23.3±7.2	0.343
Alanine Aminotransferase (U/L)	25.2±7.8	24.6±6.9	0.758

NLR- Neutrophil-to-lymphocyte ratio; PLR- Platelet-to-lymphocyte ratio

Table 3. Doppler and Carotid Artery Parameters of Groups

	Control Group (n=67) (Median. min-max)	Gestational Diabetes Group (n=65) (Median. min-max)	P value
Umbilical Artery PI	0.81 (0.51-1.49)	0.90 (0.55-1.33)	0.509
Right Uterine Artery PI	0.83 (0.55-1.06)	0.94 (0.61-1.02)	<0.001
Left Uterine Artery PI	0.77 (0.47-1.15)	0.61 (0.51-1.15)	0.485
Right Carotid Artery Max	0.06 (0.03-.09)	0.07 (0.02-.11)	0.001
Right Carotid Artery Min	0.03 (0.03-.30)	0.05 (0.01-.62)	<0.001
Right Carotid Artery Aav	0.04 (0.02-.06)	0.05 (0.02-.58)	<0.001
Left Carotid Artery Max	0.04 (0.01-.11)	0.07 (0.03-.87)	<0.001
Left Carotid Artery Min	0.02 (0.01-.04)	0.03 (0.01-.05)	<0.001
Left Carotid Artery Aav	0.02 (0.01-.10)	0.05 (0.01-.7)	<0.001

PI: Pulsatility index, Min: Minimum, Max: Maximum, Aav: Average Value

Table 4. Correlation analysis of Carotid Artery Diameters with other parameters in Control Group

		RCA max	RCA min	RCA Aav.	LCA max	LCA min	LCA Aav
Gestational Week	p	0.085	0.553	0.369	0.247	0.080	0.304
	r	0.212	0.074	0.111	-0.143	0.215	-0.127
Glucose	p	<0.001	0.021	0.005	0.013	0.025	0.071
	r	0.623**	0.281*	0.338**	0.302*	0.274*	0.222
Umbilical Artery PI	p	0.855	0.736	0.822	0.092	0.208	0.303
	r	-0.023	0.042	-0.028	-0.208	0.156	-0.128
Right Ut.A. PI	p	0.002	0.212	0.015	0.785	0.249	0.644
	r	0.379**	0.154	0.296*	0.034	0.143	0.058
Left Ut.A. PI	p	0.705	0.788	0.319	0.920	0.658	0.207
	r	0.047	-0.033	0.124	0.013	0.055	0.156

Ut. A. PI: Uterine Artery Pulsatility Index, RCA: Right Carotid Artery, LCA: Left Carotid Artery Min: Minimum, Max: Maximum, Aav: Average Value *. Correlation is significant at the 0.05 level **. Correlation is significant at the 0.01 level

Table 5. Correlation analysis of Carotid Artery Diameters with other parameters in Gestational Diabetes Group

		RCA max	RCA min	RCA Aav.	LCA max	LCA min	LCA Aav
Gestational Week	p	0.978	0.341	0.737	0.041	0.379	0.994
	r	-0.003	0.120	0.043	-0.255*	0.111	-0.001
Glucose	p	0.030	0.379	0.232	0.683	0.007	0.808
	r	0.269*	0.111	0.150	0.052	0.332**	-0.031
Umbilical Artery PI	p	0.489	0.559	0.899	0.066	0.027	0.038
	r	0.087	-0.074	0.016	-0.229	0.274*	0.258*
Right Ut.A. PI	p	0.016	0.663	0.082	0.293	<0.001	0.004
	r	0.298*	0.055	0.217	-0.132	0.444**	0.355**
Left Ut.A. PI	p	0.002	0.299	0.081	0.244	0.242	0.459
	r	0.381**	0.131	0.218	-0.147	0.147	0.093

Ut. A. PI: Uterine Artery Pulsatility Index, RCA: Right Carotid Artery, LCA: Left Carotid Artery Min: Minimum, Max: Maximum, Aav: Average Value*. Correlation is significant at the 0.05 level **. Correlation is significant at the 0.01 level

Discussion

This investigation aims to determine the effects of hyperglycemia at CIMT and doppler flow in patients with GDM. And to evaluate whether there is a difference in CIMT between patients with GDM and other pregnant women. This study compared GDM patients with healthy pregnant women. In the GDM group, the number of pregnancies and amniotic fluid index were higher. In the GDM group, thrombocytosis was significant; there was resistance in unilateral UtA blood flow; and again bilateral CIMT were high. A relationship was found between the resistance increase in UtAs and maternal CIMT, and this positive correlation was more significant in the GDM group.

Hyperglycemia, increased femur length measurement and polyhydramnios determined in the GDM group in this study could be an indicator of poor glycemic control, which is in line with the current literature. There is a vigorous association between GDM and macrosomia; it is observed more significantly in late-diagnosed mothers and pregnant women with poor glycemic control; and the probability of clavicle fractures, femur head fractures, and brachial plexus damage is higher during birth [16]. The relationship between GDM and polyhydramnios was determined, and sonographic assessments showed that fetal biometrics, as well as amniotic fluid measurements, could be used in GDM screening [17,18].

The literature includes doppler studies with GDM, indicating complicated results. This study compared pulsatility indices showing umbilical artery resistance, and no meaningful differences were discovered between the groups (Table 3). A prospective doppler study that was performed to predict GDM patients' perinatal outcomes showed that Middle Cerebral Artery Pulsatility Index could be an indicator; parallel to the current investigation, it found no important differences in umbilical artery values and reported that they cannot be used

as an indicator [19]. A case-control study that evaluated early hemodynamic changes in the fetus aged 18-22 weeks old reported a decrease in the Middle Cerebral Artery peak systolic velocity values of the GDM group, and similar to our study, umbilical artery doppler parameters indicated no differences between the groups [20]. In addition to doppler measurements, maternal UtA doppler measurements are used to predict perinatal and maternal outcomes. Our study compared both right and left UtA doppler pulsatility indices between the groups, and a resistance increase was detected in the GDM group. A prospective study that evaluated UtA pulsatility indices values in patients with GDM in the first trimester detected an increase in pulsatility indices values in the group that developed preeclampsia, and no increase was detected in the group that did not develop preeclampsia [21]. None of the patients included in this study had hypertensive or preeclamptic findings, but there was a resistance increase in the UtA doppler of the GDM group. This condition could be an early indicator of trophoblastic invasion disorders of spiral arterioles, inflammatory disorders, and placentation disorders.

While the GDM group in this study had thrombocytosis, no increase was detected in other inflammation markers such as NLR and the platelet-lymphocyte ratio (PLR). Thrombocytosis that developed in GDM patients was reported in another retrospective case-control study, and it was reported that chronic inflammation could play a role in the pathogenesis in this group [22]. This condition could be an early indicator of trophoblastic invasion disorders of spiral arterioles, inflammatory disorders, and placentation disorders.

Previous research showed that GDM patients in the postpartum period encountered type 2 diabetes, metabolic syndrome, hypertension, and cardiovascular diseases [23,24]. This study demonstrated that CIMT, a marker of atherosclerotic and vascular diseases, was increased in the GDM group. Possible inflammation-induced thrombocytosis and increased UtA

resistance may be associated with cardiovascular risks. A case-control study conducted between the 24th and 28th gestational weeks reported higher CIMT thickness and homocysteine levels in the GDM group in comparison to healthful pregnant women [15]. This finding overlaps with the outcomes of our analysis. The literature reports raised atherosclerosis and cardiovascular diseases in patients with proven systemic inflammation [25,26]. The effects of GDM continue after pregnancy as well.

Women who gave birth after GDM diagnosis had increased pulse wave velocity value in Carotid arteries, namely matrix metalloproteinase 1 levels, markers of resistance, and inflammation [27].

There are some limitations of this study. The first limitation is the limited number of patients included in the study, which is one of the obstacles to the generalization of the results to the population. Another limitation is that the CIMTs of the patients were not measured after delivery. Therefore, it cannot be commented on whether there is a change in the CIMT values of the patients after delivery.

Examining CIMT in pregnant women with GDM may be beneficial in terms of determining atherosclerotic risks. It may contribute to the prevention of future atherosclerotic diseases. In future studies, long-term follow-up of pregnant women with GDM will provide a more clear indication of the increased CIMT and the risk of atherosclerotic disease in these individuals.

Conclusion

This study showed inflammation, resistance in uterine artery flows, and CIMT increase in both groups. We found that CIMT was correlated with glucose levels free of patient diagnosis. We also found a correlation between thrombocytosis, namely inflammation, and UtA resistance in GDM patients. Uterine artery doppler data and CIMT measurements could be used as an indicator of systemic inflammation and cardiovascular disease. Thus, early detection of risk patients can be achieved. Although the evaluation of maternal vascular status seems possible with CIMT and UtA doppler flows, prospective studies with larger participation are needed to evaluate perinatal outcomes.

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ORIGINAL ARTICLE

Medicine Science
International
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Some biochemical tips in the etiopathogenesis of Pectus Excavatum

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Abstract

Pectus excavatum (PE) is the most common deformity among anterior chest wall abnormalities. Although many theories on the pathogenesis of PE have been described, the uncertainty is still going on whether it is a result of developmental, biochemical, or biomechanical reasons or their combination. The aim of this study was to evaluate the biochemical parameters that may cause or be associated with the development of PE between children with PE and their healthy peers. A total of 33 patients' medical records were retrospectively analyzed who followed up because of pectus excavatum between 2019 and 2021. A control group was formed from 32 healthy children from the hospital records with similar age and gender profiles as the patient group. The data from both groups were collected and statistically analyzed in terms of gender, age, and laboratory tests, including hemogram, Vit B12, Parathormone (PTH), Vit.D, Alkaline phosphatase (ALP), and serum Calcium (Ca) and Phosphor (P) levels. Compared to the control group, statistically, significantly higher serum ALP, P, and PTH levels with low Vit.B12 levels were detected. The significant difference in the levels of ALP, PTH, P, and Vit B12, which have an important place in the construction and development of osteochondral structures, may impair the remodeling capacity of the costosternal structure with the contribution of thoracic biomechanics. When PE deformity is noticed, if appropriate medical treatment such as vitamin and mineral supplements and diet regulation is applied to children in the follow-up process, the process can be slowed down, and the deformity can be alleviated.

Keywords: Vitamin B12, phosphorus, pectus excavatum, children

Introduction

Anterior chest wall deformities are a rare medical problem, and pectus excavation is the most common deformity among anterior chest wall abnormalities [1,2]. There are several hypotheses regarding its pathogenesis; Hypertension of the diaphragm during embryonic development [3], thickened substernal ligament [4], muscle imbalance in the anterior portion of the diaphragm [5], defects in collagen formation [6], overgrowth and biomechanical weakness of the costosternal cartilage due to a metabolic defect [7], cartilaginous overgrowth [8] or premature cartilage aging in the costosternal cartilage [9] and abnormalities in the amount of trace elements in the costal cartilage [10]. Finally, two main hypotheses remain for the pathogenesis of PE, suggesting a developmental disorder or cartilage proliferation. A summary of all studies suggests that the changes in the amounts of trace elements in the cartilage structure or the disorders in collagen synthesis, and abnormalities in type-2 collagen structure leads to PE with abnormalities in cartilage and bone chemistry [11]. Although those extensive researches are interested in the etiopathogenesis of PE, no additional approaches other than surgical treatment are recommended in the management of PE. The aim of this study was to evaluate the biochemical parameters

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that may cause or be associated with the development of PE between children with PE and their healthy peers.

Material and Methods

A total of 33 patients' medical records were retrospectively analyzed who followed up because of pectus excavatum between 2019 and 2021. A control group was formed from 32 healthy children from the hospital records with similar age and gender profiles as the patient group. The data from both groups were collected and statistically analyzed in terms of gender, age, and laboratory tests, including hemogram, Vit B12, Parathormone, Vit.D, Alkaline phosphatase, and serum Calcium and Phosphor levels. Demographic information and clinical characteristics were recorded for all participants using a data list. Laboratory findings were obtained from the medical registry system of XXX Training and Research Hospital. Biochemical tests and hemograms were obtained through Abbott Architect c16000 (Illinois, USA) and Sysmex Corporation XN-10 (Kobe, Japan), respectively. This retrospective study was approved by the Institutional Ethics Review Board for Clinical Research (2022/214).

Statistical analysis

Data analyzes of the participants included in the study were carried out with the SPSS for Windows v.25 software (IBM, New York, USA). The normality assumption of the data was checked through a Kolmogorov-Smirnov Test. The significance level (p)

for comparison tests was taken as 0.05. Since the variables did not have a normality assumption (p>0.05), the analysis was continued with non-parametric test methods. Because the assumption of normality was not provided, comparisons in independent pairs were carried out with the Mann-Whitney test. A chi-square (χ2) analysis was performed using cross tables for categorical data analysis. In the binary logistic regression analysis, the Hosmer-Lemeshow statistics were used to test the goodness of fit of the model. The model for binary logistic regression in patient and control groups' estimate of significant variables was constructed.

Results

Demographic characteristics of patients with pectus excavatum and the healthy control group

In this study, there were 8 (24.2%) girls and 25 (75.8%) boys in the PE group and 13(40.6%) girls, and 19 (59.4%) boys in the control group. Mean ages were 12.56±4.57 vs. 12.63 ± 4.17 in PE and control groups. There were no statistically significant differences regarding age between the groups. (Table 1).

Laboratory markers of pectus excavatum patients and healthy control group

A statistically significant difference was found between the groups according to the Alkaline phosphatase, Parathormone, Phosphorus, and vitamin B12. (p<0.05, Table 2).

Table 1. Comparison of the groups by gender and age distribution

Variable	Groups		Patients	Control	Total	p
Gender	Girl	n	8	13	21	
		%	24.2%	40.6%	32.3%	
	Boy	n	25	19	34	0.004*ᵃ
		%	75.8%	59.4%	52.3%	
	Total	n	33	32	65	
		%	100.0%	100.0%	100.0%	
Age	Mean±sd		12.56±4.57	12.63±4.17	12.55±4.71	0.057*ᵇ

n; frequency. %; percent. sd; standart deviation. M; Median. pa; Chi-Square Test value (χ2). pb; Mann Whitney Test Value. *; indicates statisticaly difference

Table 2. Measurements of blood parameters in both groups

Variables	Groups	Mean ± sd	M (Min-Max)	Test	p
Alkaline phosphatase U/L	patient	220 ± 51.17	212.5(115-336)	177.000	0.001*
	control	137.63 ± 65.56	120(45-261)		
Phosphorus mg/dL	patient	5.09 ± 0.47	5.1(3.8-6)	84.500	0.001*
	control	3.96 ± 0.64	4(2.7-5.6)		
Parathormone pg/mL	patient	37.81 ± 17.96	32.2(12.2-90.06)	360.500	0.042*
	control	28.59 ± 10.68	25.8(9.21-50.6)		
Vitamin B12 pg/mL	patient	327.88 ± 130.57	298.5(124-605)	327.500	0.009*
	control	427.59 ± 134.47	416.5(191-822)		
Calcium mg/dL	patient	9.67 ± 0.36	9.6(9.1-10.5)	397.000	0.084
	control	9.8 ± 0.31	9.75(9-10.5)		
Hemoglobin g/dL	patient	13.51 ± 1.37	13(11.2-17.1)	505.500	0.768
	control	13.44 ± 1.4	13.3(10.8-16.9)		
Ferritin ng/mL	patient	28.09 ± 17.54	27.6(5.99-97)	388.500	0.067
	control	40.82 ± 27.73	36(2.78-122)		
vitamin D	patient	17.58 ± 5.55	17(5.63-28.3)	490.500	0.773
	control	18.87 ± 7.44	17.7(6.81-36.1)		

sd; standard deviation, M; Median, Min; The smallest value taken, Max; the highest value taken, p; Mann Whitney Test Value, p value, *p<0.05; points a statistically significant difference between the groups

Logistics regression analysis for groups

A Binary Logistic Regression model was established in which the dependent variables of the groups, ALP, phosphorus, parathormone, vitamin B12, age, and gender, were the independent variables. In the binary logistic regression analysis (Table 3), the

Hosmer-Lemeshow statistics were used to test the goodness of fit of the model. In the established model, the groups of data (study-control) were predicted; The model established with Alkaline phosphatase, Phosphorus, Parathormone, Vitamin B12, age, and gender values was found to be a statistically sufficient model ($\chi2$ = 9.188, degree of freedom= 8 p=0.327>0.05).

Table 3. Estimated Values of the Parameters in the Model

Variables	β	SE	W	df	p (sig)	Exp(β) (OR)	95% C.I.for EXP(β)	
							Min	Max
Alkaline phosphatase	-0.022	0.013	2.915	1	0.088	0.978	0.954	1.003
Phosphorus	**-3.989**	**1.540**	**6.710**	**1**	**0.010***	**0.019**	**0.001**	**0.379**
Vitamin B12	**0.017**	**0.007**	**6.144**	**1**	**0.013***	**1.017**	**1.104**	**1.231**
Parathormone	0.040	0.045	0.806	1	0.369	1.041	0.953	1.137
Age	-0.111	0.162	0.468	1	0.494	0.895	0.651	1.230
Gender	0.531	1.151	0.213	1	0.645	1.700	0.178	16.218
Constant	**17.487**	**7.351**	**5.659**	**1**	**0.017***	**4.469**		

β; parameter estimation, SE; standard error; W; Wald statistics, df; degrees of freedom, Exp (β); odds ratio, 95% CI; confidence interval.

Discussion

Although many theories on the pathogenesis of PE have been described [1-15], there has yet to be any reliable anatomical or radiological evidence. However, it is stated that structural abnormalities of costosternal cartilage are an important factor in the development of PE. As a main structural component of costal cartilage, the Type-2 collagen metabolism and its composition are of cardinal importance in the etiology and pathogenesis of PE [16]. Bone mineral density (BMD) and bone fragility are measured when assessing bone health. Decreased vitamin B12 levels have a negative effect on BMD [17], and high levels of homocysteine are an indicator of vitamin B12 deficiency. Homocysteine prevents the formation of collagen bonds by stimulating osteoclasts and increasing osteoclast formation [18]. Alkaline phosphatase activity and osteoblast growth are both directly influenced by vitamin B12 [19]. Vitamin B12 deficiency adversely affects the construction and destruction of bone. Therefore, supplementation with vitamin B12 is crucial to maintain healthy bone structure [20].

In healthy individuals, serum alkaline phosphatase levels change with age, and its level is higher during childhood and adolescence due to the maturation and growth of the bones [21,22]. However, we found a statistically significant increase in ALP values between PE and control cases. Mean ALP values were 220 ± 51.17 vs. 137.63±65.56 in PE and control groups, suggesting increased bone resorption in children with PE compared with their healthy peers. Indeed, ALP has been proposed as a novel predictor for high-turnover bone disease [13,23,24].

Maintaining serum phosphate levels within physiological limits for various biological processes is critical. An essential

component of bones, nucleic acids, and cell membranes, phosphate is critical for cellular energy metabolism, intracellular protein phosphorylation, and hemoglobin oxygen release [25]. In this study, the serum phosphorus level was detected as higher in the PE group than in the control group. There was a statistically significant difference between mean phosphorus values in the PE group (5.09±0.47 mg/dL) versus (3.96±0.64 mg/dL) in the control group. Alkaline phosphatase level rises during early osteoblastic activity, and this increase provides local phosphate formation or its liberation in the presence of organic phosphates such as b-glycerophosphate, thus causing an increase in extracellular P concentration [26] . This situation explains the statistically significant high ALP and P values we found in the PE group. The effects of hyperphosphatemia on bone metabolism via the parathyroid gland are well known. Although vitamin D insufficiency results in PTH increase, which causes cortical thinning and, sometimes, marrow fibrosis [27], there was no significant difference in vitamin D levels between the groups in this study. However, there was a statistically significant difference in PTH levels between the PE and Control groups (Table 2).

Although the exact causes of PE are not known, the underlying mechanism may be related to corrupted collagen synthesis of costochondral structures, which may result in disrupted remodeling of ribs and sternum and, finally, the development of PE.

As a result, high phosphorus, alkaline phosphatase, parathormone, and low Vit B12 values, which are found with a statistically significant rate in PE cases compared to the control group, lead to disrupted bone and cartilage formation by complex mechanisms, possibly affecting the remodeling of the ribs and results with PE in slow progress.

In this retrospective study, routine hematologic parameters of the PE patients, which were obtained during the first and follow-up examinations, were investigated. Its retrospective design and the lack of information on protein markers, minerals, and other vitamins and sex hormones are the limitations of this study. However, differences in some biochemical markers of bone and cartilage formation could be assumed to be related to the progression of deformity, together with unknown factors. Since PE generally progresses gradually until puberty when it is noticed earlier, the regulation of biochemical abnormalities may be useful to increase the remodeling capacity of the sternum and ribs and to prevent or slow the progression of the deformity. These limited results may be inspiring for prospective randomized trials.

Patient informed consent
Signed informed consent was gathered from the participants for this study.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was endorsed by Malatya Turgut Ozal University Non-Interventional Clinical Researches Ethics Committee (Decision Date: 13/12/2022, Meeting Number: 21, Decision Number: 2022/214).

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ORIGINAL ARTICLE

Can systemic immune inflammation index measured in the first trimester predict later occurring isolated oligohydramnios?

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Abstract

The aim of our study is to determine whether the first trimester systemic immune inflammation index (SII) and other hematological markers can be useful as new markers of isolated oligohydramnios that may develop later. Two main groups were formed in this retrospective study. In the first group, 57 pregnant women with isolated oligohydramnios in their third trimester (between 28-40 weeks) were included. The control group consisted of 137 healthy pregnant women with a normal amniotic index (AFI) in the third trimester. First trimester and delivery hemogram values and newborn results of all pregnant women in both groups included in the study were noted for statistical comparison. Platelet (261.895+8.04), which is the hematological marker that best predicts IO in the first trimester, was found to be higher than the healthy group (244.390±4.79) (p=0.03). PLR was the best predictor of oligohydramnios in the third trimester. The PLR level was determined as 113,288, and the cut-off value was 64.91%, the upper limit was 95% CI, the specificity was 51.09%, the positive predictive value was 35.58%, and the negative predictive value was 77.78%. The platelet count in the first trimester and the progressive increase in the number of PLR in the third trimester are significantly related in the prediction of oligohydromnus. SII, NLR and PLR measured in the first trimester are useless in predicting isolated oligohydramnios that may develop in the future.

Keywords: First trimester, NLR, Isolated oligohydroamnios, PLR, SII

Introduction

Oligohydramnios is a condition detected at routine obstetric examination in which the amniotic fluid index (AFI) calculated by examining four quadrants at ultrasound is ≤ 5 cm or in which the longest vertical pocket length measured at ultrasound is ≤2 cm. The condition is seen in 5% of term pregnancies and is associated with poor obstetric outcomes [1]. Isolated oligohydramnios (IO) is defined as insufficient amniotic fluid (AFI≤5) in pregnant women without maternal or fetal disease. It can be seen in approximately 0.5-5% of pregnancies [2]. Oligohydramnios can result in increased mortality and morbidity, either in association with the etiology, or else as a result of a decrease in amniotic fluid [3]. Several authors have thought that the development of oligohydramnios may be a sign of uteroplacental failure or chronic fetal stress [4]. In addition, various physiological changes occurring for adaption to pregnancy in the maternal hematological system may give rise to a mild inflammatory state [5]. Pathological deviations from these physiological adaptations can be detected by examining peripheral blood specimens collected from expectant mothers during routine pregnancy follow-ups. Several indices have recently been

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developed from hematological parameters investigated in peripheral blood for showing systemic inflammation. Two such indices, the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR), are simple biomarkers widely employed for the detection of systemic inflammation [6]. Both NLR and PLR have been shown to be correlated with cancer and several inflammatory diseases, and have begun being regarded as likely inflammatory markers [6-7]. The system immune-inflammation index (SII), used as a novel inflammatory biomarker in recent years, has been shown to be associated with adverse obstetric outcomes such as placental pathologies [8-9]. To the best of our knowledge, there have been no reports to date of the importance of the SII in women with IO in the first trimester. The purpose of this study was therefore to investigate SII levels in addition to NLR and PLR for predicting the development and progression of IO among women in the first trimester.

Material and Methods

This study was planned and completed in accordance with the Declaration of Helsinki and was approved by the university ethical committee (no. 05/26 dated 29.04.2020). The research was designed as a retrospective case-controlled study at the Mengücek Gazi Training and Research Hospital (MEAH), Turkey, a tertiary institution. A total of 194 women were included in the study, 57 with oligohydramnios and 137 healthy pregnant women followed-up at the MEAH between January 2018 and January 2021. Pregnant women aged 18-40 years with gestational ages ≥28 weeks with IO and with available first trimester complete blood count results were included in the study. Women with pre-eclampsia, eclampsia, and hypertensive disease, with gestational diabetes mellitus, with anomalies determined during pregnancy follow-ups, or who smoked or used alcohol during pregnancy were excluded. In addition, all patients included in the study underwent the AmniSure(R) test, and those in whom early membrane rupture was detected were also excluded. Women with high WBC and CRP values were similarly not included. Two main groups were established in this retrospective study. The first consisted of 57 women with IO whose amniotic fluid was <2 cm in the deepest pocket or ≤5 cm in total in four quadrants at ultrasonography performed between gestational weeks 28 and 40. The control group consisted of 137 healthy pregnant women with normal amniotic index (AFI) values in the 28-40th weeks of pregnancy. The same protocols for the induction of labor were applied to both groups. Oxytocin for induction was administered by infusion at 0.002 IU/min. Additionally, women with Bishop scores <6 received 10 mg dinoprostone by the intravaginal route for cervical maturation [10]. Fetal biophysical scoring was performed and closely monitored twice weekly for fetal well-being in patients with IO in whom labor was not immediately induced. Routine hourly blood pressure, heart beat, urine output, and vaginal bleeding checks were performed postpartum to determine postpartum bleeding. Complete blood count values in both groups in the first trimester and at the time of delivery, and neonatal results were recorded.

Statistical analysis

The study data were analyzed on SPSS version 20.00 software and were expressed as mean±standard deviation or percentage values. Normality of distribution was examined using the Kolmogorov Smirnov test. One-Way ANOVA and Tukey's HSD test post hoc were used in the evaluation of hematological parameters test. Logistic regression analysis was applied to determine whether maternal PLR, WBC, and lymphocyte values measured during presentation for labor predict oligohydramnios. Receiver operating characteristic (ROC) analysis was performed to determine the platelet cut-off point for predicting oligohydramnios in the first trimester of pregnancy. ROC analysis was also applied to determine PLR, WBC, and lymphocyte cut-off points for predicting oligohydramnios in the third trimester. p values <0.05 were regarded as significant for all analyses.

Results

The records of patients diagnosed with oligohydramnios and followed-up at the MEAH between September 2010 and April 2022 were examine retrospectively and included in the study. The demographic characteristics of the study groups are shown in Table 1. The median age of the patients included was 27.21 (±5.39) years. The mean week of gestation was 26.30±4.87 for the oligohydramnios group and 28.29± 5.50 for the healthy group, and there was no statistical difference between the groups (p : 0.53). Mean birth week was 38.33±1.776 for the oligohydramnios group and 38.84±1.88 in the healthy control group, and this was statistically significant (p:0.03). Gravidity and parity values were higher in the healthy group compared to the IO group (p:0.011 and p:0.023, respectively). The rate of cesarean delivery was higher in the IO group (p:0.002). In terms of hematological parameters investigated in the first trimester, no statistically significant differences were observed between the groups' WBC, hemoglobin, neutrophil, or lymphocyte counts (p : 0.89, p : 0.95, p :0.51, and p : 0.13, respectively). Platelet counts in the first trimester were significantly higher in the IO group (261.895+8.04) than in the healthy control group (244.390±4.79) (p:0.03). No significant differences were observed between the groups in the terms of RDW, MPV, NLR, PLR, or SII values in the first trimester (p:0.13, p :0.99, p :0.35, p: 0.49, and p: 0.21, respectively) (Table 2). However, significant differences between the groups were observed in terms of the hematological parameters of WBC and lymphocyte counts investigated in the third trimester (p: 0.014 and p:0.03, respectively) (Table 3). No significant differences were observed in terms of RDW, MPV, NLR, or SII in the third trimester (p: 0.13, p: 0.99, p: 0.35, p: 0.49, and p:0.21, respectively) (Table 3). Only PLR values were significantly higher in the oligohydramnios group compared to the healthy control group (p:0.01). As shown in Table 4, first trimester the serum platelet level that best predicted oligohydramnios was 240,500. This cut-off value exhibited 63.1% sensitivity, 50.3% specificity, a positive predictive value (PPV) of 34.6% and a negative predictive value (NPV) of 76.6% with a 95% upper confidence interval (CI) (Figure 1). PLR was

the hematological index that best predicted oligohydramnios in the third trimester. A PLR level of 113,288 was determined. This cut-off value exhibited 64.91% sensitivity, 51.09% specificity, 35.58 PPV, and 77.78% NPV with a 95% upper confidence interval (Figure 1). The third trimester WBC value that best predicted oligohydramnios was 10.35, which exhibited 68.4% sensitivity, 47.40% specificity, 34.65% PPV, and 76.34% NPV with a 95% upper confidence interval (Figure 2). The third trimester serum lymphocyte level that best predicted oligohydramnios was 1.95. This cut-off value exhibited 68.42% sensitivity, 52.55% specificity, 37.50% PPV, and 80% NPV with a 95% upper confidence interval (Figure 2). As shown in terms of the neonatal results in Table 5, there was no difference between the groups in female/male fetal gender (p=0.44). Fetal weight was higher in the healthy group (3194±470.34) than in the oligohydramnios group (3046±519.02) (p:0.046). Similarly, low birth weight fetus delivery was observed in eight cases (14%) in the oligohydramnios group compared to two (1.5%) in the healthy group. The probability of low birth weight fetal delivery was significantly higher in the oligohydramnios group (p:0.002). There was no difference between the groups in terms of premature birth (p:0.92). APGAR scores at 1 and 5 min during delivery were higher in the healthy group than in the oligohydramnios group (p:0.001 and p:0.001, respectively). Fetal length was also similar between the healthy (49.68±0.14 cm) and oligohydramnios (49.21±0.25 cm) groups (p:0.120). Incubation requirements in the NICU were also similar in the two groups (p:0.162).

Table 1. Characteristics of pregnant women with and without oligohydramnios

Parameters	Oligohydramnios (n = 57)	Healthy Pregnant (n = 137)	p-value
Age [year]	26.30± 4.87(18-40)		0,53
Pregnancy; weeks	38.33±1.776	38.84+1.88	0.039*
Gravidity	2,04±1.295	2.53±1.36	0.011*
Parity	0.88±1.18	1.23 ±1.16	0.023*
Type of delivery			
Vaginal	36(63.2%)	114 (83.8%)	0.002*
Cesarean	21 (36.8%)	22 (16.2%)	

Cesarean delivery rates were given as number of percentage, and other values were given as mean ± standard deviation. *p<0.05 was considered statistically significant

Table 2. Comparison of the hematological test results measured in the first trimester of pregnant women with and without oligohydramnios between the groups

Parameters	Oligohydramnios (n = 57)	Healthy Pregnant (n = 137)	p-value
WBC (×10³/l)	8.78±0.29	8.79±0.20	0.89
Hemoglobin, g/L	12.37±0.19	12.31±0.13	0,95
Platelets (×10³ /L)	261.895+8.04	244.390±4.79	0.03*
Neutrophils (×10³ /L)	6.17+0.25	6.05±0.16	0.51
Lymphocytes (×10³ /L)	2.01±0.06	2.08±0.05	0.73
RDW	14.02+0.24	13.91±0.13	0.99
MPV	10.55±0.13	10.33±0.07	0.13
NLR	3.25±0.16	3.15±0.11	0.35
PLR	134.08±5.37	129.77±3.92	0.49
SII	817.82±50.13	775.86±32.47	0.21

*p<0.05 was considered statistically significant

Abbreviations: WBC:white blood cells; RDW=:red blood cell distribution width; MPV=mean platelet volume (MPV); NLR=Neutrophil to lymphocyte ratio; PLR= Platelet to lymphocyte ratio; SII= systemic immune inflammation index

Table 3. Comparison of the 3rd trimester haematological test results of pregnant women with and without oligohydramnios between the groups

Parameters	Oligohydramnios (n = 57)	Healthy Pregnant (n = 137)	p-value
WBC	10.06±0.36	11.41±0.30	0.01*
Hemoglobin, g/L	11.75±0.17	11.69±0.09	0.60
Platelets (×10³ /L)	232.02±6.76	225.10±5.47	0.14
Neutrophils (×10³ /L)	7.61±0.32	8.57+0.28	0.11
Lymphocytes (×10³ /L)	1.93.01±0.10	2.12±0.079	0.03*
RDW	14.56±0.27	14.65±0.22	0.49
MPV	10.66±0.12	10.56±0.84	0.76
NLR	4.35±0.29	4.72±0.26	0.81
PLR	129.82±5.21	117.70±4.13	0.01*
SII	1022.47±85.04	1063.60±72.99	0.52

*p<0.05 was considered statistically significant

Abbreviations: Wbc: white blood cells; RDW: red blood cell distribution width; MPV: mean platelet volume (MPV); NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: systemic immune inflammation index

Table 4. Diagnostic sensitivity and specificity of serum markers in study groups

Parameters	Cutoff	Sensitivity(%)	Specificity (%)	PPD (%)	NPD (%)
Plt 1	≥240.500	63.16	50.36	34.62	76.67
PLR 2	≥113.288	64.91	51.09	35.58	77.78
WBC 2	≤10.35	68.40	47.40	34.65	76.34
Lymphocytes 2	≤1.95	68.42	52.55	37.50	80.00

%: Percentage;

Abbreviations: PPD: Positive predictive value; NPD: Negative predictive value. WBC2: white blood cells(third trimester; Plt1: Platelet count in the first trimester ,PLR2 — Platelet lymphocyte ratio(third trimester); Lymphocytes 2: Lymphocytes (third trimester)

Table 5. Neonatal outcomes in pregnant women with and without oligohydraomnios.

Parameters	Oligohydramnios (n = 57)	Healthy Pregnant (n = 137)	p-value
Fetal Gender			0.442
Female	28(49.1%)	59(43.1%)	
Male	29(50.9%)	78(56.1%)	
Birth weight [grams]	3046±519.02	3194±470.34	0.032*
Low Brith Weight			
<2500 gr	8 (14%)	2 (1.5%)	0.002*
Gestational age at birth (weeks)			0.92
<37 week	4(7.0%)	10(7.3%)	
>37 week	53(93%)	127(92.7%)	
Apgar score			
1st minute	7.86±0.06	7.90±0.39	0.001*
5st minute	8.89±041	8.92±0.35	0.001*
Fetal length	49.21±0.25	49.68±0.14	0.120
Need of NICU	5(8.8%)	5(3.6%)	0.162

NICU;newborn intensive care unit, %: Percentage *p<0.05 was considered statistically significant
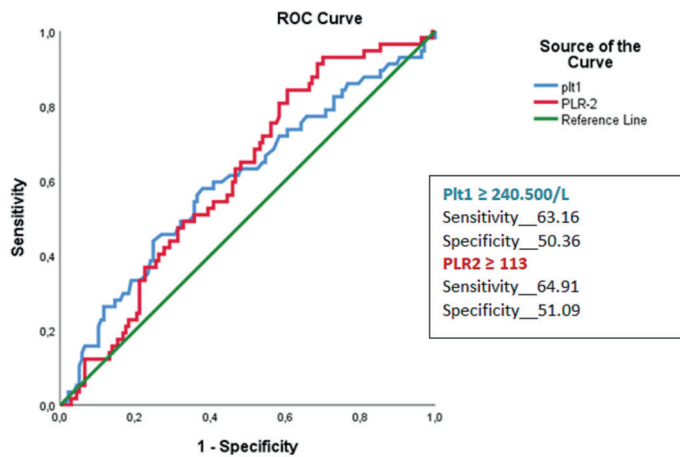
Figure 1. ROC curve of first trimester platelet and third trimester PLR
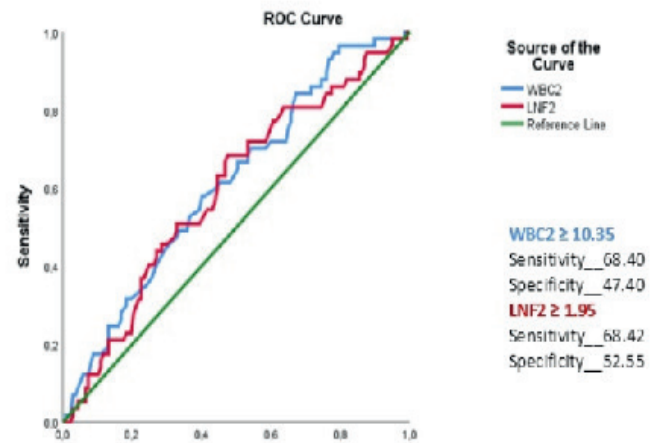

Figure 2. ROC curve of third trimester WBC and lymphocyte count

Discussion

Studies showing that poor obstetric outcomes may be a result of inflammatory processes are available in the literature [2,5,7,8]. Based on this information, in our current study, we investigated whether there is a relationship between hematological parameters measured in the first trimester and oligohydramnis that may develop later. To the best of our knowledge, this is the first study to compare women with oligohydramnios and healthy women in terms of SII, NLR, and PLR values in the first trimester. The findings showed that platelet levels, one of the serum biomarkers investigated in the first trimester, were associated with higher IO rates in the subsequent weeks of pregnancy. Additionally, they showed that WBC, PLR, and lymphocyte values investigated in the third trimester may be associated with higher IO rates.

The clinical importance of oligohydramnios derives from its exacerbation of the risk of fetal and neonatal morbidity and mortality. These poor obstetric outcomes associated with oligohydramnios are thought to be related to placental insufficiency [11]. Additionally, a progressive decrease in uteroplacental flow causes activation of neutrophils in the fetus in the subsequent stages of pregnancy and increased chemokine release by resulting in chronic hypoxia [7]. Similar to neutrophils, platelets contribute both to the initiation of inflammation by increasing the secretion of cytokines and to the continuation of inflammation by increasing the production of neutrophils and platelets. [12]. All these inflammatory processes suggest that an inflammatory process plays a role in the pathogenesis of IO [7]. Previous studies have also investigated whether hematological parameters investigated in the first trimester can predict poor obstetric outcomes [13-16]. First trimester a platelet cut-off value of ≥240,500 (62% sensitivity and 73.6% specificity) best predicted the subsequent development of IO. To the best of our knowledge, this is the first study to show an association between platelet counts in the first trimester and IO. In contrast, hematological indices such as WBC, hemoglobin, neutrophil, lymphocyte, RDW, MPV, NLR, PLR, and SII values investigated

in the first trimester yielded no significant findings in terms of predicting IO. One study involving 11,415 patients reported no significant difference in PLR and NLR values investigated in the first trimester between high-risk pregnancies and healthy pregnancies [17]. Similarly to those results, no relationship was also determined between either NLR or PLR investigated in the first trimester and IO in the present study. Consistent with the present research, a previous study from Turkey also reported no relationship between hematological indices in the first trimester and SGA or oligohydramnios [18]. In the present study, serum WBC value of 10.35 (68.4% sensitivity and 47.4% specificity) best predicted the development of IO in the third trimester. The hematological index that best predicted IO in the third trimester was PLR. The optimal cut-off value for PLR was 113,288 (64.9% sensitivity and 51.0% specificity). In agreement with our PLR findings, Erten O et al. reported significantly higher cystatin C, hs-CRP, and PLR values in the third trimester in an oligohydramnios group compared to a control group. However, again similarly to the present research, that study found no significant difference in NLR values between the two groups [7]. Smiliary to present study, another study comparing high-risk pregnant women and the normal population in the third trimester also reported no association between NLR values and adverse obstetric outcomes [18]. Higher adverse neonatal outcomes were also observed in the oligohydramnios group in the present study. More than one study has shown that increasing proinflammatory cytokine production may be associated with adverse pregnancy outcome such as uterine activation and prematurity [19-20]. It is unclear whether IO reflects an underlying pathological condition, for which reason the management of IO is still controversial. Smiliary to present study, several studies have shown that a higher cesarean section rate in patients with IO compared to healthy groups [21-22]. Effects on neonatal outcomes are also uncertain; some authors showed no adverse effects [23]. while others showed higher neonatal intensive care unit (NICU) admission rates and higher rates of meconium aspiration syndrome [16]; however, only some studies showed low APGAR scores, which is consistent with our

current study [24]. In terms of cesarean delivery rates, a meta-analysis of 12 studies in which 35,999 pregnant women were included significantly higher labor induction and cesarean rates in patients with IO, a finding consistent with the present study [16]. However, the higher rates of admission to the NICU in that meta-analysis [16] were inconsistent with our findings. In a study by Manzanares, S. et al., the cesarean delivery rate was found to be higher in the oligohydramnios group than in the control group, which was consistent with our study results. However, the demonstration that there was no difference between the groups in terms of neonatal outcomes or perinatal morbidity or mortality was not compatible with our study results [25].

Conclusion

In conclusion, this retrospective study is the first to show an association between SII values investigated in the first trimester and oligohydramnios that may develop subsequently. This study also showed an association between maternal platelet counts investigated in the first trimester and WBC, PLR, and lymphocyte values in the third trimester and oligohydramnios. However, no relationship between SII, NLR and PLR values in the first trimester and IO. We think that IO can be identified early and neonatal morbidity and mortality reduced to a minimum by evaluating women's platelet values in the first trimester and PLR, WBC, and lymphocyte values in the third trimester. However, further prospective studies with more participants are now needed to determine whether these parameters can be used to detect a pregnant woman at risk of IO and to predict whether this will lead to adverse perinatal outcomes.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

Our study was approved by the ethics committee of the university (Ethics Committee Date: 29.04.2020, Number: 05/26).

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ORIGINAL ARTICLE

Pandemic process status questionnaire: Development and psychometric properties

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Abstract

The pandemic process has caused significant changes in many areas of daily life. The aim is to develop a new questionnaire to evaluate the changes that occurred during the pandemic process and to examine the psychometric properties of this questionnaire. For face validity, 10 individuals were asked to interpret the questions. The Pandemic Process Status Questionnaire was tested with the help of a questionnaire created with the help of Google Forms. In order to evaluate the content validity, the content validity index and content validity ratio were used in line with the opinions of 7 experts. A pilot test was carried out. Exploratory factor analysis was performed for construct validity. The World Health Organization Quality of Life-brief version was used for convergence validity. A total of 25 items with an impact score of less than 1.5 in face validity were deleted. According to the content validity index, 15 items and 21 items according to the content validity rate were removed. In the pilot application, 5 items with an item-total correlation below 0.3 were deleted. The results of the exploratory factor analysis provided 6 dimensions: general status, physical status, psychological status, social and economic status, concerns about the pandemic, and eating habits. This structure explained 71.77% of the total variance. The questionnaire showed a weak correlation with the World Health Organization quality of life-Short Form (r=0.26). The Pandemic Process Status Questionnaire is a short and valid tool to summarize the situation encountered during the pandemic process.

Keywords: Questionnaire, Psychometrics, Pandemic, COVID-19, Validity

Introduction

The new SARS-CoV-2 Coronavirus disease was first seen in Wuhan in December 2019 and then spread rapidly all over the world. The COVID-19 pandemic was declared by the World Health Organization in March 2020 [1]. The pandemic has had significant impacts on society and health systems [2]. During the pandemic, house arrest has been implemented in many countries to prevent the spread of the virus. When these restrictions are considered in general terms, they have caused significant changes in many areas of people's daily lives such as health, economic status and eating habits, physical mobility [3]. The pandemic has caused difficulties in accessing healthcare, especially for those without COVID-19 [4]. The pandemic causes individuals in society to be inactive for a long time, and it also creates socio-psychological problems. As a result, health-related quality of life is affected [2]. Various studies have been conducted to understand the changes that the pandemic has brought about in the lives of individuals. Bai et al. conducted a network analysis of individuals' mental health and quality of life during the pandemic. The World Health Organization Quality of Life-brief version (WHOQOL- BREF) was used in the study [5]. In addition, the EQ-5D-5L questionnaire with sub-dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/

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depression was used to evaluate the effects of the pandemic on health-related quality of life [6]. The pandemic has brought significant changes in people's lifestyles, such as their eating habits. As a result of a study investigating eating and nutritional habits during the pandemic, it was determined that the number of daily meals, appetite, and weight of individuals increased [7]. In another study, an event effect scale was used to evaluate the effects of the pandemic on mental health and quality of life, including questions about mental health problems, social status, family support, and lifestyle changes [8]. Since the Neolithic Age and the Bronze Age, people have been struggling with pandemics and epidemics. Based on past pandemics, it is thought that similar outbreaks may occur in the future [9]. Considering the current as well as future effects of pandemics, scales that examine comprehensive and pandemic-specific difficulties are needed to examine changes in society [10].

The difficulties brought by the pandemic have caused many changes in people's lives. Considering past pandemics, it is also aimed to develop a new questionnaire to evaluate the changes caused by the pandemic and to evaluate the psychometric properties of the developed questionnaire

Material and Methods

A questionnaire has been developed to evaluate the changes brought about by the pandemic process in the lives of individuals living in Turkey since March 2020. The research was designed prospectively. The study was carried out between September 2020 and September 2022. The study protocol was approved by the local Clinical Research Ethics Committee (Approved number 2020/1095).

Instrument development

In order to create the items, first of all, a literature review was carried out with the help of the Endnote X9 software program. Web of Science and Pubmed databases were used. Keywords (quality of life or lifestyle behavior) and (COVID-19 or pandemic) were used in this search. As a result of this search, a total of 251 articles (Pubmed=144 and Web of Science=17) were found. After removing 70 duplicated articles, 181 articles remained. These articles were reviewed with the other author to create the items.

In addition, the draft version of the items was created considering the difficulties encountered during the pandemic process. First of all, all the questionnaire items were evaluated in terms of language by interviewing the linguist and the final version of the draft questionnaire was given.

Face Validity

Ten individuals over the age of 18 were asked to interpret the questions in the draft questionnaire. The items were evaluated qualitatively through face-to-face interviews with the participants. Those who scored less than 1.5 item effect score were excluded from the questionnaire [11].

Content validity

The items were evaluated in terms of content validity by 7 experts from different fields (1 psychological counselor, 1 engineer, 2 teachers, and 3 physiotherapists among whom two were experienced in developing questionnaires). For the content validity index (I-CVI) of the items, the experts analyzed the items according to their relevance on a 4-point Likert-type scale. I-CVI was obtained by dividing the number of experts who gave 3 or 4 points to each item by the total number of experts. As a result, items below I-CVI 0.78 were excluded from the questionnaire [12]. How necessary the items were for the scale was measured using a 3-point scale (1 = Not necessary; 2 = Useful but not necessary; 3 = Necessary). In addition, the content validity index (S-CVI/Ave) at the questionnaire level was calculated by taking the average of the I-CVI values of the items. S-CVI/Ave should be >0.90 [12]. As a result of the evaluation, the content validity ratio (CVR) was calculated. According to Lawshe, the suitable CVR value for 7 experts is 1.00.

Pilot Testing and Item Analysis

A pilot test was conducted before the explanatory factor analysis. The pilot application was carried out using a questionnaire created with the help of a Google form. This questionnaire includes the consent of the participants to the study. It also questions the participants' residence status in Turkey, name surname, and age information since March 10, 2020. Participants completed the questionnaires individually. If the item-total correlation was less than 0.3, the item was removed. In addition, if Cronbach alpha increased when any item was removed, the item was deleted [13].

Construct validity

Exploratory factor analysis was used to evaluate the construct validity. At this stage, it is stated that a sample of 100-200 may be sufficient [14,15]. Data were collected with a different sample from the pilot application. Survey questions were shared in class social media groups at the university and relatives or friends were encouraged to share the survey as well. Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity tests were used to evaluate the adequacy and suitability of the sample. Eigenvalue value was determined as ≥1 and screen plot graphic was used. The minimum factor load was determined as 0.4. Exploratory factor analysis and varimax rotation were used to determine the factors.

Convergence validity

At this stage, WHOQOL-BREF was used to assess convergent validity. Turkish validity and reliability of this questionnaire have been made [16]. This questionnaire consists of 25 questions covering physical health, psychological health, social relationships, and environment in addition to general health status. Each item is rated on a 5-point (1-5) scale. A higher score indicates better quality of life [17]. Correlations were considered

low (<0.40), moderate (0.40-0.59), substantial (0.60-0.79), and high (>0.80) [18].

Statistical analysis

Statistical analysis was done using Software SPSS 25.0 version. Data analysis was performed through exploratory factor analysis with the basic component method with Varimax rotation. The normal distribution of data was examined by Kolmogorov-Smirnov test. Correlation between PPSQ and WHOQOL - Bref was evaluated using the Pearson correlation coefficient for normal distribution data and the Spearman correlation coefficient for non-distributed data. The P value <0.05 was considered significant.

Results

The Pandemic Process Status Questionnaire (PPSQ) initially consisted of 93 items. The flowchart of the development process of the questionnaire is given in Figure 1.
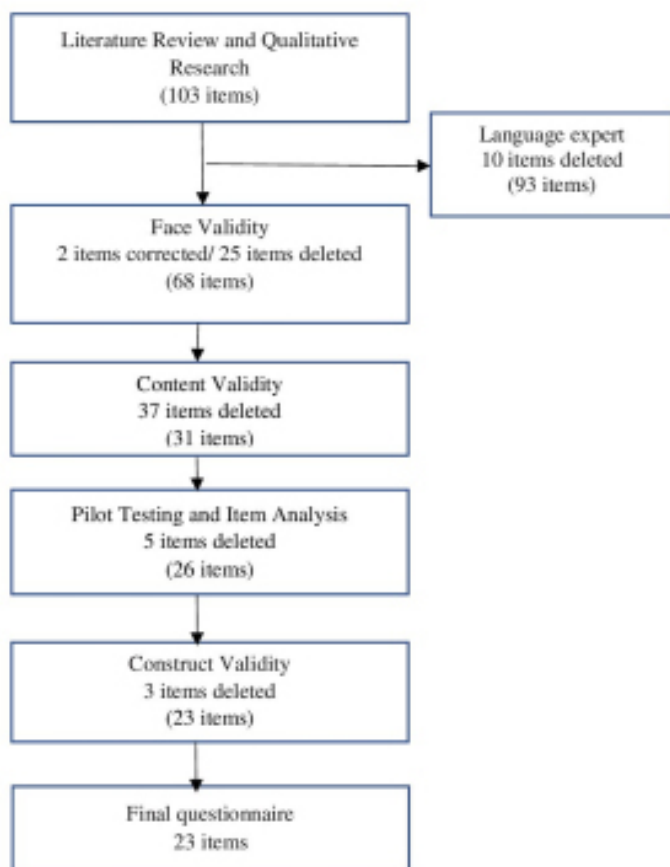

Figure 1. Flowchart for questionnaire development and validation

Face Validity

The mean age of the participants was 26.4±4.03. From a qualitative point of view, small suggestions were made for 2 items. Then, in quantitative face validity, a total of 25 items with an impact score below 1.5 were removed from the questionnaire.

Content validity

At this stage, first of all, 15 items below 0.78 according to CVI were deleted. S-CVI was found to be 0.90. Afterward, the items were examined according to the suggestions of the experts and the CVR, and 22 more items were deleted and as a result, 31 items remained.

Pilot Testing and Item Analysis

At this stage, a questionnaire was applied to 50 people. The mean age of the participants was 31.44±11.90. Cronbach's alpha was found to be 0.91. Since deleting any item would not cause an increase in Cronbach's alpha, the item was not deleted. In addition, 5 items with an item-total correlation below 0.3 were deleted. After the pilot testing, 26 items remained.

Construct validity

A total of 252 people filled out the questionnaire consisting of 26 questions. Since two of the participants did not reside in Turkey as of March 10, 2020, they were not included in the analysis. In total, analyzes were carried out for 250 participants. The mean age of the participants was 25.07±8.63. Since the value was 0.85 according to the KMO test result and Bartlett's test of sphericity test ($\chi2 = 3672,962$ df = 253, p =0.00) was statistically significant, the sample was found to be appropriate. Principal component factor analysis was performed with Kaiser Normalization with varimax rotation. As a result of factor analysis, 6 factors were obtained for the questionnaire (Table 1). The scatter plot is in Figure 2. A 6-factor solution was shown, which explained 71.17% of the variance. One item was omitted because it was not assigned to any factor (fear of being unemployed during the pandemic worries me). Two items were removed because they were loaded on 2 factors and the difference between them was small (My sleeping habits changed during the pandemic process and I think I'm starting to get obsessed with cleaning during the pandemic process.). A total of 3 items were removed from the questionnaire at this stage, and a total of 23 items were obtained.
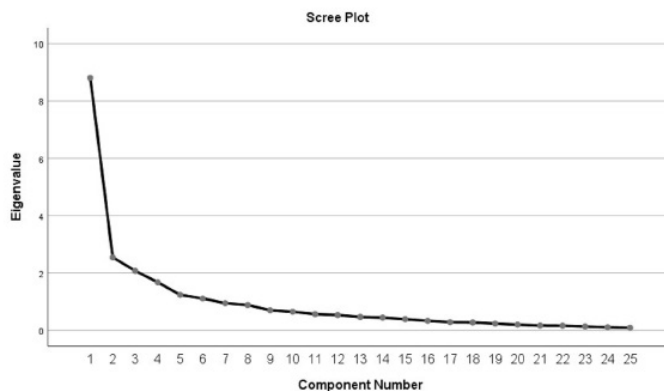

Figure 2. Scree plot for the exploratory factor analysis

Table 1. Results obtained from the factor analysis of the pandemic process status questionnaire

Code	Item	Factor Load					
		1	**2**	**3**	**4**	**5**	**6**
1	I get angry more quickly compared to before the pandemic period	0.865					
2	The pandemic process increases my anxiety level	0.833					
3	The pandemic process causes a pessimistic view of the future	0.829					
4	I feel more stressed during the pandemic process	0.741					
5	Having people around me with COVID-19 causes me anxiety		0.869				
6	I worry about the thought of being a COVID-19 carrier		0.869				
7	I'm afraid that someone from my family or close circle will catch COVID-19		0.847				
8	I'm afraid of having COVID-19		0.760				
9	My general health is adversely affected by the pandemic process			0.821			
10	The restricted life in the pandemic process negatively affects my general health			0.765			
11	Due to my various disease during the pandemic process, I have difficulties in getting health care			0.719			
12	The diseases I've had during the pandemic worry me more than usual			0.553			
13	I miss meeting my relatives and friends				0.789		
14	The pandemic process allows me to spend more time with my family				0.778		
15	I spend more time on social media than before the pandemic				0.761		
16	My social interaction decreased during the pandemic process				0.569		
17	I'm having a hard time going to work during the pandemic process				0.431		
18	The sedentary lifestyle (inactive) during the pandemic process is causing my physical health to deteriorate					0.805	
19	The sedentary and restricted life in the pandemic process reduces my physical performance					0.763	
20	Compared to the pre-pandemic period, I get tired more quickly					0.754	
21	The pandemic process makes healthy living more important for me					0.417	
22	My appetite increased during the pandemic process						0.858
23	I think I gained weight during the pandemic process						0.786
Eigenvalue		8.098	2.511	2.063	1.568	1.169	1.099
Variance explained (%)		35.208	10.917	8.967	6.817	5.082	4.780
Cumulative percentage%		35.208	46.124	55.092	61.909	66.991	71.772

Table 2. Correlation coefficient between PPSQ factors and WHOQOL ̇- BREF subscales

		PPSQ					
	Education Status	**General Status**	**Physical Status**	**Psychological Status**	**Social and Economic Status**	**Concerns about the Pandemic**	**Eating Habits**
General health	0.23**	0.08	0.19*	-0.01	0.02	0.10	
Physical health	0.40**	0.24**	0.24**	0.06	0.21**	0.12	
Psychological health	0.22**	0.16*	0.22**	0.03	0.03	0.19*	
Social relationships	0.19*	0.09	0.15*	0.01	0.11	-0.00	
Environment	0.28**	0.10	0.16*	0.05	0.06	0.08	

(WHOQOL- BREF)

PPSQ= Pandemic Process Status Questionnaire; WHOQOL ̇- BREF= World Health Organization Quality of Life-brief version

*Significant at the $p < 0.05$

**Significant at the $p < 0.01$

Convergence validity

At this stage, 166 people completed the PPSQ and the WHOQOL - BREF. The mean age of the participants was 31.76±9.86 years. The correlation between the subsections of the two questionnaires was evaluated with the Spearman test, and the correlation between the total scores of the scale was evaluated with the Pearson test. The correlations of the subsections are given in Table 2. There was a weak positive correlation between the total scores (r=0.26; p=0.00).

Scoring

The PPSQ consists of 6 sections and 23 questions. General status (4 items), eating habits (2 items), social status (5 items), and 3 questions related to physical status were scored based on a 5-point Likert scale (1=strongly agree, 5=strongly disagree). Physical status (1 item), psychological status (4 items) and concerns about the pandemic (4 items) were calculated on a 5-point Likert scale (1 = Always, 5 = Never). The lowest score on the questionnaire is 23 and the highest score is 115. Lower scores for all subsections indicate worse status. The formula was used to convert the scores into standardized scores between 0-100. According to this formula, the raw score of each section was obtained by summing the scores.

$$\text{Standardized score} = \frac{\text{Actual raw score} - \text{Lowest possible raw score}}{\text{Possible raw score range}}$$

Discussion

In this study, the PPSQ, consisting of 23 items, was developed in order to examine the changes in the COVID-19 pandemic process. It makes the interpretation of the difficulties encountered easily specific to the pandemic. In addition, the psychometric properties of the questionnaire were also tested. The questionnaire included questions about general status (4 items), psychological status (4 items), social status (5 items), concerns about the pandemic (4 items), eating habits (2 items), and physical status (4 items). The results showed that the questionnaire could evaluate the changes that occurred during the pandemic process.

The pandemic has had negative effects on many areas of life. In a study conducted in China, the first 2 items of WHOQOL-BREF were used to evaluate the impact of the epidemic on quality of life [19]. On the other hand, Chopra et al developed a survey of the impact of COVID-19 on lifestyle-related behaviors to assess the effects on eating behavior, sleep, and activity [10]. The need for different scales has also been noted to examine changes in mental health, such as fear of COVID-19 [20].

One of the factors belonging to the PPSQ is related to the psychological state. The largest factor load in this sub-dimension was related to irritability, level of anxiety, and pessimism about the future. During the COVID-19 pandemic, one in three people worldwide has been reported to have an anxiety disorder [21]. In addition, longitudinal studies after COVID-19 infection have reported deterioration in mental health and life satisfaction [22].

Looking at past pandemics, it has been reported that mental health problems such as anxiety and depression have also been reported in epidemics such as Severe Acute Respiratory Syndrome, Ebola, Middle East Respiratory Syndrome, and Zika [23].

Concerns about the pandemic were also one of the sub-dimensions. The largest factor load in this sub-dimension was related to concerns about the patients in the immediate environment, fear of contracting the disease and being a carrier of the disease. It has been stated that the biggest fears in the pandemic process are getting infected and transmitting the virus to friends or family [24]. The general health sub-dimension included the impact on the general health of the pandemic and the difficulties in accessing health services during the pandemic. One of the challenges of the pandemic was access to healthcare. Situations not related to COVID-19 have delayed access to and care for healthcare in Italy [25]. In the sub-dimension of social status, the largest factor load was related to longing for relatives and friends. The pandemic has caused great social isolation and people are driven into loneliness [26]. In addition, the item about spending more time with family members during the pandemic was also important in this sub-dimension. As a common result of disasters, there may be conflicts within the family along with psychological disorders. During the pandemic process, family members had to spend more time as a result of social isolation and restrictions. Most of the individuals included in a qualitative study reported strained family relationships [27]. Again, the item related to the increase in the use of social media in this sub-dimension also showed a high factor load. Due to the physical distance rules during the pandemic process, societies have excessively increased the use of social media for work, education, or social [28]. The item with the largest factor load in the physical health sub-dimension was related to the effect of sedentary life in the pandemic process. It is stated that sitting time and inactivity increase during the pandemic process and this situation negatively affects the quality of life [2]. In the PPSQ, there were items related to increased appetite and weight gain in the sub-dimension of eating habits. It is reported that there are many changes in lifestyle behavior during the pandemic process. One of them is eating behaviors. As a result, weight gain occurs [29].

As a result of the content validity, the S-CVI was found to be 0.90. This indicates strong validity for the questionnaire [13]. As a result of the exploratory factor analysis, the 6-factor structure explained 71.77% of the total variance. WHOQOL - BREF was used for convergence validity. This questionnaire has been used for validity in many quality-of-life scales [18,30]. PPSQ showed similar characteristics in most sub-dimensions, although not the same number of dimensions as WHOQOL - BREF. However, the correlation between the questionnaires was low. In another study, a low correlation was shown between WHOQOL - BREF and Health Protective Behavior Scale (r=0.34) [18]. This was similar to our study.

The strongest aspect of the study was that it used different samples

at each validation stage. Also, this study has some limitations. First of all, it was aimed to reach individuals in different age groups. However, due to the fact that our study was conducted online, the adaptation and interest of the older age group were less. In addition, our lack of reliability analysis was an important limitation.

Conclusion

PPSQ is a valid tool to evaluate the situation encountered during the pandemic process in detail and in a short time. This questionnaire can help healthcare professionals assess the changes brought about by the pandemic. It can also be used for evaluation in various scientific research.

Patient informed consent
Signed informed consent was gathered from the participants for this study.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical approval
The study protocol was approved by the local Clinical Research Ethics Committee (Approved number 2020/1095).

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ORIGINAL ARTICLE

Assessment of enteral nutrition through feeding stomas or gastric tubes in digestive surgery

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Abstract

Ostomy feeding remains a reference approach for enteral nutritional assistance. In Madagascar, the techniques are still conventional surgical procedures due to the lack of adequate endoscopic equipment. This study aims to evaluate the benefits and risks of enteral nutrition with a two-week follow-up. Included patients who had benefited from enteral nutrition by tube feeding using nasogastric, gastrostomy, and jejunostomy tubes over six months in Joseph Ravoahangy Andrianavalona Hospital. Prevalence, age and gender, current body mass index (BMI), weight, nutritional grade, initial pathology, psychological status, comorbidities, type of feeding stoma, and the surgical technique (gastrostomy or jejunostomy) were studied. After 15 days, the effectiveness of enteral nutrition was assessed using BMI, serum albumin, C-Reactive Protein (CRP) level, as well as postoperative complications and quality of life. The patient's outcome on the 15th day has been determined. The Chi-square test analyzed the associations and Mann Whitney test compared the effects of enteral nutrition by ostomy and gastric tube use. Forty-two patients were included, aged 47(17-78). The sex ratio was 0.5. Initially, the body mass index was 17(12-23) kg/m², the serum albumin value 3.4 (2.5-4.7) gr/dl with a median CRP level of 16 (2-74.2) mg/l. Nutritional assistance resulted in a weight variation between baseline and 15th day. Comparing enteral nutrition by ostomy and gastric tube, only variation of C Reactive Protein on the 15th day has a significative difference. Mortality was 33% (gastrostomy), 31% (jejunostomy), 24% (nasogastric tube). Nutritional support and the choice of ostomy or gastric tube for enteral nutrition were not associated with mortality. The effectiveness of nutritional assistance is still questionable in this study if the results are more promising in the literature. The death rate linked to the initial pathology and the general state of the patients is still considerable, hence the interest in decision-making in multidisciplinary consultation meetings.

Keywords: Body mass index, madagascar, enteral nutrition, nutritional assessment, ostomy

Introduction

Undernutrition reflects a mismatch between the body's protein and energy requirements, with tissue losses having deleterious consequences for the body [1,2]. Since its description in 1980 by Gauderer and Ponsky, the creation of an ostomy for enteral nutrition has been one of the alternatives for prolonged medium and long-term enteral nutrition [2]. European reviews still mention the difficulty of its indication, as the impact of the intervention on the improvement of the general state of the patients must be assessed by evaluating the benefits in terms of nutrition and the risks of the operation with a quality of life that can sometimes be poor [3]. A feeding stoma can be for palliative purposes or as a perioperative preparation for esophageal surgery.

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Indeed, the "Société française d'Anesthésie et de Réanimation" (SfAR) and the "Société Francophone de Nutrition Clinique et Métabolisme" recommend perioperative nutritional management in order to reduce the operative risks linked to undernutrition [4]. In Madagascar, techniques are still conventional with a surgical approach due to inadequate endoscopic equipment. Hence the question: "What is the impact of nutritional rehabilitation by stoma in the Joseph Ravoahangy Andrianavalona University Hospital, Antananarivo - Madagascar?" The main aim of the present study was to evaluate the benefits and the risks of enteral feeding in digestive pathologies. The specific objectives were to describe the main indications for enteral feeding, evaluate the evolution of the nutritional status of the patients and assess the quality of life of the patients.

Materials and Method

It was conducted a prospective case series, monocentric over a period of six months at the Joseph Ravoahangy Andrianavalona University Hospital (CHU-JRA). The study was approved by the University Hospital J.R. Andrianavalona and the Department of Surgery and the Department of Anesthesia and Resuscitation of the Faculty of Medicine of Antananarivo. This study included patients aged at least 18 years, all genders included, operated for a feeding gastrostomy or jejunostomy following upper aerodigestive cancers or non-oncological stenosing esophageal lesion. Also included were patients who had received enteral nutrition via a nasogastric tube. Patients who had received oral nutrition with a "homemade" diet were not included in the study. The classification of age, gender, and ASA (American Society of Anesthesiologists) was collected. In order to assess the nutritional efficacy of the feeding stomas, the team systematically took weight and height to calculate the body mass index (BMI) at the time of the study, the usual weight. Also, the initial pathology, risk factors of undernutrition such as psychological status, comorbidities (obesity, chronic inflammatory disease, autoimmune disease, long-term corticosteroid treatment, immune status, oncological pathology, treatment), and the morbidity of the surgery to determine the nutritional grade. Preoperative nutritional preparation (adapted according to the results of the preoperative check-ups [hemoglobin, blood ionogram, serum albumin, C-Reactive Protein or CRP level]) was assessed. In addition, the emergency or a scheduled characteristic of the surgery and the type of feeding stoma were assessed. In Madagascar, due to the limited technical resources, the feeding stomas were made by a surgical approach according to the Fontant or Witzel method. After a fortnight, the same parameters (weight gain, BMI, serum albumin, CRP level for adjusting serum albumin value) were reassessed. Postoperative complications were classified according to the Clavien-Dindo score. This score classifies surgery-related complications from I to V. The apparition of gastroesophageal reflux, inhalation pneumonitis, postoperative infection, and peri-stomal lesions also allowed the quality of the stoma and were assessed. Patients' quality of life according to their stomas was also assessed by the

EuroQol-5D, evaluating the level of depression and self-esteem (good, middle, bad); patients also rated their satisfaction on a scale of 0 to 10. Continuous variables are expressed as median with extremes and categorical variables as frequency. The Chi-square or exact Fisher tests were used for analyzing association between parameters. Mann Whitney comparison test was used to note the similarity or dissimilarity between enteral nutrition by ostomy or gastric tube after 15 days. Participants were not remunerated; the anonymity of the patients was respected.

Results

At the end of the study, 42 patients were included, aged 47 (17-78) years, and half (52%) of them were older than 50 years. There was no gender predominance, and the sex ratio was 0.5. The ASA score was more significant than or equal to 2 in 78% of cases (Table 1). The weight of the patients was 47 (34-67) kg with a BMI at the time of the study of 17 (12-23) kg/m². Weight loss greater than 10% of the initial weight was noted in 18 patients (42%). The serum albumin value was 3.4 (2.5-4.7) gr/dl with a median CRP level of 16 (2-74.2) mg/l (Table 2).

Table 1. Profile of study population

		n	%
Gender	Female	21	50
	Male	21	50
Age (years)	< 20	5	12
	[20-30]	9	21
	[30-40]	6	14
	[40-50]	4	10
	[50-60]	8	19
	[60-70]	9	21
	≥70	1	2
IPS[1]	IPS <2	16	38
	IPS ≥2	26	62
AFC[2]	1	23	55
	2	18	43
	3	1	2
ASA[3]	1	11	26
	2	22	52
	3	9	21
	4 à 6	0	0
Oncological diseases		30	71

[1]: Indice de Performans Status; [2]: Association Française de Chirurgie; [3]: American Society of Anesthesiologists

Table 2. Nutritional status of the study population before enteral nutrition

		n	%
Intake weight variation	Weight loss	24	57
	Weight gain	15	36
	No weight variation	3	7
Serum albumin (g/L)	≥35	13	31
	[30-35]	12	29
	<30	17	40
CRP level (mg/L)	<6	26	62
	≥6	16	38
Nutritional grade	2	17	40
	3	22	52
	1 et 4	3	7

Twenty-five (59%) patients had a feeding jejunostomy versus three (7%) feeding gastrostomies; fourteen (33%) patients were malnourished with a gastric tube (Table 3). Fifteen feeding

stomas procedures (35%) were performed under local anesthesia.
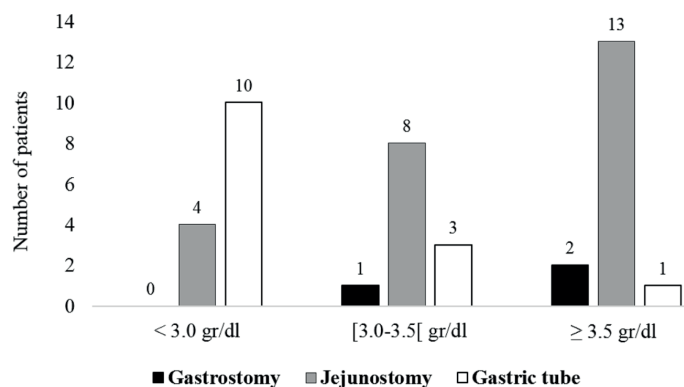
Figure 1. Serum albumin at D15

The targeted caloric intake was between 2500 and 3000 Kcal/d with hyper protein diets, fractionated (Fortimel®, Fresubin®, Supportan®, Diben®). After a 15-day follow-up, the weight gain was 2 (1-5) kg.

The indications of the route of enteral nutrition were given after multidisciplinary concertation in 74% of cases (n=31).

Table 3. Comparison of effects of enteral nutrition at the 15th day (D15)

		n (%)	Ostomy		Gastric tube	P
			Gastrostomy	Jejunostomy		
EuroQol-5D (D15)	Good		0 (0%)	6 (14%)	0 (0%)	
	Middle		2 (5%)	10 (24%)	12 (29%)	0.543
	Bad		1 (2%)	8 (19%)	3 (7%)	
Clavien Dindo Score (D15)	I		1 (2%)	19 (45%)	13 (31%)	
	II		1 (2%)	1 (2%)	2 (5%)	0.471
	III		1 (2%)	1 (2%)	0 (0%)	
	IV		0 (0%)	3 (7%)	0 (0%)	
Weight variation (D15)	Weight gain		1 (2%)	13 (31%)	1 (2%)	
	Weight loss		2 (5%)	12 (29%)	10 (24%)	0.300
	No weight variation		0 (0%)	0 (0%)	3 (7%)	
Serum albumin variation (D15)	Increased serum albumin		1 (2%)	14 (33%)	10 (24%)	
	Decrease serum albumin		2 (5%)	11 (26%)	4 (9%)	0,294
CRP variation (D15)	Increased CRP level		2 (5%)	10 (24%)	4 (9%)	
	Decreased CRP level		1 (2%)	15 (36%)	10 (24%)	0.021
Outcome at D15	Patient survival		2 (5%)	18 (43%)	10 (24%)	
	Death		1 (2%)	7 (17%)	4 (9%)	0.351

More than half (55%) of the interventions were performed in an emergency. The introduction of enteral nutritional assistance (via stoma or gastric tube) was not associated to the variation between the initial serum albumin level and the serum albumin level at D15 (p=0.115) and did not cause a change between initial and D15 CRP levels (p=0.561). At D15, serum albumin at D15 was 3.7 (2.2-5.0)gr/dl (figure 1) and CRP levels were 15 (1-68.2) mg/l. Median weight was 46 (35-69) kg BMI was 17 (10-24) kg/m² at D15. An augmentation of weight (+6 (1-15) kg) and serum albumin (+0.2 (0.1-1.5) gr/dl) were observed after nutritional support; a decrease of -3.5 (1-9) kg and -0.2 [0.1-1.1] gr/dl (serum albumin) were also noticed (Table III). Accelerated rehabilitation was recommended in 76% (n=32). This technique promotes early oral refeeding and early lifting after digestive surgery. However, complications were found; the main complications included: local infection (n=5), failure to refeed (n=2), poor tube fixation leading to tube removal (n=2), evisceration (n=1), pneumopathy (n=3). Whatever the type of nutritional support, there was no significant association with variations of weight, serum albumin or CRP levels, or with the occurrence of complications at D15, or patient outcome (p>0.05). The choice of ostomy type or gastric tube was significantly associated with variations of CRP at D15 (p=0.042) but not with the weight variations (p=0.086) nor serum albumin variations (p=0.091). The presence of an ostomy did not impaire patients' quality of life (p=0.091). Eleven (26%) patients died after 15 days, with 33% for those who had gastrostomy, 31% with jejunostomy and 24% when patients had nasogastric tube. The parenteral and/or enteral nutrition support and more specifically, the choice of enteral nutritional support by ostomy or gastric tube was not associated with the occurrence of death (p=0.487).

Discussion

Indication

In the present study, the indication for a feeding stoma (n=28) predominated over enteral feeding via the gastric tube (n=14). Ostomies are to be preferred for a predictable feeding period of more than four weeks, in particular, for home feeding, in case of esophageal or gastric obstruction, a swallowing disorder (neurological, ENT disease), or in case of severe undernutrition requiring an energy intake not covered by oral feeding [6]. A meta-analysis of data published in the literature in 2005 reviewed the issue [7]. Patients who did not receive a nasogastric tube tended to have fewer infectious pulmonary complications. Enteral nutrition is less expensive, more physiological, easier to administer at home, maintains intestinal trophic, and has less risk of infectious morbidity. Enteral feeding can be done orally with nutritional supplements through a gastric tube (nasogastric, pharyngostomy, oesophagostomy, gastrostomy), duodenal (nasoduodenal, extended gastrotomy), jejunal (nasojejunal or jejunostomy). Nutrition via a feeding stoma tube is less invasive and causes less discomfort than the nasogastric tube [7]. In the present study, the use of ostomy or gastric tube was not

associated with quality of life and in comparison with gastric tube, the difference of quality of life was similar with ostomy.

Perioperative preparation [8]

The patients had a BMI of 17 (12-23) kg/m². If the patient is undernourished with a BMI less than or equal to 18, the operative risk is high, leading to a possible report of the surgical indication. Indeed, severe malnutrition with a serum albumin level below 25g/dL is a poor prognostic factor [8]. Following a consensus conference in December 1994, the French National Authority for Health (HAS, "Haute Autorité de Santé") recommends an initial refeeding by gastric tube for a minimum of seven days if there is important stenosis in the upper digestive tract [12]. For patients at high risk of anesthesia, local anesthesia was performed in the present study under the supervision of an anesthetist.

Feeding protocol [12]

In the results presented, the diet was fractionated and high in protein. For an adult male, the recommended energy intake is, on average, 2.400 to 2.600 calories per day, depending on activity. For an adult woman, it is 1,800 to 2.200 calories. In 95% of cases, the polymeric solution with fibers (semi-elemental solution: more expensive, not more efficient, decreasing gastric emptying, increasing the risk of diarrhea, without increasing digestive tolerance and nitrogen balance). Hypercaloric solutions can reduce volumes and/or flow rates, but the risk of diarrhea is introduced too quickly. Feeding can be intermittent or by bolus over a short period, continuous at a regular rate for several hours, or possibly cyclical with continuous feeding. In principle, start with 500 ml over 24 hours, i.e., 21 ml/hour, and then, depending on tolerance, increase by 500 ml every 24 hours to reach the target in 3-4 days, i.e., an increase in the rate of 21 ml each day. In the presence of diarrhea and/or intestinal bloating, start with 250 ml/24^h and increase by 250 ml each day, i.e., 11 ml/hour [12]. Diarrhea should not be considered a failure either but should be investigated as a cause of diarrhea or as a result of poor adherence to the administration rules.

Efficiency of stoma feeding

Enteral nutrition, initially developed in France by Etienne Levy in the early 1970s, has become a primary refeeding technique [3]. More physiological than parenteral nutrition, it represents the gold standard in the administration of nutritional assistance today [3].

Van Dyck et al. [8] had shown that enteral nutrition reduced iatrogenic infectious morbidity in patients and stimulated their immune system and systemic inflammatory response. Paradoxically, a multicentre trial in Scandinavia on 453 patients conducted by Senesse P et al. [13] did not show a significant difference between enteral and parenteral nutrition. Nevertheless, about enteral nutrition, nutrition by ostomy was associated with more inflammatory phenomenon, also, comparing to gastric tube,

there was more elevation of CRP when ostomy was indicated. Feeding stomas had the highest mortality, with one-third of patients affected. The main evaluation criteria in the present study were based on: weight, BMI, Nutritional Grade, albumin, and CRP. In the literature, the Mini Nutrition Assessment (MNA) score is also recommended to assess the state of undernutrition [12]. The MNA score is based on the occurrence of anorexia in less than three months, recent weight loss in three months, motor skills, psychological stress, neuropsychological problems, and Body Mass Index [12].

Feeding stoma monitoring

Infectious complications, such as ostomy site infection (n=5) and pneumonia (n=3), followed by mechanical complications such as poor fixation of the ostomy feeding tube (n=2), were the main complications found. Possible complications are also screened when assessing the effectiveness of the digestive stoma refeeding. Complications related to the ostomy tube are nil for surgical gastrostomies, 12.1% for radiological gastrostomies, and 16% for Percutaneous Endoscopic Gastrostomies (PEG) [8,9]. The latter are mainly represented by: peristomal leakage due to delayed healing, local infection, gastric hypersecretion, a tube that is too "loose," or excessive torsion in the stoma pathway [9]. The following have also been observed: buried bumper syndrome, poor tube fixation, stoma irritation, reflux leading to pneumopathy, and failure to refeed [11]. In a meta-analysis of 5,752 patients with a feeding stoma comparing surgical, radiological, and endoscopic approaches, procedural mortality was 2.5% vs. 0.3% vs. 0.5% for PEGs, and 30-day mortality was 29% vs. 13.3% vs. 15.4% respectively [9]. According to regression analysis: independent predictors of these early morbidities were: advanced age, pressure sores, hypoalbuminemia, severe undernutrition, progressive disease, pulmonary infection, presence of comorbidities, institutionalization, and length of hospitalization before gastrostomy [11-13]. Early and late bronchopneumonia are common and are the main causes of mortality [12]. The severity depends on the cough reflex - pharyngeal reflex - ciliary transport - virulence of bacteria, their concentrations, and the host (defenses). Tubes of the ostomies promote bronchopneumonia by increasing gastroesophageal reflux, esophageal motor disturbances, alteration of the lower and upper esophageal sphincter, and an increase in the contents that may reflux [11]. Some complications were found in this study, especially aspiration pneumonitis and some lesions around ostomy.

Suggested actions according to current recommendations

The present study's monitoring criteria were based on weight, BMI, albumin, and CRP. According to the recommendations, nutritional efficacy is assessed based on compliance with the prescription, clinical monitoring (with weight measurement twice a week, body composition every 15 days), biological monitoring (albumin every 15 days, pre albuminemia with CRP, osmolality twice a week to detect possible micronutrient deficiencies) [13]. Serum albumin reflects protein metabolism. On the other hand, albumin measurement allows us to distinguish between an isolated intake deficiency where it is normal and malnutrition due to hypercatabolism, where the albumin level will fall rapidly. Hypoalbuminemia is determined when the level is ≤35 g/l [13]. CRP is an inflammatory protein. Its half-life is 12 hours. An elevated CRP (>20 mg/l) reflects an inflammatory state and, therefore, a risk of hypercatabolism and, therefore, a high risk of undernutrition, particularly in the elderly [13]. Other parameters can also reflect the evolution of the nutritional status of patients. Transthyretin reflects short-term protein synthesis (half-life =48 hours). It is, therefore, a very good marker for monitoring nutrition. Low transthyretinemia level is defined as a level ≤110 mg/l. The orosomucoid, whose pathological threshold is 1.2 g/l, the serum lymphocyte level, when it is less than 1000/mm³, although not very sensitive, indicates profound undernutrition. In addition to these main assays, more specific micronutrient assays (vitamins and/or trace elements) can be added according to the clinical context [9]. In the current Malagasy context, some of these tests are not yet available, so it would be essential to introduce them into practice to improve management.

The Nutritional Risk Index is another index for assessing nutritional status [12]. In the present study, no index was investigated other than the nutritional grade, which was easier and faster to assess. The NRI is calculated as follows: NRI = (1.489 x Albumin (g/l)) 41.7 x (Current weight / Usual weight). When the index is above 100, the nutritional status can be considered satisfactory. Mild undernutrition is defined as between 97.5 and 100, moderate undernutrition between 83.5 and 97.5, and severe undernutrition when it is less than 83.5 [1,2]. Calculating this score would allow a more refined consideration of the patient's nutritional status to assess their nutritional status.

This study was limited by cognitive biases, as patients and their relatives may have difficulty following the diet protocol, which may affect therapeutic efficacy.

Conclusion

The indication for a feeding stoma was far superior to that of feeding via a nasogastric tube in this study, with a significant impact on complications but no significant difference in efficacy. This effectiveness of feeding assistance is still debatable in the present context if the results are more promising in the literature. This could be related to the comorbidity of the patients due to the initial oncological pathology. The nutritional evaluation criteria were clinical-biological and repeated. The rate of death associated with the initial pathology and the patients' general state remains considerable in our study, hence the interest in decision-making in a multidisciplinary consultation meeting. In developed countries, these stomas can be installed radiologically, endoscopically using the "Pull" or "Introducer" method, or laparoscopically. These approaches are less invasive and more

beneficial for a patient who is already fragile from the start, hence the interest in developing these techniques locally.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was approved by the hierachy of the unity and the CHU JRA.

Patient informed consent
This study is an original article where we have studied the patients' files. The patient give their consent for the intervention. Document which is in the patient hospital file.

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ORIGINAL ARTICLE

Importance of curcumin effect and asprosin level on glucose metabolism in diabetic rats

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Abstract

Asprosin is a new hormone secreted mainly from white adipose tissue. It may be associated with the pathogenesis of obesity, diabetes and some metabolic diseases. The changes in plasma asprosin levels of experimental diabetic rats and the relation of these changes with liver glucose metabolism and some diabetes parameters were investigated, and the effects of metformin, gliclazide or curcumin treatment on plasma asprosin levels were tried. The study was designed as an animal model in diabetic rats The albino rats were divided into five groups. To induce diabetes, a single dose of STZ was injected intraperitoneally. Diabetics rats were treated intragastrically with metformin (D+Metformin group), gliclazide (D+Giliclazide group) or 20 curcumin (D+Curcumin group) for eight weeks. Fasting blood glucose, insulin levels and other parameters were measured. Plasma asporsin levels of untreated diabetic rats increased significantly (P<.001). Although the plasma asprosin levels of diabetic rats treated with the rugs were significantly lower (P<.001). Fasting blood glucose levels of diabetic rats treated with the drugs were found to be remarkably lower than the diabetic control values (P<.001, respectively). There was no significant difference in the insulin levels and HOMA-IR between these three groups. Curcumin treatment provides significant improvements in plasma asprosin level and diabetes parameters. The increase in plasma asprosin level in diabetic rats may be one of the main reasons that facilitate the development of the disease or is responsible for its pathogenesis. Our findings support the idea that curcumin may be an important treatment option for diabetes.

Keywords: Streptozotocin, Metformin, Gliclazide, Curcumin, Rat

Introduction

Diabetes mellitus (DM) is a very important metabolic and chronic disease affecting all organs and systems. Micro and macrovascular complications occur, especially in uncontrolled patients [1]. It is interesting that complications may develop in some patients despite being under medical control. Therefore, alternative appropriate treatment methods should be developed to treat the disease and prevent complications [2]. Oxidative stress has been noted in the pathogenesis of diabetes, since some complications cannot be prevented despite treatment with insulin or antihyperglycemic drugs. Based on this, it has been suggested to add various antioxidants to the treatment protocol in recent years [3].

The mechanisms involved in the pathogenesis of diabetes have

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not yet been fully clarified. In recent years, some hormones defined as adipokines/adipocytokines secreted from adipose tissues have been associated with the pathogenesis of diabetes. Asprosin, which is encoded by the Fibrillin 1 gene in white adipose tissue, is a new hormone discovered in 2016. The main source of asprosin in the blood is white adipose tissue [4]. Asprosin, secreted between meals to maintain the energy level, stimulates the release of glucose from the liver into the bloodstream [5]. As a glucogenic hormone, it stimulates the appetite center in the hypothalamus while increasing the release of glucose from the liver to maintain glucose homeostasis [6]. It is thought to be associated with the pathogenesis of diabetes, as it directly stimulates hepatic glucose secretion and appetite. However, our current literature on the effects of asprosin on glucose metabolism and its relationship with diabetes parameters is not yet sufficient.

In this study, possible changes in plasma asprosin levels of diabetic rats induced by streptozocin(STZ) and the relationship of this change with glucose metabolism, insulin resistance and other diabetes parameters were investigated. Moreover, the effects of metformin, gliclazide and curcumin, which is claimed to be an antidiabetic phytochemical agent, on plasma asprosin levels and liver enzymes related to glucose metabolism were evaluated comparatively.

Key Points

• Asprosin uses various intracellular signals and prepares the ground for insulin resistance through disruption of glucose metabolism.

• Changes in plasma asprosin levels are associated with some diabetes parameters and have a positive effect on plasma asprosin levels after clinical improvement with antidiabetic treatment.

• Treatment of diabetic rats with curcumin resulted in improvements in fasting blood glucose, asprosin levels, and insulin resistance. These results suggest that curcumin, which is known to have no known side effects, may gain a more important place among antidiabetic drugs in the future.

Material and Methods

Experimental methods

Our project was approved by Dicle University Animal Experiments Local Ethics Committee with protocol number 2019/07/4 and date 28/03/2019. In this study, thirty-five Wistar albino adult male rats (224-295 g.) were used. Subjects were divided into one control and four diabetic groups, each with 7 rats. To induce diabetes, STZ solution (single dose, 60 mg/kg) prepared in phosphate-citrate buffer (pH: 4.5) was injected in the same way 15 minutes after nicotinamide (110 mg/kg) was administered intraperitoneally. Two days later, fasting blood glucose was measured in blood samples taken from the tail vein with a glucometer (Plusmedfast test, Tyson Bioresearch

Inc., Taiwan). Those with a blood glucose level of 14 mmol/dl=250 mg/dl and above were included in the diabetic groups. All groups were fed in stainless steel cages with 12 hours light, 12 hours dark and 22±2 °C with normal pellet feed and tap water for 8 weeks without any restriction. Healthy rats and non-medicated diabetic rats were fed a normal diet, and no drugs were administered. Only placebo (tap water) was given by gastric gavage. Other diabetic rats were treated with 150 mg/kg/day metformin (D+Metformin group), 10 mg/kg/day gliclazide (D+Gliclazide group), or 200 mg/kg/day curcumin extract (D+Curcumin group) by gastric gavage for 8 weeks. Weekly decrease or increase in body weight and fasting blood glucose measurements of all groups were determined. At the end of the eight-week experimental period, rats were sacrificed by cardiac puncture under mild ketamine anesthesia after 12 hours of fasting. After the abdomen was opened and the liver samples taken were homogenized, hexokinase (HK),pyruvatekinase (PK), glucose-6-phosphatase (G6P-az) and glucose-6-phosphate dehydrogenase (G6PD) activities related to glucose metabolism were measured using appropriate kits and methods.

Chemicals and application methods

To induce diabetes, nicotinamide (Sigma Chemical, St. Louis, MO., USA) dissolved in saline was administered intraperitoneally at a dose of 110 mg/kg after 12 hours of fasting. After 15 minutes, a single dose of 60 mg/kg STZ (Sigma Chemical, St. Louis, MO., USA)] dissolved in 0.1 M phosphate-citrate buffer (pH: 4.5) was injected intraperitoneally. Eight hours after STZ injection, 15% glucose solution given to prevent hypoglycemia.

Preparation of Samples

Blood samples taken by cardiac puncture were centrifuged at 3000 rpm for 10 minutes (Heraeus Biofuge Stratos; Kendo Laboratory Products, Osterode-Germany), and their sera were separated. To obtain plasma samples, blood samples were placed in EDTA tubes. Serum and plasma samples placed in Eppendorf tubes were stored at -80°C until analysis.

After the liver tissues were rapidly homogenized, the supernatants were stored at -80°C until the enzyme activities were measured by ELISA.

Measurement methods

Insulin Level

Serum insulin concentration was measured spectrophotometrically with a rat insulin ELISA kit from Sun Red (Catalog no: 201-11-0708) Biochrom in an ANTHOS-ZENYTH200 Microplate reader.

Plasma Asprosin Level

A rat asprosin ELISA kit (Sun Red, catalog no: 201-11-2025) was used to measure plasma asprosin levels. After the absorbances were determined spectrophotometrically in a microplate reader (Biochrom®ANTHOS-ZENYTH200), the results were expressed as pg/mL.

Other Biochemical Parameters

Fasting blood glucose, TG, TC, VLDL-C, LDL-C and HDL-C levels were measured on the Abbott Architect C16000 Photometric Autoanalyzer device using Abbott Diagnostics original kits (Abbott Laboratories, Abbott Park, IL, USA). The HOMA-IR (homeostatic model assessment-insulin resistance) formula was used to determine HOMA-IR.

HOMA-IR was calculated using the formula below after measuring fasting blood insulin and glucose levels. HOMA-IR=Fasting Glucose (mg/dL) X Fasting insulin (uIU/mL)/405. In addition, parameters related to lipid metabolism, including serum triglyceride(TG), total cholesterol (TC), High-density lipoprotein-cholesterol (HDL-C),Low-density lipoprotein-cholesterol (LDL-C) and Very Low-Density Lipoprotein Cholesterol (VLDL-C) levels, were determined.

Liver enzymes

Nine milliliters of phosphate buffer solution was added to one gram of liver tissue and homogenized in a Bandelin-UW 2070 brand tissue homogenizer at 15000 rpm for 60 seconds. The homogenates were centrifuged at 5000 rpm for 10 minutes at 4°C. Supernatants were transferred to Eppendorf tubes, and liver enzymes were measured spectrophotometrically in the Biochrom ®ANTHOS-ZENYTH200 Microplate reader with HK, PK, G6P-az and G6PD Sun Red brand ELISA kits on the same day.

Statistical Evaluation

SPSS 25 version statistical program was used in computer environment for data analysis. Student's t test was used for comparisons between binary variable groups, and analysis of variance (ANOVA) was used for more than 2 comparisons. Tukey's test was used for multiple comparisons within groups. Positive or negative relationships among the data were determined with Spearman's correlation test. The results are expressed as the arithmetic mean±standard deviation, and p <0.05 was considered significant for one-way ANOVA, Tukey's test, and Spearman's correlation tests.

Results

Body weight changes of the rats

The weekly feed and water consumption and body weight changes of all groups are shown in Table 1. The feed and water consumption of all groups, except the D+ metformin group, increased significantly over the weeks. However, diabetic rats consumed more feed and water than healthy controls. While the body weights of healthy rats increased over time, the body mass of diabetic patients who consumed excessive feed and water decreased significantly.

Plasma asprosin levels

After the experimental period, the fasting plasma asprosin levels of all groups are shown in Table 2. Plasma asporsin levels of untreated diabetic rats increased significantly (P<.001). Although

the plasma asprosin levels of diabetic rats treated with metformin, gliclazide or curcumin were significantly lower (P<.001), they did not fully return to normal healthy values. When the effects of these three antidiabetic agents on blood asprosin levels were compared, no significant difference was found between them (Figure 1).
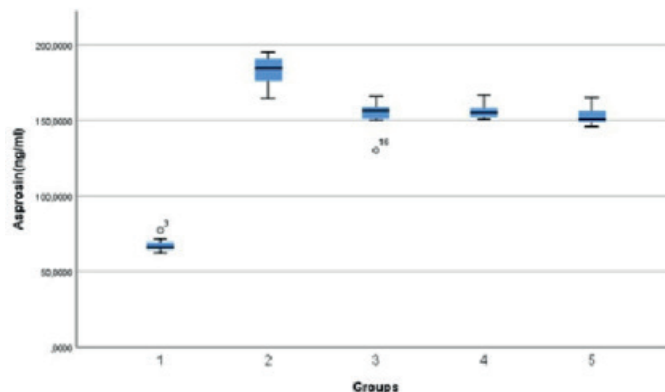
Figure 1. Plasma asprosin levels of healthy controls and diabetic rats treated with metformin, gliclazide and curcumin

Fasting blood glucose, insulin levels and HOMA-IR

As seen in Table 3, fasting blood glucose levels of diabetic rats treated with metformin, gliclazide or curcumin were found to be remarkably lower than the diabetic control values (P<.001, respectively). However, it was determined that the antidiabetics used could not provide a complete improvement in fasting blood glucose level and were effective at a rate of 18%, 27% and 19%, respectively. Although antidiabetic treatment with metformin, gliclazide or curcumin increased insulin levels in diabetic rats, this increase was not statistically significant. In addition, the insulin levels of these three groups were quite close to each other, and there was no significant difference between them (Figure 2). Thus, the effects of metformin, gliclazide and curcumin on HOMA-IR in diabetic rats were also quite similar. Antidiabetic treatments improved insulin resistance by 9%, 20%, and 13%, respectively.

Figure 2. The effects of curcumin on insulin level, glucose level and insulin resistance in diabetic rats and comparison with the effects of metformin and gliclazide

Table 1. Change in body weight (g) at the end of the 1st and 8th weeks of all groups

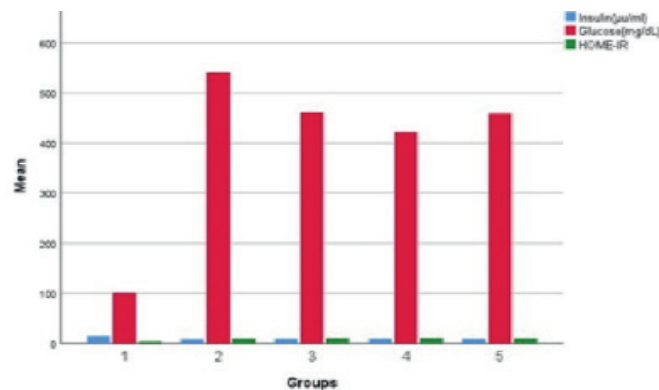| Weeks	Groups				
	Control Mean(SD)	**Diabetic (DM)** Mean(SD)	**DM+Metformin** Mean(SD)	**DM+Gliclazide** Mean(SD)	**DM+CurCumin** Mean(SD)
Week 1	450.3(44.1)[p=.971]	496.4(24.6)[p<.001*]	448.3(21.9)[p<.001*]	451.3(38.3)[p=.003*]	443.9(19.9)[p<.001*]
Week 8	449.6 (26.4)	299.6(2.6)	345.4(36.1)	341.8(63.7)	364.6(28.5)

P: Pairwise group comparisons for continuous variable *: P<.05 was considered statistically significant (Student's t test) SD: Standard deviation

Table 2. Comparison of Asprosin level between rat groups

Parameters	Groups				
	Control Mean(SD)	**Diabetic (DM)** Mean(SD)	**DM+Metformin** Mean(SD)	**DM+Gliclazide** Mean(SD)	**DM+CurCumin** Mean(SD)
Asprosin	67.5(5.2)[β]	182.3(11.1)[a]	153.1(11.4)[a,b]	156.0(5.6)[a,b]	152.9(7.1)[a,b]

All data were calculated using the Tukey test for p Multiple Comparisons (Mean difference is significant at the p<.05 level). P[a]<.001 compared with the control group, P[b]<.001 compared with the diabetic group

Table 3. Comparison of Insulin, Glucose and HOMA-IR between rat groups

Parameters	Groups				
	Control Mean(SD)	**Diabetic (DM)** Mean(SD)	**DM+Metformin** Mean(SD)	**DM+Gliclazide** Mean(SD)	**DM+CurCumin** Mean(SD)
Glucose (mg/dl)	100.3(9.3) [β]	541.3(21.3)[a]	460.7(47.4)[a,b]	421.3(10.6) [a,b]	458.4(19.7)[a,b]
Insulin (μU/ml)	14.8(0.7) [β]	7.7(0.6)[a]	8.5(0.9)[a]	8.6(0.8)[a]	8.2(0.7)[a]
HOMA-IR	3.7(0.4) [β]	8.9(0.8)[a]	9.6(1.2)[a]	10.2(0.6)[a,b]	9.3(0.7)[a]

All data were calculated using the Tukey test for p Multiple Comparisons (Mean difference is significant at the p <.05 level).The HOMA-IR was calculated as shown in the formula: HOMA-IR=[fasting insulin (μU/l)×fasting glucose (nmol/l)]/405; P[a]<.05 compared with the control group, Pb<.001 compared with the diabetic group. P[β]: one-way Anova test, P[β]<.001

Table 4. Comparison of Liver Enzyme values

Parameters	Groups				
	Control Mean(SD)	**Diabetic (DM)** Mean(SD)	**DM+Metformin** Mean(SD)	**DM+Gliclazide** Mean(SD)	**DM+CurCumin** Mean(SD)
HK(μmol/mg tissue)	262.1(7.8)[β]	130.9(8.1)[a]	255.1(6.2)[b]	246.7(3.3)[a,b]	227.7(9.5)[a,b,c,d]
G6P(μmol/mg tissue)	1064.4(3.2)[β]	2103.9(1.7)[a]	1804.7(0.7)[a,b]	1865.1(8.4)[a,b,c]	1821.1(16.4)[a,b,c,d]
G6PD(μmol/mg tissue)	514.8(2.7)[β]	260.7(1.7)[a]	409.1(0.4)[a,b]	427.3(1.1)[a,b,c]	416.1(1.2)[a,b,c,d]
PK(μmol/mg tissue)	207.1(1.9)[β]	98.2(0.9)[a]	156.3(1.4)[a,b]	155.6(3.1)[a,b]	152.9(1.5)[a,b,c]
A LP(U/L)	189.3(7.5)[β]	771.4(104.1)[a]	691.0(7.4) [a,b]	657.3(40.5)[a,b,c]	674.6(52.1)[a,b,c,d]
A LT(U/L)	44.7(4.8)[β]	95.3(9.2)[a]	87.4(5.6)[a]	90.3(6.9)[a]	90.3(10.8)[a]
A ST(U/L)	89.1(6.6)[β]	138.6(11.4)[a]	131.4(8.1)[a]	132.3(10.1)[a]	133.1(5.9)[a]
GGT (U/L)	6.6(1.5)[β]	17.3(0.8)[a]	15.3(0.5)[a,b]	15.1(09.7)[a,b]	15.4(0.5)[a,b]

All data were calculated using the Tukey test for p Multiple Comparisons (Mean difference is significant at the p<.05 level). P[a]<.001 compared with the control group, P[B]<.001 compared with the diabetic group, p[c]<.05 compared with DM+Metformin group p[d]<.05 compared with DM+Gliclazide group. P[β]:one-way Anova test, P[β]<.001

HK: Hexokinase, G6P: Glucose 6 Phosphate, G6PDH: Glucose 6 Phosphate Dehydrogenase, PK: Pyruvate Kinase, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: Aspartate Aminotransferase

Table 5. Comparison of Serum Lipid values

Parameters	Groups				
	Control Mean(SD)	Diabetic (DM) Mean(SD)	DM+Metformin Mean(SD)	DM+Gliclazide Mean(SD)	DM+CurCumin Mean(SD)
TC (mg/dL)	77.3(6.1)[β]	95.1(4.9)[a]	80.1(1.9)[b]	79.0(1.3)[b]	82.1(2.4)[b]
HDL (mg/dL)	33.6(1.9)[β]	23.2(2.6)[a]	26.2(1.3)[a,b]	28.3(1.1)[a,b]	26.3(2.1)[a,b]
TG (mg/dL)	78.0(8.3)[β]	100.4(11.2)[a]	87.9(6.7)[b]	84.9(5.4)[b]	85.7(6.1)[b]
VLDL(mg/dL)	15.6(1.7)[β]	20.1(2.6)[a]	17.6(1.3)[b]	16.9(1.1)[b]	17.1(1.2)[b]
LDL-C(mg/dL)	28.1(6.6)	51.9(4.5)[a]	36.4(1.7)[a,b]	33.8(1.6)[b]	38.7(2.9)[a,b]

All data were calculated using the Tukey test for p Multiple Comparisons (Mean difference is significant at the P <.05 level). P[a]<.05 compared with the control group, P[b]<,05 compared with the diabetic group. P[β]:One-way Anova test, P[β]<.001
TC: Total Cholesterol TG: Triglyceride, HDL: High Density Lipoprotein Cholesterol, LDL: Low Density Lipoprotein Cholesterol, VLDL: Very Low Density Lipoprotein

Liver enzymes

Liver enzymes related to glucose metabolism in healthy and diabetic rats are presented in Table 4. HK, G6PD and PK activities were significantly decreased in diabetic rats, while G6P-ase activity increased. These changes in diabetes-related liver enzyme activity were significantly improved with metformin, gliclazide or curcumin treatment and were very close to healthy control values.

Enzymes related to the assessment of liver injury, alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) activity were significantly elevated in diabetic rats (Figure 3). This negative effect of diabetes on the liver decreased significantly with metformin, gliclazide, or curcumin treatment (Table 4).
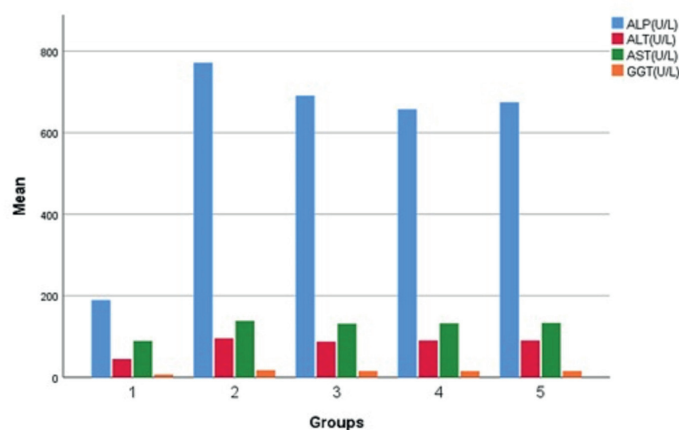

Figure 3. The comparison of liver enzymes levels related to glucose metabolism of healthy and diabetic rats

Serum lipid levels

The serum lipid parameters of all groups are shown in Table 5. Serum TG, TC, VLDL-C and LDL-C levels of diabetic control rats increased significantly compared to normal values, while HDL-C levels decreased. Metformin, gliclazide, or curcumin treatment produced significant improvements in serum lipid parameters of diabetic rats, close to healthy control values.

Correlation tests

In this study, the correlations with Asprosin and other variables are shown in Table 6. We determined that plasma asprosin levels were positively correlated with fasting blood glucose and insulin resistance but negatively correlated with insulin levels (R=.976, P<.001, R=.874, P<.001, R=-.936, P<.001, respectively). When the relations of asprosin with glucose metabolism were examined, it was observed that there was a positive correlation between plasma asprosin level and liver enzymes, G6P, and GGT (R=.965, P< .001 and R=.981, P< .001), although there was a negative correlation with G6P-ase activity (R= -.829, P<.001). In addition, our results showed that there is a negative correlation between plasma asprosin levels and liver health status. Likewise, asprosin was also found to be associated with lipid metabolism. While there were positive correlations between plasma asprosin concentration and serum lipid parameters CHOL, TG and LDL-C (R=.558, P<.001; R=.594, P<.001 and R=.696, P<.001, respectively), plasma asprosin level and serum HDL-C amount were found to be negatively correlated (R= -.826 P<.001).

Table 6. Correlation of Asprosin Level with Insulin HOMA-IR, Blood Glucose, Liver Enzymes, and Blood Lipid and Cholesterol

Parameters	Asprosin (R,P)
Insulin (µU/ml)	(R=-.936, P< .001)
HOME-IR	(R=.874, P< .001)
Glucose (mg/dl)	(R=.976, P< .001)
HK(µmol/mg tissue)	(R=-.611, P< .001)
G6PD(µmol/mg tissue)	(R=.829, P< .001)
PK(µmol/mg tissue)	(R=-.897, P< .001)
A LP(U/L)	(R=.958, P< .001)
A LT(U/L)	(R=.900, P< .001)
A ST(U/L)	(R=.862, P< .001)
TC(mg/dL)	(R=.558, P< .001)
HDL (mg/dL)	(R=-.826, P< .001)
TG (mg/dL)	(R=.594, P< .001)
LDL-C(mg/dL)	(R=.696, P< .001)
G6P(µmol/mg tissue)	(R=.981, P< .001)
GGT(U/L)	(R=.965, P< .001)

*p<0.05 was considered statistically significant
Abbreviations: WBC:white blood cells; RDW=:red blood
cell distribution width; MPV=mean platelet volume (MPV);
NLR=Neutrophil to lymphocyte ratio; PLR= Platelet to lymphocyte
ratio; SII= systemic immune inflammation index

Discussion

Asprosin shows complex important effects in carbohydrate and lipid metabolism and metabolic diseases. It plays a role in glucose metabolism and insulin resistance by using many intracellular signaling pathways [7]. It has been shown in vitro to cause inflammation, apoptosis, a decrease in insulin production and cellular dysfunction in pancreatic β cells [8]. Plasma asprosin levels were found to be higher in people with high insulin resistance, Type 2 diabetic patients and mice than in healthy controls [7-10]. Some researchers have documented an independent positive correlation between plasma asprosin levels and insulin resistance [11-14]. In addition, serum asprosin levels were recently found to be higher in the umbilical cord of pregnant women with diabetes and their babies [15].

Considering these results, asprosin seems to be a major component in glucose homeostasis. Indeed, Romere et al. showed that a single subcutaneous injection of recombinant asprosin into mice causes hyperinsulinemia after hyperglycemia, and specific asprosin antibodies ameliorate insulin resistance by normalizing blood glucose and insulin levels [11]. Considering these data, it was suggested that plasma asprosin levels can be used as a biomarker for the early diagnosis of diabetes and monitoring its prognosis.

In our study, as in many previous similar studies, plasma asprosin levels in STZ-induced diabetic rats were significantly elevated. In addition, we found positive correlations between plasma asprosin levels and fasting blood glucose, insulin levels and insulin resistance. Our findings support the majority of available literature [9,12-14]. However, it is necessary to consider the results of studies that do not confirm a positive correlation between plasma asprosin level and insulin resistance or, on the contrary, show a negative relationship [15].

Treatment of diabetic rats with curcumin or conventional antidiabetic drugs, metformin or gliclazide resulted in improvements in fasting blood glucose, asprosin levels, and insulin resistance. When the effects of these three antidiabetic agents were compared, it was seen that there was no significant difference between them. Considering the increase in plasma asprosin levels and partial recovery after antidiabetic treatment in diabetic rats, the idea that asprosin may increase insulin resistance by negatively affecting fasting blood sugar and insulin levels should be considered.

In our study, hepatic enzymes related to glucose metabolism, HK, G6PD and PK levels of diabetic rats increased significantly, while G6P-ase activity decreased. Increased glycolysis on the one hand and increased gluconeogenesis on the other, this imbalance between liver enzymes contributed significantly to the elevation of blood glucose levels in untreated diabetic rats. Metformin, gliclazide or curcumin treatment significantly reduced this diabetes-related imbalance in glucose metabolism. Moreover, the three antidiabetic agents we used in this study showed a rather similar curative effect on biomarkers of liver injury and serum ALP, ALT, AST and GGT levels in diabetic rats.

Dyslipidemia is frequently encountered in diabetic patients, especially those with Type 2 diabetes. Generally, patients have an increase in serum triglyceride, VLDL-C and LDL-C levels, while a decrease in HDL-C levels is observed [16,17]. Serum triglyceride, VLDL-C and LDL-C levels increased, while HDL-C levels decreased. The therapeutic effects of curcumin, metformin, and gliclazide on the plasma lipid profile in STZ-induced diabetic rats were quite similar, but curcumin increased HDL-C levels more than the others.

In our study, the effects of curcumin were compared with those of other antidiabetic drugs, metformin and gliclazide. Curcumin has a potential role in both the treatment and prevention of various diseases due to its antibacterial, anti-diabetic, anti-viral and anticancer effects [18-20]. It has been reported to improve pathological events, blood glucose, lipid profiles, hepatic antioxidant levels, and biomarkers of liver and kidney damage in type 2 diabetic patients through different mechanisms and multiple molecular targets [21-24]. Curcumin treatment with yogurt for one month showed antihyperglycemic and antihyperlipidemic effects in STZ-induced diabetic rats.25The same researchers observed that supplementation of 50 or 100 mg/kg/day curcumin to the diet of diabetic rats reduced hyperglycemia and vascular

inflammation [26]. Current information and the results of this study indicate that curcumin may be an alternative antidiabetic in the treatment of diabetes.

Our study was done as an experimental rat model and there are some limitations. Since our study was an animal experiment, a limited number of rats were included. Results such as serum glucose, liver enzymes, insulin resistance and cholesterol in rats may differ from humans. Another limiting factor is the inability to study the pancreatic pathology of rats.

Conclusion

Some proinflammatory adipocytokines secreted from white adipose tissue have been associated with diabetes pathogenesis or prognosis. New adipokines are being discovered every day, and the number of cytokines associated with diabetes pathogenesis is increasing. Although the pathogenesis of diabetes is not completely clear, we can say that there is a clear relationship between asprosin and the development of diabetes. If its negative effects on glucose metabolism can be controlled, asprosin may be a new target for the prevention and alternative treatment of diabetes. The available information is not yet sufficient to establish a causality between high plasma asprosin levels and diabetes. Whether the increase in plasma asprosin levels is a protective feedback mechanism for diabetes or a result of metabolic disorders has not yet been fully proven. In any case, the results of this study and many similar studies support the idea that plasma asprosin levels may be an important biomarker for the diagnosis and prognosis of diabetes.

As in many similar studies, our findings confirm that curcumin is an antidiabetic compound and show that it has similar effects on glucose metabolism as the classical antidiabetics metformin or gliclazide. Curcumin may be an alternative option in the treatment of diabetes, as it has been reported that it has no significant side effects or its anti-inflammatory and other positive effects.

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ORIGINAL ARTICLE

Evaluation of patients applying for disability determination procedures in terms of spine injury

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Abstract

Vertebral are not easily injured due to both the strength of the bone structure and the anatomical protection of the soft tissues. Traumas that cause damage to the vertebral column are often high-energy traumas such as traffic accidents. In our study, vertebral fractures seen in patients who applied for a report for disability determination; were aimed to evaluate the fracture site in terms of its sequelae and its provisions in the disability determination charts. In our study, the reports of the cases that were examined by us after applying for disability assessment in Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Forensic Medicine between the years 2019-2021 were examined. Cases with vertebral injuries were included in the study and were examined in terms of age, gender, spine region, additional traumatic findings, sequelae, treatment method, how many points they got from which disability scale, and duration of incapacity. As a result of joint range of motion examinations, in cervical vertebral fractures, limitation of cervical extension movement, in thoracic vertebral fractures, limitation of thoracic flexion movement, in lumbar vertebral fractures, it was determined that the limitation of lumbar extension movement was observed mostly. In our study, vertebral injuries were seen in 17% of the patients who applied for disability detection procedures after a traffic accident. In addition, vertebral injuries are important injuries in terms of public health and health expenditures, as well as important causes of disability and incapacity to work. Vertebral injuries resulting from traffic accidents can cause significant limitations and adversely affect people's lives.

Keywords: Vertebra, spine injury, disability, incapacity

Introduction

Traffic accidents cause general body trauma, material and moral losses, and systemic injuries that affect the vital functions of people. One of these injuries is vertebral injuries, mostly after high-energy trauma [1]. Vertebrae are deep-seated bone structures in our body and traumas that will cause fractures in the vertebrae are high-energy traumas, except for osteoporotic patients [2].

Vertebral fractures are economically important because both surgical and conservative treatments have high costs. Vertebral fractures may cause limitations in people at the end of the healing process. These limitations, which can develop after vertebral fractures, affect the social life of the person, cause material, moral losses, cause incapacity and disability [3]. Vertebral trauma patients apply to forensic medicine units for disability determination procedures, either individually or by court referral and request a report in order to seek their rights.

In our study, vertebral fractures seen in patients who applied

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for a report for disability determination; were aimed to evaluate the fracture site in terms of its sequelae and its provisions in the disability determination charts.

Material and Methods

Approval numbered 83116987-763 was received from the Tokat Gaziosmanpaşa University Faculty of Medicine Dean's Clinical Research Ethics Committee, stating that there was no ethical or scientific objection to our study.

In our study, the reports of the cases that were examined by us after applying for disability assessment in Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Forensic Medicine between the years 2019-2021 were examined. Cases with vertebral injuries were included in the study and were examined in terms of age, gender, spine region, additional traumatic findings, sequelae, treatment method, how many points they got from which disability scale, and duration of incapacity.

Statistical Analysis

Descriptive analyzes were performed to give information about the general characteristics of the study groups and Pearson Chi-Square Tests was used in comparisons. Data belonging to continuous variables are in the form of mean±standard deviation and median minimum and maximum values; Data on categorical variables were given as n (%). It was considered statistically significant when the p-value was calculated less than 0.05. Ready-made statistical software was used for calculations (SPSS 22.0 Chicago, IL, USA).

Results

Vertebral injuries were detected in 263 (17%) of the 1547 cases that were examined by us after applying for disability assessment in Tokat Gaziosmanpaşa University Faculty of Medicine, Department of Forensic Medicine. Of the cases, 163 (62%) were male and 100 (38%) were female, and the male/female ratio was found to be 1.6. The mean age of the cases was 37.2 (min:5, max:77). It was determined that 184 of the cases had in-vehicle traffic accidents, 53 of them had non-vehicle traffic accidents, 24 of them were motorcycle accidents, 2 of them were bicycle accidents (Table 1) It was determined that 102 of the cases who had in-vehicle traffic accidents were male and 82 were female. Thirty five of the cases who had non-vehicle traffic accidents were male and 18 were female. Of the cases who had motorcycle accidents, 22 were male and 2 were female. Of the cases who had a bicycle accident, 1 was male and 1 was female. (p:0.01) (Table 2).

In 92 cases, other regional traumas were found in addition to vertebral injuries. It was observed that the most common accompanying additional trauma was in the extremities with 61 cases. Additional trauma findings were detected respectively in the thorax in 47 cases, in the lower extremities in 35 cases, in the upper extremities in 26 cases, in the head region in 23 cases, in the pelvis in 15 cases, and in the face in 11 cases (Table 3). It

was found that 29 of the cases were treated surgically after the trauma, 179 cases were treated conservatively with corsets and 55 cases with a neck brace.

Table 1. Accident type

■ In vehicle ■ Non vehicle ■ Motorcycle ■ Bicycle
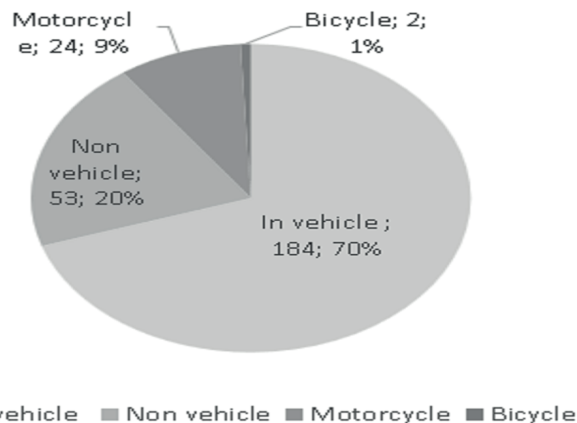
Table 2. Type of accident by gender

	In vehicle	Non-vehicle	Motorcycle	Bicycle	p
Male	102	35	22	1	0.010
Female	82	18	2	1	

Table 3. Additional trauma
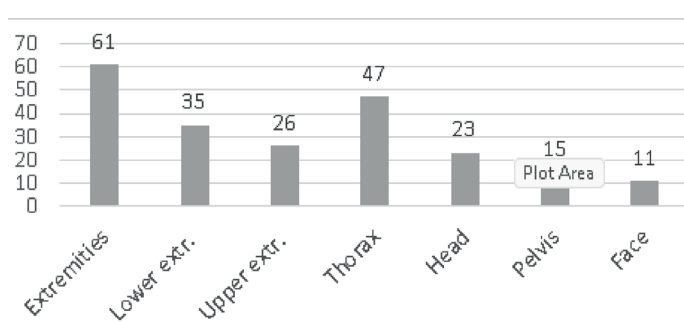
Vertebral fractures were found at one level in 58% of the cases, at two levels in 25%, and at three or more than three levels in 17%. When the vertebral column was divided into cervical, thoracic, lumbar, and sacral, the most common fracture was found in the lumbar vertebrae (L1-5) in 228 cases. Fractures were observed in thoracic vertebrae in 138 cases (T1-12), cervical vertebrae in 101 cases (C1-7), and sacral vertebrae in 7 cases. L2 vertebra (66 cases) fractures were found most frequently in lumbar vertebrae. In order of the number of cases of other lumbar vertebral fractures; L1 62 cases, L3 45 cases, L4 35 cases, and L5 20 cases. T12 vertebrae (29 cases) were the most common fractures in the thoracic vertebrae. T11 vertebral fracture in 16 cases, T8 vertebral fracture in 13 cases, T5 and T9 vertebral fracture in 11 cases, T4 vertebral fracture in 10 cases, T3, T6 and T7 vertebral fractures in 9 cases, T10 vertebral fracture in 8 cases, T2 vertebral fracture in 7 cases, T1 vertebra fracture in 6 cases was detected. Fractures were found most frequently in the C2 vertebra (20 cases) in cervical vertebrae. The number of cases

of other cervical vertebral fractures; C6 was 16 cases, C7 was 15 cases, C1, C3 and C5 were 13 cases, C4 was 11 cases. In sacral vertebrae, fractures were most common in S1 vertebra (5 cases), and fractures were found in one case each in S2 and S3 vertebrae. Most frequently fractured vertebrae are shown in Figure 1. It was determined that the lumbar vertebra was the most common injury in the patients who had an in-vehicle traffic accident, non-vehicle accident and motorcycle accident. The accident type and injured vertebral regions are given in Table 4.

Figure 1. Most frequently fractured vertebrae

Table 4. The accident type and injured vertebral regions

	In vehicle	Non-vehicle	Motorcycle	Bicycle	p
Cervikal	46	15	4	1	0.582
Thoracic	54	11	12	0	0.035
Lumbar	100	31	14	1	0.924
Sacral	6	1	0	0	0.902

Odontoid fractures were the most common in the upper cervical vertebrae (C1-C2), and lamina fractures were the most common in the lower cervical vertebrae. In the thoracic vertebrae, the most common corpus fracture, the second most common transverse process (62% right transverse process, 38% left transverse process) fracture was observed. It was observed that the most common transverse process fracture (51% left transverse process, 49% right transverse process) was developed in the lumbar region, and the second most common corpus fracture occurred. It was determined that the most common corpus fracture developed in the sacral region.

As a result of joint range of motion examinations, in cervical vertebral fractures, limitation of cervical extension movement was observed mostly. Limitations were detected respectively in bilateral rotation movement, bilateral lateral flexion movement and cervical flexion movements. In thoracic vertebral fractures, limitation of thoracic flexion movement was observed mostly. In lumbar vertebral fractures, it was determined that the limitation of lumbar extension movement was the most common. Respectively; It was observed that there were limitations in lumbar flexion, left lateral flexion and right lateral flexion movements. Neurological sequelae remained due to vertebral trauma in a total of 19 cases (%7.2), including 9 cases of cervical vertebral fracture, 5 cases of thoracic vertebral fracture, and 5 cases of lumbar vertebral fracture. It was determined that 14 of the cases with neurological sequelae were male and 5 were female. Neurological sequelae were detected after in-vehicle traffic accident in 14 cases, out-of-vehicle traffic accident in 4 cases, and after motorcycle accident in 1 case. There was no statistical significance between neurological sequels and gender (p:0.275) and type of accidents (p:0.91).

Fifty-five of the cases received rates from the Determination of Work Power and Loss of Proficiency in Occupation, 51 from the Disability Criterion, and 157 from the Adult Disability Assessment Schedule. Considering the medical recovery and rehabilitation periods due to the vertebral fracture, the duration of temporary incapacity for work, which was considered by us, was determined between the lowest 90 days and the highest 120 days (average 99 days). The average time of stay at the hospital of the patients treated surgically was determined as 11.8 days. 76% of patients treated surgically and 66% of patients treated conservatively stated that they had difficulty in doing their job and there was a decrease in their earnings.

Table 5. Avarage rate from the regulation charts

Regulation charts	Section	Table	n	Average Rate
Regulation on Disability Assessment for Adults	Musculoskeletal System 1-1.1 Injury Model and Diagnosis-related assessment	Table1.1	61	10.7
		Table1.2	31	10.1
		Table 1.3	33	10.4
	The joint range of motion model is 1-1.2	Table 1.4 to Table 1.10	32	19.3
Regulation on Disability Criteria, Classification and Health Reports to be Given to the Disabled	Musculoskeletal System 1-1.1 Injury Model and Diagnosis-related assessment	Table1.1	24	8.6
		Table1.2	8	10.5
		Table 1.3	10	11.3
	The joint range of motion model is 1-1.2	Table 1.4 to Table 1.10	9	15.5
Regulation on Determination of Working Power and Loss of Profession Loss Rate	Ruler A, spine malfunctions	10. List - 1	48	16.9
	Ruler A, spine malfunctions	10. List - 2	7	33

The disability rates of the lumbar spine under the heading Musculoskeletal System 1-1.1 Injury Model and Diagnosis-related assessment in the scale of 85 cases that received a ratio from the Disability Criterion and Disability Assessment Table for Adults are from Table1.1, and the disability rates of 39 cases of the cervical spine are from Table1.2. The disability rates of the thoracic spine for 43 cases received a ratio from Table 1.3. Disability Criterion and Adult Disability Assessment Chart, in the disability section of spine problems, based on the item 'If there is no injury, if the injury model is insufficient, or if the injury affects more than one segment in the same spine region, the joint range of motion model is used, and 41 cases were rated from the Section 1-1.2 range of motion model [4,5]. The average rate of cases that received a rate from the Regulation on Disability Criteria, Classification and Health Reports to be Given to the Disabled was 11%, and the average rate of cases that received a rate from the Regulation on Disability Assessment for Adults was 12.4%.

Twenty-four cases that received a rating from the Determination Procedures for Work Power and Loss of Proficiency in Occupation were rated for mild 1Aa (1/3 loss of vertebral height) for crushing (compression) or comminuted fractures of a vertebra. 2 cases of medium 1Ab (loss of 1/2 of the vertebral height), 9 cases of crushing or comminuted fractures of a vertebra with dislocation in the cervical region from item 1Ba, 13 cases of multiple vertebra processus spinosus, processus transversus fractures from item 1C. 7 cases of ankylosis of the vertebrae in two or more segments occurred after vertebral fractures or fusion surgeries due to their fractures from item 2 [6]. The average rate of cases that received a rate from the Determination Procedures for the Loss of Working Power and Profession Loss of Earning Power was determined as 19%. The average scores and the number of cases obtained from the regulation charts are given in Table 5.

Discussion

Vertebrae are not easily injured due to both the strength of the bone structure and the anatomical protection of the soft tissues. Traumas that cause damage to the vertebral column are often high-energy traumas such as traffic accidents and falling from a height [7].

In studies in the literature, the average age of vertebral injuries has been reported to be generally in the thirties and 80% of cases with vertebral injuries are under the age of 40 [8,9,10]. In our study, the mean age was found to be 37.2. Vertebral injuries are 2-4 times more common in male than in female [11,12,13]. Consistent with literature, in our study %62 were male and %38 were female, the male-female ratio was found to be 1.6. It was determined that male had more spinal injuries in in-vehicle traffic accidents, non-vehicle traffic accidents and motorcycle accidents. The reason why vertebral injuries are more common in men is that they are more intense in traffic than women. Vertebral fractures are more common in men up to the age of 55 and in women over the age of 55 [14].

In the literature, traffic accidents and falling from a height have been shown as the most common causes of spinal injuries [15]. In our study, all cases with vertebral fractures were injured as a result of traffic accidents due to the examination of the reports prepared for disability determination procedures. For this reason, it does not reflect the most common cause of vertebral fractures in the whole population, as our study lacks. Vertebral injuries were found to be the most common in-vehicle traffic accidents among traffic accidents. When the bone fractures caused by traffic accidents are evaluated, vertebral fractures are among the first three bones in the list of the most broken bones [16].

Injuries to other systems may occur in high-energy traumas that cause spinal fractures [10]. Skeletal traumas constitute half of the additional injuries, the frequency of which is reported between 43-78%, and various organ injuries in the other half. In our study, the frequency of additional trauma findings was found to be 34.98%. Limb injuries are the most common accompanying injuries to vertebral fractures. In one study, Concomitant trauma was found in 47% of 508 patients brought to the hospital for spinal trauma. The most common ones were head trauma (26%), chest trauma (24%), and long bone fractures (23%) [17]. In another study, it was seen that lower extremity fractures were the most frequent, and fractures of the extremities were the most [18]. In our study, areas with additional trauma were the upper extremity in 26 cases (28%), lower extremity in 35 cases (38%), extremity injury in 61 cases, thoracic region injury in 47 cases (51%), head trauma in 23 cases (25%), Pelvis injury in 15 cases (16%) and facial bone fractures were detected in 11 cases (12%).

It has been reported in the literature that the most common injury is at the thoracolumbar junction (52%), that is, at the T11-L1 level. This is followed by the lumbar region (L2-L5) with 32% and the thoracic region (T1-T10) with 16% [8]. In our study, it was found that the most common injury was in the lumbar region (L2-5), with 166 cases. The most frequently injured vertebra was L2 (66 cases). The incidence of injury is higher in the thoracolumbar junction and lumbar region due to the facet joint incompatibility caused by the lack of protective effect of the rib cage and the facet joints in the thoracic region in the coronal plane and in the lumbar region in the sagittal plane [17].

In the literature, neurological deficit is observed in 14-38% of all vertebral traumas and fractures [19]. Neurologic deficits in cervical vertebral injuries reach 40%. Neurological deficits in thoracolumbar vertebral injuries in adults are seen at rates ranging from 10-38% [20,21]. In a study, the rate of neurological deficit was 10.9% [22]. In our study, the rate of neurological deficit was 7.2%. It was found that cervical vertebral fractures were the most common cause of the neurological deficit. Neurological sequelae were found to occur most frequently in males and in-vehicle traffic accidents. In our study, it was determined that the most common lamina fracture in the cervical vertebrae, the most common corpus fracture in the thorocal vertebrae, the most common left trans vertebrae fracture in the lumbar vertebrae, and the most common corpus fracture in the sacral vertebrae as a result of traffic accidents.

It was seen that the average rate of cases that received a rate from the Determination Procedures for the Rate of Loss of Working Power and Profession, was 19%, the average rate of cases that received a rate from the Disability Criterion was 11%, and the average rate of cases that received a rate from the Disability Assessment Chart for Adults was 12.4% [4,5,6]. It is seen that the section reserved for spinal defects in Determination of Labor Force and Loss of Profitability in Occupation is less detailed than other charts. As a result, disability report issuers cannot find the exact equivalent of vertebral injuries in the charts and give results as a result on their own opinions. This situation, especially in the cases where results are obtained by using the Determination of Loss of Working Power and Profession Loss Rate, causes the rates to be different and higher.

In the literature, it is seen that the hospitalization period of the operated patients varies between 10 and 107 days [22,23]. In accordance with the literature in our study, the average time of stay at the hospital of the patients treated surgically was determined as 11.8 days. The duration of temporary incapacity for work, which was considered by us, was determined between the lowest 90 days and the highest 120 days (average 99 days).

Conclusion

All examinations should be carried out in accordance with the methods specified in the charts and in accordance with objective criteria. In addition to active range of motion, passive range of motion should also be evaluated. Medical documents and radiological results of the applied treatment should be examined in detail. In this way, both patients and insurance companies can be prevented from losing their rights regarding the event that is the subject of the lawsuit.

Our study has made significant contributions to the literature on patients with vertebral injuries who applied to Forensic Medicine Units for disability determination. In addition, vertebral injuries are important injuries in terms of public health and health expenditures, as well as important causes of disability and incapacity to work. Vertebral injuries resulting from traffic accidents can cause significant limitations and adversely affect people's lives. In our study, vertebral injuries were seen in 17% of the patients who applied for disability detection procedures after a traffic accident. Individuals with limited vertebral movements will suffer economically by staying away from most work areas. In order to reduce the loss of rights, necessary steps should be taken for these individuals to seek their rights through disability determination procedures, and by providing appropriate working conditions, it is necessary to prevent them from suffering further economic damage.

Our study was presented as an oral presentation at the 3nd International Turaz Academy Forensic Sciences, Forensic Medicine and Pathology Congress.

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ORIGINAL ARTICLE

A society, a disease, a survey and the expected result

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Abstract

COVID-19, which affects the whole world, has affected people, societies and human relations throughout the process. The COVID-19 pandemic both limited people's social lives and changed the perspective of people who carry the virus. Anxiety, fear, haste, loneliness, worry were the most common emotions. In this study, we aimed to evaluate how social warnings affect people, the effects of death risk due to the disease, the side effects of the drugs used on behavior change, and the underlying factors. 189 cases were included in the study. The study was designed in the style of a 20-question questionnaire on the effects of covid-19 and treatment options on the behavior pattern. The responses were evaluated and interpreted as percentages. Variables on family and social behavior related to anxiety, fear, panic, and loneliness caused by COVID-19 and the drugs used in its treatment were observed. Negative effects of COVID-19 were observed in family and community relations. COVID-19 has caused psychological and sociological changes in interpersonal and social behaviors all over the world. There are differences in behavioral patterns among societies. In Turkish society, behavioral changes arising from the characteristic and patriarchal characteristics of the society have been observed. A more detailed assessment of the effects of COVID-19 and subsequent pandemics on the individual and society remains important.

Keywords: Social behaviors, loneliness, death, patriarchal characteristics

Introduction

The epidemic factor, which started with a viral respiratory infection notification in Wuhan, China in December 2019 and spread across the country borders, first to the continents and then to the whole world was determined to be a beta coronavirus mutation that passed from bats to humans and On January 7, 2020, it was named as COVID-19 by the World Health Organization (WHO). COVID-19, which was accepted as a pandemic on March 11, 2020, maintains its place on the world agenda as a health problem, despite completing its second year in the world [1].

The transmission of the virus from person to person via droplets and the asymptomatic period after transmission were the main factors in its rapid spread. Again, the fact that symptoms such as fever, fatigue and dry cough in the symptomatic period of the disease were similar to other viral diseases delayed the diagnosis and contributed to its spread. Although the disease was mild at the rate of 80% at the beginning, its fatality increased with mutations in the following periods [1]. In severe cases, progressive respiratory failure developed due to virus-related alveolar damage and death resulted in 1-5% of these cases [2]. The majority of the cases that resulted in death were middle-advanced aged individuals with a previous chronic disease (such

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as cirrhosis due to liver failure, hypertension, coronary heart disease, diabetes mellitus and Parkinson's disease) [2].

There is still no specific drug used in the treatment of the disease. For this reason, countries are taking various public health measures that can prevent or slow down the transmission of COVID-19. These measures can be counted as case isolation (full closure), identification and follow-up of contacts (filiation), environmental disinfection and the use of personal protective equipment (isolation) [3]. Although successful studies were carried out on epidemic transmission and contact control in our country at the beginning, the increasing number of cases and the change in people's attitudes towards restrictions caused disruptions in epidemic control.

Many factors are effective in the occurrence of these disruptions. These can be grouped under titles such as human factor, economic reasons, climate variables and virus mutation.

Antivirals such as lopinavir, ritonavir, favipiravir, oseltamivir, various drugs such as chloroquine, azirithromycin and vitamin C and supportive treatments were used in the treatment of sick individuals [4].

In this study, considering that the side effects of some drugs used for COVID-19 are not clearly explained, we wanted to examine the effect on the course of treatment and human behavior if these side effects are explained. For this, individuals over the age of 18 were asked questions and their opinions were taken with a survey study about COVID-19. We tried to learn about the concerns of the respondents about COVID-19 and their behavior in the face of events.

Material and Method

TWe tried to examine how individuals who are citizens of the Republic of Turkey over the age of 18 have information about the COVID-19 disease in the form of questions and answers, and whether they have information about the side effects of the drugs used so far, how effective the continuous warnings are and whether there will be a change in the answers at variable times. Our questionnaire, consisting of 20 questions was carried out on randomly selected individuals living within the borders of Malatya province, regardless of whether they or their relatives have COVID-19 disease.

Approval for this study was obtained from the Health Services Directorate of the Ministry of Health with the application numbered 2020-07-25T13_35_43.

The following results were obtained in the survey conducted on 189 people.

Results

47.3% of the 189 people who participated in the survey were between the ages of 35-44 and 35.3% were between the ages

of 25-34. 55.9% of the participants were female and 76.2% were married (figure 1).72% of the participants had one or more children. 46.2% of the participants were university graduates, 31.7% were graduates and 32.1% were primary, secondary and high school graduates.
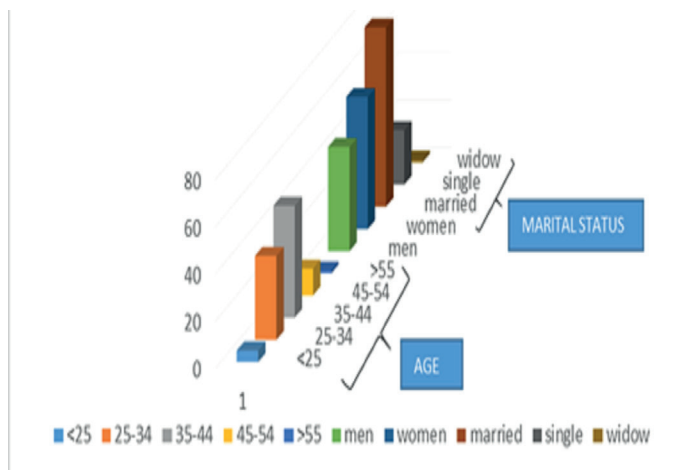
Figure 1. Demographic distribution of survey participants

In the answer to the question of how did you learn that COVID-19 carries a risk of death, although 77.9% of the participants had a university or graduate education, 39.8% stated that learned from television news, 17.2% learned through internet and research (figure 2).
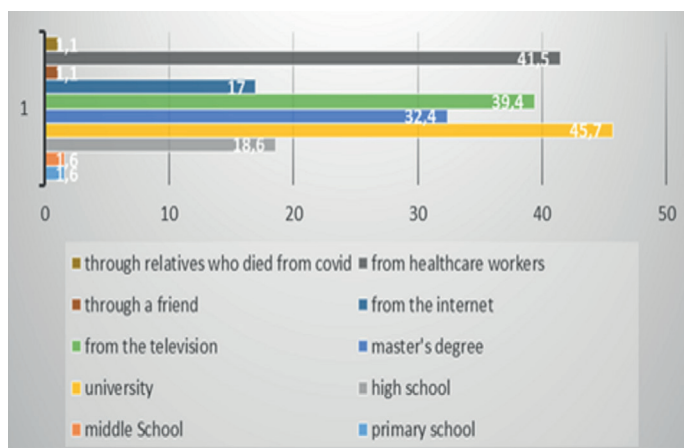
Figure 2. Education levels of survey participants and ways of accessing information

It was observed that 34.4% of the participants were not aware of the side effects of the drugs in the treatment of covid-19. It was determined that only 6.4 % of those who knew about the side effects did research on the possible side effects in case of using the drug, by researching this information themselves (figure 3).

The number of people who want to be told about the risk of death of the drugs used in the treatment of COVID-19 is 154, and the number of people who want it not to be told at all is 26. 19 people stated that after they died, they wanted their relatives to be told as the cause of death.

Would you take the drug if the risk was told? 50 people stated that they would not take the drug, 103 people stated that they would take it because they had no other choice, 48 people said they would take the drug because it was an acceptable risk.(figure 4)
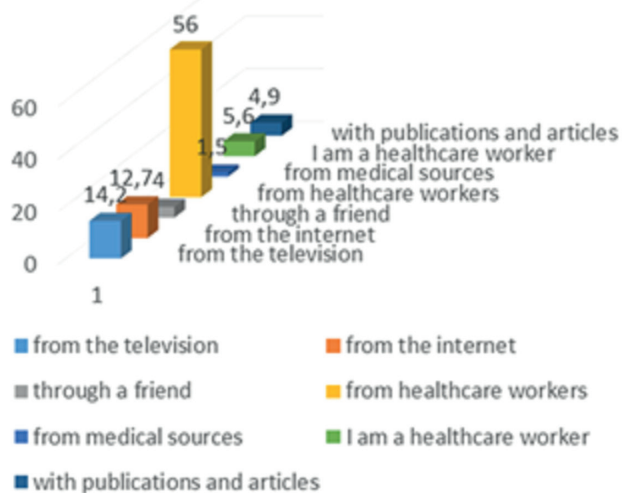
Figure 3. Behavior analysis against knowing the side effects of COVID-19 drugs
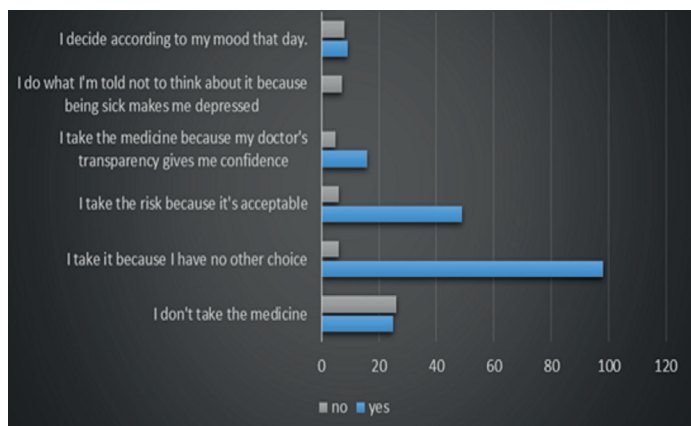
Figure 4. Behavioral analysis of participants in taking medication despite knowing the side effects of COVID-19 drugs

Again in this context, does your doctor's failure to inform you about a drug with a low risk of death in a disease with a high risk of death change your behavior? Even though they said yes to the question, there would be a change in behavior, only 12 people stated that they would become aggressive. 67 people said I get sad and 40 people said I don't care.

To the question of who would you tell first when you got COVID-19, 142 of the participants answered to their first-degree relatives and 91 of them to my wife.

To the question of what emotion you would experience when you were told that you had COVID-19, 75.4% was answered as I would have anxiety because of thinking that something would happen to my family. (figure 5) 15.6% reported that they may experience regret because they did not take full protection measures against the virus.

If you knew from whom the COVID-19 contagion came from, would your attitude towards it change? 112 of 189 participants answered this question as no.
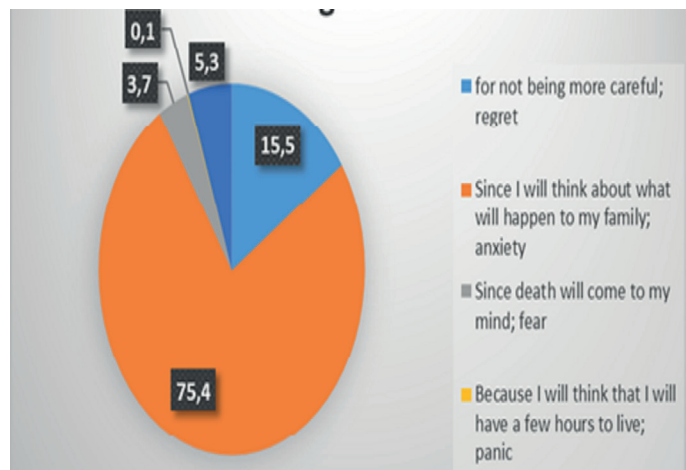
Figure 5. Behavioral analysis of participants after learning they had COVID-19

To the question in our survey about whether receiving death news frequently makes a change in the behavior of people; while 30.2% said that it makes me more aggressive, 20.9% replied that it does not affect me and 18.7% replied that it prevents me from making long plans (figure 6).
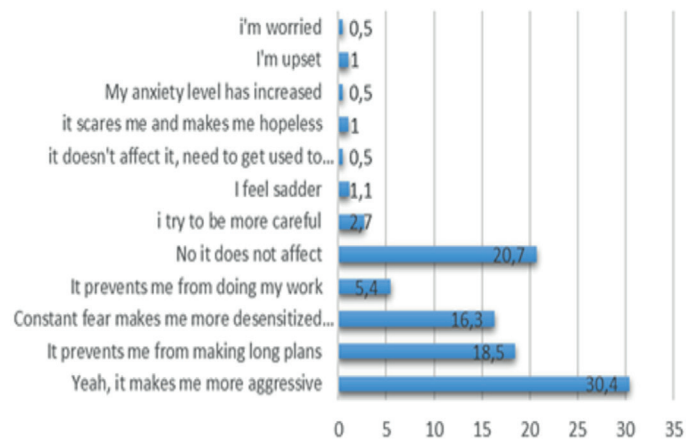
Figure 6. Examining the relationship between covid 19 deaths and mood

The rate of those who argue that videos and posts showing that there is a permanent damage left behind in survivors of the COVID-19 disease are effective in behavior was observed as 87.6%.

Although there is a high risk of death and there is still an intense spread, the relaxation of the measures is due to the desperation brought by the living standards according to 43.4% of the survey participants and the prolongation of the process according to 22.5%.

Discussion

COVID-19 pneumonia is characterized by acute onset and

rapid progression. Lung damage caused by such infections can progress further to severe acute respiratory syndrome. It has been understood that it is more important not to catch the disease with personal protective measures rather than medicine, which is contagious by droplet and there is still no effective treatment other than vaccination.

As a society, simple information about COVID-19, such as transmission through droplets, contactlessness and distance and protection information, has been known since the first day of the disease, but 17.2% of the number of people who learned this information by researching it. The scarcity of this number shows that, as a society, we are oriented towards ready-made information even on matters that concern ourselves and our lives and we are limited in applying the measures.

While the protection against patients with COVID-19 symptoms and clinics was high in the first period, the loss of people's distance from positive patients in the last period has led to an

increase in the number of patients. The reasons such as socio-economic level, educational status, lack of concrete visible results of the disease, depersonalization due to frequent warnings such as death and necessity of social life are considered as reasons for people to loosen these protection measures. This decrease in measures has caused fluctuations as in previous epidemics. In the past, the epidemic, which was called the Spanish flu in 1918, was seen in the form of the first wave in 1918 March-August and the second wave between September-December. 1957 Asian flu and 1968 Hong Kong flu spread all over the world in 12 months, but the 2nd wave was not detected in the records and it is thought that there were more than one million deaths [5]. Since December 2019, COVID-19 has infected more than 477 million people and caused the death of more than 6 million people [6].

Studies on COVID-19 continue. Keyaerts et al. showed that chloroquine was effective in covid by inhibiting intracellular SARS-CoV replication in newborn mice [7]. Vincent et al. reported that chloroquine reduces viral spread by reducing the binding of the virus to the ACE receptor [8]. In the light of such studies, the drug chloroquine was used frequently in the first period of the COVID-19 pandemic in various countries. Although it has not been shown to have a clear benefit, it was thought to be effective in the prognosis of the disease. In our country, 200 mg of chloroquine was administered twice a day for 5 days to covid-19 patients who were positive for PCR in the early stages of the pandemic [4]. Chloroquine was a drug known to have serious side effects. One of them is that it affects the heart and prolongs the QT interval, causing heart rhythm disorders and death. Considering that most of the people who use the drug do not know this information and this side effect is common, it was thought that people were not clearly informed before starting this drug. We conducted the survey by thinking that in a disease with a high fatality rate as COVID-19, there will be death due to the effect of Chloroquine, although not as much as COVID-19, if it

was clearly expressed to the people taking the drug, what kind of thought would they have.

Although the spread of COVID-19 was prevented at first with the restrictions in Turkey, the epidemic control could not be achieved as in the first months due to the prolongation of the process, the inability to continue the restrictions due to economic reasons and the fact that the living standards of the citizens did not allow the continuation of isolation. This process has revealed different psychological effects in people. Sometimes not having detailed information about the subject and sometimes being constantly warned with excessive warning (such as death) caused either a decrease in the reactions or an overreaction.

In the survey we conducted, we observed that constantly warning at the highest pitch causes desensitisation by 20%. When it comes to the question of how it would be more beneficial to warn people, although the majority in the survey did not show a clear opinion, it was observed that sharing clear and reliable information every day would lead people to be more careful. If the warnings were arranged in this way, it was thought that it would be more beneficial for the mental health of the community.

During the Covid-19 pandemic, we had the chance to observe through the media throughout the process that the social measures taken against the progression of the epidemic in the western society were high, and the reactions to those who caught the disease were excessive. It was thought in the light of this information that for the same populations, not telling about the danger of death in such life-threatening drugs or not being fully informed about the disease could lead to great reactions. However, when we look at the answers given to the survey questions in our society, we have the opinion that our society will not react as harshly as the western society shows.

The decision of 103 people who said in the survey that they would take the drug because I had no other choice, shows that, like all living things, human beings cannot go beyond their instinctive behavior to accept when their will is not sufficient. On the other hand, 48 people who consider it as an acceptable risk represent success-oriented individuals who make the necessary sacrifice in order to reach the goal in the society. The statements of these 48 people show that in our society, that is, in the Turkish Society, these individuals are too many to be underestimated. It shows that the rapid response of our society in creating unity and solidarity in collective disasters and events stems from this. The reasons for this result are that we are a result-oriented society, that some risks can be taken where there are many gains and that our empathy skills are high for the other person.

Again, unlike the western society, it is seen from the results of our survey that as a Turkish Society, the concept of family is at the forefront in the disease process and the concerns about family members are more important than how the individual will overcome the disease himself. The fact that 75.7% of the participants gave an answer of anxiety to the question of what

emotion you experienced when you first learned that you were caught in COVID-19 is an evidence that explains this. Knowing that a person will die instinctively makes him think about what will happen to those around him rather than himself. The fact that most of the participants are married and have children, and that we value our loved ones more than ourselves, are effective in the formation of these decisions. The purpose of not reporting the news of the infection to others is an effort to take precautions for our loved ones, rather than sharing the troubles.

Knowing from whom you got the disease causes many of the countries with the pandemic to take strict measures against the person who is the source of the infection, while it causes less reaction because empathy is at the forefront in our own society. Of the 100 people who answered the question in the questionnaire, 45 said that my attitude towards the person who infected me would not change, while 24 said that if they knew about the disease and did not take precautions, my attitude towards it would change.

With the answers given to the questions in the entire questionnaire, we observed that the concept of family is intensely experienced in our society, that empathy is a natural behavior, that the concept of love contains more social movements than the individual. In this case, the main reason is that we come from a patriarchal society and we have a different perspective on the concept of family. If these attitudes of the Turkish Nation in the face of events are made for other nations with similar studies, perhaps the differences between them and the Turkish nation will be understood more clearly.

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ORIGINAL ARTICLE

The effect of kinesio taping on neck pain in academicians

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Abstract

Pain in the neck is one of the oldest and most common problems known to mankind. Neck pain is generally defined as a feeling of discomfort felt in the side and back of the neck. This study aimed to investigate the effect of KT on neck pain in academicians with neck pain. We aimed to investigate the effectiveness of taping by using the Bournemouth Neck Questionnaire before and after to evaluate neck pain. A total of 40 people, 18 male, and 22 female participated in the study. Academicians with neck pain were included in our study. Demographic information such as age, height, weight, gender, regular sports habits, daily smoking, and chronic disease status was questioned. "Y" and "I" bands were applied to the participants. The "Y" band was applied to the lower end of the cervical 7th vertebra (Vertebra Prominens) with submaximal tension, and the other two ends were applied to the right end of the right end to the proc. mastoideus of and temporal bone the left end to the processus (proc.) mastoideus of the left temporal bone. The "I" band was applied to the pars transversa of the trapezius muscle with moderate tension. The applied bands remained on the participants for 72 hours (3 days). In addition, the Bournemouth Neck Pain Questionnaire consisting of 7 questions was applied to the participants, questioning the intensity of pain, inadequacy in activities of daily living, inadequacy in social activities, anxiety, emotional aspects of depression, kinesiophobia, and ability to control pain. The Bournemouth Neck Pain Questionnaire was administered twice before and 10 days after the taping procedure and the results were compared. It was observed that the Bournemouth Neck Pain Scale scores before taping were higher than after taping in the participants included in the study. The decrease in Bournemouth Neck Pain scale scores after taping was statistically significant (p<0.05). There was no statistically significant difference in the Bournemouth Neck Pain Scale scores between those who do and do not do regular sports before taping (p>0.05), but a statistically significant difference was found after taping (p<0.05). It has been concluded that KT is an effective method in the treatment of neck pain in academics who spend a long time at the computer and desk. We believe that the study will contribute to clinicians, researchers and the literature.

Keywords: Neck pain, kinesio taping, physical therapy and rehabilitation

Introduction

Computer and internet technologies have been rapidly developing and spreading over the last hundred years. This developing with technology, internet use has become an indispensable tool of life [1]. In addition, it has caused human beings to lead a much more sedentary life compared to the past [2]. Depending on technological developments, the use of computers in offices and workplaces has increased, and long-term computer use has also developed in employees, besides long-term computer use brings along some health problems [3]. These health problems include stressful lifestyle, less movement, change in eating habits, and staying in a fixed posture for a long time have caused deterioration of body mechanics and posture [2].

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Musculoskeletal system diseases due to prolonged computer use in a fixed position; repetitive stresses in the work environment of individuals working in an inappropriate posture a series of injuries involving muscle, tendon, ligament, nerve, joint, cartilage, bone, and vascular tissues belonging to the body dynamics of the arm, leg, neck, low back regions develop as a result of exposure [4]. Deteriorated body dynamics, especially in the regions exposed to continuous stress in the musculoskeletal system, such as the low back, neck, and shoulder girdle, appear with various symptoms, especially pain sensation [5].

Musculoskeletal system diseases are very common, affecting all age groups and genders, and are an important health problem that causes disability and loss of strength. Related to the musculoskeletal system, problems usually manifest as pain. Although these problems are not fatal, they reduce quality of life and decrease economic productivity [6]. In 2004 a population-based study conducted in the USA reported that 80% of the population between the ages of 15 and 84 defined musculoskeletal pain at least once in their lifetime and that the problem has reached almost epidemic proportions [7]. One of the most common health problems in individuals working at a desk is musculoskeletal pain due to repetitive stress and incorrect posture developing neck pain [8]. The neck is an important region that protects many vital structures and connects the head and body parts of our body between our jaw joint and collarbone [9]. Pain felt in the neck region is human It is one of the oldest and most familiar problems in history [5]. In the 21st century, neck pain is a problem that develops in certain periods of the lives of a large proportion of people in their daily lives. It is seen as a disorder that negatively affects their activities [10].

Neck pain is one of the most common and recurrent musculoskeletal diseases in the community after low back pain. In addition, it is a problem that can be experienced by all age and gender groups, affecting the social life of the person, and causing a decrease in productivity and an increase in treatment costs [11]. Seventy percent of people complain of neck pain at least once in their lifetime. The prevalence of symptoms lasting for one year varies between 1.7% and 11.5%. Neck pain is mostly seen in people with poor posture who work at a desk and in healthcare workers [12]. Prolonged isometric contractions cause excessive stress in the muscles and are more common in desk workers, especially those with inappropriate sitting postures position, non-ergonomic arrangements, working conditions bring problems in the musculoskeletal system. Problems related to the musculoskeletal system affect work efficiency and quality of life and cause loss of work and economic losses [13].

In the studies conducted, long-term have shown that working at a computer is a factor affecting neck pain [14]. The anatomical structure of the neck region is at the forefront in the frequent occurrence of neck pain. The neck region has a highly mobile structure due to its anatomical structure. Although the mobility of this region has many advantages, it is also a region that is open to injury [15]. Neck pain is generally defined as a feeling of discomfort felt in the lateral and posterior regions of the neck [16].

In recent years, neck pain has been observed more frequently in our society as a result of occupational diseases and in-vehicle accidents. In the literature, it is reported that the frequency of neck pain is gradually increasing and it is more common in women than in men [17]. In a study, the lifetime prevalence of neck pain was found to be approximately 67-71% and this was found in one third of the individuals two of them have encountered neck pain at least once [18]. Neck pain is observed in 22% of the population. It has been reported that 44% of patients consult a physician due to the chronicization of pain [19]. The general cause of pain in the neck region is due to strain, sprain or inflammation [20].

Today, many methods are used for the treatment of musculoskeletal pain. There are studies suggesting that Kinesio Taping, one of these methods, reduces neck pain [21]. From this point of view, KT reduces pain and improves functionality. It is thought that it may be an alternative treatment modality to increase the number of patients [22].

Especially academicians perform their work in a computer environment, so we think that they will be more prone to skeletal and muscular diseases. The aim of this study was to investigate the effect of KT on neck pain in academicians with neck pain effect on neck pain. We aim to investigate the effectiveness of taping by using the Bournemouth Neck Questionnaire before and after KT to evaluate neck pain.

Material and Method

Our study was conducted among 24-55-year-old academician (18 male and 22 female) volunteers who filled out an informed consent form. Participants were recruited from Malatya Turgut Özal University Interventional Clinic Approval from the Research Ethics Committee 2022/42 was obtained. Academicians with pain in the neck region were included in our study. In addition, attention was paid to the fact that the participants did not have a history of deformity or congenital deformity in the neck region. In the neck region; Individuals with neck joint instability, trauma in the past year, severe osteoporosis, previous neck surgery, positive "spurling" or "cervical distraction" test, neck flattening and cervical disc herniation were not included in the study. Again, individuals who received physical therapy and rehabilitation in the last six months did not participate in the study.

In the demographic questionnaire, age, height, weight, gender, regular sports habits, daily smoking and chronic disease status were questioned.

Actions taken

KT was applied to the back of the neck of the participants. Participants completed the Bournemouth Neck Pain Questionnaire to find out the effectiveness of the taping procedure.

KT was applied by a physiotherapist certified in the taping method. The kinesiological taping technique (The Kinesio Taping® technique) and kinesiological tape (Kinesio Tex® tape) were developed in 1973 by Japanese chiropractic and acupuncturist.

It is a method developed by Kenzo Kase. The kinesiologic tape has been developed to reflect the characteristics of the skin, and it is thickness corresponds to the epidermis layer of the skin. Its elasticity to the human is similar to the elastic properties of the skin. The bands are longitudinally the same as it does not show a transverse stretching feature while extending up to 55-60%. Tapes can be used for different treatment purposes and are applied in different tensions. The bands can be stretched by approximately 60%. Tension levels are defined as maximal stretching (100%), submaximal stretching (75%), moderate stretching (50%), light stretching (25%), very light stretching (10-15%), and application without stretching. The tapes, which maintain their elastic properties for 3-7 days, consist of polymer elastic fibers wrapped in 100% cotton fibers. The adhesive consists of wavy acrylic similar to fingerprints, latex-free, and heat is activated by it. The strips used for kinesiologic taping are I, Y, X, mesh, or ring-shaped. The choice of tape type depends on the technique, and the stage of the disease, the affected may vary according to the region. I and Y strips are the most commonly preferred application methods to reduce pain [23]

I and Y strips will be used for the taping process to be applied to the back of the neck area (Figure 1).
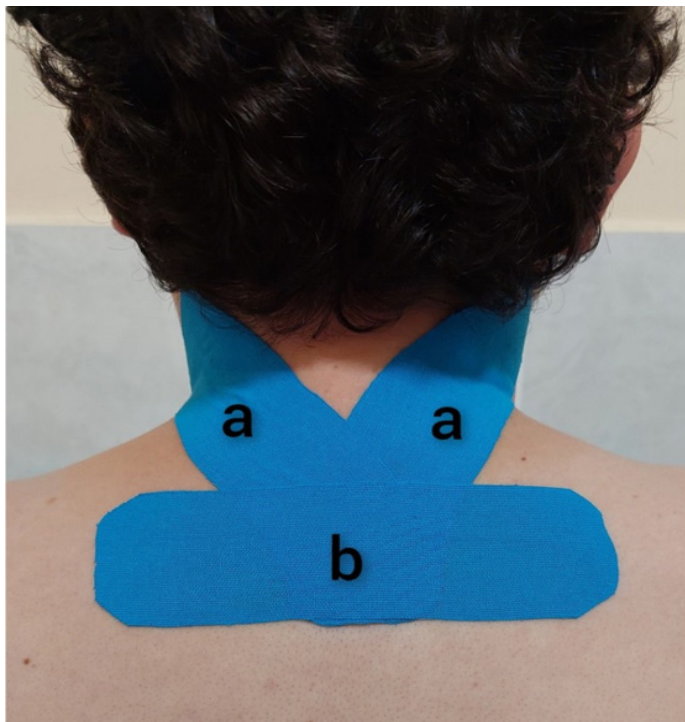
Figure 1. Kinesio taping is an application. Application of the "Y" and "I" band (a) "Y" bant and (b) "I" bant

Application of the "Y" Band

For the taping process, the bands were cut according to the length of the neck area of the people. Round shapes were given to all corners of the tape used in this process. The purpose of this is to prevent the tape from lifting from the edges during putting on and taking off the clothes and during the movements of the person. The tape was glued to the lower end of the cervical 7th vertebra (Vertebra Prominens) with submaximal tension, and the right end of the other two ends was glued to the temporal bone the left end was applied to the proc. mastoideus of right and the left end to the proc. mastoideus of the left temporal bone. No stretching was performed at the beginning and end of the band to avoid skin discomfort [23].

Application of the "I" Band

For the taping process, the bands were cut according to the length of the neck area of the people. Round shapes were given to all corners of the tape used in this process. The purpose of the tape is to prevent the tape from lifting from the edges during putting on and taking off the clothes and during the movements of the person. The tape was applied to the pars transversa of the trapezius muscle with moderate tension. No stretching was performed at the beginning and end of the band to avoid skin discomfort [23].

The applied patches stayed on the participants for 72 hours (3 days).

In addition, the Bournemouth Neck Pain Questionnaire was administered to the participants before and ten days after the taping procedure. The questionnaire included pain intensity, inadequacy in activities of daily living, inadequacy in social activities, anxiety, emotional aspects, kinesiophobia, and ability to control pain consisting of 7 questions. In addition to pain, the questionnaire assesses kinesiophobia, anxiety, depression, and the individual's ability to cope with pain specific to neck pain. The questions of the questionnaire are not about the current status of the individual, but the average severity of the symptoms present in the last week is questioned. Since it is known that the severity of symptoms related to neck pain varies over time, this questionnaire makes inquiries according to a certain time period. For this reason, the Bournemouth Neck Pain Questionnaire is designed to assess the clinical course of individuals and is quite successful in reflecting [24].

Statistical Analysis

The analysis of the data included in the study was performed with the SPSS (Statistical Program in Social Sciences) 25 program. Whether the data included in the study fit the normal distribution was checked with the Kolmogorov Smirnow Test [25]. The significance level (p) was taken as 0.05 for comparison tests. Since the variables were not normally distributed ($p>0.05$), the analysis was continued with nonparametric test methods. Wilcoxon Sign test was used for dependent dyadic groups and

Mann Whitney U test was used for dependent dyadic groups. Mean, standard deviation, median, minimum, maximum, number and percentage were calculated for descriptive data.

Results

In the participants included in the study, Bournemouth Neck Pain Questionnaire scale scores before taping were higher than after taping. The decrease in Bournemouth Neck Pain Questionnaire scale scores after taping was statisti cally significant (p=0.001<0.05, Table 2). The change in Bournemouth Neck Pain Questionnaire before and after taping in individuals The change in the scores of the scale is given in Figure 2.

When the individuals were analyzed, it was observed that there were decreases in the scale scores after taping, and some individuals dropped as low as 0 points (Figure 2).
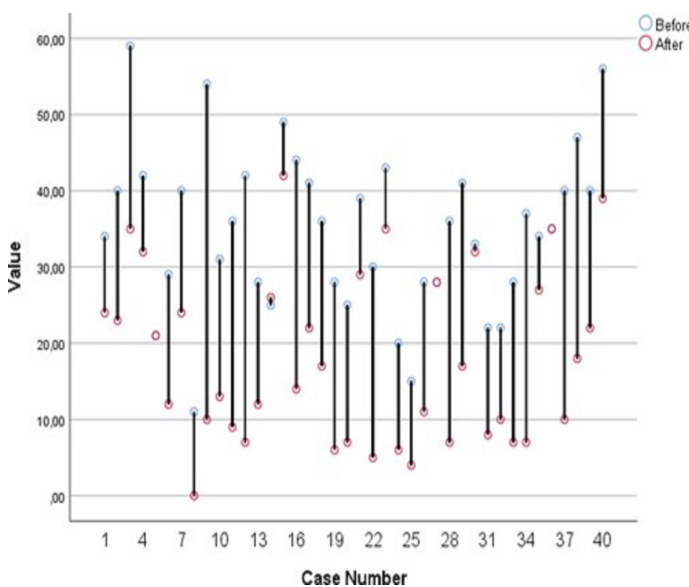
Figure 2. Before and after taping bournemouth neck pain questionnaire scale scores change

According to the Bournemouth Neck Pain Questionnaire, There was no statistically significant difference between the groups of gender, age, BMI, chronic disease variables in both pre-taping and post-taping scores (p>0.05, Table 3).

According to the Bournemouth Neck Pain Questionnaire there was no statistically significant difference in the scale scores between regular and non-regular exercisers before taping (p>0.05, Table 3), but a statistically significant difference was found after taping (p<0.05, Table 3).

According to the Bournemouth Neck Pain Questionnaire Scale scores between smokers and non-smokers before taping significant difference was found (p<0.05, Table 3). but no statistically significant difference was found after taping (p>0.05, Table 3).

According to the Bournemouth Neck Pain Questionnaire The changes in the Scale scores before and after taping were statistically significant in women, men, 22-34 years old, 35 years old and over, normal weight and overweight, regular exercisers and non-exercisers, chronic disease and non-smokers, smokers and non-smokers (p<0.05, Table 3).

Table 1. Demographic information of participants

Variable	Group	Number	Percentage
Gender	Female	22	55.0
	Male	18	45.0
Age	22-34 years old	21	52.5
	35 years and older	19	47.5
BMI	Normal	26	65.0
	Overweight	14	35.0
Regular Sports	Yes	8	20.0
	No	32	80.0
Chronic Disease	Yes	6	15.0
	No	34	85.0
Smoking	Yes	23	57.5
	No	17	42.5

Table 2. Comparison of measurements before and after taping

Variable	Ort±ss	M (Min-Max)	Test	p Value
Before Taping	34.73±10.64	35.5 (11-59)	-5.282	0.001*
After Taping	17.83±11.21	15.5 (0-42)		

Ort; mean, ss; standard deviation, M; median, min; lowest score, max; highest score, test value; Wilcoxon Test Value, p value; statistical significance, *p<0.05; there is a statistically significant difference between the groups, Before-After Taping: A statistical analysis of the answers given to the questions before and after the neck survey we applied.

Limitations of the study

In the Kinesio taping, we applied in academicians, we explained the application of Kinesio tapping to academicians who did not know this application, and some academicians did not favor the taping application.

They also said that it would not be cosmetically pleasing when lecturing.

Other participants also stated that they removed the tape while taking a bath. All these factors make it difficult to ensure voluntary participation and collect sufficient data. These reasons constitute the limitations of our study.

Table 3. Intra and inter-group comparison for sociodemographic variables

Variable	Application	Before		After		Intragroup Comparison	
		Mean±ss	M (Min-Max)	Mean±ss	M (Min-Max)	Wilcoxon Test Value	p Value
Gender	Female	35.95±11.61	35(15-59)	19.68±12.38	17.5(4-42)	-3.981	0.001*
	Male	33.22±9.42	35.5(11-47)	15.56±9.43	15.5(0-35)	-3.518	0.001*
Between groups Comparison	Mann Whitney U	182.500		163.500			
	p Value	0.670		0.350			
Age	22-34 Years	34.48±11.93	36(11-59)	17.9±12.69	13(0-39)	-3.964	0.001*
	35 Years and Over Man	35±9.33	35(21-54)	17.74±9.65	17(7-42)	-3.519	0.001*
Between groups Comparison	Mann Whitney U	199.000		185.000			
	p Value	0.991		0.690			
BMI	Normal	34.54±11.63	34.5(11-59)	18.31±12.08	17(0-39)	-4.245	0.001*
	Overweight	35.07±8.91	36.5(22-49)	16.93±9.73	15.5(6-42)	-3.182	0.001*
Between groups Comparison	Mann Whitney U	171.500		179.500			
	p Value	0.770		0.940			
Regular Sport	Yes	33.5±10.04	33(21-54)	9.75±5.04	8(5-21)	-2.366	0.018*
	No	35.03±10.92	35.5(11-59)	19.84±11.46	20(0-42)	-4.753	0.001*
Between groups Comparison	Mann Whitney U	110.500		58.500			
	p Value	0.553		0.017*			
Chronic Disease	Yes	33.5±6.02	35(22-39)	18.17±11.44	16.5(7-32)	-2.207	0.027*
	No	34.94±11.31	35.5(11-59)	17.76±11.34	15.5(0-42)	-4.843	0.001*
Between groups Comparison	Mann Whitney U	91.000		98.000			
	p Value	0.676		0.879			
Cigarette	Yes	38.3 ± 10.44	40(20-59)	18.65±11.7	17(6-42)	-4.077	0.001*
	No	29.88 ± 9.1	31(11-42)	16.71±10.76	13(0-32)	-3.410	0.001*
Between groups Comparison	Mann Whitney U	110.000		179.000			
	p Value	0.019*		0.651			

Ort; mean, ss; standard deviation, M; median, min; lowest score, max; highest score, *p<0.05; there is a statistically significant difference between the groups

Discussion

Neck pain is a problem especially seen in people who are frequently exposed to non-neutral positions, such as students and office workers. In this problem, the pressure applied to the neck muscles causes a protective spasm in the structures surrounding the neck. As a result, ischemia, extreme pain, and abnormal neck posture are observed [26]. In our study, we investigated the effectiveness of the treatment of neck problems with Kinesio Taping, which is common in academics who spend long periods in front of the computer. According to the Bournemouth neck questionnaire used in the evaluation of neck pain after treatment with KT in our study, we found a statistically significant difference between the pre-treatment and post-treatment values of the participants [27]. Thus, we determined that the pain decreased statistically significantly (p=0.001).

Studies have been conducted in many countries on the validity and reliability of the Bournemouth neck questionnaire. According to Salaree et al. [28] reported that this questionnaire is suitable for clinical and research use in the Iranian population. Geri et al. (29) reported that the Italian version of this questionnaire is suitable for clinical and research use. In the literature on the validity and reliability of the Bournemouth neck questionnaire used in our study in the Turkish population, Yılmaz et. al. [30] reported that Cronbach's alpha values were 0.877 and 0.907 before and after treatment, respectively, and were appropriate in clinical applications. Similarly, Agce et al. [31] reported that with Cronbach alpha values of 0.97 and 0.99, it is suitable for use in multidimensional, short, practical individuals with neck pain.

In the literature, KT application has a widespread use in the treatment of musculoskeletal diseases. According to Paoloni et

al. and Greig et al. [32,33] stated that taping can support lumbar muscles, provide mechanical support for body muscles, and increase body flexion by reducing pain and accelerating tissue healing. Lim and Tay [34] reported that elastic taping is an effective method for musculoskeletal system pain. According to Arpaci et al. [35] reported that KT method was effective in increasing proprioceptive recovery in female and in reducing pain during resistant wrist extension in male in patients with lateral epicondylitis.

Many studies in the literature have reported that KT method is effective in the treatment of neck, back, and shoulder pain. From these studies, it was stated that KT method is effective in patients with mechanical neck dysfunction due to cervical lordosis problems [36,37]. Lopez et al. It has been reported that KT application significantly reduces the level of pain in fibromyalgia patients and improves the comfort of the head, neck, and shoulders [38].

Similar to our study, in studies investigating the efficacy of the KT method in the treatment of neck pain, Erdoğanoğlu and Bayraklı found that there was a statistically significant difference between before and 24 hours after elastic taping in pain assessment [39]. Gonzales-Iglesias et al. reported that especially the cervical region is injured in acute whiplash injuries and that the application of elastic taping has positive results in reducing cervical pain [40]. According to Alahmari et al. applied the same form of taping as our study and placebo taping without creating tension. As a result, they reported that the pain in the VAS-taping group decreased significantly compared to the placebo group on the 3rd and 7th days [41]. Augusttsson et al. reported that short-term balanced body taping treatment had a limited, reducing effect on pain sensitivity in the neck, back, and shoulders without being compared with other treatments [42].

In the comparison of KT method used in neck pain in the literature with other treatments, Elabd et al. [26] applied the same taping method as our study in the taping group in patients with neck pain and compared it with the posture exercise group and reported that KT was more effective than postural exercises in reducing neck pain. Taylor et al. [43] reported that taping had a short-term effect on neck and upper extremity pain and that this method could be a useful alternative to other conservative methods. Saavedra-Hernandez et al. [37] reported that there was no statistically significant difference between elastic taping and other methods, and that the elastic taping method was equally effective with other existing methods in neck pain. In our study, we concluded that the KT method was effective, similar to these studies in the literature.

There are resources describing the mechanism of action of KT therapy related to physiological and neuroanatomical approaches. Regarding these mechanisms, Erdoğanoğlu and Bayraklı [39] reported that providing afferent sensory input with elastic banding provides relief in pain by activating the pain inhibitor mechanism. Regarding this mechanism, several studies have stated that the cutaneous tension stimulation provided by KT inhibits the transmission of mechanical and painful stimuli. They reported that this is due to the fact that the KT method can provide inhibition by afferent impulses according to the gate control theory. In addition, it is reported that KT application can increase lymphatic and vascular flow and increase functional abilities in patients by helping to correct possible joint alignment disorders [33, 44,45]. Gusella et al. [46] reported that KT application normalizes muscle function with two main mechanisms. The first and mechanical one of these mechanisms is that taping affects the muscle fibers. This effect occurs by shifting the length-tension curve of the muscles and changing the position of the joints. The second mechanism speculates that the amplification of proprioceptive and kinesthetic information occurs because the taping stimulates skin stimulation and affects the central nervous system.

Conclusion

In our study, We concluded that KT is an effective method in the treatment of neck pain in academics who spend a long time at the computer and desk. It may shed light on the literature and researchers that our study can be an alternative treatment for people with pain complaints and who use computers a lot.

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ORIGINAL ARTICLE

Expression of connexin 32 and connexin 43 gap junction proteins in basal and squamous cell carcinomas

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Abstract

Gap junctions play a role in intercellular communication in the epithelium, muscle and nerve tissues, and many more tissues and organs. These linking regions and the proteins forming them are called connexins (Cx). Recent studies show that cellular homeostatic equilibrium can be influenced by connexins. In this study, the expression of Cx43 and Cx32 in basal cell carcinoma (BCC) and squamous cell carcinomas (SCC) is tried studied. A total of 45 cases, 23 male and 22 female, were included in the study. Twenty of the cases were SCC and twenty-five were BCC. Retrospective data from records were examined and specimens were investigated by immunohistochemistry staining. It was determined that the results of Cx 43 and Cx 32 staining changed according to the tumor type of cases (P = 0,020). It was determined that the results of Cx43 and Cx32 staining did not change according to the sex and age, BCC and SCC subtype, and location. Losses of Cx43 and Cx32 have been shown to be associated with tumor types. We believe that it can be used as a support marker of SCC and BCC differential diagnosis.

Keywords: Basal cell carcinoma, Squamous cell carcinoma, Connexin 32, Connexin 43

Introduction

Gap junctions (GJ) between two neighboring cells have great importance. GJ are intercellular membrane channels that allow direct cell-to-cell communication, ion, small molecules, and cellular metabolites to enter and exit between neighboring cells. These linking regions and the proteins that constituent them are called connexins and show a widespread in all mammalian cells [1].

Recent studies have shown that cellular homeostatic balance can independently affect intercellular communication (GJIC), the structural premises of gap junctions [2]. These highly diverse proteins make their specific responsibilities as vital functions, such as facilitating the intracellular passage of small regulatory molecules by spreading electrical signals between cells. In many cell types, changes in the connexin family can be seen and adaptive mechanisms may develop for the continuation of function. However, these changes can lead to significant pathologies. In many cases, single-point mutations cause dramatic consequences due to insufficient quantification of the junctional regions of the connexions and non-uniform internalization [3].

The sizes of the connections are their classification criteria. Membrane proteins form extracellular and intracellular structures in the form of thread loops in the membrane due to amino acid

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sequences. These layouts form the topology of the connections. This formation has been confirmed by several investigators for Cx43, Cx26, and Cx32 [4-6].

Despite numerous linkages, evidence has been shown that these proteins are superimposed on cell and tissue proliferation [3].

First, in many tissues and cell types, two or more members of the connective family are explicitly exposed. Cx43 was observed in keratinocytes and Cx32 in hepatocytes. There are studies of the expression of connexin in mammals and in particular of Cx43 expression. It is known that Cx43 is endogenously present and contains 35 different tissues, including keratinocytes, astrocytes, endothelial cells, smooth muscle cells [3-7].

When the literature is investigated, researches are suggesting that Cx43 can stimulate invasion and metastasis by regulating the interaction between stromal cells and tumors [7]. There are also studies evaluating the expression of Cx 32 and 43 between normal tissue and neoplastic tissue [8].

In this study, the expression of basal cell carcinoma (BCC) and squamous cell carcinomas (SCC) Cx43 and Cx 32 was investigated and the relationship with clinical parameters was investigated.

Material and Method

Design of study

The study was planned retrospectively. BCC and SCC cases sent to the pathology department between 2014 and 2015 were included in the study. The location, diameter, differentiation grades and age and gender of cases were reported. A total of 45 cases were included in the study. Twenty of the cases were SCC, twenty-five of the cases BCC. 23 of the cases were male and 22 of the cases were female. Paraffin blocks of cases were selected. 3 micrometer thick sections were taken from these paraffin blocks. Sections were taken on a polylysine-coated slides.

Immunohistochemistry

Sections of 3 μm thickness were prepared from paraffin blocks consisting of skin tissues. Immunohistochemical staining was performed using a Leica Bond automatic tissue staining device . The antibody and dilution ratios are as follows; Cx32 (recombinant anti-connexin 32/GJB1) (dilution ratio 1:200) and Cx43 (recombinant anti-connexin 43/GJA1) (dilution ratio 1:200). Slides were evaluated under the Nikon Eclipse Ni U microscope for grading. The stained slides were examined and photos were taken. Cx32 and Cx43 expression were evaluated semi-quantitatively according to staining intensity as none, mild, moderate and strong (0,1,2,3). Mild, moderate and strong staining grades were combined (as positive). Data were classified as negative and positive. It was observed that positivity was found in the basal cells (Figures 1-4).
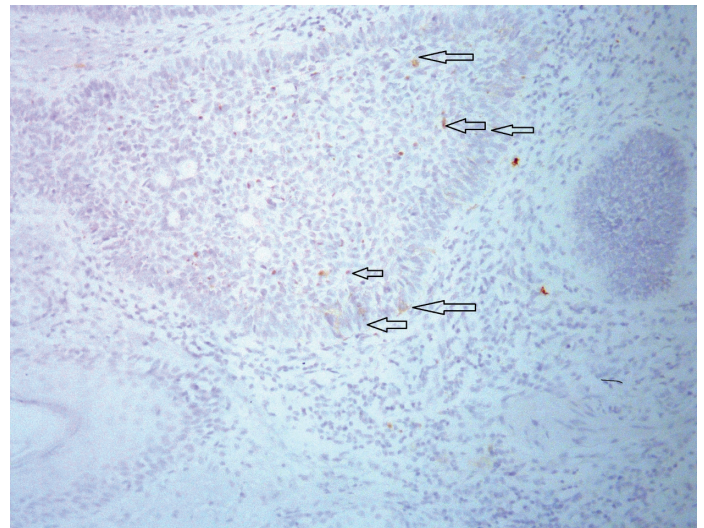
Figure 1. Connexin 43 positivity of Basal Cell Carcinomas (x200)
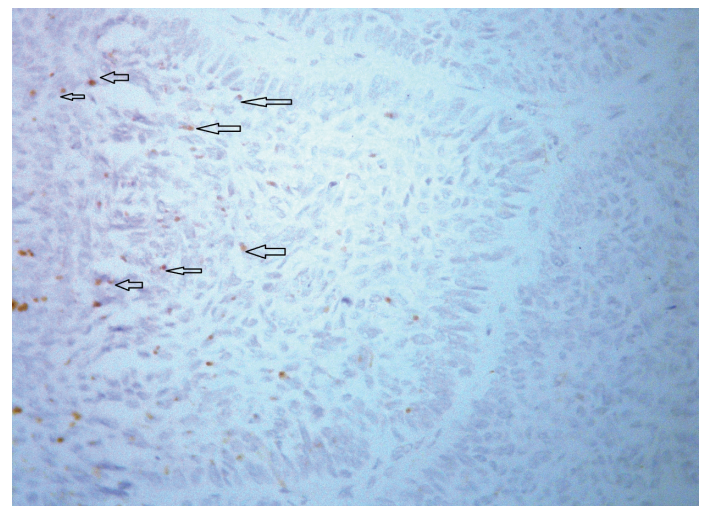
Figure 2. Connexin 32 positivity of Basal Cell Carcinomas (x400)
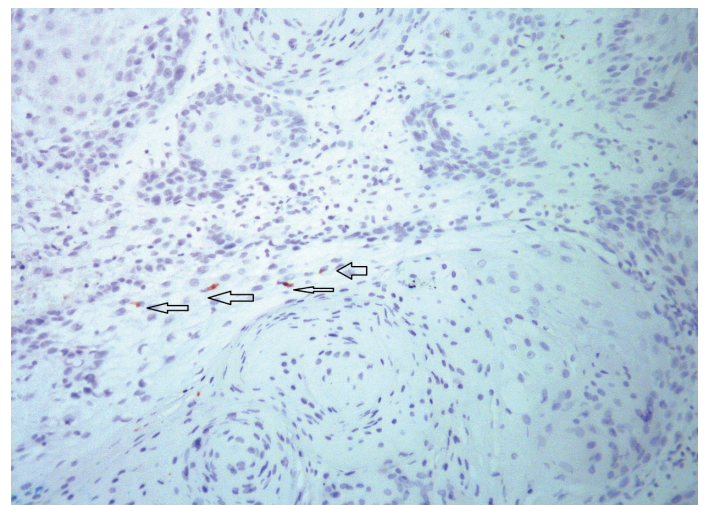
Figure 3. Connexin 43 positivity of Squamous Cell Carcinomas (x200)
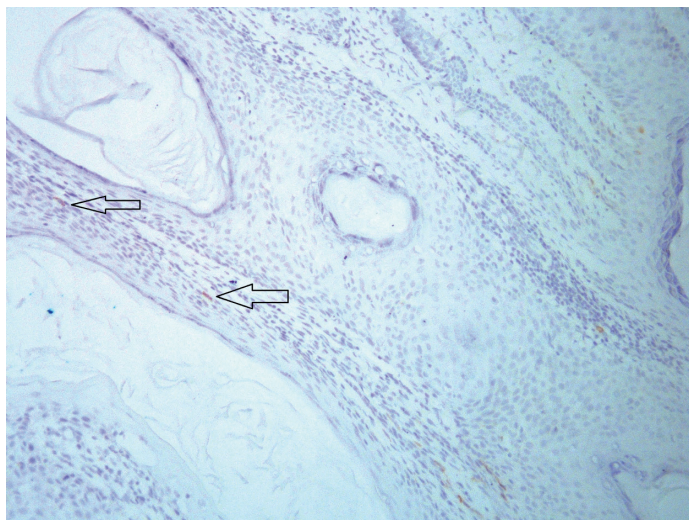
Figure 4. Connexin 32 positivity of Squamous Cell Carcinomas (x200)

Statistical analysis of data

Chi-square analysis was used to investigate the relation between sex, age, type, differentiation grade, location, and the results of the Cx43 and Cx32 staining of the cases. In this study, evaluation; below 50 years of age and 51-70 age group values were combined and evaluated. Diameter less than 5 mm and from 6 to 10 mm were combined and evaluated. SCC distribution according to the differentiation is as follows; 12 well-differentiated, 8 moderate and poorly differentiated tumors. The subtype distribution of BCC was as follows; 14 nodular, 3 infiltrative, 5 basosquamous, 1 micronodular, 1 keratotic, 1 pigmented. In both tumors, location , diameter, and age were evaluated together. The location of the nose and the upper region was 29 cases and under the nose were 26 cases. The number of cases between 6-10 mm and over 11mm is 22 and 23, respectively.

Chi-square analysis was used to investigate the relationship between gender, age, type, degree of differentiation and location of cases with Cx43 and Cx32 staining results (negative, positive).

In addition, for significant results, the effect of staining intensity was demonstrated by bivariate logistic regression analysis. In the study, multivariate logistic regression analysis was not performed because the effect of species was significant only in the presence of staining (P < 0.25).

All statistical calculations were made in the SPSS 19.0 V statistical package program and were expressed in terms of findings and percentages.

Results

Statistically, it was determined that the results of Cx 43 and Cx 32 staining changed according to the tumor type of the cases (P = 0,020) (Table-1). As a result of the bivariate logistic regression analysis performed, the intensity of staining in BCC type according to SCC type is 8,175 times more (Tables 2,3). As a result of the bivariate logistic regression analysis performed, the intensity of staining in BCC type according to SCC type is 7,071 times more.

Table 1. Results of the Cx 43 and Cx 32 according to the type of tumor

Type of tumor	n (%)		Total
Staining	Negative	Positive	
BCC	14 (56.0)	11 (44.0)	25 (100.0)
SCC	18 (90.0)	2 (10.0)	20 (100.0)
Total	32 (71.1)	13 (28.9)	45 (100.0)
x^2 :6.252	P=0.020		

Table 2. Potential risk factors associated with Cx43 staining in the univariate logistic regression equation

Variable	No	Total No	Prevalence (%)	B	S.E.	Wald	Sig.	Exp(B)	95% CIfor Exp(B)	
									Lower	Upper
Constant				-2.20	0.745	8.690	0.003	0.111		
TYPE										
SCC	2	20	10.0							
BCC	11	25	44.0	1.96	0.847	5.330	0.021	7.071	1.344	37.215

Table 3. Potential risk factors associated with Cx32 staining in the univariate logistic regression equation

Variable	No	Total No	Prevalence (%)	B	S.E.	Wald	Sig.	Exp(B)	95% CIfor Exp(B)	
									Lower	Upper
Constant				-2.20	0.745	8.690	0.003	0.111		
TYPE										
SCC	2	20	10.0							
BCC	11	25	44.0	1.96	0.847	5.330	0.021	7.071	1.344	37.215

Besides, the results of Cx 43 and Cx 32 staining did not change according to the subtype of BCC and SCC (respectively; P = 0,188, P = 0.514). Moreover, the results of Cx 43 and Cx 32 staining in the cases did not change according to the location (P = 0,322).

Cx 43 and 32 staining results were evaluated according to the diameter of the tumor. It was determined that the staining results did not change (P=0.372).

Distribution of Cx43 and Cx32 staining results according to the sex of tumor types are evaluated. It was determined that Cx32 staining results were the same as Cx43 staining results and did not change (P = 0,815).

Statistically, Cx 43 and Cx 32 staining results were evaluated according to the age of cases. It was determined that the staining results did not change (respectively; P=0.095, P=0.441).

Discussion

Some Cx's are very specific and are excreted in many tissues. One of these cases, the Cx43, has been reported to be extended in more than twenty-five tissues [9,10].

Hieber et al. have studies showing increased expression of Cx43 [11]. In the aforementioned study, they observed that carotenoids increased protein levels and Cx43 expression in the suprabasal layers of human keratinocytes in human and mouse fibroblasts and organotypic cultures [11]. As a result of this study, they concluded that it may be important in the growth of human tumor cells and claimed that Cx43 expression can potently inhibit the in vitro marker of malignancy [12].

Cx43 expression in human carcinoma cells has been shown to decrease both in vivo and in vitro [13,14].

In Bertram's study, increased Cx43 expression and decreased normal and neoplastic tissue proliferation were observed. It has been observed to decrease in displaced tissue and tumor progression [15].

In a study by Puzzo et al., they reported negative or poor expression of Cx43 expression in poorly differentiated carcinoma [16].

In this study, staining in SCC was lesser than BCC. Since SCCs are more aggressive tumors than BCC, loss of Cx staining showed results consistent with the literature with tumor type. Since the prognosis will worsen with loss of differentiation, the expected result in this study is loss of Cx staining with loss of differentiation. However, although this interpretation was made clinically in this study, it could not be proved statistically because the number of cases was small.

The study of Wilgenbus et al. investigated the expression of Cx 26, 32, and 43 gap-junction proteins in malignant and non-malignant human tissues. In their study, Cx32, the major gap-junction protein in rat and mouse liver, was also detected in the human liver and kidneys [17]. Cx26 was detected in different epithelium, whereas Cx43 was expressed in epithelial and mesenchymal tissues. All benign tumors and some malignant tumors in the study showed stable expression in gap-junction proteins. In addition, a decrease in gap-junction proteins was observed in many cancers compared to normal tissues. To give an example of these cancers; breast cancer, renal cell carcinoma and sarcoma. They observed in their study in basal cell carcinoma tissue samples [17].

Tada et al. showed that Cx expression was weak in BCC and SCC, and expression was absent in eccrine and apocrine glands [18].

In a study by Schneider et al. they report 43 cases of basal, parabasal, and middle-layer Cx [8]. In this study, it was noticed that the staining is prominent in the basal cells.

Danos et al. reported a positive correlation between the expression of Cx 43 and the patients's survival and head and neck carcinomas [19].

Limitations of the study

The sample number in this study was a few. Therefore, SCC and BCC subtype could not be analyzed separately in terms of demographic data. In this study, it was observed that the expression of Cx43 and Cx32 in BCC and SCC cases did not change with age, sex, location, and diameter. Since the study was included between 2014 and 2015, the relationship between Cx32 and Cx43 was not assessed with the survival of the cases. This is one of the limitations of this study.

Conclusion

Expression of CX32 and Cx 43 may be useful in the differential diagnosis of BCC and SCC. We believe that analysis with larger case series can yield more reliable results in order to reveal the differences between the subtypes and demographic variables of both tumors.

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ORIGINAL ARTICLE

Long-term results of laser in situ keratomileusis for myopia

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Abstract

Laser in situ keratomileusis (LASIK) is still the most popular refractive surgery in the world. The aim of the study is to assess the long term clinical outcomes of LASIK in treating patients with different types of myopia. Pre- and postoperative distance visual acuity, refractive spherical equivalent (SE) and clinical examinations of dry eye disease were recorded. Values obtained at baseline and controls were compared with each other. While preoperative mean uncorrected distance visual acuity (UDVA) of low and moderate myopic patients was 0.1±0.07 on Snellen eye chart, and it was 0.86 ±0.11 at the 6th month and 0.92 ±0.05 at the 3rd year. At the last control examination, the percentages of manifest refractive SE in the range of ±0.50D and ±1.00D were 78.3%, 88.3%, respectively. The mean UDVA of high myopic patients was 0.03 ±0.02 preoperatively, and it was 0.84 ±0.16 at the 6th month and 0.69 ±0.21 at the 3rd year. UDVA at 3 years was significantly decreased compared with 6 month postoperatively.(p=0.01) At the last control examination of this group, the percentages of manifest refractive SE in the range of ±0.50D and ±1.00D were 48.3%, 66.1 %, respectively. These also decreased from 6 month to 3 years postoperatively.The mean tear break-up time and schirmer-1 values, which decreased in the postoperative first year visits of the patients, were close to the preoperative values at the last control. There were no statistically significant difference between the preoperative and 3rd year comparisons.(all p>0.05) In conclusion, LASIK is an effective and safe procedure in patient with myopia, preoperative higher SE is a predictor of low postoperative efficacy.

Keywords: Cornea, Myopia, laser in situ keratomileusis, visual outcome, dry eye disease

Introduction

Myopia is a refractive anomaly which is a global public health issue. Glasses and contact lenses are the most preferred options for good vision in daily life. Although glasses are safe and effective methods for correction of myopia and myopic astigmatism, many patients are looking for others due to the difficulty of using glasses from a personal and social perspective. Contact lens is an alternative, but it has some disadvantages and may also cause ocular complications. Dry eye desease, discomfort, corneal infiltrates and giant papillary conjunctivitis are the most common complications of contact lenses [1]. Refractive surgery is a permanent solution which is an attractive option for many patients.

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Refractive surgery is an area that has developed rapidly in ophthalmology. The last century witnessed the development of refractive surgery, starting with manual methods such as refractive cornea shaping and curved incisions [2]. After years of radial keratotomy for myopia, Tokel et al. performed photorefractive keratectomy (PRK) on myopic eyes in 1983 using a 193 nm argon fluoride laser [3]. PRK is an effective, safe and predictable procedure for correcting different types of myopia. However, over time, problems such as postoperative pain, corneal haze, and myopic regression have emerged as disadvantages of PRK [4]. In refractive surgery, Pallikaris defined the LASIK procedure in 1989 [5]. The most important reasons for preferring LASIK over PRK are reduced post-operative pain, rapid visual rehabilitation, and minimized possibility of regression. Furthermore, the decrease in some complications in long-term follow-ups has made the LASIK procedure more popular [6]. However, some limitations remain, such as postoperative myopia regression and dry eye development [7]. The patient usually perceives dry eye symptoms immediately after surgery which are usually temporary. However, some may be more severe than others and may harm vision quality [8].

Even if different and new surgical techniques emerge, LASIK refractive surgery remains on the agenda. This study aimed to examine the change in refractive errors, visual acuity change, and possible complications in the long term follow-up of myopic cases who underwent LASIK surgery.

Material and Methods

Local Ethics Committee (Cemil Tascioglu City Hospital Ethic Committee ref no: 2022/259) allowed this study. The records of 98 patients who received myopia and/or myopia astigmatism diagnosis and had a LASIK refractive surgery between September 2008 and June 2014 at the ophtalmology departments of Okmeydani Training and Research Hospital were retrospectively analyzed through the hospital's electronic database.

A comprehensive ophtalmologic examination that including corrected and un corrected visual acuity (UDVA), manifest, fogging and cycloplegic refractions testing on Snellen eye chart, slit lamp examination of the anterior segment and retina assessment with pharmacological mydriasis. Schirmer 1 and tear break-up time (TBUT) tests were also applied to the patients before the operation and in the control examinations. Pentacam (Oculus,Wetzlar, Germany) was used for corneal topography measurements of patients. Only the individuals with myopia and myopic astigmatism included in our research. Inclusion criteria consisted no contact lens wear 3 weeks before surgery, stable refraction, an age of 22 years or older, with astigmatism of <1.50 Diopter(D) and best corrected visual acuity of at least of 0.7 on Snellen chart. Individuals with a record of a concurrent systemic diseases such as diabetes mellitus or hypertension, any ocular diseases or any history of ocular trauma were also aliminated from the investigation.

All surgeries were performed by two surgeons using the same protocol and technique. After topical anesthesia, Automated Corneal Shaper Microkeratome (Moria, Antony, France) was utilized to make corneal flap. LASIK was performed with the MEL 80 (Carl Zeiss Meditec, Jena, Germany) excimer laser system. Postoperatively, diclofenac 0.1% (Voltaren, Novartis) and tobramycin (Tobrex, Alcon Lab., Ft Worth, Texas) eye drops associated with preservative free tear substitutes were used 4 times per day for 3 weeks. Fluorometholone 0.25% was applied 4 times daily for a 3 weeks based on refraction and intraocular pressure.

One hundred and seventy six eyes were divided into two groups according to the degree of preoperative spherical equivalent (SE). Group 1 eyes had mild and moderate myopia (0 to -6.00D) ; group 2 eyes had high myopia (more than -6.00). Postoperative examination were performed at 1 day, 1 week, 1 month, 3, 6, 12 and 36 months. UDVA , best corrected visual acuity by manifest refraction, slit lamp biomicroscopy, Schirmer-1 test, TBUT and cornea topography were performed during all visits.

Statistical Analysis

For statistical analysis, the chi-square test was employed to compare the frequencies and percentages of the groups. The Kolmogorov-Smirnov test was used in the analysis of the normal distribution, and the follow-up paired t test was performed to compare the mean values of the variables for the groups. The results were displayed as mean ± standard deviation. SPSS for windows was used to conduct all statistical analysis. (Version : 21.0) Statistics were considered significant at p< 0.05.

Results

This study investigated the examination records of 176 eyes of 98 patients.The ages were between 22 and 45, and the mean age was 29.23±4.67. There were 97 eyes in group 1 and 79 eyes in group 2. No statistically significant difference was present between the groups in the comparion of gender and mean age. (p=0.08, p=0.07 respectively) (Table 1)

Table 1. Patient demographics of the 176 matched eyes that underwent LASIK treatment for different degrees of myopia

Characteristic	Group1 (Mean±SD)	Group2 (Mean±SD)
Age (years)	28.13±5.27	29.88±6.15
Gender (% female)	%61.1	%57.3
Manifest spherical equivalent (D)	- 4.29±0.52 D	-7.89±1.10 D
Cylinder (D)	-0.65±0.37 D	-0.74±0.48 D
Corneal thickness (μm)	546.62±33.29 μm	534.38±41.32 μm
UDVA (Snellen Chart)	0.1±0.06	0.03±0.02
Schirmer's 1 (mm)	20.41±4.26 mm	19.12±7.06 mm
Tear break-up time (sec)	10.2±1.8 sec	9.8±2.2 sec

The mean SE of the refractive error in the preoperative examinations of the patients in group 1 was 4.29±0.52 D. Later, it was -0.35±0.18 D, -0.38 ±0.16 D, and -0,41±0.46 D in the postoperative 6th month, 1st year, and 3rd year, respectively. There was no statistically significant difference in the mutual comparison of the values from the controls.(all p>0.05) In group 2, the mean SE of the refractive error in the preoperative examinations of the patients was -7.89 ±1.10 D. Then, it was -1.07± 0.24 D, -1.13 ± 0.36 D, and -1.41±0.48 D in the postoperative 6th -month, 1st -year, and 3rd -year, respectively. In the mutual comparison of the values in the controls, statistically significant differences were presented between the 3rd -year and 6th -month , 3rd -year and 1st -year values.(p=0.04, p=0.03, respectively) (Figure 1).
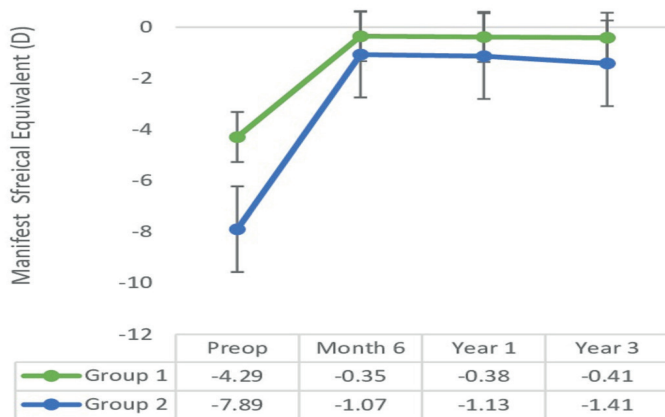
Figure 1. Mean value of SE preoperatively and 6 months, 1 and 3 years after

In the last control examination of the first group (in the 3rd -year), the percentages of manifest refractive SE in the range of ±0.50 D, ±1.00 D and ±2.00 D were 78.3%, 88.3%, and 97.9%, respectively. In the last control examination of the second group (3rd -year), the percentages of manifest refractive SE in the range of ±0.50 D, ±1.00 D and ± 2.00 D were 48.3%, 66.1%, and 84.4%, respectively. (Figure 2)
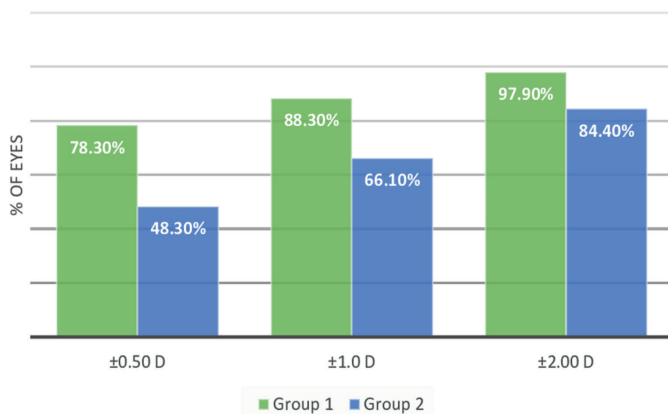
Figure 2. Percentages of eyes within ±0.50 D, ±1.00 D and ±2.00 D (in terms of SE) at 3 years after LASIK surgery

In group 1, the mean preoperative UDVA of the patients on Snellen chart was 0.1 ±0.06, while it was 0.86±0.11, 0.91 ± 0.06, and 0.92±0.05 in the postoperative 6th-month, 1st-year, and 3rd- year, respectively. There was no statistically significant difference in the mutual comparison of the values obtained in the controls.(all p>0.05). In group 2, the mean UDVA in the preoperative examination of the patients was 0.03±0.02, while it was 0.84±0.16, 0.81±0.12, and 0.69±0.21 in the postoperative 6th month,1st year, and 3rd year, respectively.In the mutual comparison of the values obtained in the controls, there were statistically significant differences between the 3rd-year and 6th-month , 3rd-year and 1st-year values.(p=0.03, p=0.04, respectively) (Figure 3)
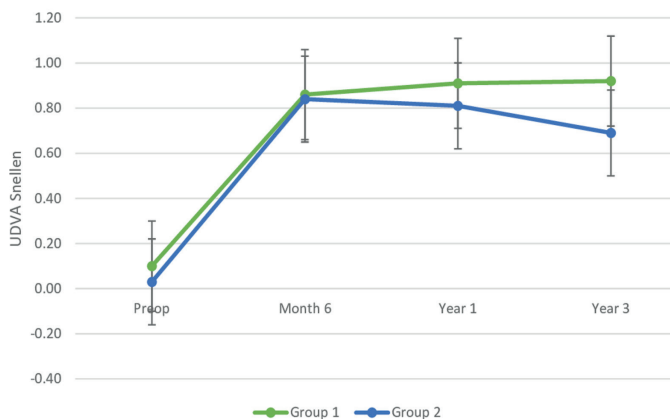
Figure 3. Time course of mean UDVA on Snellen chart after LASIK surgery. Errors bars represent the standard deviation

In group 1, the mean preoperative UDVA of the patients on Snellen chart was 0.1 ±0.06, while it was 0.86±0.11, 0.91 ± 0.06, and 0.92±0.05 in the postoperative 6th-month, 1st-year, and 3rd- year, respectively. There was no statistically significant difference in the mutual comparison of the values obtained in the controls.(all p>0.05). In group 2, the mean UDVA in the preoperative examination of the patients was 0.03±0.02, while it was 0.84±0.16, 0.81±0.12, and 0.69±0.21 in the postoperative 6th month,1st year, and 3rd year, respectively.In the mutual comparison of the values obtained in the controls, there were statistically significant differences between the 3rd-year and

Figure 4. Gained and lost lines according to the comparison of 3rd-year and 6th-month control of UDVA on Snellen chart

The mean preoperative TBUT was 10.2±1.8 sec. in group 1, it was 7.1 ± 2.9 sec, 9.4 ± 2.4 sec, and 10.1±2.3 sec in the 6th-month, 1st-year, and 3rd-year of the control examinations, respectively. After comparing the control visits and pre-LASIK values, only the 6th-month control value was statistically significantly lower (p=0.03, p=0.06, p=0.12, respectively). The mean preoperative Schirmer-1 test was 20.41±4.26 mm, while it was 14.11 ± 5.18 mm, 16.37 ± 6.26 mm, and 19.91±3.84 mm in the 6th-month, 1st-year, and 3rd-year, respectively. After comparing the control visits and pre-LASIK values, the values at the 6th-month and 1st-year controls were statistically significantly lower (p=0.03, p=0.04, p=0.08, respectively). In group 2, the mean TBUT was 9.8±2.2 sec, while it was 7.2±1.9 sec, 9.1 ± 2.1 sec, and 9.6±0.9 sec in the 6th month, 1st year and 3rd year, respectively. In the control visits and the pre-LASIK values, only the 6th-month control value was statistically significantly lower (p=0.03, p=0.06, p=0.11, respectively). While the mean preoperative Schirmer-1 test was 19.12±7.06, the mean postoperative Schirmer-1 test was 15.93±4.17, 18.06 ± 3.75, and 18.32±6.12 in the 6th-month, 1st-year, and 3rd-year, respectively. In comparing the control visits and pre-LASIK values, only the 6th-month control value was statistically significantly lower.(p=0.03, p=0.06, p=0.09, respectively) (Figures 5,6). In the first year controls, there were complaints of dry eye symptoms in eight casesin group 1 and eleven cases in group 2. In the controls, dry eye were presented in two cases in group 1 and four cases in group 2.

Figure 5. Time course of mean TBUT

Figure 6. Time course of mean Schirmer-1 test

Intraoperative and postoperative complications

Only four eyes (2.2%) had complications during the operation. These were limbal hemorrhage in two eyes (1.1%), epithelial defect during microkeratome transition in one eye (0.5%), and free flap in one eye (0.5%). Among the most common early complications in the postoperative period, forign materials were presented in four eyes (2.2%), diffuse lamellar keratitis (DLK) in two eyes (1.1%), and flap wrinkles in three eyes (1.6%). After the necessary surgical treatment and medical follow-up, there were no subjective complaints about the quality of vision. Corneal ectasia development and vitreoretinal complications did not appear in any of the cases. In the late postoperative period, the epithelial invasion was present in eleven eyes (6.2%). In 10 of these eyes, no progression to the central region was present, and therefore, there was no intervention. In one eye, progression to the central region was present in the 6th month, and the epithelium was cleaned by removing the flap.

Discussion

Refractive surgeries provide patients with refractive errors with a permanent corrective solution beyond glasses or contact lenses. Therefore, optimizing the results of these elective surgeries and avoiding complications are crucial. In the literature, Goes applied LASIK to eyes with low astigmatism values and mild-moderate myopic refractive error. He found that 60 of 68 eyes (88%) had a Snellen score of 0.9 or above, a spherical refractive error of 0.13 ±0.30 D, and 65 of 68 eyes (96%) had a targeted refractive correction of ±0.50 D during the 1-year follow-up period. One of the results of this study using the Mel 80 device, was that at one month, 17% of eyes and at one year, 13% of eyes gained two lines or more in visual acuity . Starting from the first month until the first year, all of the eyes were stable [9]. The results by O'Doherty et al. at the end of the fifth year in myopic eyes administered LASIK are also interesting. In their study, the percentage of preoperative mean SE refractive error was 81% in 49 eyes with -4.85 D, while it was within ±1.00 D in the second postoperative month and 85% in the 5th year. The rate of UDVA at 20/40 or above was 88% at 2 months, while it was 89% at 5 years. Moreover, UDVA increased by 51% in the fifth year compared to the 2nd month, while it continued at the same level in the other eyes. At the end of the fifth year, an average of -0.50 D myopic regression was present [10]. The results obtained from our study show that LASIK surgery gives effective, stable, and reliable results in low and moderate myopic errors. As a result of the 3-year follow-up, manifest refractive SE was - 0.48±0.46, while it was in the range of ± 0.50 D in 78.3% of the cases. At the end of 3-year follow-up, the mean UDVA was 0.92±0.05 on Snellen chart, and when the 6th-month control was compared, there was no change in the visual acuity in 45 (46.3%) of 97 eyes. However, 31 (31.9%) cases had a visual acuity gain, and 18 (18.4%) lost line on Snellen chart. At the end of the follow-up period, no patients required retreatment in this group. Refractive error and vision results were consistent with

the literature. Ikeda et al. noted that conventional LASIK offered good safety outcomes in mild and moderate myopic patients during the 12-year observation period. As a result of the 12-year follow-up, while mean manifest refractive SE was -0.68±0.26 D, 87.3% of the cases were in the range of ± 1.0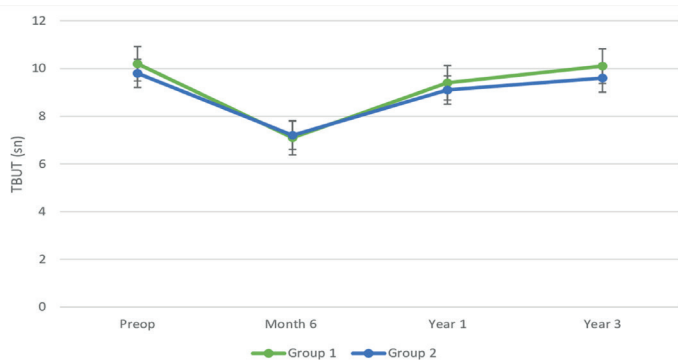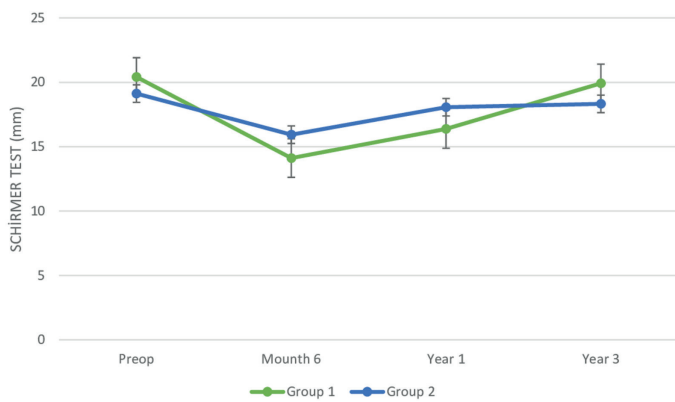0 D. In comparing the results of the last visit and the follow-up results of the first year, there was no change in UDVA on Snellen chart in 23% of the cases, while only one Snellen line of UDVA loss noted in approximately 67% of the cases [11]. Kim et al. found UDVA on Snellen chart mean 0.92±0.05 as a result of 3-year follow-ups, and manifest refractive SE was -0.68±0.26 D. At the end of the follow-up, low and moderate myopic group 59.3% of the cases were detected in the range of ± 0.50 D and 81.3% in the range of ±1.00 D [12].

The disadvantage of many corneal refractive surgeries is refractive unstability on the long term, especially in the high myopia group. In the literature, long term results after excimer laser procedures differ in eyes with high myopic refractive error. Alio et al. showed that at ten years, manifest SEs of 82 (42%) of 196 eyes were within ±1.00 D, and 119 (61%) were within ±2.00. Myopic regression decreased with time in eyes that did not undergo retreatment, with a mean rate of -0.25±0.18 D per year [13]. Lin et al., in their series of 66 cases with a mean SE of - 8.15 ± 0.94 D before the operation, noted that mean manifest refractive SE was -0.64 ± 0.95 D. As a result of the follow-up, the mean rate of patients with UDVA over 20/20 was 62.1% on Snellen chart, while 61% of cases were within ± 0.50 range and 82% were within ±1.00 range [14]. Ikeda et al. found the mean SE was -0.53 D at the end of the first year and -1.40 D at the end of the 12th year in their series of 38 cases with a mean preoperative SE - 8.15 ± 0.94 D. At the end of the first year, the average value of UDVA of patients over 20/20 on Snellen chart was 61%, while 82% of the cases were in the ± 1.00 D range. At the end of the 12th -year, the mean value UDVA of patients over 20/20 on Snellen chart was 22%, and 66% of the cases were in the ± 1.00 D range. They noted that conventional LASIK surgery offered good safety outcomes during the 12-year observation period. However, its efficacy and predictability gradually decreased due to myopic regression from corneal steeping [11]. In our results, the mean percentages of manifest refractive SE in the range of ± 0.50 D and ± 1.00 D in the 3rd-year control of advanced myopic patients were 68.3% and 76.1%, respectively. And the mean manifest refractive SE was -1.41±0.18 D in the last control. The mean UDVA of the patients was 0.81±0.16 and 0.76±0.21 in the postoperative 6th-month and 3rd-year, respectively. In UDVA, the loss rates were one line in 12 (15.1%) , two lines in 15 (18.9%), three lines in 7 (8.8%), and four lines in 5 (6.3%) of 79 eyes. No patient had a retreatment laser application for up to 3 years. In the advanced myopia group there were only 6 eyes with indication for retreatment. It is difficult to say that only one mechanism explains the regression that develops after LASIK in myopic eyes. Many possible explanations are present on this subject. High myopic eyes may respond differently to LASIK surgery than low myopic eyes due to a higher corneal elasticity

and relatively thinner sclera. Additionally, different mediators have roles in wound healing in these eyes, which show that not only epithelial changes influence myopic regression [15].

Kim et al. stated in their study that LASIK may be safe and effective on a large myopic population, but over time myopic regression occurs. Lower preoperative best corrected visual acuity and higher preoperative SE can predict low postoperative efficacy [16]. Ikeda et al. reported that LASIK offered good safety outcomes in highly myopic eyes during their 12-year observation period, however the predictability and efficacy gradually decreased with time because of myopic regression [11]. Kato et al. showed that postoperative refraction progressed statistically significantly one year after LASIK in patient with high myopia [17]. Although the exact etiology remains unclear, potential mechanisms leading to myopia regression after LASIK are as follows: stromal synthesis, keratocyte proliferation, axial elongation, corneal forward shift, epithelial hyperplasia, corneal hydration, and nuclear sclerosis [18-24]. In study of Xia et al., patients with high myopia who underwent small incision lenticule extraction (SMILE), mean residual refractive error was observed -0.02 D in the 6th-month and this value remained at the end of the 3rd-year. In the femtosecond assisted LASIK group, residuel refractive error was mean -0.15 D in the 6th-month and it progressed to an average of -0.43 D at the end of the third year. As a result of their 3-year follow-up, the mean of UDVA on Snellen chart in the SMILE group was 92.3% and above, while it was 89% in the femtosecond assisted LASIK group [25]. The systematic comparative meta-analysis study published by Fu et al focused on the results of femtosecond assisted LASIK and SMILE applied in myopic patients. There were no statistically significant differences in the results of these two procedures for patients with moderate and low myopia. However, in the high myopia group, the postoperative corrected distance visual acuity values of those who underwent SMILE were statistically significantly higher than femtosecond assisted LASIK group [26]. Yu et al. suggested that, in vivo, the excimer laser used in LASIK released more cytokines and chemokines than those released in SMILE. LASIK collected more inflammatory cells in the surgical site.[27] SMILE surgery seems to be an appropriate alternative in selected cases in the high myopic patient group.

Due to the formation of corneal flaps in LASIK, various problems may be experienced in the flap, cornea interface, and stroma. The most common problems are subconjunctival hemorrhage, epithelial defects, suction loss, foreign body, diffuse lamellar keratitis, thin flaps, buttonhole flaps, free flaps, flap decentralization, and flap wrinkles [7]. In our study, only 4 eyes (2.2%) had complications during the operation. These were limbal hemorrhage in 2 eyes (1.1%), epithelial defect during microkeratome transition in 1 eye (0.5%), and free flap in 1 eye (0.5%). Ablation continued normally in the eye that developed a free flap intraoperatively, the flap was repositioned without sutures, and the patient was followed up with a contact lens for a while. Among the most common early complications

in the early postoperative period, foreign bodies were found in 4 eyes (2.2%), diffuse lamellar keratitis in 2 eyes (1.1%), and flap wrinkles in 3 eyes (1.6%). After the necessary surgical treatment and medical follow-up, there were no subjective symptoms related to visual quality in these cases. In the late postoperative period, the interfacial epithelial invasion was presented in eleven eyes (6%). In these eyes, epithelial invasion mostly appeared in the periphery, and since only one of them had epithelial invasion toward the center and increased astigmatism, the flap was removed and washed in the 3rd month. In the long-term results of our study, no corneal ectasia and retina complications such as retina detachment, choroidal neovascular membrane, macular hole, retinal hemorrhage, and endophthalmitis were found.

Last but not least, dry eye syndrome is still the most frequent complication of LASIK [28]. After flap making combined with excimer laser photoablation the cornea is denervated, and its sensitivity decreases. Therefore, the neural impulse originating from the ocular surface and stimulating the lacrimal gland is disrupted, and tear secretion is significantly reduced [29]. This induces a decrease in tear secretion, tear film quality, epithelial wound healing and blinking rates. Tear secretion returns to its normal level as the nerves begin to regenerate in the dense cornea during the recovery period. Post refractive dry eye syndrome is an immediate issue because of patients' visual comfort and quality of life dictate their overall satisfaction [30]. In their study on dry eye detection after LASIK, Toda et al. found a significant decrease in the results of TBUT and Schirmer tests from the postoperative 1st to the 6th month than the preoperative period. However at the end of the first year, these values were close to preoperative values. They pointed out the significance of using artificial tears for patients for a long time after the operation [31]. Paiva et al. found no statistically significant difference in the dry eye ratio in their comparison between the groups determined according to nasal and superior approaches while forming a corneal flap. They found a statistically significant difference in the test results they applied for dry eye in both groups compared to the preoperative results. Hence, they reported that the risk of dry eye syndrome is correlated with high myopia and the depth of laser treatment [32]. In our study, Schirmer-1 and TBUT tests were low in the first postoperative controls. There was no statistically significant difference in comparison with preoperative values in the controls at the end of the third year. Subjective dry eye complaints were recorded in only 6 cases in the patient files. Xia et al. found significantly longer TBUT values and lower OSDI scores in the SMILE group than in the femtosecond assisted LASIK group at 1st and 3rd months postoperatively. Their data also showed a faster recovery of ocular surface damage in the SMILE group than in the femtosecond assisted LASIK. It should be attributed to the slight cornea nerve damage and a more regular corneal surface during the new flapless technique of SMILE [25]. Li et al. demonstrated that patients in the SMILE group had greater central corneal sensitivity scores and less corneal staining than patients in the femtosecond assisted LASIK group [33]. Ganesh et al. showed statistically significant lower incidence of dry eyes

in the SMILE group than in the LASIK group. They noted that although postoperative dry eye syndrome has decreased since the introduction of the femtosecond laser for flap creation; in SMILE procedure, the anterior stromal nerve plexus was signifcantly less disrupted than in femtosecond assisted LASIK [34].

One of the limtations of the study is its retrospective design. Since retrospective research may include several biases, such as information bias and selection bias, there may be some minor errors. Secondly, the sample size was relatively small. Only consecutive patients who completed thirty-six months of follow-up were presented. We know that our results can not be generalized to hundreds of thousands of patients undergoing excimer laser procedures. Thirdly, patients without astigmatism or with low astigmatism were presented in the study. It may be appropriate to conduct research with high astigmatic value. Lastly, because we conducted the study using patient records, we could not identify all predictive markers in dry eye disease. Two basic parameters were used in the research, but different parameters in the dry eye disease examination can be benefcal.

Conclusion

In summary, primary LASIK surgery is effective and safe in treating myopia and myopic astigmatism refractive errors throughout the thirty six months observation period. However, our findings show that if the amount of myopic correction is large, myopic regression occurs in several cases after LASIK. Further randomized prospective studies over longer follow-up periods in patients with high-level myopia might be beneficial.

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ORIGINAL ARTICLE

Growing concern; The relationship between screen time and behavior problems in digital era

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Abstract

Although the physical and psychological effects of digital screens have been shown in studies, its relationship with the behavior of children is still unclear. When, how, and at what ages screen time is associated with behavioral problems continues to be investigated. The study aimed to evaluate the relationship between screen time and behavioral problems. 378 children (preschooler:64, schooler:206, adolescent:108) were included in our study. The Strengths and Difficulties Questionnaire, screen and sociodemographic data were filled in by the mothers. An increase in the SDQ score (except for the social score) indicates an increase in behavioral problems. In each group, <25p screen time was evaluated as low, 25-75p as medium, >75p as high screen time. The median screen time of the preschool, school and adolescent groups was calculated as 3.00hrs.(25p-75p:1.125-5.00), 3.00hrs.(25p-75p:2.00-6.00), 5.00hrs.(25p-75p:3.00-8.00), respectively. The hyperactivity/inattention score of preschoolers who watched screen ≤1hr was significantly lower compared to those with >1hr screen time (p=0.02); In the schooler group, the social score was statistically higher and the scores of the other subscales were lower in those who watch screen ≤2hrs. While high screen time was found to be associated with behavioral problems in school and adolescents, it was found to be associated with less hyperactivity problems in preschool period in regression analysis. It was determined that low-screen time was associated with less hyperactivity in preschool period and more behavioral problems in adolescents. While moderate screen time had a positive effect on behaviors in adolescents in paired analyzes, no effect was observed in multiple regressions. Parental screen time was associated with emotional/behavioral problems of preschool and school age children. Child's screen time and parental screen time should be evaluated for intervention of behavioral problems. Large-scale studies are needed to compare the effect of low and medium-screen time on children's well-being.

Keywords: Screen time, parental screen time, behavioral problems

Introduction

Digital media plays a crucial role in the lives of the younger generation. Digital media tools are used for purposes such as entertainment, socialization, education, feeding and care [1]. In recent years, technological developments enable children to access digital devices anytime, anywhere and increase children's screen time [2, 3].

Restriction of screen time is recommended in the guidelines [4-6] but it is known that parents cannot apply the screen time restrictions [7]. The results of studies that investigate media use and children's well-being are inconsistent [8-10]. Previous studies have shown that high screen time was associated with

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physical and mental health problems [11] and low screen time positively affects the development of children [6, 8]. In recent studies, it has been shown that the relationship between screen time and mental problems is not linear, and moderate screen time has positive psychological effects compared to low screen time [10]. We know that children's screen time has been increasing, so the concerns about children's mental health have been increasing. When and how digital media affect children negatively remains a current public issue. Behavioral problems and factors affecting screen time vary between cultures. The study aimed to evaluate the factors affecting screen time and the relationship between screen time and behavioral problems in children between the ages of 2 and 17.

Material and Methods

Ethics committee approval was obtained from the Ethics Committee Toros University in Mersin, Turkey (23/9/2022 numbered 154). All parents were included in the study voluntarily, using the snowball sampling method. Inclusion criteria; being able to speak Turkish and having children between the ages of 2-17. First of all, the purpose of the study was explained and it was informed that the participation was voluntary. Mothers who agreed to participate in the study were asked to complete the Strengths and Difficulties Questionnaire (SDQ) to assess their children's behavioral problems. The mothers were also asked to fill out a questionnaire made by the researcher for the study that inquired about their children's screen time, parents' screen time, why their children watch screens, how long their children should watch screens per day, the number of books read weekly, and their sociodemographic data. Sociodemographic data; sex and age of children, parent's age, parent's education level, employment status, the number of children, birth order, and family income. Family income was asked by dividing into three groups as below the minimum wage, minimum wage, and above the minimum wage.

The children included in the study were divided into three groups according to their ages as preschoolers (2-4 years), schoolers (5-9 years), and adolescent groups (10-17 years).

In each group, screen times below 25p were classified as low screen time, 25-75p as moderate screen time, and above 75p as high screen time. Also, screen time was categorized as recommended by the guidelines, with a maximum of one hour and more than one hour daily for preschoolers; screen time was categorized as a maximum of two hours and more than two hours daily for schoolers.

Strengths and difficulties questionnaire (SDQ): Completed by parents to assess the emotional and behavioral problems of children and adolescents. SDQ consists of five subscales consisting of 25 items. The subscales are emotional problems, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. The total difficulties score includes the sum of the emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationship. Each item

is evaluated on a 3-point scale from 0 to 2. A higher score on the SDQ subscales score (except for the social score) indicates greater behavioral problems. A higher score on the prosocial behavior score indicates strengths.

Statistical Analysis

Normality control of continuous variables was evaluated with the Shapiro-Wilk test. Since the variables did not conform to the normal distribution, the Mann-Whitney U test was used in the comparison of two independent groups, and the Kruskal-Wallis test was used in the comparison of more than two groups. Spearman Rho correlation coefficients were calculated to examine the linear relationship between the variables. The Chi-square test was used in the analysis of categorical data. Multiple Linear Regression models were created for the variables affecting the Strengths and Difficulties Questionnaire subscales (Total difficulties score, emotional symptoms, hyperactivity/inattention, prosocial behaviors, conduct problems, and peer relationship problems). Data analysis was done in IBM SPSS 21 package program.

Results

As a result, a total of 378 children, 64 in the preschooler group, 206 in the schooler group, and 108 in the adolescent group, were evaluated. The sociodemographic characteristics of the participants in the study were shown in Table 1.

The median screen time for the preschooler, schooler, and adolescent groups was calculated as 3.00hrs (25p-75p: 1.125-5.00), 3.00hrs (25p-75p: 2.00-6.00) and 5.00hrs (25p-75p: 3.00-8.00), respectively. Screen time of the adolescent group was statistically higher than the other groups (p<0.001). There was a negative correlation between the number of books read weekly and screen time (r=-.329 p<0.001), and also parental education and screen time in the schooler group (maternal education: r=-.217 p=.002, paternal education r=-.156 p=.026). The numbers of televisions and siblings were positively correlated with screen time in the schooler group (r=.146 p=.036, r=.187 p=.007, respectively). According to Kruskal-Wallis analysis, the medium children's screen time was the highest compared to first and last children' screen time in the schooler group (p<0.001). By the Mann Whitney-U analysis, the screen time of the children of unemployed mothers was found to be higher than the children of working mothers (p=0.006). In the adolescent group, there was an inverse correlation between screen time and the number of books read weekly (r=-.323 p=.001), and a positive correlation between screen time and maternal age and number of televisions (r=.20 p=.038; r=.238 p=.013, respectively).

We asked parents, "How many hours do you think your child should watch screens?". In the preschooler group, 54% of the mothers answered for a maximum of 1 hour, and in the schooler group, 92% of the mothers answered for a maximum of 2 hours. When the children's screen time was examined, it was seen that only 25% of the parents applied the recommended screen time restrictions (≤1 hour) in the preschooler group. In the schooler

group, 27% of parents were able to enforce the recommended screen time restrictions (≤2 hours).

We asked parents why children use screens. The most common answers in the preschooler group were entertainment (59.4%), caregiving (20.3%), and calming the children (15.6%). The most frequently given answers in the schooler group were entertainment (71.8%), education (12.6%), and caregiving (7.3%). In the adolescent group, the answers given by the parents were entertainment (67.6%), education (21.3%), and socialization (10.2%).

In the bivariate analysis, it was found that screen time was inversely related to prosocial score in the preschooler group (r=-.255 p=0.042). In the schooler group, screen time was found to be inversely related to prosocial scores and positively related to other subscales of SDQ. We did not find a relationship between behavioral problems and screen time in the adolescent group.

In the preschooler group, children who watched a screen for ≤1 hour daily had a lower hyperactivity/inattention score than those who watched more than one hour (p=0.02). It was observed that children who watched ≤2 hours in the schooler group had higher

Table 1. Socio-demographic characteristics and screen parameters of the children included in the study

	Preschooler group N=64	Schooler group N=206	Adolescent group N=108
Age, year*	3.0(2-4)	7.0(6-8)	12.0(11-13)
Sex, M/F	33/31	96/110	55/53
Maternal age, year*	30(26-37)	35(31-39)	39(35-42)
Paternal age, year*	36(31-41)	38(34-43)	42(39-46)
Maternal education, year*	11.5(8-13,5)	12(7.5-16)	12(5-16)
Paternal education, year*	11.5(8-12)	12(8-16)	12(8-16)
Unemployed mother**	49(%76)	135(%65)	61(%56)
Family income **			
Below the minimum wage	16(25)	32(15.5)	13(12)
The minimum wage	22(34.3)	65(31.5)	28(25.9)
Above the minimum wage	26(40.6)	108(52.4)	67(62)
The number of children*	2(1-3)	2(2-3)	2.5(2-3)
Birth of the order**			
The first child	31(%48)	110(%53)	58(%54)
Middle child	5(%8)	30(%14	22(%20)
The last child	28(%44)	65(%33)	28(%26)
The number of books read weekly*	0(0-5)	2(0-5)	0(0-2)
The presence of TV in the bedroom**	9(%14)	32(%15)	57(%53)
The number of TV*	1(1-2)	1(1-2)	1(1-2)
Screen time, h/d*	3(1.12-5.0)	3(2.0-6.0)	5(3.0-8.0)
Maternal screen time, h/d*	2(1.0-3.0)	2(1.0-3.0)	2(1.0-3.0)
Paternal screen time, h/d*	2(1.25-4.0)	2(1.0-4.0)	3(2.0-5.0)

*= median (min-max) **= N (%)

prosocial scores (p=0.045) and other subscales were lower than children who watched more than 2 hours (p<0.05). We used the median screen time as the cut-off value (≤ 5 hours), as there was no recommended hour in the adolescent group. Adolescents with less than five hours of screen time were found to have lower total difficulties scores (p=0.03) and lower peer scores than those who watched more than 5 hours (p=0.01) (Table 2). The effects of low, moderate, and high screen time on behavioral problems in all three groups are shown in Table 3.

The maternal screen time was positively related to hyperactivity/inattention score in the preschooler group, and also the maternal time was inversely related to the conduct, hyperactivity/inattention, peer, and total difficulties scores in the schooler group. We did not find a significant relationship between parental screen time and SDQ subscales in the adolescent group.

The Multiple Linear Regression model was used to determine the factors related to screen time in all three groups. Sociodemographic factors such as age, sex, age of parent, parental

Table 2. Behavior problems according to the recommended screen time by guidelines

	Total difficulties	Prosocial score	Emotional symptoms	Conduct problems	Hyperactivite/Inattention	Peer relationship
Preschooler group						
Screen time ≤1hr (n=16)	8(4.5-17.5)	8(6-10)	2.5(0-4)	2(0.25-3.75)	3(1.25-5.0)	2(1.25-4)
Screen time >1hr (n=48)	12(9.25-17.75)	7(6-9)	2(1-4)	2(1-3)	5(3.25-7)	3(2-4)
p- value	0.160	0.230	0.688	0.682	0.020	0.770
Schooler group						
Screen time ≤2hrs (n=57)	9(5-13)	9(7-10)	2(0-4)	1(0-2.5)	4(2-5)	2(1-3)
Screen time >2hrs (n=149)	12(9-17)	8(6-9)	3(1-5)	2(1-3)	5(3-7)	3(2-4)
p- value	<0.001	0.045	0.013	0018	0.003	0.002
Adolescent group						
Screen time ≤ 5hr. (n=62)	11(8-14)	9(7.75-10)	4 (2-5)	2(1-3)	4(2-6)	2(1-4)
Screen time >5hrs (n=46)	15(9.75-19)	8.5(6-10)	4(2-6)	2(1-4)	4(3-6)	3(2-5)
p- value	0.03	0.065	0.288	0.442	0.324	0.010

Median (min-max) of values were given

Table 3. Children's behavior problems according to low, moderate, and high screen time

	Total difficulties	Prosocial score	Emotional symptoms	Conduct problems	Hyperactivite/Inattention	Peer relationship
Preschooler group						
Low screen time	8(4.5-17.5)	8(6-10)	2.5(0-4)	2(0.25-3.75)	3(1.25-5.0)	2(1.25-4)
Moderate screen time	12(8.5-18)	7.5(6-9)	2(0-4)	2(1-3)	5.5(3-8)	2.5(2-4)
High screen time	13.5(9.75-15.25)	6(3.75-8.25)	3(1.75-4)	3(1-4)	5(4-6)	3(1.75-4)
p- value	0.370	0.203	0.644	0.814	0.052	0.778
Schooler group						
Low screen time	9(5.5-14)[a]	9(7.25-10)	1(0-4)[c]	2(0-2.75)[e]	4(2.25-5)[g]	2(1-3)
Moderate screen time	11(7-14)[b]	8(7-10)	2(1-4)[d]	2(0-3)[f]	4(2-6)[h]	3(1-4)
High screen time	15(12-21)[ab]	8(6-9)	3(2-7)[cd]	3(2-5)[ef]	6(4-8)[gh]	2(3-4)
p- value	<0.001	0.149	0.005	<0.001	0.001	0.170
Adolescent group						
Low screen time	12(11-20.5)	9(6-10)	4(3-6)	2(0.5-5)	4(2-5)	4(2-4.5)
Moderate screen time	11(8-15)[i]	9(8-10)	3(2-5)	1 (0.5-3)	4(2-6)	2(1-4)[j]
High screen time	15.5(11-22.25)[i]	8(5.75-10)	4(2-6)	2(1-6)	5(3-6)	4(2-6)[j]
p- value	0.040	0.122	0.258	0.064	0.554	0.003

*= median (min-max) values were given

education, working status of a mother, family income, birth order; the presence of a TV in the bedroom; the number of the TV at the home; the number of books read weekly, SDQ subscales; parental screen times were joined the models. In the preschooler group, the presence of a TV in the bedroom (β=0.317 p=0.029), prosocial behavior (β=-0.416 p=0.013); in the schooler group, the number of books read weekly (β=-0.172 p=0.018); in the adolescent group; the presence of a TV in the bedroom (β:0.296 p=0.012) were found to be possible risk factors for screen time.

When the factors associated with behavioral problems were analyzed by Multiple Linear Regression analysis, sociodemographic data, parental screen time, the number of books read weekly, the presence of a TV in the bedroom, low screen time, moderate screen time, and high screen time were included in the models. In the preschool period, maternal screen time was associated with prosocial score and hyperactivity/inattention score (β=-0.273 p=0.05, β=0.245 p=0.035, respectively), presence of a TV in the bedroom was associated with prosocial behavior score (β=0.279 p=0.034). Additionally, low and high screen time were found to be associated with hyperactivity/inattention scores (β=-2.432 p=0.019,β=-2.047 p=0.047).

In the schooler group, high screen time was related to total difficulties score (β=0.227 p=0.001), emotional symptoms (β=0.155 p=0.036), conduct problems (β=0.259 p<0.001), and hyperactivity/inattention scores (β=0.194 p=0.008). Maternal and paternal screen time was related to total difficulties (β=-0.262 p<0.001, β=0.152 p=0.023, respectively). And also, paternal screen time was related to emotional symptoms (β=0.150 p=0.038), maternal screen time was related to conduct problems β=-0.228 p<0.001), hyperactivity/inattention (β=-0.258 p<0.001), and peer scores (β=-0.193 p=0.009) in the schooler group.

High screen time in the adolescent group was associated with prosocial score (β=-0.227 p=0.024), conduct problems (β=0.259 p=0.015), and peer score (β=0.298 p=0.003). Low screen time was also found to be associated with conduct problems score (β=0.287 p=0.013).

Discussion

Due to the inexorable increasing screen time among the younger generation, when and how screen time causes negative effects children's mental health is one of the health problems that are wondered. In our study, the relationship between preschoolers, schoolers, and adolescent children's screen time, risk factors, and behavioral problems was studied in detail.

The median screen time in the preschooler, schooler, and adolescent groups was 3.00 hrs. and 3.00 hrs., and 5.00 hrs. respectively. This finding was observed to be similar to previous studies [12-14]. In agreement with the literature, the screen time of the adolescent group was found to be statistically higher than the schooler and preschooler groups [13].

Guidelines recommend limiting screen time to parents to reduce the negative effects of screen time [5, 6]. However, most of the parents of the preschooler and schooler groups stated that their children should watch at or below the recommended hours, it was seen that only %25 of them could apply the recommended screen time. In previous studies, the rate of not applying the screen restrictions recommendation ranged between 20% and 75%, and in our study, the rate was found to be in the upper range [7, 15, 16].

 We expected that screen time would be associated with behavioral problems, especially hyperactivity/inattention problems, as younger children are more sensitive to environmental factors, overreact to violent events, and have insufficient self-regulation skills and insufficient skills to distinguish between reality and virtual reality [17]. Consistent with our experience and the literature, in multiple regression analysis, low screen time was found to be associated with lower hyperactivity and inattention problems in preschooler children [18]. An unexpected finding was that high screen time was associated with lower hyperactivity and inattention problems in preschool children too. In the preschooler group, parents stated that they mostly used the screen for caregiving and calming their children. We thought that since the physical activity of the child who stands in front of the screen for a long time may be decreased, therefore the hyperactivity score was found to be low according to maternal reports. In line with previous studies, the study demonstrated that high screen time was associated with emotional, conduct, and hyperactivity/inattention problems in the schooler group [11, 19]. No relationship was found between low and moderate screen time and behavioral problems in the schooler group.

In the literature, according to the Goldilock hypothesis, while high screen time causes behavioral problems in adolescents, moderate screen time does not cause negative effects, and may even have positive effects on behavior compared to low screen time [10]. It has been suggested that moderate digital screen time may positively affect the socialization and creativity of adolescents [10]. It is stated that there is no linear relationship between screen time and behavioral problems [8]. In our study, however, low screen time was associated with higher behavioral problems, moderate screen time did not affect behavior problems in the adolescent group. High screen time had negative effects on behavioral problems in adolescent group agreement with the literature [10, 20]. High screen time was associated with conduct and peer problems in adolescents. In bivariate analyzes, adolescents who watch moderate screen time had lower peer and total difficulties scores compared to those who watch high and low screen time. The effect of moderate screen time was not seen in Multiple Linear Regression. It was thought that the effect of moderate screen time might not have emerged due to the small sample size of the adolescent group.

Several previous studies investigated the effect of children's screen time on children's behavioral problems [10, 12, 13]. A

few studies investigated the effect of parental screen time on the children's behavior problems [21, 22]. The study conducted by Wong et al. [21] was shown that the problematic screen uses of parents affected the behaviors of three-year-old children by increasing the child's screen time and decreasing the interaction between parent and the child. In our study, parental screen time was found to be associated with children's behavioral problems in all groups except the adolescent group. In the preschooler group, it was observed that maternal screen time was associated with lower prosocial behaviors and higher hyperactivity/inattention problems. Also, it was found that paternal screen time was related to higher total difficulties scores and emotional problems in the schooler group. In this study, no relationship was found between the parent's screen time and the children's screen time. It is known that in early childhood, spending quality time with children and interaction between parents and children positively affect the emotional and social development of children [23]. We thought that parental screen time may negatively affect the behavioral problems of younger children by reducing quality time and interaction with the child. It is thought that parental screen time may not affect adolescents' behavior problems since the social environment gains importance in adolescence. Another unexpected finding was maternal screen time was found to be associated with lower behavioral problems in the schooler group. Since the information about screen time was obtained from the mothers, it was thought that it may be related to mothers may tend to see their screen time low.

Evaluating the effects of both parents' and children's screen time on children's behavior problems according to the developmental periods (preschooler, schooler, and adolescent) was the strength of the study. Besides the strengths, the study had some limitations. The limitations were; the study was a cross-sectional study, the sample sizes of preschooler and adolescent groups were small, and co-viewing was not investigated.

Since digital media is an indispensable part of our lives, its positive and/or negative effects on our children's mental health will continue to be investigated. Parental and children's screen time should be evaluated for the intervention of children's behavioral problems. This study showed that recommendations regarding the time spent by children and parents in front of the screen should be given according to the developmental stages of the children. Longitudinal and large-scale studies are needed to evaluate the relationship between low and moderate screen time and behavioral problems.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

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Ethical approval
Ethics committee approval was obtained from the Ethics Committee of Toros University in Mersin, Turkey (23/9/2022 numbered 154).

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ORIGINAL ARTICLE

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Evaluation of the abduction angles between hand fingers

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Abstract

This study aimed to reveal the angular values of abduction between the fingers and evaluated the right-left sides angular asymmetry and the differences between the genders. Participants were asked to place their hand fingers on a table with maximum finger abduction. Hand photographs were taken at a distance of 50 cm on the vertical axis, focusing on the metacarpophalangeal joint of the middle finger. Angular measurements between fingers on the photographs were taken by using the Image-J program. Statistical analysis was performed with SPSS software. The mean values of the abduction angles between thumb-index, index-middle, middle-ring, and ring-little fingers on the right hand were 53.94º, 19.99º, 17.29º and 27.72º in males; 48.38º, 20.78º, 18.23º and 29.41º in females, respectively. On the left hand, the mean values of abduction angles between thumb-index, index-middle, middle-ring, and ring-little fingers were 54.83º, 21.16º, 20.15º and 29.93º in males; 49.38º, 22.35º, 19.93º and 31.55º in females, respectively. The average abduction angles of the fingers are thumb-index> ring-little > index-middle> middle-ring, from largest to smallest. When the right-left sides were compared for abduction angles, a significant difference was found for the middle-ring and ring-little fingers in females and the index-middle, middle-ring and ring-little fingers in males (p<0.005). A significant difference was found in only thumb-index abduction angles in the comparison between genders, p<0.005. The normative descriptive angular data of our society obtained from the study will contribute to the literature revealing the anatomical differences between different racial and ethnic groups.

Keywords: Fingers, hand, range of motion, gender differences, thumb, abduction

Introduction

Joints are anatomical structures that allow movement to the skeletal system. Knowing the functional anatomy and biomechanics of joint movements is essential. Classical knowledge of the range of motion of the joints is written in classical anatomy books; It is likely to vary depending on racial, ethnic and geographical differences. Methods such as goniometry, pollexograph, inclinometer and spectrophotometry are used to evaluate the range of motion of joints [1, 2].

Hand fingers can perform various degrees of flexion, extension, abduction, adduction, and circumduction movements with the metacarpophalangeal and interphalangeal joints. This hand mobility is critical during daily activities, especially in tasks that require fine motor skills, such as using the keyboard [3]. In addition, the flexion and abduction angles of the thumb are significant during phone and tablet use. The flexion range at the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints are 90º, 100º, and 90º, respectively. The metacarpophalangeal and distal interphalangeal joints can perform extension 45º and 10º, respectively [4]. In the fist-shaped hand, the extension of the fingers in flexion cannot be performed

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independently due to the several juncturae tendinum located in the extensor digitorum muscle. The degree of abduction between the fingers will likely change after the movement in extension.

When the degrees of abduction movement of the hand fingers are compared, it is reported that the 2nd finger has the most abduction movement range, followed by the 5th, 4th and 3rd fingers, respectively, in terms of the range of motion in the textbooks. It has been reported that angulation is a maximum of 25º, and the range of motion slightly increases while its combination with flexion, extension, and slight rotational movements in the joint [5].

The thumb has a flexion-extension angle of 53º. The abduction-adduction movements of the thumb are different from the other fingers. The thumb performs these movements over the carpometacarpal joint, and this angulation is approximately 42º [6].

In osteoarthritis and rheumatoid arthritis, the range of movements may increase or decrease depending on the joint involvement. The flexion-extension angle was reported to decrease in both osteoarthritis and rheumatoid arthritis patients. (82º in patients with osteoarthritis, 74º in patients with rheumatoid arthritis). The same study reported that the abduction-adduction angle means value slightly increased (approximately 2.5º) in patients with osteoarthritis. In contrast, it slightly decreased (approximately 3.8º) in rheumatoid patients [6].

In the literature, there are not enough anatomical studies comparing the normative values of the joint range of motion of the fingers in individuals with different racial, ethnic, geographical and social characteristics. This study is one of the first studies in which the degree of abduction of the fingers was evaluated after simultaneous abduction movement of the fingers. This study aimed to obtain descriptive data on the abduction angles of the hand fingers and to indicate gender and side differences.

Material and Methods

This study was conducted on 91 (48 female and 43 male) adult volunteers aged between 18-5. Ethical approval of the study was obtained by the decision of the Non-Interventional Ethics Committee of Izmir Katip Celebi University, numbered 24.02.2022-0045. The individuals participating in the study were those with no acquired or congenital deformity, trauma, or surgery history in their upper extremities, and none were professional athletes. Participants signed voluntary informed consent forms after they were informed about the study. Participants were seated, instructed to place their hands with palms facing down on the table. They were instructed to keep their wrists straight and middle fingers on the sagittal axis, while the fingers were in maximum abduction. The same researcher took the photos from a distance of 50 cm focusing on the metacarpophalangeal joint knuckle at a vertical angle of the middle finger with a Canon 800D camera. For standardization, a millimetric ruler was also photographed. Abduction angle measurements were made on

the photos of both hands by using ImageJ software. The angles between the lines drawn tangentially to the lateral side of the fingers on the images were measured (Figure 1). A total of 8 angle values were obtained between the fingers of the right and left hands. The angles were measured between the thumb-index, index-middle, middle-ring, and ring-little fingers.

IBM SPSS v25 software was used for statistical analysis. Descriptive statistical data (minimum, maximum, mean, and SD) were obtained. Distribution was evaluated with the Shapiro-Wilk test. Differences between the right and left sides were obtained using the paired t-test, and the differences between the genders were obtained using the independent t-test. Correlation values between angles were obtained by Pearson correlation.

Results

The mean values of the abduction angles between thumb-index, index-middle, middle-ring, and ring-little fingers for the right hand were found to be 53.94º, 19.99º, 17.29º and 27.72º in males; 48.38º, 20.78º, 18.23º and 29.41º in females, respectively. On the left hand, the mean values of abduction angles between thumb-index, index-middle, middle-ring, and ring-little fingers were 54.83º, 21.16º, 20.15º and 29.93º in males; 49.38º, 22.35º, 19.93º and 31.55º in females, respectively. The mean and standard deviation of the abduction angles of the fingers are given in Table 1. The mean of the abduction angles of the fingers from largest to smallest are angle thumb-index > ring-little > index-middle > middle-ring (Figure 1).
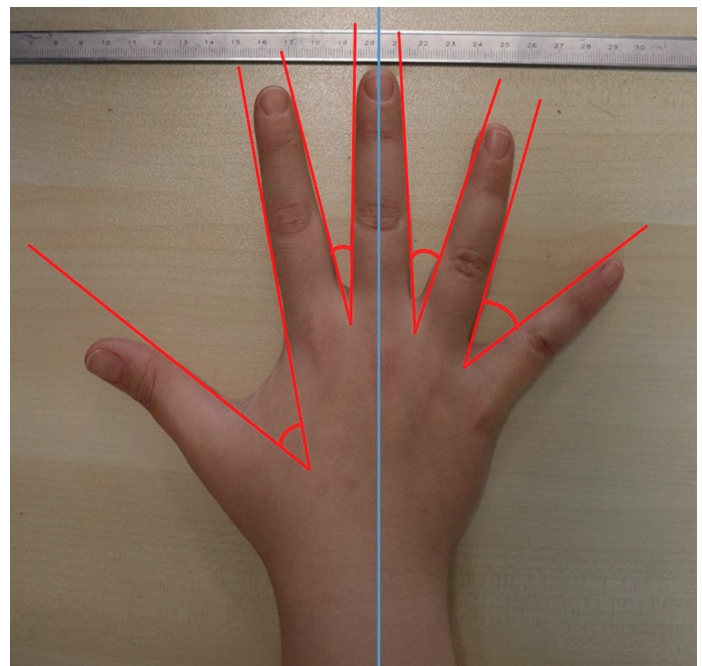
Figure 1. The abduction angles between fingers

When the abduction angles of the right and left sides were compared, a significant difference was found for the angles middle-ring and ring-little in females and for the angles index-middle, middle-ring and ring-little in males p<0.005 (Table 1).

In comparison between the genders, a significant difference was found only on the angle thumb-index $p<0.005$ (Table 1). The correlation between the corresponding abduction angles in the right and left hands were evaluated. The correlation values from largest to smallest were found in angles thumb-index > ring-little > middle-ring > index-middle in males and angles thumb-index > middle-ring > index-middle > ring-little in females (Table 2,3).
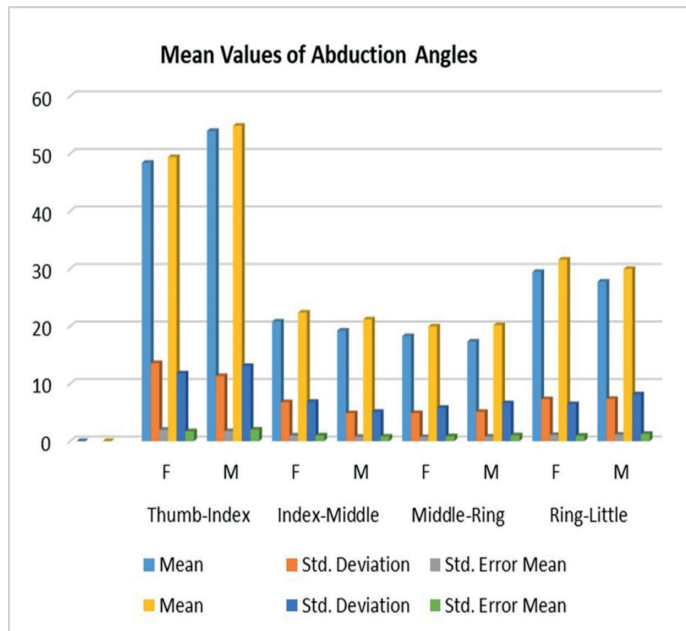
Figure 2. The mean values of abduction angles, standard deviations and standard errors in males and females

Table 1. Comparison of abduction angles of the fingers by hand side and gender

Angles	Gender	Right Mean±SD	Left Mean±SD	p value[a]
Thumb-Index	F	48.38 ±13.55	49.38±11.77	0.455
	M	53.94±11.30	54.83±13.05	0.549
p value[b]		0.037*	0.039*	
Index-Middle	F	20.78±6.75	22.35±6.82	0.091
	M	19.19±4.85	21.16±5.09	0.029*
p value[b]		0.204	0.353	
Middle-Ring	F	18.23±4.86	19.93±5.78	0.007*
	M	17.29±5.08	20.15±6.57	0.001*
p value[b]		0.372	0.866	
Ring-Little	F	29.41±7.28	31.55±6.40	0.049*
	M	27.72±7.33	29.93±8.12	0.030*
p value[b]		0.275	0.289	

SD: standard deviation
[a]p values represent Right and Left hand comparison within same gender
[b]p values represent Male and Female comparison within same handside
*Values are significantly different between groups ($p<0.05$)

Table 2. Correlations of the abduction angles between right and left sides in males

			Right				Left			
			Thumb-Index	Index-Middle	Middle-Ring	Ring-Little	Thumb-Index	Index-Middle	Middle-Ring	Ring-Little
Right	**Thumb-Index**	r	1							
		p								
	Index-Middle	r	-0.218	1						
		p	0.160							
	Middle-Ring	r	0.075	-0.024	1					
		p	0.632	0.881						
	Ring-Little	r	0.326*	-0.058	-0.138	1				
		p	0.033	0.710	0.378					
Left	**Thumb-Index**	r	0.690**	-0.098	0.064	0.290	1			
		p	0.000	0.531	0.686	0.060				
	Index-Middle	r	0.062	0.339*	0.018	0.169	-0.063	1		
		p	0.694	0.026	0.907	0.279	0.686			
	Middle-Ring	r	0.141	0.078	0.640**	0.202	0.102	0.113	1	
		p	0.369	0.619	0.000	0.194	0.516	0.470		
	Ring-Little	r	0.201	-0.107	-0.114	0.659**	0.253	0.020	-0.014	1
		p	0.196	0.494	0.467	0.000	0.101	0.899	0.929	

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

Table 3. Correlations of the abduction angles between right and left sides in females

			Right				Left			
			Thumb-Index	Index-Middle	Middle-Ring	Ring-Little	Thumb-Index	Index-Middle	Middle-Ring	Ring-Little
Right	**Thumb-Index**	r	1							
		p								
	Index-Middle	r	0.080	1						
		p	0.588							
	Middle-Ring	r	-0.230	0.367*	1					
		p	0.116	0.010						
	Ring-Little	r	0.291*	0.412**	0.327*	1				
		p	0.045	0.004	0.023					
Left	**Thumb-Index**	r	0.743**	0.057	-0.138	0.222	1			
		p	0.000	0.702	0.349	0.129				
	Index-Middle	r	0.444**	0.568**	0.157	0.459**	0.254	1		
		p	0.002	0.000	0.286	0.001	0.081			
	Middle-Ring	r	-0.083	0.477**	0.708**	0.225	-0.054	0.166	1	
		p	0.575	0.001	0.000	0.124	0.717	0.259		
	Ring-Little	r	0.336*	0.252	0.213	0.429**	0.189	0.410**	0.281	1
		p	0.019	0.084	0.146	0.002	0.198	0.004	0.053	

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

Discussion

The range of motion of the fingers is essential in performing many fine, detailed motor functions. In the literature, numerous studies in the field of health and engineering examine the degrees of flexion and extension of the fingers. However, comparing studies of different societies and races on finger abduction angles in the literature is rare. The angular values of the interdigital ranges that obtained in this study are essential for comparing different racial and ethnic groups.

Coupier et al. investigated the range of motion of the fingers in 20 healthy Belgian individuals aged 22-65 years using the spectrophotometric method. They found the abduction-adduction range of motion between fingers from thumb to little 37º, 13º, 7º, 15º and 29º in the right hand; 35º, 12º, 8º, 17º and 30º in the left hand, respectively [7]. In this study, mean values of abduction angles between fingers from thumb to little were 51º, 20º, 17º and 28º in the right hand and 52º, 22º, 20º and 30º in the left hand, respectively for all subjects. The values belonging to males and females were similar (Table 1). Jerome et al. reported that they could not find any difference between the right and left sides regarding the range of motion [7]. These results do not agree with the current study results. In this study, the middle-ring and ring-little abduction angles in both hands were found to have statistically significant differences in both genders. In addition, index-middle abduction angles in males

were statistically significantly different between the right and left sides in this study. Possible reasons for the difference between the results of the two studies include methodological and racial differences. Coupier et al. also found no significant difference between genders [7]. In current study, there was no statistically significant difference between genders in the abduction range of motion except for the thumb-index angle. In this respect, the results of the two studies are similar.

Gracia-Ibáñez et al. found 35.2º, 25.7º and 28.4º for the mean abduction angle values from index-middle, middle-ring and ring-little, respectively. They reported that the differences between angular values were not statistically significant regarding genders [8]. Angular values obtained by Gracia-Ibáñez et al. were higher than the current study findings. This may be due to the methodological difference between the two studies. They found the order of magnitude of the abduction angle as index-middle> ring-little> middle-ring. But in this study, it was ring-little> index-middle> middle-ring. Their results differed from this study in terms of mean values of abduction angles and the order of magnitude.

Barakat et al. reported that the mean value of the radial abduction angle range of the thumb was 62.9º (between 53-71º) in their study on 62 females [9]. This value is higher than the radial abduction angle of the thumb obtained from the females in this study (Table 1). This is because methodologically, they only

looked at the radial abduction angle from the fingers of the thumb. In this study, the angulation between the fingers was measured while the fingers of the hand were abducted simultaneously. Therefore, in current study, the abduction of the second finger can be interpreted as a reduction in the radial abduction angle of the thumb.

In a study conducted by Gurbuz et al. with an electronic digital inclinometer (20 male, 20 female), they reported that the lowest abduction degree was 4.12º for the metacarpophalangeal joint of the thumb. And the highest abduction degree was 80.98º for the middle finger. The abduction angle in other fingers; was reported to be 41.9º for the index finger, 41.57º for the ring finger, and 48.53º for the little finger [10]. These angular values differ from the current study's results (Table 1). However, this research did not perform an abduction angle assessment for the metacarpophalangeal joint of the thumb. In this study, the radial abduction angle of the thumb was evaluated. This angle was larger than the other angles that measured and it was approximately 50º (Figure 2). The order of abduction angle widths of the other fingers from largest to smallest was the abduction of the ring-little, index-middle, and middle-ring fingers for both genders, respectively (Figure 2). The order of largest to smallest for these 3 fingers was similar in both studies.

The active palmar abduction angle measured by the pollexograph-thumb method on 25 (9 male, 16 female and 3 left-handed) healthy individuals by Kracker et al. was found to be 62±5º (range 54-72º) on average. In the same study, they measured 57±6º (in the range of 45-70º) with a goniometer [2]. This study shows that the results of the studies conducted with two different methods are similar. However, gender differences were not evaluated in this study. In this study, unlike the palmar abduction angle of the thumb, the radial abduction angle of the thumb was evaluated. When the genders were compared, the difference between men and women in the radial abduction angles of the thumb was found statistically significant. There was no gender difference in the abduction angles of the other fingers.

Anatomy studies show a significant difference between the genders regarding hand length and width and for determining gender from hand sizes [11]. Literature information suggests that there may be a difference between the genders regarding abduction angles between the fingers. However, in this study, no gender difference was found between abduction angles for the index-middle and ring-little finger. There was a difference between the genders only in terms of thumb radial abduction angles.

White et al. found 51.1±5.5º for the abduction of the thumb in their study [12]. Although their measurement methods were different, this result was similar to ours. They reported a weak negative correlation when they evaluated the abduction angle according to age groups. The 65+age group had a 4.5º lower abduction angle than the 35-49 age group. In our study, the abduction angle was

not evaluated according to age. They also found that the thumb's flexion, extension and abduction angles did not change according to age and gender groups. Still, in our study, the thumb abduction angle showed differences between the genders [12].

The current study evaluates the abduction angles between the fingers when all fingers are abducted simultaneously (except the middle finger). This study did not assess the maximal abduction range of motion between the fingers. Studies evaluating the maximal abduction angles of each finger are planned for the future.

Conclusion

The middle-ring and ring-little fingers abduction angles in females and index-middle, middle-ring and ring-little fingers abduction angles in males were determined statistically significantly different regarding the right and left sides. In addition, only the thumb-index fingers abduction angle was statistically different in comparing the genders. Current study will contribute to the literature in terms of anatomical comparison of finger movement characteristics of people from different geographical regions.

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ORIGINAL ARTICLE

Evaluation of the findings affecting the treatment decision in cases of adhesive intestinal obstruction

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Abstract

To establish a standard approach in patient management by determining the parameters that affect the decision of surgical or conservative treatment in adhesive small bowel obstructions. 94 patients who were admitted to the emergency department with symptoms of ileus and were diagnosed with adhesive intestinal obstruction according to clinical, examination and imaging findings were grouped as patients who were followed up with conservative methods (Group 1) and patients who underwent surgery (Group 2). All patients' laboratory values (hemoglobin, white blood cell (WBC), C- reactive protein (CRP), Blodd urea nitrogen (BUN)/creatinin, sodium, potassium, Lactate dehydrogenase (LDH), lactate and amylase) and imaging findings (air-fluid level in direct abdominal X-ray, increase in small intestine diameter (≥3.95 cm) in computerized tomography), wall thickness increase (>3mm), transition zone, fecal sign, and presence of contrast in the colon) were evaluated, and criteria for early surgery and non-operative follow-up-treatment criteria were determined. 72% (n:68) of the patients were classified as Group 1 and 28% (n:26) as Group 2, and no significant difference was found between the groups according to age and gender. Surgical treatment with increased lactate (r:0.326, p=0.001), diameter increase in the small intestine (r:0.299, p=0.003) and wall thickness increase (r:0.540, p<0.001), change in air-fluid levels on direct X-ray (A significant correlation was found between r:-0.291, p=0.004) and contrast transfer to the colon on tomography (r:-0.668, p<0.001) and the decision for conservative treatment. Although adhesive intestinal obstruction is a condition that can mostly be managed non-operatively, the early surgical decision significantly reduces mortality and morbidity in cases with an operation indication. It was concluded that the standard approach protocol based on laboratory and imaging findings determined in the non-operative or operative treatment management helps in the differential diagnosis and early surgical decision and reduces the length of stay of the patient.

Keywords: Adhesive obstruction, ileus, acute abdomen, surgery

Introduction

Peritoneal adhesions are pathological bands formed between the omentum, intestinal loops and abdominal wall. They are classified as congenital or acquired according to their etiology (postinflammatory or postoperative) [1]. Postoperative adhesions are among the major unanticipated complications of surgery.

Postoperative peritoneal and intestinal adhesions are important complications that may occur after abdominal surgery [2]. Abdominal adhesions begin to form on the 5th to 7th day after surgery [3]. Although it is usually seen after abdominal surgery and cholecystectomy operations such as appendicitis, gynecological operations and colon surgery, it can also be caused by non-

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operative causes such as peritonitis and inflammatory bowel diseases. Adhesions can cause infertility, chronic abdominal pain and pelvic pain, most commonly intestinal obstruction. Since each new operation is a risk factor for the development of new adhesions, the decision for the operation to be performed due to adhesion should be made correctly [2].

Small bowel obstruction (IBO) is one of the most important reasons for admission to the surgical service in developed countries (1 of 6 patients). In most cases, improvement is observed with nonoperative treatment (70-80%), but recurrences are common (20-53%) [4,5]. IBOs often occur due to adhesions[5]. The management of adhesive IBOs is based on clinical investigations, biological testing, and imaging modalities. There is still no clear rule on the application of surgery or non-operative follow-up at the time of admission. The fact that the majority of adhesive IBOs are due to previous surgeries creates a paradox about the place of surgery in treatment[5]. Mostly, obstruction can be treated conservatively by using a nasogastric tube, intravenous fluid therapy, administration of analgesics, and correction of electrolyte imbalance [5].

The study aimed to determine the possible clinical, laboratory and radiological parameters for the standard treatment approach in cases of intestinal obstruction due to adhesion. In addition, it is to reduce the morbidity and mortality rates due to complications by making the surgical treatment decision as soon as possible in cases with surgical indications.

Material and Methods

After obtaining approval from the local ethics committee, the study was conducted on patients who applied to the emergency department of our hospital between April 2019 and April 2020 and were diagnosed with adhesive intestinal obstruction with clinical-imaging findings. All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical Faculty of XXX (Date:06/02/2019; Session Number: 2019/2; Decision No: 18)

Patients with non-adhesive obstruction etiology according to computed tomography (CT) findings, pregnant women, patients with contrast allergy and patients under 18 years of age were excluded from the study. The patients included in the study were classified according to the American Association for the Surgery of Trauma (AAST) grading and divided into Group 1 (conservative) and Group 2 (operative) (Table 1) [2]. Age, gender, examination findings, comorbidities and surgical histories of all patients were recorded.

CRP, potassium, lactate levels, small bowel wall thickness on tomographic examination, small bowel diameter ≥3.95 cm, localized air-fluid level on X-ray, and passage of contrast material into the colon were determined as potential predictors

for the surgical decision.

Surgery was performed in patients who had acute abdomen findings on physical examination or who had ischemia, necrosis or perforation according to CT findings. Oral intake of all other patients was stopped and they were followed up with nasogastric tube decompression, IV hydration and medical treatment. Follow-up patients were evaluated with physical examination, laboratory and imaging methods when necessary at maximum 8-hour intervals in terms of the need for emergency surgical intervention.

In laboratory examination, hemoglobin, WBC, CRP, BUN/creatinine, sodium, potassium, LDH and amylase and lactate values in blood gas were evaluated.

Table 1. Conservative and surgical treatment planning classification according to AAST

Stage	AAST Disease Staging	Intestinal Obstruction
I	Non-complicated Organ limited, minimal Abnormal finding	Partial Obstruction
II	Non-complicated Limited to the organ Severe abnormal finding	Complete Obstruction No intestinal ischemia
III	Complicated Local impact	Complete Obstruction Non-gangrenous reversible ischemic bowel
IV	Complicated Advanced into the surrounding tissue	Complete Obstruction Gangrenous bowel or locally limited perforation
V	Complicated Past the surrounding tissue Widespread impact	Diffuse Peritoneal contamination Developed perforation

Imaging analysis

Direct Graphs: presence, extent and location of air-fluid levels, and air-fluid level displacements at follow-up were evaluated (Figure 1). Direct radiographs were performed at 24 hour intervals. While evaluating the displacement of the air-fluid level, the abdomen was divided into 9 quadrants and the differences between localizations were compared [3,4]
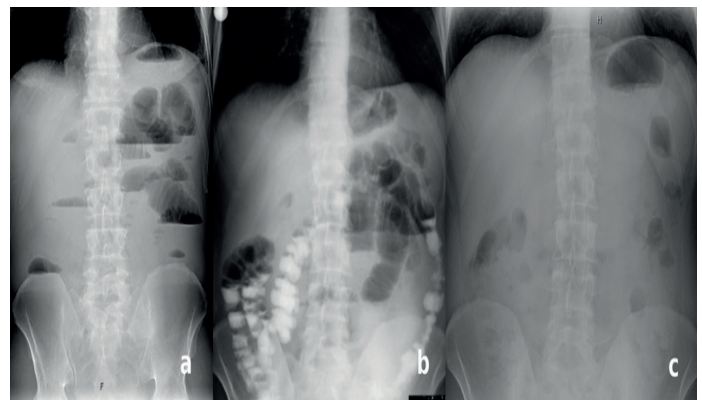
Figure 1. a) Air-liquid levels (arrows), b) Displacement of air-liquid levels and contrast transition to the column, c) Decreasing air-liquid levels

Computed Tomography: abdominal CT within the first 24-hour by applying IV and oral contrast material was performed for all patients. All CT scans were performed by Toshiba Alexion Advance device, Mas: 120 Kv, 3.0 slice thickness. 50cc urographin (a mixture of sodium diatrizoate and meglumine diatrizoate) diluted 1/10 and administered 500 ml by oral or nasogastric route. Low-volume administration was preferred because of the difficulty in oral intake of the gastrograph, and the risk of aspiration and vomiting. An average of 4-6 hours later, an abdominal CT was performed.

Small intestine diameter, wall thickness, transition zone, fecal sign and presence of contrast in the colon were evaluated with CT examination (Figure 2,3). An intestinal diameter increase of 3 cm or more was considered abnormal. For wall thickness, values of 3 mm and above were determined as abnormal wall thickening [5-7].

Figure 2. In the axial section, sudden thinning and tapering (transition zone) (arrow) in the shape of a bird's beak in lumen calibration in a segment of small bowel at the abdominal lower quadrant
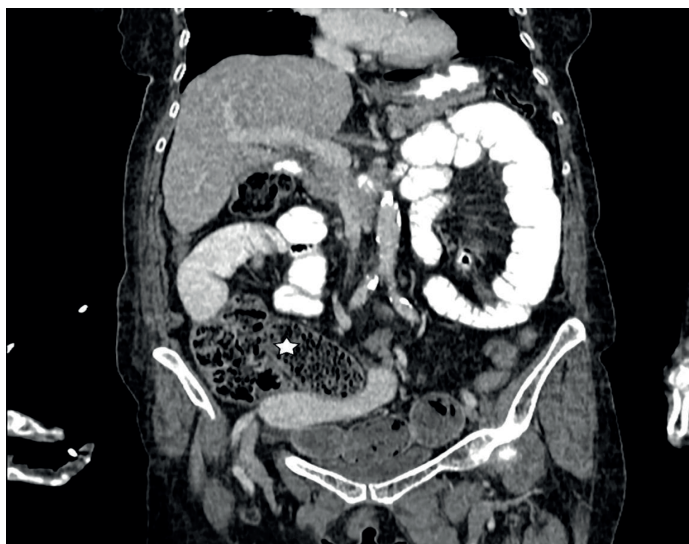
Figure 3. Sign of fecelization (white star)

Management of the patients

Patients without an indication for emergency surgery were followed up by stopping oral intake, inserting a nasogastric tube, and arranging IV hydration therapy. The patients were followed up for a maximum of 72 hours, as recommended in the literature, in terms of daily spontaneous gas-stool output, the character and amount of the contents draining from the nasogastric tube, fever, pulse, blood pressure, abdominal auscultation findings, and direct abdominal X-ray, WBC, CRP, electrolytes and other biochemical parameters. [3,8]. Patients who developed acute abdomen symptoms during their follow-up were operated, and patients whose symptoms regressed and who tolerated oral intake and had gas-stool discharge were discharged after 72 hours.

Statistical Analysis

The data obtained in the study were statistically analyzed using the IBM Statistics Package for Social Sciences (SPSS) ver 20.0 software. The conformity of the data to the normal distribution was tested using the Shapiro-Wilk test and Levene test, as well as the homogeneity of variance. Independent samples t-test and Mann-Whitney U test were used to compare numerical data. Chi-Square and Fischer's Exact tests were used to compare categorical data. Pearson and Spearman's correlation analyzes were used to evaluate the factors associated with surgery. The contribution of the factors to the surgical decision was calculated by binary logistic regression analysis. Optimal cut-off values for the surgical application of each value were determined by the Receivers operating characteristic (ROC) curves. Quantitative data were expressed in the tables as mean ± standard deviation (SD) (Maximum-Minimum) and median (25%-75% values). Categorical data were expressed as n (numbers) and percentages (%). A value of $p < 0.05$ was considered statistically significant.

Results

Among 228 patients admitted to the emergency department, 94 patients who were diagnosed with adhesive intestinal obstruction by oral and IV contrast-enhanced abdominal CT and met the inclusion criteria were included in the study (Figure 4).

Figure 4. Flowchart of the study design

The mean age of the patients was 55.14±18.74 years (18-86) in Group 1 and 56.73±17.43 years (19-85) in Group 2, and no significant difference was found between the groups (p=0.710). Although there was no statistically significant difference between the groups in terms of gender (p=0.722), the number of male patients was higher in both groups than females, and 64% of Group 1 (n=43); 66% (n=17) of Group 2 were male. The number of previous surgeries was 2.21±1.28 in Group 1 and 2.27±1.01 in Group 2, and no significant difference was found between the two groups (p=0.861). The mean duration of stool discharge in patients followed in Group 1 was 42.35±19.35 hours (8-72). The mean time to decide on surgical treatment in group 2 was 37.69±23.57 hours (range: 2-72). The mean hospital stay was 3.16±1.36 days (1-7) in Group 1, 8.69±3.37 days in Group 2 (5-16), and it was statistically significantly higher in Group 2 (p=0.001) (Table 2).

WBC was 9.68±3.52 (3.4-14.75) in Group 1, 10.53±5.29 (2.9-19.8) in Group 2, CRP was 51.58±61.62 in Group 1, 75.07±88.39 in Group 2, no statistically significant difference between the group was detected (p=0.370, p=0.149, respectively). When the electrolytes and BUN/creatinine parameters were examined, the mean K value was 4.29±0.80 mmol/l in Group 1 and 3.95±0.60 mmol/l in Group 2; The lactate level in blood gas was 1.17±0.46 U/L in Group 1, 1.71±1.10 U/L in Group 2, and K and lactate levels were significantly higher in Group 2 (p=0.045, p=0.001, respectively). There were no significant differences between the groups in terms of Na, LDH and amylase values and BUN/creatinine ratios (p=0.782, LDH p=0.353, amylase p=0.111, p=0.928, respectively) (Table 1)

While changes and regression in the localization of air-fluid levels were observed in 90% (n:61) of the patients in Group 1, it was observed that it persisted in 77% (n:20) of the patients in Group 2 (p=0.001).

There was no significant difference between the groups in terms of the incidence of intraperitoneal free fluid, the rate of visibility of the transition zone, and the finding of fecalization detected by CT (p=0.541, p=0.079, p=0.079, respectively). Contrast transfer rates to the colon in Group 1 and intestinal wall thickness were statistically significantly higher in Group 2 (p<0.001) (Table 3). When all parameters were examined, it was seen that some findings were effective in the choice of surgical treatment. When factors related to surgery are evaluated, laboratory parameters include lactate elevation (r:0.326, p=0.001), increase in small intestine diameter on tomography (≥3.95 cm) (r:0.299, p=0.003) and increase in small intestinal wall thickness (>3mm) (r :0.540, p<0.001), a positive correlation was detected. A negative correlation was observed with the displacement of air-fluid levels on the graphy (r:-0.291, p=0.004) and with the transfer of contrast material to the colon (r:-0.668, p<0.001) on the tomography. Absence of contrast transfer to the colon (OR: 8.66, 95%CI:1.34-56.09, p<0.001), increased small bowel wall thickness (>3mm) (OR:2.23, 95%CI: 1.36-14.07, p=0.023) and thin Intestinal diameter over 3.95 cm (OR: 5.53, 95% CI: 1.87-25.58, p=0.001) was found to be among the reasons that increased the probability of surgery.

Gas-stool discharge time in group 1 was calculated as 42.35±19.35 (min:8, max:72) hours on average. In Group 2, the mean time to decision on surgical treatment was 37.69±23.57 (2-8) hours.

Table 2. Clinical and laboratory findings

	Group 1 (conservative treatment) (n=68)	Group 2 (surgery) (n=26)	p
Age (years)	55.14±18.74	56.73±17.43	0.710
Gender (Female) (n/%)	25 (%36)	9 (%34)	0.722
Number of previous surgeries	2.21±1.28	2.27±1.01	0.861
BMI (kg/m²)	25.96±4.71	26.08±4.27	0.895
Stool discharge time (For conservative treatment group)	42.35±19.35	-	
Surgery time	-	37.69±23.57	
Hospitalization day	3.16±1.36	8.69±3.37	**0.001**
WBC	9.68±3.52	10.53±5.29	0.370
CRP	51.58±61.62	75.07±88.39	0.149
Na	138.16±3.58	138.38±3.17	0.782
K	4.29±0.80	3.95±0.60	**0.045**
BUN/creatinine	21.59±8.36	21.78±10.65	0.928
Lactate	1.17±0.46	1.71±1.10	**0.001**
Amylase	57.64±37.58	80.96±103.76	0.111
LDH	258.07±88.17	283.91±130.03	0.353

Table 3. Radiological findings

		Group 1 (conservative treatment) (n=68)	Group 2 (surgery) (n=26)	p
Air-fluid level displacement on X-ray	Yes	61	6	0.001
	No	7	20	
CT	Yes	35	13	0.541
Free fluid	No	33	13	
CT	Yes	15	21	<0.001
Increase in wall thickness	No	53	5	
CT	Yes	29	16	**0.079**
Transition zone	No	39	10	
CT	Yes	17	10	0.150
Feces sign	No	51	16	
CT and X-ray	Yes	60	5	**<0.001**
Contrast transition to the colon	No	8	21	

Discussion

Although hemoglobin value in the diagnosis of intestinal obstruction is significant in terms of etiologies such as inflammatory bowel diseases, malignancies and Meckel's diverticulum, it does not have specific importance in the differential diagnosis of adhesive obstruction. However, leukocytosis may indicate the presence of complications such as perforation and peritonitis and may guide the clinician in terms of operation indication or timing. The values of blood urea nitrogen, creatinine, sodium, potassium and other electrolytes are important in determining the value and severity of hypovolemia and metabolic disorders [9]. Evaluation of blood gas parameters gains more importance in patients presenting with systemic disease symptoms such as fever, tachycardia, confusion and hypotension. Metabolic alkalosis in blood gas may result from severe vomiting, but metabolic acidosis may develop as a result of severe hypovolemia and intestinal ischemia [8]. Elevated LDH is an indicator of tissue damage. Since LDH is in many tissues, it does not provide information about the location and cause of tissue damage. However, it can give an idea about whether tissue damage has developed in a patient with obstruction symptoms. Serum lactate levels are not a reliable and specific laboratory parameter for ischemia, but they are significant in terms of ischemia predictivity in patients with small bowel obstruction. Pancreatic amylase can be elevated in small bowel pathologies (such as ischemia and perforation) [10]. For this reason, it can help the diagnosis in patients who are thought to have obstruction.

The use of abdominal CT in cases of intestinal obstruction is becoming increasingly common. It has high sensitivity and specificity in determining the etiology and level of obstruction [11].

In our study, the rate of patients diagnosed with adhesive intestinal obstruction and treated conservatively was 72%, which was found to be compatible with the literature [8,12]. The fact that the number of male patients was higher than females in both groups in our study suggests that the male gender is a risk factor for acute intestinal obstruction. The mean age of the patients in our study was 55, which is relatively low compared to similar publications in the literature. The mean age of the patients in our study was 55, which is relatively low compared to similar publications in the literature. However, it has been shown in the literature that the risk of developing adhesive obstruction increases with age.

In a study on the time of follow-up and surgical decision-making by applying an oral gastrograph, the absence of contrast in the colon after 24 hours is recommended as an indication for surgical treatment [13]. However, in our study, only 46% of our patients had gas-stool discharge in the first 24 hours, and 54% had 24-72 hours of discharge, indicating that it would be more appropriate to extend the conservative treatment period up to 72 hours. Thus, it would cause surgical complications, long hospital stays, increased surgical cost and increased probability of adhesion. Thus, it would cause surgical complications, long hospital stays, increased surgical cost and increased probability of adhesion. From this point of view, we think that it would be more accurate to follow up with conservative treatments.

The aim of radiological imaging in patients with intestinal obstruction is primarily to determine the transition zone and the etiology of the obstruction. The next aim is to investigate the presence of complications such as ischemia and perforation [14]. In cases where an intestinal obstruction is suspected, the first imaging method to be performed is an abdominal X-ray. However, the place of conventional radiographs in the diagnosis of obstruction decreases to 46% despite the latest technological

developments [15].

Although ultrasonography is successful in showing especially enlarged bowel loops, bowel diameters, and intra-abdominal free fluid in patients with ileus, its use is limited in demonstrating the level and etiology of obstruction [16]. In the study of Baid et al., it was shown that CT findings overlap with the perioperative and intraoperative findings at a high rate (86.67%). CT findings are very important in the management of patients, it shows emergency operation indications such as ischemia and perforation with high accuracy and helps clinicians with their rapid examination time [15]. In a meta-analysis, CT has been shown to have a sensitivity of 92% (81-100%) and specificity of 93% (range 68-100%) in complete obstructions. However, no standard conclusion has been reached for years regarding the CT procedure, contrast agent use, and CT scan time [17]. The use of intravenous contrast is very useful in the diagnosis of strangulation and in determining the localization, etiology and degree of obstruction [18]. In addition, the use of intravenous contrast has a unique diagnostic importance in terms of possible ischemic mechanical bowel obstruction by illuminating mesenteric vascular pathologies [19]. The use of oral contrast varies according to the patient's condition and the experience of the clinics. Direct CT is performed without the use of oral contrast in patients with suspected strangulation, perforation or complete obstruction. In patients with stable general conditions, oral contrast application not only provides a more accurate determination of the transition zone, but also provides a therapeutic effect with intraluminal pressure [20,21].

Our study has some limitations. The most important limitation is that it was planned retrospectively. Since we are the tertiary reference hospital in our city, most complicated cases admit to our hospital. There are similar studies in the literature. However, despite these, the most important contribution of our study to the literature is that it provides data that will predict in which patient's medical treatment may be more successful, especially according to imaging methods.

Conclusion

As a result, radiological findings are more important than laboratory parameters in determining the decision and time of surgery in cases diagnosed with intestinal obstruction. A small bowel diameter of 3.95 cm, intestinal wall thickness greater than 3 mm, and the absence of passage of oral contrast into the colon are the most reliable radiological parameters in terms of operation indication.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The study protocol was approved by Kahramanmaras Sutcu Imam University, Medical Faculty Ethics Committee (Date: 06.02.2019 No: 2019/02-18)

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ORIGINAL ARTICLE

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Thermosensitive pluronic® F127-based in situ gel formulation containing nanoparticles for the sustained delivery of paclitaxel

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Abstract

Bone metastasis is one of the most encountered complications among cancer patients and majority of cancer types has led to bone metastasis. Paclitaxel (PCX) is an anticancer agent commonly used in cancer treatment. However, its clinical use is restricted owing to poor water solubility. PCL NPs were investigated to cope with solubility problem of PCX. The size, polydispersity index and zeta potential of PCL were 383.8±2.4 nm, 0.253±0.122 and +51.3±6.1 mV, respectively. The PCX encapsulation efficiency was 77.2±2.1%. Subsequently, in situ gellling system was prepared by using different Pluronic F-127 concentration in order to determine the optimum ratio. İn situ gel formulation containing 20% Pluronic F-127 was selected as the optimum formulation and subjected to characterization tests. The viscosity of in situ gelling system with CS/PCX-PCL NPs at room temperature (25 °C±0.1) and at body temperature (37 °C±0.1) were found 137.00 ±3.05 cP and 890.30 ±89.61 cP at 100 rpm, respectively. According to the release results, in situ gel provided prolonged release profile compared to PCL NPs alone. Consequently, in situ gel containing CS/PCX-PCL NP elucidated in detail is a promising approach for locally applicable injectable systems.

Keywords: Cancer, nanoparticles, paclitaxel, in situ gel, drug release

Introduction

Bone metastasis is a secondary complication caused by the spread of cancer to the bone. Up to 70% of people with breast cancer or prostate cancer, and 15% to 30% of those with lung, colon, bladder, or kidney cancer, encounter bone metastases [1, 2]. Paclitaxel (PCX) is an anti-tumor agent which used in the treatment various cancers including bone metastasis [3, 4]. PCX exerts its therapeutic effect by targeting microtubules during cell profileration and inhibits cells at the G2/M phase [5]. Although PCX has been accepted as an ideal option in current clinical treatments, PCX shows a broad distribution throughout the body resulting in severe adverse effects [6]. Therefore, local applicable methods stand out to decrease severe side effects of PCX. Intraarticular delivery offers many advantages for joint and cartilage related diseases because only a small amount of the drug is required to exhibit the desired therapeutic efficacy, and drug exposure to improper areas is minimized [7].

Drug delivery systems (micro/nanoparticles, liposomes, and gels) for intraarticular injection can be effective to extend release period and retention time and to target specific sites like synovial joints, cartilage, chondrocytes, to improve the efficacy of drugs [8]. Polymeric nanoparticles (NPs) are drug delivery systems in the range of 10 to 1000 nm which consisted of biocompatible polymers [9, 10]. Polycaprolactone (PCL) is a biodegradable

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semicrystalline aliphatic polyester approved by the FDA that is used as a carrier for sustained delivery of therapeutic molecules [11]. Since PCL has slow in vivo degradation, non-toxic structure and therapeutic activity and stability, it is commonly preferred to fabrication of nanoparticle systems. Application of PCL NPs with in situ gelling system for local delivery of therapeutic molecules provides NPs with extended release at the site of action [12]. Chitosan (CS) is a deacetylated derivative of chitin. It is biodegradable and biocompatible cationic polymer and has benefits on bone regeneration [13]. It has been shown that chitosan prevents the formation of secondary breast and prostate tumors in the bone [14]. Furthermore, CS has been widely used as coating material. Surface decoration with CS provides a wealth of benefits for polymeric, lipid or metallic NPs, such as improving stability, enhanced bioavailability, controlled drug release, increased bioadhesion and increased cellular uptake [15].

Because of their unique characteristics, in situ gelling hydrogel formulations have gained great interest for development of site spesific drug systems. The hydrophilic nature of hydrogels limits the delivery of hydrophobic drugs in hydrogels. To overcome this problem, before being incorporated in hydrogels, hydrophobic active substances can be encapsulated in nanomaterials or their hydrophilicity can be increased with cyclodextrin derivatives [16]. The main limitations of thermosensitive hydrogels are in the development of biocompatible and biodegradable materials with ideal properties such as heat responsiveness and controlled/ sustained release. However, increasing researches have been reported due to the advances observed in the fields of drug delivery systems, biocompatible polymers and new polymeric drug formulation approaches for biomedical applications [17-19].

The simple phase transition (sol-gel transition) in water provides simplicity and safety as there are no chemical reactions or external stimuli that form the hydrogel. The sol phase is defined as a flowing fluid, whereas the gel phase is non-flowing while retaining its integrity. The gel phase appears when a polymer's critical concentration (critical gel concentration, CGC) is exceeded [20].

Various polymers can be used for the preparation of in situ gelling systems. Among these, poloxamers are popular polymers in pharmaceutical applications due to their favorable properties such as non-toxic, non-irritant, commercial availability and a wide variety of molecular weight forms. Poloxamers are amphiphilic synthetic tri-block copolymers comprised of two poly-(ethylene oxide) units and one poly(propylene oxide) (PPO) unit. They have been approved by the FDA and are listed in the US and European Pharmacopoeia [21].

Poloxamer 407 (Pluronic F127) gels at a concentration of 20% by weight at 25°C. This rate is lower than other members of the poloxamer series. Poloxamer gels are a mobile viscous liquid that, at room temperature, transforms into a semi-solid transparent gel at body temperature from the solution (37ºC). At

the crucial temperature for micellization, PPO block dehydration results in the production of micelles. As the temperature rises, micelle formation becomes increasingly crucial, and eventually the micelles come into contact and stop moving [13].

In our previous study, PCX loaded PCL NPs coated with CS (CS/PCX-PCL) and poly-L-lysine were developed. According to the results of in vitro characterization and in vitro release studies, CS coated formulations exhibited ideal properties in terms of particle size, zeta potential and poly dispersity index [22]. In this study, Pluronic F-127 (PF127) based thermosensitive in situ gel systems were developed. The gelation characteristics of each polymer and their formulations were investigated in order to determine the best conditions for forming in situ gelling systems. Then, CS/PCX-PCL NPs were dispersed in optimized thermosensitive in situ gel. This research lays the groundwork for the development of a PCX delivery system that combines the in situ thermogelling property of F127 with the benefits of polymeric NPs.

Material and Methods

Polycaprolactone (PCL) (Mw:80.000), Pluronic F-127, Pluronic F68 and Paclitaxel (Mw:853.91) were obtained from Sigma–Aldrich (St. Louis, MO, USA). Chitosan (Type; Protasan UP G-113; Mw<200 kDa) was supplied from Novamatrix, Norway. All the other reagents were pharmaceutical grade.

Preparation of PCX-loaded CS/PCL NPs

PCX-loaded CS/PCL NPs were prepared according to the method used in our previous research [22]. Briefly, 10 mg PCL (Mw= 80.000) was weighed for each batch and 1 mg of PCX was added and dissolved in 5 mL organic phase (acetone). Pluronic F-68 (75 mg) and chitosan (2.5 mg) were added to ultra-pure water (10 mL) and stirred (500 rpm) at room temperature for preparing aqueous phase. At 800 rpm, organic phase was added dropwise to aqueous phase and stirring (500 rpm) continued at room temperature overnight to evaporate the organic phase completely. NPs were obtained by nanoprecipitation method. For 5 minutes, the dispersions were centrifuged at 3500 rpm. Finally, supernatants were filtered with 0.45 μm pore size filter to remove the aggregate from the solution.

Preparation and characterization of blank and PCX-loaded CS/PCL NPs dispersed in situ gel

Thermosensitive Pluronic F-127 and Pluronic F68 blank hydrogels were prepared with varying proportions of Pluronic F127. For the preparation of pluronic containing hydrogels, phosphate buffered saline was progressively mixed with the pluronic powders (PBS) (pH 7.4) under agitation on magnetic stirrer (750 rpm) at 4 °C. Formulations were mixed for 24 hours. The final pluronic concentration in the hydrogel for the formulations containing pluronic F-127 alone was 15%, 18%, 20%, 22%, and 25% w/w. For the preparation of hydrogels consisting of a mixture of F127 and F68 the ratio of F127/F68 in the formulation was determined as 19/1% [23]. After complete dissolution of the pluronic powder, each formulation

will be equilibrated at 4°C for 24 hours to eliminate foam and air bubbles. For the preparation of nanoparticle dispersed gels PCX-loaded CS/PCL NPs were added to optimized in situ gel and mixed at 750 rpm at 4 °C. Based on the results of rheological behavior and oxygen-reactive species generation, moist heat sterilization was chosen as the method for gel sterilization [24]. After all gels were prepared, they were sterilized at 121 °C for 15 minutes in autoclave.

Gelation temperature and time

The temperature at which the sol-gel transition takes place is referred to as the gelation temperature, and the time for the start of gelation and the subsequent transition from sol to gel are also known as the gelation times (Figure 1).
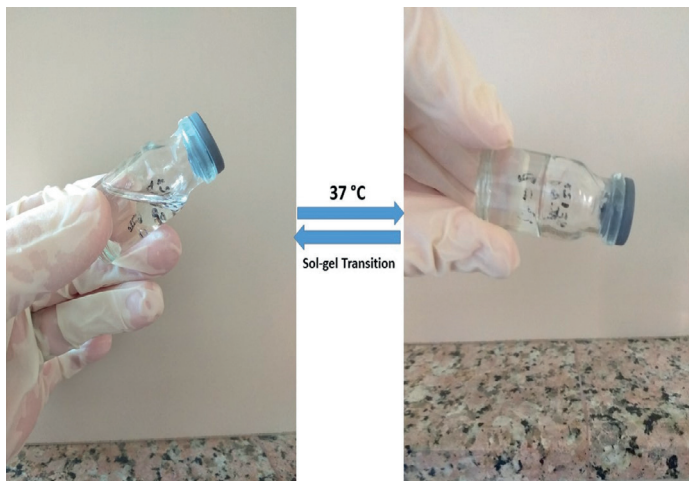
Figure 1. The sol–gel transition of a thermosensitive *in situ* gel

For gelation time, magnetic stirrer was adjusted to the range of 50-100 °C, the solutions (3 mL) were allowed to mix at 75 rpm. A thermometer was inserted into the solutions. The temperature at which the magnetic bar did not turn and the solution in the vial did not flow was determined as the gelation temperature. The gelation time was determined by taking into account the state of the gel where the solution does not flow for 1 minute after inverting a bottle. The solution (3 mL) was taken into a glass bottle and heated in a 37 ºC water bath to gel. To examine the sample's gelation after each minute, the glass vial was taken out and inverted for one minute. No flow within 1 minute after the bottle is inverted will be considered the gel state [25].

Viscosity measurements and rheological behavior of in situ gels

The viscosity measurement of the gels was determined at different rotational speeds (10-100 rpm) and constant temperature using a rotary viscometer (Brookfield DV-II) equipped with a CP52 spindle. Based on the measurements shear rate, shear stress, viscosity was determined, and flow curves were obtained.

pH and clarity

In order to determine the pH of blank in situ gel formulation and in situ gelling systems with CS/PCL NPs loaded with PCX, pH

meter (Mettler Toledo, Switzerland) was utilized. Measurements for each formulation were conducted for three times (n=3). The clarity of each formulation was analyzed by visual examination under bright light with a dark background [26].

In vitro release of PCX from in situ gel formulation

In vitro release studies of in situ gelling formulations containing CS/PCX-PCL NPs were carried out by following dialysis bag method (MWCO; 14,000 Da). Dialysis membran was soaked with NaOH (%1) for overnight prior to experiment. 1000 µL in situ gel containing CS/PCX-PCL NPs was added to dialysis membrane bag and immersed into 25 mL PBS at 37°C. At predetermined time intervals, 200 µL of the release medium were taken and replaced with fresh PBS at same volume. To analyze the amount of released PCX from in situ gel, UV spectrophotometer was used at 230 nm [22].

Statistical Analysis

IBM® SPSS Statistics® V21 program was used for statistical analysis. Student's t-test was used for pairwise comparisons. In all comparisons, it was considered significant for $p < 0.05$.

Results

Characterization of in situ gel formulations containing NPs

nanoparticle characterization

PCX loaded CS/PCL NPs were prepared using optimized nanoprecipitation method described in our previous study [22]. The average size of optimum nanoparticle formulation was 383.8±2.4 nm, the PDI was 0.253±0.122 and the zeta potential was +51.3±6.1. The PCX encapsulation efficiency was 77.2±2.1%.

Gelation temperature and time

Various concentrations of Pluronic F-127 were investigated in order to obtain the best concentration ratio. When the concentration of Pluronic F-127 was 15%, no gelling was observed below 37°C. When the ratio of Pluronic F-127 was increased to 18%, the gelation temperature was found to be 36.67°C ± 0.58. When the Pluronic concentration increased gelation time and temperature were decreased. Gelation temperatures and times of formulations were displayed in Table 1.

According to Kim et al., a suitable gelation temperature for in situ gel formulations should be in the range of 30-36°C [27]. F2 was selected due to its suitable gelation temperature and time. According to Aka-Any-Grah et al. F68 was added %1 to the F2 formulation and total polymer ratio kept constant at %20 [23]. The gelation time and temperature of in situ gel consisted of mixture of Pluronic F-127 and Pluronic F68 at 19%/1% ratio was found 30.33±0.58 sec and 41.67±0.58°C. The in situ gel consisted of mixture of F127 and F68 at 19%/1% was chosen as optimum formulation due to its favorable characteristics. The gelation time and temperature of optimum in situ gel containing CS/PCX-PCL NPs were found 41.33 ±0.58 sec and 30.67±1.15°C, respectively.

Table 1. Gelation temperatures and times of formulations

Formulation	Pluronic F-127 (%)	Pluronic F68 (%)	Total pluronic ratio (%)	Gelation Temperature (°C)	Gelation Time (sec)
F1	18	-	18	36.67±0.58	57.67±0.58
F2	20	-	20	31.67±0.58	51.00±1.73
F3	22	-	22	26.33±0.58	40.00±0.00
F4	25	-	25	22.00±0.00	30.00±0.00
Optimum Formulation	19	1	20	30.33±0.58	41.67 ±0.58

Table 2. pH and clarity results of formulations

Formulation	Blank *in situ* Gel		NP Loaded *in situ* Gel	
	pH	Clarity	pH	Clarity
F1	6.09±0.05	Clear	6.15±0.02	Clear
F2	6.07±0.03	Clear	6.14±0.00	Clear
F3	6.01±0.08	Clear	6.08±0.09	Clear
F4	5.98±0.01	Clear	6.05±0.02	Clear
Optimum Formulation	6.03±0.01	Clear	6.08±0.04	Clear

Viscosity measurements and rheological behavior of in situ gels

Viscosity measurements were performed at both room and body temperature. The viscosity of blank in situ gel and in situ gel containing CS/ PCX-PCL NPs at room temperature (25 °C±0.1) were found 135.00±2.47 cP and 137.00 ±3.05 cP respectively at 100 rpm (Figure 2).

The viscosity of blank in situ gel and in situ gel containing CS/PCX-PCL NPs at body temperature (37 °C±0.1) were found 736.57±7.97 cP and 890.30 ±89.61 cP respectively at 100 rpm (Figure 3).
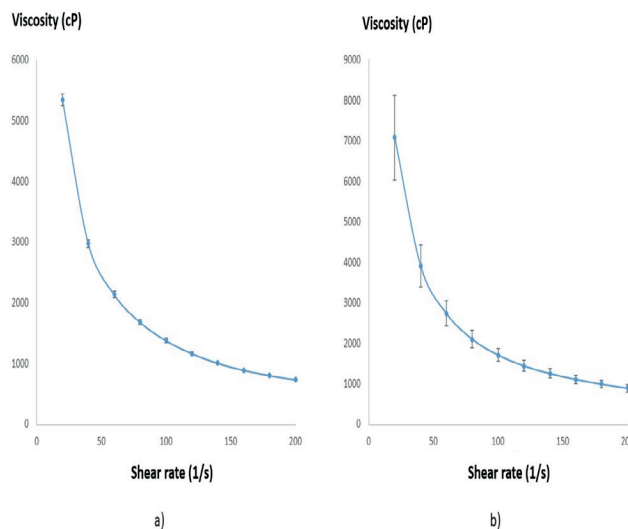
Figure 3. Flow curves of blank in situ gel a) and in situ gel containing PCX loaded CS/PCL NPs b) at 37 °C±0.1

pH and clarity

The pH and clarity results are illustrated in Table 2. The pH of our formulations varies between 5.98-6.15. According to the literature review, this pH range is accepted as suitable for injectable in situ gel formulation for bone tissue [28, 29]. Also,
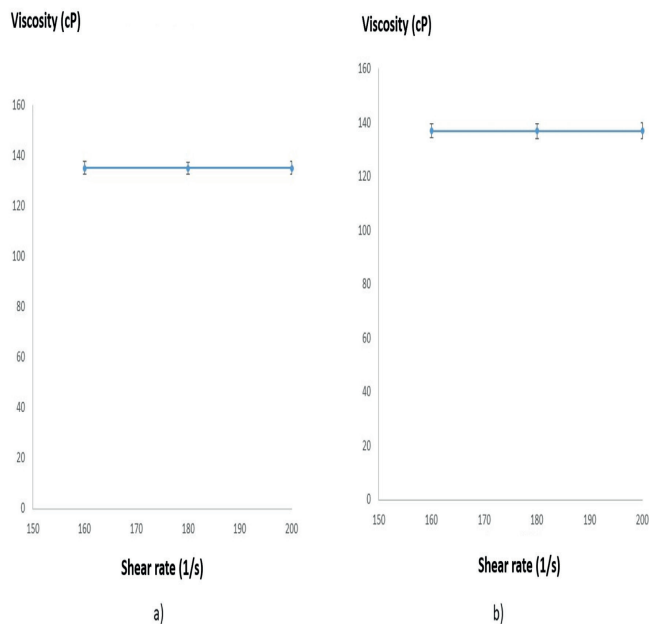

Figure 2. Flow curves of blank in situ gel a) and in situ gel containing PCX loaded CS/PCL NPs b) at 25 °C±0.1

both blank and nanoparticle loaded formulations had clear appearance. Results of clarity tests indicated that nanoparticle incorporation to in situ gel formulation did not cause a significant change in the clarity of gel.

In vitro release studies

Figure 4 demonstrates the cumulative release of PCX from PCL NPs and in situ gel containing PCL NPs. According to the in vitro release study, PCL NPs formulation released PCX faster than in situ gel containing PCL NPs. For the PCL NPs alone, higher than %70 of PCX was liberated from nanoparticle system at the end of the release experiment. İn situ gel formulation, on the other hand, still maintained approximately %40 of PCX at 96 h. It can be clearly observed that in situ gel formulation could extend the release of PCX compared to PCL NPs alone.
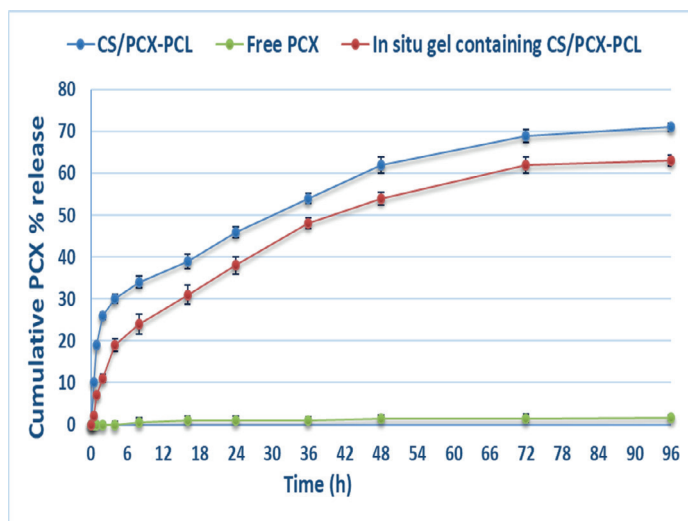
Figure 4. Cumulative release of PCX from CS/PCX-PCL and in situ gel formulations containing CS/PCX-PCL

Discussion

Local therapeutic approaches have recently aroused a great deal of attention. Since it allows to directly reach to target area, has led to low adverse effects and increases treatment efficiency, localized treatment approaches have been commonly preferred lately. İn situ gelling systems are among the most effective candidates which are able to provide localized therapy. They offer a wealth of benefits for treatment including extended-release profile, convenient administration, increased retention time on the tissue. In this context, in situ gel formulations containing CS/PCX-PCL NPs were developed to provide an effective way to be used in cancer type metastasis to bone tissue.

CS/PCX-PCL NPs were developed by following the method developed in our previous study [22]. The NPs had ideal properties in terms of size, PDI, ZP and encapsulation efficiency. According to gelation temperature and gelation time results, increased Pluronic F-127 concentration used in formulations has led to lower gelation time and temperature. Physiological temperatures will cause the

formulation to have liquid qualities if the gelation temperature is too high, which can cause leakage. Lower gelation temperatures, on the other hand, may cause application chalenges due to the viscous nature of the formulation. In the light of these information, F2 was selected as the optimum formulation. Then, to obtain lower gelation time, Pluronic F-127 and Pluronic F 68 were mixed at 19%/1%. The addition of the active substance or additives is known to change the sol-gel transition temperature [30]. Furthermore, short gelation time is important in terms of preventing drainage from the application site of the active substance and the residence time in the application area for prolonged release. However, the addition of active substance had no effect on gelation temperatures and gelation times in our in situ gels. No significant differences were found in gelation time and temperature of between blank in situ gel and in situ gel containing CS/PCX-PCL NPs ($p>0.05$).

İn situ gel formulations should ideally have a low viscosity in sol state so that the formulation can be easily injected at the application site. On the other hand, after application, the in situ gel formulation must have a high viscosity at body temperature so that it comes into contact with the bone tissue and stays longer in the defect area to ensure effective bone regeneration [31]. Based on our viscosity results, blank in situ gel and in situ gel containing CS/PCX-PCL NPs are suitable. Flow curves were shown Figure 2 and Figure 3. The results indicated that, poloxamer solution showed a Newtonian behavior at room temperature while it might be a pseudoplastic fluid when the temperature reached above gelation temperature at body temperature. Poloxamer molecules exist as monomolecular micelles in an aqueous solution at low temperatures, surrounded by a sheath of hydrogen bonded water molecules, with hydrophilic poly(oxyethylene) moieties wrapped around central hydrophobic poly(oxypropylene) moieties. There are few interactions between polymer molecules in this case the chains are highly mobile. As a result, poloxamer solutions have Newtonian flow properties in whichviscosity keeps constant when shear rate increases. Our results are compatible with literature [32]. As the temperature rises, the hydrophobic poly(oxypropylene) sections of the poloxamer chains' hydrogen bonds become unstable and eventually desolvate, allowing for widespread hydrogen bonding between poly(oxypropylene) moieties on nearby chains. The hydrophobic core of multimolecular micelles is formed by poly(oxypropylene) aggregates, with the hydrophilic poly(oxyethylene) portions interacting with the aqueous vehicle. The formation of multimolecular micelles causes a reduction in chain mobility [33] As a result, above gelation temperature, poloxamer gels exhibit pseudoplastic flow characteristics. In pseudoplastic flow characteristics, when the shear rate increased, the viscosity decreases. Our results are compatible with literature [34-36]. Furthermore, our pH and clarity results pointed out that our formulations are in acceptable range and addition of CS/PCX-PCL NPs did not result in significant changes ($p>0.05$).

When release data were examined, it is obvious that in situ gel notably increased the release time of PCX compared to CS/PCL NPs. The reason why in situ gel loaded with CS/PCL NPs exhibited

prolonged release profile can be explained by advantages provided by in situ gel systems. Process of drug release from in situ gels containing NPs carries out in two steps. At first, in situ gel disrupts gradually and collapse totally. During that time, NPs carried by in situ gel formulation liberates from gel matrix. In the second step, drug molecules release from NP system. Accordingly, in situ gel released the drug slower than CS/PCL NPs alone. When graphics were examined thoroughly, 2 stages of release are noticed; fast release in the initial of experiment and prolonged release over an extended period. In the first 6 hours, the burst effect was observed. The main reason of burst effect is because of surface modification with CS. Since CS covers the surface of the nanoparticle, drug molecules are adsorbed by CS. Therefore, after the first interaction between nanoparticles and release medium, firstly drug molecules adsorbed onto CS release from nanoparticle system and as a result, faster drug release occurs. Our results are compatible with the literature [37].

Conclusion

In the present study, the PCX with poor solubility was loaded to PCL NPs and then NPs were incorporated to in situ gel formulation in order to provide prolonged release profile, increased retention time in tissue. In this context, characterization tests of PCL NPs and in situ gel formulation were conducted. PCL NPs had optimum properties with the particle size 383.8±2.4 nm, the PDI 0.253±0.122 and the zeta potential +51.3±6.1 mV. To obtain a gel formulation with ideal gelation time and temperature various pluronic ratios were evaluated. It was seen that as concentration ratio of Pluronic F-127 was increased, gelation time and temperature were decreased. Based on the results, optimum formulation was selected as F2 containing %20 Pluronic F-127. Subsequently, in order to decrease gelation time, Pluronic F 68 was added at the rate of %1 by keeping total pluronic (Pluronic F-127 + Pluronic F 68) ratio at %20. pH and clarity results were suitable for injection to targeted tissue. According to release data, it was proven that in situ gel formulation could achieve sustained PCX release. This study has been a promising preformulation study for injectable in situ gel formulation to be utilized in bone metastasis.

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ORIGINAL ARTICLE

Machine learning-based ovarian cancer prediction with XGboost and stochastic gradient boosting models

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Abstract

Ovarian cancer is one of the most common types of gynecological malignancies with its high mortality rate, silent and occult tumor growth, late onset of symptoms and diagnosis in advanced stages. Therefore, the need to develop new diagnostic techniques to predict the course of the disease and the prognosis of this malignancy has increased. In this study, ovarian cancer and benign ovarian tumor samples will be classified to create an accurate diagnostic predictive model using the machine learning method XGBoost and Stochastic Gradient Boosting and disease-related risk factors will be determined. This current study considered the open-access ovarian cancer and benign ovarian tumor samples data set. For this purpose, data from 349 patients were included. The data set was divided as 80:20 as a training and test dataset. XGBoost and Stochastic Gradient Boosting were constructed for the classification via five-fold cross-validation. Accuracy, balanced accuracy, sensitivity, specificity, positive predictive value, and negative predictive value performance metrics were evaluated for model performance. Among the performance criteria in the test stage obtained from the XGBoost model that has the best classification result; accuracy, balanced accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F1 score were obtained as 89.5%, 88.7%, 85.7%, 91.7%, 85.7%, 91.7%, and 85.7%, respectively. According to the variable importance obtained as a result of the model, the variables most associated with the diagnosis were CA72-4, HE4, LYM%, ALB, EO%, BUN, RBC, NEU, and MCV, respectively. The applied machine learning model successfully classified ovarian cancer and created a highly accurate diagnostic prediction model. The results from the study revealed effective parameters that can diagnose ovarian cancer with high accuracy. With the parameters determined as a result of the modeling, the clinician will be able to simplify and facilitate the decision-making process for the diagnosis of ovarian cancer.

Keywords: Ovarian cancer, classification, machine learning, XGBoost, stochastic gradient boosting

Introduction

Cancer is the major cause of death in most parts of the world, and it is currently the most significant impediment to most countries achieving optimal life expectancy [1,2]. On the heels of cervical and uterine cancer, ovarian cancer is the third most common kind of gynecologic malignancy. In addition to this, it has the highest number of fatalities and the poorest prognosis [3]. Although ovarian cancer is not as prevalent as breast cancer, it is three times more likely to result in death, and it is projected that the fatality rate will significantly increase by the year 2040 [2,4]. Ovarian cancer was reported to have affected 295,414 women globally in 2018 and been responsible for 184,799 fatalities [2]. Ovarian cancer has a high mortality rate due to silent and

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secret tumor growth, delayed symptom presentation, and a lack of adequate screening, which leads to diagnosis in the advanced stages. Because of its stealthy nature, this disease has earned the moniker "the silent killer" [4,5].

Ovarian cancer incidence varies across the world, like that of many other malignancies [6]. Ovarian cancer mortality follows a varied pattern due to inequalities in access to diagnostic and treatment facilities, with African people having the greatest fatality rate [7]. Among the risk factors that cause the disease, it is thought that there are factors such demographic factors, reproductive factors, gynecologic factors, hormonal factors, genetic factors, and lifestyle Factors [8]. Despite the fact that ovarian tumors are chemo-sensitive and typically exhibit initial efficacy against platinum/taxane treatment, patients with the advanced illness have 5-year recurrence rates of 60% to 80% . Consequently, much effort has been devoted to developing new diagnostic techniques to predict the course of the disease and the prognosis of this malignancy [9].

Machine learning (ML), is a subfield of artificial intelligence that performs data-driven learning in order to achieve its goal of making predictions about new data when such data is introduced to it. In recent years, ML approaches have become one of the technologies that are widely utilized in the diagnosis of diseases and clinical decision support systems. These methods also have a wide range of potential applications in a variety of fields. The determination of genetic diseases, the early diagnosis of cancer diseases, and the identification of patterns in medical imaging are all examples of areas in which ML, which has a wide range of applications in the medical field, constitutes the basic infrastructure of application areas. In the last decade, both unsupervised and supervised machine learning methods have achieved high performance in a wide variety of situations [10,11].

In the current study, ovarian cancer and benign ovarian tumor samples will be classified using XGBoost and Stochastic Gradient Boosting, supervised machine learning method trained on 49 predictive variables, to create an accurate diagnostic prediction model. The performance metrics obtained from the 2 models used will be examined and the model with the best classification will be decided. The model with the best classification performance will be used as the diagnostic prediction model, and the variables that can be used in diagnosing the disease will be obtained with the help of the variable significance values obtained as a result of the model.

Material and Methods

Data collection and variables

The patients used in the current study consisted of patients with ovarian cancer and benign ovarian tumor. Patients who underwent surgical resection and were diagnosed by pathology after surgery were included in the research. None of the ovarian cancer patients included in the study received chemotherapy or radiotherapy before surgery. The dataset includes 349 Chinese patients, 49 variables such as demographics, blood routine tests, general chemistry, and tumor markers, and the target variable (ovarian cancer and benign ovarian tumor) [12].

XGboost algorithm

Gradient Boost is a powerful ML technique for regression and classification problems in which weak predictive models frequently produce ensemble forms of decision trees. Gradient Boost, which is based on the boosting method, aims to construct many weak learners in sequence and incorporate them into a complex model [13].

Extreme Gradient Boosting (XGBoost) is one of the applications of gradient boosting machines (GBM), one of the most effective supervised learning algorithms. Its fundamental structure is founded on gradient boosting and decision tree algorithms. When compared to other algorithms, it has a significant advantage in terms of speed and performance. XGBoost is also highly predictive, ten times faster than other algorithms, and includes several regularizations that improve overall performance while reducing overfitting or over-learning. Gradient boosting is an ensemble method for creating a robust classifier by combining a set of weak classifiers with boosting. Starting with a basic learner, the strong learner is trained iteratively. The principles of gradient boosting and XGBoost are the same. The key differences are in the implementation details. By controlling the complexity of the trees, XGBoost can achieve better performance by employing various regularization techniques [14,15].

Stochastic gradient boosting algorithm

Stochastic gradient boosting is a method developed by Friedman by incorporating randomness into the gradient boosting method. In stochastic gradient boosting, a random subsample is selected with permutation sampling strategy at each refresh. This selected subsample is used to calculate the model update instead of all learners and to reduce the correlation between trees [16]. As with other ensemble learning methods, large trees are not created in this method, but instead, each tree (usually 100–200 trees) developed during the process is summarized and each observation is grouped according to the most common classification among trees. These differences cause the stochastic gradient boosting method to differ from other augmentation methods and reduce its sensitivity to outliers and unbalanced data sets [16,17].

Biostatistical analysis

The median (minimum-maximum) and mean±standart deviation were used to summarize variables. Shapiro Wilk test of normality was used to determine normal distribution. Whether there is a statistically significant difference between the output variable and input variables was evaluated by using where appropriate Mann-Whitney U test, independent sample t-test, and Chi-square test. It was determined that a value was statistically significant if it had a p-value of less than 0.05 ($p<0.05$). IBM SPSS Statistics 26.0 was utilized in all analyses.

Machine learning modeling and performance evaluation

In the current study, XGBoost and Stochastic Gradient Boosting were used in the modeling stage for the dataset in question. The data set was divided as 80:20 as a training and test dataset. The n-fold cross-validation approach was used for the analyses. The data is separated into n parts in the n-fold cross-validation procedure, and the model is applied to n parts. One of the n parts is used for testing, while the remaining n-1 parts are used to train the model. In this study, 5-fold cross-validation was employed for the modeling process. Accuracy, balanced accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F1-score were used as performance evaluation criteria. In addition, variable importances were calculated, which gives information about how much the input variables contribute to the output variable. Modeling was done using R studio 4.2.1.

Results

The data set used in the study included a total of 349 patients with 171 ovarian cancer and 178 benign ovarian tumors. The mean age of the patients was 45.05±15.13. While the mean age of patients with ovarian cancer was 52.98±13.48 years, the mean age of patients with benign ovarian tumors was 37.44±12.5.

The results of the statistical analyses between the target variable and independent variables are given in Table 1.

According to the results obtained from the analyzes made between the independent variables and the target variable, there is a statistical difference between the target variable ovarian cancer ve benign ovarian tumors categories in terms of AFP, Age, ALB, ALP, AST, BASO%, Ca, CA125, CA72-4, DBIL, GGT, GLO, GLU, HCT, HE4, HGB, IBIL, LYM#, LYM%, MCH, MONO, Na, NEU, PCT, PDW, PLT, RBC, TBIL, TP variables (p<0.05). In addition, there is a statistically significant difference between the categories of the target variable for the menopause variable, which is a qualitative variable.

Table 2 shows the values of the performance metrics calculated for the training and test data sets as a result of the Stochastic Gradient Boosting model.

In the training stage accuracy, balanced accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F1 score obtained from the Stochastic gradient boosting model were 97.5%, 97.3%, 96.7%, 98%, 96.7%, 98%, and 96.7%, respectively. Also in the testing stage accuracy, balanced accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F1-score obtained from the Stochastic gradient boosting model were 84.2%, 81.5%, 71.4%, 91.7%, 83.3%, 94.6%, and 76.9%, respectively.

In the training stage accuracy, balanced accuracy, sensitivity, specificity, positive predictive value, negative predictive value,

Table 1. The results of the statistical analyses between the target variable and independent variables

Variables	Abreviation of Variables	TYPE				p
		Cancer		No Cancer		
		Mean±SD	Median(Min-Max)	Mean±SD	Median(Min-Max)	
Alpha-Fetoprotein	AFP	22.71±145.02	2.44(0.61-1210)	2.71±2.18	2.1(0.61-20.53)	0.013**
Anion Gap	AG	19.4±4.6	19.97(6.6-28.36)	19.24±4.1	19.74(6.2-33.33)	0.728*
Age	Age	52.98±13.49	53(18-83)	37.44±12.51	36(15-69)	<0.001*
Albumin	ALB	38.89±6.33	39.2(22-51.5)	43.2±3.97	43.4(28-50.9)	<0.001*
Alkaline Phosphatase	ALP	86.78±58.45	77(26-763)	67.67±19.88	65(29-157)	<0.001**
Alanine Aminotransferase	ALT	17.96±11.93	15(5-86)	18.06±10.57	15(4-71)	0.353**
Aspartate Aminotransferase	AST	20.98±9.47	19(9-64)	17.28±6.99	16(7-78)	<0.001**
Basophil Cell Count	BASO#	0.03±0.02	0.02(0-0.12)	0.03±0.02	0.03(0-0.12)	0.312**
Basophil Cell Ratio	BASO%	0.44±0.33	0.4(0-1.58)	0.52±0.36	0.44(0-1.94)	0.046*
Blood Urea Nitrogen	BUN	4.01±1.42	3.75(1.12-10.19)	4.02±1.15	3.88(1.52-8.31)	0.449**
Calcium	Ca	2.32±0.42	2.44(0.92-2.82)	2.46±0.28	2.52(0.95-2.83)	<0.001**
Carbohydrate Antigen 125	CA125	695.89±1068.16	241.5(7.26-5000)	51.45±79.79	22.66(3.75-515.4)	<0.001**
Carbohydrate Antigen 19-9	CA19-9	71.95±178.98	14.99(0.6-1000)	25.91±40.36	14(0.6-279.5)	0.2
Carbohydrate Antigen 72-4	CA72-4	19.84±36.61	4.83(0.63-158.5)	3.12±4.06	1.74(0.2-19.37)	<0.001**
Carcinoembryonic Antigen	CEA	5.51±16.08	1.41(0.2-138.8)	1.47±0.88	1.27(0.2-6.95)	0.103**
Chlorine	CL	100.9±3.52	101(84.6-109.4)	100.73±2.36	100.8(93.1-108)	0.340**
Carban Dioxide-Combining Power	CO2CP	24.54±2.97	24.1(16.2-34.3)	24.03±2.37	24(16.2-30)	0.077*
Creatinine	CREA	63.35±12.59	62.7(38.2-114)	65.11±10.77	64(41-94.1)	0.060**

Direct Bilirubin	DBIL	2.9±1.35	2.5(0.9-9.2)	3.35±1.48	3.15(1-12.1)	<0.001**
Eosinophil Count	EO#	0.06±0.06	0.05(0-0.34)	0.07±0.08	0.05(0-0.4)	0.421**
Eosinophil Ratio	EO%	1±0.94	0.8(0-5.1)	1.24±1.29	0.9(0-7.6)	0.134**
Gama Glutamyltransferasey	GGT	22.83±17.43	17(4-114)	19.84±18.8	15(4-176)	0.007**
Globulin	GLO	31.09±5.09	31(14.1-47.6)	29.29±3.75	28.85(20.4-40.5)	<0.001*
Glucose	GLU	5.56±1.48	5.23(3.71-12.44)	5.12±0.85	5(3.57-9.3)	0.014**
Hematocrit	HCT	0.38±0.05	0.39(0.22-0.57)	0.39±0.04	0.39(0.29-0.46)	0.033**
Human Epididymis Protein 4	HE4	342.82±517.31	140.9(29.49-3537.6)	49.17±39.07	43.77(16.71-531.8)	<0.001**
Hemoglobin	HGB	122.2±16.71	124(61.8-189)	128.34±13.7	129.5(80-158)	<0.001**
Indirect Bilirubin	IBIL	5.35±2.54	5(1.5-16)	6.56±3.2	6(1-28.4)	<0.001**
Kalium	K	4.38±0.41	4.36(3.08-5.4)	4.39±0.39	4.38(3.33-5.39)	0.918*
Lymphocyte Count	LYM#	1.41±0.54	1.34(0.35-3.2)	1.7±0.55	1.67(0.38-3.49)	<0.001*
Lymphocyte Ratio	LYM%	22.74±10.05	23.4(3.9-51.6)	29.27±9.7	29.8(5.1-49.6)	<0.001**
Mean Corpuscular Hemoglubin	MCH	28.34±2.71	28.9(17.7-33.7)	29.2±2.36	29.85(18.9-36.8)	<0.001**
Mean Corpuscular Volume	MCV	87.79±6.71	88.4(61-103.4)	88.34±5.32	89.6(65.2-107.9)	0.414**
Magnesium	Mg	0.98±0.13	0.96(0.65-1.3)	0.98±0.12	0.97(0.66-1.37)	0.571**
Mononuclear Cell Count	MONO#	0.39±0.16	0.35(0.07-0.94)	0.33±0.13	0.31(0.07-0.97)	<0.001**
Monocyte Ratio	MONO%	5.77±2.01	5.55(1.51-21.3)	5.4±1.82	5.28(0.3-12.14)	0.069*
Mean Platelet Volume	MPV	9.98±1.78	10.1(5.06-14.5)	10.1±1.7	10.4(5.98-13.8)	0.407**
Natrium	Na	140.91±3.26	141.3(125.1-147.9)	140.09±2.35	140.1(133-150.7)	<0.001**
Neutrophil Ratio	NEU	70.25±10.98	70.6(37.2-92)	59.59±9.4	59.5(42.44-81.7)	<0.001*
Thrombocytocrit	PCT	0.27±0.1	0.26(0.09-0.69)	0.23±0.07	0.23(0.07-0.42)	<0.001**
Platelet Distribution Width	PDW	13.91±3.19	13.4(8.8-22.8)	14.74±2.75	14.1(9.4-20.9)	0.002**
Phosphorus	PHOS	1.12±0.18	1.12(0.65-1.67)	1.12±0.19	1.13(0.57-1.75)	0.641**
Platelet Count	PLT	281.65±117.44	265(74-868)	230.25±57.33	223.5(88-398)	<0.001**
Red Blood Cell Count	RBC	4.31±0.52	4.32(2.62-6.74)	4.4±0.41	4.42(2.9-5.39)	0.031**
Red Blood Cell Distribution Width	RDW	13.68±2	13.1(10.92-22.2)	13.43±1.59	12.9(11.1-20)	0.376**
Total Bilirubin	TBIL	8.25±3.65	7.6(2.5-22.7)	9.91±4.47	9.2(2.7-38.3)	<0.001**
Total Protein	TP	69.62±8.88	71.9(32.9-83.8)	72.49±5.15	73(49.5-86.8)	0.015**
Urie Acid	UA	246.25±78.04	236.9(96-632)	241.26±58.18	233.25(102.3-460.6)	0.982**

*: Independent samples t-test, **: Mann Whitney U test, SD: Standart Deviation, Min: Minimum, Max: Maximum

Table 2. Performance metric values calculated from Stochastic Gradient Boosting model

Performance Metrics	Training Stage	Testing Stage
	Value (%)	Value (%)
Accuracy	97.5	84.2
Balanced Accuracy	97.3	81.5
Sensitivity	96.7	71.4
Specificity	98.0	91.7
Positive predictive value	96.7	83.3
Negative predictive value	98.0	84.6
F1-score	96.7	76.9

Table 3. Performance metric values calculated from XGBoost model

Performance Metrics	Training Stage	Testing Stage
	Value (%)	Value (%)
Accuracy	91.2	89.5
Balanced Accuracy	89.7	88.7
Sensitivity	83.3	85.7
Specificity	96.0	91.7
Positive predictive value	92.6	85.7
Negative predictive value	90.6	91.7
F1-score	87.7	85.7

and F1-score obtained from the XGBoost model were 91.2%, 89.7%, 83.3%, 96%, 92.6%, 90.6%, and 87.7%, respectively. Also in the testing stage accuracy, balanced accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F1-score obtained from the XGBoost model were 89.5%, 88.7%, 85.7%, 91.7%, 85.7%, 91.7%, and 85.7%, respectively. In Figure 1, values of performance metrics obtained from Stochastic Gradient Boosting and XGBoost models in the testing stage are shown.
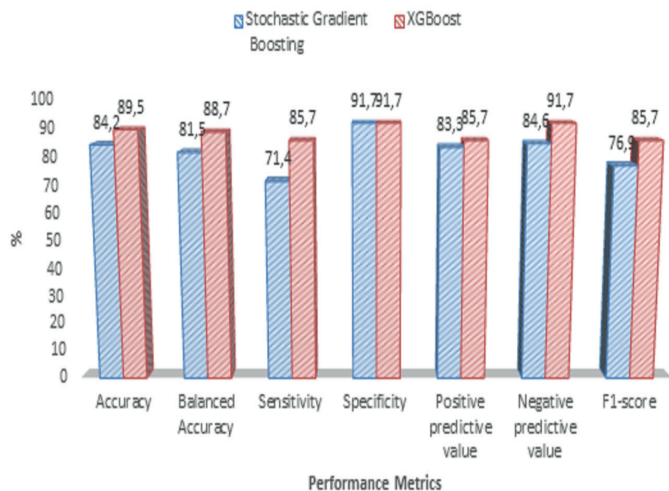
Figure 1. In the testing phase, performance metric values acquired from Stochastic Gradient Boosting and XGBoost models

When the performance metrics obtained from the XGBoost and Stochastic gradient boosting models, which are used in the modeling phase in the current study, are examined, the XGBoost model has classified the ovarian cancer data in the best way.

The variable importance values for the variables associated with the output variable obtained as a result of the XGBoost model are given in Table 4. The graph of the variable importance values calculated as a result of the XGBoost model is given in figure 2.
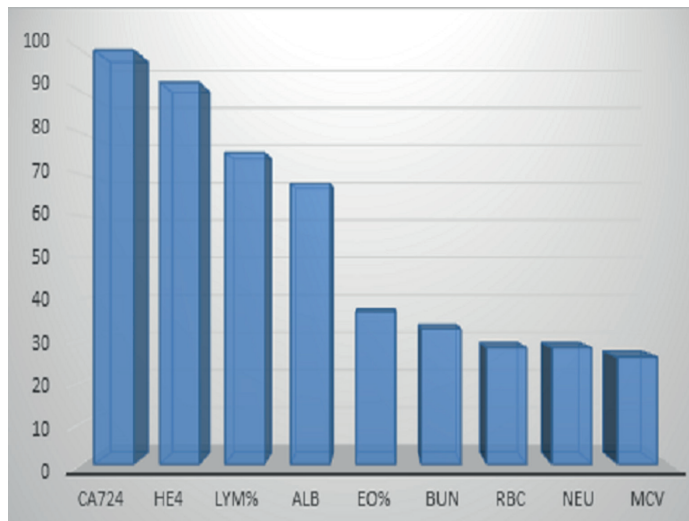
Figure 2. Variable importance values related with ovarian cancer

Table 4. The variable importance values obtained as a result of the XGBoost model

The Variables Related With Ovarian Cancer	XGBoost
CA72-4	100
HE4	92.27
LYM%	75.246
ALB	67.789
EO%	36.836
BUN	32.721
RBC	28.23
NEU	28.181
MCV	25.983

Discussion

The inability to detect the disease in its early stages and the frequency with which it recurrent make ovarian cancer the most lethal form of gynecological cancer [18,19]. Due to the lack of effective tools to detect the disease at an early stage, the disease is often diagnosed at a late stage, which can affect the overall prognosis and result in death [20]. Early-stage (I, II) ovarian cancer patients have a 5-year survival rate of over 90%, whereas late-stage (III, IV) ovarian cancer patients have a 5-year survival rate of about 20-40%. Despite breakthroughs in treatment, individuals with ovarian cancer have an overall 5-year survival rate of 45%, making it the second most fatal gynecological tumor [21-23].

When the survival rates are examined, there is a need to determine effective procedures for the diagnosis of ovarian cancer, where the survival rate is low and the diagnosis can usually be made at advanced stages. The importance of studies to be carried out in order to reveal the markers associated with the disease that can support the diagnosis in the early stages of the disease and reduce the effects of the disease with effective treatment before the prognosis progresses is increasing. Machine learning applications have become increasingly popular and applied in the diagnosis of diseases and clinical decision support systems in recent years. With machine learning techniques, which are frequently applied in the field of health, diseases detection at an early stage and revealing the factors affecting the disease are carried out [24,25]. For this reason, in the current study, the most appropriate method for classification of ovarian cancer using XGBoost and Stochastic Gradient Boosting models, which are ML methods, and the predictive factors associated with the diagnosis of the disease as a result of the classification were revealed with variable importance values.

Among the performance criteria in the test stage obtained from the XGBoost model that has the best classification result, accuracy, balanced accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and F1-score were obtained as 89.5%, 88.7%, 85.7%, 91.7%, 85.7%, 91.7%, and

85.7%, respectively. Successful results for the diagnosis of ovarian cancer, and according to the variable importance obtained as a result of the model, the variables most associated with the diagnosis were CA72-4, HE4, LYM%, ALB, EO%, BUN, RBC, NEU, and MCV, respectively.

When the variable importance results are examined, it is the variable CA72-4 that explains the target variable the most. In addition, according to the results of the statistical analysis, the CA72-4 variable differed in terms of the categories of the target variable, and it was found to be at a higher level in patients with ovarian cancer than in patients with benign ovarian tumors. In a study, it was shown that the CA72-4 value is at high levels in ovarian cancer patients [26]. In another study, it was reported that CA72-4 was positive in ovarian cancer patients [27]. The second variable that most explains the target variable according to the variable significance values is the HE4 parameter. Human Epididymis Protein 4 (HE4) is a new biomarker being studied for the diagnosis of ovarian malignant tumors. According to the results obtained in the current study, the HE4 value increased in patients with ovarian cancer. In one study, it was shown that the HE4 parameter is found to be overexpressed in ovarian tumors, particularly endometrioid ovarian cancer [28]. In another study, it was reported that HE4 increased in ovarian cancer patients [29]. When the studies for the LYM % parameter, which is another important variable, were examined, it was found that it was associated with ovarian cancer [30]. In studies, the ALB parameter has been associated with the survival of ovarian cancer patients and has been said to be a determinant of survival [31,32]. In one study, it was determined that a high NEU parameter was associated with poor survival for ovarian cancer [33]. In a meta-analysis study, 12 studies were examined and it was shown that the NEU parameter is reliable and satisfactory for predicting the prognosis of patients with ovarian cancer. And it was concluded that it is associated with survival [34].

With the machine learning models applied in this study, a prediction model has been developed to diagnose ovarian cancer. The results obtained revealed effective parameters that can diagnose ovarian cancer with high accuracy. With the parameters determined as a result of the modeling, the clinician will be able to simplify and facilitate the decision-making process for the diagnosis of ovarian cancer.

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ORIGINAL ARTICLE

Miscellaneous neuromuscular symptoms and signs in long Covid

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Abstract

We have completed the 3rd year of the Covid-19 pandemic. In the early stages of the disease, we were faced with a wide variety of symptoms and signs, including the neuromuscular system, as well as life-threatening cardiopulmonary, neurovascular and immun complications. In our study, we questioned fatigue, myalgia, arthralgia, dyspnea, headache, dizziness, neck pain, back pain, low back pain, knee-hip-foot joint pain, vascular claudication (lower extremity pain/cramp), neuropathic pain, morning stiffness, joint swelling, pernio, imbalance in walking in patients (N=111; 65 female, 29 male) aged 20-59 years, who applied to our outpatient clinic in the last 1 year and had Covid-19. The mean time after Covid-19 was 5.8 ±2.1 months. The duration of Covid-19 treatment was a minimum of 5 days and a maximum of 12 days (median=5 days). Weight loss in 14.4% (median=3.5 kg), anorexia 17.1%, myalgia 41.4% (visual analog scale, VAS=5.1±1.9 cm), arthralgia 24.3% (VAS=5.1±2 cm), fatigue 63.1%, joint swelling 1.8%, pernio sign 0.9%, morning stiffness 7.2% (median=15 min, min 5-maximum 60 min), headache 39.6%, neuropathic pain 15.3%, effort dyspnea 38.7%, 30 second chair stand test= 14.9 ±3.6, vascular claudication symptom 11.7%, neck pain 27.0%, low back pain 30.6%, back pain 36%, hip-knee-foot pain 18.0%, gait imbalance 1.8%, dizziness 18.9% were observed. While fatigue (p=0.05), headache (p=0.04), and dyspnea (p=0.021) complaints were higher in males; VAS (arthralgia) was found higher in females (p=0.026). In the post-Covid-19 period, we see many neuromuscular symptoms and signs, especially fatigue, myalgia, headache and back pain. In addition, lower extremity vascular claudication and neuropathic pain related with chronic pain should not be overlooked in these patients.

Keywords: Covid-19, neuromuscular symptoms, neuropathic pain, long covid

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, China, and spread rapidly around the world [1]. Covid-19 is an RNA virus that has a viral structural spike (S) protein that binds to the angiotensin converting enzyme 2 (ACE2) receptor in human cells. The ACE2 receptor is found in high levels in the lung epithelium, heart, kidney, pancreas, spleen, gastrointestinal tract, bladder, cornea and blood vessels, as well as in the central and peripheral nervous systems and skeletal muscle. Viral replication in human cells is followed by viral release through cell destruction. In addition, Covid-19 activates an inflammatory response that can cause a cytokine storm and consequent multi-organ damage [2].

Covid-19 can manifest in different ways, from asymptomatic clinical to mild upper respiratory tract disease symptoms to acute respiratory distress syndrome (ARDS). It is known to cause numerous extrapulmonary findings including gastrointestinal findings, liver, kidney, heart damage and acute coronary syndromes, neurological complications and skin findings. Although myalgia is common in Covid-19 infection, other

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musculoskeletal symptoms have rarely been identified early. As the number of Covid-19 patients and recoveries increases, increasing musculoskeletal complaints, neurological and rheumatic complications related to both the disease process and the post-treatment period have been reported [3,4].

Inflammation causes flu-like manifestations of the disease. When viral replication occurs, IL-6 and TNF-alpha levels increase in the blood. During viral reproduction, symptoms such as fever, weakness, cough, myalgia occur. Myalgia and fatigue, one of the most common symptoms at the beginning of the disease, occur as a result of IL-6 upregulation. Studies on myalgia in Covid-19 infection support that the symptom of myalgia is dependent on the general inflammation and cytokine response in the disease [5,6].

It is characterized by severe ischemic myalgia accompanied by physical fatigue and muscle weakness in patients in the acute period [7]. However, current data on miscellaneous symptoms and signs such as myalgia, arthralgia, fatigue, joint swelling, imbalance in walking, spinal pain, headache, pernio, neuropathic pain, dizziness etc…seen in the neuromuscular system in the long term period after Covid-19 are insufficient.

In about 10% of patients who recover after Covid-19, the symptoms may persist for a long time. Covid-19 infection negatively affects the quality of life and daily life of the person by causing many symptoms and signs in the neuromuscular system with multiple pathophysiological mechanisms (endothelial dysfunction, immune reaction, mitochondrial dysfunction, ischemia etc…) in the long term. While focusing on respiratory and cardiac problems after Covid-19, neuromuscular symptoms and signs are ignored. These symptoms and signs are also frequently seen after Covid-19 and reduce the quality of life of people. In our study, these symptoms and signs and related factors were comprehensively reported in the view of the current literature.

Material and Methods

Study design and sample

Our study was designed as cross-sectional analytical. Patients who applied to the Physical Medicine and Rehabilitation outpatient clinic and had Covid in the last 1 year (with a history of Covid-19 PCR positivity) were included in the study. Those with concomitant chronic rheumatic disease, orthopedic disorder, history of trauma, systemic disease, infection, and malignancy were excluded from the study.

Data collection

Data were recorded by the same experienced clinician through pyhsical examination and a simple questionnaire. Demographic data (age, gender) of the patients were recorded. In the questionnaire, duration after covid (months), the duration of treatment with covid (days), the presence of weight loss, the amount of weight loss (kg), anorexia, myalgia and visual analog

scale (VAS) (0- 10 cm), arthralgia and VAS (0-10 cm), fatigue, joint swelling, pernio (chillblain) findings in fingers and toes (bruising, pain, discoloration), morning stiffness and its duration (minutes), headache, neuropathic pain (assessed with PAIN DETECT), effort dyspnea, 30-second sit and stand test, vascular claudication findings such as leg cramps and pain, neck pain, low back pain, back pain, hip-knee-foot pain, gait imbalance, and dizziness were questioned.

Visual analog scale (VAS)

It is a scale used to digitize some values that cannot be measured numerically. Numbers 0-10 are written on a horizontal or vertical 100 mm long line. For the value to be measured, the person is asked to mark the point he feels and thinks. For example, for pain, a value of 0 means 'no pain' and a value of 10 means 'unbearable pain'.

Chair stand test

For this test performed to determine leg strengths; A straight-back chair with a seat height of 43.18cm (12-in) without armrests and a Casio HS-5 M stopwatch were used. The individual was allowed to sit in the middle of the chair with his back straight, feet on the ground and arms crossed in front of his chest (right hand on left shoulder, left hand on right shoulder). While the individual was in this position, he started the test with the start command and took off as fully as he could during 30 seconds. The number of full take-offs made during 30 seconds formed the score of the subject. Each subject was both shown and explained how to do the test, and the test was started after making sure that each subject had 2-3 attempts to do the test [8].

Pain detect

The PainDETECT questionnaire was first developed to detect the neuropathic component of pain in patients with low back pain. Patients with a total questionnaire score of 12 or less are considered to have no neuropathic pain component. If the total score is in the range of 13-18, the result is uncertain, but it is accepted that neuropathic component may be present, that is, possible neuropathic pain [9]. The Turkish validity and reliability study of the questionnaire was done by Alkan et al. [10].

Statistical Analysis

Statistical evaluation will be done with the Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA) program. Concerning categorical data, frequencies and percentages were applied to distinguish these values. Differences between groups were contrasted using the Chi-squared test. Numerical data will be given as ratio, mean±standart deviation (std), median (minimum/maximum). With the Kolmogorov Smirnov test and histogram analysis, it will be checked whether the data is normally distributed. According to the analysis result, appropriate parametric or nonparametric tests is used. Statistical significance level was accepted as $p < 0.05$. As a result of the power analysis, type 1 error was accepted as 0.05 and the power

of the test was 0.80, and the minimum sample size was calculated as 86 patients.

Ethics

In our study, approval was obtained from the Ministry of Health and Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Clinical Research Ethics Committee (date: 08.03.2021; protocol number: 87). The study is in compliance with Helsinki Declaration principles. A voluntary consent form was obtained from the participants.

Results

Our study included 65 women (58.6%) and 46 men (41.4%), with a mean age of 37.3±11.3 years (20-59 years), with a total of N=111 patients who had covid-19 in the last 1 year. The duration after Covid-19 was 5.8 ± 2.1 months. The duration of Covid-19 treatment was a minimum of 5 days and a maximum of 12 days (median=5 days). There was weight loss in 14.4% of the patients, with a median weight loss of 3.5 kg (2-10 kg). The prevelance of anorexia 17.1%, myalgia 41.4% (VAS=5.1±1.9 cm), arthralgia 24.3% (VAS=5.1±2 cm), fatigue 63.1%, joint swelling 1.8%, pernio sign 0.9%, morning stiffness 7.2% with median=15 minutes (min 5-maximum 60 minutes), headache 39.6%, neuropathic pain 15.3%, effort dyspnea 38.7%, 30 seconds sit and stand test= 14.9±3.6, vascular claudication symptom 11.7%, neck pain 27.0%, low back pain 30.6%, back pain 36%, hip-knee-foot pain 18.0%, gait imbalance 1.8%, and dizziness 18.9%. Descriptive data of the study are summarized in Table 1.

Table 1. Analysis of sociodemographic and descriptive data of the study

	Mean±std	Median	N/%	Minimum-maximum
Age (year)	37.3±11.3	-	111	-
Gender(female/male)			65/58.6 46/41.4	
Duration after covid-19 (months)	5.8 ±2.1	-	111	1-12
Duration of Covid-19 treatment (days)	-	5	111	5-12
Weight loss	-	-	16/14.4	
The amount of Weight (kg)	-	3.5	-	2-10
Anorexia			19/17.1	
Myalgia			46/41.4	
Myalgia VAS (0-10 cm)	5.1±1.9	-	-	-
Artralgia			27/24.3	
Arthralgia VAS (0-10 cm)	5.1±2			
Fatigue	-	-	70/63.1	
Joint swelling	-	-	2/1.8	
Pernio	-	-	1/0.9	
Morning stiffness	-	-	8/7.2	
Duration of morning stiffness (minutes)	-	15	-	5-60
Headache			44/39.6	
Neuropathic pain			17/15.3	
Effort dyspnea			43/38.7	
30-second chair stand test	14.9±3.6	-		
Vascular claudication	-	-	13/11.7	
Neck pain	-	-	30/27	
Low back pain	-	-	34/30.6	
Back pain	-	-	40/36	
Hip-knee-foot pain	-	-	20/18	
Walking imbalance	-	-	2/1.8	
Dizziness	-	-	21/18.9	

When we analyzed the whole group in terms of gender, the complaints of fatigue (p=0.05), headache (p=0.04), and effort dyspnea (p=0.021) were higher in males; VAS, arthralgia was higher in females (p=0.026) (Table 2). Other parameters were in similar distribution.

Table 2. The Comparison of the parameters according to gender (Only statistically significant parameters are indicated in the table)

	P
Fatigue	0.05*
Headache	0.04*
Effort dyspnea	0.021*
VAS (arthralgia)	0.026*

*Mann Whitney U test. p<0.05, statistically difference

Discussion

Coronavirus is a life-threatening virus that can infect humans and some animals, ranging from the common cold to serious respiratory problems in humans. Covid-19 is a virus with a high mutation ability, and the continuation of some symptoms after the disease or the emergence of other new findings in individuals who have had the disease negatively affect people both psychologically and physically. It has been observed that some symptoms persist for a while in individuals who survived the disease. While there is still no clear treatment method for acute infection, it is an important health problem to manage the symptoms and long-term complications of the disease in the post-covid-19 period of patients.

We frequently see neuromuscular symptoms and signs in the post covid period especially fatigue, myalgia, headache and back pain (in order of high frequency). Additionally neuropathic pain and vascular claudication symptoms associated with chronic pain are seen in patients in long term follow up. We think that the development of neuropathic pain is related with chronic pain; the development of vascular claudication is related to the thrombosis effect of the virus.

We also find differences in terms of gender. The complaints of fatigue, headache, and effort dyspnea were higher in males; VAS, arthralgia was higher in females. Differences in chronic pain in females vs. males are well known, and a lot of laboratory tests have demonstrated that females are more sensitive to pain than males.

When we analyzed the participants in terms of gender in our study, it was found that the complaints of fatigue, headache, dyspnea were higher in the male gender. On the other hand, arthralgia and VAS scores were higher in females. When the literature research, it was reported that post-covid fatigue and shortness of breath were more common in females [11]. In another study conducted with 1027 participants, it was found that myalgia and fatigue were more common in females [12]. In a study conducted in a tertiary hospital, it was reported that gender did not have any effect on post-covid symptoms [13]. In most of the studies conducted in the post-covid period, it was found that the female gender had more symptoms in the post-covid period than the males [14-16]. We think that the difference between the literature and our study may be due to the difference in the sample and the duration after covid.

41.4% of the participants had myalgia (VAS score 5.1±1.9), and 24.3% had arthralgia (VAS 5.1±2). Joob et al. in the study, the frequency of arthralgia was found to be over 2.5% [17]. Skyes et al. in the study, it was reported that 51.5% of the participants had post-covid myalgia [18]. In another study, myalgia was found to be between 4.5% - 36% and arthralgia was in the range of 6.0-27% [19]. Our scores were found similar to the literature.

In our study, the 3 most common musculoskeletal symptoms were fatigue in 63.1%, myalgia in 41.4% and back pain in 36%, respectively. In studies in the literature, the incidence of post-covid symptoms varies [20-26]. We think that this is due to the fact that our study consisted of not only inpatients, but also groups of patients who were hospitalized, received outpatient treatment and completed their home quarantine without any treatment, in other words, all patients with severe and mild disease.

Among the extrapulmonary symptoms associated with Covid-19, dermatological symptoms are increasingly being reported [27]. Pernio or chilblain, characterized by an acral pattern, is a localized inflammatory disease resulting from an abnormal response to cold [28]. It is characterized by a poor prognosis and is reported as an isolated cutaneous manifestation of hypercoagulable states [29]. It is thought that Covid-19 may also cause pernio by immune mechanisms as it is characterized by perivascular lymphocyte infiltration in histopathological examinations [30]. When we look at the literature, studies on pernio after covid are mostly case reports. Painful skin lesions on the hands and feet in the long term after Covid-19 should be evaluated in terms of pernio. Vascular claudication is characterized by aching pain, numbness, weakness, or fatigue in the lower extremity muscle groups. The frequency of vascular claudication in our patients was 11.7%. Vascular claudication symptoms in the lower extremities may have been caused by immobilization, lack of physical activity, and the virus itself (intramuscular microthrombosis, entodel damage, ischemia). Few publications related to Covid-19-related vascular claudication were observed in the literature [31]. The sit and stand test is a test that evaluates lower extremity muscle strength and dynamic balance. In our study, the average number of 30-second sit and stand test was 14.9±3.6.

A very common symptom of Covid-19 is pain. Since Covid-19 can often affect the peripheral or central nervous system, a number of chronic pain complications of Covid-19 are predicted to be neuropathic. A few publications were found in the literature on the relationship between Covid-19 and neuropathic pain [32,33]. Neuropathic pain refers to pain caused by nervous system pathology. Neuropathic pain reflects both peripheral and

central sensitization mechanisms. Abnormal signals originate not only from damaged axons, but also from intact nociceptors that share the innervation region of the damaged nerve [34]. We now know that chronic pain may develop due to primary damage to the central or peripheral nervous system, and that chronic pain causes neuropathic pain through sensitization [35,36]. We think that the neuropathic pain in Covid-19 patients may develop over time due to the neuroinvasiveness of the virus or other painful conditions (arthralgia, myalgia, back pain etc…) by sensitization.

The vascular endothelium provides a crucial interface between the blood compartment and tissues and is responsible for maintaining normal homeostasis. Our view of Covid-19 from the lens of endothelial disease helps us to explain the pathophysiology of a wide variety of symptoms of the disease [37]. We now know that Covid-19 causes immune response and life-threatening conditions as a result of microthrombosis and endothelial dysfunction in many vital organs. This immune reaction can trigger autoimmune diseases in the long run. In a small number of case reports, it was observed in the literature that arthritis and polyarthritis could develop in the acute / subacute period due to Covid-19 [38,39]. In our study, we detected joint swelling in 2 patients.

The limitations of the study are the patients consist of the patients who attend to Physical Medicine and Rehabilitation clinic with a complain, secondly there is no control group. Also small sample size is another limitation.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
In our study, approval was obtained from the Ministry of Health and Kahramanmaraş Sutcu Imam University, Faculty of Medicine, Clinical Research Ethics Committee (date: 08.03.2021; protocol number: 87).

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ORIGINAL ARTICLE

The investigation of dermatophyte agents in patients with dermatophytosis diagnosis

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Abstract

The aim of our study was to investigate the features and agents in patients with dermatophytosis and to evaluate the dermatophyte flora changes in our area in recent years. Patients and Methods: Patients with dermatophytosis were included in our study. The age, gender, social life area, animal contact history of the patients and the clinical types of dermatophytosis were recorded. 443 native preparation positive species were cultured and their pathogens were investigated. There were 367 cases with an age range between 1-79 years. The animal contact history was present in 23,7% and rural area living anamnesis was present in 21.2% of the species having dermatophytosis diagnosis. The ratio of clinical type distributions were determined as follows; T.pedis %41.5, T.unguium on foot+hand %29.2, T.capitis %9.9, T.inguinalis %7.2, T.corporis %6.1, T.manum %3.6, T.facialis %2.0 and T.barba %0.5. The agent could be identified in 76.5% of the species with the rates of T.rubrum 62.5%, T.mentagrophytes 16.8%, T.verrucosum 9.4%, M.canis 4.7%, E.floccosum 3.2%, T.violaceum 1.8%, T.tonsurans 0.9%, M.nanum 0.3 % and T.schonlein 0.3 %. T.rubrum was the most frequent agent causing T.pedis, T.unguium, T.inguinalis. Also T.verrucosum was the most frequent agent in T.capitis, T.corporis and T.barba and it was considered that this could be arised from our animal husbandry region. There have been differentiations in dermatophytosis and their agents today versus their status in 20 years ago in our region. Although they were decreased in comparison to the past, cases with T. capitis have remained their importance at present.

Keywords: Dermatophyte, dermatophytosis, tinea

Introduction

A significant portion of patients applying to dermatology policlinic have fungal diseases, and most of them are superficial fungal diseases. In this group of diseases, we most commonly see dermatofyte group fungi. Fungal infections on keratinized tissues such as the epidermis, hair, and nails that dermatophytes cause are called dermatophytosis [1]. Superficial fungal infections have affected more than 25% of the world's population in the last 50 years and have become one of the most common types of infections [2]. Dermatophytosis makes up about one-tenth of dermal diseases [3]. Even though epidemiologic data about dermatophytosis is limited, it is reported that dermatophytosis infections are more common than they were in the past because the number of gyms, spas, saunas, hammams and similar places have increased and the fungi's capability to change their enzyme systems and reproduction types and the ability to adapt to different conditions and spread [4].

The variety and prevalence of dermatophytosis in the world

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differs depending on the climate of the region, geographic structure, lifestyle and activity of the society [5]. Each region has its own dermatophyte flora and this flora can change over time. Things such as the development of tourism, adventures, and migration cause the spread of fungal infections, from one region to another and the settling of new species in the region. For this reason, at certain times some dermatophytes can be more dominant and gain epidemiological properties.

Significant changes have occurred in the twentieth century in the epidemiological data of dermatophytes [6]. Even in our own region, a study conducted in 1979 detected that the clinical types and species of dermatophytes have changed compared to 10-12 years ago [7]. Identifying the agent at a species level, following up on dermatophytes, determining the ecology and epidemiology and knowing the endemic areas are important for controling infections and public health. This will help contribute to treatment and actions to be taken [5]. In light of these data, we aimed to determine the recent dermatophyte flora and changes of dermatophytoses in our region.

Patients and Methods

Patients and samples

Informed consent was obtained from all patients, and the local ethical commitee approved the study protocol (Ataturk University School of Medicine ethics comitee 09.02.2007/17).

Materials for our study consisted of samples taken from 443 body parts of 367 patients diagnosed with dermatophytosis who applied to Atatürk University School of Medicine Dermatology polyclinic. Native preparations including 20% of potassium hydroxide (KOH) were prepared from the samples. After finding cases that were positive upon examination of native preparation, age, gender, clinical diagnosis (location), contact with animals, and social living spaces were recorded.

Culture methods prepared from clinical samples and diagnosis of fungi

Sabouroud Dextrose Agar (SDA), Dermatophyte Test Medium (DTM) and MDA (Mycobiyotic Dextrose Agar) and Potato Dextrose (PDA) agar medium cultivations were performed for each culture sample. To reproduce slow reproducing dermatophytes, sikloheksimidsiz SDA medium was used, too. Two mediums were used for each sample. One cultivated medium was left at room temperature (260C), and the others were incubated at 370C. Cultures were checked for fungal reproduction 2-3 times a week for at least four months. At the end of this period, cultures that showed no reproduction except dermatophytes, yeasts and other fungi were evaluated as negative. From the colony mitchels of the tubes that had complete breeding, a sample was taken with "cellophane tape" or a loop. Fungal elements were stained with Lactophenol Cotton Blue. They were examined at 400x magnification by microscope. The differentiation of species was performed by evaluating the colonies macroscopically and microscopically. To distinguish T. rubrum and T. mentagrophytes, hair perforation test was used.

Data were entered to SPSS 11.0 statistical program and evaluated with the chi-square test. Values that are $p<0.05$ were accepted as statistically significant.

Results

Our study included 367 patients diagnosed with dermatophystosis and culture and evaluation results of 443 dermatophysitosis diagnosed samples from different sites. The ages of the patients were between 1-79 years (36.67$\pm$ 12.45 mean $\pm$ standard deviation; SD). 248 patients were males (67.57%) and 119 (32.43%) were females. In 340 samples (76.5%), breeding of the cultures was obtained. 87 patients were (23.7%) from rural areas, 280 patients (76.7%) were from urban areas. 98 (26.7%) patients had history of contact with animals, and 269 (73.3%) patients had no history of contact with animals. Demographic data, history of contact with animals, living spaces and reproduction rates of the samples in the cultures are given in Table 1.

Table 1. Demographic data, history of contact with animal, living spaces and culture medium positivity of the samples

	n	%
Patients	367	
Samples	443	
Dermatophystosis In a single site/ In multiple sites	296 /71	80/ 20
Gender Female/ Male	119/ 248	32.4/ 67.6
Culture medium positivity of samples + / -	339/ 104	76.5/ 23.5
Animal contact Yes/ No	98/ 269	26.3/ 73.3
Living spaces Rural/ Urban	87/ 280	23.7/ 76.3

9 different dermatophysitoses were detected in our study. Dermatophysitoses detected clinically, factors that can be identified and their distributions are demonstrated in Table 2.

As the 339 dermatophytes total obtained from the culture results were evaluated, 311 (91.8%) of them were Trichophyton type, 17 (5%) were Mycrosporum type and 11 (3.2%) of them were determined to be Epidermophyton type. 6 species were identified as belonging to the Trichophyton type, 2 species belong to the Microsporum type, and one species belongs to the Epidermophyton type. T. rubrum was the most commonly identified agent among the dermatophytes at a rate of (62.5%). T. mentagrophytes (16.8%) was second, and T. verrucosum was third (9.4%). Distributions of the detected dermatophytes are demonstrated in Table 3.

Table 2. Dermatophytoses detected clinically, dermatophyt that can be identified and their distributions

Dermatophysitoses	Number of cases/ %	Number of cases with dermatophyt identification	Dermatophyt	number/ %
T. pedis	184/ 41.5	152	T. rubrum	116/ 76.3
			T.mentagrophytes	26/ 17.1
			M. canis	4/ 2.6
			E. floccosum	3/ 2.0
			T. violaceum	2/ 1.3
			T. verrucosum	1/0.7
T. ungium-foot	115/ 26.0	72	T. rubrum	59 /81.9
			T.mentagrophytes	11/ 15.3
			T. violaceum	2/ 2.8
T. ungium- hand	14/ 3.2	6	T. rubrum	5 /83.3
			T.mentagrophytes	1/ 16.7
T. capitis	44/ 9.9	36	T. verrucosum	15/ 41.6
			T. mentagrophytes	6/ 16.6
			M. canis	5/ 13.9
			T. rubrum	4/ 11.1
			T. tonsurans	2/ 5.6
			T. violaceum	2/ 5.6
			T. schonlein	1/ 2.8
			M. nanum	1 /2.8
T. inguinalis	32/ 7.1	27	T. rubrum	13/ 48.1
			E. floccosum	8/ 29.6
			T.mentagrophytes	5/ 18.5
			M. canis	1/ 3.7
T. corporis	27/ 6.1	25	T. verrucosum	13/ 52
			T. rubrum	6/ 24
			M. canis	4/ 16
			T.mentagrophytes	1/ 4
			T. tonsurans	1/ 4
T. manum	16/ 3.6	10	T.mentagrophytes	5 /50
			T. rubrum	4/ 40
			M. canis	1/ 10
T. facialis	9 /2.0	9	T. rubrum	5/ 55.5
			T.mentagrophytes	2/ 22.2
			M. canis	1/ 11.1
			T. verrucosum	1/11.1
T. barba	2 / 0.005	2	T. verrucosum	2

Table 3. Distributions of the detected dermatophytes

Dermatophytes	number	%
T. rubrum	212	62.5
T. mentagrophytes	57	16.8
T. verrucosum	32	9.4
T. violaceum	6	1.8
T. tonsurans	3	0.9
T. schonlein	1	0.3
M. canis	16	4.7
M. nanum	1	0.3
E. floccosum	11	3.2
Total	**339**	**100**

In our study, while dermatophysitosis was detected in a single site in 296 patients, 71 patients dermatophysitosis were detected in multiple sites. Distributions of these dermatophysitosis are demonstrated in Table 4.

Table 4. Distributions of dermatophysitosis that were detected in multiple sites in 71 patients

Dermatophysitoses	n	%
T. pedis+ T. unguium (hand)	42	59.2
T. pedis+ T. ingiunalis	8	11.3
T. pedis+ T. unguium (foot)+ T. unguium (hand)	4	5.6
T. unguium (foot)+ T. unguium (hand)	3	4.2
T. unguium (foot)+ T. ingiunalis	3	4.2
T. pedis+ T. manum	3	4.2
T. capitis+ T corporis	2	2.8
T. unguium (foot)+ T. manum	2	2.8
T. capitis+ T. facialis	1	1.4
T. manum+ T. facialis	1	1.4
T. unguium (foot)+ T. Facialis	1	1.4
T. pedis+ T. ingiunalis+ T. corporis	1	1.4
Total number of cases	**71**	**100**

History of contact with animals existed in 100% of the T.barba cases, 81.8% of the T.capitis cases, 77.8% of T.corporis cases and 66.7% of T. Facialis cases. All of the T. barba cases, 84.1% of T. capitis cases, and 67% of T. facialis cases were patients from rural areas. In the distribution of agents, T. verrucosum (93.8%), M. canis (87.5%) and T. violaceum (66.7 %) were forefront in patients from rural areas.

Discussion

Each region has its own dermatophyte flora and this flora can vary epidemiologically in time. In our study, we tried to determine recent dermatophyte flora in our region and changes of dermatophysitoses.

As the demographic data of our study were evaluated, we observed the female/male ratio to be about ½. Simlarly, in studies conducted in our country, the number of male patients was found to be higher than the number of female patients, and this ratio was found to vary in range from ½ to 1/6 in different studies [8-10]. The reason there are more male patients with dermatophysitosis is thought to be that they are in more contact with the external environment, and they meet more often with common contagious agents [11]. Also the ages of our patients were between 1-79 years in accordance with the knowledge that dermatophytosis can be seen at any age [12].

In our study, nine different dermatophysitosis were detected in 443 samples. Among these, the most common clinical state was Tinea pedis with an occurance of 41.5%. Parallel to our study, studies conducted in different regions of our country reported T. pedis as the most frequent clinical state. The close rates suggest that regional factors do not primarily affect the incidence of T. pedis [8, 9, 12-14]. In our study the dermatophysitosis that cause T. pedis were identified as T. rubrum, T. mentagrophytes, M. Canis, E. Floccosum, T.violaceum and T. verrucosum with decreasing frequency. Recently, both in our country and in other countries, the most common agents for T. pedis have been reported as T. rubrum, T. mentagrophyes and E. floccosum, which are antrophophilic species [6, 15]. As we evaluated studies conducted in our region, in the 1980s, M. canis was the dominating agent in T. pedis. T. mentagrophytes passed to the forefront in the 1990s and T. rubrum in the beginning of the 2000s [1, 16-18]. We determined that the frequency of T. rubrum increased compared to 8 years ago. M. canis was found at a lower rate than in the past in our study [16, 17]. Also in T. pedis cases, E. Floccosum, T.violaceum and T. verrucosum were detected as rare agents. Our results were compatible with the E. Floccosum rates in the study of Uslu in the recent past, and the rate of E. Floccosum has decreased when compared to the older study of Ak [16, 18]. When all the data are taken into consideration, there have been epidemiologic changes in T. pedis agents in our region.

As we compare T. pedis agents in recent studies conducted in our country, the most common agents have been detected as T. rubrum and T. Mentagrophytes similar to our results [8, 13,

19]. In our study, we determined that M. Canis, E. Floccosum, T.violaceum and T. Verrucosum are also seen as less common agents. However, in our region we did not detect M. audouinii, T. tonsurans and M. gypseum as agents of T. pedis. The observation of T. rubrum as the most common agent and T. mentagrophytes as a second agent is a change parallel within our country and across the world.

Similar to our study, numerous data have been obtained from other studies conducted in our country suggesting that T. pedis followed by T. unguium [8, 13, 19]. In other words, T. ungium is commonly seen in patients with T. pedis [11]. T. ungium on the hand is rarer than the foot. Since it's not given as a separate entity in most of the studies, it does not give us a chance to discuss in detail. In our study, the most common three agents in T. Ungium were detected as T. rubrum, T. mentagrophytes and T.violaceum. The international data for T. Unguium report that, T. rubrum was seen with higher incidences, T. mentagrophyes was the second most common agent and E. floccosum can be very rarely seen [6, 13, 15, 18]. In terms of the first two agents, it can be concluded that there wasn't any significant change compared to the past. Also we detected T. violaceum sporadically in our study. This is compatible with classical knowledge that it is a rare agent [20].

In our study, we found that T. capitis was the most common dermatophysitosis in childhood. T. capitis was seen in lower socioeconomic level societies, and zoophilic factors play an important role in this infection [6]. Our region has relatively low socio-economic conditions. 23.7% of our patients are from rural areas and a history of contact with animals was reported in 81% of patients with T. capitis. Even though we identified T. capitis as the third most frequent dermatophysitosis in our study, it was the most frequent one in the past years [7, 17,18]. Epidemiologic studies of dermatophysitosis support that the current change may be parallel to the changes in our country and region [6, 15, 21]. Similar to the older data of our region, T. capitis profunda (kerion selsi) has emerged as the most common type of T.capitis in our region [17]. A total of seven dermatophytes detected in T. capitis in our study; T. verrucosum, T. mentagrophytes, M. canis, T. rubrum, T. tonsurans, T. violaceum, T. schonlein and M. nanum. Zoophilic species were dominant in our agents. Except M. nanum isolated from only one case in our study, we observed that all these agents were also detected in previous studies in our region [17, 18]. M. Nanum was very rarely reported in studies conducted in our country [12, 13]. In our study, T. verrucosum was the main agent for T. capitis and a significant portion of patients had a history of animal contact. Parallel to our study, the most common agent in T. capitis cases was T. violaceum in Southern East Anatolia and Cukurova and T. verrucosum in Middle Anatolia and Eastern Anatolia [15]. In recent studies conducted in the Eastern Anatolia region, among the T. capitis agents, T. rubrum was reported to be approximately between 7%-23%, and the percentage of 11% in our study was found compatible with these data [18, 22]. In past studies conducted in our region, T. capitis favosa was commonly seen and T.

schonlein was detected as the first or second agent [10, 17, 23]. However, Ergenekon emphasized, even in his 1976 study, that T. capitis favosa decreased when compared to previous years [23]. In our study, T. capitis favosa was detected in only one case, and T. schonlein was cultivated in the culture. From this point, we can state that T. capitis favoza has decreased in our region and is a rare clinic type. The most recent epidemiologic studies report that T. capitis favosa and T. schonlein as agents are gradually decreasing [6]. One of the biggest reasons for this may be the socioeconomic developments in our country and region compared to 20-30 years ago. Also, we can state that the flora of T. capitis in our region has different properties and T. Capitis had epidemiologic changes in recent years. Because the characteristics of our region include working with livestock, we determined that the effects of zoophilic types are on going. While T. schonlein was once the most common in T. capitis cases, recently it became a more rare type and T. verrucosum became the most common type. Determinations of T. rubrum and M. nanum, which were not identified before, showed us that we meet with different species over time. Agents of T. capitis have changed compared to 20-30 years ago, and these changes may be the result of the development of social conditions.

Seebacher et al have mentioned that T. pedis, T. unguium and T. capitis are three epidemiologic problems that cannot be solved until recent day. While T. pedis was in first place in central and northern Europe, in southern Europe and particularly in Islamic countries, T. capitis and zoophilic types were in the forefront [6]. Our study seems to be compatible with this data from the aspect that our country is geographically settled between east and west, the existence of T. Pedis and T. unguium as the most common, and the increase of T. Capitis, particularly in the east.

Another clinical state we determined was T. Inguinalis. In our study, we made the differential diagnosis by using wood light and included only the positive native preparation samples. Thus, we only included the patients whoose clinical and laboratory findings were compatible. This method can explain the lower numbers of T. inguinalis compared to the studies conducted with sample numbers depending on preliminary diagnosis. T.inguinalis, which was determined to be the third agent in studies by Uslu and Aktaş conducted in our region, was determined as the fourth agent in our study [18, 24]. In our study, the agents in T. inguinalis cases were determined as T. rubrum, E. floccosum, T. mentagrophytes and M. canis, respectively. Generally, the most common agents in T. inguinalis cases were reported as E. floccosum, T. rubrum and T.mentagrophytes [11, 20]. When we reviewed recent studies in our country, there were studies that were determined E. Floccosum as the most common, different from our study, and in many studies, similar to our study, T. rubrum was seen as the most common agent in T. Inguinalis [8-10, 12-14, 19]. T. inguinalis occurs with contaminated properties, rarely with direct contact, and with autoinoculation when there is a dermatophysitosis in another site of the body. When transmission is by autoinoculation, the agent is commonly T. rubrum. In our

study, in 12 of 27 cases in which we produced the agent, there was dermatophytosis in another region with T. inguinalis. From this point, our rate of T. rubrum and producing T. rubrum as the first and E. floccosum as the second agent seem compatible with classical knowledge [9]. When we reviewed previous studies in our region, the first agent was seen as T. rubrum, parallel to our study [1, 18]. Different from these studies, we determined a few cases of M. canis in our study. Fındık et al determined the agent of M.canis in T. inguinalis, similar to our study. İnci et al mentioned that T.inguinalis cases due to M. canis should not be surprising [25, 26].

We determined T. Corporis as the fifth dermatophysitosis in our study. The rates in our study are close to the rates of previous studies in our country and region [7-9, 12, 14, 18,19,24]. One of the reasons we found T. corporis lower in ranking is that we did not include T. facialis to T. corporis cases methodologically, and our cases consisted of positive native preparation samples, from the cases in which differential diagnosis was made and were clinically diagnosed as dermathophysitosis. In our study, we detected the agents of T. Corporis according to frequency, respectively, as T. Verrucosum, T. Rubrum, M. Canis, T.mentagrophytes and T. tonsurans. Generally, it is reported that mostly zoophilic and geophilic agents are detected in T.corporis, autoinoculation can develop mainly due to T. rubrum, and T. mentagrophyes and rarely E. floccosum can be determined [11]. When T. corporis is seen in childhood, mostly zoophilic species are found as agents [20]. In our study, more than half of the T. corporis cases were children (0-15 years). This was compatible with the detection of T.verrucosum in our study, which is the most common zoophilic agent. In studies by Arpalı and Çakıroğlu, which are the previous data from our region, we see that zoophilic agents were determined in children, similar to our data [17, 27]. However, we can mention that even M. canis, dominant in those years, still exists, but yet isn't the dominant type today. Recently, we determined that M. canis was replaced by T. verrucosum. The reason that zoophilic agents were not detected in other studies in our region could be because there weren't pediatric patients or the number of child cases was lower [1, 18]. The second most common agent we detected in T. Corporis cases was T. rubrum. Seebacher et al reported that the most common agent in T. corporis cases around the world is T. rubrum [6]. Similarly, the most common agent in T. corporis in our country is reported to be T. Rubrum [8, 9,13,19]. In our region, both Özdemir et al and Uslu et al have determined it as the first agent [1, 18]. Determination of T. rubrum as the second agent, in our study, states that T. rubrum protects its importance in T. corporis in our region. T. corporis is the second agent among childhood cases, and as the zoophilic properties are forefront, support that age groups and regional characteristics (livestock) are important for T.corporis.

The frequency and incidence of T. Manum in our study is similar to previous data in our region and other regions of our country [12, 18, 24]. In our study, of the 10 T. manum cases,

T.mentagrophytes were detected in 5 cases, T. rubrum was detected in 4 cases, and M. canis was detected in one case. 3 cases were T. pedis et manum cases. In 2 cases, T. Unguium and T. manum were found together. In several domestic and foreign references, T. rubrum is reported as the most common agent in T. manum cases and is mentioned that this was followed by T. mentagrophytes [11, 20]. The low number of T.manum cases, and the agents we determined in our study seem to be compatible with previous data from our region and similar environments [8, 18,27]. T. rubrum, which was not detected 30 years ago, could be increasing gradually in T. manum cases.

Tinea facialis and T. Barba, rare among dermatophyitosis, are not detected in many studies clinically in our country and detected as the least common in our study [9, 11,19,25]. T. facialis was detected in 9 patients in our study. In various studies, zoophilic factors are indicated to be forefront in T. facialis cases [11]. Besides zoophilic factors, it is reported that Trichophyton species are common and can occur as a result of autoinoculation if there is dermatophysitosis in any other site [28]. The numbers we detected in our study are compatible with mentioned resources for the type of agent and frequency. Even though zoophilic factors are dominant in T. facialis in our region, it being the most frequent agent of T. rubrum is a condition that should be considered. T. Barba was detected in two cases in our study. We reproduced T. Verrucosum as the agent in both cases. It is more commonly seen in farmers, veterinarians, and in people with similar jobs that engage bovine animals. The agent is commonly reported to be T. verrucosum, followed by T. mentagrophytes [9]. Since we are in a livestock region and in light of the above knowledge, to determine T. verrucosum as the agent in both cases was an expected result. T.manum, T. facialis, and T. barba were isolated less in our study; our results seem to be compatible with the previous studies for frequency and type of agent. However, since the number of cases was insufficient in previous studies and our study, it was not possible to discuss the data in detail.

Of the total 339 dermatophyte species obtained from the culture results in our study, 91.8% belong to the Trichophyton species, 5% belong to the Microsporum species and 3.2% belong to the Epidermophyton species. In this study, the overall frequency of dermatophytes was determined as T. rubrum, T. mentagrophyte, T. verrucosum, M. Canis, E. Floccosum, T. violaceum, T. tonsurans, M. Nanum and T. Schonlein, respectively. When we reviewed studies conducted in our region, Kot et al reported this sorting in 1979 as M.canis, T. schonlein, T. violaceum, T. mentagrophytes and T. verrucosum [7]. Parallel to clinic types, the ranking of these agents are not compatible with our study and can be explained by the epidemiological change in our region since 1979. This epidemiologic change is parallel to socioeconomic developments in our country and region. T. rubrum growing in dominance among all species, similar to other studies in our country, is an important factor [8, 10, 13, 14, 21, 25]. In studies conducted in more recent years in our region, Aktaş et al reported the order of dermatophyte frequency as T.

rubrum, T. mentagrophytes, T. violaceum, T. verrucosum and M. canis. Uslu reviewed the later data and reported a distribution of 138 agents. The isolated the order of frequency as T. rubrum, T. mentagrophytes, T. schonleinii, T. violaceum, T. tonsurans, M. canis and E. floccosum [18, 24]. In these studies, T. rubrum was isolated as the most common agent and was followed by T. mentagrophytes. Our study is compatible with both studies, conducted 10 years ago, for the first two agents. We suggest that the reason we isolated more agents than the other studies is because of our high number of cases (339).

In studies conducted in our country, as we reviewed the data close to our region geographically, T. violaceumis was more common in southeast Anatolia region than our region, and T. verrucosum is more common in our region [29]. As we compared our study with studies in the Mediterranean region, the detection of T. rubrum as the most common agent in both our region and Mediterranean region studies seem to be compatible [19]. However, T. violaceum is generally more common in the Adana and Mersin region than what we detected in our study (1.8%). The ratio of T. verrucosum was 9.4% in our study and was significantly higher than the rate in the Adana and Mersin region. T. verrucosum is a zoophilic agent and particularly of bovine origin [11]. The source of livelihood is our region is farming. These reasons support the higher rates of T. verrucosum in our region. As we considered the studies conducted in the Middle Anatolia region, we see T.rubrum and T. Mentagrophytes as the first two agents [30]. This finding is supported by the other studies of this region [12]. Again, the results of the study from this region conducted in Konya by Fındık et al- the findings, number of samples that have reproduction, frequency of the dermatophysitosis, isolated agents, and number of species are similar with our study [25]. However, the detection of T. verrucosum at 9.4% in our study suggested that it originated from livestock in our region. Generally, our study seems to be compatible with studies conducted in the Middle Anatolian Region in which T. rubrumis was the more common agent followed by T. mentagrophytes. As we reviewed the studies conducted in the Black Sea region, the most common agent is T. rubrum, as in our study [8-10]. In the studies conducted in the Black Sea region, E. floccosum is more common than in ours and many other regions, and not finding M. canis is noteworthy. The lower rate of T. inguinalis cases in our study and higher rates in the Black Sea region can be explained by the high rates of E. floccosum. Besides, climate characteristics of the Black Sea region can be a factor. Studies from the Aegean Region were similar with our region's first ranking agents; however, T. rubrum was more common in the Aegean region, and T. verrucosum was detected to be more common in our region than the Aegean region [31, 32]. As we reviewed literature for the Marmara region, even though we didn't find recent or detailed data, T. rubrum and T. mentagrophytes were the most common, as in our study [32, 33].

In foreign studies, T. rubrum is epidemiologically the most common agent recently, except in underdeveloped regions [2, 15, 21]. In the United States of America, T. rubrum is reported as the most common agent except T. capitis. T. capitis is the most common agent among dermatophysitosis agents; its incidence is gradually increasing and T. tonsurans is reported as its most common agent [35]. When we look at Europe, T. rubrum was reported at 1% among the dermatophysitosis agents in Germany in 1926. By gradually increasing over the years, it reached to 82.6% in 1993 [6]. One reason partially explaining this increase is that the clinical types of T. pedis and T. unguium have become the most common clinical types. Through the recent use of systemic antifungal agents, T. schoenlein and M. audouinii seem to be eradicated in Germany. M. canis is still observed at a rate of 3.1% in a study conducted in Berlin in 1993 [6]. T.rubrum is the most common agent, and T. pedis and T. unguium are presented as the most common clinical types in central Europe and North Europe, except Poland. In Croatia, Slovenia and Italy, the Mediterranean countries of Europe, M. canis major presents as a dermatophyte. This is a strong example of the effect of climate characteristics epidemiologically [6]. In Africa, the situation is totally different from Europe. Both socioeconomic conditions and climate are thought to be responsible for this situation. In Africa, the group most affected by dermatophytes is children. T. capitis is very common. Even though it changes according to geographical conditions, M. audouinii is one the most common agents in Africa. T. violaceum and T. soudanense are also two common agents. T. pedis and onycomycosis are rarely observed in the rural areas of Africa, and the low incidence of diabetes and walking with bare feet are suggested as the reasons for this state. Rare incidences of T. rubrum and T. mentagrophytes have been linked to the lower numbers of T. pedis and onycomycosis cases [2]. In Asia, similar to Europe, T. rubrum and T.mentagrophytes are stated as the two most common agents, respectively, and T. pedis and T. unguium cases are stated as the most common two clinical types. However, conversely to Europe, in Asia the clinical types following these are T. capitis and T. corporis, and the most common agent is stated as T. violaceum [2]. In our study, the most common two clinical types are T. pedis and T. ungium, respectively, and the most common two agents are T. rubrum and T. mentagrophyte. This is compatible with both Europe and Asia from this aspect. In Europe, M. canis is the most common agent in T. capitis cases. In the western part of our country, the Aegean region, M. canis is identified as the most common agent in T. capitis. In the Southeastern Anatolian region, T. violaceum, and in the Eastern Anatolian region, T. verrucosum, are the prominent agents [21]. Like the results from the Asian continent, in our eastern neighbour, Iran, T. capitis is one of the most commonly seen clinical types, and the most common agents are T. violaceum and T. verrucosum [36, 37]. In our study, conducted in our region (on the Asian continent and in the eastern part of our country), we found T. capitis as the third clinical type and the most common agent in this clinical type was detected as T. verrucosum, similar to the study in Iran.

In our study, in about twenty percent of the patients dermatophysitosis was detected in more than one site. The

rate of having dermatophysitosis in more than one site varies between 17-37% in various studies, and, in these studies, T.pedis and T. unguium are reported as the most common comorbid dermatophysitosis, as in our study [8, 9, 14]. The rate of T. pedis+T. unguium cases in more than one dermatophysitosis patient were reported as 78.26% by Metin et al (8), 57.8% by Saniç et al (9) and 67.3% by Baysal et al [14]. Similarly, in our study, we determined that, of the cases having dermatophysitosis in more than one site, 59.2% were T. pedis+T. unguium, and this was detected as the most common comorbidity. The second most frequent comorbidity we detected was T. pedis+T. inguinalis with a rate of 11.2%. All of the three mentioned studies this comorbidity was observed in our study as the most frequent second comorbidity with a various rate between 6.52%-29.2% [8, 9, 14].

With lower and close frequencies, we detected comorbidities of T. inguinalis+T. unguium, T.pedis+T. manum, and T.unguium hand+T. unguium foot cases. From this aspect, our study was compatible with previous study data [8, 9, 14, 20].

In our study, of the 443 dermatophysitosis diagnoses, 23.7% had history of animal contact. These rates were marked significantly by 100% for T.barba, 81.8% for T.capitis, 77.8% for T.corporis and with 66.7% for T. facialis.

History of animal contact was remarkable, in 96.9% cases reproducing T. verrucosum, 87.5% cases reproducing M. canis, 66.7% cases reproducing T. violaceum, and 1 case reproducing M.nanum. Zoophilic dermatophytes are infections originating from mammals and poultry, mostly cat, dog, bovine, horse and rodents, transmitted from animals to humans and commonly seen in humans [15]. In the studies conducted, it was reported that the epidemiology of zoophilic agents may change, for instance in England, with industrial development and less contact with animals, cases occurring by T. verrucosum decreased [38]. As for zoophilic agents, in our study, we determined four species- T. verrucosum, M. canis, M. nanum, and T. mentagrophytes. The characteristic that our region deals mainly in livestock supported our findings. Particularly, in our cattle-breeding region, T. verrucosum was forefront among agents. In our study 21.2% of the cases were from rural areas, and 78.8% were from urban areas. All of the T. barba cases, 84.1% of T. capitis cases and 67% of T. facialis cases were in patients from rural areas. In patients from rural areas, T. verrucosum, M. Canis and T. violaceum were predominant as the agent. In our study, social living space, contact with animals, and zoophilic agents supported our findings.

Conclusion

Comparing previous studies, it was determined that the ethiologic and epidemiologic characteristics of dermatophysiyoses have changed in the last 8-10 years, and they have exhibited prominent differences compared to 20-30 years ago. Also, some differences in our region compared to the other regions of our country were determined. All these differences suggest that these changes may be related to lifestyles of the society, livelihood sources,

and social conditions. We hope that the results of our study can shed even a small amount of light on the measures to be taken by public health providers, preventive and curative medical services, and further studies necessary. We suggest that, in order to obtain better data, multidisciplinary and more comphrehensive studies are needed.

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ORIGINAL ARTICLE

The effect of psychodrama on anxiety levels and stress coping styles in academicians

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Abstract

This study aimed to investigate the effects of psychodrama on stress and coping with stress in people working as medical doctors and nurses academicians. This study confirmed whether psychodrama could be effective on stress and coping mechanisms for nurses and medical doctors academicians. Individuals were evaluated by the state and continuity anxiety scale, the stress coping style scale, the Hamilton anxiety scale, and the Hamilton depression scale. The Statistical Program for Social Sciences-SPSS for Windows, version 22.0, was used for statistical analysis (SPSS Inc., Chicago, IL, USA).Data are given as mean (standard deviation) and number (percentage). To test the normal distribution compliance of the data, the Kolmogorov Smirnov test, T test for independent groups in normally distributed data with two groups, ANOVA test for data with more than two groups with normal distribution, and Mann Whitney U test for data with normal distribution was used. A statistically significant difference was found in the pre-test and post-test average scores of the applied scales. Practice Implications It is recommended that this study be performed with a more homogeneous patient group. It was found that psychodrama significantly affected stress and stress coping styles in individuals who work as academicians. It was found that psychodrama significantly affected stress and stress-coping styles in individuals. The most important limitation of our study was that the participants were in the same academic community.

Keywords: Psychodrama, stress, coping stres, academician

Introduction

Although stress has a negative connotation, it is a human's adaptation response to their environment. People react to a threat in their environment by creating stress. People are exposed to stressful life events at home and work in daily life. People develop various strategies to cope with these stressful life events. Coping with stress is considered an ever-changing, cognitive, and behavioral effort to adapt to reduce the negative effects of stress [1]. The coping styles with stress are closely related to an individual's personality traits and capacity to use their possessions. Work-life is one of the environments where stressful events occur frequently. Different stressful situations may arise depending on the nature of the work done.

The academic profession is among the occupational groups with a high-stress intensity. Time pressures, long working hours, unrealistic delivery dates, lack of appropriate rest breaks, constant attention to work, making high-level decisions, and complex information may cause individuals to face stress Economic responsibilities are as important as academic responsibilities. The fact that people have to work harder to fulfil their economic responsibilities can lead to frustration and depression in employees. Irregular working hours, overtime, and

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the shift system expose employees to stress to generate more economic income [2]. All these stress sources cause the physical and mental well-being of academicians to deteriorate.

Psychotherapeutic interventions are methods known to positively affect individuals' quality of life and cope with stress [3,4]. Group therapy is also among these methods. Group psychotherapy is performed with 8-15 participants in general, where the group's principles and framework are defined and agreed upon with the participants, and the participants' consent is obtained. For healing factors to be functionally activated in group practices, an atmosphere of trust is provided by fulfilling/ensuring the fulfillment of the participants' and the manager's responsibilities, such as confidentiality, attendance, and constructive feedback, which are clarified and detailed in the agreed principles [5,6,7].

Psychodrama is an action-based group psychotherapy method that is performed by fulfilling the conditions required by the action. It is aimed to improve the role repertoire of the participants by developing the role repertoire, working on possible solutions, realizing personal and interpersonal problems, viewing themselves from the outside with the mirror technique, trying and rehearsing the new behaviors they want to implement, and gaining different and new perspectives. In-group activities allow members to see the results of different behaviors and problem-solving methods [8,9].

This study aimed to motivate the academic staff through groups to realize the negative effects of the stress they experience in their academic life on their mental health and to develop appropriate coping strategies to cope with these stressful life events.

Material and Methods

Study design and study sample

People who are working as academic staff in the field of health at a University, needing help due to problems in their field of study, not using drugs, without any psychiatric diagnosis according to DSM-5 (Structural Clinical Interview for DSM-5, SCID), who presented for psychodrama and were willing to join the group, were included in this study. The psychodrama group consisted of 12 people, four men and eight women. Participants were interviewed individually before the study, the patients were informed about the procedure (can't the participant pattern be more accurate), and their written consent was obtained. The group members who agreed to participate in the study completed the following scales before the psychotherapy process and three days after the 19 sessions.

Data collection tool

State-Trait Anxiety Scale (STAI-I and STAI-II) was developed by Spielberger et al. In 1983 [10]. Its adaptation to Turkish and its validity and reliability study were conducted by Oner and Le Compte [11]. Each of the subscales contains 20 items. Answers are scored between 1 and 4, and the total score obtained from each subscale ranges from 20 to 80. A high score indicates a high anxiety level.

The Beck Depression Scale (BDI) is a 21-item scale used by Beck and Steer to measure depressive symptoms [12]. Each item shows a depressive symptom. As a self-report tool, the BDI is a common tool used to measure depression. The total score ranges from 0 to 63, with higher scores indicating more severe depression. The internal consistency reliability coefficient in the validity and reliability study is 0.84 [13].

Beck Anxiety Scale (BAI) is a self-reporting scale that determines the frequency of anxiety symptoms experienced by individuals. It is a scale of 21 items, scored between 0 and 3. The high scores obtained from the scale indicate the severity of the anxiety experienced by the individual. Its validity and reliability study in our country was conducted in 1993 by Ulusoy et al. [14].

The Styles of Coping with Stress Scale was created by Folkman and Lazarus in 1980, based on the Ways of Coping Inventory, and is a scale used to determine the styles the individual uses to cope with stress [15]. The scale was adapted to Turkish in 1995 by Sahin and Durak [1]. The internal consistency coefficient calculated for the subscales in the reliability study of the Turkish adaptation of the SSTC is 0.80 for the self-confident approach subtest, 0.68 for the optimistic approach subtest, 0.73 for the helpless approach subtest, 0.70 for the submissive approach subtest and 0.47 for the social support subtest [1]. According to Folkman and Lazarus (1980), there are two basic styles of coping with stress: "Problem-Focused / Active Coping Style" and "Emotion-Oriented / Passive Coping Style"[15]. The Turkish adaptation of the 4-point Likert type scale consists of 30 items and 5 subscales. These subscales are the "self-confident approach" (items 8, 10, 14, 16, 20, 23 and 26), "optimistic approach" (items 2, 4, 6, 12 and 18), "desperate approach" (3, 7, 11, 19, 22, 25, 27 and 28), "submissive approach" (Articles 5, 13, 15, 17, 21 and 24) and "seeking social support" (1, 9, Articles 29 and 30) [1]. Scores for each subscale are calculated separately.

Psychodrama Group Psychotherapy Practice

Group applications were carried out in a hall suitable for psychodrama group practice at University, with a total of 19 meetings, for 4 hours a per session, twice a week. A therapist and co-therapist led each session, and each session was supervised. Although the psychodrama sessions progress spontaneously considering the existing needs of the members, the group's therapist was prepared in advance in accordance with the stages of the group. All sessions followed the warm-up, action, and sharing phases.

Sessions

The first session was aimed at determining the common goals and principles of the group. For this, the previously prepared group contract items were played with psychodramatic methods. It aimed at the group members to take responsibility for the group, adopt the principles, and create a safe environment. Some members left the group in the second session. Although the purpose and method were explained beforehand, it can be thought

that individual and group goals did not match and/or did not find the method suitable for them when they saw the application in the first session [16]. The rest of the group was asked to use play dough to express their emotions. It was thought that play dough would allow people to regress in control and make it easier to express their emotions. It was assumed that because the members worked as academicians at the same university, their relationships in the academic environment or their academic life could be reflected in their relationships in the group environment or their academic life within the group. For this reason, the game of removing hats (representing workplace relationships) was played. A meeting game was played to start a new group relationship for the group members who left their academic and social relations outside of the group and to encounter these new roles.

In the third session, the tree and wind game was played to support the trust relationship of the members of the group. It was aimed to ensure that the participants, who were in the roles of tree and wind after they became pairs, were to get to know each other with these roles and to provide trust. In the last game, the group members who went for a walk in the forest were made to express themselves and their processes by selecting living or non-living beings in the forest.

In the fourth session, the game of getting to know each other and taking off the hats was played as new members joined the group. A game was organized for the group members to choose their band names with their inner music. This game aimed to ensure that the members leave their academic and social identities outside of the group and continue with their new roles.

With the mirror game played in the fifth session, the members were asked to evaluate themselves from the eyes of others. This game also allowed them to meet again in the group. Afterward, a hello party game was played to ensure group cohesion. Members were asked to join this party as fairy-tale heroes. Thus, it was aimed to leave their academic titles and be in the group on their spontaneity.

The sixth session aimed for group members to express themselves by using body language and gain awareness about their 'self' with the group sculpture game. In addition, a group tree game was played to understand group dynamics and see their functionality.

In the seventh session, the mourning game was played with the protagonist; with this game, the members supported the protagonist with their feelings and experiences. With the chair game run first and now and then, the members could evaluate the group process and clarify their goals.

In the eighth session, the warm-up game Chinese Whispers was played. This game is a warming-up game where emotions are shared, much talking, and communication difficulties are shown, such as information, coming to us from many sources, sometimes becoming corrupted somewhere along the way. In the group in Phase 2, where conflicts were intense, they started by choosing a game to speak loudly of unspeakable sentences and unexplained feelings. Also, this game was aimed to make the group put aside their academic identity, in other words, to provide controlled regression by reminding members of childhood periods. This continued until the Protagonist game.

The ninth session started with the protagonist's game. The protagonist brought a group play regarding the intervening time and distance negatively affecting their relationships with their social environment. The play aimed to separate the group in the second phase, which is one of the forming stages of the group, to separate their conflicts from the people with whom they were transferred and to encounter them without retransmission. Therefore, they played the children's games they played with their childhood friends, both with their old friends in the role and with their bandmates. As Moreno suggested, it was planned to develop a single relationship by correcting the transference relationship [17].

In the tenth session, a group picture was made. It was aimed at the members to grow closer to each other, to feel that they are together despite their differences, and to contribute to integration as the theme of the third phase.

In the eleventh session, the protagonist group said they were angry after the picture. A protagonist-centered game was launched, and the members in the post supported the protagonist with their feelings and experiences.

The twelfth session started with a game of form and content. The goal of this game was to reinforce group cohesion. In addition, this game aimed to increase the individual differences of the group members and support group development. The game of receiving gifts from the group was played so that the group members who saw their individual differences were a member of the group with these differences and left the group with a positive feeling. At the end of the session, each member was told to ask for something from the group that would complement them and the group. The goal here was to create functional bonds between the group members. The game, which was thought to serve this purpose, was the game of asking for gifts from the group.

The thirteenth session started with the group tree game. The goal of this game was to let each group member see where and how they were in the group. While ending session 13, the members presented gifts using psychodrama objects and shared their feelings and wishes for each other.

In the fourteenth session, the picture in the frame game was played. Each member brought to the group a picture s/he remembered from the past. Each member played his/her own picture game. This game aimed to prepare the members to make new adjustments to their own lives.

The fifteenth session aimed to go to Aslantepe Mound and connect the members to a place where so many civilizations have come and gone, to support them in establishing their connections with their roots, to recognize the strong and supportive parts

that remain there, and to help them review their priorities by reminding them of the forgotten and remaining parts of human history. In this way, it would be ensured that they form their next goals according to their inner needs. Then, the reason for the transition to the social atom was to recognize its current roots and connections and allow them to make the necessary arrangements. The social atom was made for members to see their relationship networks.

In the sixteenth session, a group game called "a village tale" was played. It aimed at group members to see their strengths and weaknesses with their roles and raise awareness about these roles and social relationships.

In the seventeenth session, a protagonist-centered game was implemented. A time-themed game was played with the protagonist. In sharing, members supported the protagonist with their feelings and experiences. Afterward, the group members were allowed to go on a group journey for the second time. Thus, the changes of the group members with the roles they took in the first journey they took together and the second journey were observed. The effects of the group process were observed.

The members were asked to stage their academic troubles towards the end of the eighteenth session. After these troubles were remembered, the magic shop game continued. This game aimed to give members insight into the function of their lives and the continuation of the things they had but wanted to change. Later, it was considered to collect luggage for the members. As the group approached the end, it was planned to realize their gains here by taking the things they would like to carry and generalizing their lives outside the group.

Participants were asked to hold a farewell ceremony for the last session in the nineteenth session. It aimed to allow the members to say goodbye to the group and feel the process was completed.

Ethical principles of study

The study was approved by the Ethics Committee of the University (Approval Number: 2013-204).

Statistical Analysis

The Statistical Program for Social Sciences-SPSS for Windows, version 22.0 was used for statistical analysis (SPSS Inc., Chicago, IL, USA). Data are given as mean (standard deviation) and number (percentage). To test the normal distribution compliance of the data, the Kolmogorov Smirnov test, T test for independent groups in normally distributed data with two groups, ANOVA test for data with more than two groups with normal distribution, and Mann Whitney U test for data with normal distribution was used. The significance level was accepted as $p < 0.05$ in the evaluations.

Results

The socio-demographic characteristics of the members of the psychodrama group are given in Table 1. The average age of the participants was 28.83 (± 1.74). 66.6% of the members were women, and 33.3% were men. The ratio of married and single

people was 50%. 58.3% worked as an academic in medicine, and 41.7% in the nursing department.

Table 1. Socio-demographic characteristics of the members

		n:12
Age (average±SD)		28.83±1.74
Gender	Female	8 (66.6%)
	Male	4 (33.3)
Marital Status	Married	6(50%)
	Single	6 (50%)
Department of work	Medicine	7 (58.3%)
	Nursing	5 (41.7%)

SD: Standard Deviation

Table 2 shows the pre-test and post-test average scores of the academicians participating in the group study for the STAI-I, STAI-II, BA, and BD scales. A statistically significant difference was found in the applied scales' pre-test and post-test average scores. Average scores in all scales were found to be higher in pre-tests but lower in post-tests.

Table 2. Comparison of the STAI-I, STAI-II, Beck Anxiety (BA) and Beck Depression Scales (BD) mean scores of participants before and after psychodrama

	Pre-test	**Post-test**	**P**
STAI-I	32.16 (±5.49)	29.75 (±4.88)	0.03
STAI-II	36.83 (±7.38)	34.08 (±6.57)	0.01
BA	6.58 (±6.24)	5.5 (±6.03)	0.018
BD	6.58 (±4.66)	4.75 (±4.3)	0.04

Bold inidicated $p < 0.05$

Table 3. Comparison of the average scores of the subscales of the participants' coping styles with the stress scale before and after psychodrama

	Pre-test	**Post-test**	**P**
Self-confident	14.83 (±1.89)	16 (±2)	0.04
Optimistic	9.5 (±2.23)	10 (±1.95)	0.02
Helpless	8.25 (±3.69)	6.58 (±3.5)	0.07
Submissive	8 (±2.48)	6.66 (±3.2)	0.01
Social support	8.16 (±1.8)	9(±1.04)	0.13
Active	32.58 (±5.07)	35 (±3.61)	0.06
Passive	15.83 (±4.91)	14.66 (±7.55)	<0.01

Bold inidicated $p < 0.05$

Group members' coping styles and the pre-test and post-test average scores of subscales are given in Table 3. Self-confident and optimistic subscale scores increased, while post-test scores were lower in the helpless and submissive subscales. It was determined that there is a statistically significant difference in the four subtests. Although there is no statistically significant difference between the social support pre-test and post-test scores, post-test scores are higher. Also, as the scores obtained from the "self-confident approach," "optimistic approach," and

"seeking social support" subscales increase, one's "active coping styles"; as the scores obtained from the "helpless approach" and "submissive approach" subscales increase, they show that they use "passive coping styles" more. In our study, while active coping styles' post-test mean scores were higher, passive coping style post-test scores were lower. Statistically, the difference is significant.

Discussion

In this study, a psychodrama group was formed with the participation of academic staff working in the field of health. In our study, before starting the group, the therapist assessed the participants once by a pre-interview, and a contract was established with the participants.

Our working group consisted of young adults in their most productive period of life in terms of work and social productivity. These people are academicians working in the health field, which requires a high level of cognitive performance and an intense workload. Our research has also examined psychodramatic methods in the symptoms and attitudes of academicians against stress.

Stress is a situation that needs to be dealt with, but if coping strategies are maladaptive, psychological health deterioration and accompanying psychopathological symptoms are also inevitable [18]. Based on the stressful events and experiences in their work and social lives, the group members opened the situations, games, sharing, and feedback they perceived as stressful to the group. Through psychodrama sessions, they experienced their own emotions, mental designs, and realization processes within the group.

In our group study, the STAI-I, STAI-II, BA, BD scales were applied to the participants to measure their anxiety and depression levels before and after psychodrama sessions. Both anxiety and depression levels in-group members were found to be statistically significantly lower after psychodrama.

This study has shown that psychodrama contributes to both individual development and the improvement of depression. It has been reported that psychodrama has a healing effect on depressive symptoms by stimulating spontaneity and creativity, especially with an increase in the amount of speech, associations, and taking action [4].

In our study, we support that psychodrama may improve stress-related depressive symptoms. The Beck depression inventory, which measures the level of depressive symptoms in our study, focuses on mood symptoms rather than cognitive functions [19,20,21]. The change of attitudes that include the dimensions of emotional thoughts and behaviors can occur over a long period in human life. For this reason, the scale we used seems limited to evaluating cognitive change in individuals. However, we anticipate that changes in mood and behavior that improve with psychodrama can provide a cognitive change in the long term

and contribute to a decrease in people's pessimistic perspectives against stressors. In our study, the group members state that their emotions and changes have also changed during the feedback phase during the therapy process after the sessions.

Anxiety is situationally associated with acute-state-oriented episodes that fluctuate over time. It can last a lifetime as a personality trait when it becomes permanent. Consistent with the Trait Anxiety Theory, people's high anxiety levels cause them to become hypersensitive and psychologically hypersensitive to stimuli [10]. Our study found a statistically significant reduction in both situational and trait anxiety levels with psychodrama. Stress perception is related to the person's cognitive equipment and environmental factors. When anxiety, which may occur due to stress, becomes maladaptive, it negatively affects a person's life [10].

Our study shows that psychodrama is effective in reducing anxiety. Psychodrama increases awareness of oneself and others with whom they are in a relationship [15]. Increasing awareness and insight into the physical and emotional effects of stress will contribute to the protection of one's own mental health and social relationships, as well as professional development. Extensive research findings emphasize that effective coping strategies individuals use to cope with their stress experiences positively affect mental health [22,23,24].

Our study found a statistically significant increase in the mean scores of the self-confident and optimistic approach, considered active coping methods after psychodrama. When pre-test and post-test scores for seeking social support were compared, the difference was not statistically significant. However, it was found that there was an increase in the scores in the subgroup of seeking social support after psychodrama. A significant decrease was found in the mean scores of the helpless and submissive approach among the passive coping mechanisms. Animating previous experiences that people have difficulty overcoming with their coping methods in the psychodrama scene allows for testing reality and developing alternative thinking. With the occurrence of interpersonal learning and behavior changes, people's attitudes toward stressors also change.

Working with people having similar problems in group psychotherapy practices decreases the feeling of loneliness, understanding, and sharing prepares the ground for the development of empathy. The development of new solutions to challenging situations becomes easier [25,26,27]. In our study, while active coping attitudes increased, the decrease in passive coping attitudes supports the healing effect of psychodrama in coping with stress. The group work carried out contributed to the increase in the awareness of the members of the academicians about their stressors, improvement in anxiety and depression symptoms, as well as using more effective coping mechanisms against stressors.

The most important limitation of our study was that the

participants were in the same academic community. Even though the participants were in the same academic community, a problem of trust and internal competition was reflected in the group. When the game of excluding the workplace roles was played, it was not always easy for each participant to encounter new roles according to individual differences and to start new relationships. In this case, symbols were used more frequently. Another limitation is the number of participants included in the study is very small.

The group psychotherapy sessions in this study helped group members become aware of their stress factors and develop skills to deal effectively with stressful situations. The results show that psychodrama is very important in terms of both protecting participants' psychological mental health and in professional development. Working in health is extremely stressful and compelling. This study's results showed that psychodrama reduces anxiety and stress levels. According to the results of this research, we project that psychodrama can be applied to healthcare professionals working under intense stress, can reduce stress level and increase work efficiency.

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ORIGINAL ARTICLE

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The influence of the approach for blood loss and transfusion in total knee arthroplasty: Medial parapatellar vs. subvastus

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Abstract

The medial parapatellar (MP) and subvastus (SV) approaches are the most common approaches used in total knee arthroplasty (TKA). Blood loss and transfusion requirements during these approaches varies in different studies. This study compared the MP and SV techniques in terms of blood loss and transfusion needs. Sixty-four patients were enrolled for this retrospective, single-centre and single-surgeon study. Patients were allocated into two groups of 32 patients each: TKA utilizing a MP approach (MP group) and TKA utilizing a SV approach (SV group). The calculated blood loss, determined using the Gross method, was the study's primary outcome. Additionally, the amounts of haemoglobin and haematocrit decrease from preoperative to postoperative 3rd day as well as the need for blood transfusions were compared. The mean calculated blood loss was lower in the SV group compared to the MP group (953±362 mL vs. 1245±404 mL, p=0.003). The haematocrit decrease from preoperative to postoperative 3rd day was in favour of the SV group (7.0±2.9 % vs. 9.5±3.0 %, p=0.005). The mean units of packed red cells transfused in the MP and SV groups were 0.28±0.45 and 0.19±0.4, respectively (p>0.05). Although lower blood loss was observed in the SV approach, the postoperative transfusion rates were not affected. When selecting the approach to use in TKA, surgeons should consider that SV approach is efficient in reducing blood loss without any change in transfusion requirement.

Keywords: Total knee arthroplasty, approach, blood loss, transfusion, subvastus, medial parapatellar

Introduction

For patients with advanced knee osteoarthritis, total knee arthroplasty (TKA) is a successful major orthopaedic procedure. The medial parapatellar approach (MP), despite there are other surgical methods for the knee, continues to be the most used one [1,2].

Despite excellent exposure, the quadriceps tendon is incised and the peripatellar blood supply is compromised, which could lead to extensor mechanism complications such as avascular necrosis, patella fracture, and anterior knee pain [1,2]. Therefore, less invasive approaches such as subvastus and midvastus approaches have been investigated in comparative studies over the last few decades.

The subvastus (SV) approach was first introduced by Erkes

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in 1929 and popularized by Hoffman in 1991 [2]. As it avoids disruption of the quadriceps tendon and the insertion point of the vastus medialis, it is considered a less invasive approach that can provide better quadriceps strength, improved patellar tracking and conservation of the patella blood supply, resulting in reduced postoperative pain and shorter hospital stays [1,2]. In terms of blood loss, a significant amount may occur during TKA. The average blood loss values in different studies have been reported as up to 3030 mL [3]. This wide range depends on several factors, such as the surgical approach and technique, the use of a tourniquet and drainage, several pharmacological agents, and implant design [4].

The surgical approach is one of the main factors influencing the blood loss and transfusion requirement during or after any surgical operation, so these parameters must be considered by the surgeon when selecting the approach to be used. Several studies comparing the SV and MP approaches have revealed conflicting results and controversy remains about which approach results in lower blood loss [1,2,5-11]. The hypothesis of the current study was that the SV approach would decrease blood loss and transfusion requirements as the less invasive nature.

Material and Methods

This retrospective, single-centre and single-surgeon study was carried out in accordance with the Helsinki Declaration (as revised in 2013) and approved by the local ethics committee (Gulhane Ethics Committee, approval number 2020-525). The study's inclusion and exclusion criteria are shown in the Table 1. The patients who received unilateral TKA for primary knee osteoarthritis between January 2016 and August 2020 utilizing either the SV or MP approach were analysed from the database of the senior surgeon.

Table 1. Inclusion and exclusion criteria for the study

Inclusion and Exclusion Criteria
Inclusion
Patients who undergone unilateral total knee arthroplasty with medial parapatellar or subvastus approach
Patients aged 55-80 years
Patients within the normal range of preoperative haemoglobin, haematocrit, platelet and prothrombin time (INR, international normalized ratio) levels
Exclusion
Previous knee surgery
Patients with post-traumatic osteoarthritis or rheumatoid conditions
Patients with coagulation disorders or chronic hepatic disease
History of malignancy
Pre-operative ongoing anticoagulant therapy
Metabolic bone disease

During this period, 32 patients underwent TKA using the SV approach. A match-paired group by age, gender, the American Society of Anaesthesiologists (ASA) Physical Status Classification System score, body mass index (BMI) of 32 patients who underwent TKA using the MP approach were selected from the same database. The patients were divided into two groups of 32 patients each, according to the surgical approach used: MP approach utilized TKA (MP group) and SV approach utilized TKA (SV group).

The following data were retrieved from the medical records of the patients: age, gender, weight, height, BMI, ASA score, the side of the surgery, operation time, preoperative and postoperative first, second and third day haemoglobin and haematocrit levels, amount of intraoperative and postoperative blood transfusions, the decrease in haemoglobin and haematocrit from preoperative to postoperative day 3, and the volume of blood coming from the surgical drain.

All patients received a daily subcutaneous injection of low-molecular-weight heparin (40 mg of enoxaparin sodium; Clexane, Aventis Intercontinental, France) starting 12 hours before to surgery and continuing for 4 weeks following the procedure. All operations were performed under combined spinal and epidural anaesthesia. A posterior-cruciate-ligament-stabilized (PS) implant (Zimmer, NexGen) was used for all patients. Entry with a midline skin incision was followed by a standard MP or SV arthrotomy for exposure. The tourniquet was inflated to a pressure of 300 mmHg after sterile preparation, draping, and exsanguination. The tibial and femoral components were implanted with bone cement in each case, and no patient received patellar resurfacing. After implantation, a suction drain was placed and clamped, then the surgical layers were closed in a routine fashion. No cell saver system, bipolar sealer, or pharmacological agent such as tranexamic acid (TXA) was used in any patient.

The suction drain clamp was activated at the postoperative 8th hour. Active and passive knee range of motion and straight leg raise exercises were encouraged immediately postoperatively as tolerated after weaning from the anaesthesia. The drain and the Jones bandage were removed, and the patients were mobilized in the first postoperative day. No continuous passive motion machine was used. The same standardized postoperative rehabilitation protocol was applied to both groups. All patients' postoperative blood drainage from the drain was measured on the container scale after removing the drain.

Blood transfusions were given to patients who had haemoglobin levels below 8 g/dL or who had clinical conditions that were impaired as shown by symptoms of anaemia, tachycardia, or hypotension. Up to three days after surgery, all transfusions administered were tracked. On the first, second, and third days following surgery, the haematocrit and postoperative haemoglobin values were noted. Blood loss was calculated using the Gross formula based on patient gender, height, weight, and haematocrit values [12].

The study's data were statistically analysed using the SPSS program (IBM SPSS Statistics for Windows, Version 24.0). The mean, standard deviation, median, minimum, and maximum values were used to express continuous data, while frequency and percentage were used to express categorical variables. The Shapiro-Wilk test was used to determine if continuous variables conformed to the normal distribution, and the Student's t-test and Mann-Whitney U-test were applied to compare two independent groups. The Pearson Chi-Square test was applied to the comparisons of categorical variables. In all the statistical analyses, a value of $p < 0.05$ was accepted as statistically significant.

Results

Evaluation was made of a total of 64 patients, and no significant difference was determined between the two groups in terms of the demographic data. There was no significant difference between the two groups in terms of the operation side, operation time and ASA Score. The mean calculated blood loss was lower in the SV group compared to the MP group (953 ± 362 mL vs. 1245 ± 404 mL, $p=0.003$). The mean units of packed red cells transfused in the MP and SV groups were 0.28 ± 0.45 and 0.19 ± 0.4, respectively ($p>0.05$). The mean postoperative drainage volume within 24 h after surgery was 459 ± 39 mL in the SV group and 471 ± 31 mL in the MP group. Regarding the postoperative transfusion rates and drainage volumes, there was no statistically significant difference between the two groups (Table 2).

The preoperative platelet and prothrombin time (INR, international normalized ratio) levels were within the normal range for all the patients (range for platelet: 150.000-450.000/microliter, range for INR: <1.1). No significant difference was detected in the haemoglobin values recorded preoperatively and on postoperative days 1, 2, and 3, the preoperative to postoperative third-day haemoglobin decrease, and the postoperative first-day

Table 2. Patient demographic data and the data on the surgical side, ASA Score, postoperative drainage, calculated blood loss, transfusion and operation time

	Subvastus Group	Medial Parapatellar Group	P-value
Gender (n)-Female/Male	31 (96.9%)/1 (3.1%)	28 (87.5%)/4 (12.5%)	n.s.
Age (years) #	68.5±8.2	69.8±6	n.s.
Body mass index# (kg/m2)	30±2.8	29.2±3.8	n.s.
Side (right/left)	20/12	19/13	n.s.
ASA Score (II/III)	22/10	24/8	n.s.
Postoperative Drainage (ml) #	459±39	471±31	n.s.
Calculated Blood Loss (ml) #	953±362	1245±404	0.003*
Transfusion# (packed red cells/patient)	0.19±0.4	0.28±0.45	n.s.
Operation time (minutes)	90.5±7.25	85.5±6.25	n.s.

The values are given as mean±standard deviation. *Student's t-test

Table 3. Preoperative and postoperative haemoglobin and haematocrit values

Haemoglobin (g/dl)	Subvastus Group	Medial Parapatellar Group	P-value
Preoperative	12.9±1.1	13±1.2	n.s.
Day 1	11±1.3	11.3±1.1	n.s.
Day 2	10.5±0.9	10.3±0.9	n.s.
Day 3	10.3±0.7	10±1.0	n.s.
Hb Decrease (Pre to postop 3rd day)	2.6±1.0	3.0±1.0	n.s.
Haematocrit (%)			
Preoperative	38.8±3.0	39.5±3.6	n.s.
Day 1	33.5±3.7	34±3.6	n.s.
Day 2	32.2±2.7	30.1±2.7	0.039**
Day 3	31.7±2.2	30±2.7	0.01*
Htc Decrease (Pre to postop 3rd day)	7.0±2.9	9.5±3.0	0.005**

The values are given as mean±standard deviation. *Student's t-test, **Mann Whitney U test

haematocrit levels. Comparisons made between two groups were at the same time intervals (e.g., postoperative first-day haematocrit levels of the MP group were compared to the postoperative first-day haematocrit levels of the SV group) and a difference was detected in the haematocrit values on postoperative days 2 and 3 in favour of the SV group (p=0.039, p=0.01, respectively). The decrease in haematocrit level from preoperative to postoperative day 3 was lower in the SV group (7.0±2.9 % vs. 9.5±3.0 %, p=0.005) (Table 3).

The number of patients in both groups provided sufficient power for the comparison of the groups of the calculated blood loss (effect size, 0.7612856; α err prob, 0.05; post-hoc power, 0.914; p=0.003) and the preoperative to postoperative 3rd day haematocrit decrease (effect size, 0.8473359; α err prob, 0.05; post-hoc power, 0.915; p=0.005), according to the post-hoc power analysis.

Discussion

The main finding of this study was that the SV approach provides a lower calculated blood loss, but does not affect the postoperative transfusion rates. TKA is a successful major orthopaedic procedure for patients, however it frequently results in substantial blood loss and a high blood transfusion rate. Total knee and hip arthroplasty, as well as fracture surgeries, are the most common causes of transfusion in surgical patients, accounting for 9.8% of all transfused red blood cell units, according to Shortt et al. [13]. Following TKA, transfusion rates have been estimated to range from 20 to 40 percent [14,15].

Average blood loss reported in the current literature varies widely between 400 to 3030 mL [2,3,16,17]. This wide range depends on several factors, such as the patient demographics, surgical approach and technique, use of a tourniquet and drainage, application of several pharmacological agents, implant design, and the method used to calculate blood loss [4]. In the current study, the calculated blood loss in both groups (SV: 953 mL, MP: 1245 mL) was higher than the amounts reported in several studies but was comparable to the current literature. This could be attributed to the routine use of a tourniquet and drainage and non-usage of tranexamic acid.

Allogeneic blood transfusion rates for TKA patients reported in the literature vary greatly from 12% to as high as 87% [16-18]. Complications of allogeneic blood transfusion include haemolytic and allergic reactions, coagulopathy, fluid overload, acute lung injury, disease transmission, immunomodulation which could increase susceptibility to postoperative infections including in the surgical site, increased length of hospitalization, cost, and mortality [14,15,19]. Therefore, minimizing blood loss and consequent blood transfusions during TKA is crucial to avoid increased complications. In the present study, the postoperative transfusion rates were lower in the SV group (0.19±0.4 versus 0.28±0.45 units of packed red cells), although the difference was not statistically significant.

The haemoglobin loss in routine TKA has been reported to be between 2.8-3.8 g/dL [17,20,21]. The current study data revealed a haemoglobin drop of mean 2.6 and 3.0 g/dL in the SV and MP groups, respectively (p>0.05), which was consistent with the literature. Studies comparing the SV and MP approaches have revealed conflicting results concerning blood loss. Several studies have reported no difference [1,5-8], whereas others have reported less blood loss [2,9-11,22] using the SV approach. Higher blood loss is attributed to prolonged surgical times due to difficulty in obtaining adequate exposure. These studies concluded that further high-quality studies are needed to clarify this controversial issue. Nonetheless, in our study, there were no significant difference between the groups in terms of the operation time.

The SV method has been shown to have benefits in numerous studies, including quicker recovery, improved quadriceps strength, less lateral release, enhanced patellar tracking, preservation of the patellar blood supply, and less postoperative pain, which leads to shorter hospital stays. [1,2,7]. Despite the advantages, the long learning curve, longer surgical time, difficulties in obtaining adequate exposure, and consequent prosthesis component malalignment reported in several studies [23,24] have discouraged surgeons. The NJR (National Joint Registry for England, Wales, and Northern Ireland) 11th Annual report revealed that the SV approach was used in only 1% of TKA surgeries between 2004 and 2014 [25]. It can be considered that surgeons are reluctant to use the SV approach due to the above-mentioned difficulties.

Strengths of this study were that the operations were performed by the same senior surgeon with experience beyond the learning curves of both approaches, strict exclusion criteria (including preoperative ongoing anticoagulant therapy and hypertension, which is frequent in this age population), the same anaesthesia technique and implant utilization, and that factors related to increased blood loss were minimized in all patients. The retrospective nature of this study was its principal drawback. In addition, no conclusion can be drawn from the results in respect of cementless application, cruciate retaining design, robotic surgery, patients with rheumatoid disorders and younger patient groups. Lastly, this study did not assess the outcomes of TKA performed without a tourniquet or while using one at various pressures.

Conclusion

The SV approach yielded lower blood loss, higher haematocrit values on postoperative days 2 and 3, and lower preoperative to postoperative third-day haematocrit decrease compared to the MP approach, and the postoperative transfusion rates were not affected. The clinical relevance of this study is that when selecting the approach to be used in TKA, surgeons should take into consideration that the SV approach is efficient in reducing blood loss without any change in transfusion requirement

compared to the MP approach.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was approved by Gulhane Ethics Committee (approval no 2020-525)

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ORIGINAL ARTICLE

Association of nutrition literacy level with sociodemographic data: Case of Afyonkarahisar

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Abstract

This study was planned to evaluate the nutrition literacy (NL) levels of randomly selected individuals aged 18-65 years living in Afyonkarahisar, Turkey, and to associate the NL with some of their sociodemographic characteristics. The data of this cross-sectional study were collected through a face-to-face survey technique. In the survey form created for the study, questions about descriptive characteristics and the Evaluation Instrument of Nutrition Literacy on Adults (EINLA) were included. The study was carried out between 15 September and 1 November 2021 with a total of 1,601 participants. The study was conducted with a total of 1,601 participants. The participants' mean age was 29.40±10.04 years, and as per the Body Mass Index (BMI) classification, 14.7% were underweight, 50% were normal weight, 25.7% were overweight and 9.6% were obese. In this study, the total NL score of the participants was found as adequate in 61.4% of them and borderline in 38.6%. In the BMI classification of the participants, the group with the highest total NL score was found to be individuals with normal BMI (65.6%- p=0.003). As the BMI values of the participants increased, their NL portion knowledge levels decreased (p<0.01). Individuals with normal weight were determined to read food labels more (p<0.01). As the individuals' education level increases, the NL level increases. Underweight and normal weight individuals according to their BMI values were determined to have a higher level of NL competence than overweight and obese ones. Our study results indicate that most of the individuals with adequate levels of knowledge on NL have a normal BMI value and they integrate this knowledge into their daily lives. Organizing and providing various programs and training in order to improve the NL levels of societies may play a role in increasing the level of awareness and decreasing obesity.

Keywords: Adult nutrition, nutritional habits, nutrition literacy

Introduction

Nutrition constitutes one of the important parameters for individuals to maintain their lives in healthily [1]. In order for individuals to maintain a healthy life, nutrients should be consumed consciously in an adequate and balanced way [2]. Otherwise, they might be exposed to many health-threatening diseases [1-2]. This negatively affects the quality of life and life expectancy of the individual [2]. Obesity, diabetes, hypertension, and coronary diseases are the leading diseases that develop and/or impair the quality of life due to inadequate and/or unbalanced nutrition [3-4]. Obesity is defined as an abnormal increase in fat cells in the body, while at the same time it is an increase in scale weight [5]. Developing food technologies in the globalizing world and smart devices focused on increasing the comfort of the life of individuals have triggered the increase in obesity [6-7]. This has led to the need for individuals to act more consciously and carefully in food selection [8-9]. The development of healthy lifestyle behaviors and thus the prevention of various diseases

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are very important in terms of public health. At the same time, the length and costs of the treatment processes of these emerging diseases bring a great burden on the economies of countries [9]. The stages of access to correct information, evaluation, and making the right choice should be provided in order for an individual to gain healthy eating habits. The combination of desire, knowledge, skill, behavior, attitude and ability required for managing safe and healthy nutrition is defined as nutrition literacy [10-11]. NL, intended to measure the nutritional knowledge of the individual, is a concept that includes the level of awareness and comprehension ability. An individual with an adequate level of NL knowledge can analyze food selection and focus on the right choices of foods. They can also analyze portion control and label information together. By choosing the most suitable food for their health, they can apply the healthiest preparation and cooking methods [12]. Increasing the NL level of individuals or raising the awareness of societies about NL is extremely important for the prevention of many chronic diseases, especially obesity [10-12]. Although various studies have been conducted to measure the level of NL knowledge in our country, it is not at adequate levels. The aim of this study was to make contributions to the literature and draw attention to the importance of the subject by examining the relationship between NL level and some sociodemographic characteristics and BMI.

Material and Methods

This single-center cross-sectional study was conducted in Afyonkarahisar, Turkey, between September 15 and November 1, 2021. Afyonkarahisar is a city with a population of approximately 1 million located in the Inner Aegean region of Turkey geographically [8]. Individuals aged 18-65 formed the population of the study. The study was carried out with 1,601 volunteer individuals who agreed to participate in the survey method, were randomly selected, and did not have any obvious serious psychiatric disease and communication barriers (such as serious hearing and vision).

The individuals who agreed to participate were asked about their height, weight, age and marital status, and these data were noted. Also, their educational status, place of residence, and whether they actively use social media were questioned. Body Mass Index (BMI) (kg/m2) has been calculated according to the recorded height (m) and body weight (kg) value [BMI formula: body weight (kg)/height (m2)]. BMI values were evaluated according to the criteria set by the World Health Organization for adults. BMI ≤ 18.5 was considered as underweight, 18.5-25.0 normal, 25.0-30.0 overweight, and 30≥obese. Evaluation Instrument of Nutrition Literacy on Adults Scale was applied to the participants.

Evaluation Instrument of Nutrition Literacy on Adults (EINLA) It is a scale developed by Cesur et al. in 2015 to assess nutrition literacy. The Cronbach's Alpha reliability score of the EINLA was found to be 0.73 and the correlation coefficient was 0.85. The scale consists of 35 questions and five subsections. In addition,

the total score of the scale is calculated [13]. Subsections of the scale:

1. General nutritional knowledge (GNK) 10 items,

2. Reading comprehension (RC) 6 items,

3. Knowledge of food groups (KFG) 10 items,

4. Portion knowledge (PK) 3 items,

5. Reading food label (RFL) has 6 items.

The scoring was performed by coding the correct questions as "one point" and the questions answered incorrectly or skipped as "zero points". The total scale score from the NL is classified as an inadequate level if it is between 0-11 points, borderline if it is between 12-23 points, and adequate if it is between 24-35 points [13].

Data Analysis and Statistical Method, continuous quantitative variables are given as "n" and "percentage". Continuous variables consisting of independent measurements and showing normal distribution were analyzed with the **Independent Samples T-Test**, while the **Mann-Whitney Rank Sum Test** was used for the data that did not show normal distribution. The Chi-square test was used in descriptive statistics. The probability value of p<0.05 was considered significant. SPSS 21 package program was used in all data analyses.

Ethics Committee; Ethics Committee approval for the study (2021/445) was obtained on 03.09.2021 from the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University.

Results

The study was conducted with a total of 1,601 participants, 32.4% male, and 67.6% female. The mean age of the participants was 29.40±10.04 (18-65) years. As per the Body Mass Index (BMI) classification, 14.7% were underweight (18.96±1.74-22), 50% were normal weight (22.48±1.40), 25.7% were overweight (27.06±1.34) and 9.6% were obese (33.29±3.57). The majority of the participants in the study were single (66.5%), with an undergraduate education level (69%), not working at any job (52.5%), using social media actively (95.1%), and living in the city center (67%) (Table 1).

In this study, a significant difference was found in terms of gender and this difference was in favor of women (p<0.001). In regards to the marital status of the participants, while there was a significant difference in favor of married participants in general nutritional knowledge and the total score (p<0.001), a significant difference was found in favor of single individuals in the subsections of portion knowledge (p=0.001) and reading food labels (p<0.001). In regards to the place of residence, there was a significant difference in favor of participants living in the districts in general nutrition knowledge (p<0.01), reading comprehension (p=0.01), and the total score (p=0.01), while a significant difference was found in favor of those living in the

city center in the subsection of reading food label (p=0.021).

As the education level of the participants increased, a statistically significant increase was observed in the level of general nutrition knowledge and reading comprehension (p<0.001). In terms of the profession, the participants who were not working were found to have statistically significant higher scores in all areas of nutrition literacy, except for reading food labels. The portion knowledge level was found to decrease as BMI increased, and this was statistically significant. The reading food label values of the group with normal BMI values were found to be significantly different.

Table 1. EINLA and evaluation of sociodemographic data I

		Socio-demographic data I							
		Gender		**Marital status**			**Location of residence**		
		Female n=1083	**Male n=518**	**Married n=537**	**Single n=1023**	**Divorced n=41**	**City n=1072**	**District n=460**	**Village n=69**
General nutritional knowledge	Inadequate	53 (4.9)	32 (6.0)	16 (3.0)	65 6.4)	3 (7.3)	55 (5.1)	20 (4.3)	9 (13.0)
	Borderline	385 (35.5)	258 (49.8)	163 (30.3)	462 (45.2)	18 (43.9)	444 (41.4)	163 (35.4)	36 (52.2)
	Adequate	645 (59.6)	228 (44.2)	359 (66.7)	495 (48.4)	20 (48.8)	573 (53.5)	277 (60.2)	24 (34.8)
		p<0.001		p<0.001			p<0.01		
Reading Comprehension	Inadequate	25 (2.3)	26 (5.0)	18 (3.3)	30 (2.9)	3 (7.3)	31 (2.9)	15 (3.3)	5 (7.2)
	Borderline	335 (30.9)	207 (40.0)	132 (24.5)	395 (38.6)	15 (36.6)	374 (34.9)	134 (29.1)	34 (49.3)
	Adequate	723 (66.8)	285 (55.0)	388 (72.1)	597 (58.4)	23 (56.1)	667 (62.2)	311(67.6)	30 (43.5)
		p<0.001		p<0.001			p=0.01		
Knowledge of Food Groups	Inadequate	20 (1.8)	8 (1.5)	13 (2.4)	13 (1.3)	2 (4.9)	23 (2.1)	4 (0.8)	1 (1.4)
	Borderline	312 (28.8)	174 (33.6)	145 (27.0)	327 (32.0)	14 (34.1)	314 (29.3)	153 (33.3)	19 (27.5)
	Adequate	751 (69.3)	335 (64.9)	380 (70.6)	682 (66.7)	25 (61.0)	735 (88.6)	303 (65.9)	49 (71.1)
		p=0.145		p=0.146			p=0.254		
Portion Knowledge	Inadequate	666 (61.5)	363 (70.1)	348 (64.7)	652 (63.8)	29 (70.7)	703 (65.6)	280 (60.9)	46 (66.7)
	Borderline	342 (31.6)	138 (26.6)	174 (32.3)	297 (29.1)	9 (22.0)	307 (28.6)	155 (33.7)	18 (26.1)
	Adequate	75 (6.9)	17 (3.3)	16 (3.0)	73 (7.1)	3 (7.3)	62 (5.8)	25 (5.4)	5 (7.2)
		p=0.001		p=0.001			p=0.327		
Reading Food Label	Inadequate	243 (22.4)	156 (30.1)	163 (30.3)	223 (21.8)	13 (31.7)	249 (23.2)	122 (26.5)	28 (40.6)
	Borderline	537 (49.6)	240 (46.3)	264 (49.1)	493 (48.2)	20 (48.8)	529 (49.3)	220 (47.8)	28 (40.6)
	Adequate	303 (28.0)	122 (23.6)	111 (20.6)	306 (29.9)	8 (19.5)	294 (27.4)	118 (25.7)	13 (18.8)
		p=0.003		p<0.001			p=0.021		
NL Total Scores	Inadequate	-	-	-	-	-	-	-	-
	Borderline	363 (33.5)	255 (49.2)	169 (31.4)	428 (41.9)	21 (51.2)	421 (39.3)	157 (34.1)	40 (58.0)
	Adequate	720 (66.5)	263 (50.8)	369 (68.6)	594 (58.1)	20 (48.8)	651 (60.7)	303 (65.9)	29 (42.0)
		p<0.001		p<0.001			p=0.01		

Left margin label: V B O D A

Table 2. EINLA and evaluation of sociodemographic data II

		Socio-demographic data II							
		Education Status					Profession		
		Primary school n=55	Secondary school n=78	High school n=363	Graduate n=1105	Not working n=840	Government employee n=384	Labourer n=333	Retired n=44
V B O D A	**General nutritional knowledge** — Inadequate	4 (7.3)	9 (11.5)	32 (8.8)	38 (3.4)	30 (3.6)	20 (5.2)	33 (9.9)	1(2.3)
	Borderline	26 (47.3)	36 (46.2)	164 (45.3)	416 (37.7)	295 (35.1)	190 (49.5)	134 (40.2)	24 (54.5)
	Adequate	25 (45.5)	33 (42.3)	167 (45.9)	651 (58.9)	515 (61.3)	174 (45.3)	166 (49.8)	19 (43.2)
		p<0.001					p<0.01		
	Reading Comprehension — Inadequate	8 (14.5)	7 (9.0)	17 (4.7)	19 (1.7)	19 (2.3)	7 (1.8)	22 (6.6)	3 (6.8)
	Borderline	21 (38.2)	30 (38.5)	158 (43.6)	331 (30.0)	213 (25.4)	181 (47.1)	130 (39.0)	18 (40.9)
	Adequate	26 (47.3)	41 (52.6)	187 (51.7)	754 (68.3)	608 (72.4)	196 (51.0)	181 (54.4)	23 (52.3)
		p<0.001					p<0.01		
	Knowledge of Food Groups — Inadequate	0 (0.0)	3 (3.8)	10 (2.8)	15 (1.4)	15 (1.8)	4 (1.0)	7 (2.1)	2 (4.5)
	Borderline	22 (40.0)	32 (41.0)	129 (35.6)	302 (27.4)	275 (32.7)	97 (25.3)	101 (30.3)	13 (29.5)
	Adequate	33 (60.0)	43 (55.1)	223 (61.6)	787 (71.3)	550 (65.5)	283 (73.7)	225 (67.6)	29 (65.9)
		p=0.01					p=0.094		
	Portion Knowledge — Inadequate	35 (63.6)	48 (61.5)	235 (64.9)	709 (64.2)	517 (61.5)	261 (68.0)	217 (65.2)	34 (77.3)
	Borderline	16 (29.1)	27 (34.6)	112 (30.9)	325 (29.4)	261 (31.1)	110 (28.6)	101 (30.3)	8 (18.2)
	Adequate	4 (7.3)	3 (3.8)	15 (4.1)	70 (6.3)	62 (7.4)	13 (3.4)	15 (4.5)	2 (4.5)
		p=0.838					p=0.027		
	Reading Food Label — Inadequate	29 (52.7)	36 (46.2)	119 (32.9)	215 (19.5)	212 (25.2)	69 (18.0)	98 (29.4)	20 (45.5)
	Borderline	23 (41.8)	39 (50.0)	176 (48.6)	537 (48.6)	395 (47.0)	200 (52.1)	160 (48.0)	22 (50.0)
	Adequate	3 (5.5)	3 (3.8)	67 (18.5)	352 (31.9)	233 (27.7)	115 (29.9)	75 (22.5)	2 (4.5)
		p<0.01					p<0.01		
	NL Total Scores — Inadequate	-	-	-	-	-	-	-	-
	Borderline	33 (60.0)	48 (61.5)	174 (48.1)	361 (32.7)	258 (30.7)	180 (46.9)	154 (59.1)	26 (59.1)
	Adequate	22 (40.0)	30 (38.5)	188 (51.9)	743 (67.3)	582 (69.3)	204 (53.1)	179 (53.8)	18 (40.9)
		p<0.001					p<0.01		

Table 3. Relationship between BMI and EINLA

		BMI			
		Underweight n=229	Normal weight n=809	Overweight n=414	Obese n=149
General nutritional knowledge	Inadequate	8 (3.5)	46 (5.7)	17 (4.1)	13 (8.7)
	Borderline	87 (38.0)	339 (41.9)	164 (39.6)	53 (35.6)
	Adequate	134 (58.5)	424 (52.4)	233 (56.3)	83 (55.7)
			p=0.153		
Reading Comprehension	Inadequate	5 (2.2)	27 (3.3)	14 (3.4)	5 (3.4)
	Borderline	66 (28.8)	284 (35.1)	137 (33.1)	55 (36.9)
	Adequate	158 (69.0)	498 (61.6)	263 (63.5)	89 (59.7)
			p=0.511		
Knowledge of Food Groups	Inadequate	3 (1.3)	12 (1.5)	6 (1.4)	7 (4.7)
	Borderline	69 (30.1)	245 (30.3)	130 (31.4)	42 (28.2)
	Adequate	157 (68.6)	552 (68.2)	278 (67.1)	100 (67.1)
			p=0.194		
Portion Knowledge	Inadequate	138 (60.3)	501 (61.9)	286 (69.1)	104 (69.8)
	Borderline	71 (31.0)	252 (31.1)	119 (28.7)	38 (25.5)
	Adequate	20 (8.7)	56 (6.9)	9 (2.2)	7 (4.7)
			p<0.01		
Reading Food Label	Inadequate	81 (35.4)	119 (14.7)	134 (32.4)	65 (43.6)
	Borderline	125 (54.6)	359 (44.4)	216 (52.2)	77 (51.7)
	Adequate	23 (10.0)	331 (40.9)	64 (15.5)	7 (4.7)
			p<0.01		
NL Total Scores	Inadequate	-	-	-	-
	Borderline	89 (38.9)	278 (34.4)	179 (43.2)	72 (48.3)
	Adequate	140 (61.1)	531 (65.6)	235 (56.8)	77 (51.7)
			p=0.003		

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Discussion

Nutrition literacy is a relatively new concept all over the world. It is one of the important tools in the evaluation of nutritional habits and has gained more importance during the pandemic that has affected the whole world. Studies are showing that adequate and balanced nutrition of individuals in the pandemic increases the rate of coping with the disease and survival. This study was planned to analyze the factors affecting nutrition literacy, which is one of the methods of measuring whether individuals have adequate and balanced nutrition knowledge. In this study, the relationship between nutrition literacy and body mass index was examined. When the NL total score of 1,601 participants (32.4% male, 67.6% female) was evaluated, none of the individuals had inadequate NL levels. While 61.4% of the participants had adequate NL total scores, 38.6% had total scores at borderline. In similar studies to our study, 83.7% of the 750 participants in the study of Özenoğlu et al. had adequate levels of NL and 16.3% had NL levels at borderline [14], Cesur et al. found that 79.8% of 384 participants had adequate levels of NL and 19.9% were at the borderline [15], in the thesis study conducted by Er-Döngel with 430 participants, 59.8% of the participants had adequate levels [16], 94.4% of the 195 participants were found to have adequate levels of NL by Ünal [17], in Uzun's thesis study with 967 participants, 73.5% of them were at adequate levels [18], in their study with 320 academic participants, Demir et al. found that 50% of them were at an adequate level, 32.8% were at borderline, 17.2% were at inadequate level [19] and Ozdenk reported that 32.1% of the 225 licensed athletes had adequate levels of NL. It was thought that the differences in the results might be due to

the differences in the geographical differences where the studies were conducted, the used scales, and the population structure.

The majority of the individuals participating in our study were female (67.6%). When studies on NL were evaluated in terms of gender, many studies reported the female population with higher NL scores compared to males [15, 21-26]. The results of our study were found to be in line with the literature. The competency rate of female participants was found to be higher than male participants in the total score and all sub-sections of the NL scale we have used. There was a significant difference in all the areas except for the sub-section of knowledge of food groups of the scale. Females were observed to be more interested in nutrition.

The marital status of participants in our study was 33.6% married, 63.8% single, and 2.6% divorced. The competency rate of married participants was found to be significantly higher in the total score of the scale and general nutritional knowledge, reading comprehension, and reading food label subsections. This was thought to be because the majority of the participants were female and they spend more time in the kitchen. Besides, responsibilities related to the kitchen are often on females as a traditional structure of our country. This situation is thought to foster the NL levels of females.

In regards to the education level, NL levels of the participants were found to increase as their education levels increased. This was applicable for all sub-sections of the NL scale, and a significant difference was found in all sub-sections except portion knowledge. As the level of education increases, the NL of individuals increases. Many studies conducted on this subject support our results [21, 27-29]. In a study conducted with 1,281 participants in Greece, a positive relationship was found between education levels and nutrition literacy, and the level of nutrition literacy of individuals with low socio-economic status was reported to be inadequate [21]. Another study reported that the nutrition literacy of students whose fathers were university graduates was higher than those whose fathers were primary school graduates [29]. It can be said that as the level of education increases, analytical thinking becomes stronger, the sense of perception improves, and questioning increases.

When the BMI values of the individuals in our study were compared with the nutrition literacy, the group with the highest competency of nutrition literacy total score was found to be normal weight, followed by underweight, overweight, and obese individuals, respectively. According to our results, it can be said that individuals with normal weight are more careful about their nutrition and make an effort not to gain weight or have a healthy life. Similar results can be seen in different studies on this subject [15-16, 18, 30-31]. While individuals with inadequate nutrition literacy were reported to be more prone to obesity in one of the studies [18], another study found higher nutrition literacy scores in underweight individuals although there was no significant

relationship [25]. When the sub-sections of the nutrition literacy scale were examined in our study, the underweight individuals were found to have more portion knowledge, while individuals with normal weight were significantly more careful in reading food labels. There is a significant relationship between BMI and nutrition literacy. As BMI increases, nutrition literacy decreases.

In conclusion, individuals who are female, married, with high education levels and normal BMI were found to have higher nutrition literacy. Raising awareness of society about nutrition literacy can play an important role in bringing BMI values closer to normal, that is, in reducing obesity.

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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Preoperative biochemical values are correlated with adenoma volume, but not predictive factors for hungry bone syndrome in patients with primary hyperparathyroidism

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Abstract

We aimed to investigate correlation between perioperative biochemical values and adenoma volume, the effects of perioperative biochemical values and clinicopathological variables on postoperative hypocalcemia after parathyroidectomy. A retrospective study planned in tertiary university hospital on patients undergone surgery for primer hyperparathyroidism. Preoperative calcium (first, close to surgery, maximum), PTH (first, close to surgery, maximum), alkaline phosphatase (ALP) and phosphorus (P) values, postoperative calcium (early, late), postoperative PTH (early, late), 24-hour urinary calcium calculation, time from the first diagnosis of elevated calcium until surgery, preoperative hypercalcemia treatments, excised parathyroid gland, histopathologic diagnosis, maximum diameter and volume of the excised parathyroid on histopathologic examination, postoperative intravenous calcium supplement were analyzed. 73 patients were included in the study. The median age of the patients was 54 years (range, 18-82), and 83.6% were female. In univariate analysis, patients who were administrated intravenous (IV) calcium supplement had higher preoperative PTH (p=0.024). adenoma volume correlated moderate with preoperative PTH first (r=0.396, p=0.001), preoperative maximum parathormone (r=0.380, p=0.001), preoperative PTH CS (r=0.432, p<0.001) and preoperative first elevated calcium (r=0.240, p=0.041) levels. We conclude that biochemical parameters and adenoma size are not predictive factors in determining the requirement of IV calcium supplement. Preoperative PTH and calcium levels were moderately associated with adenoma volume.

Keywords: Primer hyperparathyroidism, calcium supplement, hypocalcemia, parathormone, adenoma volume, hungry bone syndrome

Introduction

Parathyroid adenoma is the most common cause of primary hyperparathyroidism. Surgical intervention, which aims to eliminate excessive parathormone pressure on calcium metabolism, remains the gold standard in treatment. One of the most important problems faced by clinicians after parathyroidectomy is hypocalcemia. In hungry bone syndrome, which is characterized by dramatic decreases in blood calcium levels, presents with severe symptoms that adversely affect patient comfort. [1]. There are case reports in the literature showing that hypocalcemia causes episodes of psychological illness. [2]. For this reason, studies have focused on revealing the predictive factors of hypocalcemia after parathyroidectomy. Studies with perioperative biochemical variables have shown that high preoperative Ca and PTH levels and rapid decrease in intraoperative PTH may be risk factors for the development of hypocalcemia [3,4]. There is even a study that provides a formula

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to predict the lowest postoperative blood calcium level after thyroid and parathyroid surgery. [5]. While it has been shown in different studies that the size of the excised adenoma may be a predictive factor for postoperative hypocalcemia [6-9], there are also opposing views stating that the size of the adenoma has no effect [10,11].

In this study, we aimed to investigate the effects of preoperative biochemical values, adenoma size (volume), location (parathyroid localization), and time from diagnosis to surgery on the development of postoperative hypocalcemia due to the presence of opposing views. We also investigated the effects of preoperative hypercalcemia treatment on postoperative calcium levels and the requirement of postoperative IV calcium supplement.

Material and Methods

A retrospective study planned to investigate the effects of the excised parathyroid volume, preoperative biochemical values, time from the first diagnosis to surgery, and preoperative hypercalcemia treatments on the development of postoperative hypocalcemia in patients who undergone parathyroidectomy for primary hyperparathyroidism. Tokat Gaziosmanpaşa University Clinical Research Ethics Committee approval was received. The data of patients who undergone parathyroidectomy for primary hyperparathyroidism in Tokat Gaziosmanpaşa University Faculty of Medicine General Surgery clinic between January 2010 and August 2022 were analyzed. Patients above 18 years of age were included in the study. Patients in whom the specimen was excised piecemeal, malignancy was found on histopathologic examination, data were not available and patients with familial hypocalciuric hypercalcemia were excluded from the study.

Age, sex, 24-hour urinary calcium calculation, time from the first diagnosis of elevated calcium until surgery, preoperative hypercalcemia treatments, excised parathyroid gland, histopathologic diagnosis, maximum diameter and volume of the excised parathyroid on histopathologic examination, postoperative intravenous calcium supplement were recorded. The volume was calculated by using the formula $V=A \times B \times C \times \pi/6$ (Miccoli Formula) for the dimensions given in the histopathologic examination.

Biochemical values

Following values were extracted and analyzed: First high preoperative calcium (mg/dL, pre-op Ca first), parathormone (pg/ml, pre-op PTH first), alkaline phosphatase (U/L, ALP first) and phosphorus (mg/dL, P first).

Maximum preoperative calcium (mg/dL, pre-op Ca max), parathormone (pg/ml, pre-op PTH max) and minimum preoperative phosphorus (mg/dL, P min).

Preoperative calcium close to surgery (mg/dL, pre-op Ca CS), parathormone (pg/ml, pre-op PTH CS), alkaline phosphatase (U/L, ALP CS) and phosphorus (mg/dL, P CS). Postoperative early calcium (mg/dL, post-op early Ca min), parathormone (pg/ml, post-op early PTH).

Postoperative late calcium (mg/dL, post-op late Ca), parathormone (pg/ml, post-op late PTH).

Statistical Analysis

While evaluating the findings of the study, SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Whether the scores obtained from each continuous variable were normally distributed or not were analyzed using descriptive, graphical, and statistical methods. Kolmogorov-Smirnov test was used to test the normality of the scores obtained from a continuous variable with the statistical method. Descriptive statistical methods (number, percentage, median, etc.) were used while evaluating the study data. Comparisons between the two groups in quantitative data were made using the Mann–Whitney U test; Qualitative comparisons between groups were made using Chi-Square tests (Yates's correction and Fisher's Exact Test). The level of relationship between the two continuous variables was examined with Spearman's correlation test. In the study, multivariate logistic regression modeling was used to measure the effect of independent variables on the dependent variable. The results were evaluated within the 95% confidence interval and the significance was evaluated under p<0.05. Correlations were considered strong at $r \geq 0.6$, moderate at $0.2 \leq r < 0.6$ and weak at $r < 0.2$.

Results

Totally 73 patients were included in the study. The median age of the patients was 54 years (range, 18-82), and 83.6% were female. When the clinical and pathological features of the disease were examined, the median symptom duration of the patients was 155 days (range, 14-2908), and most of them had adenoma tumor type (97.3%). The maximum pathological diameter of the adenoma was calculated as median 2 cm (range, 0.6-5) and its volume was calculated as median 1.2 cm3 (range, 0.05-26.3). Thyroidectomy surgery was performed in 19 patients (26%) in the same session. IV calcium supplement therapy was applied to 21 patients (28.8%) in the postoperative period. No statistically significant difference was found in the demographic and clinicopathological characteristics of the patients who required IV calcium supplement therapy (p>0.05). Demographic and clinicopathologic characteristics of the patients are presented in Table 1.

Univariate Analysis Results

The median preoperative and postoperative biochemical values of the patients are presented in detail in Table 2. There was a statistically significant difference in Pre-op PTH first and early postoperative Ca minimum levels according to IV calcium supplement status. Patients who were administered IV calcium supplement had higher preoperative PTH first (p=0.024) and had lower early postoperative Ca minimum (p<0.001) levels.

Table 1. Comparison of demographic and clinicopathological characteristics between research groups

Variables		Postoperative IV Calcium Supplement			
		All	Yes	No	p-Value
Number of patients, n(%)		73(100)	21(28.8)	52(71.2)	
Age#		54(18-82)	49(18-82)	55(21-76)	0.166ᵃ
Sex, n(%)	Male	12(16.4)	3(25)	9(75)	0.999ᶜ
	Female	61(83.6)	18(29.5)	43(70.5)	
Duration of symptoms (day) #		155(14-2908)	119(14-2069)	186(15-2908)	0.421ᵃ
Parathyroid localization, n(%)	Right (inferior=35/ superior=3)	38(52.1)	13(34.2)	25(65.8)	0.417ᵇ
	Left (inferior=35/ superior=3)	35(47.9)	8(22.9)	27(77.1)	
Histopathologic diagnosis	Adenoma	71(97.3)	21(29.6)	50(70.4)	0.999ᶜ
	Hyperplasia	2(2.7)	0(0)	2(100)	
With thyroidectomy, n(%)		19(26)	6(31.6)	13(68.4)	0.984ᵇ
Adenoma maximum diameter(cm)#		2(0.6-5)	2(0.7-3.5)	2(0.6-5)	0.425ᵃ
Adenoma volume (cm3) #		1.2(0.05-26.3)	0.6(0.08-7)	1.2(0.05-26.3)	0.314ᵃ
Preoperative hidration+diuretics, n(%)		40(54.8)	9(22.5)	31(77.5)	0.297ᵇ
Preoperative biphosphonates, n(%)		18(24.7)	8(44.4)	10(55.6)	0.133ᵇ

p>0.05, a:Mann Whitney U Test, b:Yates's correction, c:Fisher's Exact Test, #:median(range)

Table 2. Comprasion of perioperative biochemical values of patients between research groups

Variables	Postoperative IV Calcium Supplement			
	All	Yes	No	
	Median(range)	Median(range)	Median(range)	p-Value
Pre-op Ca first (mg/dl)	11.44(10.62-15.7)	11.6(10.62-15.7)	11.4(10.63-15.35)	0.100
Pre-op Ca-Max.(mg/dl)	11.9(10.68-16.1)	12.48(11-16.1)	11.79(10.68-15.2)	0.055
Per-op Ca CS (mg/dl)	11.4(9.7-15.5)	11.27(9.9-15.5)	11.4(9.7-13.7)	0.190
Post-op early Ca-Min.(mg/dl)	9.10(7.3-11.1)	8.3(7.3-10.67)	9.4(7.9-11.1)	<0.001*
Post-op late Ca (mg/dl)	9.3(6.8-11.2)	9.35(6.8-11.2)	9.3(8.1-10.47)	0.730
Pre-op PTH first (pg/ml)	212(57.24-1566)	260.5(103.1-1566)	174.25(57.24-1174)	0.024*
Pre-op PTH-Max.(pg/ml)	239.5(84.99-1566)	305.8(111.4-1566)	194.8(84.99-1174)	0.066
Per-op PTH CS (pg/ml)	204.1(44.55-1566)	275.45(44.55-1566)	161.25(84.99-1142)	0.119
Post-op early PTH(pg/ml) (n=68)	12.95(1.2-267.4)	12.66(1.78-267.4)	13.01(1.2-135.1)	0.819
Post-op late PTH(pg/ml) (n=58)	58.22(2.9-310)	53.17(9.1-170.9)	58.44(2.9-310)	0.489
Pre-op ALP first (n=59)	108(55-748)	109(55-748)	108(55-3649	0.639
Per-op ALP CS (n=55)	103(47-697)	111.5(55-6979	102(47-260)	0.146
Pre-op P first	2.46(1.68-4.27)	2.37(1.82-3.16)	2.51(1.68-4.27)	0.217
Pre-op P-Min.	2.38(1.13-3.9)	2.35(1.42-3.12)	2.4(1.13-3.99)	0.540
Per-op P CS	2.47(1.13-3.9)	2.44(1.42-3.24)	2.47(1.13-3.99	0.622

*p<0.05, Mann Whitney U Test, Pre-op:preoperative, Post-op:postoperative CS: close to surgery

Table 3. Multivariate regression analysis results

Variables	β	SE	Wald's	OR (95%CI)	p-Value
Post-op early Ca-Min.(mg/dl)	-2.541	0.671	14.33	0.079(0.021-0.294)	<0.001*
Pre-op Ca-Max.(mg/dl)	0.543	0.377	2.080	1.721(0.823-3.602)	0.149
Pre-op PTH first (pg/ml)	0.009	0.007	1.575	1.009(0.995-1.022)	0.209
Pre-op PTH-Max (pg/ml)	-0.009	0.007	1.597	0.991(0.977-1.005)	0.206
Constant	15.177	7.143	4.515	3.90E+6	

*:p<0.05, Multiple Logistic regression, Method=Enter, OR: Odd Ratio, CI:Confidence Interval, SE:Standard error, R2(Nagelkerke)=0.56, Model χ2=35819, p<0.001, Dependent variable: IV replacement (1=yes, 0=no), Correct classification probability of the model:86.3%, Note:OR and P-value were obtained using multivariate logistic regression analysis model

Table 4. The correlation between study parameters, adenoma volume and perioperative biochemical values

Variables	Adenoma volume (cm3)		Pre-op PTH (pg/ml)	
	r	p-Value	r	p-Value
Pre-op PTH first (pg/ml)	0.396	**0.001***	NA	NA
Pre-op PTH-Max.(pg/ml)	0.380	**0.001***	0.952	**<0.001***
Per-op PTH CS (pg/ml)	0.432	**<0.001***	0.867	**<0.001***
Post-op early PTH(pg/ml)	0.088	0.475	0.208	0.089
Post-op late PTH(pg/ml)	0.237	0.073	0.348	**0.008***
Pre-op Ca first (mg/dl)	0.240	**0.041***	0.295	**0.011***
Pre-op Ca-Max.(mg/dl)	0.184	0.120	0.475	**<0.001***
Per-op Ca CS (mg/dl)	0.032	0.787	0.106	0.372
Post-op early Ca-Min.(mg/dl)	0.204	0.084	-0.003	0.981
Post-op late Ca (mg/dl)	-0.107	0.375	0.005	0.965
Pre-op P first	-0.102	0.397	-0.435	**<0.001***
Pre-op P-Min.	-0.184	0.122	-0.425	**<0.001***
Pre-op ALP first	0.157	0.234	0.300	**0.021***

*:p<0.05, r: Spearman's correlation test, NA: not available, CS:close to surgery

In addition, preoperative calcium and parathormone maximum levels were higher in patients requiring IV Ca supplement (p=0.055 and p=0.066), which was close to statistical significance.

Multivariate Regression Analysis Results

Multivariate logistic regression analysis using the enter method was performed, including the variables (Pre-op PTH first and Pre-op PTH-Max; Pre-op Ca-Max and Post-op early Ca-Min) that were statistically significantly or nearly significantly associated with the presence of IV Ca supplement in univariate analyses. According to the results of the regression analysis, the coefficient of determination of the model was R2(Nagelkerke)=0.56. Accordingly, it was found that 56% of the variance in the

dependent variable was explained by the independent variables. Since the p value in the model (F=35.819, p<0.001) is smaller than the α value, it is determined that the model is significant at 95% confidence level. The correct classification probability of the model was 86.3%. The model correctly predicted the requirement of IV supplement 86% of the time with the biochemical values used. According to the multiple logistic regression model, the only independent variable associated with the requirement of postoperative IV supplement was early postoperative calcium minimum level (OR: 0.079, 95%CI: 0.021-0.294) (Table 3).

Correlation Between Continuous Variables

There was a statistically significant and moderate positive correlation between adenoma volume and preoperative PTH first (r=0.396, p=0.001) (Figure 1), preoperative maximum parathormone (r=0.380, p=0.001) (Figure 2), preoperative PTH CS (r=0.432, p<0.001) (Figure 3) and preoperative first elevated calcium (r=0.240, p=0.041) levels. (Figure 4) From this finding, it was determined that adenoma volume increased as preoperative parathormone and calcium levels increased.

Figure 1. Correlation between adenoma volume and Pre-op PTH first
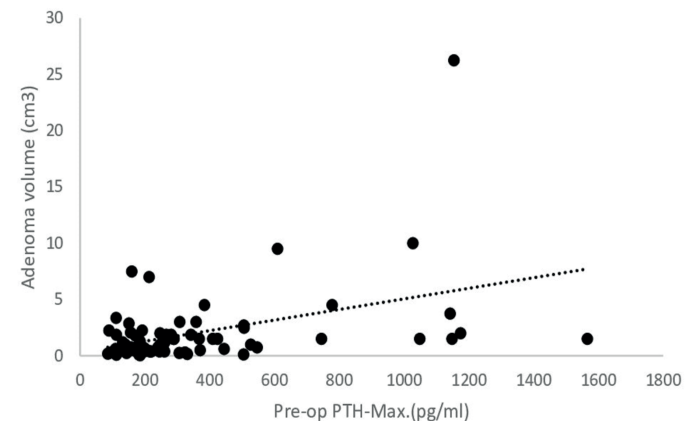
Figure 2. Correlation between adenoma volume and Pre-opPTH max

There was a statistically significant and positive correlation between preoperative parathormone level and preoperative calcium first (r=0.295, p=0.011), preoperative calcium maximum level (r=0.475, p<0.001) and preoperative ALP first (r=0.300, p=0.021), a statistically significant and negative correlation between preoperative parathormone level and preoperative phosphorus first (r=-0.435, p<0.001) and preoperative phosphorus minimum level (r=-0.425, p<0.001). (Table 4)

Figure 3. Correlation between adenoma volume and Pre-op PTH CS

Figure 4. Correlation between adenoma volume and Pre-op Ca first

Discussion

In our study, we found that demographic and clinicopathological data were not effective in determining requirement of intravenous calcium supplement in patients who were operated on for primary hyperparathyroidism. Comparing the patients with and without IV calcium supplement, both groups were similar in terms of age and sex. There was no statistically significant difference between the two groups in terms of the time from the first diagnosis to the operation, the effect of simultaneous thyroidectomy, and preoperative hypercalcemia treatments. In the univariate regression analysis of perioperative biochemical parameters, the PTH level measured at first diagnosis was found to be statistically significantly higher in patients who required IV calcium supplement. Although preoperative maximum calcium levels were higher in IV calcium supplement patients, but not statistically significant. In multivariate regression analysis, these two parameters were not independent factors

for IV calcium supplement. These results revealed the necessity of close Ca monitoring to determine the requirement of IV calcium supplement. In one study, close Ca monitoring was strongly recommended to prevent hungry bone syndrome after parathyroidectomy. [12]. There is no consensus on the risk factor of preoperative biochemical parameters in the development of hungry bone syndrome. There are studies concluding that preoperative calcium, preoperative PTH, and ALP levels that are 2 times higher than normal levels are predictive factors in hungry bone syndrome [13-15]. In a study comparing patients with and without hungry bone syndrome, no statistically significant difference was observed in terms of preoperative biochemical parameters. [16].The same uncertainty applies to adenoma weight and dimensions. Although the volume of tissue excised in patients with primary hyperparathyroidism greater than 5 cubic centimeters was shown as a risk factor in a review study, it was stated that there was insufficient data on the subject. [17]. In our study, it was revealed that the volume and maximum diameter of the removed parathyroid adenoma were not significant in terms of IV calcium supplement.

In our study, we found that the excised parathyroid volume was moderately correlated with preoperative calcium and PTH levels. A large-series study showed a moderate correlation between adenoma weight and preoperative PTH levels [18,19]. In another large-series study, it was shown that adenoma weight was statistically significantly higher in patients with PTH levels above 150 pg/ml [20].

One of the limitations of our study is that it is retrospective. Due to the retrospective nature of our study, we observed that ALP values were not analysed in some patients. In addition, the fact that histopathological examinations were evaluated by different pathologists during the long study period was another limitation of our study. This may have caused interobserver bias, especially regarding specimen sizes. However, we think that this situation did not affect our results because the averages of the removed parathyroid sizes were similar and small.

In conclusion, we believe that biochemical parameters and adenoma size are not predictive factors in determining the requirement of IV calcium supplement. For this reason, we concluded that close post-operative calcium monitoring is needed to determine the requirement of IV calcium supplement. We also concluded that preoperative PTH and calcium levels were moderately associated with adenoma volume.

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ORIGINAL ARTICLE

Frequency of GERD in women of childbearing age in Malatya region

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Abstract

Gastroesophageal reflux disease (GERD) is frequently seen not only in our country but also all over the world. GERD not only impairs health and quality of life, but also causes serious financial losses in the working population. In this study, our aim is to determine the frequency of gastroesophageal reflux disease among female healthcare professionals of childbearing age in our region. Questions were asked about demographic data such as weight, age, height, BMI, medical history, and gastroesophageal reflux of female healthcare workers, whose data were generated by us. The answers to the questionnaires were collected and evaluated retrospective. All participants in the study were women. This study was carried out on 1224 female healthcare workers of reproductive age working in Malatya Turgut Özal University training and research hospital. Approximately 1150 of the employees who were distributed questionnaires filled out the questionnaires. The mean age of the female healthcare workers of childbearing age was 30.01±5.38 years, between 19-50. The mean height of the healthcare workers was 1.64±7.8 meters, the average weight was 68.05±13.2 kg, and their body mass index (BMI) was 27.4±3.6 kg/m². The frequency of GERD in the study group was found to be positive in 24%. 38.5% of the healthcare workers had previously gone to the doctor with complaints of pyrosis and/or regurgitation. A significant relationship was found between GERD and stress, fizzy drinks, lying down after meals, and family history of GERD. There was no significant relationship between the smoking and coffee use and age of the participants in the study in terms of the presence of GERD. We think that gastroesophageal reflux symptoms are common due to stress, unbalanced diet, irregular sleep and lifestyle habits due to the COVID pandemic in the last two years due to the fact that the participants in the study were healthcare professionals. Among our healthcare professionals, both pyrosis and other GERD symptoms were found to be higher than some of the previous studies, similar to those in our country. We think that the reason for this is that the extremely stressful work of health workers in the last 2 years has contributed to this. As it is known, health workers have worked very hard in the last 2 years, they did not even use their annual leaves, even those who wanted to retire could not retire. We think that this stress environment may also contribute to GERD symptoms.

Keywords: Gastroesophageal reflu, regurgation, heartburn, GERD

Introduction

Gastroesophageal reflux disease (GERD) is frequently seen not only in our country but also all over the world [1]. It affects more than 20% of the population in the West [2]. There are many differences even in the definition of gastroesophageal reflux, in some societies it is defined as burning behind the sternum and/or esophageal escape seen once a week, while some accept it as at least once a week, some at least once every 3 months. These differences in definitions are found and interpreted differently because pyrolysis and regurgitation are interpreted differently in each language, and even in some Far Eastern languages, they cannot adequately describe regurgitation and pyrolysis [1,2].

Because of the differences in these definitions, GERD is found at different frequencies in different parts of the world and even

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in different cities of the same country. In a study by Mungan et al. in our country, the definition of GERD was defined as burning and/or acid regurgitation behind the sternum once a week, and the prevalence was found to be 19.1%, and it was stated that the prevalence was higher in those living in the Mediterranean, Black Sea, eastern Anatolia and Central Anatolia regions compared to other geographical regions [3]. Again, in an evaluation made in Sivas in our country, the frequency of GERD was found to be 19.1%, while it was found to be 21.7% in the study of the same group among medical school students in Sivas [4].

Gastroesophageal reflux is the upward movement of stomach contents from the lower end of the esophagus and even coming into the mouth. Physiologically, it is an event that can be observed for a short time 10-15 times a day, normally after something is eaten [5-7]. It does not cause symptoms and complications due to the existing protection mechanisms of the esophagus. If it occurs more frequently than normal or lasts longer, especially during sleep, it causes both clinical symptoms and histopathological damage, from gastroesophageal reflux disease [8]. In studies investigating the prevalence of GERD; In general, the frequency of symptoms is investigated. Therefore, asymptomatic patients are ignored in studies.

The prevalence of GERD is 10-20% in Western countries and the United States (USA), and 5% in Asia [9-11]. The prevalence of this disease is high, its incidence is low, it is a chronic disease with high morbidity and low mortality [9].

In a study in the USA, it was found that 42% of the participants had burning behind the sternum and 45% of them had acid and food in their mouth [9]. In the GORHEN study conducted in Turkey, erosive esophagitis was found in 35% of 1421 patients with a diagnosis of GERD, who had burning in the chest and/or passing stomach contents into the esophagus once a week. GERD is as common in our country as in Europe and the USA, but has a milder course [12]. In this study, we aimed to evaluate the prevalence of gastroesophageal reflux disease among female employees of childbearing age working in our hospital. This study is the first study to investigate the frequency of gastroesophageal reflux among female healthcare professionals in our country.

Material and Methods

In the questionnaires that we compiled from the questionnaires used in GERD studies both in the world and in our country, the participants were asked questions about demographic characteristics such as age, weight, height, BMI, education and marital status, as well as questions about their medical history and GERD. The questionnaire forms filled by the participants were evaluated retrospectively. The questionnaires used in the study were created by taking samples from the prevalence studies conducted in our country and they are valid questionnaires. The majority of those who distributed questionnaires filled out the questionnaires. In the questionnaires given to the participants, questions were asked about the frequency of GERD, age, socio-demographic characteristics, the presence of GERD symptoms,

their effects on daily life, drug use for various reasons, smoking, coffee consumption, and the relationship between the body mass index (BMI) of the employee. Burning behind the sternum and sour bitter water in the mouth (regurgitation) among the symptoms of GERD once a week or more were accepted as GERD.

In the questionnaire, patients were asked the following questions: heartburn, regurgitation, chest pain, dry cough, odynophagia, dysphagia, dysphonia, and asthma. Heartburn, regurgitation, chest pain, and dry cough were scored from 0 to 3 (0: none; 1: at least monthly; 2: at least weekly; 3: daily) and dysphagia, dysphonia, and asthma 0 (absent) to Queried as 1 (existing) and saved.

Ethics Committee Approval

The approval number 2022-94 dated 10.05.2022 was obtained from the Malatya Turgut Özal University Ethics Committee to allow the study to be conducted.

Results

All of the individuals participating in the study were women. This study was conducted among 1224 female healthcare workers of reproductive age working in Malatya Turgut Özal University training and research hospital. Approximately 1150 of the employees who were distributed questionnaires filled out the questionnaires and submitted them, 74 of them could not fill out or deliver. The mean age of the healthcare professionals in the reproductive age range was 30.01±5.38 years, between 19-50. The participants of the study consisted of doctors, nurses, anesthesia technicians, dialysis unit workers, laboratory assistants, emergency medicine technicians, cleaning personnel and x-ray technicians.

The minimum age of the study participants was 19 and the maximum age was 50. The mean age was 30.01±5.38 years. Average height is 1.64±7.8 meters, average body weight is 68.05±13.2 kg. Body mass indexes (BMI) calculated using body weight and height were found to be 27.4±3.6 kg/m² (17.2-33.2) (Table 1).

Table 1. Demographic characteristics of the participants

	Numbers (n)	Minimum	Maximum	Avarage
Age	1150	19	50	30.01±5.38
Height (cm)	1150	148	172	1.64±7.8 m
Weight (kg)	1150	39	87	68.05±13.2
BMI (kg/m2)	1150	17.2	33.2	27.4±3.6 kg/m²

Among the female healthcare professionals of childbearing age, 278 (24%) of the 1150 people evaluated were accepted as GERD if the questions investigating the presence of pain behind the sternum and/or the presence of sour bitter water in the mouth were answered once a week and/or more (Table 2). Therefore, these patients were accepted as gastroesophageal reflux patients (GERD). GERD was positive in 24% of our patients.

Participants with body mass index BMI <18kg/m2 2% (n=24) 18-24.99kg/m2 76% (n=869); 25-30kg/m2 19% (n=212); and those with >30kg/m2 were 3% (n=32) (Table 2). There was no statistically significant difference between the frequency of GERD according to BMI (p>0.05) (Table 3).

Table 2. Prevalence of GERD

GERD	Number of people (n)	Percentage (%)
Positive	278	24
Negative	872	76
Total	**1150**	**100**

Table 3. The relationship between GERD and BMI

	GERD (+) n (%)	GERD (-) n (%)	Maximum
<18 kg/m²	7(0,06)	17 (1.47)	24 (2)
18-24.99 kg/m²	202 (17.5)	667 (58)	869(76)
25-30 kg/m²	56 (4.8)	156 (14)	212(19)
>30 kg/m²	22 (1.9)	10 (1)	32 (3)
Total	**287 (24)**	**872(75.8)**	**1150 (100)**
x^2=5.6	p=0.165	p>0.05 insignificant	

Considering the relationship between GERD and age, the frequency of GERD was 0.8% in the 19-25 age group, 5.2% in the 26-35 age group, 15.6% in the 36-45 age group, and 6% in the 45-50 age group. It is observed that the frequency of GERD increases with age (Table 4). Although the frequency of GERD increased with age, the difference was not statistically significant (p>0.05).

Table 4. Relationship between GERD and age groups

Age groups	GERD (+) n (%)	GERD (-) n (%)	Total n (%)
19-25	10 (0.8)	165 (14.3)	175 (15.2)
26-35	60 (5.2)	190 (16.4)	250 (21.7)
36-45	180 (15.6)	340 (29.5)	520 (45.2)
45-50	70 (6.0)	135 (11.7)	205 (21.7)
Total	**278(24.1)**	**872 (75.8)**	**1150 (100)**
x^2=4.6	p=0.154	p>0.05 insignificant	

Among the healthcare professionals who answered the questionnaire, the frequency of regurgitation, which is one of the main symptoms of GERD, was 60% (n=691) and the frequency of those who did not have regurgitation was 40% (n=459). Of the 278 participants with GERD positive, 95% (n=265) had a complaint of sour and bitter water in the mouth (regurgitation), and 5% (n=13) had no regurgitation.

When we questioned the complaints of regurgitation, which is one of the main symptoms of GERD, among the participants with GERD positive, it was observed that 4% were observed less

than once a month, 10% once a month, 14% once a week, 9% several times a week, and 3% every day.

Among the female healthcare professionals of childbearing age, the presence of heartburn behind the chest, one of the main symptoms of GERD, was 60.7% (n=691) and 39.3% (n=459) of those who did not. The presence of heartburn was detected in 91% (n=253) of the participants with GERD positive, and 9% (n=9) of those without.

Among those with GERD positive, 4% of GERD symptoms reported the frequency of chest pain (heartburn) less than once a month, 13% every month, 16% once a week, 10% several times a week, 4% every day.

When we investigated the frequency of symptoms among GERD positive participants, only chest pain (heartburn) at least once a week was 37% (n=103), and the frequency of regurgitation at least once a week was 33% (n=92), both together. at least one frequency was found to be 30% (n=83).

When stress was questioned among female healthcare professionals of childbearing age, 85% (n=975) stated that they were positive, and when the relationship between GERD and stress was examined, 91% (n=254) of GERD (+) patients stated that they had experienced serious stress within a year. GERD and stress were found to be statistically significant (p<0.05) (Table5)

Table 5. GERD stress relationship

Stress	GERD (+) n (%)	GERD (-) n(%)	Total
Positive	254(%22)	721 (%63)	975 (%85)
Negative	24 (%2)	151 (%13)	175 (%15)
Total	**278 (%24)**	**872 (%76)**	**1150 (%100)**
x^2 =11	p=0.01	p< 0.05 significant	

5% (n=172) of female healthcare professionals of childbearing age stated that they used to smoke for a period, the rate of active smoking was 19% (n=215) in the GERD positive group, but there was no significant difference between the smoking and non-smoking groups (p> 0.05).

In terms of coffee drinking habits among healthcare workers, the rate of coffee drinking was found to be 67% (n=770) in the whole group, and 70% (n=800) in the GERD-positive group. There was no significant difference between GERD and coffee consumption (p>0.05)

When carbonated beverage habits were compared, the rate of drinking carbonated beverages among healthcare workers was found to be 52% (n=598) and 68% (n=782) in the group with GERD positive. A significant correlation was found between GERD positivity and consumption of carbonated beverages (p=0.04) (Table 6).

When asked to lie down and lie down within 2 hours after a meal among healthcare professionals, 64% (n=736) answered yes. They stated that 80% (n=56) of GERD (+) cases were hospitalized within 2 hours after eating. A significant correlation

was found between GERD positivity and lying down within 2 hours after a meal (p=0.023) (Table 7).

Table 6. The existence of a relationship between GERD and carbonated beverages

Carbonated drink	GERD(+) n(%)	GERD (-) n(%)	Total n(%)
Positive	253(%22)	529 (%46)	782 (%68)
Negative	25 (%2)	343 (%30)	368 (%32)
Total	278 (%24)	872(%75.8)	1150(%100)
x^2 =8.7	p=0.4		p< 0.05 significant

Table 7. The existence of a relationship between GERD and lying down 2 hours after a meal

Lying down two hours after eating	GERD(+) n(%)	GERD (-) n(%)	Total n(%)
Positive	223(%19)	513 (%45)	736 (%64)
Negative	55 (%5)	359 (%31)	414 (%36)
Total	278 (%24)	872(%75.8)	1150(%100)
x^2 =4.3	p=0.02		p< 0.05 significant

Among the atypical findings observed in GERD, the frequency of painful swallowing was found to be 3% (n=33) in all participants, 1% (n=13) in the GERD positive group, and 97% (n=1117) in those without odynophagia symptoms. There was no significant difference in terms of odynophagia between the group with and without GERD (p>0.05).

The frequency of dysphagia, one of the rare symptoms of GERD, was 3% (n=40) in the participants, and the frequency of difficult swallowing (dysphagia) in the GER positive group was 1% (n=16). Those without dysphagia symptoms were found in 97% (n=1110). There was no difference in the frequency of dysphagia between the GERD positive group and the negative group (p=>0.05).

When the participants were questioned about the presence of GERD in their families, the family history was positive in 35% (n=402). There is a family history in 55% (n=153) of GERD (+) cases. A significant correlation was found between GERD and family history of GERD (p=0.001) (Table 8).

Table 8. Presence of a relationship between GERD and family history

Family history	GERD(+) n(%)	GERD (-) n(%)	Total n(%)
Positive	153(%13)	249 (%22)	402 (%35)
Negative	125 (%11)	623 (%54)	748 (%65)
Total	278 (%24)	872(%75.8)	1150(%100)
x^2 =21.2	p=0.001		p< 0.05 significant

38.5% of the healthcare workers had previously gone to the doctor with complaints of pyrosis and/or regurgitation. It can be thought that working in the hospital and having easy access to health services will contribute to this. GERD was found to be significantly associated with stress, soda, lying down after a meal, and having a family history of a person with GERD

(p<0.05) (Table 5-8). No statistically significant relationship was found between age, smoking and coffee drinking and GERD.

In addition, 38.5% of those with GERD used stomach medication, 10% (n=27) antacids, 14% (n=38) PPI, 9% (n=24), H2RA, 8%. (n=22) were using PPI+ antacid, 13% (n=38) were using PPI + alginic acid, 15% (n=45) were using alginic acid, 10% (n=28) were using H2RA+antacid. About 21% stated that they did not take regular medication.

Conclusion

Among our healthcare professionals, both pyrosis and other GERD symptoms were found to be higher than some of the previous studies, similar to those in our country. We think that this is due to the fact that healthcare professionals have worked extremely stressful due to the COVID pandemic in the last 2 years, which will have contributed to this. As it is known, health workers have worked very hard in the last 2 years, they could not even use their annual leaves, even those who wanted to retire could not retire. We think that this stress environment may also contribute to GERD symptoms.

As a result, GERD is increasingly seen in all parts of the society, it is a condition that disrupts the comfort of life, reduces the quality of life and employee productivity, and increases health expenditures. Being aware of this issue, it is necessary to try to adopt the measures to eliminate the causes of GERD, both among health professionals and in the society, with lifestyle changes. Everyone diagnosed with GERD should be encouraged to adopt appropriate treatment and lifestyle changes.

Statistical Evaluation

Evaluation of the retrospective data collected in our study was done in computer environment using SPSS (Statistical Package for Social Sciences/ver:22.0) program. In the evaluation of the data obtained in the study, the Chikare test was used, and the Khikare test was used in multi-eyed schemes. All data were first entered into the Microsoft Access database, and general results were obtained with the Microsoft Excel program. The evaluation of the data was made with the SPSS 22.0 package program.

Discussion

GERD is when gastric or duodenal contents pass into the esophagus and cause symptoms. Since the symptoms of GERD are similar to many diseases, it can be easily diagnosed after excluding many diseases. It is a very common health problem in society. Although it seems innocent; Due to its symptoms, it not only impairs the quality of life of the person, but also causes complications [1, 2]. Thus, it leads to loss of workforce and cost increase in employees.

GERD is defined by the American College of Gastroenterology as the passage of stomach contents into the esophagus, causing symptoms and causing damage to the mucosa [2]. In the Montreal Classification (MC), reflux of stomach contents into the esophagus causing symptoms and complications was accepted

as GERD [1, 2]. Two important findings of gastroesophageal reflux disease are bitterness in the mouth and burning behind the sternum [4]. Heartburn may not be present in all patients [3].

In a nationwide study conducted in the United States (USA), 44% of the participants reported burning in the chest once a month [1, 2]. In a study conducted in the USA, 22% of the participants described chest pain and mouth watering in the last month, while 16% described only bitter water in the mouth [12]. The frequency of symptomatic reflux has been reported to be between 5% and 15.5% in 3 months in Europe [6]. The frequency of GERD has been reported as 10-20% in Europe and America, and 5% in Asia [8]. Although GERD is at equal rates in both men and women, complications are more common in men [13].

In many GERD epidemiological studies conducted in Turkey, the Mayo questionnaire and the GERD-Q form were used [9, 10, 14]. In the study of Bor S et al. using the Mayo score, the frequency of GERD was found to be 20% [14]. In the study conducted in Sivas province in Turkey, the prevalence of GERD was 19.3% [9], the prevalence in Bolu province was 12.5%, and the prevalence in the GORHEN study was 22.8% [12]. In the study of Mungan et al. using the GERD-Q questionnaire in the Turkish general population, the frequency of GERD was found to be 24.7% [3].

In our study, the frequency of GERD was found to be 24%, which is higher than some of the studies in our country. Our study is only female healthcare workers of childbearing age working in the hospital. One of the reasons why the results are so high may be working in a stressful field such as the health sector. Considering the COVID pandemic in the last two years, both working hours and conditions are heavier for people working in the health field, while those working in other sectors can take leave, conditions are applied differently for those working in the health field. This may have contributed to the increase in GERD symptoms by increasing the stress factor of the patients.

GERD is a common health problem in the community. Although the predisposition to reflux is physiologically more common in some people than in the normal population, dietary habits and lifestyles also play an important role in the frequency of reflux [15-17]. In some patients, GERD only manifests itself with sour, bitter water in the mouth after a meal and pain in the chest, while in others it may appear as esophageal cancer. In the diagnosis of GERD, it is an advantage to be able to diagnose the disease only by anamnesis rather than advanced methods and instruments [15, 18-20].

Using this advantage, we determined the frequency of GERD at a rate of 24% among female healthcare professionals of reproductive age in our hospital, in the study we conducted through a questionnaire on symptoms and complications to determine the prevalence of reflux in the environment we live in. This rate is higher when compared to the studies carried out at different times in the provinces around us.

The frequency of GERD, which emerged from the cumulative evaluation of other studies conducted in our country at different dates, was found to be 10-23% . The prevalence of GERD in our Konya city center is 10.9%, and it is similar to the frequency in Bolu (12.5%) [11].

The prevalence of GERD has been studied in different countries for many years, and a distinction has been made according to many demographic characteristics. Although modern life, obesity, economic status, and being old seem to increase the probability of encountering the disease more, regional studies give quite different results [21-26].

In a similar study conducted in Germany including the adult population, nutrition, quality of life, and demographic characteristics were investigated in 7124 individuals aged 18-79, and the frequency of mild reflux was found to be 25%, moderate 14%, and severe reflux 4% [23]. The female-male ratio was found to be similar when age was not taken into account; Severe reflux complaints were found to be more common in women aged 60-70 years. In the study, the frequency of reflux was found to be more common in older ages, and sufficient opinions were not expressed about socioeconomic status, BMI, and smoking. In our study, there was a statistically significant relationship between the prevalence of GERD, stress, soda, lying down after meals, and family history of GERD ($p<0.05$), but no statistically significant relationship was found between age, BMI, smoking and coffee drinking ($p>0.05$).

Since the participants in our study were health workers, they gave healthy and correct answers to the questions asked in the questionnaire, and in cases where they had difficulty, they answered correctly by getting help from more senior health workers around them. In our study, it was observed that GERD increased with age and BMI increase, but it was not statistically significant.

There were also questions in our study that questioned extraesophageal symptoms. In this study, it was determined that cough, hoarseness and hoarseness in the voice were higher in those with GERD, although it was not statistically significant.

In a study conducted in Germany, in another study examining the frequency of dysphagia in patients with reflux, the frequency of reflux was found to be 34% as a result of the evaluation of the questionnaires directed to 268 people [22]. In the study, in which men had more complaints (36%), it was found that 90% of the patients had monthly symptoms, 25% had symptoms more than twice a week, 9% had daily symptoms, and 45% had taken medication due to reflux.

In our study, the frequency of those who applied to a doctor due to reflux and were using medication was 38%. The high rate of drug users in our study, the fact that those included in the study work in hospitals, and the fact that they have easy access to physicians and drugs may also have an impact.

In a study conducted among the people in Konya, the rate of those using medication due to reflux was found to be 13.8%. In a study conducted in Konya, gender, educational status and marital status did not show a relationship with reflux, while age and BMI were found to be closely related [11]. There was no gender difference as our study was conducted only among female healthcare workers of childbearing age.

In a study conducted on minorities in the USA, weekly reflux was found to be as high as 26.2% on average [27]. In a study conducted on Caucasian, Spanish, African and Asian immigrants, 32.9% of the patients were found to be overweight and 31.7% to be obese. Among the reflux patients who were correlated with BMI, age and low socioeconomic status, the prevalence of reflux was found to be higher in African and Hispanic patients [24, 26, 28]. What is interesting here is that the prevalence of reflux was lower in similar studies conducted in their own countries. This supports the increased prevalence in Western societies. The reason for this situation, which is a problem, can be revealed with large and detailed studies [26, 29-32].

In our study, overweight people (BMI between 25-30) were 19% and obese were 3%, there was no significant socioeconomic difference between them as they were all healthcare professionals. The high prevalence of GERD in the American study can be explained by the high rates of overweight and obesity in that study [33].

The relationship between reflux and antisecretory drug use was highlighted in a survey study of 2973 people conducted in Australia. While the frequency of reflux found was 12.4%, the rate of patients using medication due to reflux symptoms was reported as 16.9%. The fact that antisecretory drug use is so high may be an indicator of the increase in the frequency of reflux in western countries [34].

In our study, the rate of those who used drugs for symptom or treatment was 38%. It is possible that our study was conducted during the COVID period and that the working conditions of healthcare workers in this period were due to the stress and related stress, because the stress rate was shown to be high in the study.

In a study conducted in Iran, a very high reflux frequency of 33% was found [35]. However, in this study, the number of samples was kept relatively low and was carried out on nomads. Still, the results found are interesting. There was no statistical difference between obese or non-obese people and gender, and it was observed that consumption of fruits and vegetables, in particular, increased reflux as a risk [35, 36].

In a prevalence study conducted in Israel; weekly reflux frequency was found to be 12.5% [37] . A total of 2027 interviews were conducted in the survey, which was conducted in the form of telephone conversations, and there was no gender difference in the evaluation like other studies [37]. While the prevalence

of reflux in the Middle East, Europe, and America is between 10-20%, data in Asia show the frequency to be between 2-7%. However, it has been shown by endoscopic studies that the prevalence, which seems to be low numerically, is higher than expected in Asia [38-40].

Some of the reasons for the difference in reflux frequency in different countries may be the inaccuracy of symptom definition and the lack of standardization in the diagnosis. Not just patients with symptoms; Patients with complications should also be included in the prevalence. So much so that in some countries, the participants were asked one-to-one survey questions, and the participants gave negative answers, especially without fully understanding the term "heartburn". In fact, the term "heartburn" does not have an exact equivalent in some Far Eastern languages [38-40].

In a study conducted among individuals who came to the hospital for routine control in Japan, the frequency of GERD was found to be 4.6% weekly, 12.8% monthly, and an average of 6.6% [39]. It cannot be generalized to the whole population, as all of the evaluations for which no gender differences were found were made on certain companies and employees.

In a study from Korea, the frequency was 3.5% per week [40]. No correlation was found with age, gender, BMI, socioeconomic status. H. pylori was presented as a protective factor in the study in which the genetic and Helicobacter pylori (H. pylori) effect on the reflux frequency difference between East and West was mentioned. However, although there is no data for H. pylori in the study, the high prevalence of H. pylori in South Asian and black races also supports the data statistically [40].

Finally, in a prevalence study conducted in patients coming to primary health care institutions in our country, patients with and without dyspeptic complaints were surveyed, and reflux was diagnosed in 38.3% of patients presenting with dyspeptic complaints, while a very high figure of 25.4% was found in the other group [41]. While it is noteworthy that the questionnaire is done by the doctor and the diagnosis is made by the doctor, it is an acceptable situation to have a high frequency of reflux in patients who have already applied to the health institution due to any ailment. In our study, the survey questions were filled by the participants themselves, but since they were all healthcare professionals, we can accept that they gave truthful answers to the questions.

After all; In all studies, GERD-related conditions include weight gain, age, diet, smoking-alcohol use, which are already mentioned in the etiology of the disease in the literature. The increase in the rate of fat in the diet as one goes to the west may explain the fact that the disease is less common in eastern countries. Contrary to expectations in almost all studies, the prevalence of reflux in women was almost equal to that in men. However, with the increase in age, there seems to be an increase to the detriment of women.

The prevalence of GERD is higher in western societies. The frequency of GERD is also increasing in Turkey. Among the reasons for this difference between regions, factors such as differences in lifestyle and dietary habits, the high frequency of Helicobacter Pylori infection, genetic factors, and the difficulty of accessing health facilities in eastern societies can be counted.

In our study, the frequency of GERD was found to be 24% among female healthcare workers of childbearing age. This result is similar to the studies conducted in Turkey. However, the frequency of GERD in our study was found to be slightly higher. The reason for this is thought to be due to the fact that the participants in our study were healthcare workers, their employees were under high stress due to the coinciding period of the COVID pandemic, irregular lifestyle and unbalanced eating habits.

This study, which we conducted among healthcare workers of childbearing age, is the first study in this field. In this study, we found a statistically significant relationship between GERD and stress, lying down after a meal, soda, and a family history of GERD. As age and weight increase, GERD increases, but it does not reach statistical significance. As in our study, other studies in which no association was found have also been reported. In this regard, more comprehensive studies are needed to clarify these relations.

The majority of people diagnosed with GERD do not receive appropriate treatment. When we consider asymptomatic cases, we see that most of the cases do not receive adequate treatment. It is seen that this disease, which causes serious complications when left untreated, should be well screened and treated in primary health care institutions.

Accurately determining the prevalence of GERD can be done with a thorough analysis and asking the right questions. After the correct diagnosis, regular drug therapy can be easily overcome with regular lifestyle changes and a healthy diet.

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ORIGINAL ARTICLE

Effect of decompressive hemicraniectomy performed within the first 48 hours on mortality in the treatment of malignant infarction of the middle cerebral artery

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Abstract

To evaluate the clinical outcomes of patients with malignant middle cerebral artery (MCA) infarction who underwent wide decompressive hemicraniectomy. Fifty-two patients with large MCA infarcts were retrospectively evaluated, and 12 patients who underwent extensive decompressive hemicraniectomy and duraplasty with a bone flap extending beyond the infarct borders were included in the study. The degree of stroke (stroke volume), preoperative and postoperative midline shift of the craniectomy area and improvement in midline shift were calculated on computed tomography. Preoperative and postoperative neurologic examination scores were determined using the modified Rankin Scale. The mean age was 63 (min: 41, max: 79) years. There was left MCA infarction in one patient and right MCA infarction in 11 patients. The postoperative follow-up period of the operated patients ranged from 14 to 90 days. The neurological examination of seven patients (58.3%) showed significant improvement. Eight (66.6%) patients survived. Postoperatively, the mean midline deviation value of 12 patients decreased from 11.04 to 4.8. It is considered that wide decompressive craniectomy performed in young patients in the early period with strict radiological and clinical follow-up can increase survival and functional recovery.

Keywords: Cerebral stroke, decompressive hemicraniectomy, middle cerebral artery infarction

Introduction

Primary injuries to the brain can lead to cerebral edema and intracranial hypertension, which are the main mechanisms of secondary brain injury, and thus important predictors of mortality and poor outcomes. With the introduction of modern neurosurgery and critical care, the classical decompressive craniectomy (DC) technique, i.e., surgical opening of the skull to reduce high intracranial pressure (ICP), has been refined, becoming a focus of clinical research in particular. In this study, we aimed to provide detailed information on the current status of DC in the modern interdisciplinary care of patients with an acute ischemic stroke, discuss the timing of surgery, and offer a seminal future perspective in terms of recovery rates using the modified Rankin score (mRS).

Material and Methods

The ethics committee of the study was obtained from Lokman Hekim University Scientific Research Ethics Committee with the decision number 2022/199. Fifty-two patients who presented to Lokman Hekim University Training and Research Hospital between January 2020 and December 2021 and were diagnosed with stroke were evaluated. Ischemic lesions were detected using cranial computed tomography (CT), diffusion-weighted magnetic

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resonance imaging (DWI-MRI), and CT/MRI angiography, and their localizations were noted. The areas of infarction were evaluated according to cerebrovascular regions, and 12 patients with extensive middle cerebral artery (MCA) infarction (infarct area greater than 1/2 of the MCA area) were included in the study (Figure 1A, B).
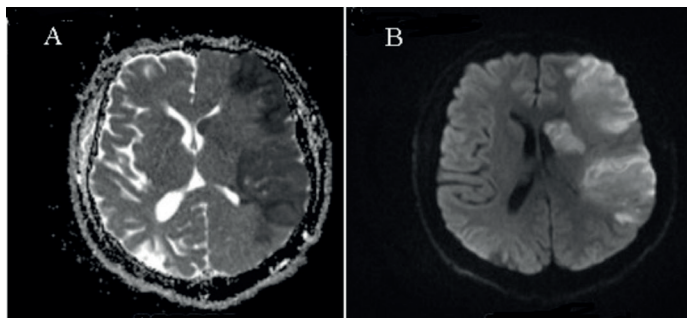
Figure 1. Left middle cerebral artery infarction. (A) ADC map, (B) diffusion-weighted magnetic resonance imaging

Surgical treatment was not planned in patients with diseases known to preclude surgical treatment, those with an mRS (pre-stroke) score of ≥2, and those with bilaterally unresponsive dilated pupils. After excluding these cases, progressive neurological deterioration and herniation were retrospectively evaluated in 12 patients that underwent wide decompressive hemicraniectomy and duraplasty with a bone flap extending beyond the infarct margins. The Detailed demographic data and neurological examinations of the patients were examined. Postoperative follow-up time, mortality rate, and disability scores were noted. mRS was used to detect functional dependence and assess recovery (Table 1).

Table 1. Modified Rankin Scale scoring

Modified Rankin score	Definition
0	No symptom
1	No significant disability despite symptoms; able to perform all normal duties and activities
2	Slight disability. Unable to perform all previous activities but able to attend to own needs without assistance
3	Moderate disability. Requires some help but able to walk without assistance
4	Moderately severe disability. Unable to walk without assistance or attend to own bodily needs without assistance
5	Severe disability. Bedridden, incontinent, requires constant nursing care and attention
6	Dead

The degree of MCA stroke was determined by examining the preoperative and postoperative non-contrast cranial CT (CT/CTA) and cranial MRI (DWI, MRI, and MRA) images of all the patients. Stroke degree (stroke volume), preoperative and postoperative midline shift of the craniectomy area, and improvement in midline shift were noted (Figure 2A, B).
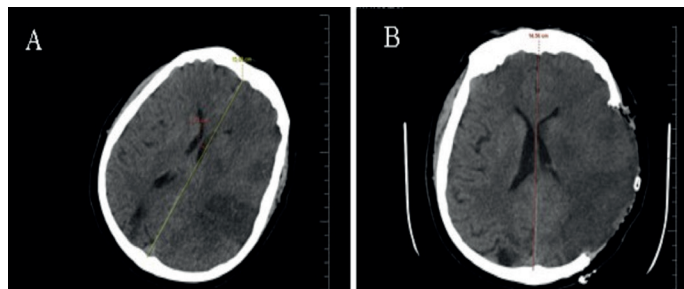
Figure 2. Axial brain computed tomography images of (A) the preoperative midline shift (13.80 mm) and (B) postoperative improvement in the midline shift

Infarct volume was calculated using the ABC/2 volume estimate of an ellipsoid, where A is the largest diameter in axial scan, B is the largest vertical diameter in axial scan, and C is the vertical diameter in coronal scan. These measurements were performed using the brain CT scans obtained within 24 hours of symptom onset (Figure 3A, B).
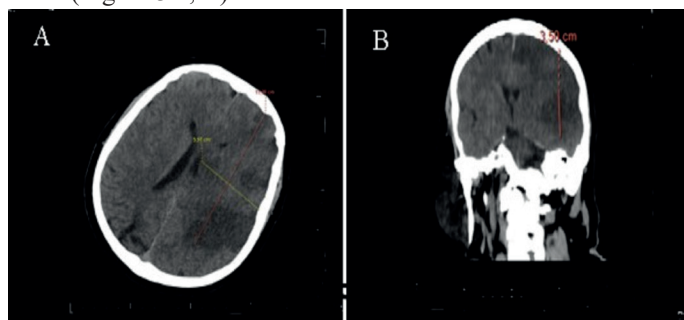
Figure 3. Preoperative brain computed tomography images showing left middle cerebral artery infarction measured using the ABC/2 method. (A) axial scan, (B) coronal scan

The length, width, and area of the craniectomy bone flap were measured on a brain CT scan obtained immediately after surgery. The bone area was defined as follows: bone flap A = D × d × π (D: anteroposterior diameter, d: the diameter perpendicular to bone flap D) (Figure 4).
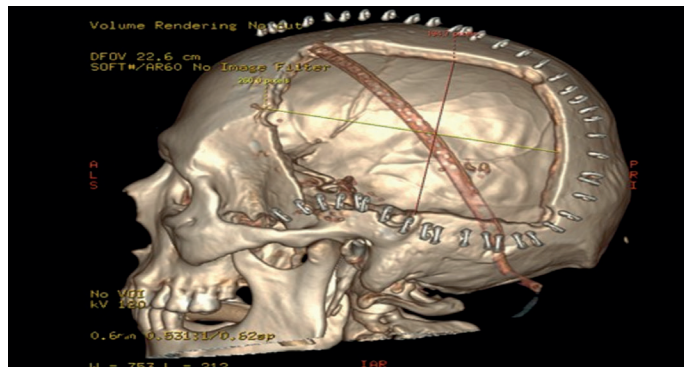
Figure 4. Three-dimensional reconstruction of postoperative brain computed tomography image showing the anteroposterior diameter and width of the craniectomy bone flap

Statistical Analysis

Statistical analysis was performed using SPSS v. 20.0. The data obtained from the study were analyzed descriptively. Central tendency measures, central distribution measures, frequency analysis, and ratio analysis techniques were applied.

Results

Fifty-two patients that presented to our center with an ischemic cerebrovascular event (CVE) were retrospectively evaluated. Twelve (24%) cases in which neurological findings were observed to deteriorate during the follow-up despite effective and appropriate medical treatment and surgical decision was made were included in the study. Wide unilateral hemicraniectomy + wide duraplasty was performed as the surgical procedure. The postoperative three-dimensional cranial CT scans of two patients are shown in Figure 4.

Decompression surgery was performed in a total of 12 patients with an ischemic CVE, six men and six women, who showed clinical progression within 24-48 hours despite medical treatment. The mean age was 63 (min: 41, max: 79) years. One patient had left MCA infarction, and 11 had right MCA infarction. The preoperative mRS was 4.4 in eight patients and 5 in four. The preoperative Glasgow Coma Scale of the patients ranged from 4 to 13. All the patients had midline shifts, and one patient also had anisocoria. The time from the diagnosis of acute ischemic stroke and admission to the hospital and surgery ranged from 24-120 hours. More than half the cases had a history of primary hypertension (66.6%) and atrial fibrillation (58.3%) (Table 2).

The postoperative follow-up period of the patients who underwent surgery varied between 7 and 90 days. The neurological examination of seven (58.8%) patients showed significant improvement. Eight (66.6%) patients survived. One patient with right MCA infarction died due to diffuse posterior system infarction. Three other patients died due to additional complications (sepsis, pneumonia).

The mean postoperative midline shift decreased from 11.08 to 4.08 in 12 patients. The mean craniectomy area was found to be 407.81 (385.9-437.3), and the craniectomy area was above average in two cases with the highest neurological and functional improvement. The mean stroke value was measured as 185.75, and four patients with the highest stroke value and preoperative midline values died (Table 3).

Table 2. Patient data

Patient	Age	Gender	GCS	Anizocoria	Mid-line shift	Surgery time	Infarct direction	HT	DM	Smoking	AF	MRS Pre-op	MRS 3.month	Thrombectomy
1	62	male	10	-	12mm	24-48	Right	+	+	-	-	4	3	-
2	55	male	11	-	11mm	24-48	Right	+	-	+	-	4	1	-
3	64	male	13	-	15mm	72-96	Right	+	+	-	+	5	-	-
4	48	female	11	-	8mm	24-48	Right	+	-	+	-	4	3	-
5	70	female	5	-	20mm	48-72	Right	+	+	-	+	5	-	-
6	67	female	6	-	13mm	96+	Right	+	-	-	+	5	-	-
7	69	male	12	-	13mm	96+	Right	-	+	-	+	5	-	-
8	79	female	4	-	11mm	48-72	Right	+	-	-	+	4	3	+
9	63	female	9	-	7,5mm	48-72	Right	+	+	-	+	4	3	+
10	67	male	10	-	9mm	72-96	Left	-	-	-	-	4	3	-
11	73	male	9	-	5mm	0-24	Right	+	-	-	+	4	4	-
12	41	female	11	+	8mm	0-24	Right	+	-	+	-	4	3	-

GCS: Glasgow Coma Scale; HT: hypertension; DM: diabetes mellitus; AF: atrial fibrillation; preop: preoperative; mRS: modified Rankin score

Table 3. Radiographic parameters of patients undergoing decompressive hemicraniectomy

| Patient no	Preoperative midline shift (mm)	Postoperative midline shift (mm)	Postoperative improvement in midline shift	Craniectomy area (cm3)	Stroke volume (cm3)
1	12	8	4	421.6	159
2	11	4	7	437.3	155
3	15	7	8	385.9	253
4	8	2	6	398.3	271
5	20	11	9	403.1	158
6	13	5	8	410.8	177
7	13	6	7	407.7	169
8	11	3	8	399.4	188
9	7,5	0	7.5	427.2	181
10	9	3	6	396.4	177
11	5	0	5	407.4	169
12	8	0	8	398.7	172
Mean	11.04	4.08	6.95	407.81	185.75

Discussion

Malignant MCA infarction is defined as a large MCA infarct that causes a space-occupying mass effect due to associated cytotoxic edema and occurs in 10% of all stroke cases. It presents with acute brain swelling within the first 48 hours after a stroke and results in elevated ICP or brain herniation. Malignant MCA infarction is associated with a mortality rate of approximately 80% despite appropriate medical treatment. There is a strong correlation between ischemic brain volume (stroke volume) and mortality (1). Clarke and Harris were the first to recommend decompressive surgery for these lesions with an intracranial mass effect [1]. Decompressive hemicraniectomy (DHC) has recently been recognized as an appropriate treatment modality for patients with malignant MCA infarction. Studies have shown the efficacy of this method in reducing mortality and morbidity associated with malignant ischemic stroke. In the literature, it has been reported that decompressive craniectomy reduces mortality from 80% to 30% [2]. However, in ischemic CVEs, there are still controversies concerning indications, timing, surgical technique to be applied, and patient selection. Nevertheless, decompressive craniectomy has been shown to reduce mortality in patients presenting with resistant intracranial hypertension and neurological deterioration despite medical treatment [3].

In the literature, there are conflicting data concerning the time of surgery, surgical procedure to be performed, and appropriate patient selection. Gupta et al. evaluated the timing of decompressive surgery. When the authors compared the clinical results of patients who underwent surgery early (within the first 24 hours) and late (after 24 hours), they found no significant difference [4]. In another study, Foerch et al. reported that loss of function was independent of surgical timing [5]. In our study, the patients were operated on in the early and late periods.

Following clinical worsening in neurological follow-ups 36 hours after diagnosis of SVO. Therefore, it is defined as late surgery. Similar to our study, Orakdogan et al. evaluated the mortality rate in patients who underwent late decompressive craniectomy (73.5%). When the two studies were compared, the mortality rate was found to be lower (18%) in our study. This was considered to be due to the differences in the demographic data of the patients participating in respective studies, comorbidities that may have been associated with mortality and morbidity, and differences in surgical techniques.

Although there are studies reporting no significant difference in the clinical outcomes of patients undergoing DHC, most clinicians state that mortality is high in operations performed after the age of 60 years [6]. In the current study, the mean age of the two patients with the highest rate of neurological and functional improvement was 58.5 years.

A decrease in mortality was observed in patients with malignant MCA infarction after DHC. Despite this surgery, the rate of herniation causing mortality in patients with malignant MCA infarction is reported to be between 11% and 22%. However, this rate has been shown to decrease with the use of a bone flap extending beyond the infarction border, extensive DHC, and duraplasty [7], as also performed in our study. In our study, consistent with the literature, mortality rate in the study was determined as 25%.

In studies evaluating the relationship between neurological improvement and mortality according to radiological parameters, a midline shift of >10 mm, presence of additional vascular space, basal ganglia involvement, large infarct volumes, and smaller craniectomy length were found to increase mortality and morbidity. In our study, complete neurologic recovery was

achieved in only one patient. This patient's mRS was determined to be 4 preoperatively and 0 at the postoperative third-month follow-up. Pullicino et al. showed that midline shift was associated with mortality [8]. In the current study, all the operated patients had a median shift of 11.24 mm on average, and all underwent extensive DHC. The preoperative and postoperative midline shift values, improvement in midline shift after DHC, craniectomy area, and stroke volume were measured. The mean shift value decreased to 4.08 in 12 patients. Consistent with the literature, the mean shift values of 12 patients decreased from to after surgery. The mean craniectomy area was above average in the two cases with the highest neurological and functional improvement. Patients with the highest stroke volume and preoperative midline shift values died. The data obtained from this study are in agreement with the results of other studies in which wide DHC was performed [9].

Malignant MCA infarction is a severe form of ischemic stroke. Severe loss of function and life-threatening conditions may occur in a significant proportion of patients that have had an ischemic stroke. Therefore, it is vital to choose the appropriate treatment method in patients with CVEs. DHC is an effective part of treatment in patients resistant to medical therapy. However, at the time of presentation, it is difficult to predict which patient will benefit from DHC, and this evaluation should be carefully performed in each case. As seen in the literature, the effect of DHC on morbidity and mortality, especially in young patients and in the first 48 hours, is clear.

In addition to DHC, approaches such as ventriculostomy to reduce intracranial pressure are also discussed in the publications. We still believe that there is a long way to go on this issue.

Limitations

This is a retrospective single-center study with a small sample. However, the majority of single-center studies evaluating mortality in the literature also have a similar sample size and retrospective design. Due to the small number of patients, we were only able to perform descriptive statistical analyses. Therefore, we could not evaluate possible relationships between parameters that could affect mortality and morbidity using basic statistical methods.

Conclusion

In light of the results of this study, it is considered that early wide DHC performed in young patients with a suitable neurological degree with combined with appropriate radiological and clinical follow-up can increase survival and functional recovery. These findings should be supported by multicenter long-term studies involving a large number of patients.

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ORIGINAL ARTICLE

Comparison of different surgical approaches for hysterectomy using the modified Clavien Dindo classification

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Abstract

This study aimed to compare the surgical approaches for hysterectomy performed in benign indications using the modified Clavien Dindo classification. Between January 2017 and December 2020, 1040 patients' clinical records who underwent a total laparoscopic hysterectomy, abdominal hysterectomy, and vaginal hysterectomy for benign causes at Istanbul Kanuni Training and Research Hospital were retrospectively analyzed. Patients were categorized into three groups; Total Laparoscopic Hysterectomy(TLH) (Group 1), total abdominal hysterectomy (TAH) (Group 2), and vaginal hysterectomy (VH) (Group 3). The demographic and clinical characteristics of the patients were classified and evaluated according to the type of surgery. Including; mean age, parity, body mass index, average uterine weight, history of prior abdominal surgery, hysterectomy indications, operation time, complication rates, amount of blood loss, and postoperative hospital stay. Modified Clavien Dindo classification was used to compare the complications. Ethics committee approval was obtained from the ethics committee of Kanuni training and research hospital. Statistical analysis of data was performed using. (SPSS Inc, Chicago, Illinois). There weren't any differences among the three groups in terms of mean age, parity, and body mass index.VH group had the lowest complication rate 17 (5.48%), compared to the other TLH 33 (9.42%), and TAH 37 (9.73%), groups $p<0.001$. The TLH group had the longest operation duration 123 ± 24.35 minutes, compared to the other VH 47 ± 14.57 and TAH (96 ± 27.64)groups. $p<0.001$). The use of the Clavien Dindo classification system enabled the comparison of clinical and surgical techniques and the correct interpretation of surgical results. Recognizing and treating complications reduces morbidity and mortality.

Keywords: Clavien Dindo classification, complication, comparison, hysterectomy, surgical approach

Introduction

Numerous conditions, including life-threatening illnesses, irregular uterine bleeding, and uterine prolapse, can be treated by hysterectomy [1]. Alternative application choices for the methods used have recently started to rise, even though the indications for hysterectomy have not changed for a long time[2]. Abdominal hysterectomy is inferior to laparoscopic hysterectomy in terms of post-operative pain, blood loss, and resume to daily activities [3,4,5]. Abdominal and laparoscopic hysterectomy technique for benign indications was shown to be inferior to vaginal hysterectomy and not advised as the first-choice modality[8]. Most surgeons avoid performing a vaginal hysterectomy in cases with a large uterus, previous pelvic surgery, history of pelvic inflammatory disease, severe endometriosis, undescended uterus, adnexal mass, or cyst [9]. A standardized classification system was required to evaluate complications in surgical approaches

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performed in the same or different centers. Clavien a general surgeon proposed a classification of complications. in 1992 and modified it with Dindo in 2004[10,11]. The modified Clavien Dindo classification has been used in the international literature in recent years to compare complications of gynecological operations[12].

Table 1. Modified Clavien Dindo classification

Grade 1 Complications in the postoperative phase that do not require medical treatment, surgical, or radiological intervention

Grade 2 Complications that necessitate the use of medication other than those prescribed in Grade 1

Grade 3A Complications that don't require general anesthesia but call for surgical, endoscopic, or imaging intervention.

Grade 3B Health problems requiring surgery, an endoscopy, or imaging intervention, combined with general anesthesia.

Grade 4A Life-threatening impacts and solitary organ damage

Grade 4B Life-threatening impacts because of numerous organ dysfunction.

Grade 5 Death

This study aimed to compare the surgical approaches for hysterectomy performed in benign indications using the modified Clavien Dindo classification.

Material and Methods

The records of 1040 women (aged 40–80 years) who underwent laparoscopic, abdominal, and vaginal hysterectomies for benign indications were retrospectively reviewed. This descriptive study was conducted at Istanbul, Kanuni Sultan Suleyman Training and Research Hospital between January 2017 and December 2020.

Patients were classified into three groups, Total Laparoscopic Hysterectomy (TLH) (Group 1), total abdominal hysterectomy (TAH) (Group 2), and vaginal hysterectomy (VH) (Group 3).

Demographic and clinical characteristics of the patients were classified and defined in each procedure according to the type of surgical approach, including mean age, parity, body mass index (BMI), uterine weight, estimated blood loss, current medical diseases, previous surgeries, indications for hysterectomy, complications, duration of surgery and length of hospital stay. We used the modified Clavien Dindo classification to compare the complications. The preoperative and postoperative hemoglobin difference was calculated. Uterus weight was measured using a precision scale at the pathology laboratory immediately after the procedure. Duration of surgery was evaluated as the time from the incision on the skin to the complete closure of the skin sutures. The length of hospital stay was determined as the time between the day of the procedure and the day of discharge from the hospital. Patients who had postoperative spontaneous micturition and defecation were discharged. The data obtained from the study were collected in 6 months. Follow-up visits were

made on the first and second postoperative days and one month after surgery. In addition, patients who developed complications were followed up until they recovered. Pelvic examinations, cervical-vaginal smears, and endometrial sampling were performed before the procedure. We included patients who were aged 40–80 years, underwent hysterectomy for benign indications, and had no missing records. We excluded patients who had malignancy, underwent a hysterectomy after a cesarean section due to postpartum bleeding, underwent a supracervical hysterectomy, or had missing records.

The management protocol (preparation and operative technique) was the same for all groups.

The hysterectomy technique that would help the patients the most was chosen after considering the presence of extra extrauterine pelvic adhesion, uterine size, and a descensus uterus. The night before the surgery, the patients underwent mechanical bowel preparation with a rectal enema. single dose of one gram cefazolin sodium was administered intravenously to all patients one hour preoperatively and six hours postoperatively. For thromboembolism prophylaxis, enoxaparin at a dose of 0.4 ml was administered subcutaneously 8 hours before the procedure and continued at 24-hour intervals throughout the hospitalization.

SPSS (SPSS Inc., Chicago, IL, USA) for Windows 24.0 was used to statistically analyze the data. Mean, standard deviation, and variance were used to present numerical data having a normal distribution. The one-way ANOVA test was used to parametrically compare three groups. Mann-Whitney U test and the Bonferroni correction were used to compare the paired groups, and the non-parametric Kruskal-Wallis test was employed to assess the significance of the difference. Fischer's precision test was used to determine whether there was a difference between the groups. Categorical data were expressed as numbers and percentages. P 0.05 was regarded as meaningful.

Results

22 patients had missing records, excluded from the study. Eight were in the total laparoscopic hysterectomy group, nine were in the total abdominal hysterectomy group, and five were in the vaginal hysterectomy group. After excluding those patients, a total of 1040 female patients were included in the study, who had undergone hysterectomies for benign indications. The modified Clavien Dindo classification is shown in table I.

Table II shows the demographic and clinical characteristics of the patients in each group. The patients in the total laparoscopic hysterectomy group had a mean age of 49,29±6,02 years and a mean parity (number of children delivered) of 3,01 ± 1,04. The body mass index was 25,40 ± 1,84. The patients in the total abdominal hysterectomy group had a mean age of 47,51 ±5,96 years and a mean parity of 2,51 ± 1,13 years. The body mass index was 28.01 ±1,82. The average age of the Vaginal hysterectomy. group was 51,82± 4.69years, and the average parity was 3,17± 6,39. The body mass index was 26.92± 1,16. In terms of mean age, parity, body mass index, uterine size, and uterine weight,

there was no significant difference between the three groups of participants in the study. Salpingectomy was the most common concurrent procedure in groups one and two. Colporrhaphy anterior was the most common concurrent procedure in group three. Table II shows the operational indications for the various procedures. The most common operation indication in the TLH and TAH groups was uterine myoma, while uterine prolapse was the most main indication in the VH group. A comparison of clinical outcomes of hysterectomy procedures is shown in table III.

Table 1. Demographic characteristics of Hysterectomy

Demographic characteristics	TLH n=350	TAH n=380	VH n= 310(%)	P
	Mean±SD	Mean±SD		
age (year)	49 (41-63)³	47 (42-62)	51 (48-80)	0.432¹
Parity(number)	3 (1-9³)	2 (1-8)	3 (1-11)	0.369
BMI (kg/m2	25.4±2.3 ⁴	28.2±2.7⁴	26.3±2.6⁴	0.571²
Uterine size(week)	12(8-14)³	12(10-16)³	12(6-14)³	0.589
Uterineweight(gr)	150 (110-160)³	155 (130-270)³	145 (70-190)³	
Previous surgery	70	80	47	0.262
Simultaneous operations	277	281	283	0.324
Salpingectomy	250	255	18	
Colporrrhapy anterior	14	15	218	
Colporrrhapy posterior	10	9	34	
Vaginal vault suspension	3	2	13	

¹ Kruskal -Wallis test
² One way anova (ANOVA) test
³mean, Minumum-Maximum
⁴ Mean, Standard deviation
 BMI:body mass index;TLH:Total laparoscopic hysterectomy

Table 2. Operation indications of hysterectomy

Indication	TLH n=350 (%)		TAH n=380 (%)		VH n=310 %		p
Myoma uteri	116	33 .14	123	32.36	40	12.90	p<0.05
Abnormal uterine bleeding	92	26.28	98	25.78	36	11.61	p<0.05
Endometrial hyperplasia without atypia	36	10.28	39	10.26	6	1.94	p>0.05
Cervical Intraepithelial neoplasia	14	4.00	15	3.94	5	1.61	p>0.05
Adnexal mass	14	4.00	15	3.94	6	1.94	p>0.05
Descensus Uteri	4	1.14	6	1.59	201	65.80	p>0.05
Endometrial Polyp	14	4.00	17	4.47	4	1.29	p>0.05
Adenomyosis	34	9.71	38	10.00	12	3.87	p>0.05
Chronic pelvic pain	26	7.42	29	7.63	-		p>0.05

Table 3. Comparison of clinical results of hysterectomy

	TLH	TAH	VH	p
	Mean±SD	Mean±SD	Mean±SD	
Operating time (Minute)	123±24.35	96±27.64	47±14.57	0.001
Mean Preoperative hemoglobin (gr/dl)	10.7.1±1.5	11±1.5	10.9±1.5	0.322
Mean Postoperative hemoglobin (gr/dl)	9.4.3±1.6	9.2±1.4	10.3±1.5	0.01
Duration of hospital stay(hour)	45(24-72)³	48(30-84)³	28 (18-48)³	0.01
Uterine weight(gr)	150(110-160)³	155(130-70)³	145(70-190)³	0.411

Table 4. Evaluation of complications in each type of hysterectomy using the modified Clavien Dindo classification

Clavien Dindo clasification	TLH n=350	TAH n=380	VH n=310
Decree 1			
Subcutaneous emphysema	2		
Preperitoneal emphysema	1		
Mild hematuria	2	4	1
Decree 2			
Port site infection	1		
High fever	1	3	1
Urine infection	4	5	4
Bleeding requring a blood transfusion	4	8	2
Mild ileus	1	2	1
Decree 4			
Pulmonary embolism	0	0	0
My cart infarction	0	0	0
Decree 5			
Death	0	0	0

Compared with TLH and TAH groups VH group had the shortest hospital stay 55±8.22(34-82 hours), 58±11.64 (32-90 hours), and 38±8.4 (28-58 hours) p<0.001 respectively. The mean operative time was 123±24.35 minutes (55-180 minutes) in the TLH group, 96±27.64(64-145 minutes) in the TAH group, and 47±1,4.57 (25-82minutes) in the VH group. Compared to the other VH and TAH groups, the TLH group had the longest operation time. 47±1,4.57 (25-82minutes) , 96±27.64(64-145 minutes), 123±24.35 (90-190minutes, p<0.001) respectively. The decrease in hemoglobin value on the first postoperative day was the lowest t in the VH group. Mean Postoperative hemoglobin (gr/dl) was 9.4.3±1.6gr/dl in TLH, 9.2±1.4gr/dl in TAH, and 10.3±1.5gr/dl in VH. Data on complications are given in table IV. Complication rates were the lowest in the VH group. It was 33 (9.42%), in the TLH group, 37 (9.73%) in the TAH group, group, and 17 (5.48%) in the VH group. Bladder damage occurred in a total of 8(0.77%) patients. We repaired the bladder injuries by suturing with a double layer of polyglactin without conversing to laparotomy. After cystography, we removed the catheter when there was no leakage and the bladder was intact. Ureteral damage

occurred in 4 (0.38%)patients. one was in TLH, 2 were in TAH, and 0ne was in the VH group. We repaired the ureteral damage by conversion to laparotomy. After intravenous pyelography, we removed the ureteral stent when there was no leakage and the ureteral was intact. A total of 14 (1.35%) patients had bleeding requiring blood transfusion due to excessive bleeding. We noticed, 2 (0.19%) bowel injuries during the operations, one was in TAH and one was in the VH group called a general surgeon to the operating room and repaired the injury without conversing to laparotomy. intra-abdominal hematoma/ abscess was detected in 4 (0.38%) patients. 1(0.28%) was in TLH, 3(0.79%) were in TLH group.

Discussion

Considering the presence of extrauterine pelvic adhesions, uterine size, and, descensus uteri the hysterectomy technique that would be most helpful to the patients was selected. Early recognition and management of complications are vital. To compare data from various institutions and analyze the risks associated with different surgical preservation procedures, standardized complication reporting is essential for future preservation surgery outcome analyses. Complications can be evaluated objectively and compared across various outcome studies using a uniform and trustworthy classification-grading system. The use of the Clavien Dindo classification system enabled the comparison of clinical and surgical techniques and the correct interpretation of surgical results

In the VH group we observed the least amount of blood loss, the shortest hospital stay, the shortest operation time, and the lowest complication rates compared to the other TAH and TLH groups. The TLH group had the longest operation time compared to the other VH and TAH groups.

Gendy et al. [13] Compared to the other VH and TAH groups, the TLH group had the longest operation time Leung[14].et al and Härkki-Sirén P et al. [15].reported that TLH requires a longer surgical time than other abdominal and vaginal hysterectomy techniques. Seracchioli et al. [16] compared TLH with TAH and couldn't find any difference in terms of operation time. In this study, compared to the other VH and TAH groups, the TLH group had the longest operation time. Aarts et al. [17]. reported the longest operative time and more urinary system complications in laparoscopic hysterectomy in their Cochrane review comparing total laparoscopic hysterectomy, abdominal hysterectomy, and vaginal hysterectomy. The best results were reported in vaginal hysterectomy. However, serious surgical complications were found to occur in 1.8% of abdominal hysterectomies and 5.1% of vaginal hysterectomies respectively. Olsson et al. [18]. compared 143 cases and found no statistical difference between TLH and TAH complication rates. Lee SH et. al [19] didnot discover any difference in complication rates in the meta-analysis outcomes comparing VH and TLH. Allam et al. [20]reported fewer complications in the TLH group using the electrosurgical bipolar vessel sealing technique than in the TAH and VH groups.

In this study. The VH group had the lowest complication rates compared to the other TLH and TAH groups. Early detection and management of intraoperative problems are crucial.

Candiani et al. [21] reported the hospital stay as 2.7 days and Morelli et al. [22]as 2.9 days in laparoscopic hysterectomy. Philips et al. [23] said that the length of hospital stay is shorter in TLH than in TAH. Garry R et al. [24] reported that the length of hospital stay was shorter in TLH than in TAH, but they could not find any difference compared to VH group . In our study among the TAH, TLH, and VH groups, the shortest hospital stay was in VH. Uterine myoma constitutes the largest indication group in TLH and TAH [25] In a vaginal hysterectomy, uterine prolapse is the largest indication group [26]. In our study, similar to the literature, uterine myoma constituted the largest indication group in TLH and TAH groups, and uterine prolapse was in the VH group. Harkki et al [27] reported the complication rate of urinary tract injury in laparoscopic hysterectomy (2.2%) and vaginal hysterectomy (0.04).In our study urinary tract injury was in the TLH group (1.43%)and (0.32%)in the VH group. In the literature, conversion rates from laparoscopy to laparotomy vary between 0.03% and 6.6% [28- 31]. TLH and vaginal hysterectomy complications have been reported to be similar for a uterus weighing up to 300 g [32] In our study conversion rate from laparoscopy to laparotomy was 0.86%

Data collected from patient files is sufficient for sample size estimation. The effects of surgical experience, which may affect each parameter, were determined in this study.

The study was descriptive and retrospective, conducted in a single tertiary hospital; These factors may have limited the generalizability of the study.

Conclusion

Our study revealed the importance of early recognition and management of complications.Early recognition and treatment complications reduce morbidity, mortality, and post-operative reoperation rates. Compared to the other TAH and TLH groups, the VH group had the least blood loss, the shortest hospital stays, the shortest operation time, and the lowest complication rates.

The hysterectomy technique that will be most beneficial to the patients should be selected.The use of the Clavien Dindo classification system enabled the comparison of clinical and surgical techniques and the correct interpretation of surgical results.

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ORIGINAL ARTICLE

A comparison of on-admission blood cell count-derived parameters on the development of contrast-induced nephropathy in acute coronary syndromes

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Abstract

Contrast-induced nephropathy (CIN) is a clinical entity closely associated with cardiac mortality and morbidity. We aimed to investigate the relationship between CIN after acute coronary syndrome and other bio-inflammatory parameters (Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, monocyte/lymphocyte ratio) as well as biomarkers such as AST/ALT, SIRI (Systemic Immnun Response Index), AISI (Aggregate Index of Systemic Inflammation), APRI (AST to platelet ratio index), SII (Systemic Immun Inflammation Index) NLR (Neutrophil to lymphocyte ratio), N/LPR (Neutrophil/ (lymphocyte x platelet), PLR (Platelet to lymphocyte ratio), MLR (Monocyte to lymphocyte ratio) and MPVLR (Mean platelet volume to lymphocyte ratio). In this retrospective cross-sectional study, we included 228 patients older than 18 years of age and underwent coronary angiography for acute coronary syndrome between January 2021 and May 2022. We applied the logistic regression analyzes to evaluate the relationship between patients' demographic, clinical characteristics, laboratory parameters, and contrast-induced nephropathy, and to evaluate the predictive power of the AST/ALT, AISI, SIRI, SII, NLR, PLR, MLR, N/LP ratio, MPVLR and other inflammatory based parameters on this primary endpoint. In the univariate analyses, prior history of coronary artery bypass, acute coronary syndrome type, prior ACEi/ARB usage, white blood cell count, hospitalization stay length, contrast amount, MLR, PLR, white blood cell to platelet ratio (WBCPR) were significantly associated with CIN. [p:0.039, p:0.017, p:0.025, p:0.044, p<0.001, p:0.003, p: 0.045, p: 0.044, p:0.044, respectively]. However, multivariable logistic regression analysis showed that WBCPR [OR 0.00 (95% CI 0.00- 0.01) p:0.005] and MLR [OR 13.522 (95% CI 2.15-84.72) p:0.005] might be statistically a significant independent predictor of CIN beside contrast amount [OR 1.92 (95% CI 01.23-3.02) p:0.004]. The WBCPR can be a new valuable independent predictor of CIN. Also, MLR and contrast amount may be a good independent predictor of CIN in acute coronary syndrome.

Keywords: Contrast-induced nephroapthy, acute coronary syndrome, monocyte/lymphocyte ratio, white blood cell/platelet ratio

Introduction

Contrast-induced nephropathy (CIN) is a clinical entity closely associated with cardiac mortality and morbidity. Despite advances in percutaneous coronary intervention (PCI) techniques in patients with acute coronary syndromes, complications such as CIN, stroke, emergency coronary artery bypass surgery, and vascular access site bleeding may occur during or after the procedure [1]. The risk of CIN increases in conditions such as chronic kidney disease (CKD), diabetes mellitus (DM), congestive heart failure (CHF), anemia, hemodynamic instability, decreased plasma volume, female gender, advanced age, contrast type, and amount [2,3].

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There are many studies in the literature on laboratory parameters associated with contrast nephropathy, especially in the acute coronary syndrome population. In a meta-analysis study, high CRP, NLR, hs-CRP and RDW levels, and low hematocrit levels, were associated with contrast nephropathy in acute coronary syndrome [4]. In other studies examining patients undergoing intervention for acute coronary syndrome, age, urea, glomerular filtration rate, creatinine, and PLR, were associated with contrast nephropathy [5-7]. Recently, it has been shown that SII was associated with CIN in non-ST elevation myocardial infarction [8]. Aspartate aminotransferase (AST) is a non-specific cardiac biomarker that increases early in acute coronary syndromes. In addition to acute inflammatory diseases, AST levels can be elevated in many chronic diseases such as inflammatory bowel diseases and chronic liver diseases [9]. The AST/ALT ratio, which is also known as the De-Ritis ratio, has been shown to predict the prognosis in cases such as bladder cancer, kidney cancer, pancreatic cancer, acute myocardial infarction, cardiac arrest, and ischemic stroke [10,11]. It has been shown in a recent study that the AST/ALT ratio also a predictor of acute kidney failure after radical retropubic prostatectomy [12]. Systemic immune response index (SIRI), calculated as neutrophil count x monocyte count/lymphocyte count, is an available parameter to predict the prognosis in acute and chronic inflammatory diseases, in endovascular interventions due to ischemic stroke, and to predict mortality in conditions such as breast cancer and lung cancer [13-15]. Moreover, there are new parameters such as AISI (Aggregate Index of Systemic Inflammation) and neutrophil/lymphocyte x platelet ratio (N/LP ratio). AISI, calculated by NLR x platelet count x monocytes, has a prognostic value, especially in respiratory tract inflammatory diseases such as interstitial fibrosis, asthma, lung cancer, or different inflammatory diseases such as COVID-19 disease [16,17]. The N/LP ratio predicts acute renal failure after abdominal surgery and cardiovascular surgery [18,19]. MLR and MPV to lymphocyte ratio (MPVLR) is also found as a good inflammatory marker in acute coronary syndromes and is a predictor of contrast-induced nephropathy [20,21]. Platelet to white blood cell count (P/WBC), is also a new inflammatory prognostic parameter predicting mortality in HBV-associated decompansated cirrhosis [22]. Since CIN is a complex porcess of inflammatory reactions including a ischemia, hypoxia, vasoconstriction, and direct toxic effect on renal tubular cells, we aimed to compare De-Ritis ratio, AISI, SII, APRİ, N/LP ratio, PLR, MLR, P/WBC and other blood derived parameters in predicting CIN in acute coronary syndromes.

Material and Methods

We evaluated acute coronary syndrome patients over 18 years old who underwent coronary angiography between 01/01/2021 and 01/05/2022. Patients who had severe chronic kidney disease (GFR<15 ml/min/1.73m2) or undergoing dialysis, chronic liver disease, died within the first 24 hours of the angiography procedure, came with cardiac arrest and were resuscitated, underwent bypass surgery after coronary angiography, had no creatinine values in the first 72 hours after admission, had acute or chronic inflammatory diseases such as autoimmune disease or cancer diagnosis, or had a history of infection or antibiotic therapy within the last one month were excluded. We recorded the demographic data, essential clinical characteristics of the patient, and serum CRP, creatinine, GFR, AST, ALT, hemoglobin, platelet count, platelet count, and hs-Trop I value before coronary angiography at admission. Contrast-induced nephropathy was defined as an increase in creatinine of >0.5 mg/dL from baseline or more than a 25% increase in creatinine from baseline within 72 hours of the procedure. Iohexol, a non-ionic, water-soluble contrast agent was used for coronary angiography. We calculated GFR with the automatic MDRD formula. We used the latest definition of universal myocardial infarction to diagnose myocardial infarction [23]. The primary endpoint targeted in our study was coronary angiography-induced contrast nephropathy. Coronary angiographic digital images of patients presenting with ACS were examined and classified as left main coronary artery, left anterior descending artery, circumflex artery, and right coronary artery, and other vessels according to the culprit lesions. The culprit lesions were treated percutaneously. The drugs used by the patients were also classified and recorded.

This study was conducted in Baskent University Hospital in accordance with the Declaration of Helsinki. Başkent University Institutional Review Board approved the study with Project no: KA21/519. The data used in the study were anonymous, so informed consent was not required.

Statistical Analysis

We analyzed the data using IBM SPSS Statistics volume 25.0 (SPSS Inc, IBM, USA). Histogram graphs, skewness-kurtosis values, and normality tests were used to check whether the data were normally distributed. In terms of descriptive statistics, it includes the mean for normally distributed parameters, the median for non-parametric quantitative variables, and numbers and percentages for categorical variables. Mann-Whitney U test and Chi-square or Fisher's exact test were used to compare non-normally distributed variables and categorical variables, respectively. Demographic, clinical, and blood count-derived parameters on admission were analyzed with univariate analysis, and the variables with a p-value <0.2 were included in a binary logistic regression analysis to determine their role in independently predicting contrast-induced nephropathy.

Results

Of 228 patients, 182 (79.8%) were male and 46 (20.2%) were female. Among the CIN-negative patients (n=198), 160 (80.8%) were male and 38 (19.2%) were female. The mean age of the CIN-negative patients was 62.39, whereas it was 61.83 in CIN-positive patients.

In the result of univariate analyses, coronary artery bypass surgery history (CABG), acute coronary syndrome type, prior ACEi/ARB usage, hospital stay length, contrast amount, MLR, PLR, and WBCPR were significantly associated with CIN in acute

coronary syndrome patients treated percutaneously [p:0.039, p: 0.017, p:0.025, p:0.044, p <0.001, p:0.003, p:0.045, p:0.044, p: 0.044] whereas De-Ritis ratio, APRI score, SII, SIRI, AISI, NLR, N to PL ratio and MPVLR were not associated with CIN in acute coronary syndrome patients treated percutaneously [p:0.605, p:0.621, p:0.116, p:0.270, p:0.213, p:0.115, p: 0.270, p:0.213, p:0.115, p: 0.246, p:0.223, respectively][Table 1]. Although

there was a significant relationship between prolongation of hospital stay and contrast nephropathy, it was thought to be meaningless in determining the prognostic value because it was a natural result of the cause-effect relationship. Thus, we found inappropriate to include the hospital stay length in the logistic regression analysis. In the binary logistic regression analysis, only MLR and WBCPR were found to be statistically

Table 1. Comparison of the baseline demographics and clinical characteristics between CIN negativeand CIN positive patients

Variables	CIN negative patients (N=198) Mean (±SD)/Median (IQR)/frequency (%)	CIN positive patients (N=30) Mean (±SD)/Median (IQR)/frequency (%)	P value
Baseline characteristics			
Age (year)	62.39 (±11.53)	61.83 (±13.76)	0.679#
Sex category (male/female)	158/40 (79.7%/20.2%)	24/6 (80%/20%)	0.980**
Hypertension	106 (53.5%)	18 (60%)	0.509**
Diabetes mellitus	64 (32.3%)	8 (26.6%)	0.537**
Hyperlipidemia	50 (25.3%)	12 (40%)	0.091**
Coronary artery disease	60 (30.3%)	11 (36.6%)	0.484**
Congestive heart failure	24 (12.1%)	4 (13.3%)	0.850**
Atrial fibrillation	8 (4%)	0 (0%)	0.262**
Prior myocardial infarction	42 (21.2%)	8 (26.6%)	0.501**
Prior CABG surgery	16 (8.1%)	6 (20%)	0,039**
Smoking	120 (60.6%)	16 (53.3%)	0.449**
Chronic pulmonary disease	22 (11.1%)	0 (0%)	0.055**
Peripheral artery disease	4 (2%)	2 (6.6%)	0.138**
Serebrovascular disease	4 (2%)	0 (0 %)	1.000**
Culprit lesion			
-LAD	80 (40.4%)	13 (43.3%)	
-Cx	44 (22.2%)	3 (10%)	
-RCA	62 (31.3%)	12 (40%)	
-LAD+ Cx	2 (1%)	0 (0%)	0.552**
-Cx+ RCA	2 (1%)	0 (0%)	
-LAD+ RCA	2 (1%)	0 (0%)	
-Saphenous	4 (2%)	2 (6.7%)	
- IM	2 (1%)	0 (0%)	
ACS type			
-Unstable angina pectoris	5 (2.5)	0 (0%)	
-Non ST elevation	45 (22.7%)	14 (46.6%)	0.017**
-ST elevation	148 (74.8%)	16 (53.4%)	
Prior BB usage	60 (30.3%)	8 (26.6%)	0.685**
Prior CCB usage	38 (19.2%)	4 (13.3%)	0.440**
Prior ACEi/ARB usage	64 (32.3%)	16 (53.4%)	0.025**
Prior Statin usage	44 (22.2%)	10 (33.3%)	0.182**
Clinical and laboratory characteristics			
Urea (mg/dL)	17 (6-51)/(8)	17 (10-31)/(7)	0.453*
Preoperative creatinine (mg/dL)	1.01 (±0.28)	1.11 (±0.35)	0.080#
GFR (mL/min/1.73m2)	78.15 (±22.19)	73.03 (±25.28)	0.250#
Serum Sodium (Na) (mmol/L)	138.06 (±2.63)	137.83 (±2.36)	0.663#

AST (U/L)	23 (10-411)/(28)	24.5 (11-174)/(21)	0.482*
ALT (U/L)	23 (8-97)/(21)	19.5 (6-67)/(23)	0.238*
CK-MB (U/L)	23.05 (0.70-558.10)/(40.95)	21,05 (7,79-123,70)/(46.53)	0.929*
Trop I (ng/L)	0.11 (0.00-213.00)/2.88	0.34 (0.01-48.79)	0.096*
Hemoglobin (g/dL)	14.77 (±1.74)	14.83 (±1.80)	0.864#
White blood cell count (103/µL)	11.35 (±3.60)	9.93 (3.42)	0.044#
Platelet (103/µL)	234 (117-673)/(94)	230.05 (139-325)/(61)	0.938*
MPV (fL)	8.05 (±1.47)	7.81 (±1.20)	0.390#
RDW (%)	12.50 (9.80-25.70)/(2,9)	12.00 (10.8-16.6)/(3.5)	0,477*
Neutrophile (103/µL)	6.63 (1.59-21.70)/(4.15)	6.37 (3.34-14.80)/(3.53)	0.280*
Lymphocyte (103/µL)	2.94 (±1.66)	2.43 (±1.59)	0.120#
Monocyte (103/µL)	0.78 (±0.32)	0.82 (±0.37)	0.533#
CRP (mg/L)	3.20 (0.30-176)/(7.05)	3.85 (0.5-120.1)/(9.90)	0.840*
HDL (mg/dL)	38 (13-93)/(11)	37 (25-79)/(13)	0.989*
LDL (mg/dL)	121.40 (±31.89)	112.77 (±31.33)	0.168#
Triglyceride (mg/dL)	129 (21-630)/(87)	156.5 (55-295)/(119)	0.269*
LV ejection fraction on admission			
>50%	84 (42.4%)	12 (40%)	
41-50%	88 (44.4%)	10 (33,.%)	0.136**
<40%	26 (13.1%)	8 (26.7%)	
Hospital stay length (day)	3 (2-9)/(1)	4 (3-8)/(2)	<0.001#
Contrast amount (mL)			
0-100	12 (6.1%)	0 (0%)	
101-200	92 (46.5%)	8 (26.7%)	
201-300	68 (34.3%)	16 (53.3%)	0.003**
301-400	20 (10.1%)	2 (6.7%)	
401-500	6 (3%)	2 (6.7%)	
>500	0 (0%)	2 (6.7%)	
De-Ritis ratio	1.179 (0.418-9.676)/(0.694)	1.000 (0.545-4.625)/(1.470)	0.605*
APRI	0.100 (0.017-1.633)/(0.139)	0.098 (0.043-0.628)/(0.088)	0.621*
SII	529.085 (139.600-4591.814)/(740.326)	645.142 (143.004-1592.752)/(761.513)	0.116*
SIRI	1.541 (0.528-29.583)/(2.129)	1.680 (0.283-10.055)/(3.583)	0.270*
AISI	356.934 (85.993-7484.658)/(496.359)	440.373 (39.685-2785.388)/(742.507)	0.213*
NLR	2.356 (0.576-19.466)/(3.158)	2.773 (0.489-7.382)/(4.373)	0.115*
MLR	0.261 (0.099-1.933)	0.321 (0.084-1.125)/(0.316)	0.045*
PLR	87.733 (32.220-440.131)/(73.261)	117.861 (39.945-282.352)/(86.089)	0.044*
NLPR	0.010 (0.001-0.166)/(0.015)	0.013 (0001-0.044)/(0.021)	0.246*
WBCPR	0.048 (±0.016)	0.041 (±0.011)	0.044#
MPVLR	3.37 (0.995-20)/(2.56)	3.75 (1.07-13.8)/(3.89)	0.223*

Abbreviations: LAD: Left coronary artery, Cx: circumflex artery, RCA: Right coronary artery, IM:Intermediate coronary artery, ACS: acute coronary syndrome, BB: Beta blocker, CCB: Calcium channel blocker, ACEi/ARB: Angiotensin converting enzymes inhibitors/ Anjiotension II receptor blockers, BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, AST: aspartate transaminase, ALT: Alanin transaminase, CK-MB: Creatinine kinase –miyocardial band, Trop I: Troponın I, MPV: Mean platelet volume, RDW: Red cell distribution width, CRP: C-reactive protein, HDL: High density lipoprotein, LDL: Low density lipoprotein, De-Ritis ratio: AST/ALT, APRI: AST to platelet ratio index, SII: Systemic Immun Inflammation Index, NLR:Neutrophil to lymphocyte ratio, MLR: Monocyte to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, NLPR: Neutrophil/ (lymphocyte x platelet), WBCPR: White blood cell count to platelet ratio, MPVLR: Mean platelet volume to lymphocyte ratio, SD: Standard derivation, IQR: Interquartile range (max-min)

#: Student- t test
*: Mann-Whitney U test
**: Chi-Square test

significant predictors of the CIN in acute coronary syndrome patients treated percutaneously [OR 13.522 (95% CI 2.15-84.72) p:0.005; OR 0.00 (95% CI 0.00- 0.01) p:0.005, respectively]. Moreover, contrast amount was also an independent predictor of CIN in this population [OR 1.92 (95% CI 01.23-3.02) p:0.004] [Table 2]. As a result of the logistic regression analysis of the parameters derived from the blood count and other statistically significant parameters predicting CIN at the time of admission to the hospital, the p-value of Hosmer-Lemeshow was found to be 0.940 and the Nagelkerke R2 value was found to be 0.293, which indicate regression model compatibility.

Table 2. Multivariable logistic regression analysis of the baseline characteristics and laboratory parameters

Variables	B	SE	Wald	df	OR	P value	95% CI	
							Lower bound	Upper bound
Baseline characteristics								
ACS type	-7.55	0.429	3.099	1	0.470	0.078	0.203	1.089
Prior CABG surgery	0.527	0.652	0.651	1	1.693	0.559	0.471	6.082
Prior COPD	-18.429	8265.394	0.000	1	1.410	0.998	0.000	.
Peripheral arterial disease	-0.848	1.076	0.621	1	2.335	0.431	0.283	19.239
Prior ACEi/ARB usage	0.715	0.475	2.266	1	2.045	0.132	0.806	5.190
LV ejection fraction on admission	0.416	0.343	1.426	1	1.516	0.225	0.774	2.969
Contrast amount	0.657	0.229	8.220	1	1.929	0.004	1.231	3.022
Laboratory parameters								
Trop I	-0.019	0.015	1.672	1	0.981	0.196	0.953	1.010
MLR	2.604	0.936	7.737	1	13.522	0.005	2.158	84.729
WBC/platelet ratio (WBCPR)	-52.115	18.626	7.829	1	2.330	0.005	0.000	0.000

Abbreviations: ACS: Acute coronary syndrome, CABG: Coronary aryery bypass greft surgery, COPD: Chronic obstructive pulmonary disease, ACEi/ARB: Angiotensin converting enzymes inhibitors/ Anjiotension II receptor blockers, Trop I: Troponın I, MLR: Monocyte to lymphocyte ratio, WBCPR: White blood cell count to platelet ratio, SE: Standard error, OR: Odds ratio, CI: Confidence interval

Discussion

There are different studies investigating many parameters, such as NLR, PLR, RDW, MPVLR, and SII, which may be associated with CIN in acute coronary syndromes. However, a recent study showed a significant association between CIN and NLR, CRP, and lower hematocrit levels, except for PLR [4-6,8]. Herein our study, MLR, PLR, WBC, and WBCPR were associated with CIN. Besides, CABG surgery, acute coronary syndrome type, contrast amount, hospital stay length, and prior ACEi/ARB usage were significantly associated with CIN. Nevertheless, there was no significant association between SII and CIN in our study. According to logistic regression analysis, WBCPR and MLR might be good predictors of CIN, in addition to contrast amount in this population.

Although there were too many studies investigating inflammatory parameters derived from blood count cells about CIN in the literature, our study is maybe the first study ascertaining and comparing other inflammatory parameters such as AISI, SII, SIRI, APRI, NLR, PLR, MLR, MPVLR, and others for CIN in acute coronary syndrome. Although there is a recent study stating that SII has a predictive value in predicting CIN in acute coronary syndrome [9], we did not find a significant association between SII and CIN. Besides, it is stated in the literature that AST/ALT ratio can be used to determine kidney damage in cancer patients or to predict post-operative acute kidney damage [10,12], we found that the AST/ALT ratio was not useful in predicting CIN in the acute coronary syndromes, as in SII.

Recently, MPVLR, a new parameter was associated with CIN and a good predictor of CIN in the acute coronary syndromes [9]. In our study, we could not find a significant association between MPVLR and CIN. Since there was a study about the association between acute kidney injury and neutrophil to platelet x lymphocyte ratio (N/LPR), we also investigated the N/LP ratio [18,19]. However, in our study, there was no significant association between the N/LP ratio and CIN. Recent studies also showed that MLR was an independent predictor of coronary inflammation and could be a good prognostic indicator of CIN in the acute coronary syndromes [20,21]. Complying with the last-cited study results about MLR and CIN, in our study, MLR was an independent predictor of CIN in the acute coronary syndromes.

It has been stated in the literature that the platelet/WBC ratio, which is a new parameter, can be a good prognostic tool in HBV-related chronic cirrhosis. There has been no study of this parameter in the literature on CIN, which is another complex inflammatory process [22]. We calculated a new formula for

white blood cell to platelet ratio (WBCPR) and found that there might be a significant association between CIN and WBCPR. In this study, we enquired the role of WBCPR in predicting CIN after percutaneous treatment in acute coronary syndrome. In this study, we aimed to investigate the role of the WBCPR in predicting CIN after percutaneous treatment in acute coronary syndromes. As a result, MLR and WBCPR were significantly associated with CIN in percutaneously treated coronary syndrome patients and could be good independent predictors of CIN in this group. The on-admission blood count-derived parameters can be calculated easily and quickly from routine blood tests in every patient with acute coronary syndromes. Thus, MLR can be a good prognostic parameter of CIN in acute coronary syndromes. WBCPR, a possibly new and independent indicator of CIN in patients with acute coronary syndromes, can be a useful parameter to predict CIN in these groups. In addition to MLR and WBCPR, contrast amount is surely associated with CIN and is a useful prognostic marker of CIN in this population.

Limitations

There were some limitations in our study. The primary limitation of the study is that it is retrospective and has a relatively small population. Secondly, we collected the on-admission data that could be affected from the timing of the patient admission to hospital. Thirdly, the comparison of patients with NSTEMI and STEMI specifically, rather than acute coronary syndrome, could have been made by including a larger patient population. Therefore, new, prospective, and larger population studies are needed to determine the true effects of blood cell-derived parameters on CIN in acute coronary syndromes.

Conclusion

CIN continues as a serious complication that may develop in acute coronary syndrome. In patients who are planned for percutaneous treatment in acute coronary syndrome, we can conclude that a new parameter, WBCPR, together with MLR, is a more valuable predictor for the development of CIN in these patients. Moreover, this study reiterates that it would be beneficial to keep the amount of contrast low.

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ORIGINAL ARTICLE

Dissoanalytic psychohistory: Dissoanalysis of the traumatic history of humanity and the construction of a new societal reality

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Abstract

In the face of all the limitations and criticisms regarding the recognition of consciousness as a psychosocial "*singularity experience*", the construction of "*Dissoanalysis Theory: Psychocommunal Therapy*" centered on "*multiple consciousness system", "multiple reality perception*" and "*multiple memory phenomenon*", that is, a new societal reality, has become an indispensability. Based on trauma and dissociation studies, i.e. modern psychotraumatology paradigms and modalities, the "*Dissoanalysis Theory*", structured by Ozturk with the aim of creating a functional society consisting of empathetic, prudent, just, peaceful, and capable individuals, made it possible for the emergence of "*dissoanalytic psychohistory*" from a psychosocial perspective. Dissoanalytic psychohistory is intervention therapy for psychosocial crises! "*Dissoanalytic psychohistory*" structured by Ozturk within the framework of the dissoanalytic school is defined as a branch of science that does researches on childhood traumas, psychosocial perceptions of childhood, chronic oppressions, child-rearing styles, dysfunctional families, dysfunctional generations, intergenerational transmission of trauma, intergenerational transfer of psychopathology, psychocommunal dissociation, dominant leaders and mass violence and develops strategies focused on especially preventing childhood traumas and wars. Dissoanalytic psychohistory, emphasizing that the neutralization of dysfunctional generations and the future can be achieved by the administration of "*psychocommunal therapy*" of all nations in the world, is an original psychology theory that consists of a holistic synthesis of modern psychotraumatology and psychohistory paradigms with the study of intergenerational transmission of trauma and intergenerational transfer of psychopathology. Dissoanalytic psychohistory, which is the dissoanalysis of the traumatic history of humanity and the construction of a new societal reality, both analyzes and integrates the dissociative components of societies with absolute reality. Dissoanalytic psychohistory creates development-oriented shifts, "*dissociative revolutions", "integrative psychosocial movements*" and "*mass predictions*" and even functional and healthy new society profiles by raising awareness of masses of human about their actions.

Keywords: Dissoanalytic psychohistory, dissoanalysis, psychohistory, dissociative revolution, intergenerational transmission of dissociation, intergenerational development

Theory of Dissoanalysis and The Age of Mass Dissociation

Dissociation, which is a psychosocial revolution against the apparent reality of oppressive systems, childhood traumas, dysfunctional generations and violent negative child-rearing styles that are perceived as unchangeable, undividable, and indestructible or unsplinterable, is both a rebellion, a search for freedom, and a harsh psychosociopolitical critique. The hypothesis of the singularity of consciousness, which is an individual experience with its subjective and objective components, in the face of encompassing dissociative reactions associated with traumatic experiences, is not an experimentally verifiable phenomenon. In the face of all the limitations and criticisms

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regarding the recognition of consciousness as a psychosocial *"singularity experience"*, the construction of *"Dissoanalysis Theory: Psychocommunal Therapy"* centered on *"multiple consciousness system"*, *"multiple reality perception"* and *"multiple memory phenomenon"*, that is, a new societal reality, has become an indispensability. Based on trauma and dissociation studies, i.e. modern psychotraumatology paradigms and modalities, the *"Dissoanalysis Theory"*, structured by Ozturk with the aim of creating a functional society consisting of empathetic, prudent, just, peaceful, and capable individuals, made it possible for the emergence of *"dissoanalytic psychohistory"* from a psychosocial perspective. Dissoanalysis theory emphasizes the beginning of an age of mass dissociation, which now spreads from individual to society, on behalf of today's oppressive systems and the directed people controlled and managed by dominant leaders. Every moment that intergenerational development yields or evolves into intergenerational fossilization is a milestone or turning point for childhood traumas, wars and genocides. The *"Dissoanalysis Theory"*, which is structured on an axis that has the closest interactional dynamic with each individual and social element of the *"multiple consciousness system"*, *"multiple reality perception"* and *"multiple memory phenomenon"* of the identity concept, which is differentiated with dissociative reactions and dissociative defenses in the face of traumatic experiences, has scientific roots in the long-term studies of *"modern psychotraumatology"* done by Ozturk, who is a trauma therapist, a psychohistorian and a dissoanalyst. Dissoanalysis provides very important theoretical and clinical contributions in the field of *"trauma and dissociation"*, both in the development of effective psychotherapy methods and in the structuring of modern psychotraumatology and psychohistory paradigms. Dissoanalysts, who have professional competence and efficiency in psychotraumatology, psychotherapy, suicidology and psychohistory, are defined as *"trauma therapists"* who conduct the treatment of trauma-related psychiatric diseases, especially dissociative disorders and post-traumatic stress disorder. As a psychotraumatologist and a psychohistorian, dissoanalysts develop effective psychotherapy models, modern psychology modalities, and dissoanalytic theories of psychohistory, as well as conducting scientific studies in the field of trauma and dissociation. As long as the dissoanalysis of traumatized individuals and societies controlled and governed by oppression cannot be carried out, no nation in the world can be freed the cycles of *"intergenerational transmission of violence"* and *"intergenerational transfer of psychopathology"* or even gain an orientation towards an integrative and developmental organization of life. The main purpose of dissoanalysis is to create integrative individuals and peace-oriented societies that are open to development in all nations of the world, and the *"dissoanalysis theory"* developed by Ozturk on this axis is the *"psychocommunal therapy"* itself! Dissoanalysis of psychosocial traumatic experiences facilitates our understanding of the dual dynamics and multiple components of encompassing oppressions, mass controls, cycles of violence, successive wars and terrorism,

and more importantly why we still attempt to control our children by both practicing negative child-rearing styles and traumatizing and dissociating them [1-8]. Dissoanalysis is a psychohistorical and psychotraumatological whole of cumulative scientific efforts, effective psychotherapy practices, and strategies to prevent short and long-term individual and social traumatic experiences in order to end both intergenerational transmission of trauma and dissociation, and intergenerational transfer of psychopathology in the operational context [1-2].

Dissoanalytic psychohistory, which is the dissoanalysis of the traumatic history of humanity and the construction of a new societal reality, both analyzes and integrates the dissociative components of societies with absolute reality. Within the framework of the trauma and dissociation-based theoretical and clinical pattern of the dissoanalysis theory developed by Ozturk, it is possible to construct modern psychotraumatology and psychohistory paradigms. The main purpose of dissoanalysis is to create a development-oriented new society, both normal and functional, composed of humanistic, empathetic, peaceful, compassionate, just, innovative and prudent individuals. As a modern theory of psychotraumatology, the psychohistorical mission of dissoanalysis is to ensure that a society of psychologically integrated individuals prevails in the intergenerational process. According to Ozturk's dissoanalysis theory, short or long-term *"functional psychotherapy approaches"*, *"effective crisis intervention programs"* and *"successful trauma prevention strategies"* cannot be developed without psychosocial analysis of violence-focused negative child-rearing styles and oppressive systems on chronic childhood traumas. From the perspective of modern psychotraumatology and dissoanalytical psychohistory, are psychodissociogenic attitudes and behaviors that function within the violence-focused negative child-rearing styles and are almost *"imprisoned"* or *"hidden"* as a *"punishment tool"* within these unempathetic, violence-focused negative child-rearing styles, with a primitive nature and intergenerational transmission [1,2,6,8]. Today, social control has become an active agent in the emergence of *"cyber dissociative experiences"* and *"cyber dissociation"* phenomenon, transforming into cyber control. In oppressive societies, digital communication networks and social media applications are used to control mass consciousness and cyber dissociative experiences are imposed on individuals. Anonymous dynamics and mobile components that prevent individuals of modern society from being authentic and individualized have been defined by Ozturk as a new dissociation phenomenon in the form of *"cyber dissociative experiences"*. According to the dissoanalysis theory, all societies of the world are now both controlled and ruled through digital communication networks and social media that cause cyber dissociative reactions. Today, traumatized societies of the digital age, which experience *"cyber dissociative experiences"* at maximal rates, have now substantiated a psychosocial transformation and even started to create directed new human and society profiles. The *"Age of Cyber Dissociation"* and even the *"Age of Mass Dissociation"* have begun, especially with the dominance of directed psychodigital

centers, which are closely related to the obedient and reversible characteristics of dysfunctional generations and conformist society profiles far from both originality and creativity that have emerged especially as of the beginning of the 21st century. The phenomenon of *"mass dissociation"* has been effective in the dominance of societies focused on *"dissociative denial"* in the face of chronic traumatic experiences and lasting oppressions. The dissociative denial created by ignoring that there are no traumatic life experiences, keeping individuals and societies away from the realization of absolute reality and imprisoning them in different and multiple realities, is the trauma of denial itself! There is nothing that distances individuals and societies from reality, from their consciousness and from themselves as much as denial, in fact, denial is a massacre of reality [9-11].

Psychocommunal Dissociation and Mass Consciousness Control

Dissociation is a camouflage focused on *"psychosocial denial"* that functions by hiding the subject in multiple consciousness and multiple memories to escape from realizing the traumatic reality or to get away from knowing this traumatic reality. In this context, dissociative reactions are psychosocial revolutionary liberation and individuation attempts of individuals and societies whose subjectivity has been taken away from them by being traumatized. According to the theory of dissoanalysis, in all times and nations of the world, the phenomenon of dissociation functions on a psychosocial dimension, so that today's *"age of dissociation"* almost imposes denial-based psychological defenses. Individuals, communities, societies and even the world are both controlled and ruled by the oppressive systems in which they exist in the space from the traumatic and dissociogenic history of humanity to the present by creating a denial-oriented *"psychocommunal dissociation"*. The denial of reality and trauma, as well as the trauma of denial, constitute the main sources of all dissociation phenomena that spread pervasively from the individual to the society [1,2,8]. However, according to the theory of dissoanalysis, social dissociation focused on the experience of the whole is actually a dystopia. Society is utopian in relation to the community and is deliberately created as inherently controllable by dominant systems. Because all individuals forming the society are not likely to be dissociated in the same time period and on the same *"external or internal reality"*. Communities come together to form society, and the communal dissociations experienced individually in these communities are transformed from psychosocial dissociation to mass dissociation. The notion that society, made up of individuals and communities, is monolithic is completely unrealistic. Just as ideas or actions that are subgroups of a mainstream thought or dominant system, communities within the same society experience their own unique dissociations. Dystopic societies and dystopian cultures are the main sources of dissociative experiences, even they are dissociogenic agents that force people into modalities of obedience and submission. Oppressive systems produce dissociating dominant cultures and coercive modalities

of submission for individuals, communities, and societies. A minor proportion of individuals, communities, and societies that do not ally with oppressive systems or oppose dominant cultures completely reject all submission and control-oriented modalities. However, a major proportion of individuals, communities and societies that are more moderate to the oppressive system may merge around a counter-subcultural focus. In certain time periods, developmentally-oriented subcultures can become widespread and even become the norm. Communities are more related to the subject directly or indirectly and establish more reciprocal bonds. Societies, on the other hand, have a more tangential and more virtual orientation in terms of direct relationship with the subject and *"social reciprocity"*. Ozturk defined the dynamics of *"communal dissociation"* experienced in communities and in the inner clusters of societies as *"psychocommunal dissociation"* because they take place and function on a psychogenic basis. Communal dissociation, psychocommunal dissociation and psychosocial dissociation are phenomena that have both function transitions and close relationship dynamics with each other and are also subgroups of mass dissociation. Ozturk emphasizes that there is a spread from dissociation of actual life to communal dissociation, from communal dissociation to psychocommunal dissociation, that *"maximal social dissociation"* or *"holistic dissociative structure"* is psychosocial dissociation itself [1,2,4,8,12]. The communal dissociation experienced in the face of mass consciousness control of oppressive societies is a struggle and reaction of the traumatized subject or subjects to remain original against standardization and de-uniquification! [1].

Violence Dystopia and Traumatic Selves in All Nations of the World

The traumatic anamnesis of the history of humanity and the intergenerational transmission of the psychological traces of dissociative experiences continue to necessitate the emergence of functional, psychotraumatologically and psychohistorically-oriented, new psychosocial paradigms, modalities and theories. *"Identity"* and *"self"*, as wholly human and long-term concepts, function as original psychosocial signatures of the interactions of individuals with both their inner and outer worlds on a dissoanalytic axis. The *"uncertainty trauma"*, experienced in the face of the impossibility of the most appropriate response to a sorrowful life adventure laden with traumatic experiences and chronic oppressions, ensures the maintenance of function transitions between identity and self and dissociative reactions. *"Psychotherapy of Identity-Discovery and Individuation"*, *"Crisis Intervention Psychotherapy"* and *"Trauma Based Alliance Model Therapy"* developed by Ozturk focus on these function transitions, and *"Dissoanalysis Theory"*, which was also structured by Ozturk in recent years, has come into play as a social and even psychosocial therapy. Psychotherapy of identity-discovery and individuation, crisis intervention psychotherapy and trauma based alliance model therapy are defined as the three pillars of dissoanalysis theory. Dissoanalysis theory is structured

on individuals, communities and societies being themselves, existing as they really are, providing their psychosocial reciprocity, and their original and independent survival. In this restructuring process, re-activating the integrative functions of the self, which was interrupted by the effects of traumatic experiences, dysfunctional family dynamics and chronic oppressions, and providing the lost optimal distance and adjustment are the most basic agents. Ozturk, the founder of dissoanalytic psychohistory, emphasizes that traumatized masses who cannot individuate are ruled by dominant leaders or dictators in herds, both by being de-uniquification and revictimized. A community or society of traumatic selves maximally adopts primitive child-rearing styles, submits to all kinds of oppression and authority, and even imprisons the countries they live in in cycles of war and violence by directing the feelings of anger and hatred made possible by their traumatic experiences, which they cannot neutralize, both to themselves and to innocent individuals, and even make mass sabotage their intergenerational destiny! A nation of maximally traumatic selves becomes pro-violent and pro-war, this proclivity for violence and war is an anger and hate-oriented projection of their negative life experiences that they cannot neutralize, with these projections the masses try to distance themselves from their own negative life experiences, and even the coverage or generalization and expansion of traumatic experiences to other people makes it possible for them to deny their real psychological pain. Traumatic individuals and societies tend to be pro-war and pro-violence in the name of trying to get rid of their negative life experiences and generalize, legalize, and even normalize traumatic experiences by directing their anger and hatred towards innocent people who are conjugated in this way, that is, they traumatize them and make them like themselves! The dissociation phenomenon associated with traumatic oscillations creates fragile human profiles that are not individuated and even individuals and societies are controlled and ruled through their traumatic experiences. Violence-oriented negative child-rearing styles, childhood traumas and chronic oppressions strike the biggest psychic impact on identity, self, consciousness, and memory. According to Ozturk's Dissoanalysis Theory; trauma and dissociation operate as a psychopathogenic and, at times, a dual and dominating force that both overlaps each other and has functional transitions with each other through disrupting the individual's interpersonal relationship dynamics, interrupting the integrative functions of identity and self, disintegrating the power of subjectivity and subjective effectiveness, forcing the person to obedience and de-uniquification modalities in the face of oppression or domination, violating personal boundaries and making them open to control and even abuse and making it difficult for the person to define and express himself [1-5].

The Birth of Dissoanalytic Psychohistory as a Psychosocial Crisis Intervention Therapy, Wounded Psychosocial Memory, and the Construction of a New Societal Reality

Dissoanalytic psychohistory is an intervention therapy for psychosocial crises! According to Ozturk, dissoanalytic psychohistory is the transformation of a major *"psychocommunal therapy"* hypothesis into reality, which is constructed at every point where the extensive traumatic components in the anamnesis of humanity, and the data obtained during the dissoanalysis process reach perfection. Ozturk defines dissoanalytic psychohistory as a scientific field which studies childhood traumas, psychosocial perceptions of childhood, chronic oppressions, child-rearing styles, dysfunctional families, dysfunctional generations, intergenerational transmission of trauma, intergenerational transmission of dissociation, intergenerational transfer of psychopathology, psychocommunal dissociation, wars, genocides, dominant leaders and psychosocial consciousness alliance and develops strategies to prevent wars and childhood traumas and is a development-oriented on creating a peaceful society. In this respect, psychohistory is actually *"psychocommunal therapy"*. *"Dissoanalytic Psychohistory"* is an original psychology theory that consists of an integrative synthesis of modern psychotraumatology and psychohistory paradigms with the studies on dissociation-based intergenerational transmission of trauma and intergenerational transfer of psychopathology carried out by Ozturk between 2003 and 2023. According to the dissoanalysis theory, psychohistory is the psychosocial identity, psychosocial memory, and psychosocial consciousness, which is transmitted from the past to the present, between generations! *"Psychosocial identity"*, *"psychosocial memory"* and *"psychosocial consciousness"* are transmitted on an intergenerational axis through interactive movements with every element of the human being that is related to and nourished by the self. The simultaneous co-consciousness or dissociative denialism of all individuals forming the community or society creates a *"social alliance"*, which determines the positive or negative group orientation in a psychosocial focus shifting from the singular to the plural in relation to absolute reality and absolute consciousness. In a nation consists of traumatized individuals, psychosocial memory is fragmented, disorganized, and symbolic. *"Wounded psychosocial memory"* is laden with elements that force to obey both traumatized subjects and dissociated masses, the major agents of which are ongoing oppressions, chronic childhood traumas, dysfunctional family dynamics and unempathetic negative child-rearing styles. Unless *"consecutive or chronic incidents of violence with variable rates"* of individual and social origin in the space from the history of humanity to the present are neutralized by psychosocial dissoanalysis method, mass consciousness controls in all nations of the world, chronic wars, colonial policies, dissociogenic, oppressive systems, unempathetic negative child-rearing styles, apparently normal families, dysfunctional generations, dominating interpersonal relationships and cycles of obedience will continue to exist at maximal rates! Ozturk underlines that the essence of dissociation experiences is the phenomenon of "*pluralization by fragmentation*", which develops as a psychosocial reaction against being controlled and ruled. Every dissociative motion of dysfunctional family dynamics and dysfunctional generations ignored or denied, which clearly

explain all the cumulative *"psychosocial maladjustments"* and *"psychosocial pathological conformism"* and even *"psychosocial sabotage"* ranging from childhood traumas fed by negative child-rearing styles to wars, causes intergenerational transfer of psychopathology and intergenerational transmission of trauma. Within the framework of the trauma-based theoretical and clinical pattern of the dissoanalysis theory developed by Ozturk, it is possible to construct modern psychohistory and psychotraumatology paradigms and to engage dissoanalysts as *"peace ambassadors", "crisis intervention specialists"* and *"psychosocial trauma experts"*. Dissoanalysis is a new theory of psychology, psychohistory and psychotraumatology that exists both as a *"psychocommunal therapy"* from a *"dualistic, dialectical and dichotomous association"* perspective and in the orientation of *"adaptive and creative evolution"* that is identical with every individual and social element. In the axis of modern psychohistory and psychotraumatology theories, chronic childhood traumas are the ones that function in violence-focused negative child-rearing styles and in fact, dissociogenic attitudes and behaviors with a primitive nature and intergenerational transmission, which are almost *"imprisoned"* or *"hidden"* as a *"punishment tool"* in these violence-focused and unempathetic negative child-rearing styles, that abusive parents ruthlessly use the reality changes they create with variable rate of their norms/normlessness and unstable attitudes both to achieve their own hedonistic interests and to control and rule their children [1-4,7,13].

The dynamic development of humanity behind its traumatic anamnesis and tragic past is a highly dissociative and complicated story, laden with multiple realities in the space from both individual and social defeats to victories! For centuries, human and society, with all their dissociative elements and dual or multiple existence, are maximally positioned against their own reality continues to be the focus of the sciences of psychology, history and psychohistory. However, in order to understand today's modern human and society, most social sciences have remained outdated, and at this regressive milestone, psychohistory, as an innovative academic discipline, came into play. A fundamental importance is given to the concept of time in all sciences, and even these sciences carry out their studies in a time focus that they dominate. Psychology looks at both the past and the future from the focus of *"present time"* and even predicts the short and long-term behaviors of individuals. History evaluates the *"old time"* from the focus of "*past time"* or *"time left in the past"*. On the other hand, *"modern psychohistory: dissoanalytic psychohistory"* pioneered by Ozturk, beyond predicting the actions of an individual, has focused on predicting the general flow of the whole vital process related to every element related to the future human being, with psychosocial analysis and even dissoanalysis of masses of people in the past and present. In today's directed societies, childhood traumas and wars come into play as mass sabotage and mass consciousness controls, and they are gradually moving away from peace and empathy-based life forms or systems. Dissoanalytic psychohistory offers much more

effective and applicable strategies than psychology, psychiatry, anthropology, and sociology to prevent childhood traumas and wars. Therefore, it is thought that dissoanalytic psychohistory will continue to progress by both dominating and comprising all other related sciences soon. Any history written excluding the science of psychology is misleading and even doomed to be forgotten! History writes the stories or histories of people, societies and countries of the past in an orientation that is far from optimal emotion, either numbly or with exaggerated enthusiasm, even ignoring absolute reality. None of the individual-centered psychological theories can make realistic deductions about society. Dissoanalytic psychohistory goes far beyond both psychology and history by making the most closely related and multi-focused analyzes with absolute truths of the masses as a psychosocial whole in the relationship between the individual and the society! Traumatized and dissociated masses write or construct a plural history rather than being singular because of their multiple memories and multiple consciousnesses, and in this direction, social realities are also multidimensional for most nations. Dissoanalytic psychohistory creates development-oriented shifts, dissociative revolutions, integrative psychosocial movements and strong mass predictions, even new functional and healthy society profiles, by analyzing the multiple realities and dissociative components of societies with an integrative approach, in the presence of absolute reality, and by raising awareness of the human masses about their actions. According to the dissoanalytic theory, the more alliances or unity there are in the psychosocial consciousness of the masses and their perception of reality, the more integrated they are [1,3,13].

Dissoanalytical psychohistory carries out its academic activities as a modern and original discipline oriented towards strategies to prevent individual and social traumas, with an integrating structure of the sciences of history and psychology, which have close relationship dynamics, that do not cover or deny each other. Ozturk redefined both psychohistory, the original and modern field of psychology that emerged with the combination of psychology and historical sciences, but differed from the combination of these disciplines and continued its progress by becoming original, and the relationship between psychology and historical sciences, with innovative *"trauma and dissociation"* paradigms and modalities. According to Ozturk, dissoanalytical psychohistory provides us all with an integrative and existential scientific experience in which we can put our thoughts as well as our feelings into transformation-centered action. However, this integrative and existential scientific experience is much more complicated than the catharsis issue, it is a development-oriented, encompassing and associative transformation experience itself! If we are not afraid of absolute reality in the focus of mass consciousness, psychohistory can easily illuminate the blurry places that have been waiting in the dark for a while, as the psychological traces of successive generations, with transparent lights. In the context of psychocommunal therapy, if we understand what past traumatic experiences the psychosocial elements exposed to this transparent light are part of, we can gain

very deep and valuable insights into our care-seeking sensitivities about which we might be vulnerable, angry and numb or, even by embracing all the children of the world with a more compassionate and virtuous heart, we can create a *"new world"* free of wars, competition, injustice and violence. We can see a lot for our future, transforming in the trajectory of the pervasive invasion of the past time into the present that we wouldn't have discovered otherwise in human history, that we've been amnesic and have ignored, or even denied or feared and exhibited phobic avoidance. Because, in the context of dissoanalytic psychohistory, it is not impossible to see the psychological traces of a single traumatic experience even after hundreds of years. From the perspective of dissoanalytical psychohistory, wars are the millennial cries of children whose hearts are broken and left to loneliness, or their revenge, or even the psychological traces of the millennial traumatic experiences of children whose smiles have been stolen! These psychological traces continue to copy and repeat themselves in a mass orientation in the history of humanity for centuries as both *"intergenerational transmission of trauma"* and *"intergenerational transfer of psychopathology"*. According to Ozturk, dissoanalytic psychohistory makes possible the existence of *"psychosocial insight"* and *"mass synthesis"* experiences, namely integration, through the analysis of identical and consecutive experiences in the *"mutual and projective relationship"* of generations! If we can evaluate the history that affects us in terms of dissoanalysis theory and encompasses all times of the world, on the psychosocial axis, we can enable the existence of a competent new human and even society model that is empathetic, compassionate, and development-oriented by overcoming both our own and social dissociative obstacles [1-3.8].

The hypothesis that individuals who experience *"consciousness interruption"*, *"memory reproduction"* and *"abdication of consciousness"* within the orbit of both traumatizing and dissociative dynamics of societies, oppressive cultures and authoritarian systems that are mesmerized by their dictators today can have an obedient, even *"impersonal"* or *"totemic"* life has already begun to transform into reality, that these experiences of *"psychosocial abdication of consciousness"* and *"psychosocial consciousness interruption"* are psychocommunal dissociation itself! The *"memory reproduction"* that Ozturk describes is the *"false positive social memory"*, in which the sum of the unreal stories and descriptions created and convinced by the masses who traumatize them but have *"hunger for affirmation"* the dictators they mesmerized are recorded! Each individual will either submit to the structure of most systems, which makes him/herself anonymous and destroys his/her *"subjectivity"*, or he/she will continue to make an effort as a dissociate, hopelessly or helplessly to try to change the system, even if they fail in their apparent solution-oriented goals, by targeting the society and the system. In fact, all neurotic disorders, especially dissociative disorders are initially adaptive reactions to abusive family, oppressive social environment, exhausting work life, and controlling manipulative systems, and as the frequency, duration

and severity of traumatic experiences increase, these adaptive reactions themselves turn into a maladaptive process, which sometimes results in a *"mass dysfunctional adjustment"* such as *"social dissociation"*. In dissociative individuals and societies, rapid transitions occur between the healthy and unhealthy parts of themselves. The healthy part represents independence, and the unhealthy part represents dependency. Fascist leaders control individuals and societies by traumatizing and dissociating them, highlighting their unhealthy parts, and oppressing their healthy parts. From a psychosocial point of view, all revictimization and fossilization cycles take place when the unhealthy part takes control, while all development and freedom-oriented dissociative revolutions take place when the healthy part takes control. Individuals and societies that are controlled and ruled by traumatizing can get rid of slavery, oppression, and abuse through dissociative revolutions that they will initiate by re-activating their healthy parts on the axis of a new societal reality they have built. Dissoanalysts can teach individuals and societies to control the rapid transitions or oscillations between dissociation and association and even to be on their healthy side for longer periods of time; neutralization of traumatic experiences is only possible when individuals and societies can stay on their healthy parts, anyway [1,2,8,14].

To comprehend dissoanalytical psychohistory more easily, it is necessary to define humanity in the space from past to present, as well as to know psychology and history, and even to analyze the people of the past by focusing on today's people, this condition is also valid for the analysis of societies. According to Ozturk, the main mission of dissoanalytic psychohistory is to make short-term and especially long-term predictions of holistic actions of post-present human masses in the direction of development or fossilization by psychosocial analysis of pre-present human masses! According to the dissoanalysis theory, individual psychopathologies in a nation are identical with social psychopathologies, that social psychopathologies that can expand and transform from this focus of individual psychopathologies are both recognizable and predictable, neutralized, and treatable in a psychohistorical context. In a society where childhood traumas, wars, oppressive systems and even genocides prevail, psychopathology is experienced at maximal rates and (also) this cumulative experience process is transformed into mass psychopathology with a strong tendency. Traumatized individuals create traumatized societies, and traumatized societies are the main source of mass psychopathologies and psychosocial abdication of consciousness, that *"totemic societies"* experiencing a psychosocial abdication of consciousness are subject to identity atrophy, identity transition, and identity penetration, tending to be attached to an abuser willing to be dominated by their dictators into whom they are mesmerize! According to dissoanalysis theory and dissoanalytic psychohistory, persons who experience identity atrophy reluctantly follow their dictator or totemic leader, whom they believe or are made to be believed as apparently saviors both individually and socially, as if in a *"collective/multiple sabotage"* orbit. Totemic leaders appeal to

the transformative, sadomasochistic, and traumatized souls of the masses, hypnotizing them in the name of violence-focused targets, that admiration for these totemic leaders however is not fueled by love, but by a trauma-related *"narcissistic fear"* or even a *"dissociative angoisse"*. At that moment, individuals in a multidimensional sabotage circle, begin to desire the domination of a dictator who shares a similar traumatic past with them to tolerate the uncertainty, frustration and anxiety brought on by traumatic experiences. The masses, who are hypnotized by the targets focused on violence, at the same time turn into the evil spirit twins, that is, their abusers, that at this stage, all kinds of traumatic experiences that are dissociated are expressed and even re-experienced, and victims who are *"focused on being like themselves"* are selected. According to the dissoanalytic theory, traumatic experiences are repeated hundreds or even thousands of times in individual and collective memory, and in a community where an outdated child-rearing style prevails, the anger and violence felt against these traumatic experiences are transferred by being paranoid to the chosen counter-community, that this transfer is accomplished through dysfunctional generations [1,2,4,8,14].

Traumatic experiences in the dissociative history of humanity enable the marginal acting outs, radical actions, sadistic thoughts, and hidden emotions of dysfunctional societies with multiple consciousness, and multiple memories to pass from fantasy dimension to real dimension, that these self-sabotaging transitions continue to revictimize individuals and societies by imprisoning them in almost endless traumatic whirlpools. As traumatic experiences and psychopathologies are suppressed without treatment, they turn into individual, and mass self-sabotage and these self-sabotages are passed on to successive generations. With this orientation, *"dissoanalytic psychohistory"* continues to embrace the principle of *"producing inclusive and functional scientific data"* for many different disciplines related to intergenerational transmission of trauma and intergenerational transfer of psychopathology, that in this direction, dissoanalytical psychohistory is focused on the goal of creating a peace-oriented society and a just world system. According to Ozturk, dissoanalytical psychohistory and modern psychotraumatology studies focusing on intergenerational transmission of trauma and intergenerational transfer of psychopathology emphasize that people can endure traumatic events through "*psychosocial dissociation*", in which multiple consciousness and memory systems are the determinant agents, activated in the face of oppression and obedience. Dissociation is a normal reaction, even a harsh manifestation with divided selves, multiple consciousness and memory systems against abusive systems that traumatize and enslave individuals, objectify, and deprive them of their subjectivity. In psychosocially experienced dissociation, people are forced into obedience through violence by dominant leaders and oppressive systems, or they volunteer for domination, that the real trauma is now the oppressive system itself, and this system has taken away both their freedom and uniqueness, as well as their selves and psychogenic identities.

Oppressive systems do not deliver what they promise to the people they make believe or even exploit and deceive or betray them. *"Deception trauma"* turns into a betrayal trauma in this process and continues to dissociate people. Dissociative experiences, which are now forced to be experienced in all kinds of oppressive systems for the individual, are not exotic processes, they are rather ordinary experiences. Dissociation is a normative characteristic of modern actual life in terms of *"experiential disconnection", "self-imprisonment", "gaining multiplicity in the psyche", "strengthening by dividing in the face of trauma", "interpersonal isolation"* and "*alienation from the environment"*, but this ordinary vitality can be transformed into technology addiction, hedonistic consumerism, marginal lives, and self-sabotage with the alienating effect of cyberspace from the social environment [1-4,8,15].

In terms of dissoanalytic psychohistory, the mirrors of luxury entertainment and shopping venues have made us believe that we all look better than we are, and brands that function as the rewards of capitalism have led us to think of ourselves as someone else and even to *"starring"* fantasies. It hurts us to appear as we are now, that in this perspective, the masses try to be what they want to be seen and show an intense effort to irresolutely accept a compulsory optional life that is almost unreal and only exists *"as"* or *"apparently"* [2,9,15]. According to Ozturk, the freedoms of postmodern people who are controlled through *"cyber dissociation experiences"* are as much as the number of alternatives offered to them by the dominant systems in the societies they live in or in the *"cyber castles"*, and these freedoms have now yielded to compulsory choices, that is, essentially single or dual-probability forms. In the digital age, illusions have taken the place of reality, our beliefs or thoughts unfortunately do not matter, in order to get everything, it is sufficient to act in accordance with the system in which one lives and to embellish what is requested to be heard [9-11]. Psychosocial control-oriented systems are easily believed, even through social media, but systems will certainly lie more or less, and once this is noticed, all illusions of the individual are destroyed, and the individual will either be a part of the system or will struggle with this system in the most appropriate way. However, this struggle is quite dissociative for the maximal rate of individuals with traumatic components, who experience the pluralization of consciousness, memory and reality with chronic oppressions, negative child-rearing styles and dysfunctional family dynamics. In this axis, *"social dissociation"* and *"psychocommunal dissociation"* as well as *"clinical dissociation"* are transformed into a mass system psychopathology by feeding on both maladaptive relationship dynamics and dysfunctional internal structures and even self-sabotage of traumatic individuals and communities. As reemphasized, the dissociation experienced by the individual is a clear, harsh and fair criticism against the system that enslaves individuals and takes away their subjectivity, independence and self [2,16,17]. Social dissociation is the holistic and successive psychopathology of childhood traumas hidden in the violence-oriented negative child-rearing styles applied to control and even

rule individuals in a nation! According to the dissoanalysis theory, just as the psychopathology in individuals is identical with the psychopathology found in the whole family, the psychopathology in the family is also identical with the psychopathology found in the society [1,2].

"Fossilization processes", which are resistant to *"development processes"* in all times and in all societies of the world, continue to operate as a dystopia of violence. At this point, psychohistory, which is a science that focuses on both the psychosocial evaluation of past events and the dissoanalysis of social violence events, is paired with psychology, comes into play with *"effective and applicable solution offers"* as a short and long term *"prevention strategy"* of childhood traumas and wars. By analyzing dysfunctional families, negative child-rearing styles, intergenerational transmissions of trauma, intergenerational transfers of psychopathology, social control mechanisms, successive wars, genocides, and nations' perceptions on children, from the past to the present in the light of modern psychotraumatology paradigms and modalities, dissoanalytic psychohistory offers us predictions of future action by the masses of people [2-5,7,8]. The analysis of the time left in the past or the present moment is valuable to the extent that it can make a prediction that turns into reality for the future, and all other evaluations that diverge from reality are nonfunctional or even unscientific! The psychohistory, which continues its development as the most systematic and comprehensive science of the modern age, is a comprehensive, objective and even synoptic view in which successive individual and mass violence events are analyzed psychosocially in a space from childhood traumas to wars. In order to create a new normal generation in the hypothesis that *"every person, every community and every society is an original psychogen"*, it is imperative that all vital masses that have prevailed from past to present undergo an adaptive positive transformation in order to reach the absolute reality in the intergenerational spaces of the integrative and creative focuses of the psychosocial consciousness alliance, otherwise: *"Individuals and societies that deny reality are doomed to live by dividing"*! Individuals, communities, and societies, and even the world, are both controlled, submitted and ruled by the motivational and oppressive systems in which they live in a wide space from the traumatic and dissociative history of humanity to the present, creating a denial-oriented *"psychocommunal dissociation"*. In this context, Ozturk proposes a *"psychocommunal therapy"* to break the cycles of *"traumatization"* and *"revictimization"* that expand on a dominant axis from the individual to the society. Provided that psychocommunal therapy is adopted and prevails in all nations of the world, all traumatic life events, especially childhood traumas, wars, and genocides, will not go beyond being a historical anecdote! [1,2].

Neutralization of Individual and Social Traumas from the Perspective of Dissoanalytic Psychohistory

In all phases of human history, individuals and societies have

been able to make sense of both themselves and the present with dissociative and associative oscillations by establishing a *"psychosocial bond"* between the past and the future. However, the domino effects of both traumatic and dissociative experiences create interruptions in the consciousness and memory of individuals and societies in these processes of interpretation. Therefore, social memories and social consciousnesses, as well as individual memories and social consciousnesses function in a fragmented way, in fact, the social identity itself is dissociative and the traumatic and dissociative psychological traces of the past are reflected in the moment lived through an intergenerational transmission! Dissoanalytical psychohistory interprets the integrative bonds and function transitions between signs and metonymy or symbols in individual and social dissociative reactions or experiences, which are dynamics of close relationship with the traumatic past of humanity, with modern psychotraumatology paradigms and modalities in a comprehensive and solution-oriented perspective. This is exactly why dissoanalytic psychohistory is a psychosocial dissoanalysis, that is, *"psychocommunal therapy"*, of the traumatic history of humanity. According to Ozturk, which is both an innovative *"science of psychology"* and a development-oriented *"society organization"* and even a *"modern mass philosophy"*, is a comprehensive dissoanalysis conducted to develop *"solution-oriented strategies"* against intergenerational transmissions of trauma and intergenerational transfers of psychopathology. The cumulative reflections of chronic and encompassing individual traumatic life experiences, which are characterized by the *"mass unconscious"* dynamics that occur on a holistic basis, create *"psychocommunal dissociation"*. The *"denial of individual trauma"* and the massive ignoring of absolute reality make it possible to experience social consciousness interruptions and memory reproductions. This process, on the other hand, creates amorphous, not-regulated, boundless, and transforming subclinical and even psychopathological *"borderline masses"* who, with their hysterical blindness, become spectators in the face of any focus of violence that expands from the individual to the society, and who allied themselves with authority figures with a *"hunger for affirmation"*, positioned in the ranks of the abusers and even bowed to them and awaited their hedonistic false rewards [1-3,7,8].

The traumas of inequality, injustice, ruthlessness and dedifferentiation traumas have turned into dissociative destinies on behalf of societies all over the world, as oppressive systems impose the rule of individuals who are marionetted by narcissistic dictators under the influence of power hunger. Psychopathogenic modalities that compel obedience in the face of oppressive systems trap both individuals and societies in childhood traumas and war whirlpools, on this axis, self-sabotage turns into mass sabotage! The forced adoption of the defense of denial in the face of mass violence in the digital age has been a major factor in the construction of a dissociated new world order and the creation of a perception of multiple reality. Psychosocial traumatic life experiences can only be neutralized by the *"dissoanalysis*

method", a *"psychosocial therapy"* developed by Ozturk within the framework of dissoanalytic psychohistory and modern psychotraumatology theories. As long as the dissoanalysis of traumatized individuals and societies cannot be carried out, no nation can get rid of its violence-oriented borderline components or even have a developmental and integrative life organization. As reemphasized, the main purpose of dissoanalysis is to create integrated individuals and societies that are open to both development and innovation. Dissoanalysis is the development of psychosocial theories focused on prevention strategies in order to both end and treat individual and social traumas as soon as possible and the structuring of clinical-based modern psychotherapy methods with psychotraumatology and psychohistory perspectives on dissociative disorders, which show the closest relationship with chronic childhood traumas that start at an early age, and neutralizing the basic dissociative components underlying these individual and social traumas with a holistic orientation. This neutralization process, which provides individual and social integration, can be carried out under the leadership of dissoanalysts, psychohistorians, psychotraumatologists and trauma psychotherapists who are peace ambassadors in all societies of the world. Natural and guiding parenting style is a short-and-long-term response to violence-oriented negative child-rearing styles, dysfunctional family dynamics, childhood traumas, trauma-related psychopathologies (dissociative disorders and post-traumatic stress disorder) and incidents of social violence that prevent the existence of both healthy parents and children and development-oriented societies on the psychosocial axis [1,2,18].

Traumatic Social Memory, Intergenerational Transmission of Dissociation, and Uncertainty Trauma

The traumatic memory of every oppression-oriented society, which is dominated by dysfunctional relationship dynamics and dependency-independency conflicts, shows intergenerational transmission with dissociative reactions, and this intergenerational transmission creates an *"uncertainty chaos"*. The uncertainty chaos begins to be experienced as an *"uncertainty trauma"* on behalf of individuals and masses when it cannot be defined, grasped, stopped, or neutralized. According to Ozturk's *"Dissoanalysis Theory"*, wars and childhood traumas co-existing in a holistic space with a close or long-term sequence with identical psychohistorical and psychosocial axis dissociative dynamics that can be strongly transformed into each other, are the two most effective agents in the transformation of this uncertainty chaos into the uncertainty trauma, but wars are both more severe and more destructive than the sum of the traumatic components that make it possible to exist! Dissoanalytic psychohistory defends the fact that it is possible to comprehend both *"the past moment"* and the *"present moment"* objectively and self-consciously through the analysis of human behaviors and motivations on a psychosocial basis that exist in the background of historical events in all times of the world and in all societies of the world [1,2]. The further one goes back in

history, the more primitive the perception of children and child-rearing styles become, and the higher the frequency, severity and intensity of wars and childhood traumas. According to Ozturk, the founder of dissoanalytic psychohistory, and deMause, who is a doyen of psychohistory, it is possible to say that, directly proportional to violence-focused negative child-rearing styles, in the past children grew up in dysfunctional families like those of today's trauma-related dissociative identity disorder cases, and that dissociative experiences were the norm. The tragic past of all humanity intersects with the traumatic and dissociative past time, almost encompassing the present with wars and childhood traumas. If the necessary psychosocial precautions are not taken, the present and the future moment will become a reality that is much more frightening than the time left in the past, even a nightmare focused on mass violence [1-3,19,20].

Psychohistory states in a clear wording, that from the existence of humanity to today's space, the references made by adults to the concept of child and the importance they give to the concept of child vary and move from period to period. Positive references to the concept of child, especially to girls, and the importance or value given to this concept show a metamorphosis or differentiation in direct proportion to the level of development of the society in different times and cultures. In this metamorphosis or differentiations, both the individual experiences of people and the experiences of the societies affected by these individuals are very effective [4,13,20]. According to Ozturk, dissoanalytic psychohistory undertakes the mission of neutralizing the traumatic memories and dissociative reactions of all societies in the world. This traumatic memory in a collective nature, that is, traumatic collective memory and dissociative reactions, operating as the *"locomotive agent"* of all kinds of violence in the space from the individual to the society, can only be effectively and successfully intervened in the short and long term with the therapeutic approaches developed by both psychotraumatologists and dissoanalysts and the strategies to prevent traumatic events constructed by psychohistorians. If a psychohistorical solution is not brought to the traumatic memories and dissociative reactions of all societies, every place and every moment of humanity will both witness the uncertainty chaos and experience the uncertainty trauma chronically in the intergenerational process. "*Traumatic social memory*" is the active agent of *"intergenerational transmission of trauma"*, *"intergenerational transfer of psychopathology"* and *"intergenerational transmission of dissociation"* [1,3,4,8]. A history that is dissoanalytically distant from psychology and even blind to a holistic psychosocial method lacks both half of its body and soul. In developmental orientation, dissoanalytic psychohistory continues its multi-focused scientific development at maximum speed already including history and psychology within its scope! [1,2].

Ozturk, who is the first psychohistorian and dissoanalyst of Turkey, emphasizes that individual traumas that cannot be intervened and treated are transformed into social traumas by

showing a cumulative change and differentiation and even gaining a holistic presence on a collective axis. Social traumas experienced with mass movements during or immediately after individual traumas gain a holistic existence on a collective axis contain intergenerational transmission of trauma and intergenerational transfer of psychopathology [1,4,7]. According to Ozturk's Dissoanalysis Theory, the wars which turn into social sabotage after staying silent in the face of individual traumas or trying to suffocate these traumas with silence are a long-term revenge of both the tragic face of all traumas and every dissociative element of the human being tried to be inauthentic, objectified or even nullified! The hidden subjects of these long-term revenges are evil parents, whose psychological traces of childhood traumas hidden in their violence-oriented negative child-rearing styles are destroyed by brutal wars and dissociative revolutions, and a new development-oriented human and society profile is created. In this new profile of people and society, primitive child-rearing styles with a dysfunctional nature are abandoned, and positive child-rearing styles with a functional nature are reached, and even a different humanistic regime is created with the original collective realities born in this process [1,2,8].

In intergenerational transmission of trauma, dysfunctional families function as an active agent together with *"apparently normal family dynamics"* and *"violence-oriented negative child-rearing styles"*, and this process itself leads to intergenerational transfer of psychopathology. The active agent of this intergenerational transfer of psychopathology is the empathy interrupted, violent, and inconsistent child-rearing styles, which also imprison childhood traumas. Intergenerational transmission of trauma and intergenerational transfer of psychopathology show an identical nature to each other in dysfunctional generations. Psychocommunal dissociation is experienced at a major rate in dysfunctional generations. According to Ozturk, *"psychocommunal dissociation"* is the isolation of individuals and masses from multiple communications, multiple stimuli and multiple realities. In psychocommunal dissociation, the process of focusing on a single reality, a single philosophy or belief system with a radical motivation is experienced, which is why parents living in the same period mostly adopt the same child-rearing style. The dominant negative child-rearing style in a society is the main source of intergenerational transmission of trauma and intergenerational transfer of psychopathology [4,5,7,21]. In terms of psychohistory, child-rearing styles both change and develop at a very slow pace, and similar psychopathologies and childhood traumas are seen at close rates in successive generations with largely identical child-rearing styles [4,18]. This dissociogenic process is the very intergenerational transfer of psychopathology and intergenerational transmission of trauma, which are the most effective agents of the emergence of wars and mass violence! Wars and incidents of mass violence condemn the traumatized and psychologically frozen borderline societies to live as voluntary slaves of their chosen totemic dictators on a vandalistic psychopathogenic axis, both by inhibiting the

dissociative revolutions and by making these borderline societies adopt outdated negative child-rearing styles! [2,4,7,22].

Dissociative Odyssey of Traumatic Childhood, Intergenerational Transmission of Destiny, and Dissociative Revolution

"Modern psychohistory: dissoanalytic psychohistory" modalities and paradigms function to create integrated individuals and societies that are not always traumatized or dissociated or even self-sabotaging. However, it is clearly understood that the further back in the history of humanity, the more tragic, traumatic, and dissociogenic, the history of childhood is [1,3,4,20]. Psychohistory provides preliminary guidance to many disciplines and fields related to individual and social traumatic experiences, especially psychotraumatology, psychiatry, clinical psychology, law, history, anthropology, forensic psychology, sociology, forensic medicine, and psychological counseling. Psychohistorians, psychotraumatologists and dissoanalysts need to know modern psychotraumatology principles and modern dissociation theories as well as be able to functionally apply trauma-centered theory and current treatment approaches of clinical psychology or witness this process to be able to conduct short and long-term theoretical and clinical studies on a *"traumatic and dissociative tragic odyssey of childhood"* or the *"real history of childhood"*. In this context, Ozturk's *"Trauma Based Alliance Model Therapy"* is one of the most up-to-date and systematic treatment models based on both psychotraumatology, dissoanalysis and psychohistory paradigms and modalities. This psychotherapy model, which has dynamics of close relationship with psychohistory such as dysfunctional family dynamics, negative child-rearing styles, and intergenerational transmission of trauma, is recommended to be used in the treatment of many mental disorders, especially trauma-related dissociative disorders, and post-traumatic stress disorder [2,4,5,8,18,23].

According to the dissoanalytic psychohistory school, the more trauma and dissociation-centered scientific research a society or nation has on the *"real history of childhood"* and "*perceptions of childhood"*, the more change and development-oriented that society or nation is. The perceptions of childhood in the past of each society penetrate their perceptions of today's childhood, and this perception changes and develops in a positive direction only in quite large time spaces. Childhood perceptions of all individuals and societies are exactly identical with those individuals and societies' perceptions of both self and humanity, that most people and masses who sabotage themselves or cannot prevent themselves from being traumatized continue to exist in a dissociogenic time circle focused on taking revenge on the other(s) for the chronic negative life experiences they have experienced or almost made their destiny. Therefore, a traumatic and dissociative, tragic odyssey of abusive identities' own childhood lies for every individual or social violence event. Wars are psychosocial sabotage of dissociated adults with chronic childhood trauma histories reflected from the past

to the present! Only integrated individuals make efforts for the peace of the community or society. The neutralization of individual and social traumas must be done immediately, which can only be achieved with *"psychocommunal therapy"*, which is emphasized by Ozturk, for the peace to be adopted and prevailed in all nations of the world. Psychocommunal therapy functions as breaking a cycle of control and obedience that extends from the individual to the society, that it is a dissociative rebellion or dissociative revolution from this perspective. Against the mainstream psychosociopolitical system that protects and glorifies perpetrators, individuals' awareness of the submissive attitudes imposed on them and their development-oriented effort not to be controlled makes it possible to perform psychosocial therapy by increasing mass awareness [1-4].

Adults, who abuse children, are attached to their perpetrators, and even identify themselves with them, that they see in each child their own traumatized state or the short-term happy childhood that they ignore, is gone or that they have forgotten or remain amnesic, and they target that innocent child whose reflection of this past their parents and society punished for thinking I am *"bad"*. On the other hand, these adults show violence and anger towards their own childhood by taking the place of their bad parents who punished them, over the child they traumatized. In fact, while most parents traumatize their own child, with whom they are still in a fusion relationship, by beating, humiliating, neglecting, or pampering, they punish the extension of themselves that they cannot break away from, that they cannot separate from and that they consider themselves to be, in a masochistic way. The anger and hatred felt towards the children they abuse is the process of pouring in the hatred and anger against their helpless childhood by transforming their *"inner poison"* into violence, that the process of pouring in this inner poison by transforming it into violence expands from children to women and the elderly, including the entire society that they thinks hates themselves. The child to whom the person is violent symbolizes his/her own childhood, the woman/women to whom he/she is violent symbolizes his/her mother who does not protect and does not love him/her, the elders whom he/she abuses symbolize his/her grandparents who do not guide him/her, and the society he/she is violent with symbolizes the mass of people who remained silent when he/she was a child. This dissociative projective process is experienced as "*intergenerational transmission of destiny*" and "*intergenerational transfer of psychopathology*". Now, the individual traumatizes innocent children and turns them into his/her likes as a revenge for his/her childhood lost in his own traumatized past in the wars of which he/she was a party, and symbolically punishes and even physically destroys the bad mothers who make him/her nothing [3-5,18].

A malevolent new generation, exposed to childhood traumas and ruthlessly raised, even sacrificed, by being trapped by negative child-rearing styles and by their own family and social environment becomes a carrier and a mediator element of both individual and social violence, and this cycle of individual and social violence shows a maximal intergenerational transmission on a dissociogenic ground. The encompassing cycle of violence extending from the individual to the society can only be explained by the phenomena of *"individual:pathological dissociation"* and *"social:mass dissociation"* [1,2,4]. Psychohistory has valued trauma and dissociation before many disciplines. The *"dissoanalytical psychohistory"* theory developed by Ozturk, can explain the chronological development, intergenerational transmissions and basic dynamics of the traumatization and revictimization processes associated with chronic dissociative reactions, which is based on childhood traumas and the phenomenon of denial, in a much wider space and with a more understandable clarity than clinical psychology and psychiatry in terms of psychotraumatology [2,3,24,25]. Ozturk, who developed the theory of dissoanalysis, emphasizes that an age of *"mass dissociation"*, which now spreads from individual to society, has begun on behalf of today's oppressive systems and directed people who are traumatized and even dissociated and controlled and ruled by dominant leaders or dictators. Individuals and societies that are controlled and even ruled by traumatizing can be freed from abuse, oppression and captivity or voluntary slavery through *"dissociative revolutions"* that they will initiate by re-activating their healthy parts. Dissociative revolutions are all actions taken by individuals and societies that have been ruled by oppression and traumatization for many years to cut their hypnotic ties with their fascist leaders and to liberate them, that with these actions, a psychosocial consciousness alliance is achieved, and a new development-oriented human and society profile is created [1].

The child-rearing styles, which are maximally dominant in all societies living in shared times or phases of the world, create people's identical destinies, identities, cultures, consciousness, and memories. On the same axis, negative life experiences and childhood traumas make it possible for people to intergenerational transfer of psychopathology that exist as identical to each other. Intergenerational transmissions of trauma and intergenerational transfers of psychopathology do not leave the individuals and societies in which they exist without being psychosocially exhausted, and they enable the existence of the directed masses that they freeze and even numb their souls and emotions! [5,7]. According to the dissoanalysis theory, traumatic experiences, which are synonymous with history of humanity, are used as a control agent by oppressive systems to create a herd psychology by generalizing and even dissociating individuals. Oppressive systems, dictators or fascist leaders rule -with *"mass traumatic experiences"*- whole societies by traumatizing them at the same time and with the same methods! By enabling social dissociation through mass traumatic experiences and chronic oppressions, in the face of these traumatic experiences and chronic oppressions, it is ensured that individuals who obey maximally exist [1,2,10,11,14]. As we go back in the history of childhood, it is seen that there is greater neglect and persecution, and that children are exposed to more violence, intimidation, sexual abuse and even murder by their families.

These incidents of major negligence, persecution, violence, intimidation, and sexual abuse are used in the past as well as today to dissociate children and take them under control. The traumatic history of childhood, which is a complete nightmare, is the history of dissociation, even anamnesis. According to dissoanalytical psychohistory, how a subject traumatized by his/her own parent traumatizes his/her own children in the same way can only be explained by the *"intergenerational transmission of trauma"* and *"intergenerational transfer of psychopathology"*. Through *"intergenerational transmission of trauma"*, *"intergenerational transfer of psychopathology"* and *"intergenerational transmission of dissociation"*, the same destiny (*"intergenerational transmission of destiny"*) is shared or experienced in successive generations [2,5,13,18,19].

Traumatic Power Hunger, Dissociative Deadlock, Mass Abdication of Mind, Iconic Totems and Psychosocial Death

According to Ozturk's Dissoanalysis Theory, traumatic experiences turn into traumatic obsessions and traumatic obsessions turn into dissociative deadlock, resulting in a dualized perception of time and lives without a self-compass. Chronic traumatic experiences, successive wars, genocides, and terrorism enable intergenerational transfer of psychopathology through dissociative deadlocks. Ozturk defines dissociative deadlock as *"mass dissociative anxiety"* created on individuals and societies by experiencing the dilemma of adapting to traumatic experiences and submission at maximum rates. According to the dissoanalysis theory, the mass dissociative anxiety that develops after the subjects' traumatic event cycles absorbs both the emotions and the souls of all people at the same time and creates obedient masses that tend to be revictimized, which is literally a psychosocial death! [1,2,7,22,26]. Anachronistic societies that experience intergenerational fossilization in the face of intergenerational development adopt violence-oriented negative child-rearing styles, simultaneously traumatizing their own children en masse and creating successive experiences of dissociative deadlock. Since societies in the intergenerational fossilization process resist change and development, they become hostile to just, modern, and compassionate people, even leaders. This mass of anti-change and anti-development is because they are chronically traumatized by their own parents through negative child-rearing styles, helplessly bond or cling to their dictators, who traumatized them, just like their own parents, or take shelter in a state of unconsciousness in order to feel a temporary sense of trust, which is called attachment to the abuser and mesmerization to their dictator in order to avoid both the uncertainty and the difficulty of control caused by their contradictory thoughts, feelings and behaviors! [1,4,5,14]. The cruel masses who succumb to oppression, admire their perpetrators, and allied with their dictators, sabotage themselves by choosing good people who are not as bad as them in the focus of being an opponent of change and development and even they move away from common sense and reality and cast their societies into wars, economic difficulties, inequalities, and injustices by voting for primitively oriented political parties without a self-compass. Individuals and societies, that are apparently committed to their dictators, but are controlled and ruled through traumatizing and dissociating by their dictators, reject a positive natural change or development by being attached to both outdated and irrational political and cultural values in a conflict of independency-dependency. The masses, who cannot neutralize their traumas and obey their perpetrators with a focus of pathological narcissism, always take their revenge from honest, innocent, and progressive people. Egoistic and self-interested individuals, who have been brought up by traumatizing, always direct their hatred and anger, which they cannot express, to good people and even they form a *"narcissistic alliance"* with any dominating power and oppressive system [2,7,14,26,27]. According to the dissoanalysis theory, individuals with denial of development or innovation and resistance to change due to their violence-oriented child-rearing style, individuals project their repressed anger against their perpetrators, whom they mesmerize by transforming the chaotic psychopathogenic dynamics associated with independency-dependency conflicts into mass dissociative anxiety and dictators, whom they believe to compensate for their loss of control and will by dominating themselves onto innocent subjects and societies they marginalize! Through the *"narcissistic alliance"* they have formed with their dictators, individuals deny their traumatized past and live in a *"dissociative power hunger (traumatic power hunger)"* focused on control! Dissociative power hunger is the main resource for dominant leaders and narcissistic dictators who have become apparently *"iconic totems"* now obeyed on behalf of the masses who have formed a narcissistic alliance with them and are experiencing a *"abdication of mind"* [1,14].

Denial Traumas: Dissociative Amnesia of Bygone Childhood and Traumatic Moments

A major proportion of individuals and societies that cannot metabolize and neutralize traumatic experiences undergo a *"denial trauma"* and make it their own *"dissociative destinies"* with an intergenerational transmission [1,2]. According to the dissoanalytic school, the denial traumas are the trauma created by ignoring or dissociating traumatic experiences! The denial traumas are one of the main elements of intergenerational transmission of trauma and intergenerational transfer of psychopathology. The denial traumas are both the architects of the empathy-interrupted negative child-rearing styles and the most fundamental agents in the formation of all cycles of violence, wars, and genocides [2,4,13,26]. Ozturk defines dissoanalytical psychohistory as *"an innovative psychology and life science"* which tries to understand today's individual and society by analyzing the past moments of humanity and the actions of its existence, life philosophies and even psychosocial dynamics, predicting the future individual and society, recording and interpreting the movement and function transitions between human and society in a wide-time and intergenerational space [3,4]. Ozturk, a psychotraumatologist, a dissoanalyst, and a psychohistorian, states that his studies of *"intergenerational*

transmission of trauma", "intergenerational transfer of psychopathology" and "intergenerational transmission of dissociation", which he pioneered in clinical psychology and especially psychotraumatology, are fundamental issues closely related to domestic violence, family psychopathology, childhood traumas, individual and social dissociative experiences in the axis of "apparently normal:dysfunctional family dynamics". Dysfunctional family dynamics in the intergenerational transmission of trauma function with violence-oriented negative child-rearing styles, and the maladaptive presence of this process or the time left in the past leads to the intergenerational transfer of psychopathology. Child-rearing styles both change and develop at a very slow pace in terms of psychohistory, and similar psychopathologies, dissociative reactions and childhood traumas are seen in successive generations. Dysfunctional families create a dysfunctional generation both by causing negative life experiences in their own children and by continuing to traumatize them with violence-oriented, inconsistent, unempathetic, and negative child-rearing styles. These merciless, self-centered, rude, and pleasure-oriented dysfunctional generations function as the primitive architects of all traumatic experiences, wars and natural massacres in today's dissociative societies [1.3-5.7].

Ozturk, a clinical psychologist, psychotraumatologist and dissoanalyst, continues to develop psychohistory, founded by Lloyd deMause, whom he considers the most valuable theorist in human history, based on intergenerational transmission of trauma, intergenerational transfer of psychopathology, intergenerational transmission of dissociation and psychocommunal dissociation by structuring it on the axis of dissoanalysis. Ozturk's psychotraumatology and dissociation-oriented style: "dissoanalytic psychohistory", which stands out with his studies on intergenerational transmission of trauma and intergenerational transfer of psychopathology, has made psychohistory quickly accepted in Turkey, making it an academically interested area [1,4,8,18,25]. deMause, who enabled psychohistory to exist and prevail at the academy of psychology all over the world, has universalized his ideas based on "social psychotraumatology" by establishing the links between trauma and dissociation and social dynamics in most of his articles [19,28]. Ozturk and deMause dealt with trauma and psychopathology transmissions that expand from the individual to the society as dual but integrative and successive processes, always considering the psychosocial part and the whole relationship in their theoretical and clinical studies [4,18,19]. Ozturk emphasizes that apart from psychoanalytic approaches, psychotraumatology paradigms and dissociation theories, namely the dissoanalytic school, are a locomotive agent in the development of psychohistory. Psychohistory targets parents, especially mothers, as the first abusers of children. Since the first moments of history of humanity, parents have sacrificed their own children by killing them and exhausted them psychologically and physically. And nowadays, although parents beat their children less often, they continue to sacrifice their children in a dissociative way by humiliating or pampering them. In this context, the ritual of sacrifice has been transformed from the dimension of physical abuse to the dimension of emotional abuse at the maximal rate. Ozturk emphasizes that today's parents continue to make their children dependent on them, traumatizing and even dissociating them by discriminating children, sabotaging their children, hindering their education, neglecting them, giving them parental denial, and pampering them. According to the dissoanalytical school, this process starts at an early age and becomes chronic, forming the basis of both borderline individuals with a false and evil nature, dissociated individuals with a focus on denial and obedience, and dysfunctional societies that are pro-war and pro-violence [1,3,4,7].

Scientists who come out of a society that was brought up with the denial traumas, become blind to traumatic realities and dissociative experiences, and they cannot even objectively analyze the human profiles of the age they live in from a psychocommunal perspective. Denial traumas enable individuals to establish a fusion and dissopathogenic communication with both other individuals and society. Individuals who establish fusion communications through dissociative projective identity transitions sabotage both themselves and other subjects and society. Because, on behalf of the individual who experiences the denial trauma, other subjects and society are unconsciously an extension of himself/herself, even a copy of himself/herself, and the person continues to torture himself/herself on a successive and chronic axis in the masochistic encompassing and self-sabotage of the denial trauma that he/she experiences by persecuting them and conveying his/her anger and hatred to them [1,2]. Parental violence, sibling violence and child-to-parent violence are among the focus topics in dissoanalytic psychohistory studies. A dysfunctional family dynamic and a dissociative negative child-rearing style, the discrimination of children, causes sibling jealousy to evolve into sibling violence. Ozturk reports that seven consecutive generations are the factor in the process of "intergenerational transmission of violence", especially that five consecutive generations are the determinant, and three consecutive generations are almost the locomotive agents. According to the dissoanalytic theory, intergenerational transmission of violence is identical with intergenerational transmission of trauma, intergenerational transmission of dissociation, and intergenerational transfer of psychopathology [1,4,5,7].

Transitioning from a violent and primitive child-rearing style, which is owned or defended and applied to one's own child, to a more empathetic and higher-level child-rearing style in an intergenerational process can only take place over centuries. The fact that this change and development process in child-rearing styles takes so long or is slow can clearly explain why childhood traumas, which are used as a punishment tool in the interruption of mass consciousness, violence-focused and unempathetic child-rearing styles from hundreds of years ago, still exist today. In order to create a global peace society in the world, this clear certainty has made it an existential, vital and scientific necessity

to associate childhood trauma prevention strategies with child-rearing styles, recognizing the function transitions and cause-effect relationships between them, and restructuring them in the direction of short and long-term *"dissoanalytic solutions"*. In the process of structuring dissoanalytical solutions, which has become a necessity, all mental health professionals, especially dissoanalysts, psychohistorians and psychotraumatologists, have important missions. Fighting against childhood traumas, misogyny, racism, wars, and genocides should be the primary duty of all virtuous people of the world [3,4,18]. Dissoanalytic psychohistory is a manifesto against both psychology schools and academics against to trauma studies, and against all outdated and oppressive societies that have adopted violent negative child-rearing styles! Long-phase trauma denials begin to be experienced as a *"denial trauma"* as soon as it prevents the processing, that is, the metabolization and neutralization of the traumatic experiences in the anamnesis of individuals and societies. Ozturk defines the trauma caused ignoring of a negative life experience as *"denial trauma"*. The denial trauma creates disintegration on individuals and societies that individuals and societies experiencing denial trauma begin to use dissociative defenses by moving away from associative experiences. Dissoanalytic psychohistory is the most realistic and most modern psychosocial analysis of people and societies, both past and present, and is therefore the longest-termed science of the future. Dissoanalytical psychohistory is a holistic whole of psychosocial and traumatic facts that the mainstream history and psychology schools deny or dissociate at maximal rates, and the denied realities drag societies into the intergenerational fossilization process. According to Ozturk, dissoanalytical psychohistory continues to develop rapidly by including modern psychotraumatology within its scope. A modern psychotraumatology away from psychohistory: trauma and dissociation studies can never reflect the absolute reality! Dissoanalytic psychohistory is both the traumatic and dissociative anamnesis of humanity revealed with absolute realities, and the construction of a new development-oriented societal reality [2,3,5,7,8].

Intergenerational Transmission of Dissociation versus Psychosocial Consciousness Alliance

"Intergenerational transmission of trauma", "intergenerational transfer of psychopathology" and *"intergenerational transmission of dissociation"* are the main fields of study of dissoanalytic psychohistory. In order to reemphasize for the last time, dissociative revolutions are all actions taken by the masses, who have been ruled by oppression and traumatization for many years, in the name of breaking their hypnotic ties with their fascist leaders and liberating them, that a psychosocial consciousness alliance is provided, and a new development-oriented human and society profile is created with these actions. According to Ozturk, psychohistory, which means *"dissoanalysis:psychosocial therapy"* of human history, is a complicated analysis and neutralization of individual and social traumas and violence incidents that feed on negative child-rearing styles and function

as a *"punishment tool"* in the tendency to *"control"* or *"rule"*. The *"silent screams", "hidden tears", "amnesic reflections", "dominant effects"* and *"psychopathological traces"* of individual and social traumatic experiences that cannot be removed like a *"dissociative boomerang"* and even show an intergenerational transmission meet us today, transforming into vandalism, terrorism, wars and even genocides. If the *"self-histories"* of individuals and societies are forgotten, their past experiences are suppressed, or if their memories are covered up with the effect of traumatic experiences, the mass psychopathological traces of these experiences will be seen as self-sabotage in the thoughtless act of individuals and societies that in any amnesic state, self-sabotage or dissociative boomerangs are doomed to be experienced again and again. That's why childhood traumas and wars ruthlessly continue to come into existence. By confronting us with our traumatic past, full of fear and shame, that we neglected, ignored, helplessly escaped, and denied, psychohistory allows us to remove our dissociative barriers and silent witnessing in order to build a better future for both our own children and all the children of the world [1,4]. Dissoanalytic psychohistory is a *"dissoanalysis: psychocommunal therapy"* of childhood traumas and wars, and is a modern psychology science based on psychotraumatology, which emerged with an integrative combination of psychology and historical sciences focused on the virtuous common goals of humanity and continues its development at a great pace. Dissoanalytic psychohistory is actually the psychosocial analysis of the difference between stated intention and actual behavior in individuals and societies, and the hypocrisy in the history of humanity, that is, saying something and doing something else [1,3,4,8].

Dissoanalytic psychohistory enables us to realize the fact that we are ruled by our dissociative barriers and traumas, even to rewrite our wounded destiny trapped in the cycle of abuse, and to experience our grief at an optimal level by neutralizing our anger to establish a more just and peaceful future for all the children of the world by confronting all of us with a harsh tone with the *"traumatic past of humanity"*, which we hide with fear and deny by drowning in silence. The motivation and hope of creating a development-oriented, compassionate, and virtuous new generation of a society whose dissociative barriers have been removed is revived [1-4,7,18]. Lloyd deMause, a science icon, makes the operational self-definition of this science with his sentence: *"Psychohistory is the science of historical motivation no more, no less"* [28]. Psychohistory, recognizing the relationship between mother and child as the most sensitive, fragile and permeable balance in life, in fact, is a long-term analysis of individual and social traumas fed by negative child-rearing styles and historical motivations in violence. Dissoanalytic psychohistory tells us in a critical and sharp way how bad-spirited mothers with borderline personality organization allied with oppressive systems turned the world into a hell and stole the smiles of humanity with venomous and hateful dysfunctional generations created by their violent

and unempathetic child-rearing styles and fascist leaders they mesmerized, that dysfunctional generations and fascist leaders, architects of these evil mothers who wrote the traumatic and dissociative history of childhood, are the active agents of the emergence of both individual and social traumas in the world. Self-focused hedonistic *"bad-spirited mothers"* in the borderline personality organization who do not adopt their children, cannot establish a secure attachment with their children and refuse to be parents, turn the destiny of the world into a real nightmare as well as their own children. In the anamnesis of every perpetrator and supporter of violence, there is definitely a mother who *"sacrificed"* or *"kept silent about the sacrifice of her children"* with a violent and unempathetic negative child-rearing style and a father right next to the mother [3-5,7].

Individual and social traumas isolate people through dissociative experiences focused on shame, somatization, regret, and denial, and even alienate them from all *"experiences of humanity"* and distance themselves from their selves [1,29]. According to Ozturk, traumatic experiences are only apparently individual because the individual is essentially a psychosocial being and traumatic reactions are experienced on a psychosocial axis and in a dissociative nature. In today's age of mass dissociation, the cycles of violence that become increasingly evident and perpetual intensify the *"shadow of society in individual traumas"*. The weight and visibility of the effects of social determinants in individual traumas lead dissoanalysts and psychohistorians to reconstruct the main components of mass violence cycles in a psychosocial and even dissoanalytic context. According to dissoanalytic psychohistory, while intergenerational transmission of trauma, intergenerational transfer of psychopathology and intergenerational transmission of dissociation occur with the transformation of individual traumatic experiences into social traumatic experiences it distances the individuals and communities it covers from their beliefs, identities, consciousness, and selves [1,3,8,24,30]. Every person or society, that cannot become the self, experiences a repetition, and turns into a copy! A subject who becomes distant from his/her natural self through traumatic experiences continues his/her life with dissociative reactions and then de-differentiate. The individual denies his/her original identity and true self, and even creates new identities and selves to adapt to traumatic experiences! According to Ozturk, dissociative individual and social traumas act in silence, steal people's smiles in silence, and walk barefoot through fires, turning their fate into a nightmare with silence, that *"silence"* and *"silent testimony"* is actually a betrayal. Anyone who remains silent in the face of trauma, are the most ruthless murderers who form self-interested alliances and kill people's souls without making good or bad judgments against all kinds of power centers with a borderline personality disorder organization! Sometimes a mother, sometimes a father, and sometimes a sibling or anyone else, who are actually soul killers, are no different from the abuser if they are *"silent witness"* to the traumatized person's life. According to Ozturk, *"Mothers are both the memory, the history and the destiny of their children and societies, and good mothers always create good generations"*. The murderers of all times and all societies in the world are ruthless parents, who are the evil actors of *"intergenerational transmission of trauma"*, *"intergenerational transfer of psychopathology"* and *"intergenerational transmission of dissociation"*. The motto of dissoanalytic psychohistory is *"one's pain is all our pain; one's mourning is all our mourning"*. Evil-spirited parents inherit hundreds of dissociative psychological traces of their own children's divided minds, which will continue to exist until they die, as well as traumatic experiences [1,2]:

"A little girl who took shelter in my memories and looks like me looks for her lost mother in the halls of my mind every day. I am startled for thousands of moments by the silence of my mother's fake smiles leaking from yesterday as a nightmare turns into reality. Most of all, I can't forgive her, I don't forgive her, and I don't want to forgive her. I want to erase that person who makes us satellites of her by suffocating us all with her silence for her own egoist interests from all my memories, but I can't erase her. My father is the man who stole my future by destroying my feelings and hopes and to whom my mother was devoted! Not being able to even feel the numbness kills me inside myself every day. When my traumatic memories both hit and loot my todays like an assassin, I can cut my body and realize that I am still alive. The pain of inflicting harm on my own body is keeping me from my planned suicide attempts. There is a woman in the mirror who always looks at my bleeding wounds and even still suffocates me with the nightmares of her silence for hundreds of years and wakes me up from all my sleeps. My childhood lost in pain is looking for me knowing that he will never find me. The shame that my family inflicted and the anger I felt towards them distance me from all people and from myself. I can no longer cry to my sacrificed old self and no longer hide, hide, and hide in my tears. Nowadays, the only thing that consoles me is my own soul wounds still bleeding, which I can endure as if experiencing someone else's pain and mourning. The never-healing wounds that both my relatives, others, and the past bleed and that surround my soul at every moment... I'm not me, I'm in places that never existed and now I'm a dead woman imprisoned in her own nothingness. I am now a completely different person in the nothingness of myself, watching the evils done to me from afar just like my mother and watching every scene of my sacrifice thousands of times in my mind!"

Quoted from a dissociative identity disorder case

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Conservative management of anal fissure accompanying constipation in school-age children

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Abstract

An anal fissure is a common problem in children and it refers to a longitudinal tear or an ulcer in the anoderm. The conventional therapy for anal fissures has been warm sitz baths and lthe ocal application of analgesic ointments, stool softeners ,and behavioral therapy as necessary. Simple wound care may often be sufficient for the treatment of anal fissure, but a comprehensive approach is required for accompanying constipation. Between 2015-2022, a total of 263 children suffering from constipation and perianal pain were diagnosed with anal fissure (AF) based on physical examination. Anal fissure and constipation (AFC) questionnaire forms were retrospectively reviewed and results of routine management protocol were assessed which was focused on local wound care and dietary regulation. The ratio of children consuming more than 2-3 cups of packed beverages containing artificial sweeteners, colorants or corn syrup was found 63,89 % (n=167). Daily water consumtion of less than five glasses was 71.1% (n=187). Daily milk consuming was 71,86% (n=189). Stool withholding and soiling was found 57,41% (n=151) and 48,67% (n=128) respectively. In only four cases (1.52%), constipation persisted for more than eight weeks despite meticulous management and improvement was achieved with anal dilatation on the tenth week. It is possible to treat anal fissures successfully and in a reasonable duration with simple local care with prednisolone pomade and a strict diet arrangement that restricts the consumption of packed foods, beverages, snacks, and milk while promoting drinking water and raw fiber intake.

Keywords: Child, anal fissure, functional constipation, conservative management

Introduction

An anal fissure is a common problem in children and it refers to a longitudinal tear or an ulcer in the anoderm. Painful defecation and rectal bleeding are the main symptoms. In the etiology of anal fissure defecation of hard stools and elevated internal anal sphincter pressure are important factors. Acute anal fissures often heal spontaneously or with simple dietary modification and stool-softening laxatives when necessary [1]. Fissures persisting for more than 4 to 6 weeks are often referred to as chronic [2-4]. AF affects all age groups with an equal incidence in both sexes [5-7]. Prolonged diarrhea or hard stool causing irritation and trauma to the anal canal are the primary and most common causes of AF [8]. In addition, secondary AF may develop in inflammatory bowel diseases, or after anal surgery.

The treatment and management of this anorectal condition are controversial. The conventional therapy for anal fissures has been warm sitz baths and the local application of analgesic ointments, adding stool softeners and behavioral therapy as necessary [10].

On the other hand, local treatment of AF alone is not sufficient. A serious approach to frequently accompanying constipation is also necessary. In the vicious cycle of constipation and anal fissure, functional constipation should be carefully considered as well as local fissure treatment. The aim of this study is to present the treatment results of anal fissures in school-age children treated with simple wound care and dietary regulation, which were evaluated together with nutrition and toilet habits.

Material and Methods

Between 2015-2022 a total of 435 school-age children who presented at the outpatient clinic with constipation and perianal pain, 263 (60,45 %) were diagnosed with AF based on physical examination. In history dietary habits, bowel habits, rectal bleeding, painful defecation and constipation were focused on with a simple AF and constipation questionnaire form. Fissure localization was also evaluated and recorded in rectal examination. Cases with known gastrointestinal diseases or who are being treated by another center due to anal fissure or constipation were excluded. This study was approved by the Institutional Ethics Review Board for Clinical Research (2022/B.96).

Diagnosis and follow-up

All cases were evaluated in the outpatient clinic during the fourth, sixth, and eighth weeks. Parents were informed to continue the treatment of constipation for one more month after the lesion healing and to continue the suggested nutrition afterward.

Treatment applied to patients diagnosed with anal fissure

All cases were started liquid paraffin 15 ml twice a day. In those with many watery stools in the first week, the dose was halved and continued. Local wound care was performed twice a day with 0.125 mg prednisolone pomade and a hot sitting bath once a day was described.

Diet regulation

All cases were informed about determined nutritional suggestions. Snacks containing sweeteners, carbonated and non-carbonated beverages, and milk consumption were prevented. Two servings of fruit and one to one and a half liters of daily water consumption were obligated. Dried or fresh apricot, unpeeled apples, and pear were preferred depending on the season. It was recommended daily to five to ten pieces of dried or fresh apricots and unpeeled apples and pears each. In addition, families were informed that the main meal should definitely contain vegetables. Instead of packaged snacks, dried apricot dried apples, and pears were recommended. Daily two or three servings of apricot kernels were recommended for children's snack needs.

Biostatistical Data Analyses

While the type error amount (alpha) was 0.05, the strength of the test (1-beta) was 0.8, the predicted effect size for the recovery time was 0.18, and the alternative hypothesis (H1) was two-way, the minimum sample size was calculated by theoretical power analysis that the minimum sample size was 236 to find a significant difference using this test [11]. The categorical variables in the study were summarized by number (percentage) and the numerical variables were summarized by the median and inter-quarter width (IQW). Shapiro Wilk test was used to match the normal distribution of the data. Mann Whitney U test, Kruskal Wallis test and Pearson chi-square tests were used where appropriate for statistical analysis. In the applied statistical analyses, the value of $p < 0.05$ was considered statistically significant. American Psychological Association (APA) 6.0 style was used to report statistical differences. All analyses were conducted with IBM SPSS Statistics 28.0 for Windows (New York; USA).

Results

A total of 263 patients included in the study, of which 147 (55.89%) were male and 116 (44.11%) were female. The median (width between quarters; WBQ) age was 115 (39) months (9.6 years). Table 1. Examination of symptoms, signs, and recovery times of cases according to gender.

Table 1. Evaluation of symptoms, signs and recovery times of cases according to gender

	Boys	Girls	p*
Bleeding	102 (69.39%)	80 (68.97%)	p>0.05
Perianal pain	128 (87.07%)	103 (88.79%)	p>0.05
Soiling	73 (49.66%)	55 (47.41%)	p>0.05
Anterior fissure	50 (34.01%)	44 (37.93%)	p>0.05
Posterior fissure	70 (47.62%)	63 (54.31%)	p>0.05
Circularfissure	27 (18.37%)	9 (7.76%)	p<0.05
Recovery time	8 weeks[a] (2)	8 weeks[a] (2)	p>0.05

*: Mann Whitney U test. a: According to the APA style, different letters in each line a,b indicate a statistically significant difference. The fact that there is only a here expresses p>0.05

Recovery time was the same in boys and girls and was found to be 8 weeks. There was no statistically significant difference between gender and recovery time (p>0.05). While there was no significant difference between fissure location and gender in anterior and posterior locations, circular lesion location was statistically significantly higher in men (p<0.05).

Table 2. Examination of the cases by stool withdrawal, toilet type preferences, and cleansing after defecation habits according to their gender. Statistically significant difference was not found (p>0.05).

Table 2. Examination of the cases by stool withdrawal, toilet type preferences and cleansing habits after defecation according to their gender

	Boys	Girls	p*
Stool witholding	88 (59.86%)	63 (54.31%)	p>0.05
Defecation position			
Crouching	36 (24.49%)	34 (29.57%)	
Sitting	93 (63.27%)	71 (61.74%)	p>0.05
No difference	18 (12.24%)	10 (8.70%)	
Cleansing after defecation			
Just washing	34 (23.13%)	30 (25.86%)	
With paper only	6 (4.08%)	5 (4.31%)	p>0.05
Washing and paper	107 (72.79%)	81 (69.83%)	

*: Mann Whitney U test

Table 3. Examination of the cases according to gender, consumption of carbonated-noncarbonated sweetened beverages, consumption of chips and similar sweetened or salty snacks, water and milk consumption habits. There was no statistically significant difference was found between the sexes.

Table 3. Examination of the cases according to their gender consumption of carbonated non-carbonated sweetened beverages, consumption of chips and similar sweetening/salty snacks, water and milk consumption

Consumption	Amount	Boys	Girls
Packed beverages	2-3 glass per week	89 (60.54%)	78 (67.24%)
	<3 glass per week	58 (39.46%)	38 (32.76%)
Packed snacks	every day	103 (70.07%)	80 (68.97%)
	1-2 times per week	20 (13.61%)	14 (12.07%)
	3-4 times per week	24 (16.33%)	22 (18.97%)
Water	<5 glass daily	105 (71.43%)	82 (70.69%)
	> 5 glass daily	42 (28.57%)	34 (29.31%)
Milk	1 glass every day	103 (70.07%)	86 (74.14%)
	3-5 glass per week	44 (29.93%)	30 (25.86%)

Discussion

Treatment of constipation is an important part of the management of anal fissures in children as the majority of fissures are believed to be due to the passing of hard stools. Approximately 35 to 50% of fissures heal with general conservative management [12,13]. In only four of the cases (1.52%) in this study, constipation persisted for more than eight weeks despite meticulous management, and improvement was achieved with anal dilatation on the tenth week. Sitz baths, topical analgesics, a high fiber diet, and adequate fluid intake as well as stool softeners are the most often advised for the initial conservative treatment of AF in the related literature. In our treatment protocol, liquid paraffin orally 15 ml twice a day was used and in those with much watery stools in the first week, the dose was administered as once a day.

According to the diet protocol we followed, apricot, unpeeled apple and pear are recommended daily as a source of fiber. At least two servings a day sun-dried apricots (fresh apricots in the season) and unpeeled apple and pear one each have been recommended.

The effect of fiber is controversial due to lack of randomized, controlled studies addressing this problem in otherwise healthy children with constipation. In some uncontrolled studies it is suggested that both normal and constipated children have low fiber intake [14,15]. In a study by Williams et al. [16] in children older than 2 years old, safe range of dietary fiber intake is suggested to be between age +5 and age +10 g/d. This formula may offer a standard, but how much of a daily amount of fiber can be obtained from a wet weight may vary for different foods. Therefore, its applicability in practice may be small. Besides the fresh fruits we also recommend to consume dried apricot and

apricot kernels to address the children' snack needs during the day. Thus, children's sweet, fiber and snack needs can be met effectively. It has also been observed that it can be a healthy and effective alternative to packaged foods containing various preservative, coloring and sweetening chemicals. In addition, families have been informed about the consumption of vegetables with protein according to the season in the main meals to provide additional fibre. On the other hand there is no significant benefit of excessive intake of fibre. In children with faecal impaction or stool witholding behaviours, excessive fibre intake should be avoided as it can worsen symptomsin [17-20].

The ratio of children consuming more than 2-3 cups of various carbonated or non-carbonated beverages containing artificial sweeteners, colorants or corn syrup was found 63,89 % (Table 3). Excessive consumption of these foods causes satiety and prevents children to eat healty foods. Additionally frequent consumption of pulp-free fruit juices also makes a negative contribution to constipation. Like fiber, sufficient water intake is necessary for the prevention and treatment of functional constipation in children [21-23]. However, evidence does not support the use of extra fluid intake [24]. It is found that 71.1% of the cases (Table 3) consumed less than five glasses of water (not fluid but water) per day. Children who were followed up were advised to consume 1-1.5 liters of water per day. In this process, children and families have been especially instructed to quit colored and sweetened liquids and to meet their water needs with just water.

When toilet habits were questioned, it is found that 71.6% of the children declared to clean by washing and drying with paper, 23.95% are only washing and 4.18% are only paper (Table 4). As described by Inan et al.[27] avoidance of toilets can be an important factor for childhood constipation. In this study stool withholding was found 54,31% (n=63) and 59,86%(n=88) in girls and boys respectively (Table 1). Withholding causes prolonged fecal stasis in the colon and with the passage of larger stools rectum becomes dilated, and fecal soiling may ocur in course of time. In this study soiling was found 47,41% (n=55) and 49,66% (n=73) in girls and boys respectively (Table 1). The main reason why school-age children avoid using school toilets other than peeing is thought to be related to the privacy, cleanliness and hygiene conditions of the school toilets and the toilet paper that is not always available [27,28]. In order to enable school-age children to use toilets for defecation, making school toilets cleaner, more comfortable and hygienic should be considered as a public health requirement and measures should be taken in this direction. Thus, the treatment of anal fissures accompanied by constipation will give faster and more successful results.

The role of other nutrients in development of chronic constipation has recently been reexamined. Intolerance to cow's milk may be another underlying cause of chronic constipation in children [29,30]. It has also recently been claimed that chronic constipation and anal fissure may often be troublesome in children who consume excessive cows milk [31]. Limiting

cow's milk consumption may ease constipation in some children, particularly if its consumption is excessive. It is supported by the evidence of inflammatory histological alterations in the colonic mucosa of children with chronic constipation. [24]. In this study a significant proportion of school-age children (72,1%) was found to consume milk regularly in every day (Table 3). In our diet protocol, we also prevented milk consumption during the treatment process. When children completed the treatment process parents were informed to consume pasteurized daily milk other than packaged, processed and additive containing milks when necessary.

Conclusion

Although several theories have been postulated, the cause of anal fissure still is obscure. Whether the concomitant functional constipation is the cause or result, anal fissure treatment, which adversely affects the quality of life of families and school-age children, gives successful results with simple wound care and a serious dietary arrangement. At this point, children's nutrition habits, water consumption and toilet habits should be carefully analyzed and regulated. Instead of sweet beverages containing sweetening and coloring chemicals or corn syrup, daily fluid needs should be met with just water. It is possible to treat anal fissure successfully and in a reasonable duration with a strict diet arrangement and a simple local care.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical approval
This study was approved by the Institutional Ethics Review Board for Clinical Research (2022/B.96).

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ORIGINAL ARTICLE

Is there a relationship between metformin-related gastrointestinal symptoms and vitamin B12 deficiency in patients with type 2 diabetes mellitus?

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Abstract

Metformin (MTF) associated gastrointestinal symptoms are fairly common side effects that adversely affect patients' treatment adherence. However, the variability of gastrointestinal symptoms in MTF-using patients has not been fully explained. In our study, we aimed to investigate the relationship between vitamin B12 deficiency with MTF-related gastrointestinal symptoms. Patients with type 2 diabetes mellitus (T2DM) using MTF were included in the study sequentially. Demographic characteristics of the patients, duration of diabetes, MTF dose and duration used, and gastrointestinal symptoms were recorded. Afterward, a hemogram, HgbA1c, and vitamin B12 measurements were performed. Patients with and without vitamin B12 deficiency were divided into two groups. The two groups were compared with statistical methods. Twenty-five percent of patients had low serum vitamin B12 levels. Patients with vitamin B12 deficiency had a longer diabetes duration, and a longer MTF usage duration (p<0.001, p<0.001) than the patients without vitamin B12 deficiency. There was no correlation between B12 deficiency and MTF dosage (p=0.590). Gastrointestinal symptoms were seen more frequently in the B12 deficiency group (p=0.025). Bloating and constipation, nausea, abdominal pain, and vomiting were seen commonly in the B12 deficiency group (p=0.002, p<0.001, p=0.014, p=0.004, respectively). Three or more symptoms were frequently seen in B12-deficient patients (p<0.001). Patients with both a MTF usage duration of 10 years or higher and vitamin B12 deficiency are found to be 434% more likely to have active gastrointestinal symptoms than all other patient groups (OR:5.343, 95%CI (2.173-13.140), p<0.001). Study results have shown that gastrointestinal symptoms seen in patients with T2DM taking MTF may be associated with vitamin B12 deficiency. MTF-related gut microbiome changes may play a role in this relationship. In particular, we recommend that patients who have been using MTF for ≥10 years and have gastrointestinal complaints should be followed more closely for vitamin B12 deficiency.

Keywords: Diabetes mellitus, gastrointestinal symptoms, metformin, vitamin B12 deficiency

Introduction

Type 2 diabetes mellitus (T2DM) constitutes the vast majority of all diabetes mellitus (DM) patients. The prevalence and incidence of T2DM are increasing rapidly all over the world. T2DM and its comorbidities have now reached epidemic proportions [1]. Metformin (MTF), a biguanide derivative, is the most widely used therapeutic agent in the treatment of patients with T2DM and has been used for nearly a century [2]. The European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) recommended the use of MTF in pharmacological treatment in addition to exercise and

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diet practices in T2DM [3]. MTF also has several other non-Food and Drug Administration (FDA)-approved indications, including gestational DM, management of antipsychotic-induced weight gain, prevention of T2DM, and treatment and prevention of polycystic ovarian syndrome. Currently, MTF is the only antidiabetic recommended by the ADA for pre-diabetes [4].

Some side effects may also develop due to the use of MTF. The most common unpleasant side effects are symptoms related to the stomach and intestinal tract, such as diarrhea, nausea, intestinal gas, abdominal pain, constipation and vomiting [5]. Gastrointestinal side effects occur in 20-30% of patients using MTF, of which approximately 5% are severe adverse events resulting in discontinuation of MTF. Although research has been done on how MTF causes gastrointestinal side effects, it is still not clear [6]. However, altered histamine or serotonin transport, localized MTF concentrations in the intestinal cell, effects due to increased bile acidity in the colon, or changes in the gut microbiome are thought to be responsible for these side effects [7]. Recent research has suggested that one of the target sites of MTF may be the gut microbiota [8].

In conclusion, MTF has a rather mixed relationship with the intestinal system in terms of both drug action and gastrointestinal side effects [7]. In addition, long-term use of MTFs can interfere with the absorption of vitamin B12 in the terminal ileum region of the intestine, resulting in a deficiency of this vitamin. The clinical significance of vitamin B12 deficiency is that it can cause megaloblastic anemia, mental status changes, and some neurological defects [9].

Our main aim in this study was to investigate whether vitamin B12 deficiency has an effect on MTF-related gastrointestinal symptoms. Our secondary aim is to determine the prevalence of vitamin B12 deficiency in our T2DM patients using MTF therapy and to compare the demographic/clinical characteristics and laboratory results of our patients with and without vitamin B12 deficiency.

Material and Methods

Study design

Ethics committee approval was obtained for the study from the Hitit University Faculty of Medicine Clinical Research Ethics Committee (Date: 20.04.2022, No: 2022-40). After obtaining approval from the institution where the research would be conducted, the research was conducted. It was planned as a observational and cross-sectional study. The research was carried out with patients who applied to the internal medicine outpatient clinic. The research population consisted of T2DM patients using MTF. With the "patient follow-up form" we prepared, demographic characteristics of the patients such as gender, age, body mass index (BMI), duration of DM, duration of MTF use, daily dose of MTF and whether they had diabetes were questioned. Neuropathy was noted. Patients meeting the

inclusion criteria were included in the research consecutively. Gastrointestinal system symptoms (diarrhea, nausea, abdominal pain, vomiting, bloating, constipation and metallic taste in the mouth) of the patients were evaluated. Gastrointestinal symptoms were evaluated according to the following criteria, and the symptoms of patients who met all criteria were considered MTF-related gastrointestinal symptoms.

MTF-related gastrointestinal symptom criteria

The onset of symptoms after MTF use, the symptom has been persistent or frequent in the last month, answering the presence of symptoms by the patients considering the last month, absence of any other medication that may cause these symptoms in the last month, and absence of acute gastroenteritis and biliary, urinary system and perineal region infections in the last month.

After the patients' data were recorded, routine evaluation tests for DM were performed. Hemogram parameters, HbA1c, and vitamin B12 values were recorded. Serum vitamin B12 measurements were made with the chemiluminescence method using Roche cobas e601 analyzers. Vitamin B12 measurements below 200 pg/mL were defined as deficiency. Patients participating in the study were divided into two groups as patients with vitamin B12 deficiency and patients without vitamin B12 deficiency. These two groups were compared in terms of demographic characteristics, clinical features, gastrointestinal symptoms and laboratory data using statistical methods.

Inclusion criteria in the study

T2DM patients who have been using MTF for at least three months, adults aged 18-80, and patients who voluntarily want to participate in the research

Exclusion criteria from the study

Patients who do not want to participate in the research voluntarily, individuals under the age of 18 and over the age of 80, patients with previous gastrointestinal complaints, patients with renal, hepatic, and chronic pancreatic insufficiency, patients with intestinal malabsorption, patients with known hematological disease or malignancy, patients with gastrointestinal malignancies, individuals with pernicious anemia, ulcerative colitis, and Crohn's disease, individuals with gastric and intestinal operations, those with cholelithiasis and those with cholecystectomy, those who are pregnant, breastfeeding, those who use alcohol, those who eat vegan and vegetarian, those who use proton pump inhibitor, H2 receptor antagonist, antacid, calcium preparation, colchicine, vitamin B12, and multivitamin drugs and patients using the extended-release oral formulation of MTF.

Statistical Analysis

All statistical analysis was performed using IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, N.Y., USA). Distribution of data evaluated by Shapiro Wilks test.

Descriptive statistics were reported as number and percentage for categorical variables, mean ± standard deviation for normally distributed numerical variables, and median value and minimum and maximum values in parentheses for non-parametric distributed variables. The relationships between the variables were investigated with Spearman or Pearson correlation coefficient in accordance with the data distribution. Comparison of numerical measurements according to research groups for two independent groups were evaluated with two sample t-tests for age only and were evaluated with Mann Whitney U test for height, weight, BMI, diabetes duration, MTF use duration, serum white blood cell (WBC), hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), Platelet (Plt), HbA1c, vitamin B12 levels in accordance with the data distribution. Categorical variables such as gender, MTF dosage, presence of gastrointestinal symptoms, bloating and constipation, nausea, vomiting, abdominal pain, metallic taste, diarrhea, number of gastrointestinal symptoms, presence of neuropathy, vitamin B12 deficiency ratio comparisons according to research groups and subgroups were evaluated by Chi-square test. A p value of <0.05 was accepted for statistical significance.

Results

The median age of 312 patients was 59 years, and 195 patients (62.5%) were female. The clinical features of these patients are given in Table 1. Of the patients in the entire group, 138 (44.23%) had no gastrointestinal symptoms during the period of MTF use, while 174 (55.77%) had one or more symptoms. Vitamin B12 levels were normal in 234 (75%) of the patients, while vitamin B12 deficiency was seen in 78 (25%) patients.

The median age of vitamin B12 deficient and non-deficient individuals was 58 and 64 years, respectively, a statistical significance was seen (p<0.001). There were no significant differences in gender, height, BMI, WBC, Hb, Hct, or Plt between patients with and without vitamin B12 deficiency (Table 1).

The median weight of patients without vitamin B12 deficiency was found lower than vitamin B12 deficient patients (80 kg vs 84.5 kg, p=0.017). HbA1c levels were higher in vitamin B12 deficient patients than in other groups (7.1 vs 7.6, p=0.015) (Table 1).

The duration of T2DM (p<0.001) and the duration of MTF use (p<0.001) were longer in the patient group with vitamin B12 deficiency compared to the patient group without vitamin B12 deficiency. There were no differences in MTF dosages between the two groups (p=0.590). The incidence of diabetic neuropathy was higher in patients with vitamin B12 deficiency (20.51%) than in patients with adequate vitamin B12 (7.26%) (p=0.001) (Table 1).

In the adequate vitamin B12 group, 52.14% of the patients had one or more gastrointestinal symptoms, this ratio was statistically higher in the deficiency group with a 66.67% symptom rate (p=0.025). Bloating and constipation, nausea, abdominal pain, and vomiting were seen more frequently in the vitamin B12 deficiency group (p=0.002, p<0.001, p=0.014, p=0.004, respectively). There were no differences in metallic taste and diarrhea between the groups (p=0.220 and p=0.078). Three or more symptoms were frequently seen in vitamin B12-deficient patients (32.05% vs 11.11%, p<0.001) (Table 1).

Evaluation of the relationship between Gastrointestinal Side Effects and MTF Dose, Duration of MTF Use, and HbA1c Level

Patients included in the study were further divided into two groups, patients with gastrointestinal side effects, and those without gastrointestinal side effects. When the MTF doses were compared, it was found that there was no statistically significant difference between the groups (p=0.753). In the subgroup analysis according to the presence of vitamin B12 deficiency, there was no significant relationship found between gastrointestinal side effects and MTF dosage in patients with normal serum vitamin B12 levels or in patients with vitamin B12 deficiency (p=0.664 and p=0.772, respectively) (Table 2).

Patients with and without gastrointestinal symptoms were compared according to the duration of MTF use. A statistically significant difference was found between these two groups (p=0.038). In the subgroup analyses, this difference couldn't be observed in patients with adequate vitamin B12 levels (p=0.595) and was much more pronounced in vitamin B12 deficient patients (p=0.005). In patients with vitamin B12 deficiency, the rate of patients who have been using MTF for more than 10 years and who do not have gastrointestinal symptoms is 23.08%, while this rate is observed as 65.38% in patients with gastrointestinal symptoms (Table 3). A patient with a MTF usage duration of 10 years or more is found to be 100.8% more likely to have active gastrointestinal symptoms than a patient with a lesser usage duration (OR:2.008, 95%CI (1.212-3.327), p=0.007). This ratio is much higher in patients with both a MTF usage duration of 10 years or higher and vitamin B12 deficiency, these group of patients are found to be 434% more likely to have active gastrointestinal symptoms than all other patient groups (OR:5.343, 95%CI (2.173-13.140), p<0.001). These significant increases in the incidence of symptoms are especially noteworthy in patients with vitamin B12 deficiency who have been taking MTF for a long time (Table 3).

When gastrointestinal symptoms were evaluated in terms of HbA1c level, no significant difference was observed in both patients with normal vitamin B12 levels and in patients with deficiency (Table 4).

The distribution of other therapeutic agents used by the patients for the treatment of diabetes mellitus, other than metformin, is given in table 5.

Table 1. Comparison between vitamin B12 deficient and adequate patients

Variables		All patients (n=312)	Adequate vitamin B12 (n=234)	Vitamin B12 deficient (n=78)	p
Age		58.95±9.65 (59)	57.89±9.53 (58)	62.14±9.38 (64)	0.001
Gender	Male	117 (37.50%)	82 (35.04%)	35 (44.87%)	0.12
	Female	195 (62.50%)	152 (64.96%)	43 (55.13%)	
Height		164 (145-187)	163 (145-187)	165 (150-187)	0.398
Weight		80 (56-125)	80 (56-125)	84.5 (63-124)	0.017
BMI (kg/m2)		30.44 (18.52-46.22)	30.18 (18.52-46.22)	31.33 (23.31-45.18)	0.096
WBC count (109/L)		7.8 (3.5-16.6)	7.8 (3.5-16.6)	7.95 (3.8-12.5)	0.896
Hb (g/dL)		13.65 (7.3-17.4)	13.8 (7.3-17.3)	13.2 (9.5-17.4)	0.177
Hct (%)		41 (19.4-84.8)	41 (19.4-50.5)	41.25 (32-84.8)	0.716
MCV (fL)		86.8 (27-115)	86 (66-115)	87 (27-110)	0.039
Plt count (109/L)		271 (80-553)	273.5 (80-553)	268 (85-440)	0.126
HbA1c (%)		7.4 (5-13.7)	7.1 (5-13.7)	7.6 (5.1-12.8)	0.015
DM duration (months)		90 (1-360)	72 (1-360)	120 (3-360)	0.001
Metformin usage duration (months)		84 (1-360)	72 (1-360)	120 (3-300)	0.001
Metformin dosage	500mg	6 (1.92%)	4 (1.71%)	2 (2.56%)	0.590
	850mg	5 (1.60%)	5 (2.14%)	0 (0.00%)	
	1000mg	41 (13.14%)	31 (13.25%)	10 (12.82%)	
	2000mg	260 (83.33%)	194 (82.91%)	66 (84.62%)	
Vitamin B12 value		280 (97-1500)	309.5 (200-1500)	164.5 (97-198)	<0.001
Known diabetic neuropathy		33 (10.58%)	17 (7.26%)	16 (20.51%)	0.001
Gastrointestinal symptoms	No symptoms	138 (44.23%)	112 (47.86%)	26 (33.33%)	0.025
	One or more symptoms	174 (55.77%)	122 (52.14%)	52 (66.67%)	
Bloating and constipation		137 (43.91%)	91 (38.89%)	46 (58.97%)	0.002
Nausea		70 (22.44%)	40 (17.09%)	30 (38.46%)	<0.001
Abdominal pain		62 (19.87%)	39 (16.67%)	23 (29.49%)	0.014
Metallic taste		36 (11.54%)	24 (10.26%)	12 (15.38%)	0.220
Diarrhea		35 (11.22%)	22 (9.40%)	13 (16.67%)	0.078
Vomiting		19 (6.09%)	9 (3.85%)	10 (12.82%)	0.004
Gastrointestinal symptoms count	No symptoms	138 (44.23%)	112 (47.86%)	26 (33.33%)	<0.001
	One symptom	79 (25.32%)	66 (28.21%)	13 (16.67%)	
	Two symptoms	44 (14.10%)	30 (12.82%)	14 (17.95%)	
	Three or more symptoms	51 (16.35%)	26 (11.11%)	25 (32.05%)	
Vitamin B12 deficiency	Normal	234 (75%)			
	Deficient	78 (25%)			

BMI: Body-mass index, WBC: White blood cell, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, Plt: Platelet, DM: Diabetes mellitus

Table 2. Crosstabulation of gastrointestinal symptoms, metformin dosage, and vitamin B12 status

Vitamin B12	Metformin dosage	No gastrointestinal symptoms	One or more gastrointestinal symptoms	p	
Adequate	500mg	1 (0.89%)	3 (2.46%)		
	850mg	2 (1.79%)	3 (2.46%)	0.664	
	1000mg	17 (15.18%)	14 (11.48%)		
	2000mg	92 (82.14%)	102 (83.61%)		0.753
Deficient	500mg	1 (3.85%)	1 (1.92%)		
	850mg	0 (0.00%)	0 (0.00%)	0.772	
	1000mg	4 (15.38%)	6 (11.54%)		
	2000mg	21 (80.77%)	45 (86.54%)		

Table 3. Crosstabulation of gastrointestinal symptoms, metformin usage duration, and vitamin B12 status

Vitamin B12	Metformin usage duration	No gastrointestinal symptoms	One or more gastrointestinal symptoms	p	
Adequate	Less than one year	17 (15.18%)	13 (10.66%)		
	1 to 5 years	37 (33.04%)	36 (29.51%)	0.595	
	5 to 10 years	33 (29.46%)	43 (35.25%)		
	10 or more years	25 (22.32%)	30 (24.59%)		0.038
Deficient	Less than one year	3 (11.54%)	4 (7.69%)		
	1 to 5 years	8 (30.77%)	7 (13.46%)	0.005	
	5 to 10 years	9 (34.62%)	7 (13.46%)		
	10 or more years	6 (23.08%)	34 (65.38%)		

Table 4. Crosstabulation of gastrointestinal symptoms, HbA1c levels, and vitamin B12 status

Vitamin B12	HbA1c levels	No gastrointestinal symptoms	One or more gastrointestinal symptoms	p	
Adequate	Less than 6	13 (11.61%)	13 (10.66%)		
	Between 6 and 8	66 (58.93%)	65 (53.28%)	0.562	
	Higher than 8	33 (29.46%)	44 (36.07%)		0.283
Deficient	Less than 6	2 (7.69%)	4 (7.69%)		
	Between 6 and 8	15 (57.69%)	24 (46.15%)	0.604	
	Higher than 8	9 (34.62%)	24 (46.15%)		

Table 5. Distribution of other therapeutic agents used in the treatment of diabetes mellitus other than metformin.

Treatment agents		n
Insulins	All types	87
Sulfonylureas	Gliclazide	49
	Glimepiride	5
Thiazolidinedione	Pioglitazone	59
Dipeptidyl peptidase 4 (DPP4) inhibitors	Sitagliptin	15
	Vildagliptin	77
	Linagliptin	28
Sodium-glucose cotransporter-2 (SGLT-2) inhibitors	Dapagliflozin	12
	Empagliflozin	24

Discussion

According to our results, we showed that the duration of DM and duration of MTF use are risk factors for vitamin B12 deficiency in patients with T2DM using MTF. More importantly, we found that MTF-related gastrointestinal symptoms were more common in patients with vitamin B12 deficiency. Especially in patients using MTF therapy for ≥10 years, the incidence of gastrointestinal symptoms increased remarkably if vitamin B12 deficiency was also present. Based on our literature review, we noticed that no other study investigated the association of vitamin B12 deficiency with gastrointestinal symptoms in T2DM patients treated with MTF. We think that our research will make an important contribution to the literature since it is the first study to investigate this subject.

The global prevalence of DM was reported as 9% in 2019 by the International Diabetes Federation (IDF) [10]. It is estimated that there will be 783 million DM patients by 2045 [11]. According to the ADA, MTF is the agent of choice for the first-line treatment of adults with T2DM [12]. Therefore, the number of patients using MTF worldwide is relatively high. It has been reported that vitamin B12 deficiency due to MTF use can be seen in an average of 6% to 30% of patients [13,14]. Different prevalence values have been reported in different studies. Prevalence of vitamin B12 deficiency was found as %6.9 in a study reported from Brazil [15], as 20.3% after 9.5 years of MTF use in a large prospective study [16], as 22% in the National Health and Nutrition Examination Survey (NHANES) [13] and as 9.5% in a study by College of Medicine of the Catholic University of Korea [9]. In our study, we detected vitamin B12 deficiency in 25% of the patients, and this rate was consistent with other studies. The reasons for the different prevalence values in different studies may be the differences in doses and durations of MTF use, differences in test methods, and differences in alcohol use. Previous studies have shown a clear relationship between the dose or duration of MTF use and vitamin B12 deficiency in patients with T2DM. Sun-Hye Ko et al. showed that patients using MTF at ≥2,000 mg/day and ≥10 years had an approximately 4-fold greater risk of vitamin B12 deficiency than patients using

MTF at ≤1,000 mg/day and <4 years [9]. Martin et al. reported in a recent study that patients using MTF for more than five years are at bigger risk for vitamin B12 deficiency [17]. Likewise, a study using NHANES data found that patients were more likely to be vitamin B12 deficient as the duration of MTF use (4.1% for 3-10 years of MTF use versus 8.1% for >10 years of use) [13]. Saqer et al. also found that the annual increase in DM duration was associated with lower vitamin B12 levels [18]. According to our study data, the duration of DM and the duration of MTF use of our patients were quite close to each other. The duration of DM and the duration of MTF use were longer in the group with vitamin B12 deficiency compared to the group without vitamin B12 deficiency. These results support other study results. However, unlike other studies, we could not detect a relationship between MTF dose and vitamin B12 deficiency.

Although an increased MCV is expected in megaloblastic anemia, it has been shown that MCV is normal in 30% of cases with a positive response to vitamin B12 therapy [19]. According to our data, although the mean MCV value was within normal limits in the group with vitamin B12 deficiency, it had a higher value than the group without vitamin B12 deficiency. HbA1c value was higher in our patient group with vitamin B12 deficiency. We think this result may be related to the longer duration of DM in patients in the vitamin B12 deficiency group. Another result of our finding was that the detected diabetic neuropathy was higher in the vitamin B12 deficient group. The fact that patients with vitamin B12 deficiency have worse glycemic control (higher HbA1c value) and longer duration of diabetes may explain this result.

Tolerability for any drug is very important in terms of treatment compliance and quality of life of patients. MTF is an antidiabetic agent that improves glycemic control with low cost and also has good safety [20]. The ADA and EASD recommend MTF as initial therapy in patients newly diagnosed with T2DM [21]. However, the majority of patients cannot adequately tolerate this drug due to side effects. Approximately 25% of patients complain of MTF-related gastrointestinal side effects and approximately 5% cannot tolerate MTF at all. [22]. In some studies, gastrointestinal symptoms such as diarrhea, nausea, or abdominal discomfort, usually mild, have been reported to occur in up to 50% of patients using MTF [23]. In our study, our rates of MTF-related gastrointestinal symptoms were found to be higher than in other studies. We think this is because, unlike other studies, a metallic taste in the mouth is also included in the symptoms. However, according to our data, we could not find a significant relationship between the dose of MTF used and gastrointestinal symptoms. Conflicting results were also found in studies evaluating the relationship between increased MTF dose and gastrointestinal symptoms. Although some studies found a positive relationship, the authors did not comment on the importance of this relationship, while some authors reported this relationship as insignificant [24,25]. In a study in which Yuxin et al. examined the safety of different doses of MTF, they found no association

between MTF dose and the incidence of gastrointestinal adverse events [26]. However, the ADA and EASD recommend reducing the dose of MTF when gastrointestinal symptoms occur, in the belief that symptoms will improve over time [27].

The clinical significance of vitamin B12 deficiency is that it can cause reversible bone marrow failure and some neurological disorders. Peripheral neuropathy may develop as a result of MTF-related vitamin B12 deficiency and may be confused with diabetic neuropathy in patients with DM under MTF therapy. It may also contribute to the exacerbation of diabetic neuropathy [28,29]. The important thing is to stop the progression of neurological damage due to vitamin B12 deficiency with early diagnosis and vitamin B12 supplementation [30]. However, permanent neurological damage can occur if neuropathic symptoms are misdiagnosed as diabetic neuropathy [29]. Therefore, detecting vitamin B12 deficiency in DM patients with neuropathic symptoms is extremely important. Already, the 2017 ADA treatment guidelines also recommend that vitamin B12 measurements be performed regularly in patients under MTF treatment [31]. With our results, we showed that the frequency of vitamin B12 deficiency is increased in patients with gastrointestinal symptoms or even three or more symptoms at the same time. We think this finding may provide benefits such as predicting patients with vitamin B12 deficiency by evaluating gastrointestinal symptoms.

The cause of vitamin B12 deficiency in people taking MTF has not been clearly clarified. Patients with T2DM have a different composition of gut microbiota compared to healthy individuals [32]. It has also been shown that daily use of 1 gram of MTF can change the microbiota after as little as three days [33]. It has also been reported that in women with type 2 diabetes, those treated with MTF have a different microbiota than those not treated with the drug [34]. It is known that disruptions in the microbiome can affect the absorption of nutrients, especially B vitamins. Therefore, changes in the gut microbiome are thought to be effective in MTF-related vitamin B12 deficiency [35]. On the other hand, changes in the microbiome by MTF may also have a potential role in gastrointestinal intolerance. Hata et al. reported a significant improvement in gastrointestinal tract symptoms after using the probiotic Bifidobacterium bifidum G9-1 in T2DM patients treated with MTF and supported this hypothesis [36]. As a result, there are highly complex relationships between MTF and the gut. Changes in the microbiome caused by the action of MTF can result in both gastrointestinal symptoms and vitamin B12 deficiency. In our study, we evaluated the relationship between vitamin B12 deficiency and gastrointestinal symptoms, which, to the best of our knowledge, has never been investigated before. Indeed, we found that vitamin B12 deficiency was more common in patients with gastrointestinal symptoms. One of our remarkable findings was that vitamin B12 deficiency was more common in patients with three or more symptoms than in patients with one or two symptoms. When we made a subgroup analysis according to vitamin B12 deficiency, we found that

this difference disappeared in the group without vitamin B12 deficiency. However, in the vitamin B12 deficient group, there was still a significant association between the duration of MTF use and gastrointestinal symptoms. The significant increase in the incidence of gastrointestinal symptoms in patients with vitamin B12 deficiency and using MTF for ≥10 years was the most striking finding of our study. According to our findings, we think that vitamin B12 deficiency may increase gastrointestinal symptoms in patients with T2DM using MTF. When we evaluate it together with the literature information, we think that MTF-related intestinal microbiome changes may be the basis of this.

Limitations of The Study

The fact that the study focused on vitamin B12 deficiency in a specific patient group increases the value of the study. However, it can be said that the study has some limitations. The inclusion of patients of single ethnicity and the fact that it is single-center is a limitation. Due to the study's cross-sectional design, the causal relationship between the variability of vitamin B12 levels over time and gastrointestinal symptoms cannot be clearly explained, but it can be speculated. At the same time, dietary habits may have an effect on gastrointestinal symptoms. However, this situation was not analyzed in the study.

Conclusion

In conclusion, our study showed that gastrointestinal symptoms seen in patients with T2DM using MTF might be related to vitamin B12 deficiency. We think that this relationship may be related to intestinal microbiome changes due to MTF. We recommend that patients who have used MTF for ≥10 years and have gastrointestinal complaints should be evaluated more closely for vitamin B12 deficiency. There is a need for multicenter prospective studies with more patients in which the causal relationship of vitamin B12 on gastrointestinal symptoms can be evaluated more clearly.

Author Contributions
F. E. Conception, design, fundings, data collection and procesing, literature review, writting, critical review
D. T. Design, fundings, data collection and procesing, analysis and interpretation, writing

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ORIGINAL ARTICLE

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Association of left atrial ejection force and obesity: A prospective study of middle-aged adults

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Abstract

Increased hemodynamic load in obese individuals leads to alterations in cardiac geometry and function, including the left atrium (LA). Left atrial ejection force (LAEF) is the force required for late diastolic filling of the left ventricle and has been shown to be associated with age, hypertension, glucose level and weight. Our aim in this study was to investigate the relationship between obesity and LAEF in middle-aged-adult individuals. For this prospective study, a total of 104 individuals, 52 healthy normal weight (BMI < 25) and 52 healthy obese (BMI>30), who were admitted to the cardiology clinic with cardiac complaints were enrolled. Detailed physical examination, anthropometric measurements, glucose levels, lipid levels, interventricular septal thickness (IVSD), left ventricular end-diastolic diameter (LVEDD) on echocardiography, left ventricular posterior wall thickness (LVPWD), left ventricular mass index (LVMI), left ventricular ejection fraction (LVEF), left atrial diameter (LAD), left atrial volume index (LAVI) and left atrial ejection force (LAEF) were calculated. Univariate and multivariate analyses were performed to determine the factors affecting LAEF. Age, male ratio, smoking rate, arterial blood pressure and lipid parameters were similar in both groups. BMI value of the normal weight group was 23.7±1.2 and 38.9±3.7 in the overweight group (p<0.001). The obese group had higher IVSD, LVEED, PWD, LVMI, LAD, LAVI and LAEF compared to the normal weight group (p<0.001 for all values). Pearson correlation analysis showed a significant and moderate correlation between BMI and LAEF (r = 0.582, p<0.001). Regression analysis also showed that BMI was a significant and independent predictor factor for LEAF (p<0.001). Higher BMI is associated with increased LAEF in middle-aged-adult healthy obese individuals.

Keywords: Echocardiography, left atrium, obesity

Introduction

Obesity can lead to various hemodynamic alterations, resulting in morphologic and functional disorders of the heart. These obesity-related disorders can eventually lead to heart failure even without co-morbid conditions such as hypertension and coronary artery disease. Although according to our traditional knowledge, these disorders are attributed to hemodynamic changes caused by obesity, recent studies provide data supporting that this condition may also develop due to neurohormonal and metabolic abnormalities [1]. Left ventricular (LV) diastolic dysfunction is especially common in severely obese individuals [2]. Pulmonary capillary wedge pressure and LV peak diastolic pressure are elevated in class II and class III obese individuals, especially during exercise, and this elevation is attributed to the decrease in

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LV compliance [3].

The left atrial ejection force (LAEF) is a known indication of both LV diastolic function and the mechanical function of the atrium. LAEF is a force applied during atrial systole to push blood through the mitral valve into the LV. In accordance with Newton's principles, LAEF is determined by multiplying the mass and velocities of the blood entering the left atrium (LA) during atrial systole. In the Strong Heart Study, LAEF was correlated with age, body mass index (BMI), hypertension, serum glucose, creatinine and insulin levels. Moreover, it has been demonstrated that an elevated LAEF is a standalone predictor of cardiovascular events [4-5].

We are unaware of any investigation examining the association between obesity and LAEF in the middle-aged obese population. This investigation was carried out to look into this connection.

Material and Methods

Study Population

For this prospective study, patients admitted to the Cardiology Outpatient Clinic of Health Sciences University Şanlıurfa Mehmet Akif Inan Training and Research Hospital due to cardiac complaints were included. After detailed physical examination and tests, according to the criteria recommended by the World Health Organization [6], 52 obese individuals with a BMI > 30 kg/m2, no other co-morbidities and 52 healthy individuals with a BMI < 25 kg/m2 a total of 104 participants were included. Cardiovascular system examinations were also performed in all patients. Blood pressures of the participants were measured in the sitting position in both arms with a mercury sphygmomanometer with a suitable cuff. Body weights, heights and waist circumferences were calculated. Using the Quetlet index, the BMI was computed by dividing the body weight by the square of the height in meters. Fasting glucose, lipid parameters, thyroid and renal function tests, and hemogram parameters were determined from venous blood samples obtained from the participants after 12 hours of fasting. All subjects underwent transthoracic echocardiographic examination and 12-lead electrocardiography (ECG).

Exclusion Criteria

•Patients with a history of coronary artery disease

•Hypertension

•Diabetes mellitus

•Metabolic syndrome

•Left ventricular wall motion defect, left ventricular ejection fraction <50%

•Valvular heart disease

•Primary cardiomyopathy

•Bundle branch block,

•Atrioventricular conduction abnormality on ECG

•Anemia

•Electrolyte imbalance

•Renal failure

•Pulmonary disease

•Poor echocardiographic appearance

In accordance with the Declaration of Helsinki, the study protocol was approved by the Harran University Faculty of Medicine Ethics Committee (HRU/22.12.22). All participants gave their written consent after being fully informed.

Conventional echocardiographic examination

All patients included in the study underwent 2-dimensional, M-mode, pulsed-wave and color flow Doppler echocardiographic examination by two cardiologists blinded to the study criteria. 2-dimensional and conventional Doppler examination was performed in the parasternal long axis and apical four spaces according to the recommendations of the American Society of Echocardiography (ASE) [7-9]. The mean value of three consecutive cycles was taken for all parameters. Left ventricular end diastolic diameter (LVEDD), interventricular septum (IVS), posterior wall (PW) and LV ejection fraction (LVEF) were calculated by M-mode echocardiography. LV mass was calculated using the Devereux formula. LV mass index (LVMI) was calculated as LV mass divided by body surface area. LA volume was calculated using the two-plane area-length method at the end of systole (maximal left atrium size) in apical four and apical two-chamber imaging, and LA volume index (LAVI) was calculated by dividing this value by body surface area [10]. 2D-mode Pulsed-wave-Doppler recordings were obtained from LV inflow velocity as recommended by ASE guidelines. Early diastolic wave (E), late diastolic wave (A), the ratio of two waves (E/A), isovolumic relaxation time, and deceleration time were calculated.

Calculation of LAEF

According to Newton's principles of motion, the product of mass and acceleration gives force. Following this logic, Manning et al [11] proposed that LAEF is equal to the product of the amount of blood passing through the mitral valve during atrial systole and the acceleration of the blood. They proved that LAEF can be calculated with the formula LAEF= $1/2 \times$ MVA $\times$ A2. However, although Newton's law applies to solids, it can lead to miscalculation if used for liquids. It has been shown in many studies that the modified version of this formula, LAEF= $1/3 \times$ MVA $\times$ A2, can be used for liquid bodies and gives more accurate results [12]. This formula was also used in this study. In this formula, MVA is the mitral valve area and A is the velocity measured during atrial systole. The mitral annulus diameter (d) was measured manually from the apical four-chamber view and MVA was calculated as $\pi d2/4$ assuming the shape of the annulus to be circular.

Statistical Analysis

The software program Statistical Program for the Social Sciences (SPSS for Windows, version 22.0, IBM Corp., Armonk, NY, U.S., 2016) was used to perform statistical analyses on the research data that had been gathered. Descriptive statistics for continuous variables were presented as mean ± standard deviation and median values in the presence of normally and non-normally distributed data, respectively.

The chi-square or Fischer's exact test was used to compare categorical variables that were reported as percentages. Whether the data was normally distributed was evaluated with the Kolmogorov-Smirnov test. Two groups were compared with the independent-samples t-test for continuous data conforming to the normal distribution. Non-normally distributed data were compared with the Mann-Whitney U test. Pearson's correlation coefficient was used for the correlation analysis between the independent indicators of LAEF. The univariate and multivariate logistic regression analyses were used to identify the independent predictors of LAEF. $P \leq 0.05$ was considered statistically significant.

Results

Baseline characteristics, echocardiographic and laboratory results of the study participants are summarized in Table 1.

Table 1. Clinical and laboratory characteristics of the study population

	Controls (n=52)	Obese (n=52)	P
Age (year)	39.2±3.5	39.9±4.1	0.312
Male, n (%)	27 (51.9%)	26 (50 %)	0.844
Smoking, n (%)	14 (26.9 %)	13 (25 %)	0.089
Weight (kg)	67.2 ±10.3	107.1 ±11.6	**<0.001**
Waist circumference (cm)	86.5±5.6	114.2±8.1	**<0.001**
BMI	23.7±1.2	38.9±3.7	**<0.001**
Systolic blood pressure (mmHg)	115.4±11.3	116.3±11.2	0.696
Diastolic blood pressure (mmHg)	77.8±5.2	79.3±4.1	0.110
Glucose (mg/dl)	85.8±10.7	92.5±7.1	**<0.001**
Total cholesterol (mg/dl)	165.4±11.9	169.2±12.9	0.130
LDL-cholesterol (mg/dl)	131.9±17.4	139.6±24.1	0.066
HDL-cholesterol (mg/dl)	50.2±5.7	48.9±7.7	0.348
Triglycerides (mg/dl)	139.8±14.6	144.3±15.9	0.139
TSH (mIU/L)	1.94±0.98	1.87±0.99	0.278
Creatinin (mg/dl)	0.95±0.8	0.88±0.2	0.278
WBC (×10³/μL)	7.3±1.8	8.43±0.8	0.216
Hemoglobin(g/dl)	13.6±1.5	14.1±1.6	0.101
Platelet (×10³/μL)	274.26±86.3	244.46±65.1	0.091

LDL: low-density lipoprotein, HDL: high-density lipoprotein,BMI:body mass index, WBC: White blood cell count, TSH:tyroid stimulating hormone

The mean age of the study population was 39.6±3.9 years and the male rate was 51%. Participants were divided into two groups according to their BMI, with those with a BMI above 30 defined as obese and those with a BMI below 25 defined as healthy. Weight (107.1±11.6 vs. 67.2±10.3, p<0.001), waist circumference (114.2±8.1 vs. 86.5±5.6, p<0.001), BMI (38.9±3.7 vs. 23.7±1.2, p<0.001) and glucose level (92.5±7.1 vs. 85.8±10.7, p<0.001) were higher in the obese group than in the normal weight group (Table 1). When the groups were compared in terms of echocardiographic parameters, IVSD (1.05±0.04 vs. 0.92±0.12, p<0.001), LVEDD (5.01±0.3 vs. 4.4±0.3, p<0.001), LVMI (89.5±13.8 vs. 77.3±16.8, p<0.001), LAD (4.1±0.2 vs. 3.5± 0.3, p<0.001), LAVI (37.4± 6.9 vs. 20.3± 1.9, p<0.001) and LAEF (7.2±1.5 vs. 5.3±1.4, p<0.001) were found to be higher compared to normal weight individuals (Figure 1).
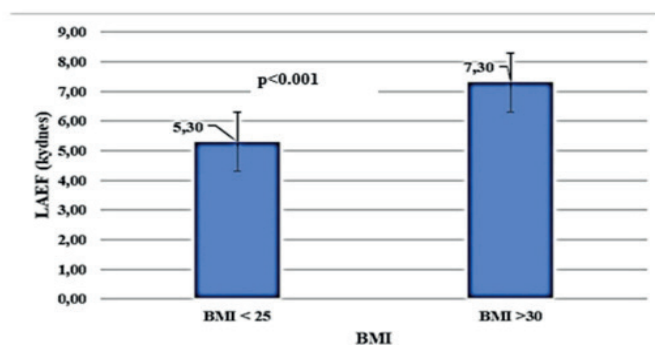

Figure 1. Comparison of LAEF of the groups

While the LVEFs of both groups were similar, peak A velocity was higher in the obese group and peak E velocity was higher in the control group. The E/A ratio was lower in the obese group (0.97±0.2 vs. 1.2±0.3, p<0.001) (Table 2).

Table 2. Echocardiographic parameters of the study population

Echocardiographic parameters	Controls (n=52)	Obese (n=52)	P
IVSD (cm)	0.92±0.12	1.05±0.04	**<0.001**
LVEDD (cm)	4.4±0.3	5.01±0.3	**<0.001**
Posterior wall thickness (cm)	0.98±0.4±	1.07±0.4	**<0.001**
LVMI	77.3±16.8	89.5±13.8	**<0.001**
LVEF (%)	60.1±5.2	62.3±4.5	0.089
LAD (cm) (anterior-posterior)	3.5±0.3	4.1±0.2	**<0.001**
Peak E velocity (cm/s)	70.01±6.4	62.8±7.4	**<0.001**
Peak A velocity (cm/s)	57.4±7.3	66.1±6.9	**<0.001**
E/A ratio	1.2±0.3	0.97±0.2	**<0.001**
Deceleration time (sec)	183.8±14	217.2±22.9	**<0.001**
LAVI	20.3±1.9	37.4±6.9	**<0.001**
LAEF(kdynes)	5.3±1.4	7.2±1.5	**<0.001**

IVSD: interventricular septal thickness, left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction,LAD: left atrium diameter, BMI:body mass index, LAVI:left atrial volume index, LAEF: left atrial ejection force,LVMI: LVMI, left ventricular mass index

The results of the correlation analysis of LAEF with echocardiographic, anthropometric and laboratory results are summarized in Table 3.

Table 3. Pearson's correlation of echocardiographic, anthropometric and laboratory parameters with LAEF

Variables	r value	p value
Waist circumference	0.516	**<0.001**
BMI	0.582	**<0.001**
LAD	0.442	**<0.001**
LAVI	0.511	**<0.001**
IVSD	0.383	**<0.001**
LVEDD	0.498	**<0.001**
Glucose	0.446	**<0.001**
LVMI	0.564	**<0.001**

Abbreviations: see Table 1 and Table 2

According to Pearson's correlation analysis results, a moderately significant correlation was observed between LAEF and BMI (r = 0.582, p<0.001), waist circumference (r = 0.516, p<0.001), LAVI (r = 0.511, p<0.001) and LVMI (r = 0.564, p<0.001), while was a significant weak correlation observed between LAD (r = 0.442, p<0.001), IVSD (r = 0.383, p<0.001), LVEDD (r = 0.498, p<0.001) and glucose level (r = 0.446, p<0.001). Logistic regression analysis revealed that waist circumference, BMI, LAD, LAVI, IVSD thickness, glucose level and LVMI were independent and significant parameters determining LAEF (Table 4).[Waist circumference: hazard ratio (HR): 1.182, 95% confidence interval (CI): 1.054-1.327, p<0.004; BMI: HR: 1.388, 95% CI: 1.087-1.772, p=0.009; LAD: HR: 1.327, 95% CI: 1.121-1.435, p<0.028; LAVI: HR: 0.801, 95% CI: 0.671-0.793, p=0.024; IVSD: HR: 1.356, 95% CI: 0.809-1.987, p=0.024; glucose level: HR: 1.197, 95% CI: 1.053-1.362, p=0.006; and LVMI: HR: 1.096, 95% CI: 1.026-1.171, p=0.007 respectively].

Table 4. Univariate and multivariate logistic regression analyses of the predictors of LAEF

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Waist circumference	1.143 (1.087-1.201)	**<0.001**	1.182 (1.054-1.327)	**0.004**
BMI	1.232 (1.140-1.331)	**<0.001**	1.388 (1.287-1.772)	**<0.001**
LAD	1.030(1.020-1.040)	**<0.001**	1.327 (1.121-1.435)	**0.028**
LAVI	1.089 (1.040-1.140)	**<0.001**	0.801 (0.671-0.973)	**0.024**
IVSD	11.801 (2.397-15.903)	**<0.016**	1.356 (0.809-1.987)	**0.049**
LVEDD	13.662 (3.652-51.113)	**<0.001**	1.805 (0.175-18.662)	0.620
Glucose	1.108 (1.053-1.166)	**<0.001**	1.197 (1.053-1.362)	**0.006**
LVMI	1.090 (1.050-1.132)	**<0.001**	1.096 (1.026-1.171)	**0.007**

Abbreviations: see Table 1 and Table 2

Discussion

Data from postmortem investigations, echocardiograms, and recently developed cardiac magnetic resonance imaging studies have been the primary sources for information on the impact of obesity on heart morphology [1]. These studies have predominantly enrolled obese individuals with comorbid diseases such as coronary artery disease (CAD) and hypertension, and thus the overlap between these co-morbid conditions and the changes in cardiac morphology caused by obesity itself has been inevitable. In light of the data from experimental studies, the effect of obesity on cardiac morphology on its own has started to be discussed [13]. Obesity causes many functional changes in addition to changes in cardiac morphology. The most common functional change is LV diastolic dysfunction [3]. Previous studies have demonstrated that impairment in transmitral inflow flow occurs with weight gain and in another study, obesity was associated with increased LAEF, cardiac output and increased left ventricular mass index in hypertensive obese individuals [14,15]. In a simple definition, LAEF is the mechanical power expended by the LA to maintain end-diastolic filling of the LV in the setting of impaired LV diastolic dysfunction [12].In this study, we investigated the relationship between obesity and LAEF in healthy obese middle-aged adults and to our clinical knowledge, this is the first study in this aspect. The demographic and anthropometric parameters of normal weight and obese individuals in our study were similar and the individuals in both groups had no other comorbidities other than obesity. Therefore, we think that this study is important in terms of clearly demonstrating how obesity can affect LA functions. Our study revealed that LAEF was higher in obese patients. There are several speculations about this situation. LV diastolic dysfunction is a very common condition in obese individuals [16]. It is only possible to compensate for the increase in LV diastolic filling pressure secondary to LV diastolic dysfunction and to maintain LV ventricular filling by increasing LAEF [17]. LV diastolic dysfunction is also thought to increase the preload of the LA, leading to a Frank-Starlig mechanism in the LA and eventually to an increase in LAEF [18]. In addition, previous studies have also shown that total blood volume and cardiac output increase in association with obesity. Volume increase may lead to an increase in all cardiac cavities including the left atrium and left ventricular cavities [19]. In parallel with this situation, in our study, obese individuals had higher LAD, LAVI, LVEDD and LVMI values compared to normal-weight individuals. Studies on obese patients have shown an increase in LVM including left ventricular hypertrophy [1] and the findings in this study were in this direction.

M. Chinali et al. [20] in a subgroup of overweight adolescents in "The Strong Heart Study" demonstrated that changes in cardiac function and morphology, including LVH, occur in proportion to weight starting from the early period. These changes are thought to be the result of increased hemodynamic load. In the early period of weight gain, LVH and LV diameters increase, whereas

in the later period, LAEF increases secondary to increased LV filling pressure. In our study, LVMI was found to be higher in the obese group although LVH was not at a pathologic level, which is parallel to these findings. In parallel with this, obese individuals were also found to have higher LAEF.

Ayer JG et al. [21] demonstrated that LAD increased in a correlated manner with BMI independent of left ventricular diameter and thickness in their large study. However, the fact that LAEF was not used in this study can be considered as a limitation and the results of the correlation analysis performed in our study revealed the presence of a significant correlation between LAEF and BMI. In addition, according to the logistic regression analysis performed in our study, waist circumference, BMI, LAD, LAVI, IVSD, glucose level and LVMI were found to be independent and significant predictive factors for LAEF. These findings are parallel with those of the Strong Heart Study [22].

Limitations of the study

The single center and small volume of the study is a limitations that can be counted first and foremost. In addition, due to the small number of patients, obese individuals were not restricted according to the degree of obesity and the changes in cardiac morphology according to obesity class could not be investigated. As is known, the measurement of LAV by three-dimensional echocardiography (3DE) provides more objective values than measurement by two-dimensional echocardiography. We think that the absence of 3DE in our clinic and its lack of use in this study is also a deficiency.

Conclusion

This study demonstrated that BMI is an independent and important factor for LAEF in middle-aged adults. This study also demonstrated that weight alone, even in the absence of comorbidities such as hypertension, DM and metabolic syndrome, which are frequently associated with obesity, can cause changes in LAD, LAVI and LVMI, especially LAEF. LAEF may provide additional insights into the pathophysiology of early diastolic dysfunction in obese individuals and the treatment of associated symptoms. LAEF, which is associated with mortality and morbidity and can be calculated noninvasively, is high in middle-aged-adult individuals in the early period of obesity and may be a guiding parameter for early action in the fight against obesity.

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ORIGINAL ARTICLE

Evaluation of the knowledge, attitudes, and behaviors of mothers of children admitted to the emergency department due to home accidents: A descriptive study from Northwest Syria

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Abstract

Accidents that occur in the home or its surroundings are called home accidents. Our aim in this study was to identify the causes of admissions due to home accidents and to assess the awareness and attitudes of mothers. This descriptive and cross-sectional study was conducted in the emergency departments of Çobanbey and Azaz Vatan hospitals. Eighty-one mothers that have an average age of 30.02±7.56 years participated in the study. 53.1% (n=43) of the children admitted due to home accidents were males and the number of applicants in the 0-6 years age group was 54 (65.8%). The most common reason for admission was falls (53.1%, n=43), followed by burns (21%, n=17). It was found that the majority kept toxic substances such as rat poison and pesticides out of the reach of children (98.8%, n=80), warned their children to stay away from water wells (92.6%, n=75), and kept ignitable substances such as matches and lighters out of the reach of children (90.1%, n=73). In addition, 92.6% (n=75) left a teapot on the stove, 88.9% (n=72) left electrical appliances in the outlet, and 80.2% (n=65) reported that children could light the stove by themselves. The mean score calculated in the questionnaire on mothers' awareness and attitude toward home accidents was 15.44±3.40. It is very necessary to carry out studies on health systems with national and international cooperation in victimized regions such as the northwest of Syria and to inform families about accident risks and safety measures.

Keywords: Children, home accident, injury, Syria

Introduction

The World Health Organization defines an accident as an event "that occurs unwillingly and causes physical and mental damage by a sudden external force [1]. Accidents that occur in the home or its surroundings are called home accidents [2]. According to the World Health Organization (WHO) data, falls, burns, and poisoning are the leading causes of morbidity and mortality in-home accidents. Therefore, home accidents are among the most serious health problems worldwide [3]. Children, especially preschool-aged children, are at high risk for home accidents because of their lack of awareness of hazards, curiosity to learn new things, tendency to imitate their parents, and sensitivity and openness to environmental hazards [4, 5].

Falls, burns, choking and blockage with solids, drowning in water, poisoning, etc., cause unintentional home accidents [4]. The types and frequency of home accidents vary depending on

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the age of the children. The home accidents that cause the most injuries in children under five years of age are falls, burns, and poisoning, respectively [2].

According to WHO, for every death from unintentional injuries, there are 34 hospitalizations and 1000 emergency room visits1. In developed countries, the mortality rate of children due to accidents is very low. Children in low- and middle-income countries account for 95.0% of injury-related deaths [6].

It is indisputable that adults are responsible for ensuring that children live in an accident-safe environment, taking protective measures, and supervising the safety of their living spaces [3]. Parents are often aware of the risk of injury at home but do not routinely consider it in their daily interactions [1]. Home accidents are closely related to variables such as region, mode of transportation, building structure, family structure, socioeconomic-sociocultural status, and psychosocial status. In underdeveloped and developing countries, injuries from falls, burns, and poisoning are twice as common as in developed countries [7]. Although prevention of home accidents is an important issue, especially in developed countries, it is observed that families in low socioeconomic status countries have poor knowledge about protection against accidents and children are at higher risk of accidents [5]. Countries are conducting studies to determine the nature and causes of accidents so that they can develop protection programs appropriate to their socioeconomic and sociocultural structures. However, in regions such as northwestern Syria, where unrest has prevailed for more than a decade, establishing an adequate monitoring system does not seem possible. Our aim in this study was to identify the causes of admissions due to home accidents and to assess the awareness and attitudes of mothers in this region, where difficult living conditions prevail.

Material and Methods

Study Design

The research was planned as descriptive and cross-sectional and conducted using face-to-face interviews with the mothers of pediatric patients admitted to the emergency departments of Cobanbey and Azaz Vatan hospitals in Syria due to home accidents between the dates of 01/06/2021-01/09/2021. On the specified dates, 134 individuals were admitted due to home accidents. A total of 81 individuals who agreed to participate and met the inclusion criteria were enrolled in the study. The Ethics Committee of Hatay Mustafa Kemal University for Noninterventional Research (meeting date: 06/05/2021, number of decisions: 18), the relevant hospital administrations, and SIG approved the study. In addition, the study was conducted by the "Declaration of the World Medical Association on the Ethical Principles of Helsinki".

Location of the study

The study was conducted in the emergency departments of Çobanbey and Azaz Vatan hospitals. Turkey established these

hospitals in 2018 and 2020 as part of humanitarian aid [8, 9, 10]. The staff of these hospitals consists of local Syrian doctors and medical personnel, while Turkish health personnel provides the consultation [11, 12]. Patients are admitted to these two hospitals from the centers of Azaz and Cobanbey, as well as from small settlements connected to these centers.

Selection of participants

Mothers of children aged 0-18 years who were admitted to the emergency departments of Azaz Vatan Hospital and Cobanbey Hospital for home accidents were included in the study. Mothers who refused to participate in the survey, who were under 18 years of age, or who had known mental disabilities or psychiatric disorders were excluded from the study. In polygamous families, the biological mother of the enrolled child was included in the study.

Data Collection

Our questionnaire was prepared in Turkish after a literature review on household accidents and translated into Arabic by sworn translators. The questions were reviewed for relevance, simplicity, and importance by Syrian specialist physicians selected for their experience and expertise in the relevant fields. After a pilot study with 20 subjects, the necessary corrections were made and the questionnaire was finalized. In the first part, the form for sociodemographic data of the participants was used, and in the second part, a questionnaire with 24 questions about the awareness of the mothers and the precautions they took. The sociodemographic data form included questions on age, gender, education level, income, number of children, place of residence, type of house and family, and history of home accidents. The home accident awareness and attitudes questionnaire asked 24 questions about home precautions and attitudes toward home accidents from the literature. They were asked to answer yes or no to the questions. The correct answer was scored as "1" and the incorrect answer was scored as "0". It was predicted that the higher the total score, the higher the awareness of home accidents. The score to be obtained on the scale ranged from 0 to 24.

Statistical Analysis

Statistical analyses of the study were performed using Statistical Package for Social Sciences version 28.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA). Descriptive statistics of the variables are given as mean±standard deviation, median (Min-Max), and n (%).

Results

A total of 81 subjects participated in the study. The frequency and percentage values of the responses given by the participants are shown in Table 1. The mean age of the mothers was 30.02±7.56 years. Twenty-two (27.2%) of the mothers were illiterate, and 33 (40.7%) had primary school graduates. The median number of children in the family was 3. The most common number of children in participants' families admitted to the emergency

department for a home accident was three. Fifty-two (64.2%) of the participants were first-time mothers between the ages of 16 and 20.

The median monthly income of the families was $100. The median number of people living in the households was 6 (3-14). 53.1% (n=43) of children admitted to the emergency department were male. The mean age of the children was 5.04±3.88 years. Fifty-four (65.8%) applicants were 0-6 years old. Twenty-four (29.6%) patients had previously presented to the emergency department because of an accident at home. The most common reason for admission was a fall (53.1%, n=43), followed by burns (21%, n=17).

When analyzing the responses to the awareness and attitude questionnaire, it was found that the majority kept toxic substances such as rat poison and pesticides out of the reach of children (98.8%, n=80), warned their children to stay away from water wells (92.6%, n=75), and kept ignitable substances such as matches and lighters out of the reach of children (90.1%, n=73). In addition, 92.6% (n=75) left a teapot on the stove, 88.9% (n=72) left electrical appliances in the outlet, and 80.2% (n=65) reported that children could light the stove by themselves (Table 2). The mean score calculated in the questionnaire on mothers' awareness and attitude toward home accidents was 15.44±3.40, with the lowest total score of mothers participating in the study being 5 and the highest being 20 (Graph 1).
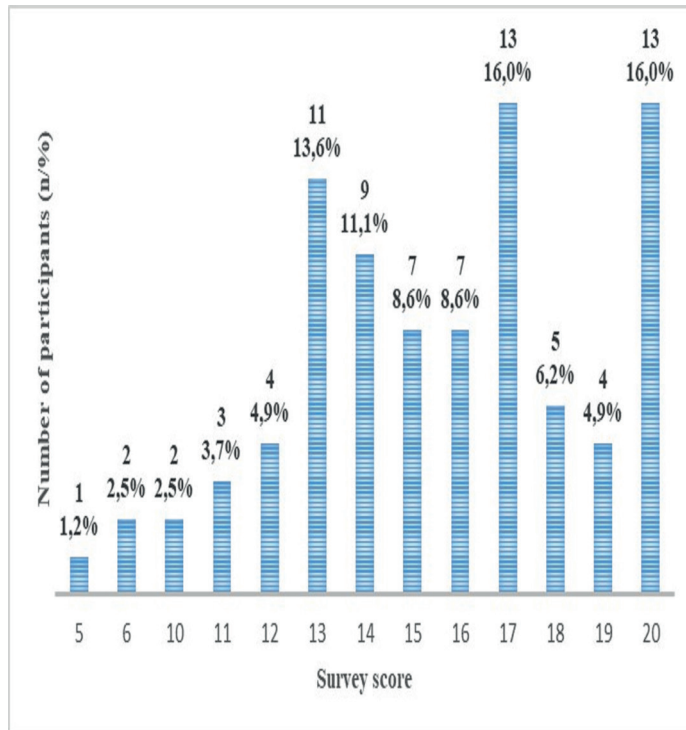
Graph 1. Distribution of the number of people according to their scores in the survey

Table 1. Socio-demographic characteristics of participants

Questions of the Questionnaire	n(%)
Total number of children in the family	
1	11(13.6)
2	12(14.8)
3	25(30.9)
4	14(17.3)
5	13(16.0)
6+	6(7.4)
Age at first motherhood	
16-20	52(64.2)
21-25	22(27.2)
26+	7(8.6)
Place of residence	
City	25(30.9)
County	42(51.9)
Village	13(16.0)
Other	1(1.2)
Family Type	
Nuclear Family	66(81.5)
Extended Family	15(18.5)
Employment Status	
Full-time	9(11.1)
Irregular	8(9.9)
Unemployed	64(79.0)
Caregiver of the Child	
Self (with support from Grandmother)	40(49.4)
Self (alone)	27(33.3)
Caregiver	1(1.2)
Nursery	1(1.2)
Other	12(14.8)
Heating method	
Diesel stove	13(16.0)
Coal stove	59(72.8)
Self-built stove with barrels or other material	1(1.2)
Electric heater	4(4.9)
Other	4(4.9)
Reason for admission to the hospital	
Fall	43(53.1)
Burn	17(21.0)
Poisoning	9(11.1)
Sharp object injury	7(8.6)
Foreign body (ear, nose)	5(6.2)
Have you ever applied to the emergency room because of a home accident?	
Yes	24(29.6)
No	57(70.4)

Table 2. Responses to the awareness and attitude questionnaire on home accidents

	Question	Yes n (%)	No n (%)
1	I keep full water buckets open at home/tent.	38(46.9)	43(53.1)
2	I keep hot water and food containers out of the reach of children.	58(71.6)	23(28.4)
3	I leave electrical appliances plugged in.	72(88.9)	9(11.1)
4	I cook food in a picnic tube at home/tent.	44(54.3)	37(45.7)
5	I keep medicines out of the reach of children.	69(85.2)	12(14.8)
6	I read the label on the bottle before giving medicine to my child.	64(79.0)	17(21.0)
7	I make children under the age of five wear jewelry such as evil eye beads and bracelets.	39(48.1)	42(51.9)
8	I put substances such as dishwashing detergent, descaler, sink opener, and bleach in high places where the child cannot reach them.	64(79.0)	17(21.0)
9	I keep the toilet and bathroom doors closed to protect my children from accidents.	66(81.5)	15(18.5)
10	I keep first aid materials for use in emergency accidents.	55(67.9)	26(32.1)
11	I keep items such as matches and lighters out of the reach of children.	73(90.1)	8(9.9)
12	I take the child out of the room when I light the stove.	27(33.3)	54(66.7)
13	I check the temperature of my child's bath water with my hand or elbow.	72(88.8)	9(11.1)
14	Children can reach boiling water on the stove.	8(9.9)	73(90.1)
15	I allow children to be in the kitchen when I cook.	54(66.7)	27(33.3)
16	I often use diesel fuel to ignite the stove.	48(59.3)	33(40.7)
17	I keep a teapot on the stove.	75(92.6)	6(7.4)
18	My children can light the stove on their own.	16(19.8)	65(80.2)
19	I let the children play on the roof of the house.	32(39.6)	49(60.4)
20	I warn children to stay away from water wells.	75(92.6)	6(7.4)
21	I prevent slippery floor surfaces from getting wet (e.g. bathroom, toilet).	70(86.4)	11(13.6)
22	I leave the children alone on the balcony.	39(48.1)	42(51.9)
23	I can leave my children under 18 alone at home.	55(67.9)	26(32.1)
24	I keep poisonous substances such as rat poison, insecticide, and fly spray out of the reach of children.	80(98.8)	1(1.2)

Discussion

In this study, mothers were found to be most knowledgeable about water wells, poisonous substances, wet floors, and ignitable substances as hazards for home accidents. In contrast, they were least knowledgeable about teapots on stoves, electrical appliances, liquid fuels, open balconies, and cooking stoves in the kitchen.

In our study, more than half of the children admitted due to home accidents were males and the number of applicants in the 0-6 years age group was 54 (65.8%). Looking at the literature, we find that boys have more home accidents in most studies [1, 2, 4, 7, 13]. Similarly, it was found that preschool children had more home accidents [13, 14]. It is believed that preschool children are more prone to home accidents because they spend more time at home and boys are more physically active and adventurous than girls.

In our study, the youngest age of the mothers was 19 years and the oldest was 45 years, and most of the mothers were primary school graduates. Similarly, in studies conducted in different countries, the age of mothers ranged from 20 to 40 years, and most mothers were illiterate or primary school graduates [1, 15, 16]. The majority of our participants had 2 or more children, and families with 3 children had the highest number of emergency department visits due to home accidents. When one examines

studies on home accidents, one finds that most families similarly have 2 or more children [1, 3, 15, 17, 18]. It is believed that as the number of children at home increases the amount of time and attention mothers devote to children decreases, increasing the rate of home accidents.

Approximately 65% of the participating mothers were 20 years old or younger when they first became mothers, and most of them were not working. In addition, one-third of them were taking care of their children alone, while about half of them were supported by their grandmother or paternal grandmother. Studies conducted in Iraq and Turkey found that most mothers did not work [1, 2, 4, 5]. In the study by Mull et al., it was found that about half of the participants received support from family members [19], and in the study by Yalaki et al., it was found that most mothers took care of the child alone [16]. In contrast to our study, a study conducted in Denmark found that the age of first maternity was mostly 25 years and older, and children born to mothers who had given birth under 25 years were found to be at higher risk of home accidents [18].

The literature has demonstrated that the risk of home accidents increases among individuals living in crowded households in rural or semi-urban areas [5, 16, 18, 19, 20]. Although studies are showing that living in a slum increases the risk compared to living in an apartment [17], it has been shown that the type of house usually does not affect the risk of home accidents [4, 18]. Also in our study, more than half of the applicants lived in rural areas and 75% lived in detached houses or apartments. As the number of people living in the home increases, the interest and attention to the child decrease. The fact that homes in rural areas are older, have more infrastructure deficiencies, and are unsafe environments increase the risk [21]. The fact that the type of home the children lived in did not affect the risk suggests that the most important factor for the occurrence of home accidents is the inadequate safety measures in the home and the parent's knowledge and awareness about accidents.

In this study, it was found that the median number of people in a family is six and the average monthly income of families is $100. According to the World Bank, the minimum per capita income in the world is $221 [22]. In our study, this value was found to be approximately $200. Consistent with the literature, the income level of the applicants with home accidents in our study was quite low. Studies have found that a low socioeconomic level increases the risk of home accidents [17, 18, 20, 23]. The region where our study was conducted is a war zone and the limited economic and social opportunities increase the risk of accidents in this region.

In a study conducted in Turkey, it was found that 67.3% of children had one home accident and 23.5% had two home accidents. In Şekerci's study, it was found that 30.2% of children were exposed to a home accident at least once and the most common cause was falls [24]. In a study that examined home accidents in the European Union, it was found that more than

half of the applications were due to falls [14]. A study conducted in the United States reported that the most common cause was falls, followed by burns [19]. Falls are the most common type of accident in children. Burns from hot water most commonly occur in children under 6 years of age [6]. In our study, similar to the literature, it was found that half of our participants had one domestic accident and about a quarter had two domestic accidents, and the most common causes were falls and burns.

Liquid fuels used for stoves pose a risk for life-threatening household accidents due to their flammable, explosive, and combustible properties [25]. In our study, the majority of families were heated with coal and oil stoves. Also, in a study conducted in Iraq, most families used diesel stoves, and very few heated with electric stoves, while in another study, families were indecisive about using electric stoves or did not want to use them [1, 5].

In our study, the majority of mothers indicated that they keep hazardous substances and tools such as chemicals, medicines, and sharp tools out of the reach of children, while they also indicated that they can leave children alone on the balcony and at home. Even though many of them use diesel oil to light the stove and have a teapot on the stove, they indicated that children cannot reach the boiling water on the stove. It can be said that the participating mothers have little awareness of this issue. In the literature, there are different findings on this issue. Similar to our findings, Aktürk et al. found that mothers keep chemicals and sharp piercing instruments in a convenient place and have a teapot on the stove [17]. A study conducted in Egypt on safety measures in home accidents found that most mothers did not store medicines in the proper place [15]. In the study conducted by Nsaif et al. in Iraq, it was reported that very few stored chemicals properly [1]. In another study conducted in Iraq, one-third of mothers reported leaving their children home alone [5]. Parents' level of knowledge and attitude is of great importance in preventing accidents in the home. Most accidents can be prevented by simple precautions. It is believed that the risk of accidents can be reduced by informing families about home accidents, especially in societies with low levels of education such as northwestern Syria.

One limitation of our study is that it reflects only Azaz and Cobanbey regions. Another limitation is that our study was conducted in a limited period and the number of participants was low due to the low access of mothers to hospitals due to the harsh conditions in the region.

Conclusion

Home accidents are a preventable public health problem. To this end, in addition to health system studies, it is very important to inform families about accident risks and safety precautions. In particular, helping families with children aged 0 to 6 years to create a safe home environment and to provide first aid practices in case of any accidents will contribute to accident

prevention. In areas where inadequate living conditions prevail, such as northwestern Syria, this public health problem should be addressed in collaboration with national and international nongovernmental organizations, and regional projects and systems should be developed.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

The Ethics Committee of Hatay Mustafa Kemal University for Noninterventional Research (meeting date: 06/05/2021, number of decisions:18), the relevant hospital administrations, and SIG approved the study.

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CASE REPORT

Medicine Science
International
Medical Journal

Our anesthesia management in a bipolar pregnant case in third trimester

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Abstract

Bipolar disorder is one of the most common psychiatric disorders during pregnancy. Electroconvulsive therapy (ECT) is a potent treatment option for pregnant bipolar cases who do not respond to medical treatment and have a high risk of suicide. In this report, we aimed to present the anesthesia management of a 34-week pregnant woman with bipolar disorder who underwent ECT due to the increase in the frequency of manic episodes despite medical treatment. Induction of labor remains an important risk in the application of ECT in third-trimester pregnant women. Further large-scale randomized controlled studies using different anesthetic agents are needed.

Keywords: Electroconvulsive therapy, pregnant bipolar, premature birth

Introduction

Bipolar disorder is one of the leading causes of psychiatric disorders with a high incidence (43%) during pregnancy [1]. Women with bipolar disorder are at increased risk for relapse during and after pregnancy. Medical management of bipolar cases during pregnancy and lactation poses a serious clinical challenge due to the changes in drug metabolism and concerns about potential teratogenicity in the fetus [2]. The use of ECT remains current due to the inadequacy and potential risks of medical treatment [3].

ECT is a potent treatment option for pregnant psychiatric patients who do not respond to medical treatment, have malnutrition and a high risk of suicide [4] .

Many studies have recommended ECT as an alternative treatment for major depression and bipolar disorder during pregnancy, and this method has been reported to be a high-effective and low-risk technique in all trimesters of pregnancy and in the postpartum period [5].

In this report, we aimed to present the anesthesia management of a 34-week pregnant woman with bipolar disorder who underwent ECT due to the increase in the frequency of manic episodes despite medical treatment.

Case Report

ECT was planned by the psychiatry clinic in a 36-year-old 34-week pregnant patient who was followed up with the diagnosis of bipolar disorder and treated with haloperidol 10 mg/day and Biperiden hidroklorür 4mg/day, because of the increased frequency of manic episodes and the lack of adequate response to drug treatment. After explaining the procedure and possible risks to the patient and her relatives, written consent was

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obtained for the ECT procedure and anesthesia. Before and after each ECT session, NST (Non-stress test) was performed by the Gynecology and Obstetrics Clinic to evaluate uterine contraction and fetal status. In addition to adequate fasting time (8 hours), i.v. H_2 receptor antagonist was administered 30 minutes before anesthesia to prevent the risk of aspiration. The 20-minute NST was performed by the Gynecology and Obstetrics Clinic before each ECT session and 6 accelerated reactive NSTs without uterine contractions were recorded. Then, the patient was taken to the ECT room before premedication in the operating room, and standard monitoring was performed with electrocardiography (ECG), pulse oximetry (SpO_2) and non-invasive blood pressure (NIBP) measurement. Case baseline vitals were recorded as heart rate: 73/min, BP: 125/81 mmHg, and SpO_2: 96. Preoxygenation was provided with 4 L/min O_2.

Propofol 1mg/kg i.v. was administered for anesthesia induction and succinylcholine 1mg/kg i.v. as the neuromuscular agent. The patient was ventilated with a mask using 100% oxygen with the $EtCO_2$ in the range of 35-40. Electrical stimulus was delivered via bifrontotemporal electrodes using a bipolar ECT device. Heart rate, oxygen saturation and mean arterial pressure of the patient were recorded before and after the induction of anesthesia, immediately after the seizure, at the 1st, 3rd and 10th minutes after the seizure, and in the postanesthetic care unit (PACU) (10th min). electroencephalogram (EEG) and electromyogram (EMG) records were kept in the follow-up of seizure activities. Eye opening time, spontaneous respiration time, orientation time, and duration of stay in the PACU were recorded. NST, which was evaluated for 20 minutes after ECT application, was reported as reactive NST with 5 30-unit uterine contractions (mild activity) and 7 accelerations. The second session was performed after 72 hours. Approximately after 24 hours the ECT application, the patient was taken to an emergency cesarean section under general anesthesia by Gynecology and Obstetrics Clinic with the pre-diagnosis of preeclampsia, due to the increase in uterine contractions and the hypertensive course of the pregnant woman. A baby with an Apgar score of 9 was delivered. The patient with stable vital signs was taken to the ward. In the postpartum period, 9 sessions of ECT were applied three times a week, the first session being on the postoperative 4th day, to create sufficient seizure time.

Discussion

Bipolar disorder is a serious chronic mood disorder characterized by episodes of mania, hypomania, and depression. It usually starts in early adulthood, and the risk of relapse is high especially in the postpartum period and in primiparous women. [6]. Psychiatric disorder that is not treated during the peripartum period can have serious consequences such as lack of weight gain, premature birth, abuse of tobacco, alcohol and other drugs, suicide and infanticide. Drug therapy is complex during pregnancy, especially in the first trimester, due to possible teratogenic effects and changes in maternal physiology. Benzodiazepines, antipsychotics, lithium and other mood stabilizers used in the treatment of bipolar disorder are among the drugs with a teratogenic risk in the first trimester [7].

Women with bipolar disorder who discontinued medical therapy before or during pregnancy have a 71% risk of relapse with new episodes, most often in the first trimester. Recurrent disease during pregnancy is associated with a 66% increased risk in the postpartum period [8].

ECT is an effective option for perinatal patients with severe mood episodes who are unresponsive to medication, unable to meet their individual needs, and for suicidal or psychotic patients [9]. Our patient with bipolar affective disorder was being treated with medication by the Psychiatry Clinic, and ECT was planned because the frequency of manic episodes increased despite medical treatment.

In his study, Miller reported fetal complications related to ECT in 28 of 300 pregnant women who received ECT. The most common fetal complication was fetal bradycardia [10].

Pompili et al. [11] examined 184 pregnant ECT cases and reported fetal arrhythmia in 9 cases and premature delivery in 7 cases.

In the case we presented, a 34-week pregnant woman was evaluated with NST before and after each session by the Obstetrics and Gynecology Clinic. As uterine contractions increased 24 hours after the second session of ECT and the patient was hypertensive, she was taken to emergency cesarean section with the preliminary diagnosis of preeclampsia.

It is aimed to create convulsions for a successful ECT application. Although the relationship between the efficacy of the treatment and the duration of the convulsion is controversial, the shortest recommended time is 25 seconds. To prevent extremity traumas that may develop during convulsions and due to respiratory problems, the procedure should be performed under general anesthesia and muscle relaxation [12,13].

Anesthetics are used during ECT application affect threshold and duration of seizures [14]. In an 18 randomized controlled study comparing the effects of intravenous anesthetic agents (Methohexital, propofol and thiopental) [15], it was reported that propofol shortened the seizure duration more than Methohexital, and there was no difference between thiopental and propofol. Propofol was found to be faster at recovery from anesthesia than thiopental. The mean durations of EMG and EEG seizure activities in our case were 32 and 34 seconds, respectively

In a meta-analysis comparing sevoflurane and i.v. anesthetics in ECT application, with a total of 12 randomized controlled studies (377 cases and 1339 ECT sessions), it was observed that sevoflurane significantly reduced EEG seizure durations compared to intravenous anesthetics [16].

Sevoflurane can be recommended, especially in the last trimester of pregnancy, as it reduces ECT-induced uterine contractions. Propofol is an ideal agent preferred for ECT in pregnant women.

It provides rapid induction and recovery and prevents nausea and vomiting [17]. In our patient, we used 1mg/kg propofol. Neuromuscular blockers are required to limit motor activity during ECT. Succinylcholine is the most preferred depolarizing muscle relaxant due to its rapid onset and short duration of action, and its transfer to the placenta is negligible due to its high water solubility. It is administered at doses of 0.75-1.5mL/kg in ECT [18]. In our patient, we used 1mg/kg succinylcholine. The time for spontaneous breathing after ECT was 107 seconds, and the time for eye opening with stimulus was 204 seconds. In our case, who was in the last trimester and had a high risk of aspiration, an 8-hour fasting period was waited and H_2 receptor antagonist was administered 30 minutes before the intervention to prevent this risk.

In a study [13], 67 adverse events were reported in 169 pregnant ECT cases, and the most common adverse event was reported as premature birth in 67 cases (19/28%). In our case, delivery was terminated by C/S due to premature labor (34 weeks) in line with the literature.

Conclusion

Induction of labor continues to be an important risk in the application of ECT in third trimester pregnant women. Therefore, there is a need for further more comprehensive randomized controlled studies in which seizure duration is taken into account and different anesthetic agents are used. In addition, the mother and fetus should be closely monitored by an experienced team after ECT.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Informed Consent
Written consent was obtained from the patient and his parents.

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