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Determination of the Relationship Between Family and Social Support and Anxiety-Depression Levels in Liver Transplant Patients

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ABSTRACT

Objective: The present study was conducted to determine of the relationship between family and social support and anxiety-depression levels in liver transplant patients.

Methods: The Introductory Characteristics Determination Form, Hospital Anxiety and Depression Scale (HADS), Multidimensional Perceived Social Support Scale (MPSSS) and Perceived Family Support Scale (PFSS) were used to question the socio-demographic characteristics of the patients.

Results: When the distribution of the mean anxiety and depression scores according to their introductory characteristics of the patients was examined, it was determined that the mean score of HADS was found to be high (HAD-A=19.71±3.29, HAD-D=15.90±1.99). The mean MPSSS of the patients was found to be at moderate level as 54.56±17.40; and the mean total score of the PFSS of the patients was found to be at high level as 35.77± 7.16. It was determined that family and social support was effective in reducing the depression levels after liver transplantation.

Conclusions: It was found that family and social support was influential in reducing the depression levels after liver transplantation.

Keywords: Liver transplantation, anxiety, depression, family support, social support.

1. INTRODUCTION

Liver transplantation is an indicated treatment for patients who have progressive and irreversible liver disease and no other treatment options (1,2) The number of liver transplantation is increasing every day in the world (1). A total of 1.610 patients underwent liver transplantation in Turkey in 2022 (3). Liver disease is considered as a chronic disease (4). Patients who have liver disease have some restrictions imposed by the disease on them. The presence of numerous symptoms (i.e. anorexia and weakness), which are usually not specific at the onset of the disease, can progress to more serious and crippling symptoms like acid and encephalopathy in the progression of liver disease. This affects the quality of life and mental health of liver transplant candidates negatively (4,5)

Important medical and surgical improvements have been made in recent years during the transplantation process (6) However, patients on the transplantation waiting list experience stress factors like life style changes, uncertainties regarding continuous waiting, surgical intervention, and postoperative treatment (7). Also, adaptation to new medical treatment, the changes in body image, family process and social life cause anxiety in psychosocial terms. After a long period following the discharge from hospital, the patient experiences anxiety and depression as s/he leaves the hospital when he tries to be used to home life (6,7).

It is considered that the importance of family and social support is great in the negativities that anxiety and depression can cause (7). Family and social support affects the well-being of individuals. These supports are a subject that is investigated in different clinical cases because of their associations with the prognosis of the disease in adverse cases like disease (8). Clinical studies show that continuously waiting for an “organ”, and changing the lifestyle in this process adversely affect the patient (7,8). For this reason, it is considered that the support received from friends and family members during transplantation process is an important factor contributing to the reduction and recovery of anxiety and depression levels of patients who are in the treatment process (7-9).

Care forms the basis of nursing. While providing nursing care, the patient should not only focus on the disease, but the patient should be considered as a whole with all its dimensions (10). Liver transplantation is a complex condition, which requires professional approach before, during and after the transplantation (11). The nurse, who is constantly on the patient’s side during the healing process,

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may be the key to implementing new applications and further individualizing patient care by determining the needs and gives the necessary care to patients. It is accepted that there is a close relation between body, mind and soul while focusing on the philosophy of the holistic care and individuality by focusing all the stages of the process (10)

In the light of these data, this study was planned and conducted to determine the effects of family and social support in patients undergoing liver transplantation on anxiety-depression.

2. METHODS

2.1. Design and Sample

This study was planned and conducted to determine the effects of family and social support in patients undergoing liver transplantation on anxiety-depression. The study was conducted with 66 patients who were qualified to answer the questions of the study, who volunteered to participate in the study, who were 18 years and older, and who underwent liver transplantation at Atatürk University, Organ Transplantation Education Research and Application Center between November 2014 and September 2017, 6 months after the date of transplantation. The universe of the study consisted of the patients who underwent liver transplantation at the specified dates, and the sample consisted of 66 patients who met the research criteria.

2.2. Instruments

The Introductory Characteristics Determination Form, Hospital Anxiety and Depression Scale (HADS), Multidimensional Perceived Social Support Scale (MPSSS), and Perceived Family Support Scale (PFSS) to question the socio-demographic characteristics of the patients in the study.

The Introductory Characteristics Determination Form: This form contained questions regarding the sociodemographic data like gender, age, educational status of the participants, and was prepared by the researcher in line with the literature (1, 2, 4-7).

The Hospital Anxiety and Depression Scale (HADS): This scale was developed by Zigmond and Snaith (11) in 1983, and its adaptation for Turkey was conducted by Aydemir et al. (12) in 1997. The Hospital Anxiety Depression Scale (HADS) includes the anxiety and depression include subscales, and it is a scale of self-notification, consisting of 14 items 7 of which investigate the symptoms of depression (even numbers), and 7 of which investigate the symptoms of anxiety (odd numbers). The answers are evaluated in the form of 4-Point Likert, and are scored between 0-3. The purpose of the scale is not to diagnose, but to identify the risk group by screening the anxiety and depression levels in patients with physical illness in a short time (11,12). It has Anxiety (HAD-A) and Depression (HAD-D) subscales. As a result of the studies conducted in Turkey, the cut-off score of the scale for the anxiety subscale was found to be 10, and 7 for the depression subscale. In this respect, the areas above these scores are considered under risk (12). In this study, the Cronbach Alpha reliability coefficient was found to be 0.78 for the subscale of anxiety, and 0.77 for the depression subscale.

Multidimensional Perceived Social Support Scale (MPSSS): The scale was developed by Zimmet (13) et al. in 1988, and the validity and reliability study for Turkey was conducted by Eker and Arkar (14) in 1995. The scale evaluates the adequacy level of social support from three different sources, and consists of a total of 12 items. There are three groups of four items each one related to the source of support: Family (Items 3, 4, 8, 11) are friends (Items 6, 7, 9, 12), and a special person (Items 1, 2, 5, 10). The scale is in the form of 7-Point Likert type, and consists of options “I totally agree” (7 points), “I mostly agree” (6 points), “I agree” (5 points), “I am undecisive” (4 points), “I disagree” (3 points), “I mostly disagree” (2 points), and “I disagree at all” (1 point) (14,15). The total score of the scale is obtained by adding the scores of the four items in each subscale; and the total score of the scale is obtained by adding all subscale points. The lowest score that may be received from the subscales is 4, and the highest score is 28. The lowest score that may be received from the entire scale is 12, and the highest score is 84 (14). A high score shows that the perceived social support (13,14). The Cronbach Alpha reliability coefficient was found to be 0.92 in the present study.

Perceived Family Support Scale (PFSS): The Perceived Family Support Scale, which was developed by Procidano and Heler in 1983 (15), adapted by Eskin in 1993 (16), and developed by Yıldırım in 1997 (17), was used to determine the level of perceived family support in the study. The scale consists of 20 questions which are answered as “Yes, No, Partly”. In the scale, questions 3, 4, 16, 19 and 20 are rated “No (2)”, “Yes (0)”, “Partially (1)”, and all other questions are rated “No (0)”, “Yes (2)”, “Partly (1)”. The Perceived Family Support Scale consists of items that can be perceived by people at almost every education level. The score received from the scale varies between 0 and 40. Increased scores show good family support (15-17). In this study, the Cronbach Alpha reliability coefficient was found to be 0.81.

2.3. Data Collection

The researcher applied the Introductory Characteristics Determination Form, Hospital Anxiety and Depression Scale (HADS), Multidimensional Perceived Social Support Scale (MPSSS), and Perceived Family Support Scale (PFSS) with face-to-face interview method to the patients who underwent liver transplantation in the 6th month after the transplantation.

2.4. Ethical Considerations

The study was commenced after receiving the approval from the Ethics board of Atatürk University, Faculty of Health Sciences on 14.11.2014 and decision number 2014/11 and was conducted according to the Helsinki Declaration principles.

2.5. Statistical Analysis

Statistical evaluation of data was done with the IBM Statistical Package for Social Sciences (SPSS) 24 program. Numbers and percentages, Mann Whitney U, ANOVA, Pearson Correlation and Multiple Regression Analysis were used. The significance level was evaluated at p<0.05 level.

3. RESULTS

The mean age of the patients who were included in the study was 43.17±14.42 years, and the mean age of the patients at transplantation was 40.45±13.70. A total of 62.1% of the patients were male, 77.3% were married, 39.4% were primary school graduates, 65.1% lived in villages, 74.2% had children, and 90.9% lived in nuclear families (Table 1). When the distribution of the mean anxiety and depression score was examined according to the identifying characteristics of the patients, it was determined that the mean anxiety and depression score was high (HAD-A=19.71±3.29, HAD-D=15.90±1.99). The gender, anxiety and depression were found to be statistically significant. The mean anxiety score of the males (20.21±1.62) was higher than the mean anxiety score of females (18.88±4.95) which was found to be statistically significant (p<.001) (Table 1).

Statistically significant differences weren't detected between the age, age of transplantation, marital status, educational status, where they lived, whether they had children, family types and anxiety and depression score averages of the patients (p>.05) (Table 1).

The total mean Multidimensional Perceived Social Support Scale (MPSSS) score was found to be at a moderate level as 54.56±17.40. When the subdimensions of the MPSSS scale were examined; 26.21±4.88 was received from the "family" dimension, which is high; 14.43±7.72 was received from the "Friend" dimension, which is moderate; 13.90±9.47 was received from the dimension of "Special One", which is medium level (Table 2).

Table 1. *Distribution of the Mean Anxiety and Depression Scores of the Patients according to Descriptive Characteristics (n=66)*

Descriptive Characteristics	Number Mean±SD	%	HAD-A Mean±SD (19.71±3.29)	Significance	HAD-D Mean±SD (15.90±1.99)	Significance
Age	43.17±14.42					
Transplantation Age	40.45±13.70					
Gender						
Female	25	37.9	18.88±4.95	MW= 3.570	16.44±2.80	MW=-0.955
Male	41	62.1	20.21±1.49	**p<0.001**	15.58±1.20	p>0.340
Marital Status						
Married	51	77.3	20.00±3.50	MW = – 0.540	15.72±1.56	MW=-1.312
Single	15	22.7	18.73±2.25	p>0.124	16.53±3.02	p>0.190
Educational Status						
Illiterate	14	21.2	19.50±6.90		16.91±2.39	
Primary School	26	39.4	20.03±1.58	F=0.811	15.42±1.20	F=1.115
Secondary School	12	18.2	19.50±1.78	p>0.546	16.08±3.36	p>0.362
High School	14	21.2	20.54±1.29		15.54±1.03	
Residence						
Village	43	65.1	19.97±3.73	F=0.401	15.67±1.43	F=0.970
City	17	25.8	19.17±2.60	p>0.753	16.17±1.91	p>0.413
Metropolitan City	6	9.1	19.00±2.68		17.00±4.60	
Having Children						
Yes	49	74.2	19.85±3.59	MW= – 0.300	15.83±1.59	MW= – 0.3738
No	17	25.7	19.31±2.30	p>0.764	16.25±2.93	p>0.710
Family Type						
Nuclear	60	90.9	19.73±3.39	MW= – 0.149	15.98±2.06	MW= – 0.628
Extended	6	9.1	19.60±2.50	p>0.881	15.40±0.54	p>0.530

Table 2. *Distribution of Mean Total PFSS, MPSSS and Subdimension Scores of the Patients (n= 66)*

MPSSS and sub-dimensions	Mean±SD
Family	26.21±4.88
Friend	14.43±7.72
Special	13.90±9.47
MPSSS Total	54.56±17.40
PFSS Total	35.77± 7.16

The total mean score of the patients in Perceived Family Support Scale (PFSS) was 35.77±7.16, which is high (Table 2).

In the study, a statistically significant, positive, weak-level relation was detected between the only HADs-A and PFSS scores; and a statistically significant, negative, meaningful, weak-level relation was detected between the mean HADs-D and PFSS scores. A significant, positive and moderate relation was detected between the only PFSS and MPSS scores (Table3).

Table 3. *The distribution of the relation between the sub-dimensions of the HADS, MPSS and PFSS scales (n=66)*

		HADs-A	HADs-D	PFSS	MPSSS
HADs-A	r	1			
HADs-D	r	0.107	1		
PFSS	r	0.364**	-0.326**	1	
MPSSS	r	0.236	-0.097	0.410**	1

**: p<0.05, **: p<0.001*

r : Correlation coefficient

When the results of the effect of the PFSS and MPSS scores of the patients on anxiety and depression were examined, it was determined that the PFSS variable, which is among the arguments, it was determined the independent variable PFSS variable had a statistically significant effect on HAD-A and HAD-D (Table 4). According to these results, a one-point increase in the PFSS variable increased the HAD-A at a rate of 0.15 points and decreased the HAD-D at a rate of – 0.10 points.

Table 4. *The effect of the mean PFSS and MPSS Scores of the Patients on Mean HADS Scores*

Variables	HAD-A (n=66)					HAD-D (n=66)				
	B	SE.	βeta	t	p	B	SE.	βeta	t	p
PFSS	0.15	3.10	0.32	2.51	0.02	-0.10	1.90	0.35	-2.64	0.01
MPSSS	0.02	2.08	0.10	0.82	0.42	0.01	1.70	0.05	0.34	0.73
Model	R=0.38; Adjusted R^2= 0.14; F= 5.18					R=0.33; Adjusted R^2= 0.11; F= 3.82				

4. DISCUSSION

The liver transplantation process is a complex process, which requires a professional approach before, during and after transplantation (18). The wait for liver transplantation and changing the lifestyles during this period can cause anxiety and depression in patients. Anxiety also increases when transplant patients are discharged from the hospital, which might be because of the loss of the security sense provided by intensive hospital care or due to the efforts to follow the medical regime after the transplantation. The anxiety and depression affect the post-transplantation treatment process in a negative way (19,20). In this study, which examined the family and social support in patients who underwent liver transplantation on anxiety-depression levels, it was determined that patients had high anxiety and depression levels (Table 1). Similarly, it was found that patients had high anxiety and depression levels before and after liver transplantations in a systematic review conducted by Young et al. (21) These findings are support other studies. (8,9,22).

When the mean anxiety and depression score was evaluated according to the introductory characteristics of the patients, it was determined that the mean anxiety score in males was higher than the average of the anxiety score in females, and this difference was statistically significant (p<.001) (Table 1). Unlike this study, 90 patients who underwent liver transplantation were examined by Yıldız and Kılınç (23), and Dąbrowska-Bendera et al. (24) examined 121 patients who underwent liver transplantation and reported that female patients had higher anxiety and depression levels compared to male patients. Annema et al. (25), on the other hand, conducted a study with 153 patients, and Paglione et al. (1) conducted another study with 153 patients, and did not find a significant difference between the anxiety and depression levels in terms gender.

In previous studies, it was reported that social and family support is effective in protecting the individual from the harmful effects of stressful life events and acts as a “buffer” against the negative outcomes of diseases (26-28). Liver transplantation increases the need for social and family support. Liver transplantation requires long-term treatment and care. It is considered that, patients’ being able to carry out their own care in the post-transplantation period depends on the motivation they can receive from their family and social circle. Increased anxiety and depression levels during transplantation cause patients to deal with the disease worse and prolong the recovery time (7,8). In the literature, it is reported that perceived support from family and friends reduces the anxiety and depression level (27-30). It is observed that the individual will decrease the anxiety and depression level with the support of the social environment and family after liver transplantation, which will affect his health, especially during the recovery process (7).

It was determined in this study that social support scores were at moderate levels, and family support scores were at high levels. Lopez et al. examined 70 patients who underwent liver transplantation in 2011 and reported that social and family support was low. However, they also found that the anxiety and depression levels were high. In the study of Okoyo Opiyo et al., it was determined that the perceived social support and optimism about the condition had positive effects on the healing process (29). in family support. Akawaza et al. (30) conducted studies and showed that family support.

In this study, it was determined that the depression level decreased with increasing family and social support. It was also determined that social support will increase with the increase is effective in the ability of transplantation patients to manage their new lives individually.

5.CONCLUSION

In the present study, the mean hospital and depression scale scores were high in all patients who underwent liver transplantation. It was determined that family and social

support is effective in reducing the depression levels after liver transplantation. It was also determined that family support is more effective in reducing this level. Patients need family and social support to minimize the complications, which can be caused by anxiety and depression during the healing process after liver transplantations. This is important when it is considered that the family structure has changed in our present day. For this reason, nurses who are with patients in all processes of liver transplantation, and who plan holistic care must ensure that alternative social support is provided to patients in case familial support is not functional. In this way, a decrease becomes possible in the anxiety and depression levels, which might develop after liver transplantations.

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Analysis of data for the study: KKS
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Clinical and Experimental Health Sciences

Effect of Digitalization on Nursing Practices Using the Lean Approach

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ABSTRACT

Objective: This study aimed to examine the effect of digitalization on nursing practices using the lean approach.

Methods: This is a descriptive observational study. The data were collected using an activity chart to record nurses' direct and indirect care practices and personal work and the Value Stream Map to compare and analyze work processes and determine both waste and value areas in the clinics. The study included a total of 15 nurses from two different internal medicine units of a hospital, including one digital clinic that uses digital applications for nurse work processes, and one partial digital clinic that has limited digital applications. The data were analyzed using current state value stream mapping, lean seven waste areas, and future state value stream mapping.

Results: In the digital clinic, 748.5 minutes were allocated for direct care, 129.1 minutes for indirect care, and 562.1 minutes for personal work. Total value-added time and non-value-added time was calculated as 1137.1 and 302.9 minutes, respectively. In the partial digital clinic, 623.9 minutes were allocated for direct care, 404.4 minutes for indirect care, and 411.1 minutes for personal work. Total value-added time and non-value-added time was calculated as 1006 and 433.4 minutes, respectively. According to the future state value stream map prepared in line with the improvement suggestions to eliminate unnecessary production, process, movement, transportation, waiting, and error waste in the current state of both clinics, it is predicted that 1354.3 minutes of value-added time will be obtained and non-value-added time will decrease to 85.7 minutes, by spending 910.9 minutes less on direct care, 190.2 minutes less on indirect care, and 259.2 minutes less on personal work.

Conclusion: The lean approach creates a repeated opportunity to review and improve processes. Analyzing nursing processes using the lean approach before and after digitalization and reviewing sources of both waste and value will contribute to implementing higher quality nursing care practices more effectively and safely and to using time and staff more efficiently.

Keywords: Digitalization, lean approach, nursing care, nursing practices.

1. INTRODUCTION

In the field of health, digitalization is defined as medical applications provided through different digital technologies to support and improve the delivery and management of health care services (1). Digitalization changes health service delivery routines to a great extent (2). Nurses constitute the largest workforce in health service delivery and have an important role in achieving quality care outcomes (3). Digitalization is used in nursing practices to increase both the quality and efficiency of care and time and cost efficacy in direct and indirect care environments such as electronic health records, bedside technologies, and drug applications (4–7). Since digitalization affects and changes the way nurses work, it is necessary to determine how nurses coordinate their workflows. Here, the critical question is to what extent digitalization contributes to patient care and how to use the time saved (8). Value and waste management are significant in radical change processes such as digitalization. The lean approach is a well-planned methodology for organizing processes and systems in such radical changes (9) and is based on the Toyota Production System. Despite its industrial origins, the philosophy of the lean approach has also encompassed healthcare (10). The lean approach focuses on eliminating waste and generating value. In the healthcare system, this means providing lean healthcare that respects and meets patient needs and preferences (11). In lean healthcare, a value is produced for patients as customers. Patient and nurse journeys are inextricably linked. In the processes analyzed, planned, and managed

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with a lean approach, the aim is to increase the time nurses spend at patients' bedsides, that is, to direct care practices, to improve patient outcomes, increase patient safety, and make patient care higher quality and more efficient (3,9,12).

Studies about the relationship between digitalization and nurse work have used observational approaches in terms of time and movement and examine processes retrospectively or prospectively. Although preferred in health services, the design, execution, and reporting of the results of movement studies are generally inadequate (6). The lean approach can be used to evaluate how effectively and efficiently digital processes are managed, whether they produce value in services, or what kinds of waste they cause (13). There are no studies about the digitalized nursing practices that compare business processes with non-digital processes in terms of time and patient safety using the lean approach and re-examine digital processes in terms of waste and value.

This study was conducted to determine and compare the sources of waste and value in two clinics, one with digital systems and one without digital systems, in nursing practices and to examine the effects of nursing practices on time and patient safety in these clinics using the lean approach.

2. METHOD

2.1. Study Place and Features

The study was conducted in two different internal medicine clinics of a public hospital, which were comparable in terms of patient type and burden. In this hospital, nursing services are delivered in three different shifts: 8, 16, and 24 hours. One of the clinics is a digital clinic that actively uses digital hospital processes in direct and indirect patient care. The digital clinic (DC) has a 42-bed capacity with a 48% occupancy rate and employs 11 nurses. In the DC, a nurse cares for an average of 10.7 patients per shift. The other is a partial digital clinic with limited use of digital applications. The partial digital clinic (PDC) has a 22-bed capacity with a 90% occupancy rate and employs 10 nurses. In the PDC, a nurse cares for an average of 10.5 patients per shift.

2.1.1. Digital Clinical Work Processes

Radiology information management system (RIMS); refers to the use of all radiology processes in a digital environment that can be processed, archived, viewed, and converted into statistical data upon user authorization.

Laboratory information management system (LIMS); refers to the system used to make, conclude, approve, and report orders and convert them into statistical data in laboratory services in digital hospital structures.

Clinical decision support system (CDSS); is used to obtain information from available sources, which are used to analyze and make decisions according to a certain situation of the patient. It streamlines decision-making processes, prevents errors with an early warning system, and supports patient-centered care. CDSS contains both written and audio information about drug interactions or administration and is used during treatment practices in the DC.

Computerized physician order entry (CPOE); refers to the entry of computerized drug orders for patients in inpatient clinics by physicians. CPOE aims to increase patient, employee, and drug safety, quality, and value, and to eliminate illegible handwriting and inaccurate and incomplete order errors. It is used by physicians in the DC.

Closed-loop drug administration (CLMA); refers to a system that starts with introducing drugs into hospital stocks and is completed with their administration to patients, providing patient and drug safety with software and hardware technology. In this system, first, the physician creates an electronic medication order. Then the drugs are packaged under the control of pharmacists, in unit doses, on behalf of the patient and sent to the clinic. When the treatment time comes, the nurse places the drugs in the treatment trolley with a computer and barcode reader and goes to the patient's room. The nurse activates the digital system using her username and password. By scanning the patient's wristband with a barcode reader, the digital patient information card of that patient is opened. The drug is verified by reading the drug barcode at the time of treatment. When the drug is confirmed, the CDSS is activated, creating written, audio, and visual stimuli about the route of drug administration, drug dose, and drug/food interactions. After the drug is administered to the patient, the treatment time is recorded in the system. The CDSS promotes administering the right drug to the right patient, in the right dose, in the right way, and at the right time. Treatment trolleys with barcode readers and computers are used in the DC.

Nurse information system; refers to the digital systems used to record nursing practices. This system is used to record nurses' measurements and follow-up processes, vital sign data, treatments, and nursing care plans in a digital environment. It is used in all nursing processes in the DC.

In the DC, admission of patients to the clinic, anamnesis data taken at hospitalization, and discharge procedures are performed electronically. To make a nursing care plan, nurses use digital systems in data collection, diagnosis, planning, application, and evaluation steps. No paper documents are used in the DC, except for those that must contain wet-ink signatures due to legal obligations, such as consent/approval forms. At the end of their shifts, nurses write a report by signing and certifying a shift log.

2.1.2. Partial Digital Clinical Work Processes

In the PDC, the digital applications are RIMS, LIMS, and an e-order system without physician support. In this clinic, paper-based documentation systems are used in nursing processes. Nurses create a daily nurse observation form for each patient. This form includes the patient's identity information, measurement and follow-up procedures, vital signs, and daily treatment plan. In addition, paper patient files

are used during clinical admission, anamnesis, and discharge. In the treatment process, the physician informs the nurse about the daily treatment plan with a paper prescription. The nurse sends the drug orders to the pharmacy through the e-order system. The drugs come to the clinic in bulk. Nurses collectively prepare the drugs for patients in the treatment room and travel to the patient for drug administration. After they administered the drug, they first record it on the nurse observation form and then in the electronic environment. Nurses use both electronic and paper documents for data collection, diagnosis, planning, application, and evaluation steps of the nursing care planning process. At the end of their shifts, nurses write a report by signing and certifying a shift log.

2.2. Study Population and Sample

The study was conducted using a total of 15 nurses, seven from the DC and eight from the PDC, who agreed to participate in the study.

2.3. Data Collection Tools

Activity chart; was used to record the content of nursing practices and the time spent on these practices. It is composed of three parts: one for direct patient care, one for indirect patient care, and one for the time devoted to personal work.

Value stream map (VSM); refers to the diagrams of both material and information flows until the delivery of an order to the customer. Several terms are used to express process information while drawing a value stream map including cycle time (C/T), processing time (P/T), value-added time (VA), non-value-added time (NVA), and lead time (L/T). Value flow mapping consists of four steps: product family selection, current state VSM for current state analysis, future state VSM for the desired destination in the future, and planning-implementation (14).

3. RESULTS

Value stream mapping, a lean technique, was used in this study. Value stream mapping steps are given below.

Selection of product family: Considering nursing activities, the work shift from 08:00 am to 08:00 am was determined as the product family, since a 24-hour shift system includes all workflow processes and has a high representative power.

Determining the main processes: In this study, the main processes for DC and PDC during a 24-hour shift were determined as direct and indirect care practices and personal work. Due to the long duration of direct care practices in nursing care, their duration is desired to be low. However, the characteristics and care needs of patients in nursing services are different from each other. Therefore, the same operations may be completed at different times in care processes or all care practices may not be performed in the same shift.

Making observations: Direct and indirect care practices and personal work of each nurse, and their repetitions were recorded using an activity chart and a stopwatch with a reversible counter. When the observation started, the stopwatch was started, and when the process was finished, it was stopped and reset. The observations took 360 hours in total, 168 hours for the DC and 192 hours for the PDC. Observations were made between September and December 2018.

Determining the processes to be included in value stream maps: Similar nursing practices in the main processes are grouped and explained as follows.

Direct care practices

***Communication with the patient*;** The processes of communication with patients in both the DC and PDC include nursing care practices such as patient education and psychological support, and were observed 135 times in the DC and 121 times in the PDC.

Follow-ups and measurements; Follow-up and measurement processes in both the DC and PDC consist of monitoring such as blood glucose measurement, weight monitoring, or patient follow-up, and were observed 108 times in the DC and 111 times in the PDC.

Vital signs follow-up; Vital signs of patients in the DC are recorded in an electronic environment via tablet computers immediately after they are measured. However, the vital signs of patients in the PDC are measured and recorded on a nurse observation form at the desk. Vital sign follow-up procedures were observed 166 times in the DC and 177 times in the PDC. Figure 1 shows images of the vital signs follow-up process.

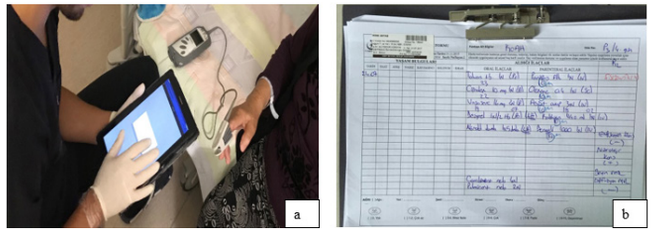

Figure 1. *Digital and partial digital clinical vital signs tracking records. a; digital clinical tablet, b; partial digital clinical nurse observation form.*

Interventional procedures; The interventional procedures in both the DC and PDC include vascular access and blood sampling, and were observed 76 times in the DC and 74 times in the PDC.

Treatment practices; Both CDSS and COPE-supported CLMA are used for treatment practices in the DC. In the PDC, the drugs prepared in the treatment room are administered collectively. Figure 2 shows treatment practices. Treatment practices were observed 16 times in the DC and 175 times in the PDC.

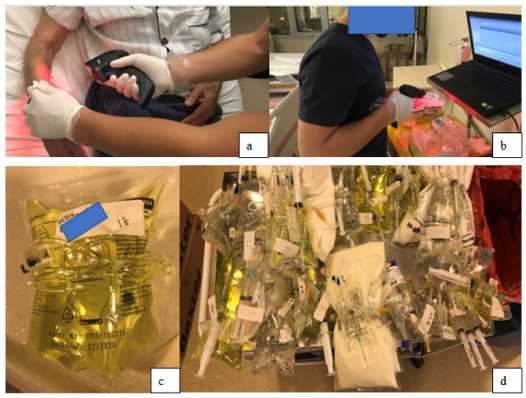

Figure 2. *Treatment practices*
a; verification of patient identity in the digital clinic, b; verification of unit dose of the drug by barcode reader in the digital clinic, c; patient's drugs in the partial digital clinic, d; collective treatment application in the partial digital clinic

Other direct care practices; Other direct care practices include processes such as feeding patients and changing dressings, and were observed 77 times in the DC and 104 times in the PDC.

Indirect care practices

Bedside visit; In the DC, bedside visits are made via a tablet computer. Nurses see all patient data, such as vital signs, follow-up and measurements, and treatment plan in the nurse information system. In the PDC, bedside visits are made through nurse observation forms and patient files. During the visit, nurses take all the files with them. Bedside visits were observed 76 times in the DC and 79 times in the PDC. Figure 3 shows the images of bedside visits.

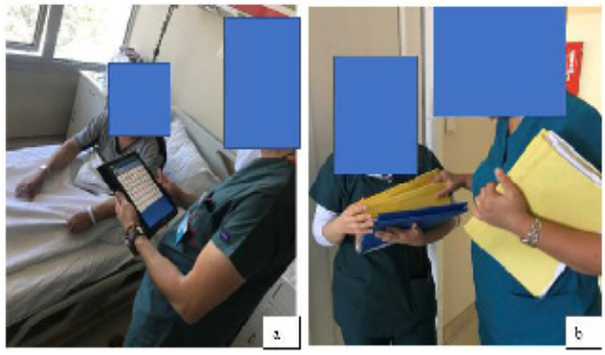

Figure 3. *Bedside visit*
a; digital clinical bedside visit, b; partial digital clinical bedside visit

Treatment preparation; In the DC, treatments are prepared and applied at patients' bedsides by CLMA systems. In the PDC, treatments are prepared collectively in the treatment room. Treatment preparations were observed 72 times in the PDC.

Communication with other persons; Communication with other persons in both the DC and PDC includes training for relatives, phone calls, and communication with other employees, and was observed 43 times in the DC and 56 times in the PDC.

Desk work; Desk work in both the DC and PDC includes nursing care planning processes, nutrition plan preparation, and consultation procedures. Several data such as blood glucose measurement, vital sign follow-up, anamnesis information, and laboratory results are used while planning nursing care for patients. All these data are accessible electronically in the DC, while nurses benefit from both digital systems and paper documents in the PDC. Desk work was observed 59 times in the DC and 73 times in the PDC.

Other work in the clinic; Other work in both the DC and PDC covers processes such as the supply of materials and devices and delivery of desk duties and was observed 36 times in the DC and 40 times in the PDC.

Paperwork; In the DC, no paperwork is used except for patient consent/approval forms, which must contain wet signatures, and a shift log. Paperwork was observed 21 times in the DC. In the PDC, a nurse observation form is prepared daily for each patient and patient files are used to record patient information. Paperwork was observed 120 times in the PDC.

Double entry; In the PDC, nurses make a nursing care plan and prepare the patient's medications both in the digital system and on the nurse observation form, making double entries. Double entries were observed 45 times in the – PDC.

Order transactions; In the PDC, nurses order medication via an e-order system. Order processes were observed 69 times in the PDC.

Personal work

Basic needs; Basic needs in both the DC and PDC covers nurses' needs such as dressing, eating, restroom, personal phone calls, and rest during 24-hour shifts. In the hospital where the study was conducted, nurses use two 20-minute meal breaks in 24-hour shifts and rest after midnight according to the suitability of their clinics. Basic needs were observed 36 times in the DC and 44 times in the PDC.

Non-productive time; Non-productive time in both the DC and PDC refers to the time when nurses wait without producing work and was observed 37 times in the DC and 24 times in the PDC.

Determining the symbols of the current state flow map: Several symbols were created to show nursing practices in the main processes on the map and are shown in Table 1.

Table 1. *Value stream map symbols*

Nurse	Communication with patient	Follow-ups and measurements	Vital sign follow-up
Interventional procedures	Treatment practices	Other direct care practices	Bedside visit
Treatment preparation	Communication with other people	Desk work	Other work in the clinic
Double entry	Paperwork	Order transactions	Basic needs
Non-productive time	Direct care	Indirect care	Personal work
Digital workflow	Workflow	Nurse flow	Time axis

Determining task times: A total of 1440 minutes was taken as a basis for determining usable times in the calculation of task time. The rates used in nurse work studies were used while calculating the daily demand. Accordingly, a nurse should allocate at least 60% of her shift time to direct care practices, 22% to indirect care practices, and 18% to personal work (15). For both clinics, task times were calculated as 864 minutes for direct care practices, 316.8 minutes for indirect care practices, and 259.2 minutes for personal work.

Determining system measurements: C/T was calculated by dividing the total time spent in nursing practices, to which the main processes are allocated, by the total number of observations. P/T was calculated by dividing the total time spent on nursing practices, to which the main processes are allocated, by the number of nurses. L/T was taken as 1440 minutes according to a 24-hour shift schedule. In addition, VA and NVA, which were determined by comparing task times in the DC and PDC processes, were used.

Drawing the current state VSM for digital and partial digital clinics:

The data obtained from observations were used to create current state VSMs to show nurses' workflows.

Figure 4 shows the current state VSM for the DC. Accordingly, in the DC, a total of 748.5 minutes were allocated to direct patient care, 129.1 minutes to indirect patient care, and 562.1 minutes to personal work. During the process, the total VA was calculated as 1137.1 minutes and the total NVA was 302.9 minutes.

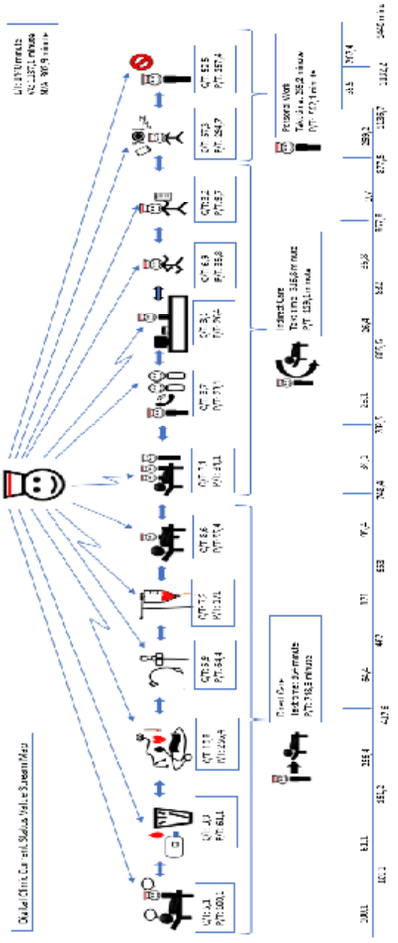

Figure 4. *Digital clinic current status value stream map*
C/T: cycle time, P/T: processing time, L/T: lead time. VA: value-added time, NVA: non-value-added time

Figure 5 shows the current state VSM for the PDC. Accordingly, in the PDC, a total of 623.9 minutes were allocated to direct patient care, 404.4 minutes to indirect patient care, and 411.1 minutes to personal work. During the process, the total VA was calculated as 1006 minutes and the total NVA was 433.4 minutes.

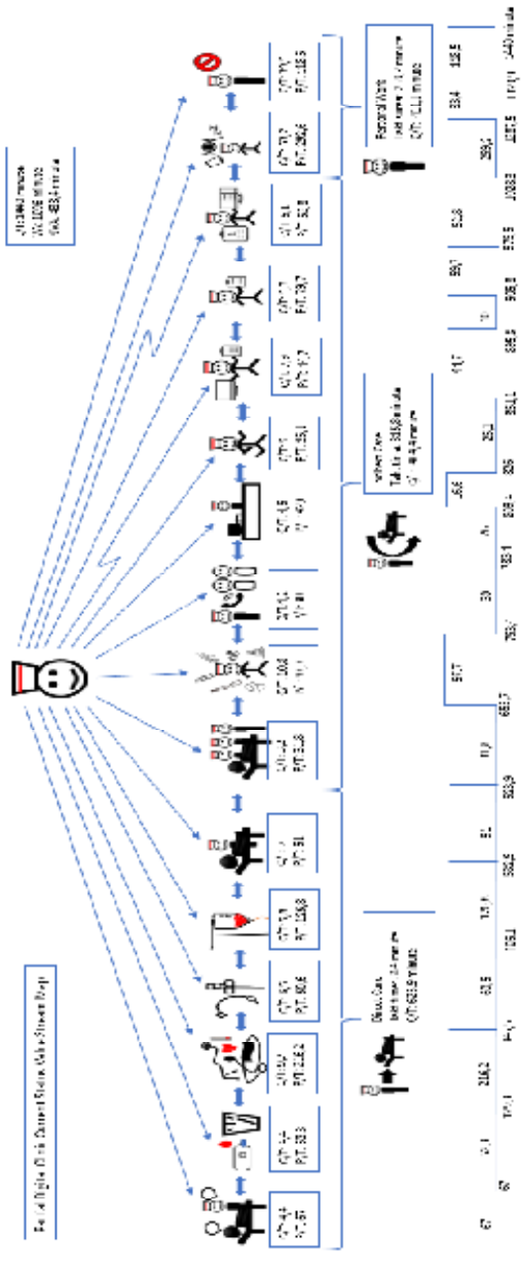

Figure 5. *Partial digital clinic current status value stream map C/T: cycle time, P/T: processing time, L/T: lead time. VA: value-added time, NVA: non-value-added time*

Determining waste areas and suggestions for improvement: As a result of the comparison of current states in both the DC and PDC, the transactions considered waste were determined according to seven waste types in the lean approach. Several suggestions are presented to eliminate the waste areas.

Direct care practices waste areas and improvement suggestions

Vital sign follow-up; According to their current state VSMs, a total of 256.4 minutes were allocated to vital sign follow-ups in the DC and 216.2 minutes in the PDC. In the DC, vital signs were measured and immediately recorded via tablet computers at patients' bedsides and then included in the direct care practice. In the PDC, vital signs were recorded on paper documents at the desk, increasing the time to perform indirect care practices. If tablet computers are used in the PDC, vital sign follow-ups can be recorded at patients' bedsides, increasing the time to implement direct care practices and eliminating paperwork.

Treatment practice; A total of 171 minutes were allocated to treatment practices in the DC and 126.8 minutes in the PDC. In the DC, treatments are administered by the CDSS-supported CLMA system, which keeps medication, drug dose, time, patient information, and route of administration closely regulated. In the PDC, treatments were applied collectively, causing unnecessary movement and transportation waste and leading to inadequate warning systems and error waste in drug safety. If treatment practices in the PDC are performed by the CDSS-supported CLMA system, the time spent by nurses on direct care practices will increase, preventing movement and transportation waste by administering drugs on a patient basis and ensuring drug safety.

Indirect care practices waste areas and improvement suggestions

Bedside visits; In the DC, bedside visits were made via tablet computers. In the PDC, nurses made bedside visits by taking all the patient's documents with them, causing unnecessary movement and transportation waste. If a tablet computer is used for bedside visits in the PDC, the transportation and movement of patient files can be prevented.

Treatment preparation; In the DC, drugs were prepared using the CDSS-supported CLMA system. In the PDC, nurses spent 97.7 minutes in the treatment room for drug preparation, causing unnecessary production and processing waste, inadequate warning systems, and error waste in drug safety. If treatment is prepared by the CDSS-supported CLMA systems in the PDC, a total of 97.7 minutes will be saved from indirect care practices, eliminating unnecessary production, process, and error waste.

Desk work; In the DC, only digital systems were used in nursing care planning and consultation processes. In the PDC, as these processes use both digital systems and paper-based documents, a total of 16.6 minutes was wasted, resulting in unnecessary processing waste. If paper-based documents are removed in the PDC, nurses will obtain all the data from digital systems, preventing the unnecessary waste of 16.6 minutes of processing.

Double recorded applications; In the PDC, nurses recorded nurse care plans and treatment practices using both paper documents and the digital system therefore spending 44.7 minutes on double entry processes, causing unnecessary production and process waste. If paper-based documents are removed in the PDC, the unnecessary production and process waste of 44.7 minutes will be prevented in the process.

Paperwork; In the PDC, a total of 69.7 minutes was allocated to prepare paper-based documents by nurses, causing unnecessary production and process waste. In addition, since all paper documents were handwritten, document standardization was considered an error waste. If paper-based documents are removed from nursing processes in the PDC, unnecessary production and process waste of 69.7 minutes spent on their preparation will be prevented, and the error waste can be prevented by ensuring document standardization.

Order transactions; In the PDC, nurses spent 52.8 minutes ordering written patient prescriptions by the e-order system, causing unnecessary production and process waste. By a transition to the CLMA system, the unnecessary production and process waste of 52.8 minutes will be prevented in the PDC.

Personal work waste areas and improvement suggestions

In both the DC and PDC, the time allocated to nurses' basic needs was excessive, whereby non-productive time leads to the wastage of waiting. Nurses in the DC spent 35.5 minutes more time than the estimated task time on basic needs, and their non-productive time was 267.4 minutes. In the PDC, nurses spent 33.4 minutes more time on basic needs and their non-productive time was 118.5 minutes. Considering the work processes of both clinics, it is suggested to move the PDC to the DC due to the high time allocated to personal work in the PDC and the low bed occupancy rate (48%) in the DC. Thus, the bed occupancy rate will increase, the time allocated by nurses to non-productive work will decrease, and the partial digital processes will be replaced by digital processes, eliminating 10 nursing positions in the PDC.

Future state mapping: A common future state VSM was drawn for both clinics. The future state VSM, shown in Figure 6, was drawn in line with the improvement suggestions to eliminate the waste types and resources determined according to both the DC and PDC current state VSMs. For the future state VSM, C/T was calculated by dividing the total observation times obtained from both clinics by the number of observations. P/T was calculated by dividing the total observation times by the total number of nurses in the DC (11 nurses: current number of nurses in the DC, as those in the PDC are recommended to be employed in the DC). According to the future state VSM drawn in line with the recommendations, it is predicted that 1354.3 minutes of VA will be obtained and NVA will decrease to 85.7 minutes, by spending 910.9 minutes less on direct care, 190.2 minutes less on indirect care, and 259.2 minutes less on personal work. Thus, unnecessary production, waiting, idle operations, movement, transportation, and error waste will be converted into value, eliminating 10 nursing positions in the PDC.

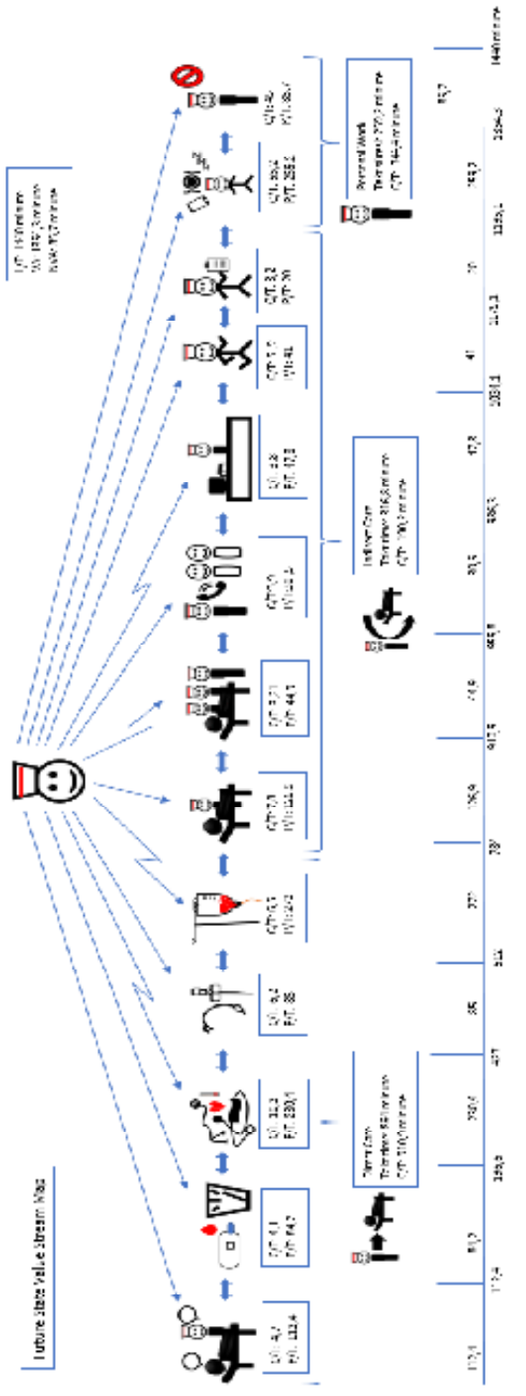

Figure 6. *Future state value stream map*
C/T: cycle time, P/T: processing time, L/T: lead time. VA: value-added time, NVA: non-value-added time

Evaluation: The process analysis for the future state was performed for both clinics, considering waste in its current state and presenting solution proposals to eliminate them. Table 2 shows the data of the processes. Thanks to our improvement suggestions, it is predicted that a non-digital clinic of the relevant institution will digitize its processes, allowing the clinics to serve at full capacity, increasing time added values in the processes, decreasing process waste, and thus saving a total of 10 nurses.

Table 2. *Analysis of digital and partial digital clinical processes*

	Direct care*	Indirect care*	Personal work*	VA	NVA
Digital clinic current state	748.4	129.1	562.1	1137.1	302.9
Partial digital clinical current state	623.9	372.6	411.1	1006	433.4
Future state	910.9	190.2	338.6	1354.3	85.7

**Time spent (MiWnute), VA: value-added time, NVA: non-value-added time*

4. DISCUSSION

This is the first study that analyzes digitalized nursing practices with lean methods, compares them with non-digital processes, determines the sources of waste and value, and establishes the desired future outcome by presenting relevant suggestions.

Our study has found that according to VSMs, more time is spent in direct care practices in DCs compared to PDCs, and this time added value to the processes in both clinics. Considering the current state of VSMs, these time differences in direct care practice work processes are caused by processes of communication with patients, vital sign follow-ups, and drug administration times. Tablet computers and CDSS-supported CLMA systems are used in vital sign follow-ups and drug applications in the DC. Using digital technologies such as CLMA significantly increased the time spent by nurses at the bedside, the communication and interaction between nurses and patients, and the time nurses spent preparing and administering ordered medications. In addition, a transition from paper-based patient records to digital applications can allow nurses to provide patient-centered, quality, and safe nursing care by securing records (6,16,17). In the future state, the use of digital systems in PDCs will increase the time allocated for direct patient care and prevent movement, transportation, and error waste.

Nursing work processes are often overloaded with NVA jobs that directly impede nursing care. Nurses work in waste-filled systems that keep them away from patients (18). This study determined that 129.1 minutes were spent on indirect care practices in the DC and 404.4 minutes in the PDC, according to their current state VSMs. All transactions add value to the process in the DC, while 281.5 minutes were spent on wasted areas in the PDC, due to drug preparation in the treatment room, preparation/use of paper-based documents, double entry of some transactions, nurses' data collection from both digital and paper systems, and additional entry of e-orders for drugs prescribed by physicians. Davies et al. (3) analyzed nurse processes by the lean approach and reported that nurses spent more time at the desk rather than bedside visits, made repetitive data entries, spent excessive time on drug preparation and orders, and therefore, allocated less time for direct patient care. Studies of digitalization processes show that digital systems save nurses' time, facilitate care processes, reduce the time allocated to desk work, prevent double entries by eliminating the use of both paper and digital systems, and reduce the time nurses spend preparing paper documents, medication prescriptions, and drug orders (19–22). In addition, digitalized applications improve nursing practices by allowing them to use a computerized doctor order entry system, have warning screens for confirming patient identity and drug names/appearance, and prevent handwriting errors, thus increasing the quality of recording systems and preventing errors (7,23–27).

Proces digitization allows for better management of resources (20). Our study predicts that a replacement of paper-based documentation systems with COPE and CDSS-supported CLMA systems in the PDC will prevent unnecessary production, movement, transportation, and error waste in the process. Bedside visits are made via tablet computers in the DC and with patient files in the PDC. Making bedside visits with paper-based documents causes unnecessary wastage of transport, movement, and error in the PDC. Bedside visits require using an effective communication process and sharing up-to-date and reliable patient information. The Joint Commission (28) introduced the bedside visit process as a patient safety target and reported that standard deficiencies in nurses' delivery and pick-up processes lead to errors. Ayaad et al. (29) reported that standardized practices in bedside visit processes, which they managed by lean principles, improved the efficiency of the delivery process and decreased error rates. Therefore, the use of tablet computers during bedside visits in the PDC will allow nurses not to use paper patient files during the delivery processes, to access all up-to-date patient data effectively, and eliminate waste areas by ensuring standardization in the processes.

Nursing services require a structured and professional organization adjusted to current medical needs and resources; therefore, there is a need for appropriate protection of resources (30). In this study, according to the current situation VSMs, the time allocated to personal work and the amount of non-productive work was high in both clinics. A transition from paper-based to digital systems is expected to eventually reduce documentation, allowing nurses to allocate more time for direct patient care (22). In the present study, digitalized systems were observed to reduce the time spent on indirect care practices, but contrary to our expectations, the time obtained through digitalized systems was not transferred to direct care practices, causing non-productive, that is, wasted waiting time. The lean approach is applied to work processes by reassigning data collection and monitoring personnel or space and redesigning the process (31). The DC and PDC had comparable patient types and burdens, but the bed occupancy rate was 48% in the DC. Therefore, it has been proposed to combine the PDC with the DC, aiming to use digital applications in PDC work processes and ensuring the use of patient beds at full capacity in the DC. Thus, 10 nurses in the PDC can be used in different areas, preventing waste of waiting time, increasing the time allocated to direct care practices, and reducing the time spent on indirect care practices and personal work. The application of lean principles enables nurses to organize their care processes by considering patients and allows hospital

managers to use personnel effectively, creating added value and high-quality patient care (9).

5. CONCLUSION

In this study, it is predicted that an analysis of clinical processes by lean techniques, determining both waste and value areas and relevant suggestions for proper workflows will increase the time allocated to direct care practices and reduce the time allocated for indirect care practices and personal work. Thus, both time and personnel are used more effectively, and patient safety is increased by reducing human-induced errors.

Analyzing nurses' digitalized workflows using lean methods provides a more accurate view of the process, creating a framework for change management.

The lean approach creates an opportunity to review and improve the processes repeatedly. Therefore, analyzing nursing processes using the lean approach before and after digitalization and reviewing sources of both waste and value will contribute to implementing nursing care practices in a more effective, higher quality, and safer manner and use time and staff more efficiently.

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Clinical and Experimental Health Sciences

The Effect of Mental Health on Health-Related Quality of Life in Adolescents

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ABSTRACT

Objective: The aim of this study was to determine the effect of mental health on health-related quality of life in adolescents.

Methods: This cross-sectional study was conducted among 1188 students studying in a public high school in Istanbul, Turkey. Data were collected using the General Health Questionnaire (GHQ-12) and the Turkish Generic Health-Related Quality of Life Questionnaire for adolescents (Kiddo-KINDL). Descriptive statistics, correlation analysis and multiple regression analysis were used in the analysis.

Results: The mean age of the adolescents was 16.61±1.17; 56.6% were female. This study shows that mental health was a negatively significantly related to all subscales of health-related quality of life (physical wellbeing, emotional wellbeing, self-esteem, family, friends, school) of adolescents ($p<0.05$). It was discovered that the adolescents' mental health, relationships with friends, participation in regular physical activity, school success, family relationships, class, economic situation, their ability to talk to people close to them about their personal problems and the presence of chronic illness were significant predictors of their overall quality of life ($R^2=0.402, p<0.001$).

Conclusion: Overall quality of life increases among adolescents who do not have a mental health problem, those who have good relationships with friends, engage in regular physical activity, achieve well at school, have good family relations, are in the upper classes, have a good economic situation, those who talk to people close to them about personal problems and those who have no chronic illness. School nurses can organize health education programs and counseling services to improve the mental health of adolescents.

Keywords: Adolescent, health-related quality of life, mental health, nurse

1. INTRODUCTION

Adolescence is the transition period from childhood into adulthood which is characterized by rapid physical growth, sexual development, and psychosocial maturation (1-3). WHO (2021) identifies adolescents as between the ages 10-19. This period is often known as a conflicted, tense, difficult period (4). The desire for independence and autonomy is the most prominent feature of this period (5). It is reported that, most common mental disorders have an onset in childhood or adolescence and with the peak incidence for common disorders occurring during adolescence (6). Today, almost one in seven young people meet diagnostic criteria for a mental illness (7). WHO (2020) reported that, mental health problems account for 16% of the global burden of disease and injury in adolescents.

Mental health problems can significantly affect the development of adolescents having an enduring impact on their health and social functioning in adulthood (9). In this period, mental health problems negatively affect adolescents' educational life, social functions and quality of life (10). It is also reported that the physical, psychological and social health of individuals is an important indicator of their quality of life (11). In many studies, it has been shown that depressive adolescents and adolescents with anxiety have lower levels of quality of life (12-15).

Quality of life is a widely comprehensive concept that covers the complexities of an individual's physical health, psychological state, social relations and characteristics related to environment (16). Health-related quality of life (HRQOL) pertains to the perception of an individual's wellbeing in the context of physical, psychological, emotional and social functionality levels (16). The importance of HRQoL assessment in adolescents stems from its ability to identify individuals at risk and detect health inequalities (17).

Studies on quality of life reveal that the health-related quality of life of adolescents is not a subject that has been widely explored and in fact, it can be seen that the quality of life of adolescents is frequently neglected. In this period, adolescents seek independence so that they can make their own lifestyle decisions. These decisions may have a long-term effect on the adolescent's health and wellbeing (13).

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The numerous factors related to on HRQoL of adolescents have been addressed previously; namely gender, age, economic status, family prosperity, physical activity and sleep (13,15,18-25).

While reviewing the literature, it was discovered that, a few prior studies have evaluated the relationship between mental health and HRQoL on healthy adolescents (13). The mental health and health-related quality of life of adolescents unfortunately is a matter that is frequently ignored. In this context, it is important to identify the relationship between mental health and health-related quality of life of adolescents if improvements are to be made in their health and wellbeing. The aim of this study in this context was to determine the effect of mental health on health-related quality of life in adolescents. The study sought answers to the following research questions:

- What is the level of mental health of adolescents?
- What is the level of quality of life of adolescents?
- Is there a relationship between mental health and health-related quality of life of adolescents?
- What are the factors associated with health-related quality of life among adolescents?

2. METHOD

2.1. Study Design and Participants

This cross-sectional study was carried out April 2014 with students attending a public high school in Istanbul, Türkiye. The school is located in a region of middle socioeconomic level in Istanbul. The choice of the school was influenced by the fact that the school was a public school and was located in a close area in terms of access to researchers. The universe of the study consisted of the students (*N*=1380) enrolled in a public high school in Istanbul over the 2013-2014 academic year. No sample selection was made since our target was to reach the entire universe of the study. In the school where this research was conducted, all of the students receive similar education and the health education is not given.

The study included students who were present on the study day and whose parents authorized participation. The criteria of exclusion were: absence on the study day, having a vision, hearing and cognitive problem, and incomplete questionnaire data. The study sample comprised 1188 students in the 9th, 10^{th,} 11th and 12th grades. Consent/assent was obtained for 1188 students (86%) who were subsequently enrolled in the study. Of the 1380 eligible adolescents, 96 (7%) did not provide written permission from their parents, 55 (4%) were absent from school on the day of the study, and 41 (3%) did not wish to participate.

2.2. Variables of the Study

Dependent variables; adolescents' mental health and health-related quality of life.

Independent variables; adolescent's gender, age, class, economic status, mother/father's education, type of family, number of siblings, work status, school success, participation in social activity, participation in regular physical activity, having a health problem in the last year, family relations, and relationships with friends and talking to people who are close about personal problems.

2.3. Measures

A socio demographic information form, the General Health Questionnaire (GHQ-12) and the Turkish Generic Health-Related Quality of Life Questionnaire for adolescents (Kiddo-KINDL) were used in the data collection.

Sociodemographic Information Form

The sociodemographic data were collected with information form. The information form contained 16 questions on the adolescent's gender, age, class, economic status, mother/father's education, type of family, number of siblings, work status, school success, participation in social activity, participation in regular physical activity, having a health problem in the last year, family relations, and relationships with friends and talking to people who are close about personal problems.

The General Health Questionnaire 12 (GHQ-12)

The GHQ was developed by David Goldberg (1970) to identify acute mental illnesses that are frequently encountered in the community. The validity and reliability studies for the questionnaire in Turkey were conducted by Kılıç et al. (1997); the form is currently used in the community to identify psychiatric cases (Cronbach's alpha: 0.78). While the questionnaire is reported to be reliable in identifying symptoms of non-psychotic depression and anxiety. Each question inquiries into the symptoms experienced in the last few weeks and have four choices of response ("never, as many as usual, more frequent that usual, very often"). Individuals receiving scores over "2" are identified as having mental problems (anxiety or depression) (26). In this study, Cronbach's alpha coefficient for the GHQ-12 was 0.83.

The Turkish Generic Health-Related Quality of Life Questionnaire for Adolescents (Kiddo-KINDL)

The Kiddo-Kindl Questionnaire was developed by Ravens-Sieberer and Bullinger (1998). The Turkish version of the scale was created by Eser et al. (2004) (27). This measure consists of 24 items on a 5-point Likert scale (from 1= "never" to 5= "always") which includes six subscales: physical wellbeing, emotional wellbeing, self-esteem, family, friends and school. The raw scores are transformed into a 0-100 scale, with higher scores indicating better HRQoL. The Kiddo-KINDL scale Cronbach alpha values were 0.83 for total quality of life, 0.70 for physical wellbeing, 0.73 for emotional wellbeing, 0.70 for self-esteem, 0.71 for family, 0.58 for friends, and 0.55 for school (27). Cronbach's alpha values for the subscales in this study vary between 0.31 – 0.79 (physical wellbeing; 0.75,

emotional wellbeing; 0.69, self-esteem; 0.79, family; 0.77, friends; 0.31, school; 0.32, total quality of life; 0.79).

2.4. Ethical Considerations

The University's Ethics Committee granted its approval for the study (approval date 09.09.2013 and number 48). Prior to the start of the research, approval for the study was first obtained from Istanbul Provincial Directorate of National Education. The researchers visited each classroom and distributed the informed parent consent and child assent forms for the students to take home to their parents. Parents signed the informed consent form at home, and then returned them to school via the students. The students completed their questionnaire after the parents gave their informed consent. The students were informed by the investigators about the nature of the study and were instructed that participation was voluntary and information was confidential and anonymous. Students completed the question forms and scales in their classrooms during school hours.

2.5. Limitations of the Research

The results of the study were limited to its own sample and therefore cannot be generalized. The data of the study were collected on the basis of self-reporting. No observations or objective evaluations were made in the study.

2.6. Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 25.0). Descriptive statistics (numbers, percentages, means, and standard deviation) were used in the analysis. Relationships between the socio-demographic characteristics, the GHQ-12 score and the Kiddo-KINDL scores were assessed with the Pearson correlation analysis. Stepwise multiple regression analysis was performed to determine factors related to health-related quality of life. The results were found to be in the 95% confidence interval and significance was assessed as $p< 0.05$.

3. RESULTS

The mean age of the students was 16.61±1.17; 56.6% were female. More details on the demographic characteristics of the adolescents are shown in Table 1. The mean scores for the subscales of the Kiddo-KINDL were found to be 54.49±22.20 for physical wellbeing, 59.98±21.24 for emotional wellbeing, 52.77±25.13 for self-esteem, 52.86±24.63 for family and 64.87±17.22 for friends, 55.46±19.23 for school, and 56.74±14.57 for the total Kiddo-KINDL. The GHQ-12 means score was found to be 2.90±3.00 (Table 2). The correlation values between sociodemographic characteristics, GHQ-12 and subscales of Kiddo-KINDL of adolescents are shown in Table 3.

Table 1. *Socio-demographic characteristics of adolescents*

Socio demographic characteristics	Min-Max	Mean±SD
Age	14-19	16.61± 1.17
Number of siblings	1-4	2.84±0.94
	n	%
Gender		
Female	672	56.6
Male	516	43.4
Grade		
9	200	16.8
10	162	13.6
11	416	35.0
12	410	34.5
Parents		
Two parents	1087	91.5
Single parent	84	7.1
No parent	17	1.4
Mother education		
Not literate	157	13.2
Literate	54	4.5
Elementary school	603	50.8
Middle School	214	18.0
High school	135	11.4
College / University	25	2.1
Father education		
Not literate	33	2.8
Literate	27	2.3
Elementary school	556	46.8
Middle School	293	24.7
High school	234	19.7
College / University	45	3.8
Monthly income		
Lowest	95	8
Middle	683	57.5
Good	376	31.6
Very good	34	2.9
Family relations		
Very good	522	43.9
Good	354	29.8
Middle	250	21
Bad	40	3.4
Very bad	22	1.9
Friend relations		
Very good	638	53.7
Good	398	33.5
Middle	128	10.8
Bad	11	0.9
Very bad	13	1.1
Talking to someone close to them about their personal problems		
Never	132	11.1
Sometimes	597	50.3
Often	235	19.8
Routinely	224	18.9

School success		
Above the class average	217	18.3
Class average	907	76.3
Below class average	64	5.4
Working status		
Yes	113	9.5
No	1075	90.5
Extracurricular social activity		
Yes	324	27.3
No	864	72.7
Sleeping problem		
Yes	597	50.3
No	591	49.7
Chronic disease		
Yes	98	8.2
No	1090	91.8
Having a health problem in the last year		
Yes	968	81.5
No	220	18.5
Regular physical activity three days a week		
Yes	619	52.1
No	569	47.9
Total	**1188**	**100**

Table 2. *The mean scores for the sub-scales and total of the Kiddo-KINDL and the GHQ-12 of adolescents*

Sub-scales of the Kiddo-KINDL	Min	Max	Mean	SD
Physical well-being	0	100	54.49	22.20
Emotional well-being	0	100	59.98	21.24
Self esteem	0	100	52.77	25.13
Family	0	100	52.86	24.63
Friends	0	100	64.87	17.22
School	0	100	55.46	19.23
Kiddo-KINDL Total	8	96	56.74	14.57
The GHQ-12 mean score	0	12	2.90	3.00

A stepwise multiple regression analysis was performed to determine the factors related to health-related quality of life of the adolescents. In the univariate analysis, the variables that had a significant relationship with health-related quality of life of adolescents were considered as independent variables. A significant relationship was seen between the physical wellbeing of the adolescents and their GHQ-12 scores (β=–0.293, $p< 0.001$), gender (β=–0.176, $p<0.001$), family relations (β=0.098, $p<0.001$), having a health problem in the last year (β=0.088, $p<0.001$), and presence of chronic illness (β=0.080 $p<0.01$), sleeping problems (β=0.061, $p< 0.05$), friend relationships (β=0.060, $p<0.05$), respectively. These variables explained 23% of total variance (R^2=0.23, $p<0.001$) (Table 4). The physical wellbeing of adolescent's increases when there is no mental health problem, the adolescent is male, family relationships are good, no health problem was experienced in the last year, there are no chronic diseases, no sleeping problems and relationships with friends are good.

A significant relationship was seen between the emotional wellbeing of the adolescents and the adolescents' GHQ-12 scores (β=-0.472, $p<0.001$), family relations (β=0.124, $p<0.001$), relationships with friends (β=0.121, p<0.001), participation in regular physical activity (β=0.068, $p<0.01$) and mother's education (β=0.061, $p<0.01$), respectively. These variables explained 35% of total variance (R^2=0.35, $p<0.001$) (Table 4). The emotional wellbeing of adolescents increases if there are no mental health problems, relationships with friends and family are good, the adolescent engages in regular physical activity and the more education the mother has.

Table 3. *Correlations between socio-demographic characteristics, GHQ-12 and Kiddo-KINDL of adolescents*

Variables	1	2	3	4	5	6	7	8	9	10	11	12
Monthly income (1)												
School success (2)	0.011											
Family relations (3)	0.187**	0.114**										
Friend relations (4)	0.139**	0.034	0.356**									
Talking to someone close to them about their personal problems (5)	0.108**	-0.017	0.138**	0.212**								
GHQ-12 (6)	0.124**	0.097**	0.376**	0.214**	0.097**							
Physical well-being (7)	0.078**	0.065*	0.256**	0.160*	0.022	-0.414**						
Emotional well-being (8)	0.149**	0.067*	0.349**	0.270**	0.128**	-0.559**	0.459**					
Self esteem (9)	0.102**	0.168**	0.216**	0.173**	0.107**	-0.334**	0.228**	0.365**				
Family (10)	0.104**	0.160**	0.199**	0.175**	0.099**	-0.316**	0.214**	0.343**	0.967**			
Friends (11)	0.155	0.075*	0.177**	0.342**	0.177**	-0.237**	0.163**	0.325	0.296**	0.300**		
School (12)	0.075**	0.221**	0.281**	0.169**	0.074*	-0.358**	0.255**	0.320**	0.232**	0.227**	0.212**	
KINDL – Total Quality of life (13)	0.161**	0.190**	0.365**	0.310**	0.146**	-0.551**	0.579**	0.695**	0.815**	0.806**	0.534**	0.535**

*Note: **p <0.01, * p <0.050.*

A significant relationship was seen between the self-esteem of the adolescents and the adolescents' GHQ-12 scores (*β*= – 0.280, *p<0.001*), class (*β*= 0.146, *p< 0.001*), participation in regular physical activity (*β*=0.145, *p<0.001*), school success (*β*=0.112, *p<0.001*), relationships with friends (*β*=0.093, *p<0.001*), and talking to people who are close about personal problems (*β*= 0.069, *p<0.05*), respectively. These variables explained 19% of total variance (R^2=0.190, *p<0.001*) (Table 4). The adolescents' level of self-esteem increased when there were no mental health problems, they were in the higher classes, and they engaged in regular physical activity, had success at school had good relations with friends and when they talked to people close to them about their personal problems.

A significant relationship was seen between the adolescents' family dimension of quality of life and their' GHQ-12 scores (*β*=–0.262, *p<0.001*), participation in regular physical activity (*β*=0.121, *p<0.001*), class (*β*=0.125, *p<0.001*), relationships with friends (*β*=0.093, *p<0.001*) school success (*β*=0.107, *p<0.001*), working at a job (*β*=–0.077, *p<0.01*), talking to people who are close about personal problems (*β*=0.065, *p<0.05*) and economic situation (*β*=0.062, *p<0.05*), respectively. These variables explained 17% of total variance (R^2=0.171, *p<0.001*) (Table 4). The adolescents' level of family dimension of quality of life increased when there were no mental health problems, they engaged in regular physical activity, they were in the higher classes, had good relations with friends, had success at school, did not work at a job outside of school, when they talked to people close to them about their personal problems, and when their economic situation was good.

Table 4. *Physical well-being, emotional well-being, self esteem and family predictors according to results of multiple regression analysis*

Variables	R^2	Adjusted R^2	F	p	B	β	t	p
Physical well-being								
Constant	0.238	0.233	52.64	0.000	40.523		9.303	0.000***
GHQ-12					-2.168	-0.293	-10.048	0.000***
Gender					-7.868	-0.176	-6.683	0.000***
Family relations					2.243	0.098	3.339	0.001***
Having a health problem in the last year					5.006	0.088	3.335	0.001***
Chronic illness					6.482	0.080	3.119	0.002**
Sleeping problems					2.693	0.061	2.213	0.027*
Relationships with friends					1.665	0.060	2.186	0.029*
Emotional well-being								
Constant	0.356	0.354	130.958	0.000	39.484		10.676	0.000***
GHQ-12					-3.342	-0.472	-18.320	0.000***
Family relations					2.723	0.124	4.700	0.000***
Relationships with friends					3.207	0.121	4.806	0.000***
Physical activity					2.904	0.068	2.865	0.004***
Mother education					1.097	0.061	2.591	0.010**
Self esteem								
Constant	0.190	0.184	34.486	0.000	15.625		2.901	0.004**
GHQ-12					-2.346	-0.280	-10.106	0.000***
Class					3.429	0.146	5.464	0.000***
Physical activity					7.309	0.145	5.381	0.000***
School success					6.000	0.112	4.196	0.000***
Relationships with friends					2.942	0.093	3.403	0.001**
Talking to someone close to them about their personal problems					1.886	0.069	2.561	0.011*
Family								
Constant	0.171	0.166	30.64	0.000	25.879		3.558	0.000***
GHQ-12					-2.150	-0.262	-9.340	0.000***
Physical activity					5.988	0.121	4.404	0.000***
Grade					2.879	0.125	4.583	0.000***
Relationships with friends					2.856	0.093	3.326	0.001***
School success					5.620	0.107	3.980	0.000***
Work in a job					-6.476	-0.077	-2.830	0.005**
Talking to someone close to them about their personal problems					1.741	0.065	2.371	0.018*
Economical situation					2.361	0.062	2.290	0.022*

GHQ-12=The General Health Questionnaire * p < 0.05, ** p <0.01, ***p < 0.001

A significant relationship was seen the adolescents' friends dimension of quality of life and their relationships with friends (*β*=0.276, *p<0.001*), GHQ-12 scores (*β*=–0.143, *p<0.001*), talking to people who are close about personal problems (*β*=0.097, p<0.001), participation in regular physical activity (*β*=0.082, *p< 0.01*) and economic situation (*β*=0.073, p<0.05), respectively. These variables explained 16% of total variance (R^2=0.167, *p<0.001*) (Table 5). The adolescents' level of friends dimension of quality of life increased when their relations with friends were good, there were no mental health issues, they were able to talk to people close to them about personal problems, they engaged in regular physical activity and their economic situation was good.

A significant relationship was seen between the adolescents' school dimension of quality of life and their GHQ-12 scores (*β*=–0.266, *p<0.001*), school success (*β*=0.178, p<0.001), family relationships (*β*=0.143, p<0.001) and sleeping problems (*β*=0.065, p<0.001), respectively. These variables explained 18% of total variance (R^2=0.187, *p<0.001*) (Table 5). The level of the adolescents' school dimension of quality of life increased when there were no mental health problems, success at school, good family relationships and no sleep problems.

A significant relationship was seen between the adolescents' overall quality of life and their GHQ-12 scores (*β*=–0.429, *p< 0.001*), relationships with friends, participation in regular physical activity (*β*=0.132, *p<0.001*), school success (*β*= 0.113, *p<0.001*), family relationships (*β*=0.102, *p<0.001*), class (*β*=0.079, *p<0.001*), economic situation (*β*= 0.060, *p< 0.01*), talking to people who are close about personal problems (*β*= 0.059, *p<0.05*), and presence of chronic illness (*β*=0.053, *p*<0.05), respectively. These variables explained 40% of total variance (R^2=0.402, *p<0.001*) (Table 5). The adolescents' overall quality of life increased when there were no mental health problems, good relationships with friends, they engaged in regular physical exercise, had success at school, good family relations, the higher their class was at school, when their economic situation was good, they talked to people close to them about personal problems and when there was no chronic illness involved.

Table 5. *Friends and school subscales and KINDL-total quality of life predictors according to results of multiple regression analysis*

Variables	R^2	Adjusted R^2	F	p	B	β	t	p
Friends								
Constant	0.167	0.163	47.258	0.000	30.449		9.578	0.000***
Relationships with friends					5.955	0.276	9.915	0.000***
GHQ-12					-0.821	-0.143	-5.132	0.000***
Talking to someone close to them about their personal problems					1.816	0.097	3.556	0.000***
Physical activity					2.155	0.082	3.013	0.003**
Economical situation					2.532	0.073	2.701	0.007**
School								
Constant	0.187	0.184	63.039	0.000	32.001		9.455	0.000***
GHQ-12					-1.702	-0.266	-9.080	0.000***
School success					7.294	0.178	6.725	0.000***
Family relations					2.832	0.143	4.944	0.000**
Sleeping problems					2.512	0.065	2.317	0.021*
KINDL – Total Quality of life								
Constant	0.402	0.398	30.64	0.000	23.574		7.330	0.000***
GHQ-12					-2.086	-0.429	-17.079	0.000***
Relationships with friends					2.809	0.154	6.248	0.000***
Physical activity					3.856	0.132	5.704	0.000***
School success					3.511	0.113	4.925	0.000***
Family relations					1.540	0.102	3.956	0.000***
Grade					1.085	0.079	3.451	0.001***
Economical situation					1.350	0.060	2.585	0.010*
Talking to someone close to them about their personal problems					0.939	0.059	2.555	0.011*
Chronic illness					2.824	0.053	2.344	0.019*

GHQ-12=The General Health Questionnaire * p < 0.05, ** p <0.01, ***p < 0.001

4. DISCUSSION

In this study which evaluated the relationship between mental health and health-related quality of life of the adolescents, the GHQ-12 mean score was 2.90±3.00. Adolescents' average GHQ-12 score above 2 indicated that they are at risk in terms of psychiatric illness. Mental health problems are seen to be quite common among adolescents (7). An estimated 10-20% of adolescents globally experience mental health problems (8). Therefore, these studies to determine mental health of adolescents are very important for determining adolescents at risk.

It is seen that the health-related quality of life of the adolescents participating in this study is slightly above the average according to the possible scores that can be obtained from the scale. While the health-related quality of life of adolescents was reported to be high in the study of Freire and Ferreira (2018), the quality of life of adolescents was reported slightly below the average values in the study of Magiera and Pac (2022) (13,28). It is stated in the literature that adolescents are generally considered to be healthy (2). It is seen that the quality of life of adolescents is similar in studies conducted with healthy adolescents in different populations.

This study shows that mental health is a significantly related to all dimensions of health-related quality of life (physical wellbeing, emotional wellbeing, self-esteem, family, friends, and school) of adolescents. The results of the study showed that as the adolescents' GHQ-12 scores rose (i.e., as the risk of mental health issues rose), health-related quality of life in all the dimensions diminished. Similar to the results of the study, Knudsen et al. (2016) it was reported that symptoms of depression were associated with low HRQoL scores (29). It has been reported that the quality of life scores of depressive adolescents are significantly lower than those of healthy adolescents (14). In a study by Freire and Ferreira (2018), it was reported that low levels of depressive symptoms are significant predictors of quality of life in all its dimensions (13). At the same time, it has been shown that anxiety is associated with low levels of quality of life (15).

Our study showed that being male was a positive predictor of quality of life in terms of physical wellbeing. In a study by Freire and Ferreira (2018), it was reported that being male was a significant predictor of physical wellbeing and psychosocial wellbeing (13). Studies on quality of life have demonstrated that men's quality of life is at a higher level than women's (19,30-31). Contrary to the results of the study, Hamby et al. (2020) and İlhan et al. (2019) found that no relationship between the gender of adolescents and quality of life in terms of physical wellbeing (2,32).

As adolescents' gain seniority at school, their health-related quality of life increases in terms of the sub dimensions of self-esteem and family and also in terms of overall quality of life. Unlike the results of the study, in a study by Karalar et al. (2017), however, no differences were detected in school quality of life according to the students' class (33). It is reported that adolescents' quality of life falls as they get older (19). This result shows that further studies are needed on the effect of the level of class on health-related quality of life of adolescents.

This study is also important in terms of showing that family and friend relationships are a significant predictor of quality of life. As adolescents' relationships with their parents improve, their health-related quality of life increases in terms of the sub dimensions of physical wellbeing, emotional wellbeing and school as well as in terms of overall quality of life. The period of adolescence is the period of transition in which an individual becomes an autonomous adult. The individual may experience conflicts with the family in this process. The fact that these conflicts are long-term and negative can harm the parent-adolescent relationship and to youths' development. (34). Conflicts between parents and adolescents during adolescence and destructive reactions to these conflicts are the main reasons that decrease the quality of life and productivity of the family (35). A family environment in which the individual can "be", "belong" and achieve "self-actualization" is of vital importance in improving quality of life (11). In order to adolescents to successfully complete this transition period, they need the thoughtful and sensitive support of their parents (35). Im et al. study (2018) showed that mothers' emotional warmth is predictors of HRQoL for adolescents (36). In a study by Williams and Anthony (2015), it was reported that family togetherness and parent behavioral expectations were associated with greater health and well-being (37). The better adolescents are able to engage in good relations with their families, the more quality of life increases.

As adolescents' relationships with their friends improve, all of the sub dimensions of quality of life outside of the school dimension as well as overall health-related quality of life improve. When adolescents are able to talk to people close to them about their personal issues, quality of life is heightened in many dimensions (self-esteem, friends) as well as on the overall scale. Friendship, togetherness and joining a group are important for the adolescent (38). Friendships in adolescence provide an important opportunity to adolescents to increase their self-esteem, support identity development, develop social skills, help solve problems, provide emotional support, and have entertainment (39,40). In a study by Williams and Anthony (2015), it was reported that friend support was associated with greater health and well-being and less school misbehavior (37). Therefore, adolescents' positive friendships should be supported (38).

As adolescents' achievement at school improves, health-related quality of life increases in many dimensions (self-esteem, family, school) as well as on the overall scale. In the study by Karalar et al. (2017), students who perceived they to be academically successful had higher quality of life scores than students who saw them to be poor or mediocre students (33). The researchers found a direct correlation between school success and school quality of life. The higher the students' academic achievement, the more their relations

with their families, teachers and friends are positively influenced and not only does their self-confidence improve in this case but they perceive school as a more positive and safe environment to be in.

In literature, socioeconomic status has been reported to correlate with individual and/or community health including HRQoL. The socioeconomic status is determined by the combination of the education level, occupation and economic status of the individual and family (22,41). The research showed that the higher the mother's level of education, the better was the adolescent's health-related quality of life in terms of emotional wellbeing. An adolescent's working at a job outside of school causes a drop in the family dimension of health-related quality of life. The better the economic status of adolescents, the more improvement was seen in the family and school sub dimensions of quality of life as well as on the overall scale. There are indications in the literature that point to the fact that income status and education status is the most significant predictor of an individual's physical, emotional, social health, and of their success and satisfaction at work and in social life, and consequently their quality of life (11).

Not experiencing any health issue in the last year increases adolescents' health-related quality of life in terms of their physical wellbeing. Additionally, when there is no chronic illness involved, adolescents' quality of life is higher, both in terms of physical wellbeing and on the total scale. In the study by Filho et al. (2018), it was found that the presence of a chronic illness and the use of medicines were significant predictors of both physical and mental health (18). Studies have shown that the quality of life of adolescents suffering from migraines, acne or functional abdominal pain was significantly lower that the quality of life of their healthier peers (42,43). In another study, a correlation was revealed between the presence of chronic illness and a low level of quality of life (31).

Suffering from insomnia lowers the health-related quality of life of adolescents in terms of the dimensions of physical wellbeing and school. One study pointed to a correlation between sleep quality and the physical functionality, vitality, mental health, body aches and general health parameter aspects of quality of life (20). Similarly, other studies have shown that people with sleep problems have poorer quality of life than individuals who have a healthy pattern of sleep and that there is a significant relationship between sleep duration and quality of life (44,45). This has a negative effect on students' quality of life.

At the end of the study, it was observed that engaging in regular physical exercise increased adolescents' health-related quality of life in terms of various dimensions (emotional wellbeing, self-esteem, family, and friends) and improved their scores on the overall scale. Filho et al. (2018) reported that vigorous physical activity is a significant predictor of physical and mental health (18). An association was found in various studies between higher levels of physical activity and higher HRQOL scores, leading to the conclusion that physically active children had a better quality of life (23-25,46).

Since the study was cross-sectional, it is limited to its own sample. The dependence of the research on the patients' self-reporting is a limitation of the study. The sufficiently large sample size was strength of the study. At the same time, in line with the results of the study, it may also be recommended that experimental studies be carried out in order to evaluate the effectiveness of nursing interventions carried out to promote adolescents' health-related quality of life.

5. CONCLUSION

This study shows that mental health is a negatively significantly related to all subscales of health-related quality of life (physical wellbeing, emotional wellbeing, self-esteem, family, friends, and school) of adolescents. It was discovered that the mental health of adolescents, their relationships with friends and family, their participation in regular physical activity, their school success, their class, their economic situation, their talking to people who are close to them about personal problems and the presence of chronic illness were significant predictors of health-related quality of life.

The school healthcare team and families have a major role in improving the quality of life of adolescents. School nurses are the most well-equipped health workers in improving the quality of life of adolescents in school. Mental health screenings and counseling services and health education programs to be performed by school nurses are especially important in adolescence. Screening should be conducted to identity adolescents that are at risk of mental health issues and these individuals should be referred for professional counseling. Other adolescents too should receive guidance and counseling. Various workshops can be conducted, group activities can be organized to improve adolescents' relations with family and friends and increase communications. Both parents and students should be provided with education about the period of adolescence and its characteristics to facilitate the transition through this period in life. The results of the research show that these interventions will contribute to improving the quality of life of adolescents.

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Clinical and Experimental Health Sciences

Determining the Image of Nursing Profession in the Society During Covid-19 Pandemia Process

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ABSTRACT

Objective: This study aimed to descriptively determine the image of the nursing profession in the society during the Covid-19 pandemic process.

Methods: The study was carried out in a district between November 2020 and February 2021. The sample of the study consisted of 1285 individuals. While collecting the data, a "Questionnaire Form" containing personal characteristics and "Image Scale for Nursing Profession" were used. Data were collected by snowball sampling method. The data were collected through an online survey.

Results: The mean score of the participants' Image Scale for Nursing Profession was found to be 150.68 ± 9.75. It was determined that the sub-dimensions of the scale, the professional qualification sub-dimension, had the highest mean score of 45.80 ± 4.45, and the other appearance sub-dimension had the lowest mean score of 11.10 ± 2.73. A significant difference was determined between the Image Scale for Nursing Profession and gender, profession, and the status of having the received care from nurses before ($p < 0.05$).

Conclusion: It was determined that the professional qualifications and professionalism of nurses came to the fore during the Covid-19 pandemic process.

Keywords: Covid-19, nursing image, pandemic, nursing

1. INTRODUCTION

Nursing is a profession that undertakes important responsibilities, such as protecting and improving the health of the individuals, family and the society, curing diseases, and preventing disabilities/rehabilitation. The evaluation of a profession by the society and the widespread acceptance of this assessment are related to the professional image and is of great importance for members of the profession (1-3). The nursing image in the society has been changed over the years in terms of political, socio-economic, cultural, and technological, aspects, etc. It is a dynamic structure that changes over time by being affected by the social, environmental or the human factors (4,5).

The perception of the nursing image in the society positively or negatively affects the members of the nursing profession and the professional quality of the profession (6). The nursing image states that it is effective in the development of the professional identity feelings of nurses, professionalization, job satisfaction, ensuring continuity to work, advising others and individuals in choosing the nursing profession (7-10). One of the important factors in determining the nursing image is gender stereotypes, whereby the nursing profession suffers from these gender stereotypes. It is stated that this situation prevents nurses' social image and professional image from being matched, thus preventing nursing from being seen as an autonomous, scientific profession and negatively affecting their legal, organizational, social and economic rights (3,11).

In addition to one of the factors affecting the nursing image in the society is the public health problems and the epidemic diseases (12). As a matter of fact, in the flu epidemic in 1918, Nightingale made great contributions to the epidemic with good hand washing, proper sanitation and regulation of the physical environment. In the following years, it has been reported that the nurses are at the forefront of some of the world's newly introduced infectious disease outbreaks, including H1N1 Swine Flu, Ebola, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (12). It has been reported by the World Health Organization (WHO) that 6.722.949 deaths and 664.618.938 cases have been detected so far with the Covid-19 epidemic that started in Wuhan, China and was declared as a pandemic in March, 2020 (13).

During the Covid-19 pandemic process, nurses are at the center of the fight against the epidemic, meeting the patients' care needs, working 24 hours with limited resources, pushing their own limits, and managing the patients' care at the expense of their lives (14-17). In the current crisis, it is stated that the nursing profession focuses on providing the highest quality, evidence-based, and the compassionate, individualized nursing care (18). During the pandemic, it

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is seen that the altruistic work of nurses and their active participation in the fight against the disease are reflected in the media. As a matter of fact, Bennett (2020) states that during the pandemic process there was a 3-fold increase in the number of news about nurses in the media (18).

The World Health Organization (WHO) declared the year 2020, which coincides with the 200th birthday of Florence Nightingale, as the "Year of Nurses and Midwives" in order to raise the nursing profile and increase the global nurse workforce. As a result of the Covid-19 pandemic, it is observed that the importance of nurses and the profession automatically comes to the fore. Considering that there are very few studies on the socially image of nurses and the dynamic nature of the nursing image, it is important to determine how this pandemic affects the image of the nursing profession. Therefore, this study was conducted to determine the image of the nursing profession in the society during the Covid-19 pandemic.

2.METHODS

This study was conducted in a descriptive district in the Western Black Sea Region between November 2020 and February 2021. The population of this study included 67245 individuals. In a study by Yazıcıoğlu and Erdoğan (2004), it is stated that the population size of 50.00-100.000 should be taken as 381-383 since the sample size is calculated with 0.05 margin of error (19). The sample of this study consisted of 1285 individuals aged 18 and over who accepted to participate in the study. Fifty-six people who filled in the survey questions incompletely were not included in the study. Data were collected by snowball sampling method. Therefore, the sample size was above the expected number. The data were collected through an online survey. After the participants gave their consent, they reached the data collection form.

The average age of the individuals participating in our study is quite young. The young average age may affect its generalizability to the whole population. This also may be a limitation of the study.

2.1. Data Collection Tools:

The data were collected using the "Questionnaire Form" developed by the researchers in line with the literature (13,15,18,20). The questionnaire form consisted of 3 parts.

2.1.1. The first part consisted of 4 questions including the individual characteristics of the individuals (age, gender, profession, and the presence of nurses in the family).

2.1.2. The second part consisted of 4 questions, including the status of individuals' benefiting from the healthcare services (previous hospitalization, the state of having received care from a nurse before, status of getting service from a nurse during the Covid-19 pandemic, status of staying as a companion in the hospital before). In the third part, "Image Scale for Nursing Profession" was used.

2.1.3. In the third part, "Image Scale for Nursing Profession" was used. The scale was developed by Dost and Bahçecik that is a Likert-type scale scored between 1 and 5, consisting of 42 items. The scale includes 6 sub-dimensions. These sub-dimensions consist of professional qualification (11 items), working conditions (10 items), gender (8 items), education (5 items), professional status (5 items) and external appearance (3 items). The Cronbach alpha coefficient of the scale was found to be 0.97 (20), and a total of 15 items were scored negatively in the evaluation of the scale. The lowest score that can be obtained from the scale is 42 and the highest score is 210, 42-75 which indicate very poor image, 76-109 poor, 110-143 medium, 144-177 good, and 178-210 indicate a very good image perception. The higher is the score obtained from the scale, the higher is the positive image perception (20). In this study Cronbach alpha was found to be 0.64.

2.2. Ethical Consideration

Before conducting the study, the approval was obtained from the Karabuk University Social and Human Sciences Research Ethics Committee (date: 10.11.2020, number: E-78977401-050.02.04-46388). The consent was obtained from the individuals participating in the study by explaining the purpose, duration, and process of the study.

2.3. Statistical analysis:

The data were analysed using SPSS (Statistical Package for Social Science) 24 package program. The descriptive statistical methods, such as number, mean, standard deviation and percentage were used to evaluate the data. Mann Whitney-U and Kruskall Wallis tests were used to compare the independent group's average in distributions that did not show a normal distribution.

3. RESULTS

It was determined that the average age of the participants was 27.28 ± 11.35 (min=18, max=75), 71.5% of them were women, 77.8% had a university or a higher education level, and 33.3% were university students. Besides, 33.3% of the participants were nurses in their families, 49.8% were hospitalized before, 82.1% received services from nurses before, and 15.3% received services from nurses during the Covid-19 pandemic (Table 1).

The average Image Scale for Nursing Profession score of the participants was 150.68 ± 9.75. When the subscale dimensions of the scale were examined, 45.80 ± 4.45 (min 15 – max 52) were from the professional qualification sub-dimension, 28.25 ± 3.45 (min 18 – max 47) were from the working conditions sub-dimension, 27.03 ± 4.81 (min 12 – max 58) were from the gender sub-dimension, education sub-dimension was 19.15 ± 2.28 (min 9 – max 25) points from the dimension, 19.32 ± 3.89 (min 5-max 25) points from the professional status sub-dimension, and 11.10 ± 2.73 (min 3 – max 15) points from the outer appearance sub-dimension (Table 2).

Table 1. *Socio-demographic characteristics of the participants*

Characteristics	n	%
Age (x̄ ±SD)	27.28±11.35 (min=18-max=75)	
Gender		
Female	919	71.5
Male	366	28.5
Educational level		
Primary education	76	5.9
High school	209	16.3
University and above	1000	77.8
Profession		
Gendarme	11	0.9
Retired	18	1.4
Engineer	28	2.2
Artisan	51	4.0
Worker	54	4.2
HealthTechnician	67	5.2
Officer	69	5.4
Teacher	72	5.6
Nurse	114	8.9
Housewife	373	29.0
Student	428	33.3
Presence of a nurse in the family		
Yes	428	33.3
No	857	66.7
Previous hospital stay		
Yes	640	49.8
No	645	50.2
Status of receiving service from a nurse before		
Yes	1055	82.1
No	230	17.9
Status of receiving service from a nurse in the Covid-19 pandemic		
Yes	196	15.3
No	1089	84.7
Previous companion ship status		
Yes	778	60.5
No	507	39.5

Table 2. *Distribution of theparticipants' mean scores for the image scale and sub-dimensions of the nursing profession (n=1285)*

Scale and sub-dimensions	Min-Max	Mean score (x̄ ±SD)
Professional qualification	11-55	45.80±4.45
Working conditions	10-50	28,25±3.45
Gender	8-40	27,03±4.81
Education	5-25	19,15±2.28
Professional status	5-25	19,32±3.89
Outher appearance	3-15	11,10±2.73
Total	**42-210**	**150.68±9.75**

In Table 3, the comparison of the participants' Image Scale for Nursing Profession and sub-dimension mean scores (n = 1285) are presented. Accordingly, a significant difference was identified between the median of the Image Scale for Nursing Profession general score and gender, profession, and previous care received from the nurses. It was revealed that the female participants had higher mean scores than men, those who had a profession other than nurses, and those who received services from nurses before compared to those who did not ($p < 0.05$).

Table 3. *Comparison of participants' image scale sub-dimension mean scores for the nursing profession according to descriptive features (n=1285)*

Descriptive Characteristics	Sub-Dimensions						
	Professional qualification	Working conditions	Gender	Education	Professional status	Outher appearance	Image Scale for Nursing Profession
	x̄ ±SD	x̄ ±SD	x̄ ±SD	x̄ ±SD	x̄ ±SD	x̄ ±SD	x̄ ±SD
Gender							
Female	46.00±4.16	28.00±3.33	28.00±4.36	19.00±2.26	19.00±3.94	11.00±2.65	155.00±9.60
Male	47.00±5.09	28.00±3.72	26.00±5.58	19.00±2.30	20.00±3.73	12.00±2.89	153.00±10.06
Statistical test and p value	Z=-1.040 p=.299	Z= – .068 p= .946	Z= – 6.499 **p<.001**	Z= – 2.419 **p= .016**	Z= – 2.176 **p= .030**	Z= – 3.928 **p<.001**	Z= – 2.831 **p<.001**
Educational level							
Primary education	49.00±5.41	27.00±3.11	24.00±5.98	19.00±2,28	22.00±2,68	14.00±2,57	156.00±8,94
High school	47.00±4.44	28.00±3.18	27.00±5.77	19.00±2,29	20.00±3,54	12.00±2,57	153.00±9.43
University and above	46.00±4.36	28.00±3.52	28.00±4.39	19.00±2.27	19.00±3.97	11.00±2.73	154.00±9.88
Statistical test and p value	KW= 8,743 **p= .013**	KW=6,470 p=0.39	KW=42,945 **p<.001**	KW=7,152 **p=.028**	KW=32,985 **p<.001**	KW=42,487 **p<.001**	KW=1,794 p=.408
Profession							
Nurse	50.00±4.04	26.00±2.38	27.00±4.30	21.00±1.68	16.00±5.16	11.00±2.64	153.00±10.05
Other	46.00±4.41	28.00±3.46	28.00±4.86	19.00±2.30	20.00±3.60	11.00±2.74	154.00±9.71
Statistical test and p value	Z= – 7.548 **p<.001**	Z= – 7.577 **p<.001**	Z= – .855 p=.393	Z= – 5.916 **p<.001**	Z= – 7.278 **p<.001**	Z= – .736 p= . 462	Z= – 2.042 **p= .041**
Presence of a nurse in the family							
Yes	47.00±4.29	27.00±3.49	27.00±4.88	20.00±2.13	20.00±4.25	12.00±2.88	153.00±8.92
No	46.00±4.48	28.00±3.38	28.00±4.73	19.00±2.34	20.00±3.69	11.00±2.66	155.00±10.13
Statistical test and p value	Z= – 4.514 **p<.001**	Z= – 6.021 **p<.001**	Z= – 4.381 **p<.001**	Z= – 2.004 **p=.045**	Z= – .270 p=.787	Z= – 1.698 p=.089	Z= – 1.695 p=.090
Previous hospital stay							
Yes	47.00±4.32	27.00±3.39	27.00±4.95	20.00±2.22	20.00±4.01	11.00±2.82	154.00±9.51
No	46.00±4.42	28.00±3.50	28.00±4.59	19.00±2.31	19.00±3.77	11.00±2.64	154.00±9.99
Statistical test and p value	Z= – 3,903 **p<.005**	Z= – 2,348 **p=.019**	Z= – 4,853 **p<.005**	Z= – 3,119 **p=.002**	Z= – 1,135 p=.256	Z= – .955 p= . 339	Z= – .170 p=.865
Status of receiving service from a nurse before							
Yes	47.00±4.38	28.00±3.39	28.00±4.79	19.00±2.24	20.00±3.96	11.00±2.77	154.00±9.60
No	45.00±4.68	28.00±3.69	27.00±4.91	19.00±2.44	19.00±3.56	11.00±2.59	152.00±10.31
Statistical test and p value	Z= – 3.145 **p=.002**	Z= – .868 p= .385	Z= – 1.013 p= .311	Z= – 1.810 p= .070	Z= – 1.116 p= .264	Z= – 1.083 p= .279	Z= – 2.366 **p= .018**
Status of receiving service from a nurse in the Covid-19 pandemic							
Yes	47.00±4.24	27.00±3.32	27.00±4.80	20.00±2.28	20.00±3.87	12.00±2.88	155.00±9.33
No	46.00±4.47	28.00±3.47	28.00±4.81	19.00±2.27	20.00±3.89	11.00±2.71	154.00±9.83
Statistical test and p value	Z= – 2.740 **p= .006**	Z= – 1,408 p= .159	Z= – 1,530 p= .126	Z= – 1,801 p= . 072	Z= – 1,733 p= . 083	Z= – 1,366 p= . 172	Z= – 1,166 p= . 243
Previous companion ship status							
Yes	47.00±4.48	28.00±3.42	27.00±4.85	19.00±2.26	20.00±3.98	11.00±2.84	154.00±9.49
No	46.00±4.37	28.00±3.48	28.00±4.74	19.00±2.29	20.00±3.75	12.00±2.56	154.00±10.15
Statistical test and p value	Z= – 3.381 **p= .001**	Z= – .423 p= .673	Z= – 2.292 **p= .022**	Z= – 1.812 p= .070	Z= – .911 p= .362	Z= – 1.470 p= . 142	Z= – .336 p= .737

KW: Kruskal-Wallis, Z: Mann Whitney U p<0.05 was accepted.

** The min and max scores that can be obtained from each sub-dimension; Professional qualification (Min 11-Max 55), Working conditions (Min 10-Max 50), Gender (Min 8-Max 40), Education (Min5 – Max 25), Professional status (Min 5-Max 25), Outher appearance (Min3-Max15)*

In the Image Scale for Nursing Profession professional qualification sub-dimension, it was showed that the education level of the individuals in the society, their profession, being a nurse in the family, having been hospitalized before, receiving services from the nurse before, receiving services from the nurses during the Covid-19 pandemic, and those who were previously accompanying patients were affected by the professional qualifications of nurses. It was determined that the mean scores of the professional qualification sub-dimension were higher than those who received education at primary education level compared to those who received education at high school and university level ($p<0.05$). It was determined that the professional qualification sub-dimension mean scores of those who were professional nurses were higher than those who were not nurses, those who did not have a nurse in their family, and those who had been hospitalized before were higher than those who were not hospitalized ($p<0.05$). In the study, it was determined that those who received service from a nurse before, compared to those who did not receive service from a nurse in the Covid-19 pandemic, had higher mean scores in the professional qualification sub-dimension than those who did not receive service from a nurse ($p<0.05$). It was illustrated that the mean scores of those who had a companion before were higher than those who did not have a companion before ($p <0.05$).

In the sub-dimension of the working conditions of the image scale for the nursing profession, it was determined that it affects the image perception in professional groups other than nurses, in the absence of a nurse in the family, and in individuals who have not been hospitalized before. In addition, it was demonstrated that the mean scores of those who were nurses were higher than those who were nurses in the family, and those who were not hospitalized before compared to those who were hospitalized ($p <0.05$).

In this study, the gender, the educational status, the presence of a nurse in the family, the previous hospitalization status, and the previous companionship made a significant difference in the perception of the image of the nursing profession, especially the perceptions of the women's image towards the nursing profession. Based on the results, the female gender was higher than males, higher than those who received university or higher education compared to those who received education at the high school and the primary school level, higher than those who were nurses in the family compared to those who were not hospitalized before, and those who did not have an accompanying person before were higher than those who stayed at the hospital ($p <0.05$).

In the Image Scale for Nursing Profession education sub-dimension, a significant difference was found in the gender, the education level, the presence of a nurse in the family, and the previous hospitalization. More specifically, it was found that the average educational scores of those who were nurses were higher than those who were nurses and were higher than those who were nurses in their family, and those who were hospitalized before were higher than those who were not hospitalized ($p <0.05$).

Further, a significant difference was found in the gender, the education level, and the profession in the image scale professional status sub-dimension for the nursing profession. Professional status means scores of men compared to women, primary school graduates and high school and university levels were found to be higher ($p<0.05$). In the study, it was determined that the other professions had higher professional status mean scores than nurses ($p<0.05$).

It was revealed that the image scale outer appearance sub-dimension of the nursing had the lowest average score in the image of the nursing profession, and the gender and educational status were effective on the image of nurses. It was found that the male gender, the female gender, and the graduates of the primary education level were higher than the high school scores and the university graduates scores ($p <0.05$).

4.DISCUSSION

In this study, the mean total score of the participants' image scale for the nursing profession was determined as 150.68 ± 9.75. Since the score range that can be obtained from the scale is 42-210 and 144-177 is considered good, it can be stated that the image perception of the society towards the nursing profession is at a good level. In their study conducted during Covid – 19 pandemia, Elmorshedy et al. (2020) reported that the public image of nurses is negative in Saudi Arabia due to the impact of the socio-cultural factors (21). In the studies in which the image of the nursing profession in the society is examined, it is reported that the image of the nurse is moderately positive. In literature reported that the social image of nursing is seen as positive, and the society respects the nursing profession, but people do not have sufficient knowledge about the nursing profession and individuals do not recommend nursing as a career choice (3,22,23). In another study, Morris-Thompson et al. (2011) state that unlike the nursing image that is influenced by prejudices, ignorance and stereotypes in the eyes of the society, the nursing image of healthcare workers is positive (24). Further, Yılmaz et al. (2019) reported that 43% of nurses, 72% of physicians, and 46% of the patients evaluated the social image of nursing at a moderate level (23). In this study, it can be argued that by determining that the social image towards the nursing profession is good, the image perception towards the nursing profession has increased during the Covid-19 pandemic.

In the "professional qualification" sub-dimension of the scale, it was observed that the mean score was 45.80 ± 4.45 and it had the highest mean score. In the image of the nursing profession, it was determined that the education level of the individuals in the society, their profession, being a nurse in the family, having been hospitalized before, receiving a service from the nurse before, receiving a service from the nurse during the Covid-19 process, and those who were previously

companions were affected by the professional qualifications of nurses. In Arthur's (1998) study, the professional nurse qualifications are expressed as a communication, job satisfaction, leadership, responsibility, flexibility, creativity, and professional practice (25). In another study, Dost (2015) mentions the ethical principles and responsibilities of nurses published by International Council of Nurses (ICN) and the Turkish Nurses Association as professional qualifications (20). Nonetheless, Hoever et al. (2014) states that although the ethical and professional definitions of nursing have been made and there is extensive knowledge of treatment protocols and guidelines as a part of the development of nursing professionalism, nursing activities are still not sufficiently recognized by the society (26). In the systematic review conducted by Girvin et al. (2016) by examining the research articles published between 2010 and 2015, it is emphasized that although the society trusts nurses, the duties and effects of the nursing profession are not realized by the public (27). Besides, Morris-Thompson et al. (2011) stated in his study that the society's knowledge about the nursing profession is insufficient and the nursing image formed in the society is based on legends, misunderstandings and stereotypes more than professional qualifications (24). Similar to the study conducted by Girvin et al. (2016), Şimşek and Alpar (2019) showed that the duties and responsibilities of nurses are not fully understood by the society, and it is stated that the nursing profession is still perceived as an auxiliary profession by the society (27, 28). In their study Li, Z et al. (2020) emphasized that the pandemic was in the forefront of nurses using their professional qualifications and professionalism during the Covid-19 epidemic, and this situation led to the understanding of the importance of the professional qualifications of nurses (29). In the news on media, Bennett et al. (2020) states that in addition to the appreciation for nurses, the nursing image reflected in the 21st century is used more than ever before with roles based on female gender, heroes and angelic images (18). It is stated that this will negatively affect the image towards the nursing profession. However, the findings of the current study showed that the visibility of the nursing profession has increased during the Covid-19 pandemic and the professional qualifications are better realized by the society.

In the working conditions sub-dimension of the image scale for the nursing profession, it was illustrated that it affected the image perception in the professional groups other than nurses, in the absence of a nurse in the family and in individuals who were not hospitalized before. Before the Covid-19 pandemic, Celik et al. (2013) reported that individuals who are self-employed and have a relative of a nurse in their family have a higher level of positive image towards the nursing profession (22). It is known that the media are an effective factor in the formation of the nursing image in the society (26). After the pandemic, Bennett et al. (2020) reported that the visibility of nurses in the media increased three times compared to 2019. It is stated that the publications in the media during the Covid-19 pandemic focus on the troubles caused by the pandemic, some realities and difficulties the nursing workforce is faced with today, as well as the publications expressing appreciation, gratitude and even love for nurses due to their contributions to the provision of healthcare services (18). During the Covid – 19 pandemic, it is stated that the wounds on their faces and the exhausted nurses' images after wearing protective masks for hours while looking after sick people during the Covid – 19 pandemic reveal the difficulties of nurses' working conditions (18). It can be argued that individuals, who do not have a nurse in their family or who have not been hospitalized before, have witnessed the working conditions of nurses during the pandemic, increased their awareness and have positively affected the image of the society towards the nursing profession. However, Garcia (2020) states that people or their relatives who were not treated at the hospital before have limited ideas about what the nurses are doing, but during the pandemic, the society have realized that the nurses are educated and qualified professional practitioners (29).

In this study, it was determined that the gender sub-dimensions of the image scale for the nursing profession, the gender, the education status, the presence of a nurse in the family, the previous hospitalization, and the previous accompanying status made a significant difference in the image perception of the nursing profession, especially the perception of women towards the nursing profession. In their study, Elmorshedy et al. (2020) state that the nursing profession is made by women, women and men work together, female nurses marry late, care regardless of gender, and other socio-cultural barriers cause the nursing profession to be negatively affected in the society (21). In another study, Bennett et al. (2020) emphasized that gender-based roles and angelic images take place on media more than ever with nursing during the pandemic process (18). Anette Kennedy, the President of the ICN during the Covid-19 pandemic conditions, states that nurses, governments and politicians are ignored by the nurses, governments and politicians in the nursing profession, which consists of 90% women, and that women and especially nurses are subjected to violence, disrespect, abuse, low salaries and are not valued (30). In another study, it was reported that this situation in which nurses were shown as heroes and angels during the Covid-19 pandemic, weakened the professionalism of the nursing workforce, strengthened the perception that nursing was an innate feminine and nurturing role, and this situation negatively reflected on the image of the profession (31).

In the education sub-dimension of the image scale for the nursing profession, a significant difference was determined in terms of gender, education level, presence of a nurse in the family, and previous hospitalization. It was revealed that the education and the professional qualification dimensions were important in the image perception towards the nursing profession for those who are nurses. This situation can be interpreted as the nurses are aware of the importance of their professional identity and professionalism. In the Chinese context, Zhuyue et al. (2020), states that a difference exists in the nursing's education levels, whereby the most common

education is at the undergraduate level, and undergraduate nurses may be more successful in combating an epidemic, probably because of their stronger abilities (31). Besides, Özsoy (2000) reveals in her study that a great majority of the participants think that nursing is a knowledge-based profession, and the nursing education should be at the university level, as well as the nursing care is vital for the recovery of patients (3). Similarly, in Yılmaz's (2019) study, it is reported that healthcare professionals believe that nursing education should be at the undergraduate level and nurses should pursue an academic career (23).

A significant difference was found in the gender, the educational status, and the profession in the professional status sub-dimension of the image scale for the nursing profession. In Celik's (2013) study, it is emphasized that the current status of a profession is closely related to the image of that profession members in the society and it is of great importance for the members of the profession (22). In addition, 58.2% of the participants think that the nursing profession has an important status in the society. Further, Tanrıverdi et al. (2014) reported that gender, education, marital status, socio-economic status, patriarchal structure and organizational levels affect the social status of the nursing profession (32). In their study, Çınar and Demir (2009) demonstrated that the lack of autonomy, the professional risks, the wages paid to nurses, and the working conditions are the reasons affecting the nursing image and the social (6). In their study, Yılmaz et al. (2019) reported that patients, nurses and physicians moderately agreed with the statement that "men's entry into the nursing profession increases their nursing status/respect". In the same study, it is stated that although the number of male nurses has increased in Turkey, women remain in a dominant position (23).

However, it was determined that the external appearance sub-dimension of the image scale for the nursing profession had the lowest average score in the image of the nursing profession, and the gender and educational status were effective on the image of nurses. In a study conducted by Celik et al. (2013), it was found that 63.2% of the participants agreed with the statement that the nurses were well-groomed and clean (22). During the Covid-19 pandemic, the nurses are mostly seen in protective equipment and this appearance can be interpreted as reflecting the difficulty of the working conditions of nurses in the society rather than being clean and well-groomed.

5.CONCLUSION

Regarding the image perception towards the nursing profession during the Covid-19 pandemic, it was found that the professional qualifications of the nurses were important. In the study, it was determined that the professional image was at a good level. In addition, it was determined that the difficulty of the working conditions of the nurses affected their nursing image by the individuals who were not nurses, the individuals who do not have nurses in their family, and individuals who were not hospitalized before. In addition, it was illustrated that the education and the professional qualification dimension are important for the image perception of the nursing profession for those who are nurses in the profession, and during the Covid-19 pandemic, the professional qualifications of nurses are affected by the nursing image of nurses. As a result, the professional qualifications and professionalism of nurses came to the fore during the Covid-19 pandemic. During this critical period, it can be argued that the working conditions of nurses are also realized by the individuals who have not received health services before, and the visibility of the nursing profession has increased.

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Clinical and Experimental Health Sciences

Determination of Attitudes Towards COVID-19 Vaccine and Affecting Factors of Individuals Applying to the Family Health Center

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ABSTRACT

Objective: This research was carried out to determine the attitudes of individuals who applied to primary care during the coronavirus disease-2019 (COVID-19) pandemic and the factors affecting the COVID-19 vaccine.

Methods: The descriptive study was conducted with individuals (n=190) who applied to five family health centers in Erzincan city center between March-June 2021. The data were collected using the "Personal Information Form" and the "Scale of Attitudes towards the COVID-19 Vaccine" by paying attention to the pandemic rules by face-to-face interview method.

Results: It was determined that 75.3% of the individuals were women, 41.1% were primary school graduates, 59.5% lived in a nuclear family and 74.2% had no chronic disease. Individuals Attitudes Towards COVID-19 Vaccine Scale mean score was 3.26±0.78 out of 5, positive attitude sub-dimension mean score was 3.32±0.99, and negative attitude sub-dimension mean score was 3.21±0.71. There is a statistically significant difference between the mean scores of the Attitudes Towards COVID-19 Vaccine Scale and the status of individuals thinking that COVID-19 vaccine is necessary for public health, worrying about getting COVID-19 infection, having COVID-19 vaccine, and following information about COVID-19 vaccine.

Conclusions: It was determined that the attitudes of these individuals towards the COVID-19 vaccine were at a positive level. The reasons for participants' concerns about the COVID-19 vaccine are fear of side effects of the vaccine and the production of the vaccine in a very short period of time.

Keywords: Attitude, COVID-19, Family health center, Vaccine

1. INTRODUCTION

Coronavirus disease-2019 [Coronavirus Disease-2019 (COVID-19)], in which the first case was detected in December 2019 in the city of Wuhan, China's Hubei province, is an infectious disease that caused the World Health Organization (WHO) to declare it a pandemic (1,2). The COVID-19 pandemic harms the lives, health and economy of individuals. Vaccination, along with hygiene practices and other behavioral measures, helps prevent the spread of infection (3). We have seen the results of the use of vaccines in the past years. The incidence of polio, measles, and other childhood diseases has decreased worldwide, and the smallpox virus has completely disappeared (4). It is stated that vaccination is important and mandatory in the control of the COVID-19 pandemic (5). In addition, vaccines have proven to be the most effective and economical way to prevent and control infectious diseases (6). Numerous COVID-19 vaccines have been developed and approved with ongoing studies since the beginning of the pandemic. Nowadays, vaccines developed against COVID-19 seem to be important in preventing and controlling COVID-19 (7). However, it is a known fact that the pandemic cannot be prevented if these vaccines are not widely accepted by the majority of the population.

There are uncertainties about whether the COVID-19 vaccine will be accepted by all communities globally. Although great progress has been made in vaccination so far, hesitation in vaccination with the COVID-19 vaccine remains a worldwide problem (6). Lack of clinical trials for the vaccine, fear of vaccine side effects, and rumors of active viruses in vaccines are some of the main obstacles hindering the success of the COVID-19 vaccine campaign (8). In a study investigating the public's acceptance or rejection of a pandemic vaccine (H1N1), people's perceived risk of infection appears to be influenced by the severity of the event, personal consequences, and previous vaccination history (9).

The coronavirus pandemic has dramatically changed people's health, economic well-being, lives and behavior of communities around the world, and has affected the health

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of individuals. Therefore, some people may be hesitant about the COVID-19 vaccine for ethical, religious, social or economic reasons (10). WHO, recommends developing strategies to overcome vaccine hesitancy and build confidence in the vaccine once a vaccine is available. In order to develop these strategies, it is important to understand the changing vaccination attitudes of different groups and geographies (11). There are studies to estimate the level of vaccine acceptance before the COVID-19 vaccine is introduced (12,13). However, no study was found to determine the attitudes of individuals who applied to the family health center towards the COVID-19 vaccine. For these reasons, the aim of our study is to determine the attitudes of individuals who applied to the family health center towards the COVID-19 vaccine and the affecting factors.

Research questions:

1. What is the attitude towards the COVID-19 vaccine?
2. What are the factors affecting attitude towards the COVID-19 vaccine?

2. METHODS

2.1. Participants

This descriptive study was conducted between March and June 2021 in five family health centers located in the city center of Erzincan, which allowed the research. The population of the study consisted of individuals who applied to the family health center for any reason between the specified dates. The study was completed with 190 individuals who did not have serious mental disorders such as any physical disorder (hearing, speech disorder), mental disability and psychotic disorder. At the time of the study, 38 people who refused to participate in the study because they did not have time to participate were excluded from the study. At the beginning of the study, the participants were informed about the study and their informed consent was obtained verbally and in writing. The data were collected by the researcher by face-to-face interview method in the waiting rooms of family health centers by taking the necessary protective measures (social distance, mask) according to the pandemic conditions.

Dependent and Independent Variables of the Research: While creating the independent variable of the research, the introductory features specific to the participants; Attitudes Towards the COVID-19 Vaccine Scale scores constituted the dependent variable.

2.2. Data Collection Tools

The data of the study were collected in 10-15 minutes by face-to-face interview method using the "Personal Information Form", which includes socio-demographic characteristics, and the "Scale of Attitudes towards the COVID-19 Vaccine".

Personal Information Form: The information form prepared by the researchers consists of 24 questions describing the socio-demographic characteristics of individuals and questioning their thoughts on the COVID-19 vaccine.

Attitudes Towards the COVID-19 Vaccine (ATV-COVID-19): This scale was developed by Genis et al. (2020). It consists of 9 items and has two sub-dimensions (positive and negative attitudes). The statements in the scale are evaluated as "Strongly disagree (1)", "Disagree (2)", "Undecided (3)", "Agree (4)", "Strongly agree (5)". A value between 1-5 is obtained by dividing the total score obtained by summing the item scores in the scale sub-dimension by the number of items in that sub-dimension. High scores obtained from the positive attitude sub-dimension indicate that the attitude towards the vaccine is positive. It is calculated after the items in the negative attitude sub-dimension are reversed, and the high scores in this sub-dimension indicate that the negative attitude towards the vaccine is less. Reverse items are coded as 1-5, 2-4, 3-3, 4-2, 5-1. The Cronbach alpha value of the scale is 0.80 (14). In this study, the reliability coefficient of the scale was found to be 0.89.

2.3. Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) for Windows 22.0 software. Number, mean, standard deviation, minimum and maximum values were used to display the descriptive statistics of continuous numerical variables, and frequency and percentage distributions were used to display categorical variables. Evaluation of the normality of the variables was done with Kolmogorov Smirnov statistical test and it was found that they showed normal distribution. Differences between the groups were evaluated with a sample t-test and ANOVA independent of parametric tests. Statistical significance was accepted as $p< 0.05$.

2.4. Ethical Considerations

Erzincan Binali Yıldırım University Human Research Ethics Committee Permission (Dated 26/02/2021 and numbered 2021/03-30) and written permission from Erzincan Provincial Health Directorate (Dated 03/03/2021 and numbered 15872173-771) were obtained. Written or verbal consent was obtained from the individuals participating in the study, and the principles of informed consent and the Declaration of Helsinki were adhered to.

3. RESULTS

The mean age of the individuals participating in the research is 39.48±12.16 (minimum: 17, maximum: 69). It has been determined that 75.3% of the individuals are women, 82.1% are married, 73.1% are not working and 50.5% of them are equal to their income and expenses. It was determined that 68.4% of the individuals had not received influenza vaccination in the past, 98.5% had not refused any other recommended vaccine in the past, 60.5% had COVID-19 infection, 91.1% of the people in their immediate environment had COVID-19 infection, and 44.2% of them did not consider having their

children vaccinated against COVID-19. When individuals were asked about the precautions, they take to protect themselves from COVID-19 infection, 92.6% of them stated that they use masks (Table 1).

It was determined that 37.4% of the individuals had concerns about COVID-19 vaccines because they were afraid of the side effects of the vaccine (Figure 1).

Table 1. *Socio-demographic and Covid-19 vaccine characteristics of individuals*

		n	%
Sex	Female	143	75,3
	Male	47	24,7
Marital status	Married	156	82,1
	Single	34	17,9
Working status	Working	51	26,9
	Not working	139	73,1
Income status	Income less than expenses	62	32,6
	Income equal to expenses	96	50,5
	Income more than expenses	32	16,8
Have you had the flu vaccine in the past?	Yes	60	31,6
	No	130	68,4
Have you refused the recommended vaccine in the past?	Yes	20	10,5
	No	170	98,5
Were you diagnosed with COVID-19	Yes	115	60,5
	No	75	39,5
Has anyone in your close circle been diagnosed with COVID-19 infection?	Yes	173	91,1
	No	11	8,9
Are you considering getting your child vaccinated for COVID-19?	Yes	36	18,9
	No	84	44,2
	Undecided	28	14,7
Measures taken by ındividuals to protect themselves from COVID-19 ınfection *	Using a mask	176	92,6
	Washing hands	153	80,5
	Continuously ventilate the workplace and home environment	149	78,4
	Not meeting people, not going out	98	51,5
	Consuming healthy food, drinking water, resting, taking vitamin supplements	84	44,2
	Continue a normal life	3	1,5
Age	Mean: 39.48±12.16 years (minimum: 17, maksimum: 69)		

** Participants gave more than one answer*

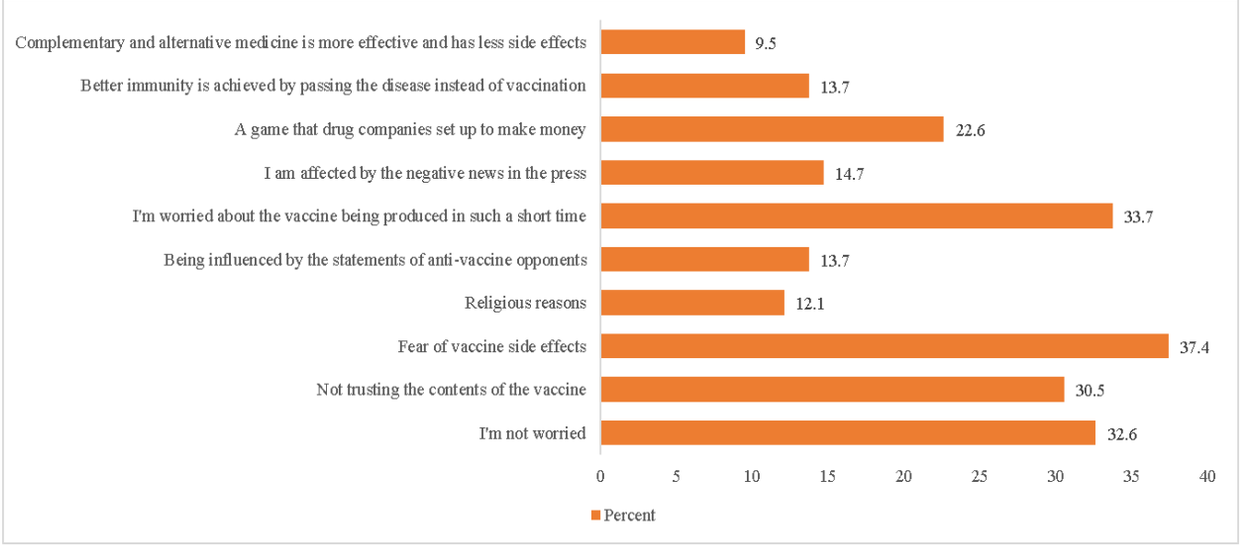

Figure 1. *Reasons for individuals' concerns about vaccination*
**Participants gave more than one answer*

A significant difference was determined between the number of children, educational status, family type, and chronic illness and the mean scores of the attitudes towards the COVID-19 vaccine scale. A significant difference was determined between the mean scores of the attitudes towards COVID-19 vaccine scale according to the individuals' thinking that the COVID-19 vaccine is beneficial for public health, being worried about getting COVID-19 infection, having the COVID-19 vaccine, the preferred type of vaccine, and following the information about the COVID-19 vaccine ($p<0.05$) (Table 2).

The values for the participants' attitudes towards the COVID-19 vaccine were 3.26±0.78 out of 5, 3.32±0.99 for the positive attitude sub-dimension, and 3.21±0.71 for the negative attitude sub-dimension (Table 3). When the mean scores of the scale are evaluated, it can be said that the positive attitudes of the participants towards the vaccine are above the average. As the scores obtained from the sub-dimension in negative attitudes increase, it can be said that the negative attitudes are below the average, since the level of negative attitudes decreases.

Table 2. *Distribution of ATV-COVID19 score averages according to socio-demographic and Covid-19 vaccine characteristics of individuals*

Thoughts on COVID-19		n	%	Positive Attitude score		Negative Attitude score		ATV-COVID 19 score	
				Mean±Sd	Test and p	Mean±Sd	Test and p	Mean±Sd	Test and p
Number of children	1 and 2 children	82	43.2	3.47±1.02	t*=2.56	3.32±0.78	t*=2.37	3.39±0.82	t*=2.655
	3 children and above	66	34.7	3.04±1.01	p=0.011	3.03±0.72	p=0.019	3.03±0.80	p=0.009
Educational level	Primary school	78	41.1	3.35±0.98		3.29±0.66		3.32±0.75	
	Secondary school	24	12.6	3.42±1.00	F**=5.05	3.37±0.76	F**=5.34	3.39±0.81	F**=5.859
	High school	52	27.4	2.95±0.85	p=0.002	2.89±0.64	p=0.001	2.91±0.67	p=0.001
	University	36	18.9	3.75±1.02		3.40±0.76		3.55±0.79	
Family type	Nuclear family	113	59.5	3.48±0.95	F**=3.651	3.30±0.69	F**=2.265	3.38±0.74	F**=3.435
	Extended family	63	33.2	3.11±1.01	p=0.028	3.08±0.74	p=0.107	3.09±0.80	p=0.034
	Broken family	14	7.4	3.03±0.97		3.05±0.77		3.04±0.81	
Chronic disease	Yes	49	25.8	3.07±0.97	t*=2.083	3.07±0.77	t*=1.593	3.07±0.82	t*=1.995
	No	141	74.2	3.41±0.98	p=0.039	3.26±0.69	p=0.113	3.33±0.75	p=0.048
Do you find the vaccination application necessary for public health?	Yes	161	84.7	3.57±0.82	t*=12.52	3.35±0.05	t*=7.13	3.45±0.66	t*=12.229
	No	29	15.3	1.93±0.61	p=0.000	2.43±0.52	p=0.000	2.21±0.46	p=0.000
Worried about contracting COVID-19 infection?	Very worried	77	40.5	3.50±0.91	F**=5.34	3.33±0.69	F**=3.44	3.40±0.76	F**=5.092
	Little worried	73	38.4	3.38±0.91	p=0.006	3.22±0.66	p=0.034	3.29±0.69	p=0.007
	Not worried	40	21.1	2.89±1.16		2.97±0.799		2.93±0.88	
Have you had the COVID-19 vaccine?	Yes	144	75.8	3.68±0.77	t*=11.34	3.40±0.64	t*=1.31	3.52±0.63	t*=2.135
	No	46	24.2	2.21±0.75	p=0.000	2.61±0.61	p=0.100	2.43±0.60	p=0.035
Which vaccine do you prefer?	Sinovac	29	15.3	3.86±0.74		3.46±0.66		3.64±0.63	
	Bion Tech	37	19.4	3.33±0.75	F**=23.63	3.19±0.57	F**=12.80	3.25±0.59	F**=21.794
	Local vaccine (Turcovac)	52	27.5	3.62±0.80	p=0.000	3.44±0.60	p=0.000	3.52±0.62	p=0.000
	Idon't mind	26	13.7	3.84±0.74		3.48±0.58		3.64±0.60	
Where do you follow the information about the COVID-19 vaccine?	TV	28	14.7	3.41±0.93		3.25±0.58		3.32±0.66	
	Internet/social media	65	34.2	3.66±0.86	F**=4.58	3.45±0.69	F**=4.75	3.54±0.71	F**=5.679
	Ministry of health website	92	48.5	3.07±1.02	p=0.003	3.03±0.72	p=0.003	3.04±0.80	p=0.001
	Don't follow	5	2.6	3.15±1.15		3.20±0.80		3.17±0.81	

**Student T-test; **ANOVA*

Table 3. *Distribution of Individuals' Attitudes Towards COVID-19 Vaccine Sub-Dimension Mean Scores*

	Min-Max	Mean±Sd
Positive Attitude	1-5	3.32±0.99
Negative Attitude	1-5	3.21±0.71
Total Scale	1-5	3.26±0.78

4. DISCUSSION

In this study, it was aimed to evaluate the attitudes of individuals who applied to the family health center towards the COVID-19 vaccine and the affecting factors. In this study, it was found that the participants had a positive attitude towards the vaccine. In the studies on this subject in the literature, it has been determined that individuals have positive opinions about the COVID-19 vaccine (15-17). The results of our study are similar to the literature. Vaccination provides the prevention of diseases that will prevent the progression of the disease (18).

The 2019 Novel Coronavirus (2019-nCoV), the causative agent of COVID-19, is transmitted through droplets and contact. In this study participants stated that they were protected from COVID-19 infection by using masks and washing their hands. In a study, it was determined that 97.3% of individuals wear masks and wash their hands (19). In the case of coughing and sneezing, infectious particles enter the body through the mouth and nose when the hands come into contact with the mouth, nose, eyes and face after contact with the particles on the surfaces. The way to prevent this type of contamination is to use face masks, practice hand hygiene and ensure the cleanliness of the surfaces (20).

In our study, individuals stated that they were worried about COVID-19 vaccines because they were afraid of the side effects of the vaccine. In a study conducted jointly in 7 European countries, it was reported that 55% of the participants were concerned about the possible side effects of the vaccine. The reasons for these concerns are mistrust of vaccines and the health system, lack of knowledge about vaccines, lack of information about vaccine-preventable diseases and misconceptions (21-23). Misinformation leading to vaccine refusal can put public health at risk instead of improving the current situation. In order to prevent this, individuals should be provided with appropriate education on the safety and efficacy of vaccines.

Another noteworthy finding in this study is that the participants stated that they do not plan to vaccinate their children against COVID-19. In contrast to this result, a study shows that parents are willing to have their children vaccinated against COVID-19 (24). In a different study, parents agree for their children to participate in a clinical trial of the COVID-19 vaccine (25). The results of our study differ from the literature. Since parents have the right to decide whether their children should be vaccinated, the mild or asymptomatic course of COVID-19 among children may have caused parents to be less anxious and reluctant to vaccinate their children (26).

In this study, a significant difference was found between educational status and the mean score of the Attitudes Towards COVID-19 Vaccination Scale. Studies have shown that those with a bachelor's degree or higher are more willing to be vaccinated, and there is a significant difference between education level and vaccination status (27,28). It can be thought that the awareness of individuals increases with education and this situation also affects the attitude of being vaccinated.

In this study, it was seen that people who have children and live with their nuclear family have a positive attitude towards the vaccine. The same results were found in the study of Kaplan et al (29). In another study, individuals stated that they wanted to be vaccinated against COVID-19 to protect themselves and their families (30). Accordingly, we can say that vaccination positively affects individuals' attitudes towards vaccination to protect their families from the negative effects of the pandemic.

In our study, it was determined that individuals with chronic diseases had a positive attitude towards the COVID-19 vaccine. In the study conducted by Williams et al., 86% of the elderly and individuals with chronic respiratory diseases stated that they wanted to be vaccinated against COVID-19 (31). We think that individuals with chronic diseases are more at risk for COVID-19 complications and therefore want to be vaccinated against COVID-19.

Most of the participants think that the vaccine against COVID-19 is necessary for public health and it is seen that individuals have positive attitudes towards the COVID-19 vaccine due to the concern of contracting COVID-19 infection. As a result of the studies, it has been observed that individuals who feel a certain level of anxiety about a subject reach a better solution about that subject (32,33). Head et al. found that the intention to receive SARSCoV-2 vaccine increased with increasing anxiety (34). Several factors contribute to vaccine-related concerns. These include perceived risks and benefits, certain religious beliefs, lack of knowledge and awareness levels of individuals (19).

It was determined that 75.8% of the individuals participating in our study had the COVID-19 vaccine. In a study conducted in the USA, 70% of adults and 71% of individuals in France stated that they wanted to be vaccinated against the COVID-19 pandemic (16,35). The acceptance of the vaccine by individuals varies according to culture, social class, time and human behavior (17).

It was found that the participants wanted to receive the Turcovac vaccine, which is a local vaccine. In addition, it was found that there was a significant difference between the mean scores of the attitude scale towards COVID-19 vaccine and the preferred vaccine. In a different study, the same conclusion was reached (24). Individuals' preference for the Turcovac vaccine shows that the positive opinion towards the local vaccine has increased.

It has been determined that the individuals participating in our study follow the information about the COVID-19 vaccine from the website of the Ministry of Health and have a positive attitude towards the COVID-19 vaccine. In a study, the sources of information that individuals trust the most about COVID-19 are the university/training-research hospitals in their province, the World Health Organization and the Ministry's Coronavirus Science Board, respectively (2). In another study, it was concluded that the participants who stated that they did not trust social media platforms such as Facebook, Twitter and Instagram had a positive attitude towards the vaccination (36). Government agencies and health professionals have made the most significant impact of information resources on individuals' attitudes towards vaccines. Trusting government agencies, health authorities and experts is critical in reducing vaccine resistance (37). People may find scientific information difficult to understand and may adopt rumors that are easier to understand but of unclear origin. Therefore, the explanations about the vaccine should be in a way that the public can understand and

institutions should carry out vaccine studies transparently (24).

5. CONCLUSION

As a result of this study, it was determined that individuals' attitudes towards COVID-19 vaccine were positive. They stated that they were protected from COVID-19 infection by using masks and washing their hands. It was determined that individuals thought that the COVID-19 vaccine was beneficial for public health, but the production of the vaccine in a very short time and fear of the side effects of the vaccine caused them to be concerned about the COVID-19 vaccine. Participants reported that they had been vaccinated against COVID-19 and that they did not plan to vaccinate their children against COVID-19. It was determined that the participants followed the information about the COVID-19 vaccine on the website of the Ministry of Health and wanted to receive the Turkovac vaccine, which is a local vaccine. We believe that it would be beneficial to inform individuals who experience anxiety and hesitation against the COVID-19 vaccine in the society, taking into account the reasons for fear and anxiety, and to take measures before the social and economic consequences increase.

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Clinical and Experimental Health Sciences

Skin Care and Colour Cosmetics in Patients with Sensitive Skin

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ABSTRACT

Objective: Sensitive skin is a dermatological condition that is frequently observed and causes discomfort in individuals. Therefore, individuals with sensitive skin must carefully choose skin care and makeup habits. Our aims in this study were to conduct the first sensitive skin prevalence study in Turkey and to identify skin care and makeup habits.

Methods: An online prospective controlled survey study was conducted among 1037 women. Participants with and without sensitive skin aged >18 years were included in the 3-month study.

Results: Of the participating women, 82.73% were found to have sensitive skin. The most sensitive part of the face was the cheek ($p < 0.001$). Therefore, blush was the least frequently used by individuals with sensitive skin ($p = 0.008$)

Conclusion: Sensitive skin is an important social and medical problem. The skin care and makeup habits of individuals with sensitive skin should be examined in detail and more help should be provided by dermatologists to these individuals.

Keywords: colour cosmetics, sensitive skin, skin care, skin barrier

1. INTRODUCTION

Symptomatic sensory findings such as burning, stinging, tightness, tingling, pain, and itching of the skin are defined as "sensitive skin" (1). These findings can be triggered by physical, thermal, or chemical stimuli that do not cause discomfort in normal healthy skin (2). Sensitive skin is a frequently observed and, therefore, important social problem. In the study of Misery et al., the European prevalence of sensitive skin was 38% (3), which increased to 70–80% in women when evaluated on the basis of their self-reported observations but was slightly lower (50–60%) in men (4).

Prevalence studies on sensitive skin have been conducted in many countries. In previous survey studies, participants described themselves as having "sensitive skin." While the prevalence rates of sensitive skin in European countries (3), the United States (5), Russia, and Brazil (6) are approximately 40%, similar rates were observed in Japan (7), whereas lower rates were found in China (8). Prevalence studies were conducted in various geographical locations, both sexes (9), and different age groups (10), comorbid facial skin diseases (11), hormonal changes (12), anatomical regions (genital, scalp, and cornea) (13-16), and triggering factors (4).

A survey study by a special interest group of the International Forum for the Study of Itch has clarified that triggering factors of sensitive skin, along with environmental factors (hot and cold weather, temperature changes, and sun exposure), include emotional stress and cosmetic and skin care products (17). Before "sensitive skin" was defined, Maibach defined similar clinical findings as cosmetic intolerance syndrome (18). Therefore, cosmetics and skin care products have been frequently examined as trigger factors of sensitive skin (19-21). Nevertheless, previous studies showed that participants were never questioned about which cosmetic products caused more discomfort and how they used skin care products and sunscreen.

While data from many countries on the prevalence of sensitive skin are available, no data have been obtained from studies in Turkey. Thus, our aim in this study was to investigate the prevalence of sensitive skin in Turkey and evaluate the cosmetic and skin care product and sunscreen use habits of participants with sensitive skin.

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2. METHODS

2.1. Study participants

This is a nationwide online prospective survey study among 1037 women aged >18 years that was conducted from July 2020 through September 2020 using the Google Forms platform through WhatsApp, e-mail, and social media. Participants who had neither facial dermatological disease, atopy, and allergy nor a familial history of atopy, allergy, and sensitive skin were excluded from the study. Participants were selected using the quota method (age and region). All the participants provided information through the online survey and permitted the use of this information in the study. Ethics committee approval was obtained from the University of Health Sciences Istanbul Training and Research Hospital Scientific Research and Publication Ethics Board (diary number: 2485, date: July 24, 2020).

2.2. Questionnaire

The questionnaire used in the study consisted of three parts. The first section collected demographic and clinical data. Section 2 was on skin care and makeup habits. The questionnaire was designed using the hybrid method (open-ended and multiple-choice questions). First, the participants were divided into the sensitive (slightly, moderate, and very) and non-sensitive skin groups based on self-assessments. Then, the first part of the questionnaire included age, place of residence (rural, urban, and metropole), marital status (single and married), Fitzpatrick skin type, and skin type (oily, dry, normal, and combination), in this order.

The second part of the questionnaire included the following: frequency of face washing (never, every day, 2 or 3 days/week, and 2 or 3 days/month), types of facial cleansing products used (open-label question), frequency of makeup use (never, every day, 2 or 3 days/week, and 2 or 3 days/month), frequency of cleansing face to remove makeup (never, and always), makeup products that can be used without causing skin sensitization on the face (foundation, blush, lipstick, eyeliner, mascara, perfume, and powder), frequency of using sunscreens and sunscreen cleansers (for both: never, every day, 2 or 3 days/week, and 2 or 3 days/month).

The third part consisted of questions on sensitivity localizations on the face (cheeks, forehead, nasolabial grooves, eyelids, chin, upper lip, and upper nose), duration of skin sensitization on the face (open-label question), course of skin sensitization on the face (episodic or constant), triggering factors of skin sensitization on the face (exposure to water, cold weather, hot weather, dry weather, temperature changes, air conditioning, air pollution, and the sun; consumption of spicy foods, coffee, tea, alcohol, and smoking; and emotional stress), seasons that trigger skin sensitization, rashes and scaling on the face with sensitization, and any visit to the dermatologist for skin sensitization within 1 year (dichotomous question).

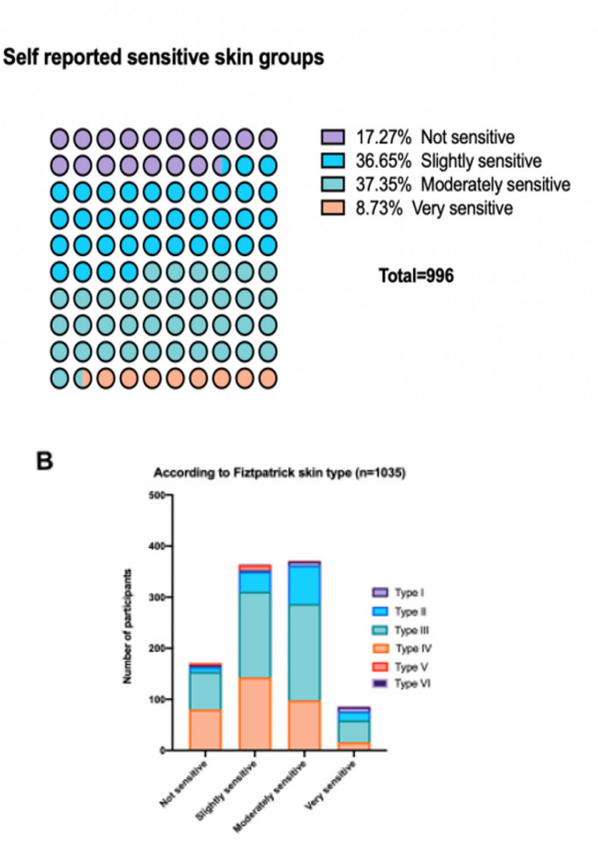
2.3. Statistical analysis

The SPSS 22.0 program for Windows was used for the statistical analysis. The descriptive statistics used included the numbers and percentages of categorical variables and numerical variables expressed as mean, standard deviation, minimum, maximum, and median values. The rates in the independent groups were compared using the chi-square test. The numerical variables had an abnormal distribution, so more than two groups were compared using the Kruskal-Wallis test. Subgroup analyses were performed with the Mann-Whitney *U* test and interpreted with Bonferroni correction. A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Demographic and Clinical Data

The mean age was 31.3 ± 11.6 years (range, 18–68 years) in the sensitive skin groups and 35.2 ± 11.2 years (range, 18–66) in the non-sensitive skin groups (p = 0.522). The distribution of the participants according to skin sensitivity is shown in Fig. 1a. The duration of skin sensitization on the face was 5.3 ± 2.9 years in the sensitive skin groups. Moreover, the discomfort felt on the faces of those who were “very sensitive” were longer-lasting than those in the other groups (p < 0.001). Sensitivity according to the Fitzpatrick skin type, and normal, combination, dry, and oily skin types are presented in Fig. 1b and 1c.



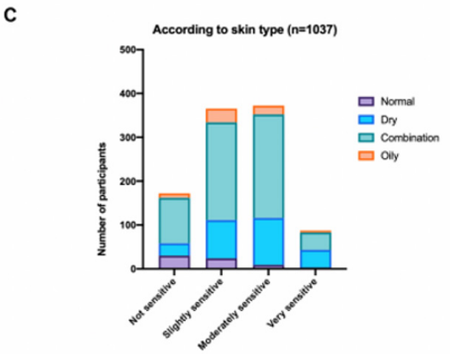


Figure 1. *Self-reported sensitive groups. Distribution of participants according to sensitivity (A). Of 172 (17.3%) participants are reported that not sensitive; 365(36.6%) slightly sensitive, 372(37.3%) moderately sensitive and 87(8.7%) very sensitive. Sensitivity according to Fitzpatrick skin type, and normal, combination, dry and oily skin (B and C) Those with Fitzpatrick skin type 1-2, combination skin and dry skin were significantly higher in moderately sensitive and very sensitive skin groups (p<0.001 for both) but Fitzpatrick skin type 4-5, normal skin and oily skin were significantly higher in slightly sensitive and not sensitive skin groups (p<0.001 for both).*

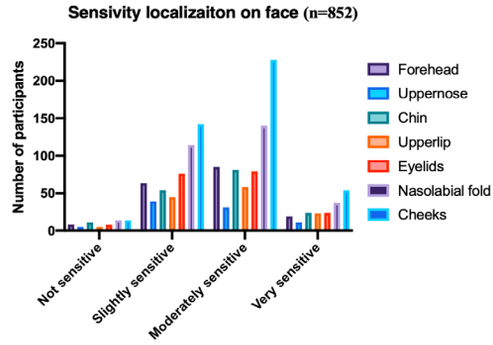


Figure 2. *Sensitivity localization on face (n=852)*

The chin (p = 0.030), upper lip (p = 0.006), and cheeks (p < 0.001) in the "very sensitive skin" group were more sensitive than the forehead (p = 0.216), upper nose (p = 0.754), eyelids (p = 0.274), and nasolabial folds (p = 0.060; Fig. 2). Only 12.4% of the participants in the group used topical facial cream, but most of them had very sensitive skin (p < 0.001). Antibiotic (p = 0.001), immunomodulation (p = 0.023), corticosteroid (p < 0.001), and hydroquinone creams (p = 0.007) were significantly more frequently used than acne creams in the "very sensitive skin" group (p = 0.362).

3.2. Skin Care and Makeup Habits

No statistically significant differences in the frequency of face washing (p = 0.055) and types of cleansing products (cleansing gel, soap, cleansing makeup remover wet wipes, and makeup cleansing oil and micellar water). Furthermore, the participants who were "not sensitive" and "slightly sensitive" frequently applied makeup every day (p = 0.015), and those who were "moderately sensitive" and "very sensitive" used blush significantly less frequently (p = 0.008). Most (67.1%) of the participants reported "definitely removing makeup," but no significant differences were found between the sensitive skin groups (p = 0.799). Daily use of sunscreen was more frequent among the "very sensitive" individuals than among the other groups (p = 0.043). Of our participants, 616 (60.6%) did not use a sunscreen facial cleanser. We found no significant differences between the sensitive skin groups (p = 0.367; Table 1).

Table 1. *Makeup habits of patients according to severity of sensitive skin*

	Total n (%)	Not Sensitive n (%)	Slightly Sensitive n (%)	Moderately Sensitive n (%)	Very Sensitive n (%)	p value
Frequency of doing makeup (n=1036)						
2-3 days/month	225(21.7)	33(19.2)	86(23.6)	80(21.5)	19(21.8)	
2-3 days / week	323(31.2)	54(31.4)	105(28.8)	122(32.8)	27(31.0)	
Everyday	275(26.5)	60(34.9)	106(29.1)	78(21.0)	19(21.8)	**0.015**
None	84(8.1)	11(6.4)	21(5.8)	37(9.9)	12(13.8)	
2-3 days /year	**129(12.5)**	14(8.1)	46(17.6)	55(14.8)	10(11.5)	
Cleaning of makeup (n=1002)						
Sometimes I clean, sometimes I don't	303(30.2)	48(28.7)	112(31.2)	108(30.3)	22(26.8)	
Definitely clean	670(66.9)	112(67.1)	239(66.6)	238(66.9)	56(68.3)	0.799
Never clean	29(2.9)	7(4.2)	8(2.2)	10(2.8)	4(4.9)	
Used Makeup products (n=1037)						
Foundation	336(32.4)	59(34.3)	122(33.4)	114(30.6)	28(32.2)	0.805
Blush	346(33.4)	73(42.4)	127(34.8)	108(29.0)	23(26.4)	**0.008**
Lipstick	541(52.2)	89(51.7)	191(52.3)	196(52.7)	43(49.4)	0.957
Eyeliner	567(54.7)	106(61.6)	194(53.2)	191(51.3)	49(56.3)	0.147
Mascara	647(62.4)	101(58.7)	241(66.0)	217(58.3)	56(64.4)	0.134
Parfume	602(58.1)	104(60.5)	214(58.6)	215(57.8)	46(52.9)	0.699
Powder	76(7.3)	12(7.0)	31(8.5)	22(5.9)	8(9.2)	0.512
Use of sunscreen (n=1036)						
2-3 days/month	139(13.4)	20(11.6)	47(12.9)	53(14.2)	10(11.6)	
2-3 days / week	229(22.1)	27(15.7)	87(23.8)	95(25.5)	16(18.6)	
Everyday	145(14.0)	73(42.4)	149(40.8)	161(43.3)	44(51.2)	**0.043**
None	446(43.1)	18(10.5)	24(6.6)	24(6.5)	8(9.3)	
2-3 days /year	77(7.4)	34(19.8)	58(15.9)	39(10.5)	8(9.3)	
Cleaning of sunscreen (n=1017)	401(39.4)	57(34.1)	142(39.3)	147(40.4)	39(44.8)	0.367

3.3. Triggering Factors

No significant differences in triggering factors were found between the sensitivity groups in our study. Other triggering factors are shown in Fig. 3.

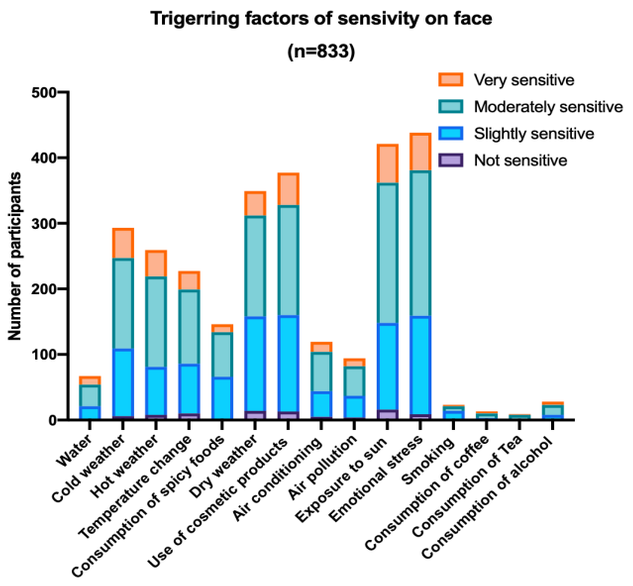


Figure 3. *Sensitivity according to triggering factors (n=833). There was a statistically significant difference in terms of water(p=0.015), cold weather p (<0.001), hot weather (p<0.001), temperature changes (p=0.018), consumption of spicy food (p=0.024), use of cosmetic products (p=0.006), exposure to sun (p<0.001) and emotional stress (p<0.001).*

4. DISCUSSION

The prevalence of sensitive skin and its triggering factors have been investigated in many studies in the last decade. As a result, the importance of sensitive skin as a dermatological disease has been recognized. The prevalence rate of sensitive skin varies according to geographical region, with moderately sensitive skin accounting for 44% of cases in Europe, 38% in the United States, 35% in North America, and 31% in Asia. In our study, the prevalence of moderately sensitive skin is nearly similar to the US and North American data (22).

To our knowledge, our study is the first to investigate skin care and makeup habits in individuals with sensitive skin. Important results that may show social differences were also obtained. Whereas individuals with oily-combination skin type were found to be affected more by skin care and makeup habits in a study conducted in patients with rosacea(23), individuals with a dry-combination skin type were more affected in our study with individuals with sensitive skin.

In the rosacea study, taking into account the affected areas, the cause of rosacea was related to excess sebum secretion, whereas in our study, the most affected areas were the chin, upper lip, and cheek, which have dense nerve fibers, sensitive skin may be compatible with the pathophysiology (24).

Basic skin care is evaluated using a three-step approach as follows: cleansing, moisturizing, and sun protection (25). However, little is known about the benefits and clinical significance of skin care to dermatological diseases. Excessive face cleansing and washing, using cleansing gels with high surfactant contents and soaps with high pH levels may damage the skin barrier (26). However, as no significant difference was found between the sensitivity groups in terms of cleaning frequency and cleaning products used, we can infer that the patients with sensitive skin in our study may have learned to pay attention to these features over time while applying basic skin care.

Makeup products are often composed of a complex blend of various inert materials, as well as perfumes, emulsifiers, sunscreens, pigments, metals, resins, and preservatives. Such complex products can trigger skin sensitization. Individuals with very sensitive skin seem to avoid applying makeup. Their use of blush may also be infrequent owing to the erythematous appearance that develops in the cheek area, and published case reports of contact dermatitis warn against the use of blush cosmetics containing carmine (27, 28), which may cause discomfort in individuals with sensitive skin.

Sun protection is important in the management of dermatological disorders. In our study, the participants with sensitive skin reported that their feeling of discomfort increased during sun exposure. The use of sunscreen was frequent in those with sensitive skin. However, awareness that sunscreens can also cause skin sensitization is important (29). In our study, the participants with sensitive skin used sunscreens but not routinely and never used sunscreen cleansers.

While sensitive skin was first shown to be the same entity as or a subgroup of rosacea in a previous study (30), it can now be distinguished from rosacea through diagnostic methods (e.g., reflectance confocal microscopy) (30). In our study, sensitive skin was frequently observed in the patients with rosacea, but the prevalence rates of allergic contact and photocontact dermatitis were also high in the patients with sensitive skin, probably due to the use of makeup and skin care products or skin care habits (31).

Limitations of the study

The limitations of this study include the comparison of different products for the evaluation of skin care and makeup habits. In future studies, the same products should be used to better evaluate the severity of skin sensitization.

5. CONCLUSIONS

The etiological and triggering factors of sensitive skin are still unclear, and the pathogenesis of sensitive skin has not been fully elucidated yet. Finding many products that will not cause skin sensitization by trying each of them is difficult for persons with sensitive skin. This is because the development of epidermal barrier dysfunction can increase the risk of skin

sensitization and those with sensitive skin should be given recommendations about skin care and makeup products and habits.

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Clinical and Experimental Health Sciences

Assessment of the Chronotypes of Nurses Working in Shifts and the Quality of Their Lives

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ABSTRACT

Objective: This research was conducted to identify the relationship between the chronotypes of nurses working in shifts and the quality of their lives.

Methods: The research sample that was designed as a descriptive study comprised 267 nurses working in shifts. The research data were collected with the descriptive survey form, the Morningness–Eveningness Questionnaire, and the Short-Form Health Survey (SF-36).

Results: As per the breakdown of the nurses by chronotype, 68.9% of the nurses were intermediate-type (n=184), 15.7% of the nurses were morning-type (n=42), and 15.4% of the nurses were evening-type (n=41). The evening-type nurses had a higher number of night shifts than the morning-type nurses ($p<0.05$). It was found that the evening-type nurses had a lower quality of life than the morning-type and intermediate-type nurses ($p<0.05$).

Conclusion: In conclusion, it was ascertained that the evening-type nurses working in shifts had a lower quality of life. Nurses' shifts can be organized by taking into consideration their chronotypes.

Keywords: Circadian Rhythm, Naps During Night Shifts, Shift Nurse, Night Work, Shift Worker

1. INTRODUCTION

Due to the 24-hour services offered uninterruptedly in healthcare facilities, the health staff working in this sector are obliged to work in shifts. Particularly the nurses work alternately in different shift hours. The person's circadian rhythm is affected as a consequence of being assigned to duties performed in shifts that alternate day and night and last long hours, and the degree of this effect can change as per personal characteristics (1–3). The circadian rhythm disorders affect the individuals physically and socially (4,5).

The circadian rhythm refers to the physiological and biological changes occurring in the organism in 24 hours. The circadian rhythm is the main determinant of the sleep-wake cycle in individuals. The chronotype refers to the individual differences in the circadian rhythm. The individuals can be categorized into three different circadian types, namely, morning-type, intermediate-type, and evening-type. The morning-type individuals wake up and go to sleep early and perform better in the early hours of the morning. The evening-type individuals go to sleep late and have difficulty in waking up early and, in general, they perform better physically and mentally in the afternoon (2,4,6). In terms of the sleep-wake patterns and performance, the intermediate-type individuals have traits somewhere in the middle (6).

The employment of an evening-type individual on the morning shift or the employment of a morning-type individual on the night shift gives rise to circadian misalignment (7). In connection with working in shifts, patterns of sleep duration and timing change, and this, in turn, brings about misalignment in social life and work duration. Defined as social jetlag, this situation can lead to the development of chronic health problems and a decrease in the quality of life (8–10).

The quality of life is a multifaceted concept and serves as a crucial factor to understand the individual's well-being that includes the physical, mental, and social aspects of life. Moreover, examining the associated factors is of importance as it accounts for the physical, psychological, and social support needed by human beings while performing daily life activities as per how they perceive their health (11). Particularly, the individuals that are affected by the changes in their work hours and have work patterns misaligned with their circadian rhythms have difficulty sustaining their lives normally and become more physically and psychosocially sensitive groups (5,8,12).

Numerous studies performed up to the present with the participation of nurses analyzed the explicit effect of chronotype

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on the sleep pattern, the quality of life (12–14), the physical activities (14), the mood (15), and the shift work disorder.

In the relevant literature, there are studies indicating that working in shifts affected the quality of nurses' lives. However, it was discerned that these studies did not adequately address the effect of nurses' chronotypes on the quality of their lives (16,17). Identifying the factors affecting the nurses working in shifts and their modifiable characteristics is important to improving the quality of their lives and hence, enhancing labour productivity. This research was conducted to find out the relationship between the chronotypes of nurses working in shifts and the quality of their lives.

2. METHOD

2.1. Study design and procedures

This is a descriptive study. The research was conducted on 430 nurses who worked at a training and research hospital in Istanbul province of Turkey in October-December 2020. The sample size was found to be [Ntpq/d2(N-1) + t2pq] 203 with a probability of 50%, 95% confidence interval and 0.05 deviation using the sampling method with a known population. Nurses worked in two shifts, one from 08:00 to 16:00 and the other from 16:00 to 08:00, at the hospital where the research data were collected. However, as 82 nurses who did not work in shifts were not included in the research sample, the research proceeded with 348 nurses. Besides, 22 nurses who did not volunteer to participate in the research, 46 nurses who were on a leave of absence for a variety of reasons (childbirth, sickness, and annual leave), and 13 nurses who submitted forms with missing data were also excluded from the sample. Thus, the analysis was based on data collected from 267 nurses (76.7% of the sample). After the nurses consented to participate in the research upon being informed about the study, the forms were delivered to the nurses, and on the next day, the nurses submitted the forms back.

2.2. Measures

In the collection of research data, the descriptive survey form, the Morningness–Eveningness Questionnaire (MEQ), and the Short-Form Health Survey (SF-36) were used.

Designed to gather sociodemographic data, the descriptive form had questions addressing nurse's age, gender, marital status, the service unit where the nurse worked, duration of work, number of night shifts per month (for the last month), state of sleeping before and during the shift, and effects of shift work on the nurse (12–16).

The MEQ is utilized for self-evaluation to identify the morning-type individuals and evening-type individuals as per each individual's circadian rhythm. It examines the individuals' physical and psychological performance within 24 hours and identifies the period when the performance is at its peak. Designed as a four-point Likert-type scale, the MEQ has 19 questions. The minimum and maximum scores to be obtained from the MEQ are successively 16 and 86 points, and the individuals are categorized as evening-types (16-41 points), intermediate-types (42-58 points), and morning-types (59-86 points) based on their scores. As per the reliability and validity study performed in Turkish, Cronbach's Alpha coefficient was found as 0.81 for the MEQ (18). In this study, Cronbach's Alpha coefficient was 0.68.

Designed as a Likert-type scale, the SF-36 evaluates two main components, namely, physical component summary and mental component summary, and comprises 36 questions. The two aforementioned main components have a total of eight sub-scales. The scores to be obtained from the main components and the sub-scales range between 0-100. A high score obtained from the SF-36 refers to high health-related quality of life. As per the reliability and validity study performed in Turkish, Cronbach's Alpha coefficient was found for the physical and mental components summary as 0.87 and 0.89, respectively (19). In this study, the physical component summary of Cronbach's Alpha coefficient was 0.70, and the component summary of Cronbach's Alpha coefficient was 0.73.

2.3. Ethical Aspect of the Research

For the research conducted in conformity with the principles of the Helsinki Declaration, the ethical endorsement was obtained from the ethics committee (Endorsement date: 08/10/2020, No: 46418926-050.01.0434981). After the nurses consented in written format to participate in the study upon being verbally informed about the research, the forms were delivered to them to collect the research data.

2.4. Statistical analysis

The research data were analyzed with SPSS 25.0 (IBM, Armonk, NY, USA). The measures of Skewness and Kurtosis were utilized to test whether the scores obtained from the measures were normally distributed, and in this regard, the acceptable range was set as (-1, +1). Descriptive statistics, chi-square test, one-way analysis of variance (ANOVA) and Tukey HSD test were used in the statistical analysis. The chi-square test was used to analyze categorical variables, one-way ANOVA was used to compare more than two independent groups and the Tukey HSD test was used to find between-group significance. The statistical significance was identified if the p-value was below 0.05.

3.RESULTS

The mean age of the nurses was 30.08±6.34 years. Of the nurses, 85.4% were female, and 62.9% were single. Upon the review of the nurses' education levels, it is discerned that 71.2% held bachelor's degrees, 15% held master's degrees, 9% held associate degrees, and 4.9% were high school graduates (Table 1). Of the nurses, 18% had chronic diseases, 12% regularly used medications, and 23.6% smoked. Of the nurses, 63.3% told that they slept before the night shift, only 14.6% reported that they could nap during the night shift, and 19.9% said that they were late to work once or more for the last month due to falling asleep.

Table 1. *Demographic variables of nurses*

Demographic variables	N	%
Age (year)*	30.08±6.34 (21-49)	
Gender		
Female	228	85.4
Male	39	14.6
Marital status		
Married	99	37.1
Single (or divorced)	168	62.9
Education		
College	13	4.9
Vocational school	24	9.0
Undergraduate	190	71.2
Postgraduate/PhD	40	15.0
Chronic diseases		
Yes	48	18.0
No	219	82.0
Smoking		
Yes	63	23.6
No	204	76.4

**(Mean ± standard deviation; min-max)*

Of the nurses, 68.9% were intermediate-type (n=184), 15.7% were morning-type (n=42), and 15.4% were evening-type (n=41). It was found that the morning-type nurses had a higher mean age than intermediate-type and evening-type nurses (p<0.05). It was ascertained that there was a statistically significant relationship between marital status and nurses' chronotypes (p<0.05) (Table 2).

Table 2. *Relationship between socio-demographic characteristics and chronotypes*

Demographic variables	Chronotype			Statistic	p
	M-types n (%)	I-types n (%)	E-types n (%)		
Age (year)*	32.79±7.07[a]	29.98±6.22[b]	27.73±5.10[c]	F:6.950	**0.001***
Gender					
Female	36 (15.8)	162 (71.1)	30 (13.2)	χ^2:5.950	0.051
Male	6 (15.4)	22 (56.4)	11 (28.2)		
Marital status					
Married	23 (23.2)	61 (61.6)	15 (15.2)	χ^2:6.849	**0.033**
Single (or divorced)	19 (11.3)	123 (73.2)	26 (15.5)		
Education					
College	1 (7.7)	7 (53.8)	5 (38.5)	χ^2:9.666	0.139
Vocational school	3 (12.5)	19 (79.2)	2 (8.3)		
Undergraduate	28 (14.7)	134 (70.5)	28 (14.7)		
Postgraduate/PhD	10 (25.0)	24 (60.0)	6 (15.0)		
Chronic diseases					
Yes	6 (12.5)	33 (68.8)	9 (18.8)	χ^2:0.827	0.661
No	36 (16.4)	151 (68.9)	32 (14.6)		

** Significance between a – b; a – c (Tukey HSD test)*
F: One-way ANOVA; χ2: Chi-squared test

It was discerned that the morning-type nurses had a higher mean of total work duration in years than evening-type and intermediate-type nurses, and this difference was statistically significant (p<0.05). Besides, there was a statistically significant difference in the number of evening-type and morning-type nurses' monthly night shifts, and the evening-type nurses had a larger number of night shifts per month than morning-type nurses (p<0.05). Furthermore, there was a statistically significant relationship between the state of sleeping during the day before the night shift and nurses' chronotypes (p<0.05) (Table 3).

Table 3. *The relationship between nurses' weekly working hours, number of night shifts, sleeping before and during night shifts and chronotype*

	Chronotype				
	M-types Mean±SD	I-types Mean±SD	E-types Mean±SD	Statistic	p
Experience as a nurse (years)	**10.79±7.68[a]**	**7.77±6.89[b]**	**5.41±5.09[c]**	**F:6.598**	**0.002***
Working hours per week	**45.07±5.00**	**45.65±5.27**	**45.24±5.50[c]**	**F:0.264**	**0768**
Night shifts per month (days)	**5.95±3.07[a]**	**6.84±2.90[b]**	**7.59±3.04[c]**	**F:3.185**	**0.043****
	n (%)	**n (%)**	**n (%)**		
Department					
Services	**27 (20.6)**	**87 (66.4)**	**17 (13.0)**	**χ^2:5.075**	**0.079**
Intensive care unit	**15 (11.0)**	**97 (71.3)**	**24 (17.6)**		
Sleep before night shift					
Yes	**22 (13.0)**	**114 (67.5)**	**33 (19.5)**	**χ^2:7.512**	**0.023**
No	**20 (20.4)**	**70 (71.4)**	**8 (8.2)**		
Nap during night shift					
Yes	**6 (13.3)**	**35 (77.8)**	**4 (8.9)**	**χ^2:2.289**	**0.318**
No	**36 (16.2)**	**149 (67.1)**	**37 (16.7)**		
Being late to work due to falling asleep					
Yes	**9 (17.0)**	**37 (69.8)**	**7 (13.2)**	**χ^2:0.272**	**0.873**
No	**33 (15.4)**	**147 (68.7)**	**34 (15.9)**		

** Significance between a – b (Tukey HSD test)*
*** Significance between a – c (Tukey HSD test)*
F: One-way ANOVA; χ2: Chi-squared test

It was identified that the evening-type nurses obtained lower means of scores from the SF-36 mental component and SF-36 social functioning sub-scale than the morning-type

nurses; also, they obtained lower means of scores from the SF-36 physical main component, physical functioning, physical role functioning, and vitality sub-scales than both morning-type and intermediate-type nurses, all these differences were statistically significant (Table 4).

Table 4. *Comparison of nurses' chronotypes and quality of life*

	Chronotype				
	M-types Mean±SD	I-types Mean±SD	E-types Mean±SD	Statistics	p
Physical component	67.51±13.10[a]	62.41±14.37[b]	55.39±18.22[c]	F:7.029	**0.001***
Mental component	64.53±16.29[a]	58.44±14.41[b]	55.63±18.15[c]	F:3.848	**0.023****
Physical functioning	85.48±19.34[a]	80.97±19.90[b]	66.46±20.25[c]	F:0.654	**0.000***
Physical role functioning	83.33±27.35[a]	74.32±35.11[b]	57.92±30.84[c]	F:1.925	**0.001***
Bodily pain	55.05±24.92	53.60±20.76	54.02±28.39	F:0.071	0.931
Vitality	55.47±17.90[a]	48.17±16.76[b]	40.12±24.17[c]	F:0.918	**0.001***
General health perception	58.21±18.17	55.00±16.77	58.41±20.80	F:1.008	0.366
Social functioning	64.88±22.29[a]	57.47±20.29[b]	49.69±23.46[c]	F:1.769	**0.005****
Emotional role functioning	83.33±31.45	75.72±33.82	74.79±33.14	F:0.975	0.379
Mental health	60.76±18.89	55.82±15.11	55.12±18.55	F:1.737	0.178

** Significance between a – c; b – c (Tukey HSD test)*
*** Significance between a – c (Tukey HSD test)*
F: One-way ANOVA

4.DISCUSSION

In general, nurses working in shifts are awake and work actively in the period when they are supposed to sleep as per their circadian rhythms (1,2). This study was performed to identify the relationship between the chronotypes of nurses working in shifts and the quality of their lives.

It is set forth that age was a significant factor associated with chronotype and had effects on the chronotype categorization and the wake-up time (20). As adults age increases, they become more inclined to be the morning-type (21–23). Likewise, as per the results of this current study, it was found that the morning-type nurses had a higher mean age than evening-type and intermediate-type nurses.

In the current study, it was ascertained that there was a statistically significant relationship between marital status and chronotype. Moreover, it was discerned that a larger percentage of married and a smaller percentage of single nurses were morning-type. In a study performed in a different culture, no statistically significant difference was identified in nurses' chronotypes as per marital status. In this respect, it is considered that the relationship found between marital status and chronotype in this current study may have been linked with married nurses' family roles and responsibilities and the fact that the married nurses had a more regular life (8).

Upon the review of the relationship between work duration in years and the chronotype in the current study, it was identified that the participants who worked for long years as nurses were morning-type. It was put forward that the senior nurses could tolerate the morning shift better than the junior nurses, and senior nurses' sleep patterns were affected less by the morning shift (24,25). Alongside this result, it is predicted that, as the inclination to be morning-type moves in tandem with age, these nurses tend to be morning-type (26,27).

In the current research, it was found that the evening-type nurses had a higher mean number of night shifts. Likewise, the study by Vedaa et al. demonstrated that the evening-type nurses had more night shifts for the last two years (28). The morning-types prefer waking up early and being awake during the early hours of the day. While the evening-types prefer going to sleep late, they have a better work performance in the afternoon and evening (13). Therefore, it can be said that the evening-types were less well-aligned with morning shifts and better aligned with night shifts (15,29).

As the nurses are supposed to stay awake for a long time during the night shift, they try to compensate for this period of sleeplessness by sleeping during the day. While the morning-types prefer going to bed early to have enough sleep before the morning shift, the intermediate-types and evening-types have difficulty in going to sleep before morning shifts as they are more inclined to go to sleep late at night (4). In general, the evening-type individuals go to sleep late at night and wake up late in the morning (5) whereas the morning-type individuals have difficulty in going to sleep during the day (4). In the current study, it was ascertained that a higher percentage of evening-type nurses working in shifts slept during the day before the night shift. Likewise, in a study conducted on intensive care nurses, it was discerned that the morning-type nurses slept for a shorter period before the night shift than the evening-type nurses (8). It is considered that a higher percentage of evening-type nurses working in shifts slept during the day before the night shift in this current study because the duration of the night shift was long (16:00-8:00) at the hospital where the research data were collected and evening-type nurses had more night shifts.

In the current study, it was identified that there was no statistically significant relationship between napping during the night shift and the nurses' chronotypes. In a similar vein to this current study, a previous study did not find a relationship between napping at night shift and chronotype (8) whereas another study emphasized that napping at night shift would contribute to the sustainability of the circadian rhythms of nurses having rapid-rotation shift work (30). However, it can be considered that a large part of the nurses participating in this current study did not nap during the night shift due to the institutional policies and the high volume of workload.

In general, the individual's physical and mental performance varies throughout the day depending on their chronotypes. As the nurses work in shifts, they have irregular sleep and wake patterns. By sleeping before the night shift, the nurses want not to suffer from sleeplessness at night shift, and after the night shift, they want to sleep and rest. Working in shifts and the long work hours affect the nurses' daily lives and the quality of their lives together with their circadian rhythms. The current study found that the morning-type nurses obtained higher means of scores from the SF-36 and its physical and mental main components. Urban et al. ascertained that the evening-type nurses obtained a lower mean of scores from the SF-36 physical functioning sub-scale, and the morning-type nurses obtained a higher mean of scores from the SF-36 physical functioning and social functioning sub-scales (5). There are also studies indicating that working in shifts negatively affected the quality of nurses' lives. Besides, certain studies assert that the evening-type nurses were more sensitive to emotional disturbances (12), their physical activities decreased, and the nurses working in shifts that were misaligned with their chronotypes were more affected by the social jetlag (4,8). In the current study, it is considered that, as the nurses worked for long hours and in shifts that were misaligned with their chronotypes, the quality of their lives was negatively affected.

The limitations of the current study were that the study was performed only in one center, a high number of nurses were on leave of absence for various reasons, and the number of female nurses was relatively high in the research sample. Also, since the study is a survey study, the results of the research are based on the reports of the individual.

5.CONCLUSION

In the study, it was found that as the age and work duration in years went up, there was a higher inclination to be morning-type, and a higher percentage of evening-type nurses working in shifts slept during the day before the night shift. They had a lower quality of life.

In this context, making an assessment of individuals' chronotypes can be identified their circadian alignment with shift work, particularly the night shifts. Thus, employing nurses in appropriate shifts may contribute to their ability to maintain their quality of life at an optimal level by increasing their adaptation to shifts. Moreover, performing further studies with more participants working in shifts is recommended.

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Acquisition of data for the study: AO, GA
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Clinical and Experimental Health Sciences

The Effects of Petroleum Jelly Perineum Massage on Episiotomy and Perineum Healing in the 1st Stage of Labour: A Randomised Controlled Trial

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ABSTRACT

Objective: The aim of this study was to investigate the effect of perineal massage on petroleum jelly episiotomy and perineal healing in nulliparous women.

Method: The single-blind randomized controlled trial was conducted on 90 nulliparous women. In the interventions group, perineal massage was performed with petroleum jelly and without petroleum jelly from the active phase of labor. Control group no interventions were performed.

Results: Perineal massage with petroleum jelly in the intervention group significantly decreased the rate of episiotomies (40%) compared to another group ($p<0.01$). In the control group, the mean labor time was 10 hours 52 min, while in the perineal massage group with petroleum jelly, this duration was determined to be 9 hours 32 min ($p<0.01$). The rates of redness (30%), edema (13.3%), and ecchymosis (3.3%) were statistically significantly higher in the control group ($p<0.01$).

Conclusion: Perineal massage with petroleum jelly could be suggested as an effective method to decrease the rate of episiotomy and labor time in vaginal labor.

Keywords: Perineal massage, episiotomy, perineal healing, nulliparity, petroleum jelly

1. INTRODUCTION

Perineal trauma caused by birth is defined as spontaneous or episiotomy-induced damage in the genital area during childbirth. Spontaneous perineal traumas are often classified by the authorities as follows. In this classification;

1st-degree tear; rupture of the perineal skin along with the vaginal epithelium;

2nd-degree tear; rupture of the perineal muscle (the anus sphincter is intact),

3rd-degree tear: the injury includes the complex of the anus sphincter,

4th-degree tear: complex rupture of the anus sphincter and this rupture is recognized as one extending to the rectal mucosa (1,2).

Listed in the group of non-spontaneous trauma, episiotomy involves the same muscle and tissue as a 2nd-degree tear. But in countries where episiotomy is frequently performed, it is reported that the perineal trauma rate is higher (3,4). According to current statistics, 65% of multiparas and almost all nulliparous (over 95%) are routinely performed episiotomies in our country (4). Whereas, according to WHO's Safe Motherhood Report, there is no reliable evidence that routine use of episiotomy is beneficial (5).

Episiotomy leads to such complications as postpartum perineal pain, dyspareunia, pain and infection in the perineal region, risk of contamination with urine and stool, pain and prolongation of the healing process, the relationship between mother and infant, and postpartum sexual life being affected adversely (6,7). Furthermore, the repair of episiotomy prevents skin-to-skin baby contact and early breastfeeding in the first half hour, which is highlighted as the golden time according to SOGC (8,9). Therefore, it is recommended to limit the routine use of episiotomy to reduce non-spontaneous perineal traumas. According to WHO, episiotomy is an initiative that should not be applied unless it is mandatory, causes more damage than its benefits, and should be used only on limited indications and not exceed 20% (5).

It is reported that perineal massage, kegel exercises, yoga, and plates in childbirth that are performed at any time starting from the gestational week 35 until the labor will reduce spontaneous/ non-spontaneous perineal trauma and episiotomy. One of the frequently used methods of reducing perineal trauma in childbirth is perineal massage, and important studies on its effectiveness are also available (4,10). Inconsistent studies have been reported on perineal massage techniques, timing, and effect (11,12). It appears

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that more research is needed to examine the effect of perineal massage on perineal area injuries during labor.

Petroleum jelly (Ministry of Health product) has the feature of locking moisture and accelerating the natural healing process of the skin, helping to heal from the inside, and creating an impermeable barrier between the cells on dry or damaged skin. Its occlusive function allows it to protect dry skin, cracked skin, minor cuts, and scraps (13). It is anticipated that petroleum jelly can be used for perineal massage due to its intense lubricity effect, immediate adaptation to body temperature, and safety. Perineal massage during childbirth is cheap and safely can be done. To the best of our knowledge, a limited study was conducted on the effect of petroleum jelly massage on perineal trauma. This study was designed to examine the effect of perineal massage with petroleum jelly on episiotomy and perineal healing in nulliparous women in active stages of labor. To our knowledge, only a limited number of studies have examined the effect of perineal massage with petroleum jelly during the first stage of labor on the second stage of labor. This study was designed to examine the effect of perineal massage with petroleum jelly on episiotomy and perineal healing in nulliparous women in the active stage of labor.

2. METHODS

2.1. Design

This single-blind randomized clinical trial was executed from November 2018 to April 2019. In this study, participants in the experimental group and the massage practitioner were aware of which group they were in due to the nature of the study. However, the physician who managed the childbirth did not know which group the participants were in. REEDA scores and perineal tears were assessed by physicians. Furthermore, experimental and control groups were coded to eliminate statistician bias. The sample size was estimated at 30 participants in each group considering a 95% confidence interval ($\alpha = 0.05$) and power of 90% ($\beta = 0.1$). This study was designed to determine the effect of perineal massage performed using petroleum jelly from the first stage of childbirth (active phase) until its second phase on perineal trauma and the level of perineal healing.

Inclusion criteria

In the inclusion criteria, homogeneity was ensured by excluding any woman who had a risk in her pregnancy and who was predicted to have a risk in her labor. Inclusion criteria were to become a volunteer, not to any risk in pregnancy (bleeding, hypertension, diabetes, excessive weight gain, etc) and labor (EMR, pelvic measurement, pain dysfunction, fetal distress, psychic problems ETC), to be in a singleton pregnancy, to be at weeks 37-40 of the pregnancy.

Exclusion criteria

Those with a birth weight of more than 4000 g (according to ultrasound calculation) and those with HPV and similar infections were excluded from the study.

2.2.Setting and Sample

The research was executed at Maternity State Hospital at Arnavutköy. All participants were informed about the aim of the study, and the necessary written consent forms were obtained. In the study conducted by CONSORT 2010 manual (14), randomization was created using the Random org site (https://www.randomizer.org/) (15) (Figure 1). The flow of the research is presented in Figure 2.

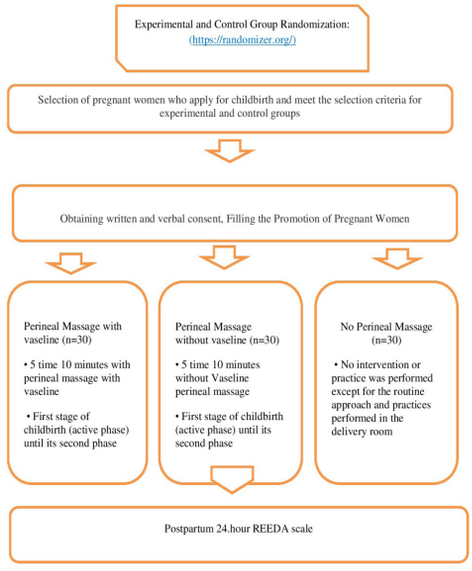

Figure 1. *Research flow chart*

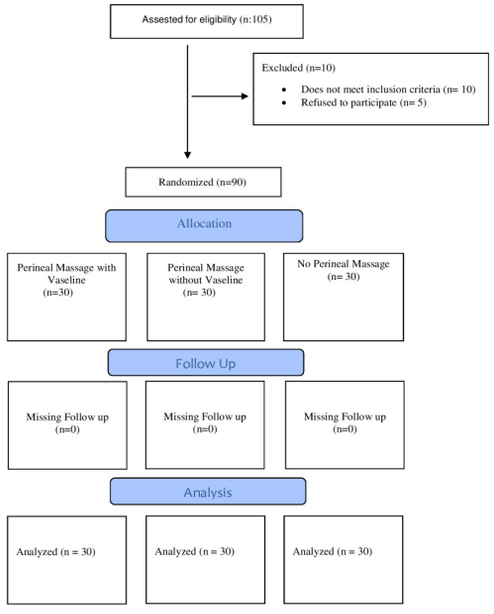

Figure 2. *Consort flow chart*

2.3.Ethical Consideration

Approval of the Marmara University Faculty of Medicine Ethics Committee (02.11.2018/ 09.2018.709) was obtained for the study.

2.4.Measurements/Instruments

Among the participants included in the experiment groups, those with a cervical opening of 4-5cm and above performed a 10 cc syringe with liquid petroleum jelly perineal massage using and not using petroleum jelly (2 groups) in the active phase of the labor until the second phase by the researcher when no contractions. The perineal massage was performed with the pregnant women in a supine position and with their bladders empty. The perineal massage was performed five times in total until full dilatation was achieved. The researcher sit on the right side of the pregnant woman facing the participant and performed the massage by moving two fingers (index and middle fingers) in a 'U' shape from one edge of the vagina to its other side for 10 minutes (Figure 3). Only hospital protocols were applied to the control group and no additional interventions were performed. All women gave birth in a lithotomy position. None of the participants had labor induction and crystal maneuvering. The childbirth was practiced by obstetricians who were blinded to the study groups. Redness, ecchymosis, edema, discharge, and approximation in the perineum based on the REEDA scale on the postpartum hours 24th were evaluated by an obstetrician who was blinded to the study groups.

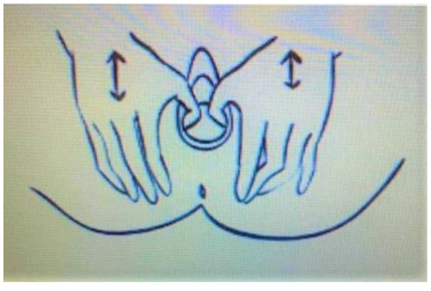

Figure 3. *Perineal massage*

Only hospital protocols were applied to the control group and no additional interventions were performed. All women gave birth in a lithotomy position. None of the participants had labor induction and crystal maneuvering. All childbirth presentations were occiput anterior, there was no scar, inflammation, edema, etc. in the perineal area and mediolateral episiotomy was performed by physicians when necessary.

Redness, ecchymosis, edema, discharge, and approximation in perineum based on the REEDA scale the postpartum hours 24th were evaluated by an obstetrician who was blinded to the study groups (Table 4).

2.5. Data Analysis

The data obtained from the research were statistically analyzed using the Statistical Package for Social Sciences (SPSS) Subscription trial version. Data were analyzed using Chi-square, t-test, and Mann-Whitney.

3. RESULTS

The socio-demographic characteristics of the women participating in the study are presented in Table 1. The results of this study showed that all three groups were homogeneous in terms of demographic characteristics at the beginning of the study ($p<0.05$) (Table 1). Results showed that episiotomy in the perineal massaged with petroleum jelly group was significantly lower (40%) than in the control group ($p<0.01$) (Table 1).

In this study, 1st-degree (3 petroleum jelly massages, 1 without petroleum jelly massage) and 2nd-degree (2 control) perineal trauma occurred. However, there were no statistically significant differences in perineal trauma in the three groups (Table 2).

Table 1. *Characteristics of the participants (n=90)*

Characteristics	Perineal massage with petroleum jelly (n=30)		Perineal massage without petroleum jelly (n=30)		No perineal massage (n=30)		Total (n=90)		Analysis
Age Mean±SD	24.43 **±4,40**		23.50 **±3.55**		22.62 ±3.87		23.52 **±4.00**		F=3.15* p> 0.45
Gestational Week Mean±SD	38.40 **±1.16**		38.53 **±0.97**		38.60 **±1.07**		38.51 **±1.06**		F=0.86* p> 0.42
Infant Birth Weight Mean±SD	3106.83**±594.87**		3046.80**±403.46**		3086.83**±409.40**		3175.53**±500.10**		F=.00* p> 1.00
Gestational Weight Gain Mean±SD	12.50**±3.35**		13.10 ± 3.74		11.38**±3.15**		12.33**±3.48**		F=0.83* p> 0.92
	n	%	n	%	n	%	n	%	
Educational Level									
8 years ↓	13	43.3	19	63.3	16	53.3	48	53,3	χ^2 =2.79 p> 0.10
9 years ↑	17	56.7	11	36.7	14	46.7	42	46.7	
Body Mass Index									
25-31	7	23.3	8	26.6	15	50	30	33.3	χ^2 =15.30 p> 0.15
32-40	23	76.7	22	73.4	15	50	60	66.7	

**One-way ANOVA*

Table 2. *Comparison of perineal trauma grades (n=90)*

Perineal Trauma Grades	Perineal massage with petroleum jelly (n=30)		Perineal massage without petroleum jelly (n=30)		No perineal massage (n=30)		Total (n=90)		Analysis
	n	%	n	%	n	%	n	%	
1st degree									
No	27	90.0	29	96.6	30	100	86	95.5	χ^2 =2.55 p> 0.27
Yes	3	10.0	1	3.4	0	0	4	4.5	
2nd degree									
No	30	100	30	100	28	93.3	88	97.7	χ^2 =6.45 p> 0.40
Yes	0	0	0	0	2	6.7	2	2.3	
Episiotomy									
No	18	60	13	43.3	8	26.7	39	43.3	**χ^2 =6.652 p< 0.01**
Yes	12	40	17	56.7	22	73.3	51	56.7	

There is a statistically significant difference among the groups in terms of duration of labor. In the control group, the labor mean-time was 10 hours 52 min, while in the perineal massage group with petroleum jelly, this duration was determined to be 9 hours 32 min (p< 0.05) (Table 3).

Table 3. *Comparison of participants in terms of labor duration*

Labor Duration	Perineal massage with petroleum jelly (n=30)	Perineal massage without petroleum jelly (n=30)	No perineal massage (n=30)	Analysis
	Mean±SD	Mean±SD	Mean±SD	
First stage duration (from 4-5 cm to 10 cm)	516.00±38.11	570.00±45.93	579.00±43.97	**F=19.01** p< 0.01**
Second stage duration	43.2±7.36	47.6±8.39	52.5±4.76	**F=18.70** p< 0.01**
First & second stage duration	559.2±45.47	617.6±54.32	631.5±48.73	**F=8.02 p< 0.01**

**Minutes **One-way ANOVA*

Redness, edema, ecchymosis, discharge, and approximation did not develop in perineal massage with the petroleum jelly group at all based on the REEDA scale. The rates of redness (30%), edema (13.3%), and ecchymosis (3.3%) were statistically significantly higher in the control group (p< 0.05) (Table 4).

Table 4. *Comparison of participants in terms of the REEDA scale*

REEDA Scale	Perineal massage with petroleum jelly (n=30)		Perineal massage without petroleum jelly (n=30)		No perineal massage (n=30)		Analysis
	n	%	n	%	n	%	
Redness							
Yes	0		5		9		**χ^2 =39.05 p< 0.01**
No	30		25		21		
Edema							
Yes	0		1		4		**χ^2 =5.506 p< 0.04**
No	30		29		26		
Ecchymosis							
Yes	0		0		1		-
No	30		30		29		
Discharge							
Yes	0		0		0		-
No	30		30		30		
Approximation							
Yes	0		0		0		-
No	30		30		30		

4. DISCUSSION

In our country, episiotomy is routinely performed in nulliparous and frequently in multiparas. Midwives and obstetricians perform episiotomy thinking that it will expand the birth canal and facilitate childbirth (17). In the present study, the rates of episiotomy that developed in the group of perineal massage with petroleum jelly, the group without petroleum jelly perineal massage, and the control group that was not performed perineal massage were 40, 57%, and 74%, respectively. The results showed that perineal massage with petroleum jelly in the intervention group significantly reduced episiotomy compared to the other group. Geranmayeh et al. (13) performed perineum massage with petroleum jelly in the second phase of birth and found a higher rate of intact perineum in the massage group (p<0.01). The finding of perineal massage to reduce trauma is in parallel with similar studies in the literature (18,19). Studies are reporting that the perineal massage performed increases perineal flexibility and decreases perineal traumas and episiotomy application (20,21). On the contrary Harlev et al. (22) conducted a study where they compared the use of fat rich in vitamins (vitamins B1, B2, B6, E) with liquid wax (jojoba oil) for perineal massage performed at the second stage of labor and found no difference between the oils used in the latter. A study showed that perineal massage with gel was safe in terms of maternal and neonatal results, but it did not significantly contribute to perineal integrity (23). This difference may be due to the phase of labor, parity, patient position, and the lubricant used in perineal massage.

In our study, no tear rates were found in the 2nd, 3rd, and 4th grades of women who underwent perineal massage. In the literature in parallel with our findings, Shahoei et al. (10) and Magoga et al. (24) similarly found that the rate of perineal trauma of 2nd degree was lower in the experiment group (22.4%). The findings of eight randomized studies by Aasheim et al. (21) that included 11.651 women who were performed perineal massage showed that the perineal massage reduces the rate of tears of 3rd and 4th degrees and the need for episiotomy (p>0.05). It was shown that perineal massage and hot application reduce the perineal traumas of third and fourth degrees (21,25). It appears that a slow and gentle massage can increase perineal stretch with increased blood circulation. Unlike these findings in a clinical trial by Albers and Borders (26), Mei-dan et al. (27) and Ashwal et al (23) found no significant difference between the intervention and control groups regarding the effect of perineal massage on perineum health (27). These dissimilarities can be associated with racial differences, differences in the quality and duration of the massage, and material used in massage or patient position.

Perineal trauma and lacerations delay perineal healing. In the present study, according to the perineal area evaluation based on the REEDA scale, higher rates of redness (30%) edema (14%), and ecchymosis (4%) developed in the control group (p< 0.01). The massage stimulates the peripheral receptors on the skin, which reach the brain through the spinal cord (28). Thus, massage promotes the release of endorphins, reduces local ischemia, increases blood supply, lymph circulation, and oxygenation of tissues, and promotes the dilatation of arterioles (28,29). Also, less perineal trauma may accelerate perineal healing.

In the current study, it was determined that the duration of labor in the perineal massage with the petroleum jelly group was the shortest compared to the other two groups. The findings of the present study are in parallel with the literature (13). Akhlaghi et al. reported the mean durations of the second stage of labor in the control and perineal massage groups were 55 and 45 minutes, respectively whose findings are consistent with our results (29). One study inconsistent with the results of this study showed that perineal massage with a water-soluble lubricant during the first stage active phase of perineal massage did not affect labor time (30). The shortening of labor time may be due to the content of the petroleum jelly. For all these reasons, perineal massage during childbirth appears to be a challenging issue that requires more research given the confusing factors.

5. CONCLUSION

The findings determined that the perineal massage with petroleum jelly in the first stage of labor increases perineal integrity and decreases perineal traumas. So, perineal massage can be an effective way to maintain intact perineum during labor. It is recommended that midwives working in the childbirth room should be trained to reduce episiotomy attempts with in-service training programs, perineal massage with petroleum jelly should be taught and applied in trauma, petroleum jelly can be used in the second stage of labor, and randomized controlled studies investigating the efficacy of substances other than petroleum jelly that can be used in the perineum to prevent perineal trauma should be conducted.

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Clinical and Experimental Health Sciences

Platelet Activating Factor Acetylhydrolase (PAF-AH) Activity: Could It Have a Role on Coagulation in Covid-19 Patients?

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ABSTRACT

Objective: Abnormal immune inflammatory response and cytokine storm play an important role on the aspect of increasing mortality in Covid-19. We aimed to investigate whether the Platelet Activating Factor Acetylhydrolase activity (PAF-AH) and hematological parameters have prognostic and predictive value in determining the disease severity.

Methods: A total of 84 Covid-19 patients, 52 of whom were hospitalized in the ward and 32 in the intensive care unit (ICU), and 38 control patients were included in this study.

Results: Lymphocyte and serum albumin levels were significantly lower ($p < .001$) and age, neutrophils, CRP, procalcitonin, LDH, INR, D-dimer levels were significantly higher ($p < .001$) in Covid-19 patients compared to the control group. ICU patients had significantly lower ($p < .001$) lymphocyte, albumin values and significantly higher ($p < .001$) age, leukocyte, neutrophils, CRP, INR, aPTT, D-dimer levels compared to ward patients. PAF-AH activity was significantly increased in ICU patients compared to the control group ($p < .05$). A positive correlation was found between PAF-AH and D-Dimer in the ICU group.

Conclusion: We found increased PAF-AH activity in patients with Covid-19. It's important to spot the PAF-AH activity in cardiovascular events that develop due to coagulation problems, which are likely to be seen on these patients in the future.

Keywords: Hematological parameters, D-Dimer, INR, aPTT.

1.INTRODUCTION

An outbreak of pneumonia, the cause of that is unknown, which began in Wuhan, China in December 2019, has led to the identification of a new beta coronavirus, called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV – 2 is the seventh member of the identified RNA coronavirus family that can infect humans (1). According to WHO data, as of May 9, 2021, 156.496.592 confirmed cases of Covid-19 have been reported in 223 countries and regions all over the world, causing deaths in 3.264.143 patients (2). It has been observed that the clinical findings of the infection caused by Covid-19 are in a broad spectrum, starting from mild manifestations such as asymptomatic disease and mild upper respiratory tract infection to severe viral pneumonia that can be associated with respiratory failure and can result in acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) and MOF (3) and finally, death. It has been revealed that advanced age, underlying diseases, abnormal immune inflammatory responses, and cytokine storms play an important role in the progression and the increasing rates of mortality of this infection, which does not yet have specific antiviral treatment other than supportive therapy (4).

It is thought that two different mechanisms run together during the process of this disease: Firstly, the pathogenicity caused by the virus itself; and the second is the inflammatory response of the body to this condition (5). Excessive inflammation leads to a predisposition to the formation of venous and arterial thromboembolic diseases as a result of endothelial dysfunction, platelet activation, hypoxia, immobilization (6). Therefore, the detection of circulating biomarkers that can represent immune status and inflammation is of critical clinical importance for early recognition of the systemic hyperinflammatory process in Covid-19 and predicting the progression of the disease. It is known that the systemic inflammatory process causes changes in leukocyte, lymphocyte, neutrophil, monocyte and platelet levels (2). Some studies have shown that peripheral blood parameters are markers of systemic inflammatory response and elevated values of these markers may lead to poor prognosis (7,8).

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PAF is one of the most powerful lipid mediators associated with inflammatory events, synthesized by various cells, including macrophages, neutrophils, lymphocytes, basophils, eosinophils, platelets, fibroblasts and vascular endothelial cells, which are at the center of most of the inflammatory systems (9). It plays a role in smooth muscle contraction, platelet activation, chemotaxis and degranulation of polymorphonuclear leukocytes and monocytes, and increases vascular permeability by altering vascular tension (10). Platelet Activating Factor Acetylhydrolase (PAF-AH) is a highly specific antioxidant enzyme released from mast cells that neutralizes both the acetyl group of PAF, which is a powerful pro-inflammatory lipid mediator, and the short-chained fatty acids of oxidized phospholipids by hydrolyzing and it also regulates inflammatory responses. Many studies show that PAF-AH plays an important role in reducing PAF-induced damage and terminating the signals of phospholipids such as PAF and oxidized PAF, which yield products unable to be recognized by the PAF receptor (11,12).

Due to its highly contagious nature, Covid-19 has placed a huge burden on hospitals. A group of laboratory tests will be useful for the efficient use of limited isolation facilities in outbreaks and for early classification, follow-up and therapeutic follow-up of patients. It has been reported that hematological parameters are significantly abnormal in most patients with Covid-19. Studies have shown that the development of coagulopathy in these patients is one of the poor prognostic features and most of the expired patients have DIC (13). Decreased PAF-AH activity is known to be accompanied by sepsis, inflammation, and coagulation (14). Determining the levels of PAF-AH activity, which has both antithrombotic and antioxidant properties, may be important for shedding light on the coagulation mechanism in these patients. There is no study in the literature yet in which hematological parameters and PAF-AH activity were evaluated together in Covid-19. We aimed to determine whether there is a relationship between them by evaluating PAF-AH enzyme activity and coagulation parameters in Covid-19 patients in this study. In addition, we wanted to determine the effectiveness of these parameters in predicting patients who should be admitted to the ICU and to investigate the usability of PAF-AH as a predictive and prognostic indicator in Covid-19 patients.

2.METHODS

2.1. Study Design and Participants

For this study, approval from the Ordu University Faculty of Medicine Ethics Committee with the date of 28.05.2020 and number 112 was obtained, as well as informed consent from all participants or their relatives.

This retrospective study was conducted with patients who visited the Emergency Room of İstanbul Bağcılar Training and Research Hospital between the dates of 15.03.2020-01.04.2020. In the study, a total of 84 adult patients that are aged 18 years and older, 52 of whom were treated in the ward and 32 in the ICU were included. The diagnosis of Covid-19 was confirmed by clinical examination, CT and rRT-PCR test positivity in nasal and/or pharyngeal swab samples. Patients with hematological disease or those who underwent blood transfusions while hospitalized were excluded. Again, 38 adult patients who were found to be negative with clinical examination, CT, and rRT-PCR tests and still admitted to the hospital on the same dates were treated as control patients. Inclusion criteria for the control group were determined as rRT-PCR test negativity, and those with the comorbid disease were once again excluded.

The routine parameters examined were analyzed retrospectively and the PAF-AH activities of these patients were studied from blood samples taken for routine tests and stored at-80ºC.

2.1.1. Clinical Classification

Covid-19 cases were evaluated according to the T.C. Ministry of Health's COVID-19 (SARS-CoV-2 infection) guidelines (15) and case classification was made. 52 patients who meet at least one of the following criteria were admitted to the ward; a. Fever, cough, nasal congestion, sore throat, muscle/joint pain, and tachypnea (≥30/min), SpO2 level below 90% in room air and b. Bilateral diffuse pneumonia findings detected on chest radiography or tomography 32 patients who meet one of the following criteria were transferred to the ICU;

Dyspnea and respiratory distress, respiratory rate>30/min, PaO2/FiO2 < 300, increased oxygen need during follow-up, PaO2 < 70 mmHg or SpO2 < 90% despite 5 L/min oxygen therapy, hypotension (systolic blood pressure < 90 mmHg and a decrease from usual SBP more than 40 mmHg) and tachycardia > 100/ min, mean arterial pressure < 65 mmHg, confusion, acute liver function tests disorder, acute kidney injury, arrhythmia and increased troponin, development of acute organ dysfunction and immune suppression, lactate > 2 mmol, capillary return disorder and cutis marmoratus.

The demographic, epidemiological, clinical, radiological data, and laboratory results of the patients were obtained by using data collection forms from electronic records. The parameters of the Covid-19 positive patients treated in the ward and ICU were compared to Covid-19 negative healthy control group.

2.2. Biochemical Study

Routine parameters taken when patients received their current diagnosis were studied in the Laboratory of Bağcılar Training and Research Hospital. For the complete blood count of the patients, blood samples were taken into a tube with EDTA and hematology analysis of the samples was performed by absorption photometry and fluorescence flow cytometry method on XN-900 (Sysmex, Japan) automatic analyzer. For coagulation parameters, with the plasma separated from the

blood samples taken into the citrate tube by centrifugation at 3500 rpm for 10 min, by immune turbidimetric and chromogenic substrate methods, on the SF-8200 (Succeder, China) automatic coagulation analyzer; biochemistry parameters, with serum obtained by centrifuging blood samples taken into the gel tube at 3500 rpm for 10 minutes were performed with the photometric assays in the AU 480 (Beckman coulter, USA) automatic biochemistry analyzer by utilizing. PAF-AH activity was analyzed from the blood samples taken for routine tests, by the enzymatic method using a spectrophotometry device, and stored at-80ºC in the Research Laboratory of Ordu University Faculty of Medicine Biochemistry.

PAF-AH activity levels have been determined spectrophotometrically by the method of Stafforini et al. (16). 2-thio-PAF (Cayman Chemical) was used as a substrate in the study. It is based on the spectrophotometric determination of 5-thio2-nitrobenzoic acid formed as a result of reaction with DTNB of free thiol groups, formed by hydrolysis of acetyl thioester bond in position sn-2 at of by at 412 nm. The molar absorbency coefficient for 5-Thio-2-nitrobenzoite acid was taken as (Ɛ= 13600 m-1cm-1). The unit of PAF-AH activity is defined as the amount of enzyme that hydrolyzes one micromole of 2-Thio PAF per minute. The detection range of the test is 30-300 nmol/min/mL.

2.3. Statistical Analysis

Data with normal distribution were expressed as the mean ± standard deviation (SD) while data with abnormal distribution were expressed as median ± IQR. Kolmogorov-Smirnov test was used to control the normal distribution of our data. Levene test was used to control the homogeneity of group variations. The group averages were compared using a one-way analysis of variance (ANOVA) when the normality assumption was provided. In addition, the Kruskal-Wallis test was also performed for assessing abnormality. Following these analyses, different groups were identified using Dunn tests or Duncan's multi-range. In the correlation analysis of parameters, Pearson or Spearman correlation test was used for parametric or nonparametric data. The statistical significance level was accepted as $p < .05$. SPSS.20 software (version 20.0) statistical package program was made using the for calculations.

3.RESULTS

3.1. Demographic Features

A total of 84 COVID-19 patients consisted of 52 in the ward and 32 in the ICU and 38 healthy people participated in the study. There was a significant difference between the groups in terms of age distribution ($p<0.001$). In the ward group, 25 of the patients were female, 27 were male, the average age was 53.3 ± 18.6; in the ICU hospitalized patients, 13 females, 19 males, mean age 72.5 ± 12.5 and Covid-19 negative control group, 24 females, 14 males, mean age 38.3 ± 11.2 was determined as ($p < .001$).

56% of the patients (n = 84) had comorbidity and the most common comorbid diseases were spotted as diabetes (34.91%, n=28), hypertension (26.19%, n=22) and coronary artery disease (17.86% n=15). (Table 1).

Table 1. *Demographic characteristics of the patients and control group.*

Groups	Control group (n=38)	Ward group (n=52)	ICU group (n=32)	p value
Age (mean ± SD)	38.3±11.2	53.3±18.6	72.5±12.5	<0.001
Gender				
Male (n) (%)	14 (36.84%)	27 (51.92%)	19 (59.38%)	
Female (n) (%)	24 (63.16%)	25 (48.08%)	13 (40.62%)	
DM		9 (17.31%)	19 (59.38%)	
HT		6 (11.54%)	16 (50%)	
CAD		3 (5.77%)	12 (37.5%)	
COPD		5 (9.62%)	5 (15.63%)	
Chronic renal failure		1 (1.92%)	6 (18.75%)	
Cerebrovascular disease		0	1 (3.13%)	

For age; data is presented as mean ± standard deviation (SD) and n (%).

3.2. Routine Parameters of the Covid 19 Ward and ICU Groups

Between the ward group and ICU group, there were various differences found in the routine hematological blood parameters and routine biochemistry parameters that show anti-inflammatory capacity. ICU patients had significantly lower lymphocytes (0.9±0.6; 1.5±0.7 $p < .01$) and lower albumin (2.8±0.5; 3.5±0.6 $p < .001$) levels compared to ward patients.

Compared to the levels of admitted ward patients', ICU patients had significantly higher Leukocyte 11.6 (0.6-36.4); 7.2(3.3-20.9) $p < .001$), higher neutrophils 10.0 (0.5-33.3); 4.84 (2.0-18.0) $p < .001$), higher CRP (132.5±104.8; 54±67.9 $p < .001$), higher LDH (384±168.5; 293.6±118.4 $p < .001$), higher INR 1.2(0.8-2.1); 1.1(0.9-2.1) $p < .001$), higher aPTT (37.7±12.2; 20.9±17.6, $p < .001$), higher D-dimer (2.41±2.5; 1.05±1.6 $p < .001$) (Table 2). PAF-AH levels were also statistically significantly increased in ICU patients (111.9 ± 26.6; 129.2 ± 27.6) ($p < .05$) compared to the control group. There was no significant difference in terms of PAF-AH levels between the patient groups. PAF-AH levels were statistically significantly increased in ICU patients, compared to the control group patients (111,9±26,6; 129,2±27,6) ($p < .05$) (Figure 1).

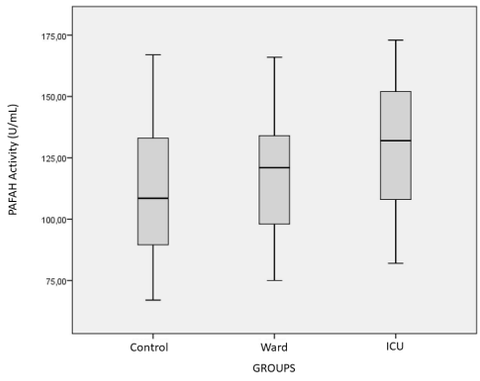

Figure 1. *Distribution of PAFAH Activity averages by groups*

Table 2. *Comparison of biochemical parameters according to Covid-19 patients and control groups.*

	Control group (n= 38)	Ward group (n= 52)	ICU group (n= 32)
Age (years)	38.3±11.2	53.3±18.6 [e]	72.5±12.5 [e, f]
Glucose (mg/dl)	90.7±26.2	111±64.6	164.6±101.8
Urea (mg/dl)	32.5±10.7	38.2±26.8	86.8±86.8 [a]
Albumin (mg/dl)	4.3±0.2	3.5±0.6 [e]	2.8±0.5 [e, f]
AST (U/L)	22.8±10.2	34.3±25 [a]	76.7±177.8
ALT (U/L)	22±19.2	30±33.9	44.2±87.5
GGT (U/L)	7.1±13.4	25,8±31	66.6±46.3
ALP (U/L)	75.3±20.8	91.2±40.1	117.5±66.8 [c]
Creatine Kinase (U/L)	92.5±16.2	88.4±93.1	127.1±165
Hemoglobin(g/L) (mg/dl)	12.2±3.4	12.1±3	10±2.4
Leucocytes (×10^9 per L)	7.5(4.1-12.4)	7.2(3.3-20.9)	11.6 (0.6-36.4) [e]
Neutrophils (×10^9 per L)	4.01 (2.1-6.8)	4.84 (2.0-18.0)[c]	10.0 (0.5-33.3) [c,f]
Lymphocytes (×10^9 per L)	2.4±0.9	1.5±0.7 [e]	0.9±0.6 [e,d]
Monocyte (×10^9 per L)	0.5±0.1	0,6±0.4	0.6±0.4
Basophil	0.05(0.02-0.1)	0.02(0.01-0.08) [c]	0.04(0.01-0.15)
Eosinophil (×10^9 per L)	0.1±0.2	0.1±0.5	0.1±0.5
Platelet (×10^9 per L)	269((158-422)	250(1.02-459)	314(102-683) [b]
CRP (mg/dl)	2.3±1.8	54±67.9 [e]	132.5±104.8 [e,f]
Procalcitonin (ng/ml)	0.02(0.01-0.09)	0.07(0.02-47.8)	0.7(0.05-100.4)
Ferritin (ng/ml)	37.7±48	169.5±320.6 [a]	542.8±749.9 [a,b]
Pt (sn)	13.3(12.3-16.6)	14.1(11.1-28.1) [a]	15.7(11.4-27.5) [c,f]
Inr	1.03(0.9-1.3)	1.1(0.9-2.1)[c]	1.2(0.8-2.1) [e, f]
aptt (sn)	32.8±8.2	20.9±17.6 [e]	37.7±12.2 [f]
D-dimer (µg/ml)	0.24±0.3	1.05±1.6 [c]	2.41±2.5 [e,b]
Fibrinogen (mg/dl)	349.3±111.3	287.2±254	391.7±255.8
Pafah (U/ml)	111.9±26.6	118±25.4	129.2±27.6 [a]
LDH (U/L)	192.4±38.1	293.6±118.4 [e]	384±168.5 [e,b]

Data is presented as mean ± standard deviation (SD) or median (interquartile range (IQR))
ap < 0.05 compared with control group
bp < 0.05 compared with Ward group
cp < 0.01 compared with control group
dp < 0.01 compared with Ward group
ep < 0.001 compared with control group
fp < 0.001 compared with Ward group

3.3. Comparison of the Relationship Between PAF-AH and Routine Parameters of the Control and Covid19 Group at Admission Ime

There was a significant positive correlation between age and ferritin (r = 0.370, p = .022), between PAF-AH-INR (r = 0.318, p = .045), between PAF-AH-ALT (r = 0.341, p = .031), between CRP-Fibrinogen (r = 10.701, p = 0.000), between CRP-D-Dimer (r = 0.814, p = .000), between ALT-INR (r = 0.580, p = .000), between ALT-Albumin (r = 0.417, p = .031), between AST-INR (r = 0.416, p = .009) in the control group. A significant negative correlation between age and aPTT (r =-0.356, p = .028) was present in the control group.

A significant positive correlation between CRP and INR level (r= 0.284, p= .042) was found in the ward group. There was a positive correlation between PAF-AH-D-Dimer (r= 0.376, p= .044), between ALT-D-Dimer (r= 0.376 p= .044), between Ferritin-D-Dimer (r=0.535, p= .03), between Ferritin-ALT (r=0.462, p= .008), between AST-Leukocyte (r=0.497, p= .004), between AST-Neutrophil (r=0.504, p= .003), between AST-Monocyte (r=0.572, p= .001), between ALT-Monocyte (r=0.381, p= .031), between Monocyte-INR (r=0.566, p= .001), between Monocyte-Ferritin (r= 0.421, p= .017) in the ICU group. A significant negative correlation between ALT-aPTT (r= – 0.579, p= .001) was present in the ICU group.

4.DISCUSSION

In this study, hematological parameters and PAF-AH enzyme activity levels were examined and compared in patients of SARS-CoV-2 in the ward and ICU. Abnormal routine results of hematological, biochemical parameters, and PAF-AH levels were available in patients with Covid-19. We found that examining PAF-AH and peripheral blood count, especially lymphocytes and neutrophils, would help to predict severe Covid-19 cases. Increased age, leukocyte, neutrophil, CRP, albümin, and D-Dimer levels as well as increased PAF-AH levels can be considered as independent biomarkers to show a deteriorating clinical picture. There was a significant positive correlation between D-Dimer and PAF-AH levels. Our findings may be useful as an earlier indicator for determining the disease severity and to help classify patients for ICU transfer. We ponder the reason for the changes in the measured parameters as the developing inflammatory process. It can be thought that PAF-AH is expressed and affected differently from post-transcriptional and post-translational mechanisms at different stages of systemic inflammation.

In three COVID-19 patients who underwent minimally invasive autopsies, marked irregularity of the lymphohematopoietic system, a decrease in lymphocytes in the spleen, necrosis, and cell degeneration was observed in addition to severe lung lesions (17). SARS-CoV-2 is a RNA coronavirus that enters human cells by binding to angiotensin-converting enzyme 2 (ACE2), which is highly expressed in lung alveolar cells, vascular endotelium, cardiac myocytes, and various cells (18). The binding of SARS-CoV-2 to the ACE2 receptor causes a high expression of ACE2, which can lead to damage

in alveolar cells. Damage to Alveolar cells can cause a range of systemic inflammatory responses, often involving varying degrees of hematopoietic system abnormalities and hemostasis activation. Especially in some COVID-19 patients, excessive inflammatory cytokine increase, which can lead to a "cytokine storm" such as increasing levels of IL-6, has the potential to cause severe diseases such as ARDS, DIC, MOF, shock as a result of uncontrolled inflammation (19).

In our study, in parallel with other studies, most of the patients were male. Also, the cases were older in comparison to other studies' patients and more likely to have underlying diseases as a result of poorer immune functions (3). Similar to other studies, more than half of the patients had comorbidity. Diabetes was the most common comorbidity, followed by hypertension, CAD, and COPD (20). Qin et al. stated that hypertension and cardiovascular disease are found at a higher rate in severe cases compared to mild cases (21). It has been stated that hypertension may play a role in the progression of COVID-19 by causing abnormal immune function as a result of immune activation (22).

In addition to the various parameters used to detect systemic inflammation, simple, low-cost and easily accessible hematological markers, which are widely used, are important (19). Lymphocytes play a decisive role in sustaining the inflammatory response and maintaining immune homeostasis. Potential mechanisms that could lead to lymphocyte deficiency were regarded as; lymphocytes being infected with the virus as a result of expressing ACE2, lymphocytic dysfunction, inflammatory cytokines leading to lymphocyte apoptosis and translocation of lymphocytes from peripheral blood to lungs (19). It has been stated that survival in COVID-19 may depend on the ability of lymphocytes killed by the virus to regenerate (23). Therefore, lymphocyte count in Covid-19 is extremely important as a clinical predictor of disease severity and prognosis. In the study of Zhou et al. it was shown that lymphocytopenia was seen in 40% of patients and the initial lymphocyte level was significantly higher in survivors than in non-survivors. This study confirmed that elevated IL-6 levels and lymphopenia were more common in severe patients, and increased age in patients with Covid-19 was related associated with increased mortality (3). Age-related defects in B and T cell function and excessive type 2 cytokine production have been shown to cause viral replication control difficulties and prolonged proinflammatory responses (24).

Regardless of whether leukocytosis represents neutrophilia, lymphocytosis, or both, it has been reported to be a harbinger of bacterial infection or superinfection for patients with COVID-19 (25). Our study showed that, unlike some previous studies, Covid-19 is associated with leukocytosis rather than leukopenia (26,27). We think that leukocytosis reflects severely increased inflammation. In one study, while an increase in leukocyte count was slightly seen in patients with severe disease, a significant increase was shown in patients who passed away (23). Consistent with the results we found in our study, it was suggested that the significant increase in leukocytes in patients with severe disease may indicate clinical worsening (23). In a study conducted on 75 patients, the leukocyte levels of the severe group were found to be higher than the moderate group (28). Leukocytosis is not correlated with lymphopenia, it is caused by the high amount of neutrophils, and lymphopenia may emerge in both inclining-declining cases of leukocyte count (23). In our study, leukocytosis was accompanied by lymphopenia and an increase in neutrophil count. In a study of Huang et al. involving 140 COVID-19 patients, he stated that leukocytosis, neutrophilia, and lymphopenia are important determinants of ICU admission (26). In our study, similar to other studies, ICU patients generally had deeper lymphopenia and neutrophilia (29,30).

Decreased lymphocyte count indicates immune system damage, while an increased neutrophil count indicates the intensity of the inflammatory response (20). Neutrophils are immunity cells that are increased in certain lung diseases, including viral respiratory infections. (31). Neutrophils may exit into the airways from the circulation via postcapillary venules in the systemic circulation or via the capillaries in the pulmonary circulation. Neutrophil production may be triggered by virus-related inflammatory factors such as interleukin-6, interleukin-8, interferon-gamma factors, tumor necrosis factor-alpha, and granulocyte colony stimulating factor (19). In one study, peripheral routine blood parameters of the severe and critical groups were analyzed, the inflammatory neutrophil count in the critical group was significantly higher than the severe group, lymphocyte count was found to be significantly lower than the severe group (29). Our results show that lymphocyte and neutrophil levels at the moment of admission are related to the prognosis of the ailment. These data propose that the degree of infection and inflammation triggered by the virus, becomes more intense, augmenting the storm of inflammation and leading to increased tissue and cell damage. Our results are consistent with previous studies that found a relationship between prognosis and disease severity (25,28).

In COVID-19 infection, the virus damages bone marrow cells directly or with the effect of overproduction of proinflammatory cytokines, and this leads to the suppression of hematopoiesis, which explains low hemoglobin, leukopenia, lymphopenia, eosinophilic cytopenia, thrombocytopenia as a result of a series of immune responses in patients. It has been stated that this critical condition may be related to the ICU patients' tendency towards low immune response and sepsis (32). There was no significant difference in hemoglobin levels between patient groups in our study. Although the number of thrombocytes decreased in ward patients, it was not statistically significant. There was significant thrombocytosis in the ICU group compared to the control group. Thrombocytopenia is common in critical patients and indicates severe organ damage, and it has been noted that there is a greater decline in platelet count, especially in those mortal cases (33). The mechanism of thrombocytopenia in COVID-19 patients is multifactorial. Chen et al. reported that some of the patients had thrombocytosis (27). One study found that patients with significantly higher platelets and PLRs had longer average hospitalization days. It

has been stated that this turn of events may be caused by the release of excessive cytokines that stimulate the formation of megakaryocytes (34). Platelets trigger the degranulation of mast cells, leading to inflammatory responses and tissue damage.

SARS-CoV-2 directly attacks vascular endothelial cells, initiating localized inflammation, endothelial activation, irregular cytokine release, and tissue damage. Vascular endothelial damage causes hypercoagulability in infected patients by COVID-19, as a result of excessive thrombin production and inhibition of fibrinolysis (35). Tang et al. found higher levels of longer PT, APTT, and D-dimer values in those who could not survive the disease compared to survivors in their study. These results suggested that patients have a tendency for hypercoagulability and supported microthrombosis (36). Wang et al. showed that D-Dimer levels were significantly higher in the ICU group in line with our results (20).

Mast cell degranulation has been reported in the alveolar septa of those who died due to COVID-19 (37). Mast cells are immunity cells that can be activated by many factors, including viruses, and have the attribute of PAF secretion (38). Recently held responsible as a factor for COVID-19 pneumonia severity, mast cells have been shown as one of the rich sources of pro-inflammatory cytokines in the lungs (39). It is also known that PAF activates platelets and promotes clot formation. PAF is known to be one of the most potent lipid mediators involved in various physiological occasions. Activation of cells responsive to pathogens, cytokine response, free radicals, and the formation of oxidized phospholipids recognized by the PAF receptor cause uncontrolled systemic inflammation and DIC by activating the coagulation system. Increased vascular permeability, plus increased leukocyte count and platelet aggregation lead to hypoperfusion and tissue hypoxia, which are the main cause of multiple organ dysfunction (11). There is evidence that the PAF signaling system is irregular in traumatic injuries, sepsis, and shock, and that interruption or termination of effector responses has beneficial consequences and thereby regulates the inflammatory response (14). PAF-AH is an enzyme that inactivates PAF and oxidized phospholipids with proinflammatory and prothrombotic features and controls systemic inflammation. PAF-AH levels increase with the stimulation of inflammatory agonists and lipopolysaccharides, however, decrease with anti-inflammatory drugs and cytokines. Circulating PAF-AH levels are found to be decreased in systemic infection and multiple organ failure. In oxidative stress-based diseases such as asthma, sepsis, stroke, acute CVH, and MOF; PAF-AH levels have been found to be low and it has been reported to contribute to organ dysfunction (40).

In one study, low PAF-AH levels in severe patients admitted to the ICU, and showed that the enzyme level increased over time. But, in this study, high PAF-AH activities were reported in the nonsurvivors group compared to survivors, and no significant predictive value was found (41). It has been reported in previous studies that PAF-AH plays an important role in controlling systemic inflammation as part of the compensatory anti-inflammatory response (42). It has been recommended that it is possible that there are a number of variations in the enzyme activity of patients (41). An earlier study had shown that plasma PAF-AH activity did not decrease in the ARDS risk group and ARDS patients, on the contrary, in bronchoalveolar lavage (BAL) fluid, increased PAF-AH levels were spotted in the acute phase of ARDS, compared to patients with ARDS risk and control patients (42). It is thought that PAFAH is increased by the leakage into the alveoli as a result of increased pulmonary capillary endothelial and alveolar epithelial permeability, release from injured cells, or by active synthesis of local PAFAH in the lungs of patients with ARDS by alveolar macrophages, alveolar type 2 pneumocytes. Previous studies also suggest that an extracellular form of PAF-AH may be vital in the local regulation of inflammation in the lung by inactivating PAF and related phospholipids released in the airways (43).

In their study, Benli et al. detected that PAF-AH level is increased in patients with high PSA levels and in the group diagnosed with prostate cancer compared to the control group. They expressed their belief that this variation may be caused by the increased inflammatory process (44). Similarly, in our study, although PAF-AH levels were increased in patients in the ward compared to the control group, it was not statistically significant. However, there was a statistically significant increase in the ICU group compared to the control group. A statistically significant positive correlation was found between D-Dimer and PAF-AH in our ICU patients. Macrophages, megakaryocytes, and dendritic cells each respond to inflammatory and hemostatic signaling factors (45). Moreover, conditions such as inflammation and sepsis play a role in controlling acute inflammation caused by PAF and oxidized phospholipids by increasing plasma PAF-AH expression and synthesis. This suggests that endogenous PAF-AH is a systemic circulating marker of inflammation that is regulated temporarily and expressed differently. In our study, the increase in PAF-AH activity in the severe (ICU group) course of the disease compared to the moderate severe (inpatient group) course of the disease is an important discovery due to the antioxidant and antithrombotic effect of the enzyme. In cardiovascular events that develop due to clotting problems that are likely to occur in patients in the future, it becomes important to determine how PAF-AH levels and PAF levels are affected. PAF has many potent biological effects on almost all tissues and organs (46). Therefore, considering these findings, it was stated that it would be reasonable to try to prevent the effect of PAF with various treatments (47).

There were some limitations in this study. Our control patients were younger than the COVID-19 patients. However, this study was the first to determine PAF-AH activity in Covid-19 patients as far as we know. In new studies to be designed, we believe that determining PAF levels as well as PAF-AH activity will provide better knowledge of the literature. More large-scale and well-designed and qualified clinical studies are needed to elucidate coagulation mechanisms in COVID-19 patients.

5.CONCLUSION

In summary, COVID-19 causes abnormalities in hematological parameters and PAF-AH activity. Therefore, measurement of PAF-AH and routine peripheral blood parameters shows that it can have an important reference value in determining the inflammatory process, predicting the patients who should be admitted to the ICU at the initial stage, classifying the patients, and evaluating the progression and prognosis of COVID-19.

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Design of the study: AB, GS, TB
Acquisition of data for the study: ESG
Analysis of data for the study: TB, AB
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Clinical and Experimental Health Sciences

Reliability, Concurrent Validity, and Minimal Detectable Change of a Smartphone Application for Measuring Thoracic Kyphosis

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ABSTRACT

Objective: To assess the intra – and inter-rater reliability and concurrent validity, and to estimate minimal detectable change of a smartphone application for measuring thoracic kyphosis angle.

Methods: A total of 80 healthy university students were evaluated. Two raters measured the thoracic kyphosis angle using a digital inclinometer and the smartphone application. Intra – and inter-rater reliability were assessed using the intraclass correlation coefficient (ICC) with 95% confidence interval. The standard error of measurement (SEM) and the minimal detectable change at the 95% confidence level (MDC_{95}) were also calculated. The concurrent validity between the digital inclinometer and the smartphone application was assessed by the linear regression analysis and Bland and Altman's 95% limits of agreement method.

Results: The intra – and inter-rater reliability were excellent for the digital inclinometer and the smartphone application (ICC > 0.75). The SEM values for the digital inclinometer and the smartphone application were close together. The MDC_{95} values for the smartphone application were 5.11 and 6.30 degrees, and 9.02 degrees for intra – and inter-rater, respectively. The digital inclinometer and the smartphone application showed a positive correlation (R^2 = 0.85). The Bland-Altman plot showed a good agreement between the instruments.

Conclusion: The smartphone application used in this study is a cost-effective, practical, reliable, and valid instrument for measuring the thoracic kyphosis angle. More than 9 degrees in the value of the thoracic kyphosis angle measured by the smartphone application can be considered as a true change.

Keywords: Reliability; validity; kyphosis; smartphone; spine

1. INTRODUCTION

Thoracic kyphosis is defined as spinal angulation between the T1 and T12 vertebrae in the sagittal plane (1). An increase or decrease in the thoracic kyphosis angle may cause adverse changes in the shoulder range of motion (2), balance (3–5), pulmonary functions (6), and quality of life (5); therefore, evaluation of the thoracic kyphosis angle is important to determine the negative effects caused by the changes in the thoracic kyphosis angle and to identify appropriate treatment strategies (7).

The gold standard method to measure the thoracic kyphosis angle is measurement of the Cobb angle on lateral radiographs (8). The disadvantages of radiographic methods are clinical impracticality, high cost, and high exposure to radiation (7). Hence, indirect measurement methods and instruments, such as Debrunner kyphometer (9), flexible electrogoniometers (1), Flexicurve index and Flexicurve angle (10), Spinal Mouse (11), goniometers (12), seventh cervical vertebrae wall distance (13), are applied. The digital inclinometer is one of these methods. The validity and intra – and inter-rater reliability of the digital inclinometer compared with the Cobb angle measurement on lateral radiographs were found to be high (14).

In recent years, one of the methods used to measure range of joint motion is smartphone applications. The use of software applications in clinical practice has increased because they are fast and practical (15). The reliability and validity studies were conducted on the use of smartphone applications for measuring range of motion of different joints (16–18). In addition, the reliability and validity of smartphone applications to measure thoracic kyphosis angle were investigated (19,20); however, the reliability and validity of a measurement instrument are not enough for an interpretation of change scores, the standard error of measurement (SEM) and the minimal detectable change should be determined (21). A smaller SEM is an indicator of a good reproducibility (22). The minimal detectable change is also an important benchmark associated with reliability, and shows the smallest change in score that can be interpreted as a true change beyond measurement error (21).

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The aim of this study was to assess the intra – and inter-rater reliability, and concurrent validity, and to estimate the minimal detectable change of a smartphone application for measuring the thoracic kyphosis angle.

2. METHODS

2.1. Participants

In this cross-sectional study, a total of 80 healthy university students participated. The inclusion criteria were as follows: older than 18 years, and able to stand independently without using any auxiliary devices. The exclusion criteria were as follows: any pain or pathology of the musculoskeletal system of the spine, and lower and upper extremities; low back pain; and having a previous surgery of the musculoskeletal system.

All participants were informed about the study, and they signed the informed consent form before participating in the study. The Non-Interventional Research Ethics Committee of European University of Lefke (17/07/2018 and UEC/17/02/07/1718/01) approved the study.

2.2. Instruments

A digital inclinometer (Baseline, 12-1057, Fabrication Enterprises, NY, USA) and a smartphone application (Clinometer, Plaincode) were used to measure the thoracic kyphosis angle of the participants.

2.3. Procedures

The measurements were performed by two physiotherapists with 13 and 19 years of experience. Before the study began, the physiotherapists practiced the procedures on volunteer subjects. As recommended in the literature, two reference points were determined to measure the thoracic kyphosis angle: the spinous processes of the 1st and 2nd thoracic vertebrae (the first reference point), and the spinous processes of the 12th thoracic and 1st lumbar vertebrae (the second reference point) (23). The total thoracic kyphosis degree was obtained by summing the angle values for each reference points (23).

The thoracic kyphosis angle was measured with the digital inclinometer and the smartphone application by each rater. Once the first rater completed the first session, the participants were rested for ten minutes prior to performing the measurement with the second rater. The second session was performed on the same day. The first and second sessions were performed three times for each instrument by each rater, and a mean value of the three measurements was used for further analysis.

2.3.1. Digital inclinometer measurement

The participants were asked to remove outer clothing to identify the spinous processes, and to assure proper positioning of the instruments. The participants were requested to stand in their normal postures and with their arms resting alongside their bodies, and remain as still as possible to avoid deviation from the angular values during the measurement. The reference points were determined by palpation, and marked. The feet of the inclinometer was initially placed at the first reference point, and a value was recorded. The inclinometer was then placed at the second reference point to measure a second value. The thoracic kyphosis angle was the sum of the values (Figure 1).

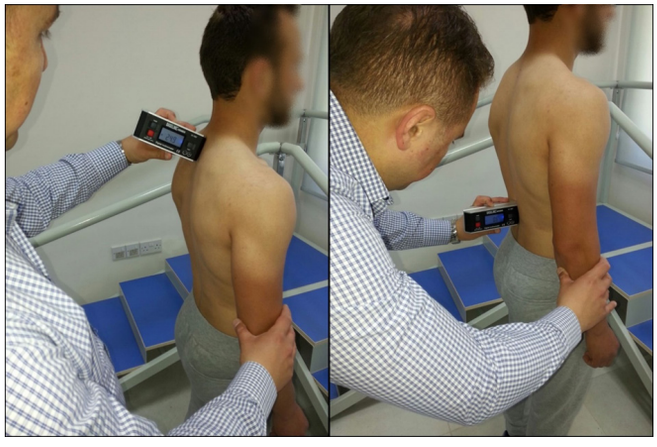

Figure 1. *The measurement of the thoracic kyphosis angle with the digital inclinometer.*

2.3.2. Smartphone application measurement

The instructions to the participants were as stated previously. The top side of the smartphone was placed at the first reference point with screen facing laterally, and a value was recorded. A second value was obtained from the second reference point in the same way, and the sum of both values was deemed the thoracic kyphosis angle (Figure 2).

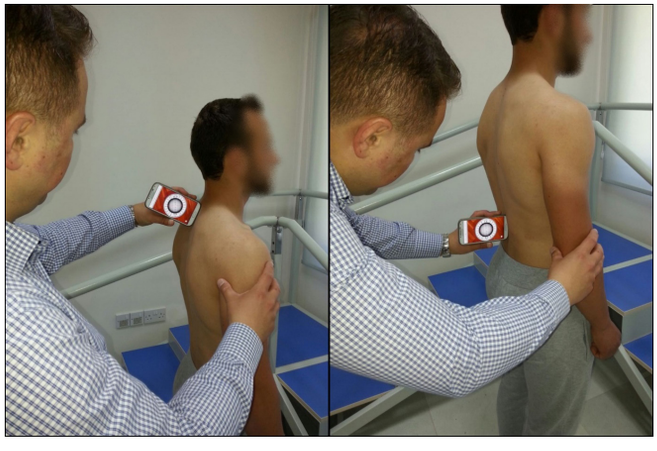

Figure 2. *The measurement of the thoracic kyphosis angle with the smartphone application.*

2.4. Sample size estimation

The sample size was calculated based on the sampling method recommended by Walter et al. for reliability studies using

the intraclass correlation coefficient (ICC) (24). The minimal acceptable and expected levels of ICC were set at 0.70 and 0.85, respectively. From this calculation, with α = 0.05 and *b* = 0.20 for two raters, the minimum number of participants required was 43. Assuming a drop-out rate of 20%, the final sample size was calculated to be 54 participants.

2.5. Statistical analysis

All statistical analysis and graphical representations were performed using the SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). Variables determined by the measurement were expressed as arithmetic mean and standard deviation.

The intra – and inter-rater reliability of the instruments were examined by calculating the ICC with 95% confidence interval. The ICCs were calculated based on a two-way mixed model (3, *k*) with an absolute agreement type (25). The ICC values were interpreted as follows: < 0.40, poor; 0.40–0.59, fair; 0.60–0.74, good; and 0.75–1.00, excellent (26). The SEM for the intra – and inter-rater were calculated by √mean square error and √(mean square error) + (mean square subjects × raters), respectively (27). The minimal detectable change at the 95% confidence level (MDC_{95}) was calculated by 1.96 × SEM × √2 (28).

The concurrent validity between the digital inclinometer and the smartphone application was assessed by the linear regression correlation and the limits of agreement proposed by Bland and Altman (29). The 95% limits of agreement were calculated as mean difference ± 1.96 × SD (29).

3. RESULTS

The demographic characteristics of the participants are presented in Table 1. The measurement results of both raters are given in Table 2. The intra – and inter-rater reliability are presented along with the SEM and MDC_{95} values in Table 3 and Table 4, respectively. The intra – and inter-rater reliability were excellent for the digital inclinometer and the smartphone application.

Table 1. *The demographic characteristics of the participants.*

	N = 80
Age (years) (Mean±SD)	20.42±1.40
Gender (in %)	
Male	42 (52.5)
Female	38 (47.5)
Weight (kg) (Mean±SD)	66.58±13.39
Height (m) (Mean±SD)	1.71±0.09
Body mass index (kg/m²) (Mean±SD)	22.58±3.16

SD, standard deviation

Table 2. *The measurement values of the digital inclinometer and the smartphone application for the first and second raters.*

	First session Mean±SD (range)	Second session Mean±SD (range)
First rater		
Digital inclinometer (°)	30.01±6.65 (14.30–48.10)	29.58±6.53 (14.20–47.70)
Smartphone application (°)	30.47±6.74 (15.20–49.40)	29.93±6.84 (14.10–49.30)
Second rater		
Digital inclinometer (°)	29.01±5.39 (15.60–44.80)	28.66±5.72 (15.40–44.10)
Smartphone application (°)	28.73±5.36 (16.90–44.80)	28.40±5.17 (17.10–44.30)

SD, standard deviation

Table 3. *The intra-rater reliability of the digital inclinometer and the smartphone application.*

	Digital inclinometer			Smartphone application		
	ICC (95% CI)	SEM (°)	MDC_{95} (°)	ICC (95% CI)	SEM (°)	MDC_{95} (°)
First rater	0.92 (0.88–0.95)	2.44	6.76	0.94 (0.90–0.96)	2.27	6.30
Second rater	0.94 (0.91–0.96)	1.81	5.04	0.93 (0.89–0.95)	1.84	5.11

ICC, intraclass correlation coefficient; CI, confidence interval; SEM, standard error of measurement; MDC95, minimal detectable change at the 95% confidence level

Table 4. *The inter-rater reliability of the digital inclinometer and the smartphone application.*

	ICC (95% CI)	SEM (°)	MDC_{95} (°)
Digital inclinometer	0.82 (0.73–0.89)	3.03	8.39
Smartphone application	0.80 (0.68–0.88)	3.25	9.02

ICC, intraclass correlation coefficient; CI, confidence interval; SEM, standard error of measurement; MDC95, minimal detectable change at the 95% confidence level

Figure 3 and Figure 4 provide graphical representations of the linear correlation and the limits of agreement, respectively. The linear regression correlation between the digital inclinometer and the smartphone application showed a positive correlation (R^2 = 0.85) (Figure 3). A mean difference on the Bland-Altman plot was –0.46 degrees, and the limits of agreement ranged from –5.60 to 4.67 degrees (Figure 4). When interpreted according to Bland and Altman (29), it can be said that the Bland-Altman plot showed a good agreement between the instruments.

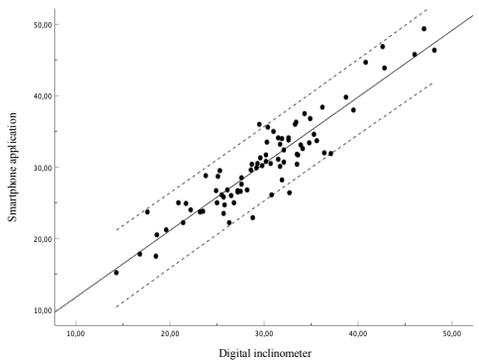

Figure 3. *The linear correlation between the digital inclinometer and the smartphone application (y = 2.38 + 0.94*x, R^2 = 0.85). The solid line is the linear regression line, the dashed lines are the 95% confidence limits.*

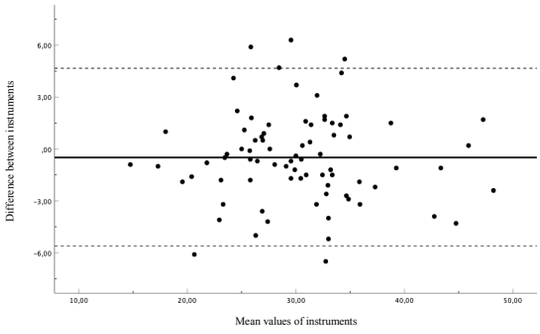

Figure 4. *The Bland-Altman plot comparing the measurements of the digital inclinometer and the smartphone application (SD = 2.62). The solid line is the mean difference (–0.46), the dashed lines are the 95% limits of agreement (–5.60 to 4.67).*

4. DISCUSSION

The present study shows that the smartphone application used in this study has high reliability and concurrent validity for measuring the thoracic kyphosis angle, and hence is an appropriate instrument to be used in clinic practice as an alternative to other instruments.

This study provides novel findings about the reliability of a smartphone application for measuring the thoracic kyphosis angle. In clinical practice, reproducibility of a measurement is an important concern when assessing a patient. A high ICC value and a smaller SEM in repeated measurements reflect a greater reproducibility (22). This study revealed that reproducibility of measuring the thoracic kyphosis angle with the smartphone application is high. Furthermore, the SEM values for the smartphone application were very close to those of the digital inclinometer (see Table 3 and Table 4); therefore, it can be argued that the smartphone application is an instrument as precise as the digital inclinometer for measuring the thoracic kyphosis angle. In this study, the MDC_{95} values of the smartphone application for intra-rater were 5.11 and 6.30 degrees, and for inter-rater was 9.02 degrees, meaning that if a clinician detects a change of more than 9 degrees in the value of the thoracic kyphosis angle measured by the smartphone application in a patient, the clinician can assume it as a true change.

The intra – and inter-rater ICC values determined by the present study are consistent with a recent study with a similar age group (20). In another study evaluating the intra-rater reliability of a smartphone application for measuring the thoracic kyphosis angle, the ICC and SEM values were found as 0.80 and 11.80 degrees, respectively (19). These findings are pretty different from those in the present study. There could be several possible explanations for discrepancies between studies. Firstly, in the mentioned study, the first and second measurement were made in standing and sitting positions, respectively (19). The angles in the vertebral arrangement showed a significant difference in sitting and standing positions (30). The different position of the participants in repeated measurements would probably affect the results. Secondly, the time period between the repeated measurements was different in studies. The second measurement was performed one week later in the mentioned study (19), while it was performed on the same day in the present study. This factor also could explain this difference.

The smartphone application showed similar reliability levels for measuring the thoracic kyphosis angle compared to other indirect measurement instruments which have been previously studied. Greendale et al. found the intra – and inter-rater ICC values as between 0.96 and 0.98 for the Debrunner kyphometer, the Flexicurve kyphosis index, and the Flexicurve kyphosis angle (10). Similarly, Roghani et al. found the intra-rater ICC value for the Spinal Mouse measurement instrument as 0.89 in subjects with normal kyphosis and as 0.94 in subjects with hyperkyphosis (11); however, while the population of the present study consisted of young and healthy subjects, the average age of subjects was ≥ 60 years in the mentioned studies (10,11). Elderly subjects showed more postural stiffness in the thoracic region compared with younger subjects (31). This factor might make a difference in repeated measurements; therefore, the differences in characteristics of the study population between the present study and the mentioned studies should be considered when comparing results. This issue should be addressed in future studies.

In previous studies, the concurrent validity of some indirect measurement methods and instruments has been studied (1,13). In these studies, the validity among methods or instruments was assessed with a correlation analysis (1,13). Such an approach has not been followed in the present study because Bland-Altman analysis is recommended to compare methods instead of correlation analysis (29). In the present study, the coefficient of determination obtained by using the linear regression was used to reveal the proportion of variance that the two instruments, but in addition, the Bland-Altman plot was presented to describe agreement between the instruments. In this study, the Bland-Altman analysis demonstrated a small mean difference with narrow limits of agreement. This means the smartphone application can be used instead of the digital inclinometer for measuring thoracic kyphosis angle. Shahri et al. compared a smartphone application with the Cobb angle on lateral radiographs and reported that an acceptable agreement between the smartphone application and the Cobb angle (20); however, the limits of agreement were wider than those calculated in the present study, and in our opinion, reported intervals in the mentioned study were not small enough to reach a conclusion that the methods could be used interchangeably. It was probably caused by a small sample size (n = 31) of the mentioned study; sample size is a factor that affects the limits of agreement (29,32). If it was performed with a larger sample size, in our opinion, the limits of agreement would come closer to the intervals obtained the present study.

Smartphone applications has a substantial advantage in clinical practice. It is not as expensive as other indirect

measurement instruments. Applications can be downloaded for free via the Internet. Clinicians, on the other hand, may not want their personal phone to come in contact with others' skin (33). This may be a barrier to use of smartphone applications in clinical practice.

This study has some limitations. Firstly, the concurrent validity of the smartphone application was not assessed by comparing measurement of the Cobb angle on lateral radiographs, which is accepted as the gold standard method for measuring the thoracic kyphosis angle. The radiographic method was not preferred in the present study because it would expose participants to excessive radiation and, in turn, pose ethical problems (1). Nevertheless, the digital inclinometer was used as a reliable and valid indirect instrument for measuring the thoracic kyphosis angle (14). Furthermore, the generalizability of the results is limited to a young, active, and healthy population, so the findings may not apply to other populations.

5. CONCLUSION

The smartphone application used in this study is a cost-effective, practical, reliable, and valid instrument for measuring the thoracic kyphosis angle in clinical practice. More than 9 degrees in the value of the thoracic kyphosis angle measured by the smartphone application can be considered as a true change. Future studies should assess the reliability and validity of smartphone applications for measuring thoracic kyphosis angle in different populations.

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Research idea:EŞ,GE,SB
Design of the study: EŞ,GE,SB,BÜ
Acquisition of data for the study: GE,SB
Analysis of data for the study: EŞ,GE
Interpretation of data for the study: EŞ, GE, SB, BÜ
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Clinical and Experimental Health Sciences

Evaluation of *in vitro* Antioxidant, Antimicrobial and Cytotoxic Activities of Crude Ethanol Extract and Fractions of *Achillea sintenisii* Hub. Mor.

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ABSTRACT

Objective: The *Achillea* species have been used to treat various ailments due to its anti-inflammatory, hemostatic, spasmolytic and cholagogue effects in the Turkish traditional medicine. However, there is no biological activity studies on some *Achillea* species except for the well-knowns. This work aimed to determine the antioxidant, antimicrobial and cytotoxic activities of the crude ethanolic extracts and fractions of *Achillea sintenisii* using in vitro methods.

Methods: The antioxidant activity was investigated by DPPH (1,1´-diphenyl – 2-picrylhydrazyl), ABTS (2,2´-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) radical scavenging, total phenol and total flavonoid content, and iron chelating methods. Antimicrobial activity evaluated by micro-plate dilution method against five test organisms. Cytotoxicity was determined by MTT method using MCF-7 breast cancer cell line and PC-3 prostate cancer cell line. Apoptosis was also measured by AO/EB staining.

Results: The n-Hexane fractions showed the highest antimicrobial and cytotoxic activities, respectively. Administration of the extracts on the cancer cells showed a concentration dependent inhibition on cell proliferation. The anti-proliferation effect could be via apoptosis and associated with the cell death.

Conclusion: The results showed that the extracts demonstrated antioxidant, antimicrobial, and cytotoxic activity, also supports the claims of traditional usage.

Keywords: *Achillea sintenisii*; antioxidant; microdilution; cytotoxicity

1. INTRODUCTION

The genus of *Achillea* (Asteraceae) is represented in the flora of Turkey by 42 species and 23 of which are endemic in Turkey (1). A list of Anatolia's most important indigenous economic plants includes *Achillea* species. They are frequently used against abdominal pain, and diarrhea as well used as diuretic, emmenagog and wound healing agents in Turkey (2). In phytochemical studies on *Achillea* species, it has been reported that these species are rich in flavonoids, triterpenes, essential oils, fixed oils and sterols (3-12). A wide range of scientific studies on the biological activities of *Achillea* species have been carried out: antioxidant (4,10-11,13-17), antimicrobial (18–22), anti-inflammatory (23-24), wound-healing (25), cytotoxic (15, 26) and insecticidal activities (5).

In recent years, interest in finding antioxidants from natural sources is increasing day by day. The antioxidant-effective phytochemicals such as flavonoids and other polyphenols obtained from plants have been reported to protect the human body from the disease by inhibiting lipid peroxidation and preventing the spread of free radical reactions. In addition, some adverse effects on human health resulting from long-term use of synthetic antioxidants have limited their use. For this reason, research efforts on the potential natural antioxidants that could replace these synthetic antioxidants, began to attract much attention in a couple of years. Therefore, we evaluated antioxidant activities of different extracts prepared from *A. sintenisii* herbs using various *in vitro* antioxidant methods.

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The natural plant origin compounds with antimicrobial activity, have been investigated and used as additives in large quantities in foods (27). Because of their antibacterial effects against a wide spectrum of foodborne pathogens, compounds obtained from natural sources have the potential to be employed for food safety (28). Many antibiotic drugs are showing drug-resistance against human pathogenic bacteria. As a result, more research is needed to evaluate the antibacterial capabilities of plant extracts that can be used in food products without causing harm.

In both industrialized and developing countries, cancer is a major public health issue. In cancer, there is an abnormal growth of cells in the body that could result in death (29). The use of natural sources as anticancer agents is based on very old dates. Nowadays, many drugs used in chemotherapy are of natural origin or derived from natural products, especially from plants (30). Therefore, there is an intense interest in anticancer activity research from natural sources. In recent years, many studies have been carried out on the cytotoxic activity of medicinal plants (31–34).

There was very limited study on the essential oil and extracts of *A. sintenisii* for their antioxidant and antimicrobial activity (35). The antioxidant, antibacterial, and cytotoxic activity of this plant has not been thoroughly investigated. Due to a lack of comprehensive data, the current study was designed to investigate the biological potential of this well-documented plant. Therefore, the aim of the present study was to investigate the quantification of total phenolic and flavonoids as well as *in vitro* antioxidant, antimicrobial and cytotoxic effects of different fractions of the crude hydroalcholic extract of aerial part of *A. sintenisii*. Phytochemical screening was also performed on the extracts to evaluate the presence of phytochemical elements.

2. METHODS

2.1. Plant materials

The plant material was collected during the flowering period in the years of 2016 from Sivas province (Figure 1). Plants were identified by Mehmet Tekin, Ph.D. (Locality, B6 Sivas: Ulaş, Ziyarettepe, N35 33 08,9; E37 01 12,1; 1406 m, 12.06.2016). Voucher specimens were kept for record with the collect number of M. Tekin 1712, in the CUFF Herbarium of Sivas Cumhuriyet University, Faculty of Pharmacy, Department of Pharmaceutical Botany, Turkey.

2.2. Chemicals

DPPH, ABTS, quercetin, Butyrylhydroxy toluene (BHT), ferrous sulphate, ferrozine, EDTA and MTT were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Gallic acid, Folin-Ciocalteu's reagent and 2,3,5-Triphenyltetrazolium chloride (TTC) were obtained from Merck (Germany). The rest of the chemicals and reagents were of analytical quality.

Figure 1. *Habitat image of Achillea sintenisii Hub. Mor.*

2.3. Preparation of crude ethanolic extract and fractions

The shade dried and coarsely powdered aerial parts of *Achillea sintenisii* (100g) were macerated with 80% alcohol (1000 mL) at a water bath with temperature of 40ºC for 48 h. The residue was then filtered using filter paper and extracted twice with ethanol. Following this procedure, all of the extracts were combined and condensed under vacuum using a rotary-evaporator (Büchi, Switzerland) to afford the alcoholic extract (Yield: 12.44%, w/w), and then 10 g of the alcoholic extract after suspending with 500 mL of distilled water, was extracted successively with n-hexane, chloroform, n-butanol and water by separating funnel (The extract from each agent was then filtered, concentrated under vacuum to generate hexane (10.66 %), chloroform (12.93 %), n-butanol (28.7 %) and the final aqueous fractions (26.3 %).

2.4. Phytochemical screening

The prepared crude ethanol extract and partitioned sub-extracts were evaluated by phytochemical qualitative screening tests for herbal secondary metabolites such as terpenoids, alkaloids, antraquinones, flavonoids, tannins, saponins, coumarins, and phenolic compounds. The formation of specific color or the precipitation was regarded as positive for these tests (36).

2.5. Antioxidant activity

The ABTS assay was based on the method of Re et al. with some modifications (37).

Iron chelating activity is one of the commonly used methods to investigate the antioxidant activity, and the complexity of ferric oxide with bivalent iron ions is based on the reduction of the absorbance at the wavelength of 562 nm. Iron ion chelation method was performed according to the method of Salma et al. (38). The ability of ethanolic crude extracts and fractions of *A. sintenisii* to scavenge 1, 1´-diphenyl-2-picryl-hydrazyl (DPPH) free radicals was measured as previously described (39). The total phenolic content of extracts was evaluated using a method described by Lee et al. (40). The

total phenolic content was expressed as milligrams of gallic acid equivalents (GAE) per gram of extract. The flavonoid content of each extract was measured based on methods described by Eruygur et al. (41). The results were expressed as milligrams quercetin equivalents (QE) per gram of extract (mg QE/g extract). The reducing power of the plant extract was analyzed according to the method of Oyaizu (42).

2.6. Antimicrobial Activity

Microbial strains: Antimicrobial and antifungal activities of the extracts and fractions were evaluated against two Gram$^+$ and two Gram– bacteria and one fungus by microdilution method. Test microorganisms were *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Pseudomonas aeruginosa (*ATCC 27853), *Escherichia coli* (ATCC 25922), and *Candida albicans* (ATCC 10231). Geometric dilutions of the extracts were performed in a 96-well microtiter plate. Plates were incubated at 37°C for 24 hours for bacteria and 30°C for 48 hours for yeasts under normal atmospheric conditions. At the end of the incubation period, in order to make breeding visible, each well received 50 µL of 2,3,5-triphenyltetrazolium chloride (Merck, Germany) at a concentration of 2 mg/mL and incubated at 37 °C for 2 hours. The first wells without color change were accepted as MIC values. The test was repeated twice, and the same results were achieved.

2.7. Cytotoxic activity

2.7.1. MTT assay

Cancer cells: Human prostate cancer (PC-3) and human breast adenocarcinoma (MCF-7) cell lines were provided from the American Type Culture Collection (ATCC, USA) were used for the cytotoxicity test for the extracts. The cells were cultivated in RPMI 1640 media containing 10% fetal bovine serum, 100 µg/mL penicillin, and 100 µg/mL streptomycin. Cancer cells were cultured at 37 °C in a humidified environment containing 5% carbon dioxide (43). The cells were treated with different concentrations of different extract of *A. sintenisii*. Then plates were incubated for 24 h, the medium was discharged from the 96-well plate, 10 µL of 3-(4,5 – dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) was added per well, and the plate kept for 2 h in 5% CO_2 humidified incubator at 37°C to allow reaction of yellow colored MTT reduced by mitochondrial dehydrogenases in viable cells to form pink to purple colored formazan. Excess MTT was sucked off, and the resulting formazan crystals were dissolved in 100 µL of dimethyl sulfoxide (DMSO). Using a microplate reader, the absorbance of purple formazan, which is proportional to the number of live cells, was measured at 560 nm (Epoch, USA). The tests were carried out in triplicate. The percentage of cell viability was calculated the following formulae:

% Cell viability= Absorbance of treated cells / Absorbance of the untreated cells × 100

Table 1. *Phytochemical screening results of ethanolic crude extract and fractions of A. sintenisii*

Phytochemical compounds	Phytochemical screening tests	Different fractions of *Achillea sintenisii*				
		n-Hexane Frc.	Chloroform Frc.	Ethanol Ex.	Butanol Frc.	Water Frc.
Carbonhydrates	Molish test	-	-	+	+	+
	Benedict test	-	-	+	+	+
Alkaloid	Dragendorff	–	–	–	–	–
	Mayer	–	–	–	–	–
	Marquis	–	–	–	–	–
Steroid	Salkowski	+	+	–	–	–
Protein	Biuret test	–	–	–	–	–
	Millon's test	–	–	–	–	–
Glycosides	Börntrager	–	–	–	–	–
	Killer-killani	+	+	+	–	–
	Baljet	–	+	+	–	–
Fatty acids	Filter paper stain test	–	–	–	–	–
Saponins	Forth test	–	–	–	–	–
Tannins and phenolics	%5 $FeCl_3$	+	+	+	+	+
	Lead acetate	+	+	+	+	+
	Salted Gelatin	–	+	+	+	+
Flavonoid	Shinoda	+	+	+	+	–
	NaOH	+	+	+	+	–
Coumarin	$FeCl_3$ +HNO_3	–	+	+	–	–
	NaOH + UV	–	+	+	+	–
Essential oil	Sudan III	+	+	+	–	–

2.7.2. Determination of Apoptosis

MCF-7 and PC-3 cells were treated in triplicate with 10 µg/mL concentration of plant extracts in 12-well plates at density of 2 × 10^4 cells/well for 12 hours. A Zeiss Axio inverted microscope (10X) imaging system was used to capture images of cell growth. Quantification of cell growth was done using Methylene blue staining. Acridine orange and ethidium bromide (AO/EB) were used to evaluate apoptosis in MCF-7 and PC-3 cancer cell lines. After a 24 – hour incubation period, 10 µg/mL concentrations of plant extract were applied in triplicate to 12-well plates at density of 2 × 10^5 cells per well. After that, cells were stained with 1µg/mL AO/EB solutions and the fluorescence intensity was measured using a microscope (Zeiss). Apoptotic cells are grouped with red intensity, while living cells are grouped with green intensity.

3. RESULTS

In this study, the ethanol crude extract and different fractions were investigated regarding their phytochemical composition by different phytochemical screening tests. Phytochemical screening of the tested extracts revealed the presence of flavonoids, phenolics, tannins and reducing sugar. Essential oil was also present in the hexane, chloroform fractions and ethanol extract.

The ethanol crude extract and different fractions of the aerial parts of *A. sintenisii* were screened against antioxidant, antimicrobial and cytotoxic activity. Antioxidant activity of the extracts were determined by DPPH, ABTS radical scavenging assay, ferric-reducing antioxidant power (FRAP), ferric ion-chelating, total phenol and total flavonoid content assays. The antioxidant and cytotoxic activity assays were tested at the concentrations of 0-1000 µg/mL. The detailed information about the results of antioxidant activities were given in Table 2 and Figure 2-3.

The Folin-Ciocalteau method was used to determine the total phenol contents (TPC) of the extracts and the TPC was expressed as Gallic acid equivalents (GAE). The TPC of the extracts ranged from 73.67 ± 3.87 to 192.41 ± 1.60 mg GAE /g extract according to our findings (Table 2). The extracts' total flavonoid content was determined using $AICl_3$ colorimetric method and representeded as quercetin equivalents (QE). According to the results, total flavonoid content ranging from 5.09 ± 5.84 to 117.69 ± 6.88 mg QE/g dry extract and the content was found in the decreasing order of n-butanol Frc.>Hexane Frc. >Chloroform Frc. > ethanol extract > aqueous fractions.

As for antimicrobial activity, the n-hexane fractions showed stronger inhibitory activity against tested gram-positive and gram-negative microorganisms and the MIC value ranges from 0.31 to 5 mg/mL, while other fractions showed no activity (Table 3).

The cytotoxic activity of the extracts was evaluated by MTT assay, the observed results strongly profile that there was a concentration dependent cytotoxic effect of the extract against MCF-7 and PC-3 cancer cells (Figure 4-5). The apoptosis of the cancer cells treated with the 100 µg/mL concentration of different extracts was determined staining with acridine orange (AO) and ethidium bromide (EB) dual staining and observed by fluorescence microscope. The fluorescence images of AO/EB staining are given in Figure 6 and the staining ratio of MCF-7 and PC-3 cells are shown in Figure 7.

Table 2. *Extraction yield, total phenolic, flavonoid content and antiradical activities of ethanolic crude extract and fractions of A. sintenisii.*

Extract or fraction	Yield of extract (%, w/w)	Total flavonoid content (mg QE/g)	Total phenol content (mg GAE/g)	DPPH radical scavenging activity IC_{50} (µg/mL)	ABTS radical scavenging activity IC_{50} (µg/mL)
Ethanol extract	12.44	41.46 ± 1.61	118.91 ± 1.91	895.42 ± 0.09[a]	590.26 ± 0.55[a]
Hexane Frc.	10.66	98.92 ± 7.35	73.67 ± 3.87	553.56 ± 0.81[b]	337.92 ± 0.93[b]
Chloroform Frc.	12.93	76.71 ± 3.18	176.91 ± 2.39	585.78 ± 1.48[b]	468.83 ± 0.29[c]
n-butanol Frc.	28.70	117.69 ± 6.88	192.41 ± 1.60	394.39 ± 1.04[c]	398.07 ± 1.25[d]
Water Frc.	26.30	5.09 ± 5.84	76.85 ± 2.92	513.17 ± 1.07[b]	429.53 ± 0.51[c]
Ascorbic acid				106.17 ± 0.97[d]	
Trolox					65.53 ± 0.57[e]

Values are expressed as mean ± SD of triplicate experiments. Different letters in the same column were significantly different (p<0.05) from each other.

Table 3. *Minimum inhibitory concentrations (MIC) of different extracts of A. sintenisii aerial parts*

S/No.	Microorganisms	Ethanol extract and fractions from ethanol extract of *A. sintenisii* (Concentration mg/mL)				
		Hexane frc.	Chloroform frc.	Ethanol ext.	n-Butanol frc.	Water frc.
1	*E. coli*	>5	>5	>5	5	5
2	*S. aureus*	0.31	5	>5	>5	>5
3	*P. aeruginosa*	>5	>5	>5	>5	>5
4	*E. faecalis*	>5	>5	>5	>5	>5
5	*C. albicans*	1.25	5	>5	>5	>5

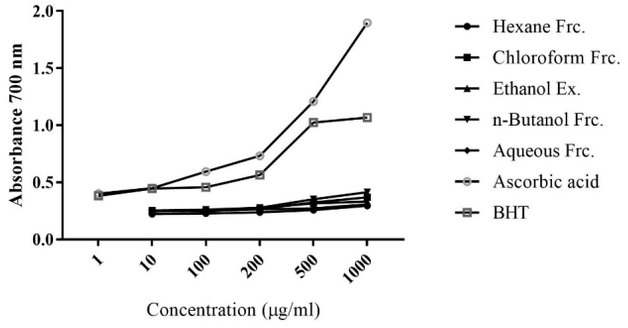

Figure 2. *Ferric reducing power of A. sintenisii extracts*

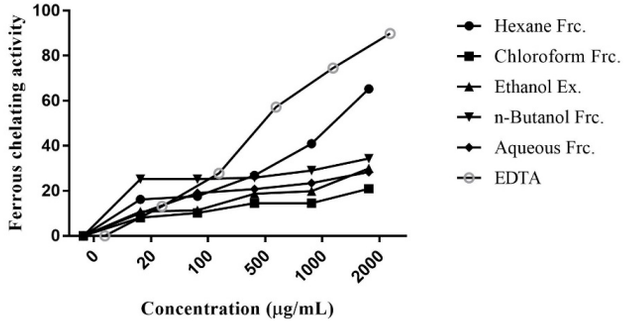

Figure 3. *Iron chelating activity of A. sintenisii extracts*

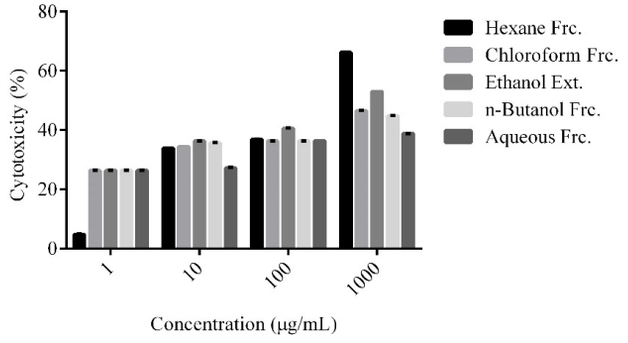

Figure 4. *Cell growth inhibition results of MCF-7 cells treated with A. sintenisii extracts after 24 hours*

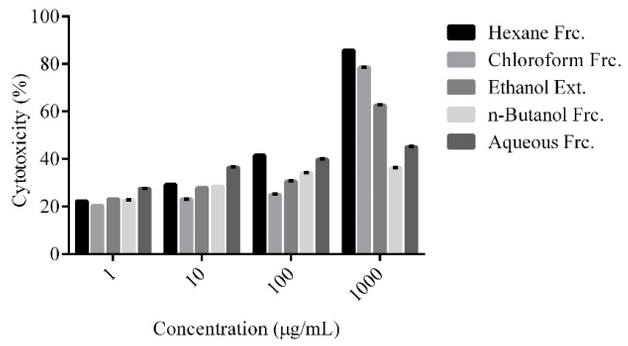

Figure 5. *Cell growth inhibition results of PC-3 cells treated with A. sintenisii extracts after 24 hours*

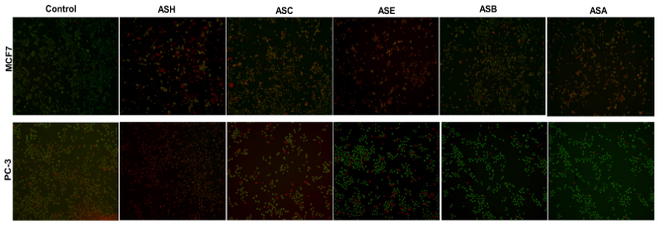

Figure 6. *AO/EB staining fluoresce images of MCF-7 and PC-3 cells treated with different A. sintenisii fractions after 24 hours (100 µg/mL)*

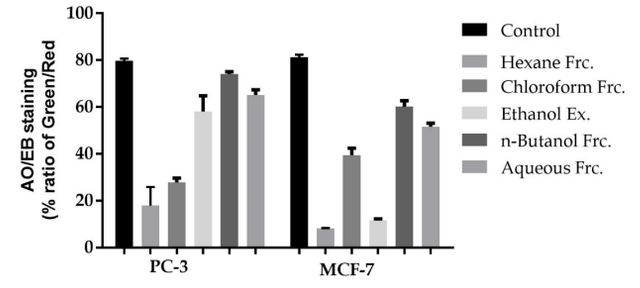

Figure 7*. AO/EB staining ratio of PC-3 and MCF-7 cells treated with A. sintenisii extract (100 µg/mL) for 24 hours*

4. DISCUSSION

Plant extract's antioxidant properties play a vital role in the prevention, treatment, and management of a variety of diseases and disorders associated with inflammation and oxidative stress. The over-releasing of reactive oxygens species in the biological system led to developing of chronic disease. This study showed the *in vitro* antioxidant activity of different extracts obtained from *A. sintenisii* using different antioxidant assays. The radical scavenging activity of different extracts obtained from *A. sintenisii* was determined by DPPH and ABTS radical scavenging assay. The DPPH radical scavenging activity of the different evaluated extracts found to be as n-butanol frc. > aqueous frc. > hexane frc. > chloroform frc. > Ethanol extract. The ABTS radical scavenging activity of the different evaluated extracts found to be as hexane frc. > n-butanol frc. > aqueous frc. > chloroform frc. > ethanol extract. The redox characteristics of flavonoids and phenolics, as well as the structural interactions between different portions of their chemical structure, are primarily responsible for their radical scavenging activity (44). In the Folin-Ciocalteu's assay, the n-butanol fraction was found to be the most polyphenolic enriched extract of TPC (192.41 ± 1.60 mg GAE /g extract) compared to the other fractions. Moreover, there was no data is available on the previous investigations on the TPC of different extracts of *A. sintenisii*. Phenolic contents in extracts obtained from other *Achillea* species were also reported. Agar et al. reported that the total

phenolic content of *A. coarctata, A. kotschyi* and *A. lycaonica* was expressed as mg gallic acid equivalent of 55.16 ± 0.96, 148.00 ± 0.92 and 76.49 ± 1.67 g dry extracts, respectively (26). These results are in agreement with our TPC results found in different extract of *A. sintenisii.* The variance in total phenolic amounts may be related with different parameters such as pretreatment, extraction method, plant species, geographical location and harvesting time etc. In a previous study, phenolic composition of *A. sintenisii* was determined by HPLC method and luteolin, vitexin, and schaftoside were found as the major phenolic compounds in water and aqueous ethanol extracts (45).

Table 3 shows the MIC of different extracts of *A. sintenisii*. All tested bacterial strains were not sensitive to the extracts except for the *S. aureus* and the yeast *C. albicans.* Previously, several *Achillea* essential oils were reported for their antimicrobial activity. The essential oil of *A. teretifolia* and *A. nobilis* were found to be active against the tested human pathogen microorganisms with the MIC value of 0.5-2 mg/mL (18). In another study of *A. teretifolia* essential oil was studied against fourteen microorganisms and showing MIC values of 0.28 to 2.25 mg/mL (46). Karaalp et al. reported antimicrobial properties of thirteen *Achillea* species flower extract and found that hexane extract of *A. coarctata* and *A. setacea* showed antibacterial activity against *E. faecalis* with 31.25 and 62.5 µg/mL MIC values. *A. teretifolia*, *A. multifidi* were found to have antimicrobial activity ranging from 50 to 75 µg/mL against *S. aureus, S. epidermidis* and *S. typhymurium* (47).

Further, we studied the *in vitro* cytotoxicity of the different extracts of *A. sintenisii* against two different human cancer cell lines by commonly used MTT cytotoxicity assay. The extracts all we studied showed cell growth inhibition in a dose-dependent manner up to 1000 µg/mL. In fact, the anticancer activity of *A. sintenisii* has not been shown in the literature. In a previous study, the methanolic extract of *A. odorata* showed strong dose dependent *in vitro* cytotoxicity against MCF-7, HepG2, and WEHI cell lines (48). The ethanol and methanol-chloroform extracts of *A. coarctata* and *A. monocephala* were evaluated for cytotoxic activity against Hela cells and found that the cells highly inactivated over the concentration of 100 µg/mL (49). A recent study has showed that of *A. kotschyi* and *A. lycaonica* have high cytotoxic effect on MCF-7 cancer cells lines (15).

Nevertheless, this is the first report on the *in vitro* antioxidant, antimicrobial and cytotoxic activity of *A. sintenisii* crude ethanol extract and different fractions. Some fractions showed more active than the crude ethanol extract. Further phytochemical investigations are underway to identify the possible active constituents responsible for the biological activity by bioassay-guided isolation techniques.

5. CONCLUSION

The results of the current study reports that all the extracts of *A. sintenisii* have shown significant antioxidant and cytotoxic effects and moderate antimicrobial activity. A significant difference in antimicrobial activity was not observed between the tested extracts except for hexane fraction. The findings of this study point to the possibility of using *A. sintenisii* as a source of antioxidants. Furthermore, the active fraction of *A. sintenisii* may lead to the presence of new cytotoxic active ingredients by phytochemical studies based on its cytotoxic activity.

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Clinical and Experimental Health Sciences

Comparison of the Rapid Antigen Test to RT-qPCR in Diagnosis of SARS-CoV-2: A University Experience in Northern Cyprus

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ABSTRACT

Objective: As an alternative to RT-qPCR assays used in the diagnosis SARS-CoV-2, antigen-detecting rapid diagnostic tests (Ag-RDTs) are available for the qualitative detection of SARS-CoV-2 in nasopharyngeal swab samples. The aim of this study was to assess the accuracy and reliability of Ag-RDTs as a diagnostic method of detecting SARS-CoV-2 positive cases within a given population.

Methods: In first phase of this investigation, 357 nasopharyngeal swab samples were screened for SARS-CoV-2 using Ag-RDTs. For the purposes of this study RT-qPCR was then applied to the same 357 nasopharyngeal swab samples in order to compare the reliability of the two detection methods. In the second phase of this investigation, Ag-RDTs were applied to an additional 75 nasopharyngeal swab samples that were already known to be RT-qPCR positive.

Results: In the first phase of this investigation, of the 357 samples screened using Ag-RDTs 14 samples were positive for SARS-CoV-2, in contrast, when RT-qPCR analysis was applied to the same 357 samples no SARS-CoV-2 samples were detected. Therefore, the false antigen positivity was determined to be at 3.9%. In the second phase of this investigation 75 RT-qPCR positive samples were re-evaluated with a rapid antigen test. Twenty-four of the 75 RT-qPCR positive sample were undetected.

Conclusion: Solely relying on rapid antigen tests to detect SARS-CoV-2 infections in the community could consequently result in infectious individuals remaining in the population. The impact of false negative rapid test results can be reduced by implementing confirmatory RT-qPCR analysis particularly in symptomatic patients.

Keywords: SARS-CoV-2, RT-qPCR, Antigen, Test, Northern Cyprus

1. INTRODUCTION

The COVID-19 (Novel Coronavirus Disease 19) pandemic, caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), led to an unprecedented public health crisis (1). While the pandemic continues worldwide, rapid and reliable tests are urgently needed for the diagnosis of COVID-19 (2). Nucleic acid amplification tests (NAATs), such as real time reverse transcription polymerase chain reaction (RT-qPCR) assays, are referred to as the gold standard test used in the diagnosis of SARS-CoV-2 acute infection. Although standard RT-qPCR protocols have high sensitivity and specificity, they can be time-consuming and expensive (3,4).

As an alternative to PCR assays, antigen detecting rapid diagnostic tests (Ag-RDTs) are available for qualitative determination of SARS-CoV-2 associated antigen (5). Antigen based tests are inexpensive and can return results within 15-30 minutes. These tests are designed to directly detect SARS-CoV-2 proteins (4,6,7). The accuracy of Ag-RDTs depends on several factors, such as the time elapsed from the onset of infection and symptoms, the viral load in the specimen, the processing of the specimen, and the quality of the reagents in the test kits (7). Sensitivity of Ag-RDTs in the detection of SARS-CoV-2 compared to NAATs SARS-CoV-2 detection sensitivity in nasal/nasopharyngeal swab samples were found to be highly variable. Their sensitivity ranging from 0-94%, while specificity is >97% (4). According to data by the World Health Organization (WHO), Ag-RDTs may generate false negative results in COVID-19 patients with low viral load. Consequently the need for further development of these tests is essential and are therefore not recommended for use in clinical diagnosis (5,8).

The aim of this study was to determine the accuracy of the SARS-CoV-2 Ag-RDT that is currently used in several countries as a diagnostic tool for the detection of SARS-CoV-2 found in nasopharyngeal/oropharyngeal swab samples.

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2. METHODS

Ethics committee approval was obtained for our study with the project number NEU/2021/95-1411 at the meeting held by the Near East University (NEU) Scientific Research Ethics Committee on 30.09.2021.

2.1. Study Groups and Study Design

The study involved two types of analyses. Initially, in the first phase of the study, Ag-RDTs and RT-qPCR were performed on 357 specimens that were collected from Near East College students and teachers between 1st and 30th April 2021. In the second phase of our study, Ag-RDTs were applied to 75 SARS-CoV-2 positive patients' samples, which were verified by direct swab specimen and RT-qPCR at the DESAM Research Institute, COVID-19 Diagnostic Laboratory between 28th May and 30th June 2021. For the second phase of the study, following the identification of 75 SARS-CoV-2 positive samples using RT-qPCR, Ag-RDTs were also applied immediately to the same swab samples collected from the 75 SARS-CoV-2 positive patients. All samples were collected as part of the routine COVID-19 screening protocol as set out by the Ministry of Health of Northern Cyprus.

2.2. Ag-RDT and RT-qPCR Analyses

The SARS-CoV-2 (COVID-19) Antigen Test (Softec, in-vitro diagnostic, Istanbul/Turkey) kit represented the selected Ag-RDT used in this investigation. This test is an immunological test that detects the nucleocapsid antigen (N) of the SARS-CoV-2, based on the principle of the double antibody sandwich technique. The sensitivity and specificity of the rapid antigen test kit according to the manufacturer was 96.38% and 99.17% respectively.

The Ag-RDT was performed in accordance with the recommendations of the manufacturer using nasopharyngeal/oropharyngeal swab samples collected from individuals. Briefly, nasopharyngeal swabs which were collected from individuals were transferred to a viral transport media immediately and 50 µl of the specimen was taken directly from the transport tube and applied onto the antigen test cassette, the results were evaluated after 15 minutes.

All RT-qPCR tests were performed using the Bio-speedy SARS-CoV-2 Double Gene RT-qPCR (Bioeksen, Ar-Ge Tekn. A.Ş., Istanbul/Turkey) kit. In accordance with the manufacturer's instructions, the kit was designed to detect *ORF1ab* and the *N* gene of SARS-CoV-2. In accordance with the FDA, a cycle threshold (CT) value less than 38.00 in a given RT-qPCR run of a sample was considered negative to the presence of SARS-CoV-2 (9). Each RT-qPCR study included a negative and positive control for quality control purposes.

The 75 RT-qPCR positive specimens which were also re-evaluated with Ag-RDTs were initially categorized into groups based on the samples Ct value. The groups were as follows: Group A: Ct of 10-19.99; Group B: Ct of 20-29.99; Group C: Ct of 30-38.

2.3 Statistical and Simulation Analysis

Statistical analysis of the data obtained was conducted using SPSS (Statistical Package for the Social Sciences) Demo Version 22.0 (SPSS Inc., Chicago, IL, USA) program. Pearson Chi Square and One Way ANOVA were used to determine the statistical significance and $p<0.05$ values were considered statistically significant.

The simulation analysis was used to simulate the collective results of SARS-CoV-2 positive cases which were detected in the DESAM Research Institute, COVID-19 Diagnostic Laboratory using RT-qPCR and Ag-RDT. A total of 865 SARS-CoV-2 RNA positive cases which were diagnosed using RT-qPCR between 01 July 2020 and 25 June 2021 were included in the simulation analysis. The SARS-CoV-2 RNA positive cases were separated into 3 groups (Group D: 10.00-19.99, Group E: 20.00-29.99, Group F: 30.00-38.00) based on their Ct values. A Ct value above 38.00 were not included into the groups. One Way ANOVA test were used to determine similarities among the groups (D to F).

3. RESULTS

In the first phase of this study, a total of 357 Ag-RDTs samples were re-evaluated for SARS-CoV-2 using RT-qPCR. Initially a total of 14 Ag-RDTs positive samples were obtained, however the RT-qPCR results of these 14 antigen positive samples together with the remaining 343 samples all tested negative for SARS-CoV-2 using the extracted RNA (as the template) from the specimens. Thus, the false positive rate of the antigen test (Ag-RDTs) used was 3.9%.

To further assess the reliability of rapid antigen tests in the detection of SARS-CoV-2, 75 RT-qPCR positive samples were re-evaluated with a rapid antigen test. While 51 (68%) of the 75 RT-qPCR positive samples included in the study were antigen positive, 24 (32%) were negative. These 75 SARS-CoV-2 RT-qPCR positive samples were assessed and categorized according to the Ct values (Table 1). The mean Ct values in antigen positive and negative samples were 20.46±3.95 (between 12.05-31.40), 26.03±3.28 (between 18.84-31.60) respectively. The difference between the mean Ct values of antigen positive and negative patients was statistically significant ($p=0.001$) (Figure 1). Accordingly, it was determined that the antigen test may not detect patients with a low viral load (Ct: 30.00-38.00) and in turn giving a false negative result. Table 2 displays the sensitivity, specificity, PPV (positive predictive value) and NPV (negative predictive value) of the antigen kit tested.

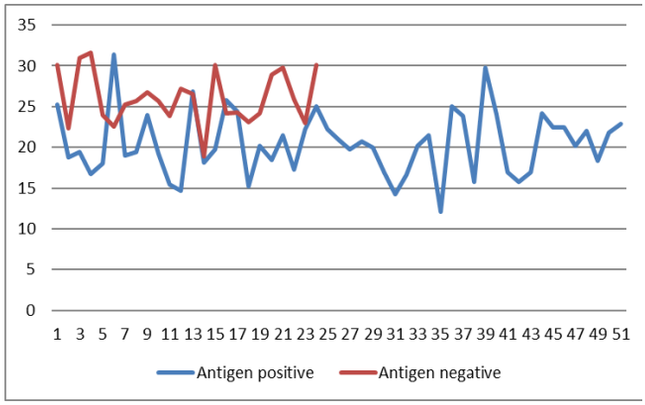

Figure 1. *Distribution of Ct values in antigen positive and negative samples*

These RT-qPCR positive samples were further separated into three groups based on the Ct values; in such group A: Ct of 10-19.99, group B: Ct of 20-29.99, group C: Ct of 30-38, respectively. None of the Ct values of the 75 samples were higher or equal to a Ct of 38. Group A was composed of 25 samples, 24 of which tested both positive for SARS-CoV-2 by RT-qPCR and antigen testing. On the other hand, Group C contained six samples, five of which are RT-qPCR RNA positive and antigen test negative (false negative). The false negative rate of Group A, B and C were determined and shown in the Table 1. The false negativity rate of the antigen test in patients with low viral load was 83.3%. According to Table 1, as the Ct values increase, the false negative rate of the antigen test also increases significantly (p=0.001).

Table 1. *Comparison of Ct values of SARS-CoV-2 RT-qPCR positive samples with antigen test results, n (%)*

Group	RT-qPCR RNA Positive / Antigen Test Positive	RT-qPCR RNA Positive / Antigen Test Negative	Total	False Negative Rate
Group A (Ct: 10.00-19.99)	24	1	25	4.0%
Group B (Ct: 20.00-29.99)	26	18	44	40.9%
Group C (Ct: 30.00-38.00)	1	5	6	83.3%

RT-PCR: Real time polymerase chain reaction; RNA: Ribonucleic acid; Ct: Cycle threshold

Table 2. *Performance evaluation of the tested antigen kit*

	RT-qPCR positive	RT-qPCR negative	Total
Antigen positive	51	14	65
Antigen negative	24	343	367
Total	75	357	432
Sensitivity	68.0%		
Specificity	96.1%		
Positive predictive value (PPV)	78.5%		
Negative predictive value (NPV)	93.5%		

RT-qPCR: Real time reverse transcription polymerase chain reaction

Based on the results of this study, a simulation was conducted to predict the reliability of the rapid antigen test in a larger sample size. A total of 865 RT-qPCR positive samples were grouped based on the Ct values of the samples and separated into groups D, E, F (Table 3). The Ct values of Group A and Group D, Group B and Group E, Group C and Group F were separately compared between against each other and there were no statistical differences among the compared groups based on the Ct values (p=0.994, p=0.195, p=0.260 respectively).

In the simulation context, Groups A, B and C false negative antigen test rates can be used to simulate Group D, E and F accordingly. The patients were categorized into A, B and C based on Ct values, this is an indication of the viral load. Thus, if all 865 RT-qPCR positive samples were re-tested with a rapid antigen test, it is predicted that, 402 positive cases (46.53%) would not to be detected as a positive case. In summary, the false negative rate of rapid antigen tests based on real data would be 46.53%.

Table 3. *Simulation analysis results*

Ct Values Range	Antigen Test False Negative Rate (%)	SARS-CoV-2 RNA Positive Cases (n)	If only antigen test was used amount of false negative cases (n)
10.00-19.99 Ct	4.00 (Group D)	120	4.80
20.00-29.99 Ct	40.91 (Group E)	526	215.19
30.00-38.00 Ct	83.33 (Group F)	219	182.49
Total	-	865	402.48

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RNA: Ribonucleic acid; Ct: Cycle threshold

4. DISCUSSION

COVID-19 pandemic has brought about the need for rapid and sensitive diagnostic tests to detect the SARS-CoV-2 as quickly as possible in order to avoid the spread of the virus and manage patients infected with SARS-CoV-2 appropriately. Rapid antigen tests are cost-effective, easy to use, and can be manufactured in large quantities (10). Ag-RDTs as their name suggests are quick in providing a result, but as this study has confirmed, the performance is dependent on the viral load, the quality of the specimen and the processing phase (11). In this study, the performance of the antigen test used in the routine screening of SARS-CoV-2 was determined by re-confirming the antigen test results with RT-qPCR and vice versa. Although the sample size in each Ct group is not evenly distributed, the preliminary data at hand suggests that the sensitivity of the antigen test may be dependent on viral load.

The sensitivity and specificity of the Softec SARS-CoV-2 Antigen Test (Turkey) kit as advertised by the manufacturer is 96.38% and 99.17%, respectively. The first phase of this study comprised 357 asymptomatic individuals who were part of a routine screening process of college students and teachers for SARS-CoV-2, as part of the Northern Cyprus COVID-19 public screening program. To further assess the

sensitivity and specificity of the antigen test kit, 75 SARS-CoV-2 RT-qPCR positive samples which were initially detected with RT-qPCR as part of routine public screening, were also tested with the antigen test kit. Collectively, based on these results, the sensitivity and specificity of the Softec SARS-CoV-2 Antigen Test kit was 68.0% and 96.1%, respectively. Our study suggests that the antigen test kit sensitivity was relative to the patient's viral load, that is, the patients with relatively higher Ct values (Ct>26) were more likely to generate false negative rapid antigen test results. These findings suggest that rapid antigen tests are less effective amongst asymptomatic individuals, when compared with RT-qPCR results. In addition, the PPV of antigen testing amongst asymptomatic individuals was calculated to be 78.5%. The correlation between lower viral loads and false-negative results by rapid antigen tests has also been noted by others (12,13). Previous studies have also demonstrated that PPV and sensitivity being particularly low in asymptomatic individuals. In the study of Barrera-Alvalos et al., 55 patient samples with positive RT-qPCR results at different Ct values were investigated. Ag-RDTs was performed on all of these samples, and none of the samples above >30 ct values were found to be positive. The sensitivity of the Ag-RDT was 90% in samples with RT-qPCR Ct value between 20≤Ct<25, 10% between 25≤Ct<30 and 0% in samples with >30 Ct value (14). In accordance with these collective findings, the WHO has announced that the sensitivity of antigen tests varies and negative diagnostic testing results should be assessed depending on the circumstances of the population and should be considered as presumptive results (15).

Phase 2 of this investigation is summarized in Table 3. The Ct values in Group A (10.00-19.99), B (20.00-29.99) and C (30.00-38.00) is representative of 865 SARS-CoV-2 RT-qPCR positive patients and is an indication of the reality of viral load in the North Cyprus population. According to statistical simulation the false negative rate following rapid antigen testing of real data is predicted to be 46.53%. To further validate the results from the current study a larger sample number of SARS-CoV-2 PCR positive samples with Ct values between 30-38 is required.

5. CONCLUSION

In this study, it has been demonstrated that antigen test kit sensitivity appears to be dependent to the patient's viral load, higher Ct values (Ct>26) were more likely to generate false negative rapid antigen test results. As indicated by the second phase of the investigation, relying solely on rapid antigen tests to detect SARS-CoV-2 infections could consequently result in infectious individuals remaining in the population. In agreement with the recommendation by the CDC (2021), the impact of false negative rapid test results can be reduced by implementing confirmatory RT-qPCR particularly in symptomatic patients.

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Author Contributions:

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Acquisition of data for the study: EG, FT, EŞ, MÇE, PT, BD, CSÖ, GT

Analysis of data for the study: EG, FT, EŞ, MÇE, PT, BD, CSÖ, GT

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Clinical and Experimental Health Sciences

The Relationship of Trunk Control with Lower Extremity Sense, Balance, and Walking in Individuals with Stroke

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ABSTRACT

Objective: This study was conducted to investigate the relationship between trunk control and lower extremity sense, balance and gait in stroke individuals.

Methods: Thirty subacute and chronic stroke patients were included in the study (mean age 52. 2 ± 14.4 years). Trunk Impairment Scale (TIS) and Turkish version of Postural Assessment Scale for Stroke Patients (PASS-T) was used for evaluating the body control, and Tinetti Balance Test (TBT) was used for evaluating balance. Tinetti Gait Test (TGT) and Ten Meter Walking Test (TMWT) were applied for evaluating walking. The light touch sense and proprioception, Fugl-Meyer Assessment of Sensorimotor Function (FMASF) for lower extremity were used. Furthermore, neglect, plantar pressure sense and stereognosis for lower extremity were evaluated.

Results: There was a significant positively strong correlation between TIS and TBT, TGT and FMSMFT, and negatively strong correlation between TIS and TMWT ($p<0.05$). There was a significant positively strong correlation between PASS-T and TBT, TGT and FMSMFT, negatively strong correlation between TMWT ($p<0.05$). TIS, PASS-T, TBT and TGT values were found significantly high in the presence of plantar pressure sense and stereognosis; and significantly low in the presence of neglect ($p<0.05$).

Conclusion: Trunk control is related with lower extremity sense and affects balance and walking.

Keywords: Stroke, postural balance, lower extremity, sensation, walking

1. INTRODUCTION

Stroke is characterized by the loss of neurons in the brain as a result of a decrease or interruption of blood flow. Although stroke ranks third as the cause of death in developed countries, it ranks first among neurological diseases in terms of mortality and disability (1). In general, stroke patients have a lack of physical function. In this respect, patients and their families face economic, social, and psychological distress and the quality of life of patients is affected negatively (2).

In stroke individuals, postural control affects functional status. The trunk is among the key points of the body. Proximal trunk control must be provided in terms of distal extremity movements, balance, and functional activities. Although trunk control provides static and dynamic posture, it also ensures the upright posture of the body and selective trunk movements (3). Peripheral input occurs in trunk balance, during sitting up and standing up from sitting. Extremity functions are associated with sensory information. Previous studies reported that sensory loss in the lower extremities affects standing, gait speed, balance during ambulation, and symmetrical gait negatively (4,5).

Sensory-perception disorders are among the problems experienced by individuals with stroke. This can be seen as the inability to perceive the senses or the inability to distinguish these senses. Sensory problems of patients must not be ignored during evaluations (6). Although the control of our movements is controled by the primary motor cortex area, the sense of position is controled by the sensory cortex (7). The initiation, continuity, and coordination of the movement are controlled by the sensory field. Adaptation to the environment is achieved with the development of perception (8). Previous studies reported that sensory impairment has effects on walking speed, gait symmetry, standing, and walking balance (9).

Balance is one of the important factor that affect standing and walking in stroke patients. The activity of daily life and social activities is provided by motor functions. Patients face difficulties in performing many motor functions e.g. walking with the deterioration of balance. In the literature, the effect of balance on many motor functions e.g. walking was investigated in stroke (10). However, studies that examine the relations between foot balance and gait with trunk control and lower extremity sense are limited. For this reason, it is important to evaluate the balance in detail. The hypothesis of the study is that presence of lower extremity sense increases

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trunk control, and increased trunk control improves balance and walking ability in stroke individuals.

The purpose of the present study was to evaluate the relations between trunk control and lower extremity sense, balance, and gait in stroke patients.

2.METHODS

2.1. Participants

The study was planned as a cross-sectional study. A total of 30 patients followed up with the diagnosis of stroke in two private hospitals between January 2021 and June 2021, were recruited voluntarily in the study. Those two hospitals were selected across by using a random sampling method. Individuals with stroke, who were 30-85 years old, able to walk 10 meters without assistive device, lower extremity functions in the 2-6 stage according to Brunnstrom Recovery Stages, patients having subacute and chronic stroke, those with 7 ≥ on Hodkinson Mental Score were included in the study. Individuals with neurological and orthopedic problems that may affect walking other than stroke, those who had a history of cardiovascular and rheumatological diseases that prevent their daily activities, with lesions or fractures in the lower extremities, lower extremity spasticity 4 according to the Modified Ashworth Scale (MAS), aphasia and communication disorders were not included (Fig. 1).

The Ethics Committee approval of the study was taken from SANKO University, Non-interventional research ethics committee on 07.07.2020 with the number 2020/09. The study was registered at ClinicalTrials.gov (NCT05244850).

2.2. Measurements

2.2.1. Trunk Impairment Scale (TIS)

The Trunk Impairment Scale consists of 3 parts; static sitting balance (3 items), dynamic sitting balance (10 items), and coordination (4 items). The total score of TIS is between 0 and 23. High scores show good trunk control (11). Turkish validity and reliability study of TIS was conducted by Sag et. all (12).

2.2.2. Postural Assessment Scale for Stroke Patients – Turk (PASS-T)

It is used to measure balance in individuals with stroke inadequate in terms of physical performance and includes 12 items measuring balance performance according to the degree of difficulty.

In general terms, it includes conditions in changing positions, which are transitions e.g. lying down, sitting, standing up, and going from standing to sitting. There are two main headings in the scale; maintaining and changing the posture. The scale is scored between 0-36 points. The ability to move is tested between 0-3 points. “0” shows the lowest value and “3” the highest value (13). Kandemir et al. conducted the Turkish validity and reliability of this scale in 2018 (14).

2.2.3. Tinetti Balance and Gait Test (TBT and TGT)

Tinetti Balance Test and Tinetti Walking Test are often used in clinical practice (15). This test consists of two parts and a total of 16 questions, which are balance in 9 questions and walking in 7 questions. Score calculation is made by observation, 2 points show that the movement is performed correctly, 1 point shows that there are adaptations in the movement, and 0 points show that the desired movement cannot be performed. A total score of 18 or less after the test shows a high fall risk, 19-24 shows a moderate fall risk, and a score above 24 shows a low risk of falling. The Turkish version of the scale was studied by Ağırcan (16).

2.2.4. 10-Meter Walking Test (TMWT)

The patient is asked to walk at a normal walking speed for a distance of 10 meters and the time is noted in the 10-Meter Walking Test (17). Increased time shows slow walking speed.

2.2.5. Fugl-Meyer Assessment of Sensorimotor Function (FMASF)

Fugl-Meyer Assessment of Sensorimotor Function consists of 12 items; 4 assessing light touch, 8 assessing proprioception sense. The total score is between 0-24. The sense of light touch is tested from lef and foot subjectively. Position sense evaluation of the lower extremities is tested on the toe, ankle, knee, and hip joints (18). The therapist first asks the patient to move up and down by making joint movements on the unaffected side in the proprioception evaluation, then asks the patient to answer by making 4-5 repetitions on the affected side with the eyes closed, within the limits of approximately 10 degrees of joint range of motion.

2.2.6. Neglect, Plantar Pressure Sense (PPS) and Stereognosis

Clock drawing test was used for neglect. In this method, the patient is asked to place numbers from 1 to 12 in a circle drawn earlier. If the numbers do not scatter in the circle and add up in one half, it is considered to be a neglect.

PPS is evaluated with a stick. The patient is asked to tell the localization of the stick placed horizontally on the plantar surface. When the stick localization is not correct, the sense is considered absent.

Stereognosis is the ability to recognize an object from its shape, size and structural features. During the examination, the patient’s eyes should be closed. In the meantime, he is asked to name objects such as keys, pens, lighters that he can easily recognize (19). If the object are not identified correctly, it is considered asteregnosia (no stereognosis).

2.3. Analysis

The conformity of the data to the normal distribution was tested with the Shapiro Wilk Test. The Mann Whitney U Test was used to compare the two independent groups. The relations between numerical variables were tested with the Spearman rank correlation coefficient. As descriptive statistics, mean ± standard deviation was given for numerical variables, and number and % values were given for categorical variables. The Statistical Package for the Social Sciences (SPSS) for Windows version 24.0 was used for statistical analysis and $p<0.05$ was considered statistically significant.

According to the 'Trunk performance after stroke and the relationship with balance, gait and functional ability' study (20), when the effect size was 0.73, the required minimum number of patients was determined as 12 ($\alpha=0.05$, and the power of the test=0.80). When Post-hoc power analysis was examined according to the relationship between TIS and FMSMFT, PASS-T and FMSMFT, the power of the study was found to be 0.99 (G*Power 3.1, Düsseldorf, Germany).

3.RESULTS

The demographic data, disease information and presence of plantar pressure sense, stereognosis and neglect, results of TMWT, TBT, TGT, TIS, PASS-T, and FMASF of the individuals are given in Table 1.

Table 1. *Socio-demographic characteristics and clinic features of the participants*

Variables		n (%)	Mean±SD	Median (Min-Max)
Gender	Male	17 (56.7)	-	-
	Female	13 (43.3)	-	-
Age (years)		-	52.17 ± 14.44	52 (30 – 82)
Height (cm)		-	167.23 ± 8.8	169 (153 – 180)
Weight (kg)		-	76.7 ± 19	72.5 (40 – 110)
BMI (kg/cm^2)		-	27.49 ± 6.96	27.05 (15.63 – 44.85)
Smoking	No	23 (76.7)	-	-
	Yes	7 (23.3)	-	
Alcohol	No	28 (93.3)	-	-
	Yes	2 (6.7)	-	-
Dominant Side	Right	27 (90)	-	-
	Left	3 (10)	-	-
Affected Side	Right	12 (40)	-	-
	Left	18 (60)	-	-
Stroke Type	hemorrhagic	9 (30)	-	-
	Ischemic	21 (70)	-	-
Stroke Stage	Subacute	6 (20)	-	-
	Chronic	24 (80)	-	-
Other disease	No	11 (36.7)	-	-
	Cardiovascular Disease	3 (10)	-	-
	Hypertension	4 (13.3)	-	-
	Hypertension and Diabetes Mellitus	5 (16.7)	-	-
	Other	7 (23.3)	-	-
PPS	Yes	25 (93.3)	-	-
	No	5 (16.7)	-	-
TIS		-	18.23 ± 4.07	19 (6 – 23)
PASS-T		-	27.9 ± 6.19	28 (12 – 36)
Stereognosis	Yes	20 (66.7)	-	-
	No	10 (33.3)	-	-
Neglect	Yes	4 (13.3)	-	-
	No	26 (86.7)	-	-
FMASF		-	6.62 ± 2.05	7 (2 – 11)
TMWT		-	44.53 ± 15.04	40.5 (21 – 77)
TGT		-	13.16 ± 3.67	13.0 (6-19)
TWT		-	5.47 ± 1.98	5.5 (2 – 9)

BMI: Body Mass Index, PPS: Plantar Pressure Sense, TIS: Trunk Impairment Scale, PASS-T: Turkish version of Postural Assessment Scale for Stroke Patients, FMASF: Fugl-Meyer Assessment of Sensorimotor Function, TMWT: Ten Meters Walk Test, TBT: Tinetti Balance Test, TGT: Tinetti Gait Test.

The TIS values were found to be significantly higher in the presence of PPS (p=0.002) and stereognosis (p=0.001) and the absence of neglect (p=0.001). The PASS-T values were significantly higher in the presence of PPS (p=0.002) and stereognosis (p=0.001) and the absence of neglect (p=0.001) (Table 2).

Table 2. *Comparison of TIS and PASS-T Values with and without PPS, Stereognosis, and Neglect*

n=30		TIS Mean±SD	p	PASS-T Mean±SD	p
PPS	Yes	19.28 ± 3.05	0,002*	29.44 ± 5.24	0,002*
	No	13 ± 4.85		20.2 ± 4.92	
Stereognosis	Yes	20.1 ± 1.97	0,001*	30.9 ± 4.04	0,001*
	No	14.5 ± 4.7		21.9 ± 5.4	
Neglect	Yes	12 ± 4.55	0,001*	16.75 ± 3.4	0,001*
	No	19.19 ± 3.1		29.62 ± 4.49	

**p<0,05, Mann Whitney U testi.*
PPS: Plantar Pressure Sense, TIS: Trunk Impairment Scale, PASS-T: Turkish version of Postural Assessment Scale for Stroke Patients

A positive correlations was found between TIS and TBT (r=0.542, p=0.002), TGT (r=0.641, p=0.001) and FMASF (r=0.730, p=0.001). Although negative significant correlation was found between TMWT (r=-0.736), p=0.001) (Table 3), a positive correlations were found between PASS-T and TBT (r=0.646, p= 0.001), TGT (r=0.769, p=0.001), FMASF (r=0.695, p=0.001), and a significant negative correlation was found with TMWT (r=-0.862, p=0.001) (Table 3).

Table 3. *Correlations between TIS and PASS-T to TMWT, TBT, TGT, PASS-T and FMASF*

n=30		TBT	TGT	FMASF	TMWT
TIS	r	0.542*	0.641*	0.730*	-0.736*
	p	0.002	0.001	0.001	0.001
PASS-T	r	0.646*	0.769*	0.695*	-0.862*
	p	0.001	0.001	0.001	0.001

**p<0,01, Spearman rank correlation coefficient.*
TIS: Trunk Impairment Scale, PASS-T: Turkish version of Postural Assessment Scale for Stroke Patients, FMASF: Fugl-Meyer Assessment of Sensorimotor Function, TMWT: Ten Meters Walk Test, TBT: Tinetti Balance Test, TGT: Tinetti Gait Test.

The TBT values were significantly higher in the presence of PPS (p=0.001) and stereognosis (p=0.014) and the absence of neglect (p=0.001) and TGT values were found to be significantly higher in the presence of PPS (p=0.001) and stereognosis (p=0.004) and the absence of neglect (p=0.026) (Table 4).

Table 4. *Comparison of TBT and TGT Values with and without PPS, Stereognosis, and Neglect*

n=30		TBT Mean±SD	p	TGT Mean±SD	p
PPS	Yes	20.32±3.96	0.001*	5.96±1.74	0.001*
	No	15±5.74		3±1	
Stereognosis	Yes	21.45±3.1	0.014*	6.2±1.74	0.004*
	No	15.4±4.7		4±1.63	
Neglect	Yes	10.75±2.99	0.001*	3.5±1.29	0.026*
	No	20.77±3.17		5.77±1.9	

**p<0,05, Mann Whitney U Test. PPS: Plantar Pressure Sense, TBT: Tinetti Balance Test, TGT: Tinetti Gait Test*

4.DISCUSSION

In the present study, in which we aimed to examine the relations between trunk control and lower extremity sense, balance, and walking in stroke individuals, it was found that trunk control was associated with lower extremity sense, balance, and walking.

Many studies were conducted on the loss of postural control in individuals who had a stroke before (21,22). In a study that was conducted by Çekok et al., 42 stroke patients were included and postural control was evaluated by using the PASS-T Scale (23). Postural control was found to be weak in previous studies. In the present study, postural control was evaluated with PASS-T, and postural control was found to be weak in parallel with the literature data.

The common opinion reached in studies is that sensory impairments are found in most stroke individuals. The somatosensory function impacts on activity performance and length of hospital stay (24). In their study, Sommerfield et al. evaluated regression and deterioration in sensory functions and observed them in 40% of individuals who had a stroke (24). Approximately half of the stroke patients face sensory impairments, mainly tactile sense and proprioceptive sense. In general, they face problems in receiving, interpreting, and responding to sensory inputs. Impaired proprioception sense was detected in approximately 50% of stroke patients (25). It was reported that because of sensory impairment, patients cannot adequately feel the extremities of the affected side, perceive it as a foreign limb, and for this reason have difficulty in performing functions (26). Previous studies reported that patients with stroke had impaired balance because of loss of PSS (27). In a study conducted by Kafa et al., it was found that the time to stand in balance and the sense of light touch showed a significant relation (28). In another study, it was found that different environmental conditions cause different effects on the body. Different surfaces used in this study affected sitting balance to varying degrees although lying down. it was reported in another study that individuals with stroke could not transfer enough weight to the affected side because of

low muscle strength and sensory problems, and for this reason, exhibited poor sitting. In another study, it was found that the contact surface of the sole and the back of the thigh changed the center of gravity (29). For this purpose, the relations between trunk control and lower extremity sensation were examined in the present study where we used FMASF for lower extremity sensation, it was found that trunk control increased as sensation increased. Although there are few studies on trunk position sense in patients with neurological problems, it was concluded that trunk or extremity position sense affects balance and functional activities. For this reason, it was emphasized that trunk training must be included in rehabilitation programs (30-32). The data obtained from the present study show parallelism with the results of the literature, and as a result, as lower extremity sensory impairment increased, walking speed and ability decreased.

In the present study, both the light touch and proprioceptive sense of the lower extremity were assessed with FMASF, which was used to evaluate the lower extremity sense along with PSS and stereognosis. It was found that there was a significant relationship between lower extremity sense and trunk control and postural control. It was also found that hemiplegic side sensory impairment affects gait and balance. As a result, the central nervous system needs as much enhanced environmental information as possible to initiate and maintain motor activity. The central nervous system adjusts the joint angles, the position of the extremities, and the body according to the information it receives from the senses. For this reason, the importance of sensory education in stroke rehabilitation must not be overlooked.

The evaluation of balance in stroke patients gives clinicians an idea of the severity of the stroke. In this respect, the most appropriate physiotherapy method is determined and the treatment results are evaluated (33,34). Clinically useful, short, and sensitive measurements are preferred. In clinical settings to reduce the burden of evaluation that forces patients and assessors to assess balance (35).

In the present study, trunk control was evaluated with TIS and PASS-T, the balance was evaluated with TBT, and trunk control was found to be associated with balance in parallel with the literature. We believe that it is important to create rehabilitation programs for trunk control in balance training in stroke patients.

The main target in the rehabilitation of stroke individuals is to ensure independent walking (36). Approximately 85% of patients walk with an assistive device after stroke (37). The problems faced by such people regarding walking are decreased walking speed and asymmetric gait pattern (38). The main target of gait training is to provide a normal gait pattern and speed (37). The criteria for successful walking in hemiplegic patients have not been identified fully, however, the positive effect of rehabilitation in terms of endurance and walking speed has been proven (39).

There are many methods employed to evaluate gait. These scales are often preferred because of their low cost and easy application. For walking to be effective, neural and non-neural structures must continue in a coordinated manner. To ensure this agreement, somatosensory input must be provided with proper postural control. Also, muscle tone and muscle strength must be normal, a normal range of motion must be provided and cognitive control is necessary. Gait function is significantly affected by the involvement of these structures. In hemiplegic patients Verheyden et al. examined the relations between trunk performance, balance and walking, and functional abilities in 21 chronic stroke patients. When the results of the study are evaluated, it was concluded that there is deterioration in trunk stability in stroke individuals and this affects walking, balance, and functional skills (19). Similarly, in a study that was conducted by Kim et al., 23 individuals with chronic stroke, TIS was used to assess trunk impairment along with the Berg Balance Scale, TMWT, and Timed-Up Go Test (TUG) to evaluate balance and walking ability. As a result of their study, they reported that trunk performance affects balance and walking activities in individuals with stroke (40). Isho et al. examined the relations of trunk control with mobility performance and gait in their study using TIS, Berg Balance Test, and TUG. They found a significant relationship between the total score of TIS and TUG. Takuya Isho et al. concluded that trunk impairment affected mobility performance and trunk stability in walking negatively (41).

As a result, they reported that dynamic balance increased with the improvement of trunk control. They also mentioned the necessity of trunk control for extremity movements (42).

In this regard, present study had some limitations. First, due to the crosssectional design of the study, the long-term causal relationships between various factors, could not be evaluated. Also the included individuals with and without sensory loss, stroke type and stage are not equal. Therefore, our study findings may not be generalizable to the all stroke patients.

5. CONCLUSION

In conclusion, not only motor disorders but also sensory disorders must be considered in the evaluation and treatment of balance and postural stability problems in individuals with stroke. As well as the treatment programs focusing on motor problems, treatment methods aimed at improving the trunk control must also be included. We believe that the results of our study will contribute to the studies to be conducted in this field and will give a different perspective to those who want to work in this field.

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Clinical and Experimental Health Sciences

Nasal Sprays Containing Mometasone Furoate Can Be Used Prophylactically in COVID-19 Infection and Related Smell Disorders

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ABSTRACT

Objective: We aimed to emphasize the possible beneficial effects of intranasal sprays containing mometasone furoate, especially for preventive treatment or supportive treatment in patients with olfactory disorders due to damage to the olfactory area, or for regular use in healthcare workers with a high risk of close contact.

Methods: Preventive and therapeutic scientific studies are continuing around the world for viral spread and viral damage associated with the Coronavirus disease 2019 (COVID-19) pandemic. We investigated the attachment of the COVID-19 virus in the nose and entry into the body with the crystal structure of the spike and Angiotensin-Converting Enzyme 2 (ACE-2) proteins, a molecular docking study. This scientific study is the first in-silico study to investigate the possible antiviral effects of Mometasone furoate molecules on spike protein and to show the antiviral effect of mometasone furoate on COVID-19.

Results: We think that nasal sprays containing mometasone furoate can be used prophylactically in patients with COVID-19 infection due to its antiviral effect, and it may be beneficial to use sprays containing mometasone furoate before the symptoms of upper respiratory tract infection begin in patients.

Conclusions: The role of these molecules in the treatment of acute smell disorders associated with COVID-19 infection and their antiviral effects on coronavirus should be investigated by conducting extensive scientific studies on the subject.

Keywords: Anosmia, Coronavirus, Mometasone furoate, Prevention, Olfactory disorders

1. INTRODUCTION

Mometasone furoate (9α,21-dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,2-dione) is an organic heterocyclic corticosteroid containing functional groups such as hydroxyl, furoate and chlorine. It is used in medicine to treat skin problems such as atopic dermatitis, psoriasis, and allergies. Mometasone furoate is used intranasally in the treatment of patients with allergic rhinitis, and intranasal use has reduced side effects compared to oral use (1). As for pharmacokinetics, no dangerous situation of Mometasone furoate has been reported like other corticosteroids in the literature (2,3). Furoate functional group decreases the possibility of systemic side effects by increasing the destruction of the particles participating in the systemic circulation in the liver. The systemic absorption of mometasone furoate nasal spray has been proven to be minimal and bioavailability <1%. Thus, given that Mometasone furoate has a relatively higher binding affinity to the glucocorticoid receptor than fluticasone furoate and corticosteroids such as Fluticasone propionate, Budesonide and Triamcinolone acetonide, the amount of unbound Mometasone furoate nasal spray in the body has never been detected in plasma (3,4).

Since the COVID-19 pandemic began, many researchers have focused on research into the symptoms of this viral infection, preventing the spread of infection and possible tissue damage associated with coronavirus infection. There are several scientific studies discussing the effects of using nasal sprays containing mometasone furoate on patients with COVID-19 infection and loss of smell, and the possible effects on recovery of olfactory loss (5,6). However, in our current literature review, we did not find any scientific study conducted on humans that directly investigated the antiviral

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effect of mometasone furoate on coronavirus. According to the results of our virtual docking study, we think that the early use or prophylactic use of nasal sprays containing mometasone furoate, especially in patients with COVID-19 infection, can reduce the existing sensory damage with its antiviral effect.

This study aims to investigate the possible antiviral effects of mometasone furoate on the COVID-19 virus, and to use it as a nasal spray in people infected with the COVID-19 virus, besides its known anti-inflammatory effects; It is emphasized that its possible antiviral effects may also be effective in reducing damage to the olfactory mucosa.

The use of mometasone furoate as a nasal spray as soon as the diagnosis is made, without waiting for any smell disorders to occur, can also benefit from its local anti-inflammatory effects as well as its antiviral effect, and reduce the bilateral obstructive inflammation of olfactory clefts. Again, we think that it may be appropriate to use nasal spray forms prophylactically, especially for health personnel who are in close contact with coronavirus, and quarantined individuals with COVID-19 contact.

2. METHODS

In a molecular docking investigation, Autodock Vina v.1.2.0 software (7,8) was used to assess the binding affinity for Mometasone furoate. The spike and ACE-2 proteins' X-ray crystal structures (9) were determined using the X-ray diffraction technique with a resolution factor of 2.45, which was obtained from the RCSB Protein Data Bank (https://www.rcsb.org/). The molecular structure of Mometasone furoate (Deposition Number: 299143) was obtained from the CCDC (https://www.ccdc.cam.ac.uk/) and was used for molecular docking (10). Water molecules were removed from the protein structures and polar hydrogens and Kollman charges were added. Using Discovery Studio Visualizer 2021 v21.1.0.20298 (Dassault Systèmes; San Diego, CA, USA: 2021), the amino acids in the catalytic domain of receptors were determined (11). As a docking engine, the Lamarckian Genetic Algorithm was used, with all docking settings set to default. From ten conformations obtained by docking calculations, the inhibitors with the lowest energy docking score were chosen. For the depiction of 3D figures, UCSF Chimera 1.16 (University of California, CA, USA: 2021) was used (12).

3. RESULTS

Mometasone furoate was tested on spike protein, one of the most critical proteins of the coronavirus, using the *in-silico* method. Two calculations were performed, namely the spike protein and its contact with the ACE-2 receptor, and the results were compared (Figure 1).

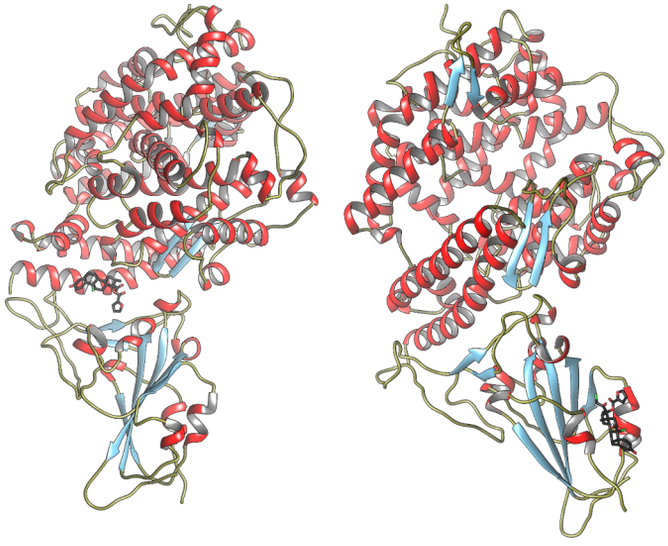

Figure 1. *Demonstration of the interaction of mometasone furoate with both the spike protein and its contact site with ACE2.*

When the spike protein results were evaluated, the binding affinity of the macrocyclic mometasone furoate to the enzyme was – 7.00 kcal/mol and it formed conventional hydrogen bond type interactions with the catalytic domain. One of these conventional hydrogen bond interactions is between ASN343 (Asparagine) and the carbonyl, and the length of the interaction is 2.29Å. again, one of the hydrogen bonds is between SER371 (Serine) and the carbonyl close to the furan ring, and the length of the interaction is 2.15Å (Figure 2).

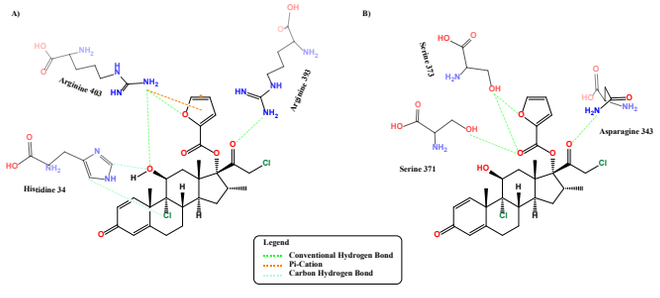

Figure 2. *Mometasone furoate and amino acid interactions diagram. A) Contact zone, B) Spike S1.*

According to the spike protein and ACE-2 contact site docking results, the binding affinity is – 8.2 kcal/mol. In this catalytic region, the carbonyl group of mometasone furoate formed two conventional hydrogen bond interactions with ARG403 (Arginine), and the furan ring formed a π-cation interaction. And again, it formed a conventional hydrogen bond interaction with ARG393 (Arginine). The HIS34 (Histidine) carbons, on the other hand, tend to carbon-hydrogen bonds with the hydroxy and chlorine atoms of mometasone furoate. All conventional hydrogen bond interactions have lengths in the 2.24 – 2.72Å range. π-cation bond electrostatic interaction length is 3.56Å. The carbon-hydrogen bond lengths are 3.53 and 3.64Å, respectively.

4. DISCUSSION

In the current literature, the effect of intranasal corticosteroids on the prevention of olfactory loss associated with COVID-19 infection or the treatment of emerging olfactory loss is not clear. There are limited studies evaluating the treatment of olfactory disorders after COVID-19 infection with intranasal corticosteroid spray therapy (13,14).

The frequency of smell disorders in COVID-19 varies widely between studies. The frequency of anosmia in COVID-19 patients ranges from 22% to 68% (15). However, patients who reported smell disorders were significantly more likely to test positive for COVID-19. As part of the pretest screening of suspected patients, it may be appropriate to use smell disorders as a highly specific manifestation of COVID-19 (5,6-13,14). There are two proposed mechanisms by which COVID-19 causes anosmia. Coronaviruses are known to infect the olfactory epithelium. The human angiotensin-converting enzyme 2 receptor, the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor, is present on olfactory epithelial cells, particularly sustentacular cells, within the olfactory cleft. Inflammation of the olfactory cleft mucosa can reduce airflow, causing conductive ophthalmic disorder (16).

According to the results of our study, we think that nasal sprays containing Mometasone furoate can both reduce edema in the olfactory area by reducing mucosal inflammation in this region with their local anti-inflammatory effects and reduce viral damage due to its reducing effect on viral binding.

Dr. Abdelalim *et al*. emphasized that, unlike other studies, the use of mometasone furoate nasal spray as a topical corticosteroid in the treatment of post-COVID-19 anosmia did not provide superiority over olfactory training regarding olfactory scores, anosmia duration, and recovery rates (6).

Dr. Rashid *et al*. emphasized that the use of nasal betamethasone drops in the treatment of smell disorders associated with COVID-19 infection is beneficial (17). Dr. Singh et al. emphasized that the use of fluticasone nasal spray may be beneficial for smell disorders (18).

Dr. Kasiri *et al*. emphasized that when mometasone furoate nasal spray was used, there was a higher improvement in severe chronic anosmia with COVID-19, as a result of their scientific study on adult patients with COVID-19 infection who developed severe microsomia or anosmia within two weeks (5).

The SARS-CoV-2 virus uses the spike protein S1, which allows the virion to interact with the host ACE2 receptor and adhere to the cell membrane. ACE-2 is a functional receptor for SARS-CoV-2, and its expression and distribution in the nervous system indicate that SARS-CoV-2 can directly or indirectly cause neurological manifestations (19).

The cell surface protein ACE-2 and the protease Transmembrane protease, serine 2 (TMPRSS2) are expressed in sustentacular cells of the olfactory epithelium, but absent or much less in most olfactory receptor neurons. These data show that sustentacular cells are involved in SARS-CoV-2 virus entry and impaired sense of smell in COVID-19 patients (20). According to our study result, nasal sprays containing mometasone furoate can reduce the sustentacular cell damage associated with COVID-19.

Dr. Eliezer *et al*. stated that there may be the sudden and complete loss of smell as a possible symptom in COVID-19 infections, and they emphasized the bilateral inflammatory occlusion of the olfactory clefts in computed tomography and Magnetic resonance imaging (MRI) in patients who described the loss of smell after coronavirus. In the scientific study they published, they defined bilateral obstructive inflammation or inflammation of olfactory clefts while olfactory bulbs are normal (21). In their study, although it was emphasized that corticosteroids should be avoided in patients infected with SARS-CoV-2; according to the results of our virtual docking study, we think that nasal sprays containing mometasone furoate should be used in the early period, especially in patients with acute coronavirus infection, before the symptoms of viral upper respiratory tract infection begin, due to their anti-inflammatory effects and antiviral properties.

Coronaviruses can invade the brain through the cribriform plate, which is close to the olfactory bulb and olfactory epithelium. In this case, there may be some structural changes in the olfactory bulb that cannot be detected in MRI results (19,20). In addition, Yao *et al*. reported that olfactory bulb volume decreased in patients with postinfectious olfactory loss and was inversely related to the duration of olfactory loss (22).

It has recently been emphasized that inhaled corticosteroids not only have anti-inflammatory effects but also have antiviral effects. While ciclesonide and mometasone suppress the *in vitro* replication of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Middle East respiratory syndrome coronavirus (MERS-CoV); It was determined that dexamethasone, cortisone, prednisolone, and fluticasone had no antiviral effects (13) Dr. Miyazawa emphasized that clinical studies are required to determine the preventive effects of nasal mometasone sprays in the treatment of early-stage COVID-19 (23). Since Mometasone has a smaller particle size than other molecules, it may be possible to reach small alveoli as an inhaler (24) and it can also be used as an inhaler in treatment due to its possible antiviral properties. Therefore, there is a need for comprehensive scientific studies on the subject. In the current literature, we did not find any other scientific study that directly evaluated the antiviral effects of mometasone furoate on the COVID-19 virus.

5. CONCLUSION

According to the results of our study, we think that nasal sprays containing mometasone furoate can be used prophylactically in patients with COVID-19 infection due to its antiviral effect, and it may be beneficial to use sprays containing mometasone furoate before the symptoms of

upper respiratory tract infection begin in patients. The role of these molecules in the treatment of acute smell disorders associated with COVID-19 infection and their antiviral effects on coronavirus should be investigated by conducting extensive scientific studies on the subject.

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Clinical and Experimental Health Sciences

Comparison of the Hall Technique and Conventional Compomer Restorations: A 60-Month Follow-up

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ABSTRACT

Objective: The Hall Technique is one biological strategy for sealing carious lesions with preformed metal crowns in primary molars. This study aimed to compare the Hall Technique's survival rate with conventional compomer restorations in caries management in primary molars for 60 months.

Methods: Children with preformed metal crowns placed with Hall Technique and conventional compomer restorations were invited to Pediatric Dentistry Clinics for a 60-month follow-up. The restorations of these children were evaluated clinically and radiographically. Dental health records of 12 and 24-month follow-up appointments were obtained from the electronic archive. The survival rate of the restorations was evaluated by Kaplan-Meier analysis and the success/failure of the restorations by the Chi-Square test. Restorations with finding such as secondary caries, pulpitis, restoration wear/fracture/loss, crown perforation, inter-radicular radiolucency, and internal root resorption were scored according to major and/or minor failure criteria, while satisfactory ones were scored as successful.

Results: Twenty-six primary molars were included in the study. There was no significant difference in the survival rates of preformed metal crowns placed with the Hall Technique (92.3%) and conventional compomer restorations (84.6%) at 60-month follow-up ($\chi^2 = 2.455$, $p = .48$). The Hall Technique (84.6%) was found significantly more successful clinically and radiographically compared to conventional compomer restorations (23.1%) according to the success or failure criteria in 60-month follow-up ($p < .01$).

Conclusion: The Hall Technique was clinically and radiographically more successful than conventional compomer restorations according to the success or failure criteria at 60-month follow-up. The Hall Technique had a similar survival rate to the conventional compomer restorations as well as low failure findings in caries management in primary molars.

Keywords: Carious dentin, dental caries, Hall Technique, pediatric dentistry, primary molars

1. INTRODUCTION

Cavitated carious lesions are an increasing and constant problem, especially in developing countries (1). The conceptual framework regarding the ideal management of carious lesions changed in the last decades (2). Current guidelines recommend combined techniques that have more preventive and less restorative treatment for the treatment of carious lesions in primary teeth (3,4). Conventional restorative techniques have been replaced by less invasive biological approaches that control the cariogenicity of the biofilm and caries (5).

Hall Technique (HT) is a treatment approach introduced by Dr. Norna Hall, which has the biological approach philosophy and includes sealing caries with preformed metal crowns (PMCs) (6). It is a low-tech option for managing early and moderately active carious lesions in primary molars without any signs or symptoms of pulp involvement (7,8). Food residues and debris are removed from the tooth without local anesthesia, caries excavation, or tooth preparation. The appropriate size PMC is cemented to the tooth (6). When the carious lesion is sealed under PMCs, the caries progression in primary teeth may arrest or at least slowdown, and the carious primary teeth may be preserved until exfoliation (9,10). During the COVID-19 pandemic, international guidelines have also recommended minimizing aerosol generation procedures to reduce the risk of viral cross-infection. The Hall Technique, one of the biological caries management techniques recommended for this purpose and has a strong recommendation quality, has become more popular (11).

In conventional procedures, if sufficient resistance and retention can be achieved for the success of the restoration after complete caries removal, primary molars can be treated with restorative materials such as resin-modified glass-ionomer cement, resin-based composite, and compomer. In cases where the carious lesion is more extensive, conventional PMCs that require extra tooth preparation can be applied instead of intracoronal restorations (12). Since intracoronal restorative techniques are more sensitive, they may require general anesthesia or sedation depending on the cooperation of the children (13).

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Hall Technique is more acceptable than conventional restorations by children and parents for reasons such as causing less anxiety in children, and no need to local anesthesia and drilling (14). Also, the effect of the technique is evident in primary teeth, consistent with studies of the biological approach in managing caries (6). A randomized controlled trial reported that major failure at 23 months was 2% in the Hall Technique and 15% in conventional restorations (14). It also reported a 95% survival rate after 12 months (15) and 73% after 36 months for the Hall Technique (7). Although this technique has been reported to be more successful and acceptable by children and parents, general dental practitioners do not routinely prefer PMCs in their clinical practice (16,17). It was shown that 92.3% of 709 pediatric dentists knew about the Hall Technique, but only 50.6% of them applied it (18).

To date and the best of our knowledge, there are no studies evaluating the survival rate of the Hall Technique for 60 months in comparison to the conventional compomer restoration of primary molars. The primary outcome of this study was the survival rates of conventional compomer restorations compared to the Hall Technique in carious primary molars. The null hypothesis tested was that there was no statistical difference in the survival rate between primary molars restored with the Hall Technique and conventional compomer restorations. The secondary outcomes of the study were the success and failure rates of both treatment techniques.

2. METHODS

2.1. Study Subjects

The Clinical Research Ethics Committee of the Marmara University, Faculty of Dentistry gave study approval (Date: 23.12.2019 /Protocol no: 2019-361). The study was registered in the ClinicalTrials.gov under the identification number NCT04818658. The study was conducted in accordance with the principles of medical research involving human subjects described by the Declaration of Helsinki.

The present study is a cohort study evaluating clinical and radiological follow-up of treated primary molars with two different techniques including the Hall Technique and conventional compomer restorative treatments in the Pediatric Dentistry Clinics, Faculty of Dentistry, Marmara University.

First, dental health records in the electronic archive between January 2016 and January 2017 were scanned by the dental software program (Uni-Dis, SDD, Istanbul, Turkey) in March 2021 and 16 children were found that their primary molars treated with the Hall Technique. Of them, 14 children had also conventional compomer restorations in primary molars. A total of 8 children with 26 teeth met the following inclusion criteria (Figure 1): children who were aged five to eight years at the time of dental treatment; had primary molars treated with both Hall Technique and conventional compomer restoration; had primary molars with matching caries sizes in radiographic caries scoring for both techniques in the initial indications (Hall Technique = conventional compomer restoration = 2 or 3); have available records for both 12 and 24-month and agree to come 60-month follow-ups. The children were invited to the Pediatric Dentistry Clinics for their approximately 60-month follow-up appointment.

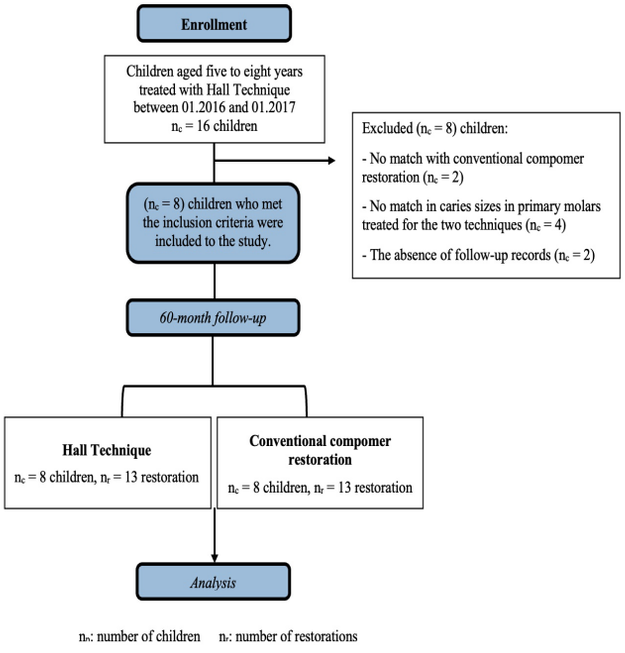

Figure 1. *The flowchart diagram presenting the procedure for selecting primary molars for the study*

The parents and their children who came to the follow-up appointment participated in the study voluntarily and accepted the informed consent verbally and in writing were selected for the study. Baseline radiographs were examined in terms of the extent of the carious lesion and the absence of pathology in the inter-radicular region (follicle of the successional permanent tooth was assessed in terms of differential diagnosis) by a well-trained pediatric dentist (B.S.Y.) under the supervision of the study director (B.K.). Evaluation of the extent of caries was done by modifying the following radiographic criteria: 0: no radiolucency; 1: radiolucency at the enamel-dentin junction; 2: radiolucency in the outer half of dentin; and 3: inner half of radiolucent dentin (19). The treated molars were classified as score 2 or 3 based on the initial dental record.

The sample size was calculated based on the study of de Menezes Abreu et al. (20) 24 teeth (12 teeth for each group) were calculated to be necessary to obtain the power (1 − β) of the test of 85% in the 95% confidence (1 − α) interval.

2.2. Treatment Procedures

Hall Technique procedures have been performed and recorded in the Department of Pediatric Dentistry since the

publication of a treatment protocol by Innes et al. in 2015 (17). PMCs placed using the Hall Technique were cemented at a single visit and no orthodontic elastic was used in any crown. GC Fuji TRIAGE ® (GC America, Alsip, IL, USA) glass ionomer cement was used for the cementation of 3M™ ESPE™ Preformed Metal Crowns (3M ESPE, St Paul MN, USA).

For conventional compomer restorations, the infected carious tissue is completely cleaned with a rubber dam, and local anesthesia is applied if necessary. Glasiosite (Voco, Cuxhaven, Germany) compomer was used in conventional restoration.

The children were invited to the control visit and the teeth included in the study were evaluated clinically and radiographically at each follow-up appointment by the same pediatric dentist (B.S.Y.) with four years of clinical experience under the supervision of the study director (B.K.) according to the success or failure criteria reported by Innes et al. (14). Restorations are considered successful if restoration is satisfactory, no additional treatment required, no clinical signs and symptoms of pulpal pathology or exfoliated tooth. Minor failures include restoration wear/fracture/loss (restorable) or crown perforation, secondary caries or new caries, reversible pulpitis treated without requiring extraction or pulpotomy. Major failures include broken tooth down (unrestorable), inter-radicular radiolucency or internal root resorption, signs or symptoms of irreversible pulpitis requiring extraction or pulpotomy.

Moreover, the occlusal vertical dimensions of the children were evaluated pre-treatment, post-treatment, and after 24 months by modifying a previously described technique (21). On the Hall Technique side, with Image J Version 1.42q (NIH, USA) software, a line parallel to the occlusal plane was drawn from the upper canine cusp tip on the lower canine, and the distance of this line to the gingival zenith point of the lower canine was measured. It was noted whether the increase in this distance after 24 months returned to its initial status.

In the survival analysis, the restorations were assessed as successful or failure. Primary molars that did not show major failure were considered to survive.

2.3. Statistical Analyses

Statistical analysis was performed with SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL., USA) and MedCalc statistical software version 19.8 (MedCalc Software Ltd, Ostend, Belgium). Relationships between categorical variables were tested with the Chi-Square (χ^2) test. Bonferroni correction was performed when comparing the success rates of the two groups. The Kaplan-Meier survival analysis using a Mantel-Cox log-rank model was carried out with 95 percent confidence intervals (CI) to evaluate the survival time for each group. The difference between survival curves was determined using the log-rank test. The significance level was assumed at .05.

3. RESULTS

3.1. Study Population Characteristics

The mean age of the children was 6.23 years (standard deviation (SD): ± 0.72). The number of boys and girls was equal. Fifteen of these restorations were performed on the first primary molar and 11 were on the second primary molar (Table 1). All restorations were placed by the same pediatric dentist (B.S.Y.). It was also observed that all treated teeth had dentin caries involving at least 2 surfaces at the beginning of their treatment. The mean of the total follow-up period of the restorations was 59.8 months (SD: ± 3; between 52 to 62 months).

Table 1. *Distribution of tooth types at baseline per treatment groups*

		Hall Technique n (%)		Conventional Compomer Restoration n (%)	
Initial	Maxillary first molar (n = 8)	3 (23.1)	χ^2 = 0.846 **p** = .83	5 (38.5)	χ^2 = 3.923 **p** = .27
	Maxillary second molar (n = 6)	4 (30.8)		2 (15.4)	
	Mandibular first molar (n = 7)	2 (15.4)		5 (38.5)	
	Mandibular second molar (n = 5)	4 (30.8)		1 (7.7)	

*χ^2 = Chi-square; * = p < .05*

3.2. Clinic and Radiographic Assessment

The 12-month, 24-month, and 60-month follow-up results for clinic and radiographic assessment of restorations were summarized in Table 2. At 60-month follow-up, it was determined that there was a statistically significant difference between the groups (p < .01). Although the success rate of the Hall Technique decreased to 84.6% after 60 months, it was still statistically more successful than conventional compomer restorations (p < .01). When the restorations were compared according to the dental arch they were in, no statistically significant difference was observed between the upper and lower teeth in both techniques (Table 3). When the types of teeth treated were investigated, the success rate in conventional compomer restorations was higher in first primary molars than in second primary molars. However, this difference was not statistically significant (p = .17). When the margin fit of PMCs was assessed, it was found that only one (7.7%) tooth (lower second molar) was unsatisfactory at 60-month follow-up. The 60-month evaluation showed the following minor failures: one restorable crown loss in the Hall Technique, four new caries and four restoration loss in conventional compomer restorations (Table 4). There was one conventional compomer restoration with new irreversible pulpitis requiring pulpectomy in the following 12 months. While internal root resorption accompanying inter-radicular radiolucency was observed in one molar treated with Hall Technique, irreversible pulpitis requiring pulpectomy was observed in one molar treated with conventional compomer restorations in the following 24 and 60 months.

Table 2. *The clinic and radiographic assessment results of the treatments according to the success or failure criteria*

		Successful n (%)	Minor failure n (%)	Major failure n (%)	
12-month	Hall Technique (n = 13)	12 (92.3)	0	1 (7.7)	$\chi^2 = 11.035$ **p** = .004*
	Conventional Compomer Restoration (n = 13)	7 (53.8)	6 (46.2)	0	
24-month	Hall Technique (n = 13)	12 (92.3)	0	1 (7.7)	$\chi^2 = 12.674$ **p** = .002*
	Conventional Compomer Restoration (n = 13)	5 (38.5)	7 (53.8)	1 (7.7)	
60-month	Hall Technique (n = 13)	11 (84.6)	1 (7.7)	1 (7.7)	$\chi^2 = 11.397$ **p** = .003*
	Conventional Compomer Restoration (n = 13)	3 (23.1)	8 (61.5)	2 (15.4)	

*χ2 = Chi-square; * = p < .05*

Table 3. *The assessment results of the treatments by tooth type at 60 months*

		Successful n (%)	Minor failure n (%)	Major failure n (%)	
Hall Technique	Upper teeth (n = 7)	6 (85.7)	1 (14.3)	0	$\chi^2 = 2.787$ **p** = .24
	Lower teeth (n = 6)	5 (83.3)	0	1 (16.7)	
	First molar (n = 5)	4 (80)	0	1 (20)	$\chi^2 = 2.903$ **p** = .23
	Second molar (n = 8)	7 (87.5)	1 (12.5)	0	
Conventional Compomer Restoration	Upper teeth (n = 7)	1 (14.3)	5 (71.4)	1 (14.3)	$\chi^2 = 0.768$ **p** = .68
	Lower teeth (n = 6)	2 (33.3)	3 (50)	1 (16.7)	
	First molar (n = 10)	3 (30)	5 (50)	2 (20)	$\chi^2 = 3.460$ **p** = .17
	Second molar (n = 3)	0	3 (100)	0	

*χ2 = Chi-square; * = p < .05*

Table 4. *The status of the restorations at follow-up appointments by the treatment groups*

Outcomes		Hall Technique			Conventional Compomer Restoration		
		Months					
		12	24	60	12	24	60
Successful	Satisfactory	12	12	7	7	5	1
	Tooth exfoliated	-	-	4	-	-	2
Minor failure	Caries	-	-	-	4	5	4
	Restoration loss (restorable)	-	-	1	2	2	4
Major failure	Irreversible pulpitis	-	-	-	-	1	2
	Inter-radicular radiolucency	1	1	1	-	-	-
	Internal root resorption	1	1	1	-	-	-

3.3. Survival of Restorations

A Kaplan-Meier survival curve was presented for the 60-month follow-up of the Hall Technique and conventional compomer restorations (Figure 2). The primary molars still at risk of failure at the time were censored. At all follow-up appointments, the mean survival rate of the Hall Technique was 92.3% (SE: ± 7.4), and there was no significant difference in the survival rates of the Hall Technique by tooth type (Table 5). The mean survival rate of conventional compomer restorations at 12, 24, and 60-month follow-ups was 100%, 92.3% (SE: ± 7.4), and 84.6% (SE: ± 10), respectively. Also, there was no significant difference in the survival rates of conventional compomer restorations by tooth types at 24-month and 60-month follow-ups (χ^2 = 3.333, p = .34; χ^2 = 2.455, p = .48; respectively). The average survival times at 60-month follow-up were 56.3 months (SE: ± 3.5; CI 49.3 – 63.2) for the Hall Technique and 57.2 months (SE: ± 3.7; CI 49.8 – 64.6) for conventional compomer restorations. There was no statistically significant difference in survival rates between the groups by the log-rank (Mantel-Cox) test (p = .57).

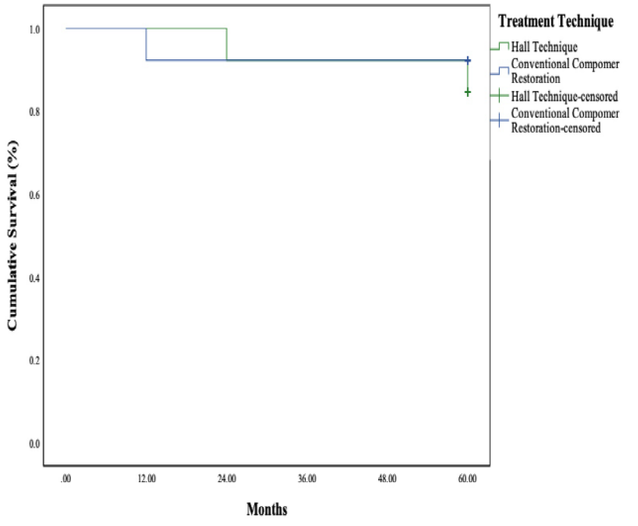

Figure 2. *The survival rates of the two techniques according to the Kaplan-Meier curve*

Table 5. *The survival rates of the treatments according to tooth type at 60 months*

		Hall Technique n (%)		Conventional Compomer Restoration n (%)	
60-month	Maxillary first molar (n = 8)	3 (100)	$\chi^2 = 0.667$ **p** = .88	4 (80)	$\chi^2 = 2.455$ **p** = .48
	Maxillary second molar (n = 6)	4 (100)		2 (100)	
	Mandibular first molar (n = 7)	0		4 (80)	
	Mandibular second molar (n = 5)	4 (100)		1 (100)	

*χ^2 = Chi-square; * = p < .05*

4. DISCUSSION

The philosophy of how to manage dental caries, previously based on complete caries excavation, has changed significantly to the understanding that dentin caries within a selectively isolated environment can be arrested, slowed, and maybe even reversed (22). The effectiveness of the Hall Technique, which was developed as a result of this philosophy, depends on the caries being arrested within an isolated environment when sealed with the PMC (9,23). When the caries is completely sealed, the bacteria cannot reach dietary carbohydrates and the biofilm cannot be metabolized. Since the bacteria cannot produce acids, the cariogenicity of biofilm becomes less (5). In addition, when primary molars were treated with Hall Technique, it has been observed that although the hardness and elastic modulus of tissue was low, the calcium and phosphorus values to support remineralization were higher than the amount in the carious tissue without treatment (24).

The main objective of the present study was to observe whether the Hall Technique or conventional compomer restorations used to restore primary molars showed different survival rates. In this study, the Kaplan-Meier survival curve was used to compare the survival of two different techniques similar to some previous studies comparing the Hall Technique with traditional PMCs (13,15).

The amount and quality of evidence for PMCs fitted using the Hall Technique is increasing (25,26). In retrospective analyzes evaluating the success of PMCs applied with the Hall Technique, the success rate of the Hall Technique was reported 97% at 12 months (13), 97.4% clinically at 20.1 months, 94.9% radiographically at 20.1 months (12), 93.5% at 24 months (27), and 93.4% at 36 months (28). Similar to these studies, the success rate of the Hall Technique in the current study was 92.3% at 12 and 24-month follow-ups; it was also 84.6% at 60-month follow-up and was more successful than conventional compomer restorations. However, the clinic and radiographic success of conventional compomer restorations in this study was 53.8% at a 2-year follow-up and 38.5% at a 5-year follow-up. In the 2-year follow-up study of Santamaria et al., in which the Hall Technique, conventional compomer restorations, and Non-Restorative Caries Treatment were followed in different patients, the success was 67.2% for conventional compomer restorations (29). This success was higher than in the present study. This difference in the success of conventional compomer restorations may be due to the diversity in caries risk in populations. On the other hand, the Hall Technique seals the tooth with PMC and reduces the effect of factors related to individuals such as caries risk factor (30). In support of this view, the success of the Hall Technique is similar in several reported studies (12,13,27-29). The high success of the Hall Technique can be also attributed to the contribution of glass ionomer cement to the remineralization of the carious lesion (31), as well as crown durability and an isolated environment (23). In this study, as in the study of Santamaria et al. (29), PMCs were cemented with GC Fuji TRIAGE glass ionomer cement. Moreover, the cementation with hydrophilic glass ionomers in the Hall Technique may have tolerated the disadvantage of lack of excellent moisture control (32).

When fitting a PMC with the Hall Technique, orthodontic separator elastics could be used for three or four days to place the crown comfortably in teeth with very tight contact. However, it was shown no relationship between the use of orthodontic separators and the margin fit of PMCs in the Hall Technique (14). In this current study, orthodontic separators were not used, and the margin fit in one (7.7%) PMC was unsatisfactory at 60-month follow-up.

Some studies have shown that the Hall Technique has a negligible effect on the temporomandibular joint, masseter muscle activity, and occlusal vertical dimensions (21,33-36). No signs or symptoms of temporomandibular dysfunction were observed 12 months after the Hall Technique (33). Abu Serdaneh et al. investigated the effect of the Hall Technique on masseter muscle activity by surface electromyography. They reported that the rest activity did not change in the sixth week, the clench activity returned to normal in the second week, and increased in the sixth week with no negative effects (34). After PMC cementation, premature contact may cause an increase in the occlusal vertical dimension but is not a problem in situations such as fitting one single crown. The balanced occlusion usually has been re-established within a few weeks (14,35). Supporting these results, Van der Zee et al. (21) and Kaya et al. (36) reported that occlusal vertical dimensions were spontaneously corrected after almost one month following the cementation of PMC. Children may tolerate occlusal changes more than adults. However, the occlusal vertical dimension was observed to be the same as at initial during follow-up visits in the current study.

According to the study comparing PMCs and conventional restorations (CR) including compomer, composite, glass ionomer, resin-modified glass ionomer, and amalgam referenced in the Cochrane database published in 2015 (25), neither group reported pain or major failure in the short-term. Long-term outcomes of the Hall Technique had a lower risk of major failure and pain, but the evidence was of moderate quality (37). Another study reported that both major (CR: 15%, HT: 2%) and minor (CR: 46%, HT: 5%) failure rates were higher in conventional restorations such as compomer, composite, glass ionomer, resin-modified glass ionomer, amalgam, and fissure sealant at 23 months compared to the Hall Technique (14). In this study, like these findings, major and minor failures in conventional compomer restorations were higher. The reason for the high failure rate of conventional compomer restorations might be the high risk of new or secondary caries due to poor oral hygiene (38).

In a randomized clinical trial comparing PMCs placed using the Hall Technique with conventional PMCs, the survival probability of the Hall Technique at 12-month follow-up was 94.5% (15); in a retrospective study, it was 97% at 15-month follow-up (13). In another retrospective analysis, when PMCs are placed using the Hall Technique on teeth with dentin caries on the approximal surface, the survival rate without

tooth extraction was reported as 86% for three years and 80.5% for five years (7). The present study found a 2-year survival rate of 92.3% in dentin caries treated with the Hall Technique, similar to the study of Elamin et al (15). It is remarkable that the survival rates are higher in the Hall PMCs with no caries removal compared to conventional compomer restorations in where all caries is removed. Also, the 5-year survival of first and second primary molars treated with the Hall Technique was not statistically different, similar to the results of Innes et al (7). Although the difference in survival rates is not statistically significant, there might be a biologically significant difference for practitioners.

When the studies on the Hall Technique were analyzed, it was found successful from all the methods compared such as glass ionomer restoration, conventional PMCs, and non-restorative caries treatment (NRCT) (14,15,39). There are three studies in the literature comparing the Hall Technique with compomer restorations (28,30,40). Santamaria et al. stated that the Hall Technique has a higher success rate at 24 months (30) and a higher survival rate at 33 months (29) compared to NRCT and compomer restorations. Kaptan and Korkmaz (40) also reported that the 1-year survival of the Hall Technique is greater than that of compomer restorations.

It might be thought that the force applied when applying PMC to unprepared teeth, may cause discomfort. However, the acceptability of the Hall Technique to children was researched, it was observed that the method was acceptable and there was no discomfort feeling. Instead of applying force by the dentist, the child's biting the PMC keeps the pain the child feels low and makes the Hall Technique more successful (37).

According to the best of our knowledge, there is no study evaluating the long-term survival rate of up to 60 months of the Hall Technique compared to conventional compomer restorations in the caries management of primary molars. Most of the studies on the Hall Technique have evaluated minor and major failures of the techniques (12,13,37). However, the survival study comparing conventional compomer restorations and the Hall Technique for the longest time is a 2.5-year follow-up study (29). Therefore, in this study, investigating the survival rate of techniques was planned as the primary outcome and investigating the success and failure rate of techniques was a secondary outcome.

In summary, with the limitations of the study, the Hall Technique is a successful minimally invasive treatment option with a high survival rate for managing early and moderately active carious lesions in primary molars. The null hypothesis was accepted because it was observed that the survival rate of conventional compomer restorations was not statistically different from the Hall Technique. In addition, it was observed that the success of conventional compomer restorations decreased compared to the Hall Technique, and major and minor failures increased in the long follow-up period. Minor failures that may seem trivial accelerate the restorative cycle of the tooth and translate into major failures in the long term and reduce the survival probability of the restoration. In the long term, the Hall Technique should be considered to be a better option than conventional compomer restorations. The small sample size in the study is a limitation of the study. Another limitation of the study is that the caries size was matched only with the radiographic score, without the International Caries Detection and Assessment System criteria in the allocation to the groups. In addition, the retrospective aspect of the study and therefore the small sample size did not allow for strict inclusion criteria regarding the localization of the lesion.

5. CONCLUSION

This cohort study found that the 60-month survival rate of both techniques was similar when comparing conventional compomer restorations with PMCs placed using the Hall Technique. Furthermore, Hall Technique had more successful results with low failure findings in clinical and radiographic assessment.

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Research idea: BSY
Design of the study: BSY and BK
Acquisition of data for the study: BSY
Analysis of data for the study: BK
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Clinical and Experimental Health Sciences

The Relationship Between Academic Performance and Physical Activity, Smart Phone Use and Sleep Quality in University Students

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ABSTRACT

Objective: Our study was planned to examine the academic achievement, physical activity, smart phone use and sleep quality of university students.

Methods: Young individuals between the ages of 18-25 studying at a vocational school were included in the study. While recording the demographic information of the participants, individuals were classified as "heavy users" and "light users", taking into account the duration of smartphone use during the day. In addition, the physical activity levels of the individuals were evaluated with the International Physical Activity Questionnaire-Short Form (IPAQ-SF), the smartphone usage level with the Smartphone Addiction Scale-Short Form (SAS-SF), and the sleep quality with the Pittsburg Sleep Quality Index (PSQI).

Results: A total of 424 people, 326 of whom were women, with a mean age of 20.30±1.34 years, participated in the study. It was determined that 70.3% of the participants used smartphones for more than 4 hours a day. It was determined that there was a weak negative correlation between the academic success of the students and their physical activity levels, and that their academic success was not affected by smart phone use and sleep quality. However, it was determined that there was a weak positive correlation between the sleep quality of the students and their smartphone use. It was observed that the physical activity levels of male students were higher, while the academic success and sleep quality of normal education students were better.

Conclusion: We think that active life, adequate and conscious smartphone use and quality sleep habits can affect academic success in university students.

Keywords: Academic performance, physical activity, sleep quality, smartphone, students

1.INTRODUCTION

Academic performance, which reveals the level of achievement of individuals' targeted behavior in school life and is generally measured by exams, is a result of education (1). Students' performance is affected by psychological, economic, social, personal and environmental factors (2). In addition, it is stated that the physical activity level and sleep quality of the university students, provided that each of them is a separate factor, can affect academic success (3-6).

Physical activity is anybody activity that requires energy expenditure and is caused by the contraction of skeletal muscles (7,8). In addition to the contribution of physical activity to health, it is thought that it can have a positive effect on academic achievement, as it increases self-esteem in individuals (9,10). The World Health Organization recommends at least 150 minutes of moderate-intensity physical activity per week or 75 minutes of vigorous aerobic exercise per week for adults aged 18-64. (11). Many studies have attempted to determine the relationship between physical activity and academic achievement, and conflicting results have been obtained. While some findings show that there is a positive relationship between academic achievement and physical activity, on the contrary, there are studies that reveal that there is no relationship, or even a weak, negative relationship (3-5).

Advances in technology in the last 20 years have increased the use of internet, smartphones, and social media, and have led to the adoption of a sedentary lifestyle by keeping individuals away from physical activity (12-14). Apart from the convenience that smartphones provide in many areas of life such as business, education, entertainment, communication and commercial activities, the increasing time spent in front of the phone has brought concerns about addiction in individuals (14,15). Studies have shown that the use of smartphones increases the level of phone addiction in individuals, causes many physical and mental problems, but increases academic assistance and success because it increases cooperation and information sharing among students (16-18).

University students experience insomnia and sleep problems due to environmental change, intensive education

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and exams, friendship, messaging and time spent on social media accounts. Quality sleep is defined as feeling rested when the individual wakes up in the morning and feeling ready for the new day both physically and mentally (19, 20). It has been stated that quality sleep facilitates memory, thus facilitating learning, helping to preserve the individual's concentration, cognitive functions, sensoriomotor integration and memory (6).

Studies have shown that academic achievement is positively or negatively affected by physical activity and phone use. On the other hand, studies indicate that quality sleep increases student achievement. Increasing use of technology and spending more time in front of the phone in recent years may cause young adults to adopt a sedentary life away from physical activity. In different studies on this subject in the literature, contradictory results have been revealed. For this reason, our study was planned to reveal the relationship between academic performance of young adults with physical activity, smartphone use and sleep quality with comprehensive research among university students.

2. METHODS

2.1. Individuals

Students were informed about the study. 424 students who voluntarily accepted to participate in the study between November 2019 and January 2020 and who were able to communicate verbally and using smartphones were included in the study. Individuals who were not health vocational college students and had communication and cooperation difficulties were excluded from the study. Our research was conducted with students studying at a health vocational school in the 2019-2020 academic year. This cross-sectional study was approved by the Ethics Committee of the Ankara Yıldırım Beyazıt University (16.10.2019-50).

2.2. Measurements

Academic success

The academic achievement of all students participating in the study was evaluated by recording the year-end Academic Grade Point Average (AGPA).

Physical activity

The International Physical Activity Questionnaire-Short Form (IPAQ-SF) was used to determine the physical activity levels of individuals (21). The questionnaire consists of seven questions questioning the frequency of walking, moderate and vigorous activities, the time spent during the activities, and the sitting time. Using the sum of the duration and frequency values of the activities, the MET values corresponding to basal metabolism were evaluated as the total score. In the calculation of the total score, walking was considered as 3.3 MET, moderate activity 4, vigorous physical activity 8, and sitting activity 1.5 MET.

Smartphone use

Smartphone Addiction Scale-Short Form (SAS-SF) was created by Kowan et al. (22). The scale, whose Turkish validity and reliability was carried out by Noyan et al. in 2015, includes a total of 10 questions (23). The total score ranges from 10-60, and it is stated that as the total score increases, phone addiction increases. The cut-off score of the scale was determined as 31 for women and 33 for men, and the Cronbach alpha coefficient was calculated as 0.867. In addition, those who use a smartphone less than 4 hours a day are classified as "light use", and those who use more than 4 hours a day are classified as "heavy use" (24).

Sleep quality

Pittsburgh Sleep Quality Index (PSQI), which provides information about the sleep quality of individuals in the last month and the type and severity of sleep disorder, was developed by Buysse et al (25). The Turkish validity and reliability of PSQI made by Ağargün et al. 19 of the 24 questions are answered by the person himself, and the remaining 5 questions are answered by the person's bed partner (26). There are 7 sub-dimensions: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime dysfunction. The score of each sub-dimension ranges from 0 to 3. Sleep quality of those with a total score of 5 or less is considered to be "good".

Statistical Package for Social Sciences (SPSS) version 22 software was used for the statistical analysis of the data obtained. The compliance of the variables to normal distribution was evaluated by Shapiro-Wilks test, Q-Q Graphs, and histograms. The mean, standard deviation, frequency, and percentage values of the data were recorded by statistical analysis. Spearman Rho Correlation Analysis was used for the relationship between the evaluation scores, and the Mann Whitney U test was used for the difference analysis between groups. In the post hoc analysis, the power of the study was determined as 99% ($\alpha = 0.05$ for $r = 0.3$). Significance level was accepted as $p < 0.05$.

3.RESULTS

Of the 424 individuals participating in the study, 76.9% were women and 26.3% were men, and the average age of the individuals was 19.53 ± 2.134 years. It was determined that 70.3% of the participants had more than 4 hours of smartphone use during the day, and 51.7% were studying in normal education (Table 1)

It was observed that there was a weak negative correlation between the academic achievement and physical activity levels of individuals (r: – 0.147; p = 0.002), and a weak positive correlation was found between smartphone addiction level and PSQI total scores (r: 0.190; p = 0.000). On the other hand, it was found that academic success was not affected by sleep quality and phone use (p> 0.05) (Table 2)

It was determined that the phone usage levels of the participants did not affect the academic achievement, sleep

quality and physical activity level (p>0.05). It was determined that the academic success rate of women and the level of physical activity of men were higher (p<0.05). In addition, it was found that the academic achievement and sleep quality of the normal education students were better (p<0.05). The comparison of AGPA, PSQI, IPAQ-SF and SAS-SF of the participants' phone usage, gender and educational status is shown in Table 3.

Table 1. *Demographic information and scale averages of the participants (n=424)*

Variable	X±SS
Age (year)	19.53±2.134
AGPA	2.47±0.67
IPAQ-SF	2251.78±2874.169
SAS-SF	29.88±10.313
PSQI	6.55±2.48
Sex	**N (%)**
Female	326 (76.9)
Male	98 (26.3)
Education status	
Normal education	219 (51.7)
Secondary education	205 (48.3)
Daily phone use	
Under 4 hours	126 (29.7)
Over 4 hours	298 (70.3)
Smartphone usage reasons	
Speech and messaging	150 (35.4)
Entertainment (internet, game, TV-movie-video watching, video-photography)	135 (31.8)
Social media (facebook, twitter, instagrametc.)	135 (31.8)
Health (pedometer, calorieetc.)	4 (0.9)
Sleep quality of the participants (based on PSQI scores)	
Healthy sleep (0-5 points)	160 (37.7)
Poor sleep (6-10 points)	239 (56.4)
Advanced sleep problems (over 10 points)	25 (5.9)
Physical activity status of the participants (based on IPAQ scores)	
Inactive group (<600 METs)	112 (26.4)
Minimal active group (600-3000 METs)	205 (48.3)
Active group (> 3000 METs)	107 (25.2)

mean ± standard deviation; Number (Percent); Academic Grade Point Average; Physical Activity Questionnaire-Short Form; Smartphone Addiction Scale-Short Form; Pittspurg Sleep Quality İndexRelationship between participants' AGPA values and IPAQ-SF, SAS-SF and PSQI scores

Table 2. *Relationship between participants' AGPA values and IPAQ-SF, SAS-SF and PSQI scores*

Variable	IPAQ-SF		PSQI		SAS-SF	
	r	p	r	p	r	p
AGPA	**-0.147**	**0.002**	-0.062	0.205	-0.077	0.112
IPAQ-SF			0.020	0.686	-0.045	0.358
PSQI					0.190	**0.000**

Academic Grade Point Average; Physical Activity Questionnaire-Short Form; Smartphone Addiction Scale-Short Form; Pittspurg Sleep Quality İndex; Spearman rho correlation coefficient; significance level Comparison of participants' phone use, gender and teaching status with AGPA, PSQI and IPAQ-SF

Table 3. *Comparison of participants' phone use, gender and teaching status with AGPA, PSQI and IPAQ-SF*

Variable	Light use (n=126)		Heavy use (n=298)		Test statistic	
	IQR	Min; Max	IQR	Min; Max	z	p
AGPA	2.62 (0.79)	0;3.92	2.49 (0.78)	0;4	-1.907	0.057
PSQI	6 (4)	2;14	6 (3)	1;13	-1.203	0.229
IPAQ-SF	1173 (2341)	0; 25200	1245 (2531)	0;15192	-0.052	0.958
	Female (n=326)		**Male (n=98)**			
AGPA	2.57 (0,74)	0;4	2.27 (0.80)	0;3.90	-4.713	**0.000**
PSQI	6 (3)	1;14	6 (3)	2;13	-1.065	0.287
IPAQ-SF	990 (2246)	0;25200	2368.50 (3510)	0;15768	-5.541	**0.000**
SAS-SF	29.50 (16)	10;56	29 (12)	10;59	-1.552	0.121
	Day teaching (n=219)		**Evening teaching (n=205)**			
AGPA	2.55 (0,83)	0:4	2.48 (0.82)	0;3.90	-2.106	**0.035**
PSQI	7 (4)	2;14	6 (4)	1;13	-3.681	**0.000**
IPAQ-SF	1356 (2143)	0;15057	1104 (2826)	0;25200	-1.745	0.081
SAS-SF	30 (13)	10;56	28 (15)	10;59	-1.244	0.214

Academic Grade Point Average; Physical Activity Questionnaire-Short Form; Smartphone Addiction Scale-Short Form; Pittspurg Sleep Quality İndex; İnterquartile range Spearman rho correlation coefficient; significance level

4. DISCUSSION

In our study, it was found that there was a weak negative relationship between the academic achievement of university students and their physical activity levels, while smartphone usage levels and sleep quality did not affect academic success. In addition, it was determined that there was a weak positive correlation between the sleep quality of university students and their phone usage levels. On the other hand, it was observed that the academic achievement of women was higher than that of men, and normal education students compared to secondary education students. It was found that the physical activity levels of the men were higher than the women, and the sleep quality of the normal education students was better than the secondary education students.

The results between physical activity and academic achievement, which is one of the indicators of personal success, are remarkable. In a study conducted with high school students, it was determined that there was no correlation between the physical activity level of the students and their academic performance (27). In a study conducted between students who are involved in physical activity and those who do not, a positive significant relationship was found between physical activity and academic performance, and it was stated that increasing physical activity can increase academic achievement (28). Another study stated that 2-3 hours of physical activity per week increased academic performance, 4 hours or more did not contribute to academic success (3). On the other hand, in a study conducted with 324 university students in Malaysia, it was observed that there was a weak negative relationship between the students' maximum oxygen consumption and their academic achievement (29). In our study, it was observed that there was a negligible negative relationship between the academic achievement

of the students and their physical activity levels, albeit weak. The fact that 75% of the individuals participating in our study led an inactive or minimally active life made us think that the individuals lead a more sedentary life, and that the duration of smartphone use may have increased because of this. We believe that the use of objective measurement parameters in determining the duration, intensity and type of physical activity, long-term monitoring and control of physical activity habits in individuals, and the relationship between academic achievement and physical activity can be revealed more clearly.

In addition, studies have shown that gender affects physical activity. In a study with 101 female and 106 male participants between the ages of 18-25, it was determined that the physical activity levels of men were higher than women (30). In a study by Kızar et al. examining the physical activity levels of university students, it was stated that men had more physical activity levels than women (12). Similar to the literature, in our study, it was observed that male students had a more active lifestyle than female students.

Smartphones can make mobile learning more attractive and easier through mobile applications by minimizing the disadvantages of traditional applications or in-class activities in schools and universities (31). In addition to the life-enhancing effects of smartphones, excessive use among young people also brings some risks (15). It is still unclear to what extent smartphone use, also widespread among students at higher education levels, affects their academic achievement (13). In a study conducted in 2015, it was reported that students who use mobile phones more frequently on a daily basis have lower grade point average (32). In studies conducted with medical school students, it is also stated that increasing the time spent by phone negatively affects academic performance (33,34). Smartphone addiction not only affects individuals' behavior, communication skills, and social lives, but also negatively affects their academic performance (35,36). Contrary to the literature, it was seen in our study that smartphone usage levels did not affect academic achievement. We believe that the differences in the reasons individuals use smartphones may be related to this situation.

Many factors, such as coffee habits, social media and phone use and drug use, can change sleep habits, and the resulting table of insomnia can affect the physical, cognitive and emotional functions of individuals (23, 37). Insufficient sleep has been associated with decreased academic success, and sleep quality can negatively affect the health and emotional state of college students (38,39). In a study conducted with medical faculty students in 2020, it was stated that students' sleeping habits affect academic success (17). The academic success of the individuals participating in our study was not affected by their sleep quality. However, similar to the literature, in our study, it was found that as the sleep quality of the students decreased, the level of phone addiction increased. It was observed that as the sleep quality of the students decreased, their phone addiction levels increased. The literature also showed similar findings in our study that there is a positive weak relationship between smartphone usage levels and sleep quality, and it has been reported that sleep problems may occur with an increase in the time spent in front of the smartphone (15,40). We believe that the adoption of a sedentary life with the technological development in recent years, the increase in interest in virtual environments and the fact that more time is spent may be the reason for this situation.

It can be said that the educational status of the students also affected their sleep quality. In our study, it was found that the sleep quality of the normal education students was better than the secondary education students. The reason for this may be that secondary school students generally stay awake at night and prefer to sleep during the day.

Our study has some limitations. Our research was carried out with students studying health-related education in a single center. Sleep quality, physical activity and smart phone usage habits were evaluated with scales. The use of quantitative assessment methods with different student populations in further studies may reveal more reliable results.

5. CONCLUSION

Although the effect of physical activity on academic achievement has not been clarified yet, it is very important to plan appropriate physical activity with the guidance of a physiotherapist on certain days of the week and for the development of cognitive functions. It should also be taken into account that academic performance can be increased by gaining conscious smart phone usage habits for academic activities in young individuals who are the guarantee of our future. It should not be forgotten that ergonomic recommendations and preventive rehabilitation are important for reducing the time spent on the phone and correcting the postural posture during the time spent. It should be known that quality sleep will play a role in success in young individuals who progress with academic success and set goals. We believe that increasing the activities suitable for young people's research, learning, acquiring knowledge and social skills and providing the necessary guidance and information in order to make conscious use of the time outside of sleep will contribute to the personality and academic development of the youth.

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Clinical and Experimental Health Sciences

Assessment of the Effects of Quince Seed Mucilage and Wheat Germ Oil on Wound Healing in Rats

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ABSTRACT

Objective: People have used traditional herbal medicines for wound care since the dawn of time. This study aimed to assess the cutaneous wound healing effects of wheat germ oil (WGO) and quince seed mucilage (QSM) in rats.

Methods: Adult female Wistar albino rats were allocated to one of the three groups: rats treated with topical WGO (n=6); topical QSM (n=6); and topical saline (n=6) as the control group. Two circular, full-thickness wounds of 0.6 mm diameter were created on the dorsal thoracic region of each rat. Test and control solutions were applied twice daily for 14 days. Wound healing was assessed by measuring the wound contraction rate and the time needed for complete epithelialization.

Results: When compared with the control group, rats in the WGO group had reduced wound closure rates in the first four days, but considerably greater rates in the 8th, 10th, and 12th days, as well as a shorter duration of time needed to complete epithelialization (11 days vs. 13 days). The wound closure rates of the rats in the QSM group were not substantially different from the control rats and the duration of time needed for complete epithelialization was not significantly different from the control group.

Conclusion: WGO use has been shown to improve wound healing. It may be used as an alternative or complementary approach for wound treatment depending on the severity of the wounds. On the other hand, QSM was not found to improve wound healing.

Keywords: Wound healing, wheat germ oil, quince seed mucilage

1. INTRODUCTION

Wound healing is a complex body activity that helps to preserve the integrity of the skin after trauma (1). Wound healing has broad-reaching impacts that go far beyond medical, influencing many areas of personal and social life. Wound infections and delayed wound healing have become a major source of financial strain on healthcare systems around the world in the modern age (2). Wound healing consists of three sequential phases: hemostasis/inflammatory phase, proliferative phase, and remodeling phase. Aberration of wound healing disrupts normal physical activity (1).

Plants may help manage and heal wounds in a variety of different ways. In many cultures, tribal and traditional treatments use a wide range of herbs to heal wounds. Several plants have been utilized in research studies to treat skin problems and wound damage (3). New wound healing therapy research is a growing field in modern biomedical sciences. Various plant extracts were studied for significant wound healing activity using experimental models, and many of them have still to be investigated (4).

Traditional wound healing treatments are commonly applied to the wider population. Among the substances used by the public in wound healing are wheat germ oil (WGO) and quince seed mucilage (QSM). Linoleic acid (18:2 n6), an essential fatty acid, accounts for around 56% of WGO content. WGO has anticancer and antioxidant properties (5). Quince seeds have been shown to include phenolic compounds, organic acids, free amino acids, and pectin (6). QSM is known as cydonin, a condensed colloidal solution with quince seeds comprising 20%-22% of its weight (7).

There are few studies on the effect of QSM on wound healing. The present study aimed to assess how WGO and QSM influenced cutaneous wound healing in rats.

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2. METHODS

2.1. Animals

Adult female Wistar albino rats (n=18) weighing 200-300 g (Marmara University Experimental Research and Animal Laboratory) were used. Following the creation of the wound model, all animals were kept in separate sections under laboratory conditions with constant temperature and humidity. During the experiments, all animals were subjected to the same stress under the same conditions. The Marmara School of Medicine Animal Care and Use Ethics Committee authorized all methods for this study's experimental protocols (15.02.2013-99.2012.mar).

2.2. Experimental Groups

All rats were randomly allocated to one of the three groups: rats treated with topical wheat germ oil (WGO) (n=6); topical quince seed mucilage (QSM) (n=6); and topical saline [ie. sérum physiologique] (SP) (n=6) as the control group, and the study was conducted on these groups.

2.3. Materials

QSM: The seeds were extracted from the quince fruit and dried for one day at room temperature. 20 ml distilled water was added to 5 g of dried quince seeds. It was heated at 50–60 ◦C and mixed for 30 min as described by Hemmati et al. (7). The mucilage part of the mixture was used. QSM was prepared freshly every other day following the same procedures.

WGO: A commercial product (Tabia Pure Nature®) of WGO *(Triticum sativum)* that was obtained by supercritical carbon dioxide extraction technique was used.

Other materials used during the experiment: Physiological saline (Eczacibasi Pharmaceuticals), formaldehyde (Aksan), ether sulfuric (Pure Chemistry), distilled water, ketamine HCl (Ketalar®, Pfizer Pharmaceuticals), 0.2% chlorhexidine (Klorhex®, Drogsan Pharmaceuticals), chlorpromazine (Largactil ®, Eczacibasi Pharmaceuticals).

2.4. Wound Model and Treatment

Ketamine (100 mg/kg body weight, intraperitoneal [IP]) and chlorpromazine (5 mg/kg body weight, IP) were used to anesthetize the rats. The anesthetized rats' dorsal hair was then shaved using an electrical clipper, and the short hairs were removed with a depilatory cream. The wound site was cleaned with saline to remove any cream leftovers, then disinfected with a 0.2% percent chlorhexidine solution. Then, using a punch biopsy tool, two circular, full-thickness excisions of 0.6 mm in diameter were formed on the dorsal thoracic region of each rat. The wounding day was enumerated as day 0. Following wound excision, all groups received twice-daily applications of the test and control solutions (WGO, QSM, SP) for 14 days until the end of the study.

2.5. Wound Closure Measurements

The wound-healing rate was assessed by measurement of the wound contraction rate and the time needed for complete epithelialization by methods described by Apikoglu-Rabus et al. (8).

The wound area was measured daily planimetrically for each animal, resulting in a total of 12 wounds for each group per measurement day.

Wounds were first traced on transparent paper with a millimeter-scale to estimate the wound contraction rate. Then, traces on the transparent paper were transferred to photocopy papers of 80 g ⁄m2 weight. The wound traces were cut out and weighed by a precision balance to get more accurate measurements. The matching surface area values in mm2 were calculated using the weights. Wound closure was reported as percentage closure and calculated by the following formula: % closure = [(area on day 0 – open area on day n)/area on day 0] × 100; n represents the day of the measurement. The wound healing rate was calculated for days 2, 4, 6, 8, 10, 12, and 14.

Complete epithelialization time was the other wound healing parameter evaluated visually during the study. 'Complete epithelialization' was considered to be reached when the scar slid off the skin, leaving no raw wound behind. Whether or not complete epithelialization happened was evaluated on the 8th, 10th, and 12th days.

Signs of infection (redness, swelling, wound inflammation, the appearance of a red line around the wound), weight loss, and dehydration were visually assessed.

2.6. Histological Evaluation

At the end of the 14-day experiment, rats were sacrificed by cardiac puncture under ketamine anesthesia. Afterward, the wound tissues were excised and fixed in a 10% formaldehyde solution for light microscopic examination by immersion fixation. Tissues dehydrated by routine histological tissue follow-up by increasing alcohol series (70%, 90%, 96%, 100%) were later made transparent with toluene and blocked by embedding in paraffin. 5 µm sections were taken from the tissue blocks with a microtome (Leica RM2125RT). To evaluate the general structure of the histological sections, hematoxylin-eosin and Gomori's triple staining were applied to determine the changes in the connective tissue structure. All of the preparations were examined and photographed under a light microscope (Olympus BX-51 / Olympus DP72).

2.7. Statistical Analysis

Continuous variables were expressed as mean ± standard error (SE) of the mean, or median (min-max). The

difference between the two groups was analyzed using the nonparametric Mann–Whitney U test. Binomial data were expressed as n (%) and analyzed using Pearson's chi-square test. Various p values were used to detail the power of statistical significance ($p<0.001$, $p<0.01$, $p<0.05$). Statistical significance was set at $p<0.05$. The analyses were performed using the statistical software package SPSS (version 11.5; SPSS Inc., Chicago, IL, USA).

3. RESULTS

3.1. Wound Healing in Rats Treated with WGO

In the first four days, rats treated with WGO exhibited poorer wound closure rates than the control group (significantly lower on the fourth day, $p=0.01$). However, it was found to be significantly higher than the control on the 8th, 10th, and 12th days ($p<0.05$, $p=0.01$, $p<0.05$, respectively). The median time of complete epithelialization was 11 days (ranging from 11 to 13) for the WGO-treated group and 13 days (ranging from 13 to 13) for the control group ($p<0.05$) (Table 1). WGO treatment improved wound healing by reducing the time required for full epithelialization compared to the control group.

3.2. Wound Healing in Rats Treated with QSM

There was no significant difference between SP and QSM groups in terms of complete epithelialization times ($p>0.05$). The QSM group had a median complete epithelialization time of 13 days (ranging from 11 to 13), which was not significantly different from the control group (Table 1).

Table 1. *Wound closure rates (wound closure rate percentage, median, (minimum-maximum))*

Group	2nd day	4th day	6th day	8th day	10th day	12th day	14th day
Control	48.0 (11.8-58.8)	53.4 (26.0-70.8)[a]	64.3 (31.2-83.9)	83.0 (70.5-93.7)[b]	91.8 (86.8-97.4)[a]	94.9 (92.4-98.5)[b]	100.0 (95.7-100.0)
WGO	31.0 (11.2-55.3)	27.0 (9.56-60.6)[a,b]	64.5 (24.1-100.0)	92.7 (82.9-100.0)[b,a]	97.7 (93.2-99.9)[a,b]	100.0 (92.8-100.0)[b]	100.0 (98.0-100.0)
QSM	28.5 (1.44-55.7)	46.7 (24.1-68.7)[b]	62.1 (37.9-78.1)	83.9 (69.5-91.4)[a]	94.4 (88.6-98.0)[b]	97.3 (92.0-100.0)	100.0 (91.6-100.0)

There is statistical significance between values marked with the same letter in each column. ap=0.01; bp<0.05; WGO: wheat germ oil; QSM: quince seed mucilage.

3.3. Histological Findings

After wound creation, it was observed that the general structure deteriorated only in the control group animals treated with SP. Papillae loss in the epidermis layer and thinning of the epithelium were detected. It was determined that the wavy distribution of collagen bundles accompanied the loss of connective tissue, which is observed intensely in the dermis layer. In addition, a decrease was observed in the cellular content of the tissue (Fig. 1-2).

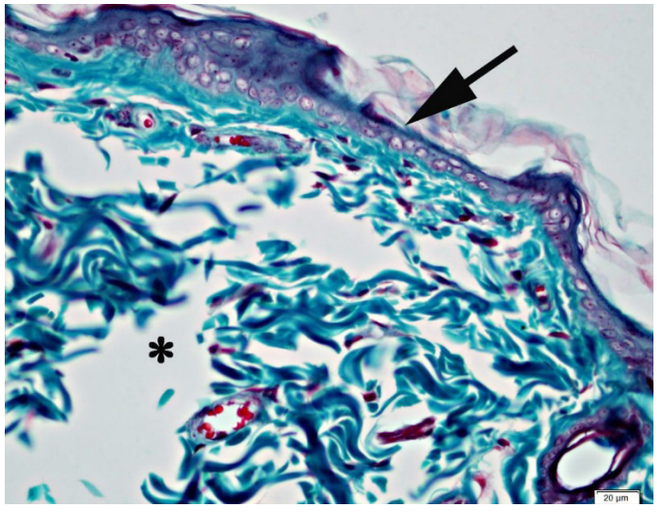

Figure 1. *Micrographs obtained from control group tissues are shown. Asterisk: scattered connective tissue loss in the dermis. Arrow: Distorted epidermis structure with irregular and thinned keratin layer. Stain: Gomori trichrome stain.*

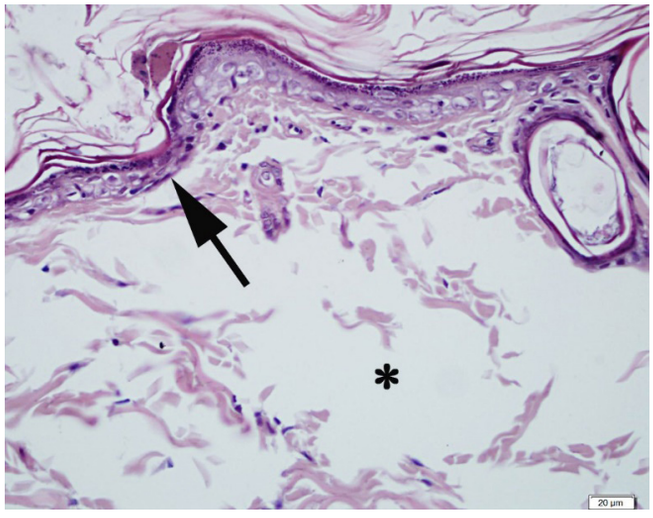

Figure 2. *Micrographs of the tissues taken from the control group are shown. Asterisk: Collagen bundles with irregular organization and intense loss of connective tissue in the dermis. Arrow: The flattened and quite thinned epidermis layer. Stain: Hematoxylin-Eosin stain.*

When tissues from the group that received WGO for wound treatment were analyzed, it was discovered that the overall structure was more regular than in the control group. In terms of histological structure, however, there was no significant difference between the groups in which QSM was administered. In addition to epidermis layer loss and flattening, an epithelial structure with degraded cells was identified. The epithelial layer has been found to produce papillae in the dermis on occasion. The collagen fiber bundles in the dermis layer, on the other hand, were found to be unevenly dispersed (Fig. 3-4)

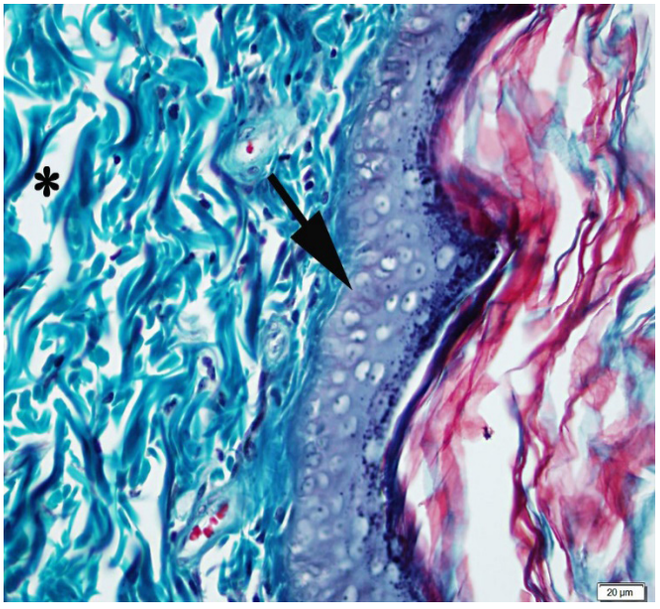

Figure 3. *Micrographs of tissues taken from the wheat germ oil group are shown. Arrow: Flattened endothelial layer. Asterisk: The dermis layer with wavy collagen bundles and localized loss of connective tissue. Stain: Gomori trichrome stain.*

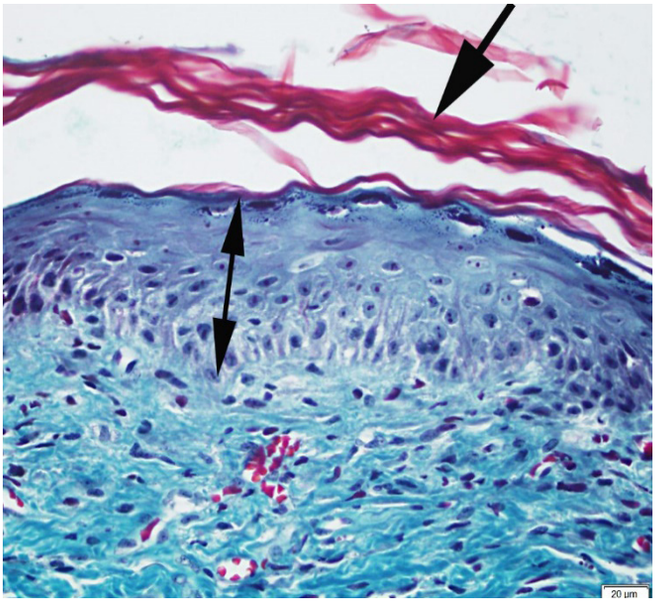

Figure 5. *Micrographs of the sections obtained from the quince seed mucilage group are shown. Arrow: A more uniform keratin layer compared to the control group. Double-headed arrow: Epithelial formation similar to normal structure. Stain: Gomori trichrome stain.*

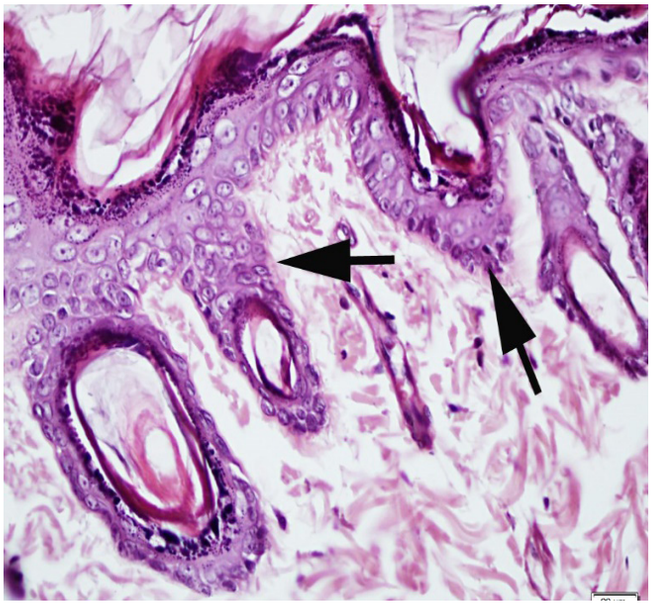

Figure 4. *Micrographs obtained from the wheat germ oil group are shown. Arrow: Papillae formation in the epidermis layer. Stain: Hematoxylin-Eosin stain.*

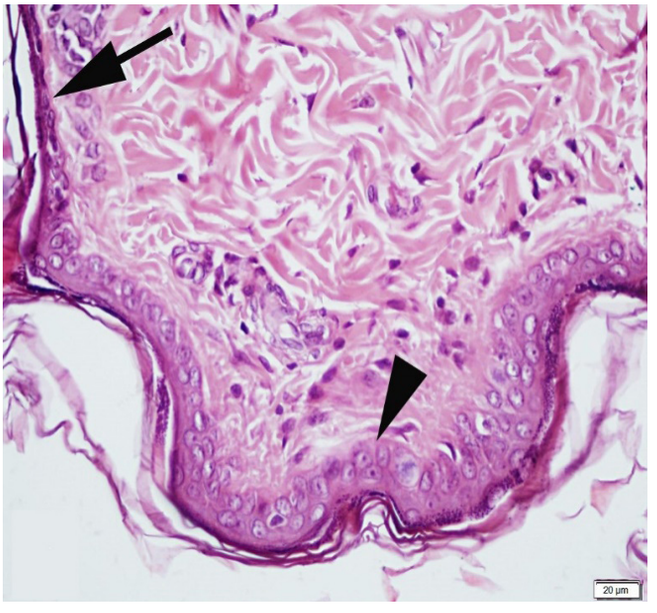

Figure 6. *Micrographs of the tissues obtained from the quince seed mucilage group are shown. Arrow: Thinning and degeneration of the epidermis. Arrowhead: Epithelial structure consisting of several cell layers observed in some parts of the epidermis. Stain: Hematoxylin-Eosin stain.*

It was observed that the samples taken from the QSM group for wound treatment had a more uniform structure than the control group. It was observed that the keratin layer was more regular in the epidermis layer and the epithelium contained more cell lines. It was observed that papillae structures began to form into connective tissue in the epithelial layer. While less connective tissue loss was in the dermis layer compared to the control group, an irregularly wavy sequence was observed in the collagen fiber bundles (Fig. 5-6).

4. DISCUSSION

Wounds are undesirable life events that might occur as a result of harm, but healing is a survival strategy that reflects an attempt to repair the tissue's natural anatomical structure and function. Various plant extracts were studied for significant wound healing activity using experimental

models, and many of them have still to be investigated. Hence, wound-healing medications that can improve the healing process are still limited (4).

This study evaluated the possible wound-healing effects of WGO and QSM rats using planimetric measurements and histological analysis in a full-thickness wound model on Wistar albino rats. When compared with the control group, although WGO-treated rats exhibited lower wound closure rates in the first four days, the rates were significantly higher after the 8th day. It was also observed that WGO treatment significantly reduced the time required for complete epithelialization when compared with the control group.

In a 2020 research by Sui et al., the macroscopic view of wound healing on days 0, 4, 7, and 10 administered by a wheat germ-derived peptide (YDW) and epidermal growth factor (EGF) showed dramatically increased wound closure compared to the control group. On the 10th day after the injury, the wound areas of the EGF-treated animals were entirely healed, the wound areas of the YDW-treated animals were nearly completely closed, and the wound areas of the control animals were still 19.3% ± 2.4% ($p<0.01$) of the original wound area (9).

Early wound cellular processes trigger acute inflammatory responses. However, chronic activation of the pro-inflammatory factors is probable to arise in persistent tissue damage, wound repair inhibition, and pathological or excessive wound healing (1). Fatty acids may regulate the healing process, which includes sequential stages (inflammation, new tissue production, and tissue remodeling) (10).

When compared to the control group, WGO prolonged the inflammatory phase, which is the initial step of wound healing. WGO's anti-inflammatory activities may reduce inflammation, which is a critical stage in wound healing, causing the process to be extended. After the extended anti-inflammatory phase, epithelialization and granulation tissue development begin with the start of the proliferative phase. WGO may have improved healing by acting at this stage, which is sensitive to oxidative damage and boosting epithelialization.

Antioxidants are utilized in wound healing to neutralize the damaging effects of free oxygen radicals. Antioxidants make the ultimate sacrifice by cleaning up free radicals and becoming less reactive and hence less damaging than the radicals themselves. As a result, antioxidants enhance wound healing (11). The antioxidant properties of cereal products often are associated with the phenolic components that comprise the cereals. In their study, Zou et al. observed that the phenolic components in WGO exhibit antioxidant effects (12).

Wheat bran (WB) and wheat germ (WG) contain 3%–4% and 7%–9% oil, respectively. An oil high in unsaturated fatty acids and a high concentration of minor components is considered to provide health benefits (13). WGO has diverse biological activities, including anticancer and antioxidant capabilities (5).

Unsaturated fatty acids are precursors of arachidonic acid. In the absence of essential fatty acids, cutaneous wound healing is hampered in mice, rats, and infants (14) but linoleic acid and other essential fatty acids can help prevent and treat pressure sores (14,15). With its chemotactic and neutrophil stimulating effects, linoleic acid, which has been linked to cell proliferation and inflammatory processes, operates as a modulator of leukocyte activities (16). Because of their impacts on pro-inflammatory cytokines, linoleic and oleic acids have been shown to speed up wound healing (14). The active component linoleic acid methyl ester extracted from Chinese and German calendula extracts has an enhancing effect on wound healing and epithelialization, according to Zimmer et al. (17).

Fatty acids can affect inflammation, lymphocyte function, and cell-mediated immunity (18). On the other hand, unsaturated fatty acids, such as omega-3, can influence the gene production of pro-inflammatory cytokines by affecting cellular membrane fluidity, cell-to-cell signaling, cell mobility, receptor interaction with their agonist, membrane function, and secondary signal generation (19).

The skin absorbs Vitamin E acetate quickly and transforms it into vitamin E (tocopherol) with the enzymes in its structure. Topical formulations of vitamin E are thought to accelerate wound healing due to their ability to suppress collagen formation and reduce fibroblast proliferation and inflammation (20). A study in diabetic rats found that tocopherol treatment significantly increased wound closure rate and total protein amount, positively affecting the wound healing process, and epithelial and collagen fibers were better organized with this therapy (21).

According to the studies, the level of vitamin E in different tissues increased immediately, and there were changes in lipid peroxidation in rats fed WGO (22). One of the components of WGO, beta-sitosterol, has been shown to have antioxidant (23,24) and anti-inflammatory (25,26) properties. Furthermore, beta-sitosterol promotes epithelialization (27). Several studies have shown that antioxidant compounds are beneficial to wound healing. In accordance with these findings, the components of WGO have antioxidant activity and are thought to have a favorable effect on wound healing in the current study as well (5,13,28).

According to a study on WG by Brandolini and Hidalgo, the pharmaceutical importance of WGO would increase considerably and gain value (28). More research is needed to produce higher-quality WGO, such as the use of additional creative and optimal ways to increase its utilization after more health benefits have been explored.

QSM was another component whose impact was investigated in the current research. Quince seed has been popularly used in some communities to heal skin wounds and reduce pain and inflammation (29).

The mucilage and gum produced from quince seeds are used to treat wounds. It's worth mentioning that extracting gums or isolating secondary plant components requires higher ethanol levels of 70%-90%, whereas mucilage is formed when the seeds are immersed in water, and a large amount of clear gelatinous substance is immediately released (30). According to Tamri et al., mucilage is a long-chain mucopolysaccharide that can act as a reservoir due to its high water absorption capacity, and when applied to a wound, it keeps the wound moist (31). Hydration improves wound healing by providing a wet wound surface on which epithelial cells may move more easily than a dry scab, protecting protease and growth factors in the exudate fluid, and increasing oxygen partial pressure (32).

Although studies have shown that mucilage can aid in healing skin wounds (closed wounds) (7,29,30), it cannot be used on exudative wounds due to its impermeable character and the risk of bacteria growth and infection spread. Mucilage reduces cell-to-cell interactions and inhibits wound healing. An impermeable structure is formed as the saturation of the gel with water affects the pores in the quince seed gel matrix. It is worth mentioning that long-term storage of QSM is inconvenient due to mold growth in the gel (30).

Quince seeds have been shown to include phenolic compounds, organic acids, free amino acids, and pectin (6). The increased proliferation of fibroblasts indicates that QSM may include growth factor(s). According to Ghafourian et al., these components are potential candidates for the effects of QSM on fibroblast growth (29). Quince seed contains phenolic compounds. One of these components, caffeoylquinic acid, is a potent antioxidant. The acceleratory impact of QSM on fibroblast proliferation might be explained by the radical scavenging and antioxidant activities of quince seed.

The wound closure rate in rats administered QSM was similar to those of control rats in our study. While the components in it are expected to improve wound healing, the finding that it has similar effects to physiological saline may be due to the insufficiency of the applied concentration.

According to a study using the microculture tetrazolium test, QSM increased the proliferation of human skin fibroblasts after 48 hours, even at low concentrations (50 g/mL) (29). Additionally, Tamri et al., studied 5%, 10%, and 20% Quince seeds mucilage cream (QSMC) with eucerin on white Iranian rabbits and reported that QSMC (20%) cream completely healed skin wounds after a 13-day therapy (31).

5. CONCLUSION

The current study revealed that WGO improved wound healing. It may be used as an alternative or complementary approach for wound treatment depending on the severity of the wounds. On the other hand, QSM was not found to improve wound healing.

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Author Contributions:
Research idea: CÇ, SA
Design of the study: CÇ, SA
Acquisition of data for the study: CÇ
Analysis of data for the study: CÇ, SA
Interpretation of data for the study: CÇ, ZÜG, AS
Drafting the manuscript: CÇ, ZÜG, AS, SA
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Clinical and Experimental Health Sciences

The Relationship between Smartphone Addiction and Functional Neck Disability among University Students during COVID-19 Pandemic

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ABSTRACT

Objective: This study aimed to determine the prevalence of smartphones addiction, and to investigate the relationship between smartphones addiction and functional neck disability among the students of Taif University during a Covid-19 pandemic.

Methods: A 1060 students from Taif University participated in this study. The smartphones addiction was evaluated by using the short version of the smartphones addiction scale (SAS-SV) and functional neck disability was measured by the neck disability index (NDI).

Results: About 83 % of the students reported smartphones addiction, 50% were suffering from mild neck disability, and 84% used their smartphones for more than 4 hours/day. Female students represented one and half times more than male to develop a smartphones addiction ($p< 0.05$). There was a significant association between smartphones addition and neck disability ($p< 0.05$). Moreover, female students had a functional neck disability significantly greater than male students ($p= 0.001$). Students with smartphones addiction represented three times more than students without addiction to develop functional neck disability ($p= 0.001$), and female students represented two times more than male students to develop functional neck disability ($p= 0.001$).

Conclusion: During a COVID-19 pandemic, more than four-fifth of the students showed smartphones addiction. The female students are more predictive to smartphones addiction than male. The smartphones addiction and female students were found to be the predictors for functional neck disability.

Keywords: Functional disability, neck pain, smartphones addiction, students

1. INTRODUCTION

Before 2 or 3 decades smartphones had a limited role that was only about receiving calls and messages, but this role has progressively developed over time to give people various benefits from smartphones through utilizing and the development of technology. Smartphones have become a very reliable resource of information for almost everyone. They are used in many ways, such as communication, learning, and playing games (1).

Nowadays, personal computers and smartphones are widely used in homes and businesses (2). Before COVID-19 pandemic research, Saudi Arabia ranked third in the world in terms of smartphone usage, with 72.8% of the population using them (3). Besides, 27.2% of Saudi university students spend more than 8 hours per day (h/day) on using their smartphones (4).

Smartphones offer many benefits, but also it has a bad impact after prolonged use, upsetting aspect is such as smartphone addiction. Smartphone addiction is a phenomenon of smartphone uncontrollable excessive use. People with this problem experience social, psychological and health problems (5). The prevalence of smartphone addiction is much higher among teenagers than adults (6). Before a COVID-19 pandemic a study conducted on undergraduate students reported that the smartphone addiction was slightly higher among males (30.3%) in comparison to females (29.3%) (7). In Saudi Arabia, 21.6% of the participants are suffering from headache, 4% sleep disturbance, 3.9% tension, 3% fatigue and 3% dizziness (8).

Furthermore, subjects with smartphone addiction had fewer sleeping hours, lack of energy the next day and there was a great impact of smartphone addiction on their academic achievement (9), and an increased risk of musculoskeletal problems, due to the excessive use of smartphones (10). The rates for shoulder disorders ranged from 46 to 52%, and 68% for neck symptoms (11). Furthermore, a 40% of 2575 young mobile phone users suffering from neck and shoulder pain (12).

During a COVID-19 pandemic, the smartphone usage increased dramatically, which was understandable due to the adoption of “lockdown” and “work from home” strategies

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to limit the virus transmission. People spent their time by searching the internet, utilizing social media, watching television shows, playing games, chatting with friends and/or family and shopping online (13). The prevalence of smartphone addiction is higher among people aged from 20 to 34 years (14). Moreover, recent studies showed an association between smartphone use and musculoskeletal symptoms among medical residents (15), and university students(16).

However, during the crisis, it seems there is no enough research that has investigated the relationship between musculoskeletal disorders and smartphone addiction among university students. Furthermore, it is worthy to study the physical disorders associated with smartphone use and identify whether they are a risk factor for musculoskeletal disabilities or not, with consideration of the students' gender, age (7,9,11,15,17), and college categories as, most of the previous studies were conducted on medical students (3,4,7,15,18–20). So, the aim of this study was to determine the prevalence of smartphone addiction and to investigate the relationship between smartphone addiction and functional neck disability among the students of Taif University during a COVID-19 pandemic.

2. METHODS

2.1. Participants

The sample size was calculated initially to be 374 participants according to Yamane formula n= [N/ (1+N (e) 2](21), Where: n signifies the sample size, N signifies the population under study, e signifies the margin error (0.05). The number of Taif University students was (N= 13579). About 5000 students received the link of the questionnaire through E-mail and social media application that was made in Google form. A valid responses of 1060 students were received and analyzed (461 male and 599 female).

The study was conducted between February and June of 2021. The students were recruited from Taif University, their age ranged from 17 to 35 years. The exclusion criteria were; students with cervical or shoulder pain before the COVID-19 pandemic, upper extremity trauma or spinal cord injury, which were verified via phone call before sending the link to the questionnaire. Additionally, some participants were excluded; 74 students off Taif university campus, 84 participants above 35 years old, 11 participants failed to complete the questionnaire, 37 participants did not mention their university or college, and 3 secondary school students (Fig. 1).

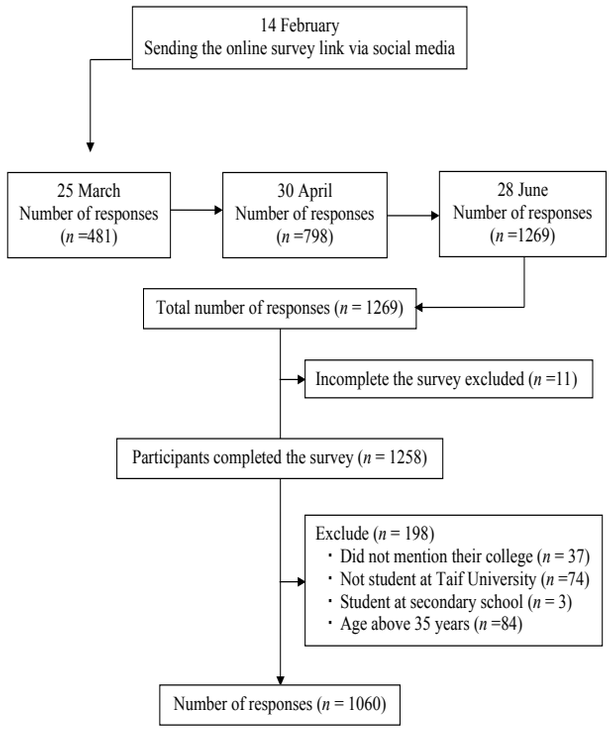

Figure 1. *Flow diagram of the study*

2.2. Ethical Considerations

Prior the commencement of the study, the students received a clear explanation of the study aim and procedure, confidentiality of the data obtained, and their legal rights, who provided an informed written consent. An ethical approval was taken from the Taif University's Ethical Committee (No. 2021-42-0102).

2.3. Assessment procedure

The data were gathered through the questionnaire which was split into three sections; the first section concerned with participants' demographic data; age, sex, height, weight, university, faculties, department and specialty. The second section was the scale-short version of the smartphone addiction scale (SAS-SV) that was used to discover the prevalence of smartphone addiction, and the third section was neck disability index (NDI) that used to assess the effect neck pain on functional disability.

Smartphone addiction scale (SAS): The SAS is a self-report scale that is used to evaluate smartphones addiction. It is a ten-item survey with a six-point Likert scale ranging from one to six , with 1 indicating strong disagreement and 6 indicating strong agreement. Higher scores imply addiction. The overall score goes from 10 to 60, and the cutoff values of smartphone addiction are 31 for male, and 33 for female (10). It was reported to be a valid instrument and has excellent reliability (22). Appendix 1.

Neck disability index (NDI): It is the most frequently used and validated instrument for evaluating the impact of neck pain on patients' functional activities and measuring outcomes in

clinical and research settings. For usage in a foreign language, the NDI questionnaire has been suitably translated, culturally adjusted and verified (23). The NDI in Arabic is a dependable, valid, and responsive instrument. Because it is made up of basic and easily understandable terms. It can be used to assess neck pain among Arabic-speaking patients in various Arabic nations (23). The Oswestry low back pain disability questionnaire was used to develop NDI. It is made up of ten questions. The first four categories are about subjective symptoms (pain intensity, headache, concentration, sleeping), the next four are about activities of daily living (ADL) (lifting, work, driving, recreation), and the final two are about discrete ADL (personal care, reading) (24). Appendix 2.

Each item is graded on a scale of zero (no disability) to five (total disability), with a maximum score of 50. NDI, on the other hand, is typically normalized to 100 and expressed as a percentage. A higher NDI score indicates a greater neck disability. To demonstrate the severity of neck impairment, the following criteria were followed: No neck disability is 0-4 points; mild neck disability is 5-14 points; moderate neck disability is 15-24 points; severe neck disability is 25-34 points; and full neck disability is > 34 points (25).

2.4. Statistical analysis

The version 20 of the Statistical Package for Social Sciences (SPSS. Armonk, NY, IBM Corp.) was used to analysis the collected data. The association between smartphone addiction, functional neck disability, college categories, gender and age were determined by Chi-square test (χ^2). Moreover, the multivariable logistic regression analysis was conducted. Odds ratios (ORs) with 95% confidence intervals (CIs) were expressed relative to a reference baseline category. The significance level ($p< 0.05$) was used for all tests.

3. RESULTS

A total of 1060 students (461 male and 599 female, 43.5% and 56.5%, respectively) from Taif University participated in this study. Their age ranged from 17 to 35 years (991; aged from 17-25 years and 69; aged from 26-35 years). A16.2% of students used their smartphone for less than 4 h/day, 28.9% used it for a duration ranging from 4-7 h/day, and 54.9% used it for more than 7 h/day. Four-hundred eighty of the students (45.3%) belonged to the medical colleges, 153 (14.4%) belonged to the humanities and education colleges, 180 (17.0%) belonged to the laws and administration colleges, and 247 (23.3%) belonged to the sciences and engineering colleges.

The percent of students who reported smartphone addiction was significantly higher than students with no smartphone addiction ($p= 0.001$, X^2 value= 451.57). The smartphone addiction percent was 82.6% (876; 363 male and 513 female) and the non-addiction percent was 17.4% (184; 98 male and 86 female). There was no significant association between smartphone addiction and college categories ($p= 0.477$). There was a significant association between smartphone addiction, and both gender and age ($p= 0.003$, 0.009 respectively), as shown in table 1.

Table 1. *The association between smartphone addiction and college categories, gender and age*

		Smartphone addiction		X^2 value	p-value
		Addicted, n (%)	Non-addicted, n (%)		
College categories	Medical colleges	401 (44.8)	79 (42.9)	2.49	0.477
	Humanities and education	129 (14.7)	24 (13.0)		
	Laws and administration	150 (17.1)	30 (16.3)		
	Sciences and engineering	196 (22.4)	51 (27.7)		
Gender	Male	363 (41.4)	98 (53.3)	8.65	0.003
	Female	513 (58.6)	86 (46.7)		
Age	17 to 25 years	8.11 (81.8)	180 (18.2)	6.88	0.009
	26-35 years	65 (94.2)	4 (5.8)		

X^2: Chi-square; n: number; p-value < 0.05 means significant difference

Female students are 1.58 more than male students to develop a smartphone addiction (OR: 1.58; 95% CI: 1.153-2.189; p = 0.005) and students aged from 26-35 years are three times more than 17 to 25 years to develop a smartphone addiction (OR: 3.499; 95% CI: 1.256-9.744; p = 0.017). Table 2 shows the multivariate analysis involving college categories, gender and age.

Table 2. *The predictors of smartphone addiction among the university students*

$R^2 = 0.026$	B	S.E.	Df	p-value	Odds ratio	95% CI for OR	
						Lower	Upper
Gender (1)	0.463	0.163	1	0.005	1.58	1.153	2.189
Age (1)	1.252	0.523	1	0.017	3.499	1.256	9.744
Constant	1.263	0.118	1	0.001	3.536		

R^2: Nagelkerke R Square value; B: Unstandardized regression weight; SE: standard error, df: degrees of freedom, CI: confidence interval; OR: odds ratio; p-value < 0.05 means significant difference

Fifty percent of the students (531; 209 male and 322 female) were suffering from a mild neck disability; 36% (383; 212 male and 171 female) had no neck disability; 11% (117; 33male and 84 female) had a moderate neck disability, 2.4% (25; 5 male and 20 female) had a severe neck disability and 0.4% (4;2 male and 2 females) had complete neck disability. Table 3. showed a significant association between smartphone addiction and neck disability ($p= 0.001$). Meanwhile, female students had a functional neck disability significantly greater than male students ($p= 0.001$). The was no significant association between age category and functional neck disability ($p= 0.477$).

Table 3. *The association between smartphone addiction and functional neck disability*

		Functional neck disability		X^2 value	p-value
		No disability, n (%)	Disability, n (%)		
Smartphone addiction	Non addicted	106 (57.6)	78 (42.4%)	44.50	0.001
	Addicted	277 (31.6))	599 (68.4%)		
Gender	Male	212 (46.0%)	249 (54.0)	34.33	0.001
	Female	171 (28.5)	428 (71.5)		
Age	17 to 25 years	361 (36.4)	630 (63.6)	0.58	0.447
	26-35 years	22 (31.9)	47 (68.1)		

X^2: Chi-square; n: number; p-value < 0.05 means significant difference

The students with smartphone addiction are 2.785 more than students with no smartphone addiction to develop a functional neck disability (OR: 2.785; 95% CI: 1.999-3.879; p = 0.001), and female students are two times more than male students to develop a functional neck disability (OR: 2.034; 95% CI: 1.568-2.638; p = 0.001). Finally, students age was not a significant predictor for the development of functional neck disability (OR: 1.017; 95% CI: 0.595-1740; p= 0.951). Table 4 shows the multivariate analysis involving SAS, gender and age.

Table 4. *The predictors of functional neck disability among the university students*

R^2 = 0.09	B	S.E	df	p-value	Odds ratio	95% CI for OR	
						Lower	Upper
Smartphone addiction	1.024	0.169	1	0.001	2.785	1.999	3.879
Gender (1)	0.710	0.133	1	0.001	2.034	1.568	2.638
Age	0.017	0.274	1	0.951	1.017	0.595	1.740
Constant	-0.648	0.165	1	0.001	0.523		

R^2: Nagelkerke R Square value; B: Unstandardized regression weight; SE: standard error, df: degrees of freedom, CI: confidence interval; OR: odds ratio; p-value < 0.05 means significant difference

4. DISCUSSION

In the current study about 83% of the participants reported smartphone addiction, which was higher than the rates reported in previous studies in Saudi Arabia 36.5%, and 27.2% (3,26), 44.6% in Lebanon (27), 31.7% in Tunis (28), 10% in Belarus (14), 24.8% in South Korea (10), 29.8% in China (7), 17.3% in Sudan and 8.6% in Yemen and Jordan was 59.8% (26). Although Sethuraman et al. (18) conducted their study before the COVID-19 pandemic on 192 medical students, their findings were nearly similar to the present results as they reported that the addiction rate was 85.40%.

The higher level of the smartphone addiction in the current study could be attributed to the COVID-19 pandemic, which led to lower levels of social connection and well-being (29). Furthermore, the reason for the higher percent of smartphones user could be owing to the lack of other sources of outdoor entertainment among university students and preoccupied with studying and academic activities which make smartphone the only means of entertainment to relieve stress and anxiety. Adding to that, there is a constant obsession among the young population about taking a selfie and posting them on social media, besides various applications of chatting, gaming and social interaction (18).

The wide variation of smartphone addiction between different researches could be attributed to various sample sizes, as well as different age, sex, level of education and culture of Saudi population, the extent of 4G Wi-Fi coverage and the use of several techniques for determining the severity of smartphone addiction. Another viewpoint, suggested that the inconsistency between the previous researches could be referred to the variation in smartphone addiction liability could be due to the personality traits of individuals such as playing sports, schooling and purpose of using smartphone (30).

This study revealed the prevalence of females smartphone addiction is higher than males (41.4% males, 58.6% females) which was supported by previous studies (31,32). These findings are consistent with a number of international studies were conducted to evaluate the prevalence of smartphone addiction among students, which have revealed that females reported higher percent of smartphone addiction in comparison to males (31,33,34). However, the finding of Kwon et al. (10) disagreed with the current findings which may be explained by their small sample size (197 participants), their participants age ranged from 18 to 53 years, or may be due to conduction of their study before the COVID-19 pandemic, through the period from November 2011 to January 2012. The present study was conducted during the crisis, where the use of electronic learning and smartphone has dramatically increased. In the same context, many studies which had been conducted before the crisis, showed no differences in the incidence of smartphone addiction between females and males (7,10).

The contradiction with the findings of Chen et al.(7) may be explained by recruitment of medical students only, without consideration of other tertiary education, while the sample of the current study was recruited from all colleges of the university. Moreover, their study was conducted in September 2016 before the COVID-19 Pandemic, whereas, e-learning has not expanded as much as it is now. Moreover, Aljomaa et al.(35) concluded that smartphone addiction was significantly associated with the male gender. Contrary to the present study, many studies reported that smartphone addiction was not related to gender (5,7,36). However, Abo-Jedi (37) reported that 26% of Jordanian university students showed smartphone addiction and the number of females with smartphone addiction was twice that of males, which was slightly greater than the current findings.

In addition, the pattern of smartphone using of males and females is different. As voice chats, text messages and social media are the most problematic applications for females, but

males' usage is more diversified, including text messages, voice conversations and gaming application (38). The result of this study matching with the nature of the society of Saudi Arabia, as males more active than a females who spent most of the daytime at home. Moreover, a study conducted on undergraduate students showed that the use of game apps, anxiety and poor sleep quality were linked to smartphone addiction among male students, and the use of multimedia programs, use of social networking sites, sadness, anxiety and poor sleep quality were significant factors for female students (7).

The current study demonstrated an increased prevalence of smartphone addiction (81.8%) in the participants aged from 17 to 25 years, which was backed up with the evidence of Csibi et al.(14) who showed the age group of 20-34 years old has received the highest score in SAS. However, Lane et al.(39) found that the smartphone use is more common among older people with higher education. It appears that this elder age group uses smartphone largely to communicate with family and friends.

The results of this study showed that no relationship between the smartphone addiction and college categories, which comes against the findings of most of the previous studies (3,7,19); Eldesokey et al.(19) reported that the prevalence of smartphone addiction was 53.6% of the undergraduate students, which was common among medical students. Chen et al. (7) found a low percent of smartphone addiction (29.8%), although they concluded that the smartphone addiction was common among the medical college students. Moreover, a study conducted on the sixth-year medical students, King Abdulaziz University, Saudi Arabia showed that the prevalence of smartphone addiction was higher among medical students. They attributed this finding to longer duration of daily smartphone usage (3). This contradiction could be attributed to the COVID-19 pandemic, which prompted all students to use smartphone excessively.

Other research studies (40,41) reported that using the smartphone for a duration exceeding the 4h daily is considered as a smartphone addiction, which could lead to musculoskeletal disorders. Thus, individuals are more likely to show smartphone addiction if they spend more time on smartphones (3,35,40,42). The present study showed that during the COVID-19 Pandemic, a 83.8% of students used their smartphone for a duration exceeding 4h/day. This finding coincides with Aljomaa et al.(35) who found a significant increase in the smartphone addiction in students used smartphone for more than 4h/day. In Saudi Arabia, 34.2% of students spent more than 8h/day (9) and 55.8% used smartphone more than 5h/day (3). Sixty-six percent of the students use their smartphones for a duration longer than 3h/day in Malaysia (20), while the Indian study showed that 30% of the students use smartphones for more than 3h/day (43). Also, Walsh et al.(44) reported that there are increases in the number of smartphone users who tend to gain the latest devices and applications, which make them unable to live without smartphones and spend more time in smartphone use. This means that smartphone addiction is likely to become one of the most common types of addiction in the future. Alhazmi et al.(3) indicated a significant correlation between smartphone addiction and daily smartphone usage hours. Moreover, one-third of students who had smartphone addiction spent 4 to 5 h/day using their devices, and half of those who had the addiction spent more than 5 h/day using them.

The current study found a relation between smartphone addiction and functional neck disability. This finding comes in line with the findings of a Saudi Arabian survey of adolescents (45), which discovered a relation between smartphone addiction, and various degrees of neck pain. Moreover, Shah et al.(46) reported an association between smartphone addiction and musculoskeletal disorder among physical therapy students aged from 20 to 25 years. A study conducted on 2435 participants in Saudi Arabia, their ages ranged from 14-18 years old, found a positive correlation between neck pain, dysfunction and smartphone addiction (47).

Furthermore, the current finding was supported by Gustafsson et al.(17) who conducted a longitudinal cohort research with Swedish young adults aged from 20 to 24 years. The information was gathered using a web-based questionnaire at the baseline (n= 7092) and five years later (n= 7092), its results revealed long-term effects on musculoskeletal disorders of the neck and its function. In addition, a cross-sectional Indian study conducted upon 306 medical students; their ages ranged from 21to 23 years, showed that using smartphones takes a prevalent part in the daily lives of medical students and would affect ADL (48), which agreed with the current study in relation to the ADL around the neck region.

Additionally, during the COVID-19 epidemic, the smartphone addiction is linked to a higher prevalence of musculoskeletal pain in the neck, shoulders, elbows, wrists/hands, lower back, and upper back (15). However, the findings of Akodu et al.(34) did not concur the result of the current study, which could be attributed to conduction of their study before a COVID-19 pandemic. Another reason for this contradiction may be the recruitment a medical student only, while the sample of the current study was collected from all colleges of Taif university. Finally, the increased functional neck disability due to smartphone use was assigned to the respondents' poor positioning, which decreased the neck angle, and assumed the forward head posture which led to higher pain-related disability of the neck (49).

This study was limited to the following. First, it was conducted on Taif University students without consideration of other universities in Saudi Arabia, or other age categories. Second, the results were surveyed-based outcomes due to the COVID-19 pandemic that pushed people to social distancing. Therefore, the addition of functional outcomes could be helpful to detect the musculoskeletal adverse effects of smartphone addiction. Third, this study explored the effect of the smartphone on functional disability without

investigating its effect on shoulder, hand function and hand grip strength. So, future studies may wish to examine the physical and mental health, social and psychological variables related to smartphones addiction during the COVID-19 pandemic. Fourth, the sample was convenient. Moreover, it did not accurately represent the population from which it was drawn. As a result, given the potential of recruiting a selected sample, the extremely high prevalence of smartphone addiction should be highlighted. Also, caution should be implemented when applying the current study's findings to other situations. Fifth, because the participants were not examined directly, they may have indicated more or less disabled than was actually the case. Sixth, anxiety, depression, general motor or cognitive impairments and relational difficulties were not taken into account. More research will be looked-forward to study the adverse effect of smartphones addiction on the students' satisfaction about the learning and teaching process, which was in need to be improved before the COVID-19 pandemic, especially students of medical sciences (50). Future research is needed to look into the impact of a home-exercise program on the students' functional neck disabilities.

5. CONCLUSION

During the COVID-19 pandemic, more than four-fifth of the students reported smartphones addiction ion. Fifty percent of the students were suffering from mild neck disability. About 84% used their smartphones for more than 4h/day, and 50% utilized them for more than 7 h/day. The smartphones addiction was higher in female than male, especially in the age group ranged from 17 to 25 years. Also, the smartphones addiction is associated with functional neck disability, with female students experiencing it at a higher rate than male students. Therefore, the university should incorporate awareness programs directed to students to learn how to use smartphones properly to avoid its negative physical effects during the COVID-19 pandemic. Which will decrease the prevalence of smartphone addiction, and its related functional neck disability, which will improve the well-being of the university students.

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Design of the study: AA, ID

Acquisition of data for the study: AA, MA, HM, ZA, MA

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Appendix 1. *Smartphone addiction scale*

No.	Items	Strongly disagree (1)	Disagree (2)	Weakly disagree (3)	Weakly agree (4)	Agree (5)	Strongly agree (6)
1	Missing planned work due to smartphone use						
2	Having a hard time concentrating in class, while doing assignments, or while working due to smartphone use						
3	Feeling pain in the wrists or at the back of the neck while using a smartphone						
4	Won't be able to stand not having a smartphone						
5	Feeling impatient and fretful when I am not holding my smartphone						
6	Having my smartphone in my mind even when I am not using it						
7	I will never give up using my smartphone even when my daily life is already greatly affected by it.						
8	Constantly checking my smartphone so as not to miss conversations between other people on Twitter or Facebook						
9	Using my smartphone longer than I had intended						
10	The people around me tell me that I use my smartphone too much.						

Appendix 2. *Neck disability index*

Section 1: Pain Intensity		Section 2: Personal Care (Washing, Dressing, etc.)	
1	□ I have no pain at the moment.	1	□ I can look after myself normally without causing extra pain
2	□ The pain is very mild at the moment	2	□ I can look after myself normally, but it causes extra pain
3	□ The pain is moderate at the moment	3	□ It is painful to look after myself and I am slow and careful
4	□ The pain is fairly severe at the moment	4	□ I need some help but can manage most of my personal care
5	□ The pain is very severe at the moment	5	□ I need help every day in most aspects of self-care
6	□ The pain is the worst imaginable at the moment	6	□ I do not get dressed, I wash with difficulty and stay in bed
Section 3: Lifting		**Section 4: Reading**	
1	□ I can lift heavy weights without extra pain	1	□ I can read as much as I want to with no pain in my neck
2	□ I can lift heavy weights, but it gives extra pain	2	□ I can read as much as I want to with slight pain in my neck
3	□ Pain prevents me lifting heavy weights off the floor, but I can manage if they are conveniently 4placed, for example on a table	3	□ I can read as much as I want with moderate pain in my neck
4	□ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned	4	□ I can't read as much as I want because of moderate pain in my neck
5	□ I can only lift very light weights	5	□ I can hardly read at all because of severe pain in my neck
6	□ I cannot lift or carry anything	6	□ I cannot read at all
Section 5: Headaches		**Section 6: Concentration**	
1	□ I have no headaches at all	1	□ I can concentrate fully when I want to with no difficulty
2	□ I have slight headaches, which come infrequently	2	□ I can concentrate fully when I want to with slight difficulty
3	□ I have moderate headaches, which come infrequently	3	□ I have a fair degree of difficulty in concentrating when I want to
4	□ I have moderate headaches, which come frequently	4	□ I have a lot of difficulty in concentrating when I want to
5	□ I have severe headaches, which come frequently	5	□ I have a great deal of difficulty in concentrating when I want to
6	□ I have headaches almost all the time	6	□ I cannot concentrate at all
Section 7: Work		**Section 8: Driving**	
1	□ I can do as much work as I want to	1	□ I can drive my car without any neck pain
2	□ I can only do my usual work, but no more	2	□ I can drive my car as long as I want with slight pain in my neck
3	□ I can do most of my usual work, but no more	3	□ I can drive my car as long as I want with moderate pain in my neck
4	□ I cannot do my usual work	4	□ I can't drive my car as long as I want because of moderate pain in my neck
5	□ I can hardly do any work at all	5	□ I can hardly drive at all because of severe pain in my neck
6	□ I can't do any work at all	6	□ I can't drive my car at all
Section 9: Sleeping		**Section 10: Recreation**	
1	□ I have no trouble sleeping	1	□ I am able to engage in all my recreation activities with no neck pain at all
2	□ My sleep is slightly disturbed (less than 1 hr sleepless)	2	□ I am able to engage in all my recreation activities, with some pain in my neck
3	□ My sleep is mildly disturbed (1-2 hrs sleepless)	3	□ I am able to engage in most, but not all of my usual recreation activities because of pain in my neck
4	□ My sleep is moderately disturbed (2-3 hrs sleepless)	4	□ I am able to engage in a few of my usual recreation activities because of pain in my neck
5	□ My sleep is greatly disturbed (3-5 hrs sleepless)	5	□ I can hardly do any recreation activities because of pain in my neck
6	□ My sleep is completely disturbed (5-7 hrs sleepless)	6	□ I can't do any recreation activities at all

Clinical and Experimental Health Sciences

Correlation Between the Level of Atherosclerosis and Pathological Features of Coronary Artery Disease: A Study of 100 Autopsy Cases

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ABSTRACT

Objective: Atherosclerosis is a generalized, chronic disease of large and medium-sized muscular elastic arteries. Relation between intensity of atherosclerosis and coronary artery disease, and risk factors of atherosclerosis could not been revealed completely by autopsy studies. We aimed to renew this shortage of knowledge with our autopsy study prospectively.

Methods: One hundred cases were autopsied within 48 h after death. Atherosclerotic risk factor data were collected including age, gender, height, weight, smoking and any chronic coronary artery disease. Atherosclerosis severity was evaluated macroscopically by examining the inner surfaces of the vascular lumens and revealed with postmortem pathological findings of coronary artery disease.

Results: The mean age was 42 ± 22 years. Seventy-four percent of cases were male, while 26% were female. Smoking duration ranged from 1 to 50 years with a mean duration of 17 ± 12 years. Existence of atherosclerosis in main vessels were also in correlation with age, duration of smoking and BMI (Body Mass Index) ($p<.05$.) significantly. Existence of coronary artery disease at autopsy were in correlation with existence of atherosclerosis in thoracic aorta, abdominal aorta and subclavian artery significantly ($p<.05$.), but not in correlation with those in carotid artery ($p>.05$.).

Conclusion: Atherosclerosis in main arteries except those in carotid artery was a good indicator of coronary artery disease.

Keywords: Atherosclerosis, Coronary Artery Disease, Forensic Pathology, Autopsy.

1. INTRODUCTION

Atherosclerosis is a generalized, chronic disease of large and medium-sized muscular elastic arteries. Plaque growth results in a reduction in lumen size and encroachment on the media. Thus, myocardial infarction, stroke, peripheral vascular disease and aneurism in aorta occurs (1). Coronary artery disease known as atherosclerotic heart disease is the largest contributor of cardiovascular diseases and maintain as a predominant cause of death worldwide. Many atherosclerotic factors such as hyperlipidemia, smoking, BMI, ageing, family cardiac diseases had been shown to be risk factors for coronary artery disease. Every vascular system has different cellular reactions to atherosclerotic risk factors (2). The correlated findings of atherosclerosis of the vascular system with the coronary artery disease will be a guide for the evaluation of obscure cardiovascular deaths at autopsy. The aim of the current study was to explore correlation between coronary artery disease and atherosclerosis in main arteries.

2. METHODS

2.1. Cases

The institutional ethics committee approved by Ethics Committee of Forensic Council of Turkey, numbered 237/2009 ATK in 2009, and informed consent was obtained from the relatives of each case. The subjects were prospective random cases in the East Black Sea Region Morgue of the Council of Forensic Medicine in where autopsied within 48 h after death. Atherosclerotic risk factor data were collected including age, gender, height, weight (BMI= weight/height) during autopsy and cigarette usage and information related to any chronic family disease or any evidence of clinical atherosclerotic disease (coronary artery disease, myocardial infarction, ischemic cerebral infarct, and peripheral vascular disease) from relatives of cases before autopsy.

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2.2. Vascular Pathology

The large-artery specimens examined including the common carotid artery, subclavian artery and aorta subdivided into the thoracic and abdominal aorta. After en bloc extirpation of the cervical, mediastinal, abdominal, retroperitoneal, and pelvic organs at autopsy, the large arteries were cut open and fixed in 10% formalin solution. The severity of atherosclerosis was evaluated macroscopically by examining the inner vessel surfaces, which were evaluated on cut sections (right common carotid artery from the bifurcation of the brachiocephalic artery to the bifurcation of the external and internal carotid artery; right subclavian artery from the bifurcation of the brachiocephalic artery to the exit point from the right clavicle as the axial artery; thoracic aorta from the aortic arch beneath the first costal artery exit or at the level of the ligamentum arteriosum to the entry of the aortic hiatus in the diaphragm; abdominal aorta from the exit of the aortic hiatus in the diaphragm to the aortic bifurcation at the pelvis). Atherosclerosis severity was evaluated macroscopically by examining the inner surfaces of the vascular lumens and calculated with stereological method (3). The term "atheroma" was used in a broad sense and included fatty streaks, fibrous plaques, complicated lesions, and calcification. One pathologist with extensive experience in the visual grading procedures evaluated the raised lesions. The degree of atherosclerosis in the sections was graded as follows: 0, no evidence of atherosclerosis, i.e., normal and consistent thickness and diameter of the vessel without intimal or medial thickening; 1, minimal changes and/or fatty streaks causing slight increases in vessel thickness, usually without affecting the lumen; 2, fibrous or atheromatous plaques, thickening of the intima, between the endothelial cell layer and the internal elastic; 3, advanced atherosclerotic plaques with fibrous deposition or complicated plaques with necrosis, ulceration, thrombosis, or hemorrhage; and 4, calcified plaques causing vessel wall stiffness. To compare atherosclerosis in these four vessels with other variable data, grade 0 and 1 was used for the absence of atherosclerosis, while grades 2, 3, and 4 accounted for the presence of atherosclerosis. The sum of all vascular luminal areas also was manually measured macroscopically and ratio of atherosclerotic area to total vascular area was calculated for each vessel on two-dimensional images with stereological method (3). All data including atherosclerotic area in all vascular area represented in numeric data as percentile. During the macroscopic and microscopic examination at autopsy, obstruction in more than 70% of the coronary arteries was due mainly to coronary atherosclerosis and hemorrhage and/or scarring in cardiac tissue also supported with microscopic examination but was also identified as acute and/or chronic myocardial infarction.

2.3. Statistical Analysis

All data were evaluated using the SPSS 25.0 program (SPSS, Inc., Chicago, IL, USA). The group data comparison was conducted with the Mann-Whitney U and chi-square tests. Correlations among numerical data were identified with Spearman's correlation test. A p level of <0.05 was accepted as statistically significant.

3. RESULTS

Four hundred vessel samples (thoracic aorta, abdominal aorta, right common carotid, and right subclavian artery from each of 100 cases) were evaluated. The mean age was 42 ± 22 years. Presence of atherosclerosis in each artery of the cases in relation to their age was shown in Table 1.Seventy-four percent of cases were male, while 26% were female. The smoking status of the cases was unknown (35%), nonsmoking (37%), and smoking (28%). Smoking duration ranged from 1 to 50 years with a mean duration of 17 ± 12 years. 31% of cases were found to have findings of coronary artery disease macroscopically and/or microscopically (Figure 1-4). Results of atherosclerosis in main vessels of cases with and without coronary artery disease and/or myocardial infarction wereshown in Table 2. Results of statistical correlation in between atherosclerosis in main vessels and age, gender, duration of smoking, BMI, anamnesis of family coronary artery disease were shown in Table 3.

Results of statistical correlation with and without coronary artery disease and/or myocardial infarction,with age, gender, duration of smoking, BMI, anamnesis of family coronary artery disease were shown in Table 4.

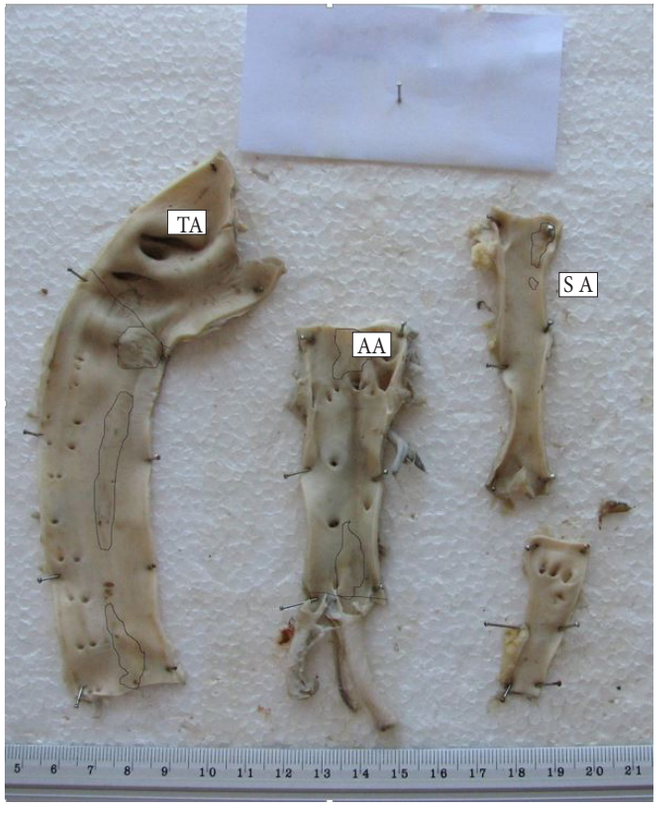

Figure 1*.Minimal changes and/or fatty streaks in arterial lumen TA: Thorasic Aorta, AA: Abdominal Aorta, SA: Subclavian Artery, CA: Carotid Artery*

Table 1. *Presence of atherosclerosis (Ath) in each artery of the cases in relation to their age.*

Artery (n) / Age (Years)	Thoracic Aorta	Abdominal Aorta	Subclavian Artery	Carotid Aorta
0-10				
Existence of Ath	0	0	0	0
Lack of Ath	8	8	8	8
11-20				
Existence of Ath	1	4	0	1
Lack of Ath	8	5	9	8
21-30				
Existence of Ath	3	8	1	3
Lack of Ath	9	4	11	9
31-40				
Existence of Ath	10	13	10	5
Lack of Ath	7	4	9	12
41-49				
Existence of Ath	9	10	7	5
Lack of Ath	5	4	7	9
51-60				
Existence of Ath	12	14	7	8
Lack of Ath	4	2	9	8
61-70				
Existence of Ath	10	10	6	6
Lack of Ath	1	1	5	5
71-80				
Existence of Ath	9	9	5	5
Lack of Ath	0	0	4	4
81-90				
Existence of Ath	2	3	2	2
Lack of Ath	1	0	1	1
> 90				
Existence of Ath	1	1	0	0
Lack of Ath	0	0	1	1
Totally	100	100	100	100

Table 2. *Presence of atherosclerosis in main arteries were compared to microscopic findings of cases with and without coronary artery disease and/or myocardial infarction.*

	Existence of coronary artery disease and/or myocardial infarction (n)	Lack of coronary artery disease and/or myocardial infarction (n)	p
Carotid artery	10	25	NS
Subclavian artery	18	20	0.02.
Toracic aorta	26	31	<.001.
Abdominal aorta	28	44	<.001.

NS: Nonspecific statistically; P<.05. is significant

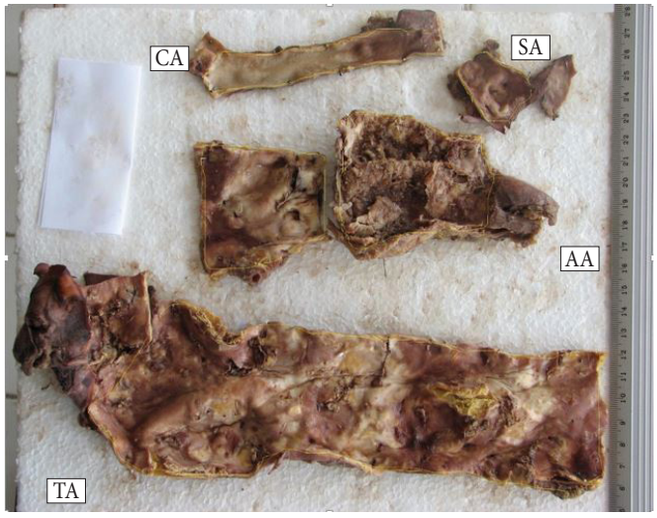

Figure 2*.Fibrous or atheromatous plaques in arterial lumen, TA: Thorasic Aorta, AA: Abdominal Aorta, SA: Subclavian Artery, CA: Carotid Artery*

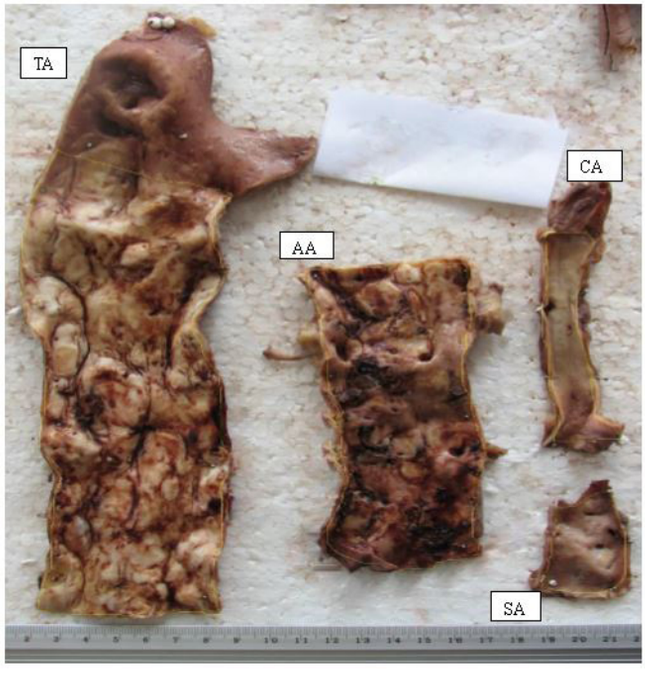

Figure 3. *Complicated plaques in arterial lumen TA: Thorasic Aorta, AA: Abdominal Aorta, SA: Subclavian Artery, CA: Carotid Artery*

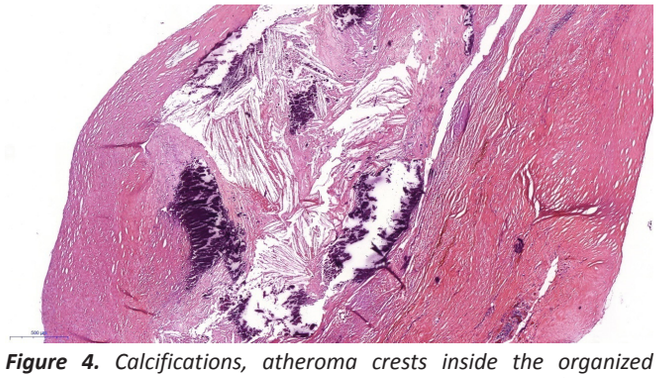

Figure 4. *Calcifications, atheroma crests inside the organized atheroma plaque has been shown in longitudinal section of coronary artery (3.5 X H&E).*

Table 3. *Correlation in between existence of atherosclerosis in main arteries and age, gender, duration of smoking, BMI, anamnesis of family coronary artery disease.*

	Existence of atherosclerosis in carotid artery	Existence of atherosclerosis in subclavian artery	Existence of atherosclerosis in thoracic aorta	Existence of atherosclerosis in abdominal aorta
Age	p<.001.	p<.001.	p<.001.	p<.001.
Gender (F/M)	NS	NS	NS	NS
Smoking (Year)	p=.006.	p=.015.	p=.009.	p=.036.
BMI	p<.001.	p=.023.	p=.001.	p<.001.
Family cardiac disease	NS	NS	NS	NS

NS=Non-significant; P<.05. is significant

Table 4. *Characteristics of cases with and without coronary artery disease and/or myocardial infarction. NS: Nonspecific statistically.*

	Existence of coronary artery disease and/or myocardial infarction	Lack of coronary artery disease and/or myocardial infarction	p
Age	61 ± 15	34 ± 20	<.001.
Gender (F/M)	7/24	19/50	NS
Smoking (year)	29 ± 12	12 ± 9	.002
BMI	27.16 ± 3.31	25.85 ± 5.42	NS
Family coronary artery disease	57%	24%	.023

NS=Non-significant. P<.05. is significant

4. DISCUSSION

Autopsy studies assess more valuable information about atherosclerotic lesions than that of clinical studies. Macroscopic and microscopic examination of a vessel on a postmortem specimen allows for exact lumen area measurements (4-6). In the current study, atherosclerosis in main vessels except carotid artery was found to be a significant marker of the coronary artery disease. Coronary atherosclerosis is generally less severe than aortic atherosclerosis but parallels the process in the aorta and explains the low incidence of coronary artery disease despite severe aortic atherosclerosis. Of all vessels, the aorta (both abdominal and thoracic) was the most affected by atherosclerotic plaques in relation with coronary artery disease (7-11). Complicated and calcified plaques were most clearly discovered on the intimal surfaces of the aorta at the sametime with fibrous plaques in other vessels (8). We also noticed that cases without raised atherosclerotic plaques in the aorta did not have coronary artery disease. Assessing plaques may be a more useful predictor of risk in cases without known coronary artery disease.

In our study, significant atherosclerotic disease in the carotid arteries did not predict significant coronary artery disease (12, 13). Some clinical and autopsy studies have shown that atherosclerotic disease of carotid artery was directly correlated with the degree of coronary artery disease which was unlikely in the current study (7, 14).

In our study, the subclavian atherosclerotic stenosis was positively associated with other markers of atherosclerosis and coronary artery disease (15,16) contrary to study which has stated that subclavian artery atherosclerosis was infrequent and especially combination of it with coronary artery disease was even rare (17). Engelhorn et al have stated that the right subclavian artery atherosclerosis could be considered to be as a risk factor for the assessment of cardiovascular risk by CCA-IMT(Common Carotid Intimal Medial Thickness) (18). Gongora – Riveraet et all. stated that coronary atherosclerosis and myocardial infarction were highly prevalent in patients died from a stroke due to atherosclerosis in the carotid and cerebral arteries (19). In literature, although the carotid artery bifurcation lesions are associated with the development of a positive coronary artery calcification after taking into account cardiovascular risk factors, body mass index and ethnicity, the absence of carotid artery plaque, does not exclude the possibilty that a coronary artery disease (20). In other study, the coexistence of carotid or intracranial atherosclerosis with coronary artery disease was confirmed in about 16% of patients (21). The exact correspondence between the carotid artery and the coronary artery is unclear, with some contradictory study results (11). More research is needed to identify the full extent of all risk factors for severe stenosis and cardio – or cerebral vascular events, among which, inflammatory biomarkers such as CRP, ESR, cytokines and also prior vascular events are likely to play a key role (22). Also, There is a concept that atherosclerosis affects both carotid and coronary systems, although not always in identical phenotypic manner (23, 24). We assume that autopsy studies find out more valuable and evident data about vessels compared to studies with imaging techniques (25).

A multivessel approach in patients with a single clinical manifestation of atherosclerosis is needed as atherosclerosis is a systemic disease and the clinical manifestation of it is associated with multiple factors like etnicity, diet, body mass index (21). Age, smoking and BMI were also found to be as

risk factors for atherosclerosis in vessels (26-28). Older age was a risk for both raised atherosclerotic lesions in the four vessels and coronary artery disease. The atherosclerotic process began in childhood and develops inconspicuously for many decades before cardiovascular complications such as coronary artery disease, myocardial infarction occur in middle and late age (5,14).

Some studies have reported no discernible differences in atherosclerosis before the age of 30, by which time virtually all individuals display some degree of intimal disease (15). Raised lesions were also not commonly determined in our cases before the age of 30 (29). However, autopsy studies have shown that the first atherosclerotic lesions actually begin to develop in the abdominal aorta, similar to our findings (15, 11). We did not detect any differences in atherosclerotic lesions of vessels and coronary artery disease between females and males due to the small number of females (n = 24) in the study.

Age, smoking and family coronary artery disease were risk factors for coronary artery disease (30,31).

In our study, smoking increased the incidence of coronary artery disease because of its vessel constrictive and ischemic effects, and also a significant correlation existed between smoking and raised atherosclerosis in the four vessels (27, 28, 32). Nakashima et al. suggested that a correlation have not existed between smoking and coronary artery disease (31). A large series autopsy case study is needed to predict the effects of smoking on atherosclerosis.

We found that the raised plaques in the four vessels increased arithmetically by surface extent when the weight to height ratio increased due to an increased fatty diet (15, 27, 28,). However, an increase in the weight to height ratio was not correlated with the incidence of coronary artery disease.

Reliable information about chronic family disease (any cardiac disease and/or diabetes mellitus) could not be obtained from the relatives of all cases before autopsy. When reliable information was obtained, a strong relationship existed between family coronary artery disease and coronary artery disease.

Atherosclerosis in aort and subclavian artery was found to be as risk factor for the assessment of coronary artery disease with association of well defined risk factors such as age, smoking, family coronary disease at our autopsy study. Age, smoking and BMI were also formatives for atherosclerosis in the main arteries.

5. CONCLUSION

Atherosclerosis in aorta and subclavian artery was found to be a risk factor for the assessment of coronary artery disease in our autopsy study. Age, smoking and BMI were also formatives for atherosclerosis in the main arteries.

Limitations

Female cases (n=24) were small in number because of randomized sectional study. So, we could not evaluate statistically correlation of gender with other data. Medical record data and smoking status of some cases couldn't be obtained completely from their relatives. Their record data had been shown as unknown. The evaluation of vessel lumens and cardiac tissue both macroscopically and microscopically had been performed by the same pathology specialist.

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Peer-review: *Externally peer-reviewed.*
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Research idea: NTY
Design of the study: NTY
Acquisition of data for the study: NTY, HCK
Analysis of data for the study: NTY, HCK, SE
Interpretation of data for the study: NTY, SE
Drafting the manuscript: NTY
Revising it critically for important intellectual content: SE, NTY
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Clinical and Experimental Health Sciences

Do The Core Stability and Position Sense of Trunk Affect Balance in Patients with Multiple Sclerosis?

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ABSTRACT

Objective: The trunk is known to be the most important key point where sensory inputs are received and motor responses occur, necessary for the maintenance of balance and postural control. The aims of the present study were to investigate the relationship between balance with core stability and position sense of trunk in patients with Multiple Sclerosis (PwMS) and to compare core stability, position sense of trunk and balance in PwMS and healthy controls.

Methods: The study was completed with 45 PwMS and 29 healthy controls with matching age and gender. Balance was assessed with Postural Stability Test (PST) and Modified Sensory Organization Test (MSOT) by using Biodex Balance System®. Core stability was evaluated with core endurance tests according to McGill procedure. Position sense of trunk was evaluated with the lumbosacral (LS) reposition tests by using Dualer IQTM digital inclinometer.

Results: PST, MSOT and LS repositioning tests scores were higher ($p<0.001$) and the trunk flexor, extensor, right and left lateral endurance tests scores were lower ($p<0.001$) in PwMS compared to healthy controls. PST and MSOT were found to be correlated with core endurance tests scores ($rs=-0.406/-0.602$, $p<0.05$) and LS reposition test scores ($rs= 0.357/0.510$, $p<0.05$) in PwMS.

Conclusion: This study suggested that core stability and position sense of trunk were affected and caused imbalance in PwMS. Therefore, clinicians should consider assessments and interventions directed at decreased core stability and trunk position sense in PwMS.

Keywords: Balance, core stability, multiple sclerosis, position sense of trunk

1. INTRODUCTION

The trunk is one of the most important key points responsible for balance. The trunk plays an important role in the organization of postural reactions (1,2). Optimal postural control of the trunk relies on intact motor, somatosensory, musculoskeletal systems, which are frequently compromised in patients with Multiple Sclerosis (PwMS) (3). Trunk control, affects standing and sitting, and is necessary to maintain body position, to remain stable when the position changes, and for the mobility function (4).

Postural control of the trunk is mainly achieved by the activation of core stability muscles. The core stability, which is formed by the power, strength, and endurance of the core muscles, is shown as the most important factor that ensures the balance of the individual in different conditions and environments during functional activities (1,5,6). Hodges and Richardson (5) reported that core muscles are activated as anticipatory before the movement begins, in order to maintain balance. Impaired core muscle activation, decreased postural control, less effective anticipatory postural adjustments, and increased reliance on compensatory postural adjustments have been indicated in PwMS (7,8).

In recent years, it has been seen that core stability trainings in patients with MS have begun to be included in physiotherapy programs, based on the knowledge that core stability is important in the development of postural control and balance. (9-12). However, there is only one study examining the relationship between core stability and balance in PwMS (13). In this study, core stability was evaluated with core endurance tests, one of its sub-parameters, and it was stated that there is a relationship between core endurance and postural control, but additional studies are needed.

Although core stability is an important motor component of balance, it is not the only factor in maintaining balance. Sensation, which is the first step in the formation of motor responses and in the formation of corrective orders by controlling the responses for the continuation of balance, is often overlooked. Perceiving sensations from the body and

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the environment and creating balanced responses suitable for the task is possible with sufficient sensory input from the somatosensory, vestibular and visual systems (14,15). In particular, the importance of the proprioceptive sense in maintaining balance is known (14,16). Like core stability, position sense of trunk, a sub parameter of proprioception, is also a significant component of trunk stability. Trunk musculature provides some core stability; however, the trunk cannot be stable without adequate position sense. Finally, we can say that trunk stability requires appropriate neural control and muscle strength as well as adequate sense of position to provide a stable foundation for movement (17-19). Additionally, we thought that the loss of sensation in the core region might affect the activity levels of the core muscles. Therefore, we also wonder about the relationship between balance and position sense of trunk. Previous studies examined the relationship between balance and position sense of trunk in patients with stroke, elderly persons, patients with ataxia, and patients with low back pain (20-23). These researches are important in terms of showing the relationship between balance disorders with the loss of position sense of trunk. However, there are no studies showing the relationship between balance and position sense of trunk in PwMS.

Therefore, the primary purpose of the study was to investigate the relationship between balance with core stability and position sense of trunk in PwMS. The secondary purpose was to compare core stability, position sense of trunk, and balance in PwMS and healthy controls.

2. METHODS

2.1. Participants

Ethical approval of the study was obtained from Gazi University Clinical Research Ethics Committee (Approval Date: 25.04.2016/Decision number: 228). Fifty PwMS with a clinically definitive diagnosis of MS by a neurologist were referred from the University Hospital, Neurology Department to Physiotherapy and Rehabilitation Department. The inclusion criteria for PwMS were being 18 to 65 years of age, 1-4 points on the Expanded Disability Status Scale (EDSS) (24), walking independently, and being a volunteer to participate in research. The exclusion criteria for PwMS were history of a MS attack in the previous 3 months, having circulatory system problems which causes muscle weakness or decrease of sense, orthopedic problems, visual impairment, pain in the ankle, knee, hip or spine, and having a score of 24 points from the Standardized Mini Mental Test (25). Additionally, 30 healthy controls were recruited from a local community center as control group through poster advertising. The inclusion criteria for healthy controls were being a volunteer to participate in research and being 18 to 65 years of age. The exclusion criterion for healthy controls was having neurological, orthopedic, circulatory, or visual problems, which may cause balance disorder, pain and biomechanical limitations in spine, hip, knee, and ankle. The study protocol was registered at ClinicalTrials.gov (NCT03566251). The study was conducted according to the Helsinki Declaration.

2.2. Procedure

The level of disability was assessed by a neurologist using the EDSS. Mental status was evaluated by the same neurologist using the MMSE. Characteristics of participants and duration of the disease were recorded. Between the measurements, 2-minute rest periods were given.

2.3. Outcome Measures

Measurements were performed with the following sequence.

2.3.1. Balance

Balance was assessed using Biodex Balance System® (Biodex®, Inc., Shirley, NY, USA), which is a reliable measure for assessing balance, by Postural Stability Test (PST) and Modified Sensory Organization Test (MSOT) (26).

2.3.1.1. PST: With this test, the static balance of the patient while standing is evaluated by the ability to keep the gravity center on the support surface. The test was performed on the right and left one foot, on a firm surface and with the eyes open. During the test, the patients are asked to keep the black dot they see on the screen in the middle of the target throughout the test. The tests were applied for 10 seconds, and a rest period of 10 seconds was given. As a result of the tests, the overall postural stability index score was obtained. Low scores indicated better performance.

2.3.1.2. MSOT: MSOT evaluates the effects of vestibular, visual, and somatosensory senses on balance during the standing position. It assesses the sensory component of balance on two different support surfaces and in two different visual conditions; condition 1: firm surface-eyes open, condition 2: firm surface-eyes closed, condition 3: foam surface-eyes open, and condition 4: foam surface-eyes closed. During all tests, patients were asked to stand as still as possible. All conditions were performed two times for 30 seconds and 30-second rest period was given between tests. At the end of the tests, sway index scores were obtained for each condition. Low scores indicated better performance (27,28).

2.3.2. Core stability

Core stability was evaluated with core endurance tests according to McGill procedure. The core endurance tests evaluated are trunk flexor test, trunk extensor test, and the left and right trunk lateral endurance tests. The purpose of core endurance tests is to maintain a static position for as long as possible. A stopwatch was used during the assessments, and the scores were recorded in seconds. One practice trial was performed, then each test was performed twice, and the best measurement score was recorded.

In order to avoid the effects of fatigue, the practical trial test was applied for a maximum of 5 seconds (29,30) (Figure 1).

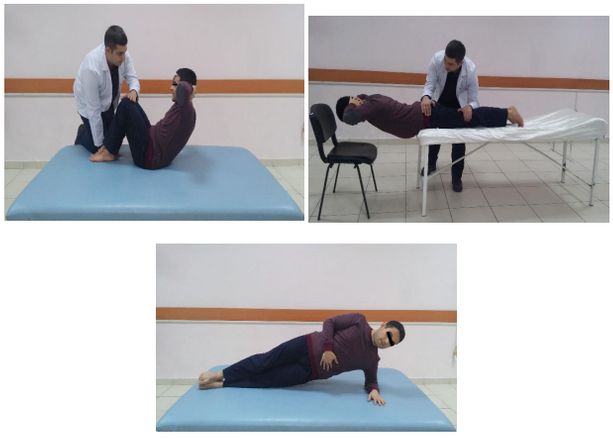

Figure 1. *The core stability tests.*

2.3.2.1. Trunk flexor test: The hips and knees were at 90º flexion position, the trunk was at 60º flexion, the feet were fixed, and the arms were bended across the chest with the hands placed on the opposite shoulder. The trunk support was removed, and the participants were asked to maintain their positions for as long as possible. The test was terminated as soon as the patients could not maintain their positions.

2.3.2.2. Trunk extensor test: The participants were positioned on the treatment table in the prone position with the hips, pelvis, and knees fixed. The upper extremities and trunk were supported by a chair at the same height as the treatment table. The chair support removed, and the patients maintained the horizontal body position as much as possible by crossing the arms behind the neck. The test was terminated as soon as the patients could not maintain their horizontal positions.

2.3.2.3. Trunk lateral endurance test: The participants were positioned in the side-lying position to make the elbow at 90º flexion position, forearm on treatment table, the lower arm in vertical position on the ground, the top arm bended across the chest with the hand placed on the opposite shoulder, the top foot in front of the lower foot and lower extremities in extension on the treatment table. The test was terminated as soon as the patients could not maintain their positions, or when the pelvis and hips returned to the mat. The test was evaluated both on the left and right sides. The test was terminated as soon as the patients could not maintain side-lying position.

2.3.3. Position sense of trunk

Position sense of trunk was assessed with the lumbosacral (LS) reposition tests by using Dualer IQ™ digital inclinometer (JTECH Medical Salt Lake City, UT, USA) (31). The tests were performed under three different visual-surface conditions while standing: 1; eyes open-firm surface, 2; eyes closed-firm surface, 3; eyes open-foam surface. The density of the foam surface was 44.85 kg/m^3. Participants placed the trunk in a 30° flexion position in the sagittal plane and held the position for 3 seconds (position 1) (Figure 2). The three seconds given for patients to describe the position are long enough, but not long enough to cause fatigue during testing and trial (32). After returning to the starting position, the patients were asked to repeat the previously attained angle. The patients verbally expressed when they felt that they had reached the angle and maintained their position (position 2) (Figure 2). The angular degree difference between the position 1 and position 2 was defined as the degree of trunk repositioning error (TRE). TRE is a reliable and valid method for measuring sense of trunk position. All conditions were performed five times. The lowest and highest scores were discarded for each condition, and the average of the remaining three scores was recorded as the TRE score. (22,31,33).

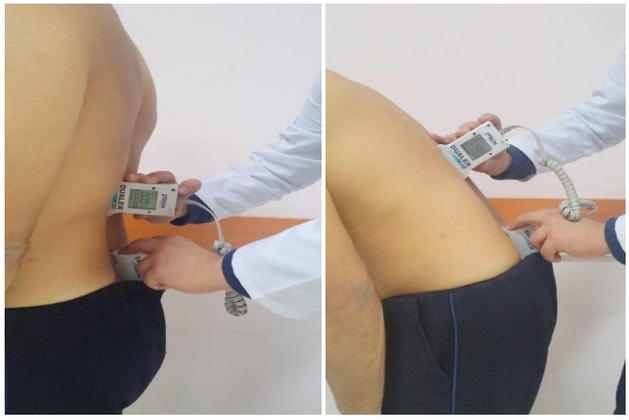

Figure 2. *The lumbosacral reposition test.*

2.4. Statistical Analysis

G*Power software package (G*Power, Version 3.0.10, Franz Faul, Universität Kiel, German) was used to calculate the sample size required for the study. According to the flexor endurance test scores of the study, it was calculated that 38 patients with MS were needed to obtain 90% power with α = 0.05 type I error, and β = 0.10 type II error (34). For statistical analyses, SPSS 15.0 (SPSS Inc., Chicago, USA) was used. Data normality was tested using the Kolmogorov–Smirnov test. Data were expressed as means (±SD) and medians (IQR 25-75). Demographic data of patients with MS and healthy participants were compared using an Independent Sample T Test. A Mann Whitney U Test and an Independent Sample T Test and were used to compare the assessment results of the patients with MS and healthy controls. A Spearman and Pearson correlation analyses were used to determine the relationship between the variables in PwMS. Statistical significance was set at alpha <0.05.

3. RESULTS

Fifty PwMS were screened for the study; 5 cases were excluded, 2 of whom did not want to participate in the study and 3 of whom did not meet the inclusion criteria. Thirty healthy volunteers were screened for the study; 1 of whom did not meet the inclusion criteria.

Demographic and disease characteristics of persons were given Table 1. There was no difference between groups regarding demographic characteristics including age, gender, and BMI (p>0.05, Table 1).

Postural sway was found to be increased according to PST and MSOT when PwMS were compared with healthy controls (p<0.001, Table 2). The trunk flexor, extensor, right and left trunk lateral endurance test scores were lower in PwMS compared to healthy controls (p<0.001, Table 2). In addition, the LS repositioning test error degree was higher in PwMS compared to healthy controls (p<0.001, Table 2).

Core endurance test scores were found to be correlated with PST-right, PST-left, MSOT-Condition 1, MSOT-Condition 2, MSOT-Condition 3, and MSOT-Condition 4 in PwMS (p<0.05) (Table 3). Similarly, LS reposition test scores were shown to correlate with PST-right, PST-left, MSOT-Condition 1, MSOT-Condition 2, MSOT-Condition 3, and MSOT-Condition 4 in PwMS (p<0.05) (Table 4).

Table 1. *Demographic and clinical characteristics of the multiple sclerosis patients and healthy controls.*

Characteristics	MS Group	Control group	p
Age, years (X ± SD)	36.71 ± 9.16	35.66 ± 9.60	0.556
Gender, female/male n (%)	34 (75.6)/11 (24.4)	21 (72.4)/8 (27.6)	0.763
BMI, kg/m^2 (X ± SD)	24.82 ± 4.03	23.93 ± 3.54	0.275
EDSS, score (X ± SD)	2.12 ± 1.07	-	-
Duration of illness, years (Median (IQR)	4 (3-7)	-	-

p>0.05; MS: Multiple Sclerosis; BMI = Body Mass Index; EDSS: Expanded Disability Status Scale.

Table 2. *Comparison of balance, core stability and trunk position sense test results of multiple sclerosis patients and healthy controls.*

		MS Group		Control Group		
		Median (IQR)	Minimum-Maximum	Median (IQR)	Minimum-Maximum	p
Balance Tests						
Postural Stability Tests (point)	Right	0.80 (0.60-2.00)	0.30-4.00	0.50 (0.40-0.60)	0.30-0.70	**<0.001**
	Left	0.90 (0.60-1.70)	0.30-4.00	0.50 (0.40-0.50)	0.20-1.10	**<0.001**
Modified Sensory Organization Test (point)	Condition 1	0.48 (0.36-0.66)	0.17-2.77	0.30 (0.27-0.44)	0.19-0.60	**<0.001**
	Condition 2	0.89 (0.76-1.51)	0.44-2.91	0.59 (0.38-0.76)	0.21-1.54	**<0.001**
	Condition 3	0.95 (0.75-1.38)	0.43-2.65	0.59 (0.50-0.70)	0.35-1.02	**<0.001**
	Condition 4	2.90 (2.06-3.34)	1.18-5.32	1.63 (1.42-1.87)	1.01-2.28	**<0.001**
Core Endurance Tests (s)						
Trunk Flexor Test		17.52 (6.76-29.63)	0.73-86.25	44.04 (29.00-56.50)	20.00-93.11	**<0.001**
Trunk Extensor Test		24.24 (16.04-44.26)	6.29-72.46	59.77 (49.50-66.99)	30.00-110.29	**<0.001**
Trunk Lateral Endurance Tests	Right	13.51 (5.69-22.56)	0.69-55.31	34.57 (29.19-60.86)	7.06-121.06	**<0.001**
	Left	11.77 (7.30-28.81)	0.00-59.30	37.55 (24.73-61.23)	11.61-90.16	**<0.001**
		X ± SD	**95% CI**	**X ± SD**	**95% CI**	**p**
Trunk Reposition Test						
Lumbosacral Reposition Tests (degree)	Condition 1	3.57 ± 1.36	3.17-3.98	1.87 ± 0.93	1.51-2.24	**<0.001**
	Condition 2	3.70 ± 1.25	3.32-4.08	2.03 ± 0.74	1.71-2.26	**<0.001**
	Condition 3	3.83 ± 1.17	3.47-4.18	2.21 ± 1.05	1.81-2.64	**<0.001**

p<0.05; Condition 1: Eyes open-firm surface; Condition 2: Eyes closed-firm surface; Condition 3: Eyes open-foam surface; Condition 4: Eyes closed-foam surface; CI: Confidence Interval

Table 3. *The investigation of the relationship between balance and core stability in patients with multiple sclerosis.*

		Core Endurance							
		Trunk Flexor Test		Trunk Extensor Test		Tunk Lateral Endurance Tests			
						Right		Left	
		r	p	r	p	r	p	r	p
PST	Right	-0.536	**<0.001**	-0.456	**0.002**	-0.518	**<0.001**	-0.463	**0.001**
	Left	-0.584	**<0.001**	-0.406	**0.006**	-0.502	**<0.001**	-0.500	**<0.001**
MSOT	Condition 1	-0.574	**<0.001**	-0.538	**<0.001**	-0.552	**<0.001**	-0.482	**<0.001**
	Condition 2	-0.447	**<0.001**	-0.421	**0.001**	-0.437	**<0.001**	-0.429	**<0.001**
	Condition 3	-0.562	**<0.001**	-0.538	**<0.001**	-0.536	**<0.001**	-0.465	**<0.001**
	Condition 4	-0.572	**<0.001**	-0.542	**<0.001**	-0.602	**<0.001**	-0.584	**<0.001**

p<0.05; PST: Postural Stability Test; MSOT: Modified Sensory Organization Test; Condition 1: Eyes open-firm surface; Condition 2: Eyes closed-firm surface; Condition 3: Eyes open-foam surface; Condition 4: Eyes closed-foam surface.

Table 4. *The investigation of the relationship between balance and trunk position sense in patients with multiple sclerosis.*

		Lumbosacral Reposition Test					
		Condition 1		Condition 2		Condition 3	
		r	p	r	p	r	p
PST	Right	0.508	**<0.001**	0.500	**<0.001**	0.404	**<0.001**
	Left	0.440	**<0.001**	0.510	**<0.001**	0.406	**<0.001**
MSOT	Condition 1	0.375	**0.002**	0.357	**0.004**	0.362	**0.003**
	Condition 2	0.386	**0.002**	0.368	**0.003**	0.429	**<0.001**
	Condition 3	0.406	**0.001**	0.417	**0.001**	0.448	**<0.001**
	Condition 4	0.458	**<0.001**	0.450	**<0.001**	0.400	**0.001**

p<0.05; PST: Postural Stability Test; MSOT: Modified Sensory Organization Test; Condition 1: Eyes open-firm surface; Condition 2: Eyes closed-firm surface; Condition 3: Eyes open-foam surface; Condition 4: Eyes closed-foam surface.

4. DISCUSSION

This study shows that core stability, position sense of trunk and balance are affected in PwMS compared to healthy controls. In addition, it indicates a relationship between imbalance and insufficient core stability and position sense of trunk in PwMS.

Patients with MS were found to have less core endurance in comparison to healthy controls in our study. Yoosefinejad et al (35) showed that core endurance decreased in PwMS with EDSS between 1.0 and 4.5, and also proposed that it was necessary to examine the relationship between balance and core endurance in PwMS. In our study, the relationship between core endurance and balance suggests that as the core endurance decreases, postural sway increases in PwMS. The decrease in core endurance seems to be a disadvantage when balance is maintained. Hodges and Richardson (5) reported that the first active muscles are transversus abdominus, internal-external oblique, rectus abdominus and lumbar multifidus muscles with lower limb movements in healthy people. They stated that this sequential contraction of core muscles reduced the perturbations caused by lower extremity movements and thus maintained postural control and balance. This study is important in terms of showing the importance of core muscles in maintaining balance. There is only one study examining the relationship between core endurance and balance in PwMS in the literature. Freund et al (13) showed that isometric flexion endurance of trunk was correlated with several measures of postural control, and isometric extension endurance of trunk was correlated with only one postural control parameter in PwMS. We also evaluated the right and left trunk lateral endurance tests in our study and we found all components of core endurance associated with balance.

Although studies examining the relationship between core stability and balance in PwMS are insufficient, there are studies showing that core muscle strength, core endurance and balance improve at the end of core stability-based training (9, 10, 12). The case series study by Freeman et al (10) demonstrated improvement in balance in ambulatory PwMS following eight weeks of individualized core stability training. Arntzen et al. reported that core stability training for 6 weeks improved trunk control and balance in the long and short terms compared to standard care in PwMS (9). Bulguroglu et al (12) showed that core stability based instrumented and mat Pilates were improved core muscle strenth, core endurance and balance in PwMS. These studies showed that balance and trunk could affect each other in PwMS. Although these studies are training studies, it is important to show that the balance is related with trunk performance in PwMS.

Patients with MS were found to have decreased position sense of trunk in comparison to healthy controls in our study. The decrease in position sense of trunk was found

to be associated with balance impairment. This study is the first to show that position sense of trunk of PwMS is less in comparison to healthy controls, and the position sense of trunk is related to the balance in PwMS. The relationship between PST and lumbosacral reposition tests is important in terms of demonstrating the importance of position sense of trunk in maintaining balance in PwMS. In addition, the relationship between MSOT and lumbosacral reposition tests shows that position sense of trunk is important in maintaining balance whenever proprioceptive, visual, and vestibular senses are used together and these senses are reduced separately in PwMS. Previous studies examined the relationship between balance and position sense of trunk in patients with stroke, patients with ataxia, elderly persons, and patients with low back pain (20-23). Ryerson et al (20) reported that position sense of trunk was less in patients with stroke compared to the non-neurologically impaired subjects, and position sense of trunk is associated with balance in patients with stroke. Onursal Kılınç et al (21) indicated that position sense of trunk was less in patients with ataxia in comparison to healthy people, and position sense of trunk was associated with postural control in patients with ataxia. Goldberg et al (22) indicated that position sense of trunk was less in balance-impaired older adults in comparison to young adults and unimpaired older adults. Additionally, they reported that position sense of trunk was correlated with balance in balance-impaired older adults. Radebold et al (23) indicated that when the proprioceptive sense was reduced, the activation of trunk muscles was delayed, and postural control was disturbed in lumbar spine in patients with low back pain. Similar to these studies, position sense of trunk was associated with balance in the present study. This suggested that loss of position sense of trunk reflected balance impairments in PwMS.

The inclusion of only mild to moderate PwMS could be a limitation of this study. As the disease progresses, both the endurance and strength of the core muscles and the position sense of trunk may decrease with the increase of central nervous system involvement. This will cause limitations in all daily life activities related to balance. Therefore, evaluation and training of core stability and position sense of trunk should be kept in mind in PwMS with advanced EDSS level.

5. CONCLUSION

Balance, core stability and position sense of trunk were affected in PwMS in comparison to healthy controls, and balance was related to core stability and position sense of trunk in PwMS. These results suggest that approaches to improve core stability and position sense of trunk should be included in rehabilitation programs for improving balance in PwMS.

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Author Contributions:

Research idea: TO, AGG, FS
Design of the study: TO, AGG
Acquisition of data for the study: TO, AGG, CO, YA, KE, Cİ
Analysis of data for the study: TO, AGG, CO, YA, KE, Cİ
Interpretation of data for the study: TO, AGG, FS, CO, YA, KE, Cİ
Drafting the manuscript: TO, AGG
Revising it critically for important intellectual content: TO, AGG
Final approval of the version to be published: TO, AGG, FS

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Clinical and Experimental Health Sciences

Eating Attitudes From a Cardiometabolic Risk Perspective: Psoriasis Sample

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ABSTRACT

Objective: In this study, we aimed to compare psoriasis patients with healthy controls in terms of impaired eating attitudes and to investigate the relationship of eating attitudes with cardiometabolic and clinical parameters, anxiety, depression, and quality of life.

Methods: 45 psoriasis patients and 45 healthy controls were included in the study. Personal and clinical information form, eating attitude test (EAT-40), body mass index (BMI) and MetS criteria were used for all participants. Psoriasis patients were evaluated with clinical information form, hospital anxiety and depression scale (HADS), dermatological quality of life index (DQLI), psoriasis area and severity index (PASI).

Results: The data of the patient and control groups differed in terms of doing sports, impaired EAT, BMI groups, and metabolic syndrome (MetS). Abnormal eating attitudes such as negative body image, inability to control oneself in eating, overeating, and some restrictive attitudes were significantly higher in the psoriasis group. Overeating, overeating or stress-induced emotional eating, presence of MetS, weight dissatisfaction, frequent dieting to lose weight, some compensatory behaviours, and loss of self-control were significantly higher in patients with BMI>25. EAT points; showed a positive moderate correlation with BMI and HAD-Anxiety. DQLI results; showed a moderate positive correlation with HAD-Anxiety and PASI scores.

Conclusion: Our study is the first to reveal what kind of disordered eating attitudes are at risk for cardiometabolic diseases in psoriasis patients. In psoriasis patients, the rate of not being able to control their eating behaviour is high. Our results primarily highlight the relationship that can be explained by autonomic reactivity between anxiety and difficulty resisting food cravings. Professional support including psychoeducation, cognitive behavioural therapy, and acceptance-based therapies should be provided to reduce maladaptive reactions and anxiety by improving self-regulation skills.

Keywords: anxiety, eating attitude, psoriasis, metabolic syndrome, obesity

1. INTRODUCTION

Psoriasis is a disease with systemic manifestations, typically characterized by erythema, plaque formation, and scaling on the skin, mediated by chronic autoinflammatory changes that are thought to develop with the interaction of endogenous and environmental factors on a genetic basis (1). Systemic changes in inflammatory modulators such as keratinocyte proliferation in the skin increased levels of inflammatory cytokines and adipokines such as TNF-α, IL-23, IL-17, hypothalamic-pituitary-adrenal axis, and autonomic dysregulation are described chronically in the severity of psoriasis (2). These systemic proinflammatory changes; It is a key factor for a number of comorbidities including psoriatic arthritis, inflammatory bowel disease, increased hyperlipidemia, hypertension, atherosclerosis, cardiovascular risk, type 2 diabetes mellitus, obesity, metabolic syndrome (MetS), skin cancer, lymphoma, and depression (2,3). MetS is multiple components of risk factors such as hypertension, impaired glucose regulation, abdominal obesity, and dyslipidemia and is seen as a common precursor to the development of diabetes mellitus and cardiovascular disease (4). The prevalence of MetS in patients with psoriasis varies between 20% and 50%, and the risk of developing MetS in psoriatic patients is at least two times higher than in healthy controls (5). Emerging evidence suggests that the genetic background and pathogenic links shared by psoriasis and MetS can be accelerated by multiple factors, such as unhealthy lifestyles, and eating attitudes (6).

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Eating attitude; consists of people's feelings, thoughts, and behaviours about eating and nutrition, and impaired attitudes pave the way for the formation of eating disorders. Eating behaviour; appetite and food intake are regulated by the control of many peripheral hormones, including adipokines (7). When the psychological aspects of eating habits are followed; Emotional eating is defined as the shaping of binge eating behaviour to alleviate the emotional tension caused by anger, boredom, depression, anxiety, or feelings of rejection (8). Some of the pathophysiological changes that are common today have revealed that obesity should be interpreted as food addiction. Therefore, it is reported that information about the neurobehavioral connections of reward processes associated with food stimuli is of strategic importance for a better understanding and proper management of obesity (9). A recent cohort study showed a positive and strong bidirectional relationship between psoriasis and any eating disorder, especially in women (10). This study investigates eating attitudes in psoriasis patients. Secondly, it aimed to investigate the relationship between impaired eating attitudes and demographic characteristics, clinical parameters such as psoriasis severity, quality of life, depression, and anxiety, and cardiometabolic parameters such as obesity and metabolic syndrome. As far as we know, there is no study in the literature that deals with all these variables collectively.

2. METHODS

2.1. Sample

The study was designed as a cross-sectional, randomized, and controlled study. Approval for the study was obtained from the ethics committee of Atatürk University Faculty of Medicine (approval document dated 09.06.2017 and numbered B.30.2.ATA.0.01.00/154). Forty-five patients, aged between 18-65 years, who applied to the dermatology outpatient clinic and were diagnosed with psoriasis, were included in the study. A control group was formed with 45 healthy participants with similar sociodemographic characteristics as the study group. Patients with uncontrolled DM, HT, presence of systemic disease, multimorbid conditions with morbid obesity, illiterate, advanced hearing, vision, and speech problems were not included in the study.

2.2. Process

All participants were asked to fill out a questionnaire including sociodemographic and health-related behaviours, after obtaining written and verbal consent. Body mass index (BMI), waist circumference, triglyceride level, HDL cholesterol level, blood pressure, and fasting blood sugar were recorded with the Eating Attitude Test (EAT-40). Dermatological examinations of psoriasis patients were performed by the same physician; The psoriasis area and severity index (PASI) was scored and evaluated with the clinical information form, the Dermatological Quality of Life Index (DQLI), and the Hospital Anxiety and Depression Scale (HADS).

2.3. Data collection tools

Socio-demographic and clinical data of the participants including age, weight, height, BMI, gender, education, economis status, profession, smoke-alcohol consumption, weight satisfaction, effort to maintain weight, dieting to maintain weight, the effect of stress on nutrition, psychogenic eating habits, restrictive eating, emotional eating, state of doing sports were evaluated.

Eating Attitude Test (EAT-40) was used in order to identify the eating disorders of the participants**.** It is a six-point Likert-form self-report scale with 40 questions used all over the world to screen for problematic eating behaviours. The cut-off point for impaired eating behaviour is accepted as 30 points (11).

Hospital Anxiety and Depression Scale (HADS) was used in order to determine the risk in terms of anxiety and depression in the patient. It is a four-point Likert-type scale to measure the level and change in severity, and is preferred because it does not contain items related to somatic symptoms. The cut-off points of the Turkish version of the HAD scale were determined as 10 for the anxiety subscale and 7 for the depression subscale (12).

Dermatological Quality of Life Index (DQLI) was used to evaluate the quality of life of psoriasis patients. It is a dermatology-specific, simple, short, understandable, patient-oriented questionnaire and can be used in daily routine clinical studies. If DQLI Scores > 10, it was considered severe(13,14).

Psoriasis Area and Severity Index (PASI) was used to rate the severity of psoriasis. The index evaluates disease severity from 0 to 72 by assessing the percentage of skin/body parts and the three target symptoms, erythema, induration, and desquamation; PASI>10 indicates severe psoriasis (14).

Patient Body mass index (BMI) (kg/m2); calculated as weight(kg) / height(m2) ratio according to World Health Organization(WHO) 2008; overweight is considered as BMI ≥25 kg/m2, and obesity as BMI ≥30 kg/m2 (15).

MetS Diagnosis; based on the presence of ≥3 criteria from the modified National Cholesterol Education Program (NCEP) Adult Treatment Panel-III; waist circumference>102cm in men or >88cm in women, hypertriglyceridemia≥150mg/dL, HDL cholesterol men<40mg/dL or women<50mg/dL, blood pressure≥130/85mmHg, and fasting plasma glucose≥100mg/dL (16).

2.4. Statistical Analysis

Participants' data were presented as mean±standard deviation, median, minimum, maximum for numerical variables, percentage, and number for categorical variables. Data were visually assessed for normality using Kolmogorov Smirnov test, histograms and Q-Q plots. Additionally, data were checked for the presence of skewness, kurtosis and outliers before proceeding with the inferential analysis.

Statistical inference is based on 95% confidence intervals (CIs), and the significance level was set at 0.05. The data of the study were analyzed using the independent sample t-test, Mann-Whitney U-test, Chi-square test, Fisher's exact test, and Pearson correlation tests in the SPSS20 program.

3. RESULTS

3.1. Comparison of sociodemographic and lifestyle variables of psoriasis and control groups

Gender, marital status, cigarette consumption, alcohol consumption, weight satisfaction, weight maintenance effort, dieting to maintain weight, effect of stress on nutrition, psychogenic eating habits, restrictive diet, and emotional eating were similar in psoriasis and control groups. There was a significant difference between the groups in terms of occupation, education, and doing sports (Table 1).

3.2. Clinical features of psoriasis patients

The most common vulgar involvement was in the psoriasis group, the rate of use of systemic agents in the treatment was high, and 87% of the patients had moderate or severe psoriasis. (Table2).

Table 1. *Comparison of sociodemographic and lifestyle variables of groups*

		Psoriasis group		Healthy controls		t	df	p[a]
		n:45	%100	n:45	%100			
Gender	Male	28	62.2	24	53.3	0.729	1	.393
	Female	17	37.8	21	46.7			
Marital Status	Single	18	40.0	26	57.8	2.846	1	.092
	Married	27	60.0	19	42.2			
Profession	Working	31	68.9	40	88.9	5.404	1	**.020***
	Not Working	14	31.3	5	11.1			
Education	Primary	19	42.2	7	15.6	7.805	2	**.020***
	Middle	16	35.6	24	53.3			
	High	10	22.2	14	31.1			
Smoke consumption	Smokers	23	51.1	15	33.3	2.232	1	.135
	Not Smokers	22	48.9	30	66.7			
Alcohol consumption	Drinkers	3	6.7	1	2.2			.616
	Not drinkers	42	93.7	44	97.8			
Weight satisfaction	Pleased	23	51.1	18	40.0	1.120	1	.296
	Not glad	22	48.9	27	60.0			
Effort to maintain weight	Yes	22	48.9	18	40.0	0.720	1	.396
	No	23	51.1	27	60.0			
Dieting to maintain weight	Often	10	22.2	4	8.9	0.741	1	.389
	Sometimes	6	11.0	16	35.6			
	Rarely-never	29	64.4	25	55.6			
The effect of stress on nutrition	Effects	34	75.6	30	66.7	0.865	1	.352
	Does not affect	11	24.4	15	33.3			
Psychogenic eating habits	Yes	33	73.3	34	75.6	0.058	1	.809
	No	12	26.7	11	24.4			
Restrictive eating	Decreased or absent appetite	13	39.4	16	47.1	0.458	1	.499
	No	32	71.1	29	52.9			
Emotional eating	Binge eating too much or more than usual	20	44.6	18	40.0	0.182	1	.670
	No	25	55.6	27	60.0			
State of doing sports	Yes	8	17.8	11	24.4	16.312	2	**<.001*****
	No	36	80.0	20	44.4			
	Done left	1	2.2	14	31.1			

*Chi-square test, significant p values were bolded in the table*p<.05,**p<.01,***p<.001*

Table 2. *Clinical features of psoriasis patients*

Age		Min-Max 18-53 year	Mean ± SD (34.36± 10.773)
Psoriasis onset age		Min-Max 1-52 year	Mean ± SD (20.04±12.46)
Disease duration		Min-Max 2-47 year	Mean ± SD (14.46±10.35)
Psoriasis type	Vulgaris	32(n)	71.11(%)
	Guttate	3(n)	6.6(%)
	Pustular	2(n)	4.4(%)
	Erythrodermic	1(n)	2.2(%)
	Nail involvement	8(n)	17.6(%)
	Joint involvement	1(n)	2.2(%)
Treatment	Local	18(n)	40.0(%)
	Systemic	27(n)	60.0(%)
Stress factor	Yes	18(n)	40.0(%)
	No	27(n)	60.0(%)
PASI group	Mild	6(n)	13.3(%)
	Middle	18(n)	40.0(%)
	Severe	21(n)	46.7(%)
DQLI	> = 11	24(n)	53.3(%)
	<11	21(n)	46.7(%)
HADS risk	Yes	24(n)	53.3(%)
	No	21(n)	46.7(%)
Mental disorder before psoriasis	Yes	2(n)	4.4(%)
	No	43(n)	95.6(%)
Mental disorder after psoriasis	Yes	9(n)	20.0(%)
	No	36(n)	80.0(%)

Hospital Anxiety and Depression Scale=HADS, Dermatological Quality of Life Index=DQLI, Psoriasis Area and Severity Index=PASI

3.3. EAT variables

From the expressions of eating attitude; trying not to eat when hungry, cutting food into small pieces, post-meal nausea, only thought is to become thinner, liking to eat meat, getting up early in the morning, like to eat at a restaurant, self-control about food, feeling pressure from others about eating, sugar-oily in the reports of liking to try foods, it was seen that the psoriasis group differed statistically from the control group. The difference was in the psoriasis group; it was due to high rates of binge eating, overeating, and restrictive eating behaviours shaped by negative body image, effort to lose weight, and loss of self-control. (Table 3)

3.4. Chi Square Test Results of Groups

When psoriasis patients and healthy controls were examined with the chi-square test; it was found that there were differences in terms of impaired eating attitude, BMI groups, and MetS. (p values: .030, .042, .004, respectively) (Table 4).

3.5. Comparison of means of metabolic variables in psoriasis and control groups;

While the mean age, BMI, glucose, HDL, Tg, cholesterol, and LDL values were similar between groups, the waist circumference and EAT scores were significantly higher in the psoriasis group (Table 5).

EAT score of 30 and above

Eight patients (17.8%) and 1 (2.2%) control were identified who exhibited impaired eating behaviours, including efforts to maintain weight, binge eating, binge eating, emotional eating, and restrictive eating changes. In those with impaired eating attitude; the rate of smoker was low (p=.022), but the rate of doing sports was high (p=.039). When the relationship between the clinical and demographic data of 8 patients with eating attitude disorder was examined by chi-square test, 8 patients had a disease duration longer than 3 years (p=.568), 6 had severe psoriasis clinic (p=.699), 4 had a history of systemic treatment (p=.694) reported. In these patients, increased BMI, MetS diagnosis, stress factor positivity, increased risk of anxiety depression, and poor quality of life were found that did not reach statistical significance (p>.05 for each).

Table 3. *EAT variables of psoriasis and control groups*

		Psoriasis group		Healthy controls		t	df	p[a]
		n	%	n	%			
I try not to eat when I'm hungry	Always – very often-often	15	33.3	5	11.1	6.852	2	**.033***
	Rarely	8	17.8	8	17.8			
	Never	22	48.9	32	71.1			
I like to eat meat	Sometimes-rarely	22	48.9	36	80.0	13.887	2	**.001****
	Never	10	22.2	8	17.8			
	Always-very often-often	13	28.9	1	2.2			
I like to eat at the restaurant	Always-very often-often	18	40.0	32	71.1	12.206	5	**.007****
	Sometimes	9	20.0	5	11.1			
	Rarely	6	13.3	6	13.3			
	Never	12	15.6	2	4.4			
I can control myself about food	Always	4	8.9	9	20.0	19.113	2	**<.001****
	Very often-often	4	8.9	19	42.2			
	Sometimes-rarely	37	82.2	17	37.8			
Sugary. I like to try fatty foods	Never	8	17.8	24	53.3	16.648	3	**.001****
	Always-very often-often	11	24.4	11	24.4			
	Sometimes	9	20.0	6	13.3			
	Rarely	17	37,8	4	8.9			

*Significant p values of the chi-squared test were bolded in the table *p<0.05,**p<0.01,***p<0.001*

Tablo 4. *Chi square test results of groups*

		Psoriasis group		Healthy controls		t	df	p[a]
		n:45	100%	n:45	100%			
EAT	30 and above	8	17.8	1	2.2			**.030***
	29 and below	37	82.2	44	97.8			
BMI group	<25	21	46.7	27	60.0	6.750	2	**.034***
	>25<30	18	40.0	18	40.0			
	>30	6	13.3	0	0.0			
Glucose	<100	36	80.0	44	97.8	7.200	1	**.007****
	>100	9	20.0	1	2.2			
Waist circumference	Normal	27	60.0	44	97.8	19.281	1	**<.001****
	Male >102 Female>88	18	40.0	1	2.2			
HDL	Normal	21	46.7	28	62.2	2.195	1	.138
	Male<40 Female<50	24	53.3	17	37.8			
Tg	<150	26	57.8	36	80.0	5.184	1	**.023***
	>150	19	42.2	9	20.0			
MetS >3 criterion	Yes	10	22.2	1	2.2	8.389	1	**.004****
	No	35	77.8	44	97.8			
Presence of metabolic risk	Yes	19	42.2	7	16.3	7.110	1	**.008****
	No	26	57.7	36	83.7			

*BMI=body mass index, Eating Attitude Test=EAT, High density lipoprotein=HDL, Metabolic syndrome=MetS, Triglyceride=Tg, a Significant p values of the chi-squared test were bolded in the table, *p<.05,**p<.01,***p<.001*

Table 5. *Comparison of means of metabolic variables in psoriasis and control groups*

	Psoriasis group	Healthy controls	t	p[a]	Means	Standard error
	(Mean ± SD)	(Mean± SD)				
Age	34.36± 10.77	30.87± 10.74	-1.538	.128	-3.49	2.268
BMI	25.47± 4.53	24.32± 3.22	-1.393	.167	-1.15	.82801
Waist circumference	93.64± 14.92	79.80± 10.53	-5.084	**<.001*** **	-13.84	2.72303
Glucose	88.39±17.02	84.62± 6.86	-1.375	.173	-3.77	2.73905
HDL	44.978±10.84	46.93± 8.22	.957	.341	1.95	2.04493
Tg	142.49±80.99	112.62±52.64	-1.958	.054	-29.87	15.25599
Cholesterol	175.20±40.72	167.58±35.58	-.916	.362	-7.63	8.32395
LDL	116.56±30.75	107.89±27.32	-1.342	.184	-8.67	6.46036
EAT score	20.24± 8.80	13.18± 6.47	-4.339	**<.001*** **	-7.07	1.62880

*An Independent sample t test was used to compare between groups, significant p values were bolded in the table*p<.05,**p<.01,***p<.001*

In patients with BMI>25;

19 were married(p=.005), 17 were male(p=.203), 17 showed severe psoriasis (p=.526), 17 had increased waist circumference(p<.0001), 14 had triglyceride value was over 150(p=.019), and 12 of them had MetS(p<.0001). Weight dissatisfaction, frequent dieting to lose weight, binge eating, overeating, and stress-induced emotional eating were significantly higher: Emotional eating changes triggered by stress and binge eating were found in 15 of them(p=.009), and 15 of them were dissatisfied with their weight(p=.051). 13 reported that they frequently dieted to lose weight(p=.005) and 13 reported that they smoked(p=.661). 5 of them had an impaired eating attitude(p=.705); Dividing food into small pieces from eating attitudes showed a significant increase in the BMI>25 groups(p=.003), and trying not to eat when hungry showed a significant increase in the BMI<25 groups(p.011).

3.6. In Pearson correlation analysis;

EAT scores; Positive moderate correlation between waist circumference (r=.311*,p=.04) and HAD anxiety (r=.352*,p=.019), and DQLI results and HAD anxiety (r=.311*,p=.040) and PASI scores (r=.442**,p=.002) was found to have a positive, moderate correlation.

4. DISCUSSION

In our study investigating the relationship between cardiometabolic risks and impaired eating attitudes in psoriasis patients, obesity rates in psoriasis patients were higher than in healthy controls. Obesity, one of the most important components in MetS, has been detected in psoriasis patients at higher rates than in the general population. Meta-analyses of cross-sectional and case-control studies have shown, similar to our results, that patients with psoriasis are 50% more likely to be obese compared to the general population (17,18). Although there is great variation between countries and ethnic groups, the prevalence of metabolic syndrome increases as body mass index(BMI) increases. In our study, a significant difference was found between the patient and control groups in terms of MetS frequency, high fasting blood glucose, high triglyceride, and high waist circumference. The recent systematic review reported that the odds ratio (OR) for MetS and psoriasis ranged from 1.39 to 4.49 (19).

In our study, binge eating, overeating, and restrictive eating behaviours shaped by negative body image, effort to lose weight, and loss of self-control were found to be high in the psoriasis group. It has been reported in the literature that eating disorders can be considered as a psychogenic cofactor contributing to the development of obesity and MetS in psoriatic patients (6). Studies in overweight and obese people have shown that negative body image with increased body dissatisfaction and shape and weight concerns leads to weight gain over time compared to those who are not overweight (20). In the study of Crosta et al.; in the psoriasis group, especially in the obese patients, higher scores were found in the eating disorder subscales of 'body dissatisfaction' and 'interpersonal distrust' compared to patients without psoriasis (21). In our study, in patients with BMI>25; although EAT scores do not differ; MetS, weight dissatisfaction, frequent dieting to lose weight, and some compensatory behaviours, binge eating too much or more than normal, and emotional eating triggered by stress were found to be significantly higher. In our study, it is consistent with the literature that emotional eating behaviours, among the eating attitudes reported in patients with weight gain, have a stronger relationship between higher BMI and MetS (22,9).

Diet is an effective factor in the etiopathogenesis of psoriasis. In our study, attitudes such as 'eating meat', 'eating out', 'trying sugary and fatty foods' were found to be high in the psoriasis group. The high avoidance states we identified are; may be associated with worsening of the psoriasis clinic if the foods mentioned by the patients are consumed (23). Meat is a food source of arachidonic acid, one of the n-6 polyunsaturated fatty acids. Eicosanoids derived from arachidonic acid have been implicated in psoriatic skin lesions by exacerbating

inflammatory processes by increasing IL-1 production and tissue sensitivity to cytokines (24). Schwarz et al. It has been reported that healthy foods such as vegetables positively affect psoriasis, and processed foods, sweets, and alcohol have negative effects on the psoriasis clinic (18). Although there are not enough randomized controlled studies in the literature to confirm the benefit of diet regulation, the patients' own experiences have been instructive in this regard. On the other hand, patients' expression "I feel bloated after meals" may also be associated with inflammatory bowel disease symptoms, which are 4 times more common in psoriasis than in the general population (25). However, while all of these attitudes are expected to be protective for obesity, obesity and metabolic risk increased in the psoriasis group in our study. The significant increase in the expression 'not being able to control oneself about food' in the psoriasis group may explain this situation. According to our results, despite the understanding of psoriasis triggering foods and/or obesity risk, insufficient self-control of eating behaviour seems to increase the risk of obesity.

It is thought that autonomic reactivity plays a role in the pathophysiology, primarily due to psychological reasons, including anxiety, about the difficulty of resisting urges to eat (26). In addition, the difference in appetite characteristics may also be effective. There is increasing evidence that an increase in appetite due to changes in neurohormones, particularly an increase in leptin levels and/or a decrease in regulatory adipokines, is associated with the occurrence of obesity in psoriasis (7). These neuroendocrine changes may also be effective by promoting hunger and the urge to eat and increasing activity in the reward cycle. In our study, the significant increase in the parameter of trying not to eat when hungry in the psoriasis group with BMI>25 may again be an indicator of increased appetite and hunger. In individuals with obesity, lack of satiety response or motivation to eat with hypersensitivity to reward, impulsivity and food-seeking appetite characteristics such as eating faster and more, and poor self-regulation are considered to be risks for excessive calorie consumption and weight gain (20). The increase in activities such as binge eating and emotional eating as pleasurable activities with changes in reward sensitivity in the psoriasis group with BMI>25 is also consistent with the literature.Impulsive eating behaviour, another disordered eating attitude, can explain emotional eating, as it is followed as fast, unplanned reactions regardless of the negative consequences of the behaviour. However, in impulsive eating, excessive compensatory behaviours are expected, which are added to the table together with the feelings of regret experienced later. Only in the psoriasis group with BMI>25, the behaviour of 'I break my food into small pieces' is scored as unhealthy or excessive weight control compensatory behaviour on the scale, but it seems to be an intervention to provide diet and weight control with awareness. At the same time, the significantly lower rate of "I like to eat at the restaurant" compared to the controls can be interpreted as avoidance behaviours associated with psychological symptoms such as social anxiety when combined with the statement "I feel that others pressure me about food". The positive correlation of EAT scores with HADS-A justifies this interpretation. A systematic review of recent observational studies and clinical trials found that prevalence of anxiety disorders and anxiety symptoms among adult patients with psoriasis using the HADS-A limits, 20-50% of participants had significant anxiety levels and 7-16% were diagnosed with clinical anxiety (27). The psychosocial burden of somatic and anxiety symptoms in psoriasis patients and the relationship between BMI and quality of life have been demonstrated (28,29). In the literature, it has been reported that individuals with high depression and anxiety levels have an increased risk of obesity-associated with their eating attitudes. At the same time, a higher cardiovascular risk is reported in common mental disorders such as depressive disorder and anxiety disorder due to inflammatory changes and autonomic dysfunction, as well as life changes such as smoking, alcohol use, inactivity, and unhealthy diet (30).

This study has many strengths. its prospective nature and the existence of a control group. The severity of psoriasis was accurately assessed using a validated clinical index, cardiometabolic risks were reported with objective criteria, not only the EAT scale scores but also the questions were evaluated and how it was affected was also evaluated. The limitations of this study are the relatively small number of participants, single-centre, and cross-sectional design. Moreover, not excluding patients treated with systemic drugs harbors the possibility of drug influence on the outlook of MetS in psoriasis.

5. CONCLUSION

It is important to raise awareness about impaired eating attitudes in psoriasis patients who are at high risk for cardiometabolic diseases. Our results primarily highlight the relationship that can be explained by autonomic reactivity between anxiety and difficulty resisting food cravings. Professional support including psychoeducation, cognitive behavioural therapy, and acceptance-based therapies should be provided to reduce maladaptive reactions and anxiety by improving self-regulation skills. The severity of psoriasis is associated with deterioration in diet and exercise. Weight loss of psoriasis patients will play an important role in both targeted treatment of psoriasis and reducing their metabolic risks. Supportive interventions for healthy lifestyle changes such as exercise and dietary changes in psoriasis patients; are seen as an unmet medical need. Prospective studies examining the role of lifestyle changes and psychological interventions in patient groups are needed.

6. Ethical considerations

This study was performed in accordance with the Declaration of Helsinki. We have obtained written consent from the patient and approval from the ethics committee of Atatürk University Faculty of Medicine (document dated 09.06.2017 and numbered B.30.2.ATA.0.01.00/154).

7. Conflict of interest

The authors have no conflict of interest to declare.

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Clinical and Experimental Health Sciences

Young Men's Perceptions about Sexual Health and Sexual Education: A Qualitative Study

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ABSTRACT

Objective: For healthy sexuality and effective sexual health education, it is important to know the sexual health perception of individuals, their sexual education needs, and the affecting factors. The purpose of this research is to learn in-depth the perceptions of young men about sexual health and sexual education.

Methods: This study was carried out in a health vocational school of a foundation university. The study was constituted using an in-depth interview method, and interviews were conducted with 16 students, 2 of whom were pilots. Content analysis was used to assess the obtained data.

Results: Sexual education with sexual behavior and health were determined as the main themes. The male students indicated level of sexual knowledge was insufficient, and they needed to receive comprehensive sexual education from a qualified specialist.

In addition, they stated that education should be given to men and women separately, and in small groups. It was also found that friends, religious and cultural values were important factors in sexual knowledge and behavior.

Conclusion: As a result, it has been revealed that male university students need sexual education, and the correct information can only be learned through a comprehensive and socio-cultural norms-sensitive education.

Keywords: Young men, perceptions, sexual health, sexual education

1. INTRODUCTION

Sexuality is defined as an integrated state of a series of emotions that provides the individual with physiological, spiritual, and positive emotions, as well as ensuring his/her integration with society and contributing to his/her personality development (1,2). Sexual health (SH) is a process that begins before the birth of an individual and continues until death, however, it has an impact on an individual's life and its significance can only be recognized with appropriate education (3). SH and sexuality-related subjects are limited presence in Turkey's educational curriculum (4). When the sexual information sources of the youth are examined, it can be seen that the internet, media and friends are at the top of the list (5,6). It is stated that this condition can lead to young people receiving incorrect information from improper sources which can lead to early pregnancies, sexually transmitted infections (STIs), and a variety of sociological and psychological issues (7). There are differences between genders in sexual interest and knowledge. Studies have shown that men are less aware than women in practically every issue related to sexuality and are more reluctant to receive education from reliable sources (8,9). There are few studies examining SH and influencing factors among young males in Turkey (10).

In order for SH education to be effective, it is important to know the factors that affect SH and to integrate them into the education program (11). In studies conducted in Turkey, the factors affecting men's SH are expressed as the age of first sexual intercourse, age of first marriage (12), and contraceptive use (13). Although studies reveal some of the factors affecting SH, an in-depth examination of the subject will provide detailed data for SH promotion programs and interventional studies (14). Most of the studies on sexuality in our country were conducted with women. In this respect, we believe that this study, which reveals the thoughts of males on sexual health and sexual education, will contribute to a more detailed understanding of the subject. The goal of this qualitative study is to ensure a deeper understanding about the perception of young males on SH and sex education.

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2. METHODS

2.1. Research Design and Participants

This research was conducted with male students who are studying first and second years at the Vocational School of Health Services of a University in Istanbul and gave consent to participate in the research. The sample was chosen using the purposive sampling method (15). The sampling approach must be the continuous accumulation of data until the ideas and processes that could be the reply to the study question began to appear on a regular basis (16). The researchers agreed that they had collected sufficient data when the ideas and processes began to appear over and over. At this point, the sample consisted of 16 male students, 2 of whom were pilots. No one refused to participate in the study. There is no relationship that would create a conflict of interest between the participants and the authors.

2.2. Data Collection

Semi-structured interview questions and the conceptual framework of the study were created as a result of discussions with professionals and literature review (17). Before this study first author took a course in qualitative research.

The data were collected by the first researcher using the "Individual Interview Form" with face-to-face in-depth interview technique between January and March 2020. In-depth interview technique was used to obtain more detailed data based on feelings, ideas, and experiences (18).

The following four questions were contained in the interview form:

- *Can you tell me a little bit about yourself, your family, and your surroundings?*
- *When, where, and by whom do you think sexual education (SE) should be done?*
- *What topics should be included in SE programs? Why?*
- *What do you think about sexuality, sexual act, and SH? How does our culture or environment guide us in terms of sexuality?*

A pilot study of the form was implemented with two students. The results of the pilot study were used to make the necessary changes to the form. Individual in-depth interviews were held in a private room with the researcher and the student seated across a table from each other. There was no one else in the room during the interview.

Necessary permissions for audio recording were obtained from all participants, and the conversations during the interviews were recorded on a voice recorder by the researcher. All of the information collected from the students was kept private. The interviews lasted approximately 28 minutes to 52 minutes, with an average duration of 38 minutes. Since the COVID-19 pandemic broke out right after the interviews were completed, transcripts could not be returned to participants for comment and/or correction.

2.3. Data Analysis

After all the interviews were completed, the raw data was written using the Microsoft Word software (Microsoft Office Professional Plus 2019). To ensure credibility, raw data were analyzed by four experts 2 of whom were article authors. Codes and themes were predetermined in line with the conceptual framework created before starting the research. Consensus was formed with the discussions made by the authors and experts on the extracted codes and results. A content analysis was carried out while doing a qualitative analysis of the data recorded in an electronic environment. The similarity of the explanations in the answers, the number of participants who made the same explanation and used similar words, the real purposes of the explanations and the originality of the answers were taken into consideration. The answers given by the students to each topic discussed were interpreted one by one. The answers given by the students to the same questions were classified according to their differences and similarities. Following each author's careful reading of the raw data, coding was done according to the main concepts. The generated codes were grouped according to the themes created before the interview. The themes that emerged as a result of this study were SE along with sexual behavior and health. After the study data was written with the Microsoft Word program and analyzed according to the themes, the data was sent to two independent persons experienced in qualitative studies to control the process. The implementation of all the steps related to this stage of the study was carried out in accordance with the relevant literature (15,19). Conduct and assessment of the study were evaluated with the COREQ qualitative design checklist.

2.4. Ethical Considerations

Before beginning the study in a state University's scientific research evaluation ethics committee provided written approval (approval number: 09.2019.727, 26/07/2019), as well as institutional approval from the university where the study was conducted. The purpose of the research and other relevant details were explained to the students, and their verbal and written consents were obtained.

3. RESULTS

According to the findings, 11 of the students were between the ages of 19-21, 12 of them had a girlfriend before, and 11 of them had previously received sexual education (Table 1).

Two main themes emerged in this study, namely SE and sexual behavior and health.

Table 1. *Socio-Demographic characteristics of the participants(n=14)*

Age	n	%
19-21	11	78.6
22 and above	3	21.4
Longest lived place		
Provincial center	7	50.0
District center	7	50.0
Marital status		
Married	1	7.1
Single	13	92.9
Does he currently have a girlfriend?		
Yes	2	14.3
No	12	85.7
Has he had a girlfriend before?		
Yes	8	57.1
No	6	42.9
Has he received sex education before?		
Yes	3	21.4
No	11	78.6

3.1. Theme 1. Sexual Education

The majority of students stated that SE should be given by a specialist, that it would be more appropriate to teach women and men separately and in small groups, and that teaching in a classroom would be more effective. The SE theme in the study is consists of two sub-themes: educator, location, time, method, and content of SE, and the impact of the student's department on his or her level of sexual knowledge.

3.1.1. Place, Time, Content, and Educator of SE

Most of the students stated that SE is necessary. Three students claimed that they received SE in high school, but that it was not sufficient and appropriate for their needs. According to the majority of students, SE should be given by experts. Students generally think that SE should be given during or after adolescence. They stated that it would be reasonable to provide education during high school years. In addition, most of the students stated that it was appropriate to conduct the training in small groups separately for women and men. They emphasized that the education should cover the issues such as male-female relations, STIs, birth control methods, infertility, sexual abuse, and violence against women. The statements of two students on this subject are as follows:

"People without SH education should not have sexual intercourse. We studied reproduction in biology class, but we did not receive a clear education on sexual diseases or sexual intercourse. I think it should be given in schools, when should it be? After puberty, in the first or second year of high school, it can be provided." (P2)

"Considering that there are women between the ages of 17-18 who have abortions in our country, students should be made aware of this issue. I think SE can be given in schools, but it should not be given to women and men together because this will prevent students from receiving an effective education. In my opinion, the male and female reproductive system, sexual diseases and methods of protection from sexual diseases should be explained in education." (P6)

3.1.2. The Effect of the Department He Studied on the Level of Sexual Knowledge

The students indicated that have more information about SH issues due to the studied at health department and have learned anatomical structures, contraception methods and infectious diseases in the lessons. However, students stated this was not enough. The following are three students' opinions on the matter.

"We may be better equipped about sexuality since we have studied in a health school. For example, in a physiology and anatomy lesson, the lecturer inevitably brought up such topics." (P14)

"In our department, basic topics related to sexuality were explained, but we also learned them in high school. It covered organs, their functions and protection methods. They do not go beyond these topics, so it is extremely limited. In my opinion, this is not enough to explain it in this way, it should be more comprehensive." (P7)

"I believe the issues discussed were not about sexuality; just its anatomy was mentioned, which we were already familiar with." (P8)

3.2. Theme 2. Sexual Behaviors and Health

The theme of sexual behaviors and health is consists of three sub themes: The meaning of sexuality and the relationship between sexuality and health, The effect of religion, socio-cultural environment on sexual behavior and the attitudes towards extramarital affairs and the red light district, brothel, and masturbation. In this theme sexual behaviors and health, the influence of religion and socio-cultural environment on sexual decision-making, sexual satisfaction without sexual intercourse, and attitudes towards sexual harassment and brothels were mentioned.

3.2.1. The Heaning of Sexuality, and the Relationship Between Sexuality and Health

The majority of the students participating in the study defined sexuality as reproduction, need and pleasure and stated that sexuality and health had a connection. Furthermore, it was noted that the students avoided using the word sexuality during the interview.

When asked "what should be done to protect SH?" the majority of the students replied as monogamy, abstinence from sex, and the use of condoms. The statements of two students on the subject are as follows:

"I would like to explain the relationship between sexuality and health by giving an example. When we greet someone,

even with our hands, we may still face the risk of getting a germ. On the other hand, because there is such close contact, if someone with herpes on their lips has sexual intercourse with a healthy person, the disease is spread to the other one immediately." (P7)

"In my opinion, to protect human health, one should not have intercourse with anyone until they get married or choose their life partner. Something like this is so wrong when you spend the weekend with one woman and the following week with another". (P13)

3.2.2. The Effect of Religion, Socio-Cultural Environment on Sexual Behavior and the Attitudes Towards Extramarital Affairs

Almost all the male students admitted to having limited knowledge on religious issues, and that the religious part of sexuality should be emphasized in education. Furthermore, the majority of students believe that there is too much misinformation and prejudice regarding sexual matters in society, that discussing sexual matters in the family is considered embarrassing, and that there is a lot of social pressure on this issue. According to the students, there are remarkable differences in the society's view of men and women who have extramarital affairs. While women are expected to abstain from sex until marriage, men are not expected to do so. Students stated that the media has a deterrent effect on sexual harassment and rape but the punishments are insufficient. The statements from three students on this subject are as follows:

"Religion says fornication is haram, but a man has a desire to have sexual intercourse during adolescence which is hard to deal with it. Instead of obeying the religious rules, prefers to do something more enjoying for himself." (P11)

"When you open the wallets of most young men in Turkey, you'll find at least one condom, and when you consider that they're separated from their families, I believe that environmental elements and their social surroundings have an impact". (P14)

"I think it's important for people to be able to restrain themselves when it comes to rape. There are also those who do it not only for the opposite sex, but also for their fellows. Such incidents should not go unpunished, as they do most of the time. In order to improve awareness in our society, I believe there should be more sexual harassment and rape news in the media."(P6)

3.2.3. Red Light District, Brothel, and Masturbation

The students who participated in the study stated that places such as brothels should be, although they are not recommended places. Most of the students specified that this is a religious sin, and the risk of infection is high in such places they were also asked what they thought about masturbation, pornographic web pages, and erotic movies. Most of the students stated that they were aware that these activities were prohibited by religion and that their culture did not consider them reasonable, but such a thing can be done instead of sexually damaging someone else.

The statements of two students on this subject are as follows:

"In my opinion, such places should not be used, who knows how many people have sexual intercourse with a woman there every day. Therefore, the probability of getting an infection is very high. Why would anyone want to be ill?" (P7)

I think a person can decide where to go and what to watch or not with his own free will. However, those who want to see such movies can do so through different banned sites and channels." (P2)

4. DISCUSSION

It was observed that the students participating in the research were reluctant to use the word sexuality, and defined the concept of sexuality as reproduction, and enjoyment. SH was perceived by the students to mean protection against infectious illnesses and using condoms. According to WHO, SH is an extremely broad concept and includes safe abortion, prevention and control of infectious diseases, fertility care, prevention of gender-based violence, contraception counselling and comprehensive education (20). In the literature, the concept of sexuality is discussed as gender, sexual preference, gender identities and roles, intimacy, pleasure, reproduction, and eroticism (3,21). The students' limited responses to the questions are regarded to be a result of their lack of knowledge as well as the social pressure they felt on them.

Despite having received a university education in the realm of health, the participants stated that they did not have enough understanding regarding sexuality and SH. Similarly, studies conducted in Turkey demonstrates that students' sexual knowledge levels are not sufficient (22,23). Inadequate SH education may pose a risk for STIs (24), unwanted pregnancies (25) and problems between couples (26). SH education does not encourage early sexual intercourse, according to the literature, and individuals who acquire SH education protect themselves at higher rates (27). Students pointed out that it is better to provide SE during adolescence and high school years. According to the literature, SE should be given as a long-term program that contains specific information for each age period from birth (28). Since sexual development has the most evident phase in adolescence, preparation for this period is also important. In our study, the participants said that SE should be given by experts in their field. WHO also mentions SE among sexual rights, and states that accurate, age-appropriate and up-to-date information should be provided about sexuality as well as the physical, psychological and social aspects of reproductive and sexual diseases (29).

Systematic review and meta-analysis studies on SE emphasize that SE should be given as comprehensive SH education

(30,31). Nurses are health care professionals who are qualified to provide comprehensive health education (32).

Students in this study believe that it's better to provide sex education for women and men separately and in small groups. The underlying reason for this preference could be as the majority of the population in Turkey is Muslim, the SE is limited, and sexuality is an avoided issue to be discussed in the family. For the effectiveness of the education, it is necessary to consider the characteristics and demands of the target group. According to a study in the literature, it was mentioned that education on sexual issues should be given separately to men and women due to the preference of Muslims (33).

Most of the students in the research, indicated that the content of SH education is limited to STIs and contraception methods. In the literature, while age-related issues may vary, it has been reported that comprehensive SE during adolescence and beyond should cover the topics like dating, sexual online behavior, physical health, relationships, sexual pleasure, sexual coercion and contraception (35,36) as well as STIs, teen parenting, religious beliefs, abortion and birth control (37).

Moreover, in the present study, the students expressed that it would be beneficial if the education included religious rules and prohibitions about sexuality. Some of the students used expressions indicating that they were in dilemma between the religious prohibitions and their sexual desires. Incorporating religious rules and prohibitions in SE can be helpful in the prevention of risky behaviors. Because many religions emphasize the sacredness of marriage and forbid extramarital affairs, it can be expected that the students have this viewpoint (34). Extramarital affairs are considered a sin according to the Islamic religion. For this reason, it is seen that individuals belonging to the Islamic religion are less inclined to have premarital intercourse (35).

Most of the students mentioned that their living environment and their friends are effective in their sexual decision-making. They also pointed out that the environment is determinative in terms of facilitating and complicating risky behaviors. It can be clearly seen in the literature that friends are effective in many risky behaviors starting from adolescence (36). It is also noted that risky behaviors are related to each other (37). According to a study, factors such as tobacco or alcohol exposure, risky peer behaviors, flirting, intention to have sexual intercourse are effective in individuals' sexual decision-making and are characterized as facilitating elements for an individual's sexual life relationship (38).

Our research has shown that according to the perception of male students, society does not treat men and women equally in sexual matters, males can live their sexuality more freely, and religion is also effective in these issues. Men are freer and dominating than women in both sexual and many other social issues due to the fact that Turkey's social and political framework is male-dominated, which ranks 54th out of 189 countries in terms of gender equality (39). Similar to our findings, it is stated that society in Turkey views men and women in premarital relationships quite differently, and that there is a double standard in this regard (40).

In the current study, another issue that should be taken into consideration is social desirability. Social desirability is the expression of the attitudes and behaviors that the individual thinks will be more accepted in the society, not what he/she did (41,42). The researchers were aware that the subject of sexuality was very sensitive, and that the participants were likely to state some thoughts and events that were not experienced and did not belong to them as if they were. In order to cope with this situation, it was suggested by the researchers to address the participants by code names, and the interview was held in a private room.

In this study, students stated that sexual harassment and sexual rape are unacceptable and there should be places such as brothels and red-light districts. Although these kinds of places are legal and individuals visit them to unwind sexually, some have claimed that going there is a religious sin. It is true that the state regulates the activities of brothel-style establishments, making them lawful under certain circumstances (such as being over 18 years old) (43). Even though brothels are legal and regulated, participants are aware that such places are risky for STIs. According to the WHO, sex workers are facing an increased burden of STIs and blood-borne infections. It is estimated that female sex workers are 30 times more likely to live with HIV than other women of reproductive age, and the average HIV prevalence among sex workers is 36% (44). In addition, the students emphasized that it would be beneficial for social awareness to publish the punishments for sexual harassment and rape in the media. According to a study, the rise in reports of sexual harassment and rape in the media and on social platforms has comprised a sense of solidarity among victims (45).

5. CONCLUSION

It was concluded that the students perceived the concept of sexual education and sexual health as incomplete. The sexual education to be given to students should be done to protect their privacy. It was also indicated that parents, friends, religious values and social culture are important factors in sexual knowledge and behavior. These factors should be considered when administering SE to individuals.

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Clinical and Experimental Health Sciences

Effect of Different Birth Balls Used at the First Stage of Labor on Birth Outcomes and Maternal Satisfaction: A Randomized Controlled Trial

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ABSTRACT

Objective: This study aimed to determine the effectiveness of different birth balls used at the first stage of labor on fetal head descent, pain intensity, and maternal satisfaction.

Methods: This study used a single-blind, randomized controlled experimental design. It was conducted with 180 primipara women in a maternity hospital in Erzurum, Turkey between October 2018 and December 2019. Women were randomized into 3 groups: A=Control group (n=60), B=Spherical birth ball group (n=60), and C=Peanut ball group (n=60). Birth balls were initiated in the active phase in the first stage of labor when cervical dilatation was 4 cm. Data were collected using the Personal Information Form, the Visual Analogue Scale (VAS), the Verbal Rating Scale (VRS), Partograph, and the Scale for Measuring Maternal Satisfaction in Birth (SMMSB).

Results: In the active and transitional phases of labor, the VAS and VRS scores for labor pain perception of Group B were statistically significantly lower than the scores of Group A and C ($p<.05$). Compared to other groups, Group B had a faster rate of fetal head descent. Group B also had the highest maternal satisfaction rate (83.3%), and the difference between the groups was found to be significant ($p<.05$).

Conclusion: This study revealed that different birth balls reduced pain, accelerated the rate of fetal head descent, and increased maternal satisfaction at the active and transition phases of the first stage of labor.

Keywords: Labor pain, birth balls, satisfaction, non-pharmacological methods

1. INTRODUCTION

Women can experience some negative effects, particularly labor pain (slowdown of labor, anxiety, fear, increase in uterus contractions, etc.) due to the physiological and psychological factors experienced during labor (1). Expansion and strain of the cervix during labor cause uterus muscles to contract and push the fetus out, making the mother feel pain (2). Defined as acute pain during the labor process, labor pain is the most severe type of pain known (3).

Pharmacological or nonpharmacological methods can be utilized to relieve this pain during the labor process. When the potential adverse effect on the mother and the fetus is taken into consideration, the use of pharmacological methods may not be the first option. Therefore, trying effective nonpharmacological methods is often the primary option for the management of labor pain. Exercises done using birth balls may increase blood flow to the uterus and relax muscles and therefore decrease pain (2). Besides, focusing the pregnant woman's attention on the movements and positions during the exercise may also decrease the perception of pain (1,4). In addition, birth ball exercises can relax back muscles, increase comfort, and decrease pain (1). Birth ball exercises are reported to decrease pain in the pelvic region and back during labor (5-7), facilitate the progression of the fetus in the birth canal, shorten the latent phase, and decrease the need for epidural analgesia and cesarean section (5,6). Labor motivation can be increased by decreasing pregnant women's anxiety or bringing it under control (8,9). Birth balls can be utilized to increase maternal comfort and expand the pelvic outlet during labor (10,11).

Sitting and swinging on a ball helps the woman to feel comfortable and increases the endorphin release because the flexibility of the ball stimulates receptors responsible for endorphin release in the pelvis (10). Besides, the effect of gravity helps the progression of birth and expansion and relaxation of pelvic muscles and bones, which enhances fetal descent. The use of birth balls during labor also prevents the mother from staying in the supine position all the time during labor (2,12). Large, long peanut balls are an alternative to traditional round balls, which are used by placing them between legs in a side-lying position during labor (14-16). Vertical use of this position out of bed is known to enhance the expansion of the pelvis as well as fetal descent with the effect of gravity (12,13).

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The literature reports the use of peanut balls and spherical birth balls as nonpharmacological methods for providing relief (such as a decrease in labor pain and duration, increase in cervical dilatation, decrease in fear and stress, and distraction with ball exercises) to laboring women (14-16). Most studies have focused on spherical birth balls (6,8,14,17). Only a limited number of studies have investigated the use of peanut balls, indicating the need for more evidence-based, randomized controlled trials on this topic (14-16,18). In addition, there is limited evidence on the comparative effectiveness of birth balls. Therefore, this study aimed to provide a valuable contribution to the literature by investigating both birth balls.

This study aimed to determine the effectiveness of different birth balls used at the first stage of labor on fetal head descent, pain intensity, and maternal satisfaction. Birth balls could offer an alternative midwifery practice for the management of labor.

2. METHODS

2.1. Design

This randomized controlled single-blind experimental study was conducted in the only public maternity hospital that provided secondary care services in a city located in eastern Anatolia between October 2018 and December 2019. The delivery room in the hospital includes five beds separated with curtains between them.

2.2. Participants

Approximately 8583 deliveries take place in a year in the hospital where the study was conducted, and the number of natural deliveries was 450 in the month the data were collected. The target population of the study consists of primipara pregnant women who applied to the maternity hospital for labor between October 2018 and December 2019. Those who were admitted to the delivery room and met the study inclusion criteria were included in the research.

2.3. Sample

A G*power (3.1.9.6) analysis was conducted to calculate the number of participants to be taken into groups (19,20). The sample size in this study was similar to that of Taavoni et al. (2016) taking the pain scores in their study as reference, effect size (0.64), 5% margin of error (α=0.05) and 99% power (1-β=0.99) were calculated as 54 participants for each group (21). Considering possible data losses, the number of samples was increased by 10% and it was aimed to include 60 participants for each group.

2.3. Inclusion Criteria

Inclusion criteria for the study were as follows: being aged 18 and above, having term pregnancy (38-40 weeks), having an estimated fetal weight of less than 4000 g based on ultrasound and clinical examinations, having a normal pelvic diameter based on vaginal examinations, being primiparous, having a singleton pregnancy, carrying a live fetus, having 4 cm of cervical dilation, having no risks regarding the pregnancy and the fetus, and having a head presentation.

2.4. Exclusion Criteria

Reluctance to participate in the study and undergoing an emergency cesarean section were the exclusion criteria.

2.5. Randomization

The single-blind randomized play-the-winner (PW rule) was applied for randomization (22). According to this rule, the same type of paper on which A, B, C were written were placed in a box (inside of the box could not be seen). The box had 60 A, 60 B, and 60 C papers, a total of 180 papers inside. Each pregnant woman chose a random paper from the box and was assigned according to the group written on the paper. The paper randomly chosen by the pregnant woman was put back after the procedure was completed. This process was continued until the target number of samples for each group was reached. When the number of samples in a group was reached, the papers belonging to that group were removed from the box. Each group included 60 primipara pregnant women. The CONSORT 2010 (23) flow diagram was created with a sample of 180 primipara pregnant women (Fig.1). As a result of the Post hoc power analysis made with the data obtained from the study, the power of the study was found to be 81%, sufficient in the number of 180 samples.

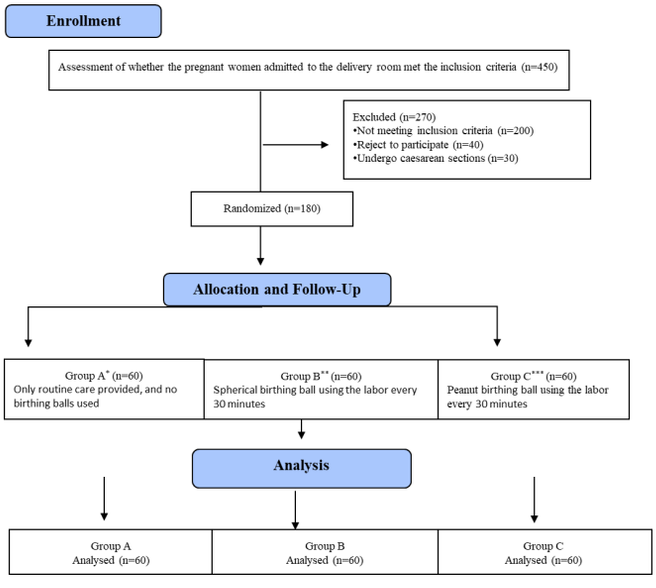


Figure 1. *Study diagram*
**Control Group*
*** Spherical Ball Group*
****Peanut Ball Group*

2.6. Data collection tools

Data were collected using the "Personal Information Form", the "Visual Analogue Scale (VAS)", the "Verbal Rating Scale (VRS)" (Since pain is a subjective phenomenon, a verbal rating scale (VRS) was added to allow pregnant women to express them verbally, considering the possibility that they could not evaluate it visually (VAS), "Partograph", and the "Scale for Measuring Maternal Satisfaction in Birth (SMMSB)".

The Personal Information Form: The form consisted of 7 questions about participating women's sociodemographic (age, education level, employment, and income level) and obstetric characteristics (number of pregnancies, miscarriages, abortions).

The Visual Analogue Scale (VAS): The scale was utilized to determine the intensity of labor pain (24). It was developed by Hayes and Patterson in 1921 (25,26). It has a 10cm long vertical line, with 0 at the bottom end (no pain) and 10 at the top end (very severe pain) (1). VAS is a very easy, efficient, cost-effective, and repeatable pain severity measurement method that determines the perceptions of women regarding pain experiences. Participating women were asked to mark the number corresponding to their pain intensity on the line. Cronbach's alpha value of the scale is .92 (27). Labor pain data were collected by VAS during labor.

The Verbal Rating Scale (VRS): The scale developed by Melzack and Targerson is intended to determine the severity of the participants' pain. Participants are asked to describe the severity of pain as mild (1), discomforting (2), distressing (3), horrible (4), and excruciating (5). Respondents are asked to select the option that best describes their pain (28).

Partograph*:* Partograph is used for routine monitoring of labor, helps in identifying slow progress in labor, and also initiates appropriate interventions to prevent prolonged and obstructed labor. It is a single sheet of paper which includes information about the fetal heart rate, uterine contraction, state of membranes and colour of fluid, cervical dilatation, and fetal head descent. Partograph was utilized to determine the fetal head descent in the first stage of labor (active and transition phases). Partograph is started when the cervical dilatation is 4 cm, and data are recorded on the form until delivery (29).

The Scale for Measuring Maternal Satisfaction in Birth (SMMSB): The scale is utilized to assess maternal satisfaction in normal delivery. The scale consists of 43 items responded on a 5-point Likert scale with options including "1-Disagree, 2-Partly agree, 3-Undecided, 4-Agree and 5-Strongly agree". Cronbach's alpha reliability coefficient of the scale was found 0.91. Higher total scores on the scale indicate higher maternal satisfaction with the hospital care provided during normal delivery (≥150.5 high satisfaction rate, <150.5 low satisfaction rate) (27). Cronbach's alpha reliability coefficients of the scale according to the groups were found as 0.85 for the control group, 0.89 for the spherical ball group, and 0.85 for the peanut ball group.

2.7. Interventions

In Groups B and C

While the women in Group B were given spherical birth ball, the women in Group C were given peanut ball; in each group, pregnant women's height was taken into consideration for the size of the balls to be given. Pregnant women used delivery balls (spherical or peanut balls) during the active period in the first stage of labor (cervical dilatation was started when it was 4 cm and continued until it reached 9 cm).

The researcher participated in a course for the training of trainers for Pilates during pregnancy and received a certificate. Positions and movements to be performed with birth balls were designed based on the information obtained during the literature review (1,2,6,8,12,16,30-32). Before the implementations started, the positions and movements to be performed by women were introduced and demonstrated by the researcher according to the groups the participants were included. Round birth ball exercises were composed of 4 different positions (sitting on a round birth ball leaning in front, kneeling on the floor and leaning on the birth ball, sitting on the ball, and side-lying position in bed) and movements to be performed with these positions (swing hips right-left, front-back, round the circle, jumping on the ball) (Group B). Peanut ball exercises included five different positions (half-sitting position, tucked side-lying position, hands and knee fire hydrant position, straddling position, forward-leaning position) and movements suitable to these positions (jumping, right-left, front-back on the ball) (Group C). It is clearly stated in the literature which positions and movements to be made with birth balls during labor. Changes were made between positions and movements according to the baby's position and the mother's comfort. These positions and movements done using birth balls realize pelvic rotation, increase pelvic mobility, and relax pelvic muscles and joints, which decreases labor pain and helps the baby to descend to the birth canal more easily (1,2,6,8,12,16,30-32). Positions and movements were performed every 30 minutes. The pregnant women were allowed to rest when they were tired or wanted to take a break. Partograph was started when the cervical dilatation was 4 cm. Fetal head descent level was evaluated and recorded on the partograph every hour until delivery. Evaluation of the cervical dilation and partograph record of the fetal head descent level was performed by the midwife. The VAS and VRS were assessed at the end of each phase of labor by the researcher.

The SMMSB was administered to the mothers within 1-4 hours in the postpartum period. All data were collected by the researcher. Midwives provided support to both pregnant women and the researcher in this process.

In Control Group (A)

Only routine midwifery care including cervical dilatation and effacement, contraction, fetal heart rate and vital signs monitoring was applied to the control group during labor. No other non-pharmacological method was applied to the control group. All data were collected by the researcher.

2.8. Data Analysis

The data were analyzed using the SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) software program. The statistician who analyzed the data was blinded to the groups (single-blind). The data were assessed using numbers, percentages, means, chi-square, One-Way ANOVA, and Repeated Measures. The Bonferroni test was utilized to determine the source of significant differences. Statistical significance was taken p-value of <.05.

2.9. Ethical Considerations

Before the study was conducted, ethics committee approval was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (B.30.2.ATA.0.01.00/237 numbered and 04.10.2018 dated) and the Erzurum Provincial Health Directorate of Nenehatun Maternity Hospital, where the study was conducted (44827528-604.02 numbered and 11.16.2018 dated). Written and verbal consent was received from all participating women. All the procedures were carried out in accordance with the principles of the Helsinki Declaration. In addition, this study was registered to the ClinicalTrials.gov with the ID number of NCT04827797.

Table 1. *Comparison of sociodemographic and obstetric characteristics according to groups.*

		Group A*		Group B**		Group C***		Test and p value
		n	%	n	%	n	%	
Socio demographic Characteristics	**Age** 18-24 25 and older	39 21	65.0 35.0	42 18	70.0 30.0	37 23	61.7 38.3	X^{2a}=0.93 p=0.62
	Education Level Elementary Secondary Higher	21 31 8	35.0 51.7 13.3	26 19 15	43.3 31.7 25.0	25 20 15	41.7 33.3 25.0	X^2=6.962 p=0.13
	Employment Status Employed Unemployed	5 55	8.3 91.7	7 53	88.3 11.7	6 54	10.0 90.0	X^2=0.37 p=0.83
	Income Status More income than ex. Income equal to ex. Lower income than expenses	16 41 3	26.7 68.3 5.0	10 42 8	16.7 70.0 13.3	21 31 8	35.0 51.7 13.3	X^2=8.45 p=0.076
		n %		n %		n %		Test and p value
Obstetric Characteristics	**Number of Pregnancies** 1 2	55 5	91.7 8.3	54 6	90.0 10.0	57 3	95.0 5.0	X^2=1.08 p=0.581
	Number of Miscarriages 0 1	55 5	91.7 8.3	54 6	90.0 10.0	59 1	98.3 1.7	X^2=3.75 p=0.15
	Number of Abortions 0 1	60 -	100.0 -	60 -	100.0 -	58 2	96.7 3.3	X^2=4.04 p=0.13

a: Chi square test
**: Control Group*
***: Spherical ball group*
****: Peanut ball group*

3. RESULTS

The groups were found to be homogenous as they had similar sociodemographic and obstetric characteristics. As shown in Table 1, there is no statistically significant difference between the groups (p>.05).

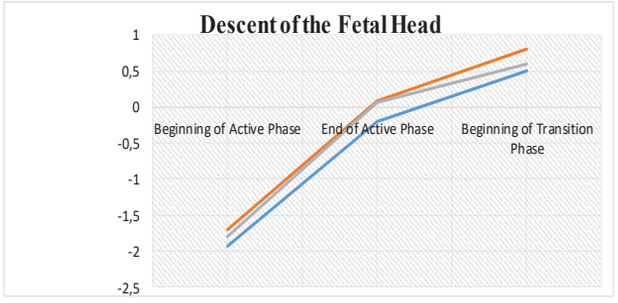
When the VAS and VRS mean scores were analyzed, a statistically significant difference was found in the VAS and VRS mean scores of the groups in the active and transition phases (p<.05). Further analysis showed that Group A was the source of the difference between VAS and VRS mean scores (Bonferroni test) (Table 2). Paired comparisons were also performed in the analyses. VAS and VRS analyses performed in the active and transition phases found that the control group's mean score was higher in comparison to other groups, and the difference was significant (e>f, e>g, f>g, h>ı, h>j, p<.05). However, the mean scores were found to be similar in the comparison of the peanut and round ball, but the difference was not significant (e≈f, ı≈j, p>.05) (Table 2).

Table 2. *Comparison of mean scores on the VAS and VRS according to groups.*

Pain perception intensity				
VAS Application Time	**Group A* (n=60)**	**Group B** (n=60)**	**Group C*** (n=60)**	**Test and p value**
	$\bar{X}$ ± SD	$\bar{X}$ ± SD	$\bar{X}$ ± SD	
Active phase	7.40±1.59[e]	5.64±1.60[f]	5.11±1.70[g]	F=32.11 **p=.000**
Transition phase	9.53±0.63[h]	8.31±1.30[ı]	8.74±1.06[j]	F=21.39 **p=.000**
Test* and p value	F=387.48, **p=.00**	F=249.31, **p=.00**	F=304.12, **p=.00**	
VRS Application Time	**Group A (n=60)**	**Group B (n=60)**	**Group C (n=60)**	**Test and p* value**
	$\bar{X}$ ± SD	$\bar{X}$ ± SD	$\bar{X}$ ± SD	
Active phase	3.51±0.77[e]	2.83±0.82[f]	2.85±0.65[g]	F[c]=15.98 **p=.001**
Transition phase	4.75±0.59[h]	3.78±0.80[ı]	4.03±0.55[j]	F[c]=37.46 **p=.001**
Test[b] and p[d] value	F=225.09, **p=.001**	F=175.63, **p=.001**	F=181.44, **p=.001**	

**: Control Group*
***: Spherical ball group*
****: Peanut ball group*
[b]Bonferroni test
[c] One-Way ANOVA
[d]p<0.05
[e](Active phase-Group A)
[f](Active phase-Group B)
[g](Active phase-Group C)
[h](Transition phase – Group A)
[ı](Transition phase-Group B)
[j](Transition phase-Group C)

The rate of fetal head descent was compared by the groups, and it was found to be faster in Group B in comparison to other groups (0.8). The rate of fetal head descent was statistically significant at the end of the active phase (p<.05). Further analysis showed that Group A was the source of the difference between the level of fetal head descent scores (Bonferroni test) (Fig. 2).



	Beginning of Active Phase	End of Active Phase	Beginning of Transition Phase
Control Group (A)	-1.93	-0.2	0.5
Spherical Ball Group (B)	-1.7	0.08	0.8
Peanut Ball Group (C)	-1.8	0.06	0.6
Significance	0.38	0.04	0.08

Figure. 2. *Comparison of descent of the fetal head for the pregnant women*

When the level of satisfaction was compared by the groups, the women in Group B were found to have the highest satisfaction levels (83.3%), and the women in Group A had the lowest satisfaction levels (58.3%); the difference between the groups was found to be significant (p<.05) (Table 3). The level of satisfaction was also compared and the results showed that while the participants in Group B had the highest satisfaction levels (83.3%), the participants in Group A had the lowest satisfaction levels (58.3%); the difference between the groups was found to be significant (p<.05) (Table 3).

Table 3. *Comparison of the pregnant women's total mean scores and cut-off point percentages for the SMMSB k*

	Group A* (n=60)	Group B** (n=60)	Group C*** (n=60)	Test and p value
	$\bar{X}$ ± SD	$\bar{X}$ ± SD	$\bar{X}$ ± SD	
Total scale point	145.66±18.30	171.20±19.44	157.90±15.09	F=31.18 **p=.001**

Scale Cut-Off Point	**Group A**		**Group B**		**Group C**		**Test and p value**
	n	**%**	**n**	**%**	**n**	**%**	
Satisfaction level Low (<150.5)	35	58.3	10	16.7	19	31.7	X^2=23.32 **p=.001**
High (≥150.5)	25	41.7	50	83.3	41	68.3	

**: Control Group*
***: Spherical ball group*
****: Peanut ball group*
[k]*SMMSB: Scale for Measuring Maternal Satisfaction in Birth*

4. DISCUSSION

Both birth balls utilized in this study were found to affect the pain perception levels, but the spherical birth balls were found to have the highest effect. Several studies that investigated the effect of the use of birth balls on pain have shown that the use of the balls reduced labor pain significantly (7,9,17,30,32-39). A randomized study indicating that nonpharmacological methods reduced the severity of labor pain reported that the use of a peanut ball in 4-5 cm cervical dilatation, massage application in 5-6 cm cervical dilatation, and a hot shower after 7 cm cervical dilatation reduced labor pain significantly (40).

A clinical study showed that free positioning with birth balls could directly reduce women's labor pain by enlarging the dimensions and mobility of pelvic and fetal positions (38). Another study reported that the use of birth balls in midwifery and nursing could relieve pain and enhance smooth delivery (41). There are several mechanisms to explain the labor pain process. The first one is the endogenous mechanism gate-control theory, which is composed of the transmission of pain-free messages to the painful area. This mechanism has a key role in the sensory distinguishing components of pain by blocking some of the nociceptive messages in the spine. The soft surface of birth balls can support and massage the perineum and the back, relieving some pressure. When women rock the pelvis on the ball, they stimulate normal somatosensory input to the projector neurons, which may relieve the pain perception (5). According to this theory, a birth ball supports the perineum and decreases pressure. Besides, some studies indicate that compared to the supine position, movement freedom and upright positions assisting gravity like sitting on a swinging chair during labor, sitting on a birth ball or toilet enhance the fetus descent, decrease contractions and labor pain, and increase the quality and efficiency of the labor (5,6,12,17,42,43). In this way, women's being in comfortable positions helps them to cope with uterus contractions during the labor process.

The present study found that the participants in spherical birth ball had a faster rate of fetal head descent and was statistically significant at the end of the active phase. This faster rate of fetal head descent could be attributed to the increase of dilatation thanks to the birth balls and the downward movement of the fetal head due to gravity. Studies show that due to the use of gravity, even with the patient in semi-flexed postures and the lateral decubitus position, there is a favor in the descent of the fetal pole into the pelvic cavity, helping to dilate and efface the cervix (44-46). Studies that investigated the effects of the use of birth balls indicate a statistically significant correlation between the groups regarding the level of fetal head descent (9,30,33,47). Mercier and Kwan (14) conducted one of the first studies that investigated the effects of peanut balls on the active phase of labor and specifically examined these effects in terms of descent and rotation of the fetus. The results of the study indicated that although the intended aim of the peanut ball was to facilitate better descent and rotation of the fetus, there

was no difference between the groups. Movements such as swinging and jumping with a birth ball by stimulating the pelvic floor increase pelvic outlet by 30%; relax connectives, sacroiliac joints, and muscles in the pelvic region; decrease pressure on the bladder, back, and coccyx; increase the blood flow to the uterus; optimize the fetal blood circulation; and enable the descent of the fetus easily and rapidly with the effect of gravity (2,35,45). Therefore, the birth balls used in this study are believed to accelerate the duration of fetal head descent.

In our study we found that the control group had lower levels of satisfaction and the spherical ball group had high levels of satisfaction. According to the results of the studies examined in the literature, the use of birth balls significantly increased maternal satisfaction levels (37,48). A study done at Bellarmine University (17) and examined how participants felt about the use of the peanut ball in the first and second stages of labor found that the feedback was positive in the participants who used a peanut ball for labor. Tussey et al. (13) reported that the peanut ball was well received by the patients who expressed satisfaction during labor and did not cause discomfort. By focusing the attention on moving with a ball, the use of birth balls decreases stress and tension during labor and increases satisfaction. Besides, movements done on the ball enable endorphin release because the flexibility and slope of the ball stimulate receptors responsible for endorphin release in the pelvis, which increases the mother's feelings of relaxation (2,47). It could be concluded that mothers' satisfaction levels increased as a result of the movements of the sitting position on the ball.

5. CONCLUSION

This study found that in comparison to usual care, the pain level was lower, fetal descent was faster, and mother satisfaction was higher in the groups that utilized different birth balls in the active and transition phases of labor. Round birth ball reduced pain more than the peanut ball. Pregnant women in the round birth ball group had higher satisfaction compared to other groups. Midwives can utilize birth balls in care practices in the labor process.

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Clinical and Experimental Health Sciences

Fear of Getting Pregnant Scale Development Study

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ABSTRACT

Objective: This study was carried out to develop a measurement tool that determines the factors that may be effective in women's fear of getting pregnant and to test its validity and reliability.

Methods: The sample of the study, which was carried out with a methodological design, consisted of 240 sexually active women who presented to the obstetrics clinic of a hospital in the Anatolian side of Istanbul between February 1 and June 1, 2021. The draft of the Fear of Getting Pregnant Scale was created by the researchers. The item pool for the draft scale consisted of 22 items. After the validity and reliability analyses, the final form of the scale contained 18 items. The scale consisted of three dimensions: "physical reasons" (5 items), "psychological reasons" (6 items), and "social reasons" (7 items). After evaluating the content validity of the scale, its test-retest reliability, internal consistency, and construct validity were examined. Explanatory factor analysis, confirmatory factor analysis, Bartlett's test of sphericity, Cronbach's alpha test, and Shapiro-Wilk test were used in the development of the scale.

Results: In the validity and reliability study of the Fear of Getting Pregnant Scale, the Content Validity Index (CVI) was found to be .83. The total Cronbach's alpha value of the scale was determined as .95, and the Cronbach's alpha values of the dimensions were .91 for "physical reasons", .89 for "psychological reasons", and .90 for "social reasons".

Conclusion: In line with these data, it was determined that the "Fear of Getting Pregnant Scale" is a valid and reliable scale.

Keywords: Pregnancy, fear, scale, development.

1. INTRODUCTION

Pregnancy is defined as a natural but complex period that causes physiological, psychological, and social changes and requires an adaptation process to these changes. In this process, the woman tries to adapt first to pregnancy and then to motherhood. The perception of pregnancy is individual and differs for each woman and her family (1). The perception of pregnancy by women differ based on their personal experiences, expectations about pregnancy, attitudes of towards pregnancy, desire for pregnancy, readiness for motherhood, dreams, education level, pre-existing diseases, risky situations experienced in current and previous pregnancies, current number of children, and social support systems, as well as the pregnancy-related attitudes, socioeconomic status, and positive reactions of their environments and families (2). The body and pregnancy perceptions of women who feel ready for pregnancy, think that pregnancy is a special period for them, and are happy to bring a baby into the world are positively affected (3).

Pregnancy is an event that has given women a significant cultural meaning in terms of social status throughout history, and at the same time, the feeling of being a mother. However, some reasons such as not having planned a pregnancy or becoming pregnant at an advanced age cause their perception of pregnancy to be negatively affected (4). Women may be undecided about having a child due to reasons such as fear of coping with the complications that arise in pregnancy with advanced age, the necessity of taking care of the baby to be born, the thought of being away from work, the thought of losing academic status, and the thought of not being able to meet the needs of the child to be born due to the existing economic conditions (5).

In the literature review, it was seen that there are many measurement instruments developed to measure pre-pregnancy childbirth stress, childbirth anxiety, and fear of childbirth (5-7). On the other hand, there is no measurement instrument developed to measure women's fears of getting pregnant before they get pregnant.

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1.1. Objective

This study aimed to develop a measurement instrument that will determine women's fear of getting pregnant and contribute this instrument to the literature.

The research questions were as follows:

- Is the "Fear of Getting Pregnant Scale" developed to assess women's fear of becoming pregnant a valid scale?
- Is the "Fear of Getting Pregnant Scale" developed to assess women's fear of becoming pregnant a reliable scale?

2. METHODS

2.1. Design and population

This study was planned with a methodological design. The study was carried out between 1 February and 1 June 2021 with women who presented to the gynecology outpatient clinics of a gynecology and pediatrics hospital serving on the Anatolian side of Istanbul for routine follow-ups.

These women presented to the gynecology outpatient clinic to get smear tests, and they did not have active health problems. The sample of the study consisted of women who had an active sex life, were not pregnant and not in menopause, did not have a history of tubal ligation, were not infertile, and did not have a communication barrier that would affect their response to the questions to be asked. The number of participants to be included was calculated based on the recommendation that the sample size of a scale development study should be 10 times the number of scale items. It was aimed to reach at least 220 women for the scale that initially consisted of 22 items, and the study was completed with 240 women who met the inclusion criteria. The sample size was 13.3 times the final number of scale items reached after the analyses.

2.2. Measurements

Personal Information Form: The form created by the researchers included 8 questions about the introductory characteristics of the participants (1-4).

Fear of Getting Pregnant Scale: A five-point Likert-type draft scale consisting of 22 items was created by the researchers based on their review of the relevant literature and previous scale development studies (1-4). An item pool was created based on guidelines and drafts that had not been validated.

2.3. Data collection

To determine the fears of women arising from problems that may arise in case of getting pregnant, an item pool of 22 statements was created based on studies and observations in the relevant literature (1-5). The Lawshe method was preferred for the content validity analysis of the scale (8). For the item pool, expert opinions were obtained from 14 midwife and nurse academicians, 12 of them in the field of gynecology nursing and 2 in the field of psychiatric nursing. While assessing the suitability of each item, the experts were asked to mark one of the options "essential", "useful but not essential", and "not necessary" and write down their opinions and recommendations for the scale items according to the criteria of relevance for the purpose, intelligibility for the respondent, and usage of clear expressions. The number of draft scale items was revised as 21 after the evaluations of the experts and the calculations of the content validity ratio (CVR) values, using which the content validity index (CVI) was found as the average of all CVR values. The resulting 21-item scale was administered to 42 people as a pilot implementation, based on the consideration to include at least two times participants as the number of items. These 42 participants were determined based on inclusion and exclusion criteria from the main sample. While applying the scale, the face-to-face interview technique was used, and the opinions of the participants about the clarity, intelligibility, and difficulty of the items were obtained. At this stage, no items that were difficult to understand and required detailed explanation were identified. After the data were collected, item analyses were applied to all items to determine whether there was a problem in terms of item-total correlation or internal consistency.

In the literature, it is stated that in scale development studies, the sample size should be at least 5 times the number of scale items, ideally 10 times (9,10). Apart from this method, which is determined based on the number of items, Preacher and MacCallum stated that the minimum sample size in scale development studies should be between 100 and 250 (11). A sample of 240 women was reached for the number of 21 items so that the minimum criteria reported in the aforementioned studies were met.

2.4. Data analysis

While the exploratory factor analysis and reliability analyses of the study were performed with the SPSS 26.0 package program, the confirmatory factor analysis was performed with the AMOS 22.0 software. In all statistical analyses conducted within the scope of the study, the level of statistical significance was accepted as 0.05. In the evaluation of expert opinions, the content validity index (CVI) was determined by calculating the content validity ratio (CVR) for each item and taking the average of the calculated CVR values. To determine the construct validity of the scale, exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) were performed. The Kaiser-Meyer-Olkin (KMO) test and Bartlett's test of sphericity were conducted to understand whether the scale items and the sample were suitable for factor analysis. In the EFA, the limit value was taken as 0.50 for the load values in the factor in which the items were included, and the items with a factor load value below 0.50 were excluded. CFA was performed after the EFA. To determine the reliability of the scale, the Cronbach's alpha reliability coefficient was

calculated. To determine the time-invariance of the scale, the Pearson product-moment correlation coefficient was calculated for the total scale and its dimensions using the test-retest method. For a test-retest analysis, a period of 2 to 6 weeks is recommended to eliminate the effect of responses staying in memory and avoid problems in reaching individuals (12). Additionally, since it is recommended in the literature that the number of individuals to be tested-retested should not be smaller than 30 (13), the scale was re-administered to 129 women who agreed to respond to the items for the second time 4 weeks after the first application. The split-half reliability testing method was used to identify potential problems in the items. This method divides the form into two equal parts, and after the simultaneous application of the two halves to the subjects, the correlation between the scores of the subjects from the halves (correlation coefficient of the half test), reliability estimation (if the conditions are met, again Pearson Product of Moments) with Correlation Coefficient) (14). If the scale has sub-dimensions, each dimension can be applied as a whole in itself. Spearman-Brown formula is applied for the reliability coefficient of the whole scale (15).

The Fear of Getting Pregnant Scale finally consisted of 18 items and three dimensions. There was no inversely scored item in the scale, and the scale had a 5-point Likert-type scoring system where each item was scored as 5 for the option of Strongly agree, 4 for Agree, 3 for Undecided, 2 for Disagree, and 1 for Strongly disagree. The minimum and maximum total scores of the scale were 18 and 90. Higher scores indicated higher levels of fear of getting pregnant.

2.5. Ethical considerations

To carry out the study, approval of the ethics committee of a foundation university was obtained (decision dated: 23.12.2020 and numbered: 130/9), followed by obtaining the permission of the institution where the study would be carried out. Written informed consent was obtained from the women who agreed to participate in the study.

2.6. Limitations

The scale was developed for women who do not have a condition that prevents getting pregnant (menopause and infertility) and have an active sex life/partner. The data were limited by the accuracy of the answers given by the participants to the scale items.

This scale may not be suitable for women who are not sexually active or those who do not have a partner. Since these women do not have a risk of becoming pregnant, the possibility of experiencing the fear of becoming pregnant is almost non-existent. For this reason, the scale was applied to individuals who were sexually active.

3. RESULTS

Results of the Validity Tests of the Scale

The mean age of the participants in the study was 31.52±7.42. It was determined that 74.6% of the participants were married, 78.3% had a university or higher education level, 70.0 % worked in an income-generating job, and 74.6% had income equal to their expenses. While 54.2% of the participants had children, 79.2% spent most of their lives in the city center, and 55.8% used an effective contraceptive method.

For a total of 22 items, the CVR values were calculated according to the evaluations made by 14 experts, and item 7 was excluded from the scale since it had a low CVR value (.42 < Critical CVR = .51). After removing this item, CVI (Content Validity Index) was calculated as the average of the CVR values as .83. As a result, a 21-item construct was obtained because the inequality CVI ≥ Critical CVR was statistically significant (Table 1).

Table 1. *Expert opinions and CVR values for each item*

	Necessary	Useful/ Insufficient	Unnecessary	CVR
Item 1	11	2	1	.57
Item 2	13	1	0	.85
Item 3	11	3	0	.57
Item 4	14	0	0	1.0
Item 5	14	0	0	1.0
Item 6	14	0	0	1.0
Item 7	**10**	**2**	**2**	**.42**
Item 8	12	2	0	.71
Item 9	13	0	1	.85
Item 10	14	0	0	1.0
Item 11	11	2	1	.57
Item 12	13	0	1	.85
Item 13	14	0	0	1.0
Item 14	13	1	0	.85
Item 15	14	0	0	1.0
Item 16	14	0	0	1.0
Item 17	13	0	1	.85
Item 18	14	0	0	1.0
Item 19	12	1	1	.71
Item 20	11	2	1	.57
Item 21	12	2	0	.71
Item 22	13	1	0	.85

CVR: Content Validity Ratio

Table 2. *KMO value of Fear of Getting Pregnant Scale and Bartlett's test of sphericity results*

Kaiser-Meyer-Olkin (KMO)		.92
Bartlett's Test of Sphericity	χ^2	3354.55
	df	153
	p-value	.000*

*χ^2: Chi-squared, df: degrees of freedom, * p< .001*

The KMO statistic of the scale was found to be .92. Thus, it was seen that the sample size was sufficient for applying factor analysis. As a result of the Bartlett's test of sphericity, it was concluded that there were significantly high correlations between the variables, and the data were suitable for applying factor analysis (p<.05) (Table 2).

The "Social reasons" dimension explained 25.85% of the total variance, the "Psychological reasons" dimension explained 22.28% of the total variance, and the "Physical reasons" dimension explained 20.64% of the total variance in scale scores. Together, the three factors of the scale explained 67.78% of the total variance in the measured variable (Table 3).

Table 3. *Variance explanation rates of factors*

Factor	Initial Eigenvalues			Total Factor Loads (Rotated)		
	Total	Explained Variance %	Cumulative %	Total	Explained Variance %	Cumulative %
Social reasons	9.81	54.53	54.53	4.65	25.85	25.85
Psychological reasons	1.55	8.61	63.14	4.01	22.28	48.13
Physical reasons	1.01	5.63	68.78	3.71	20.64	68.78

Table 4 shows which items were included in the dimensions of the Fear of Getting Pregnant Scale dimensions and the factor loading values of each item. As seen in Table 4, no item had a factor load below .40. Items 5, 8, and 9 in the Fear of Getting Pregnant scale were excluded from the analysis because they were overlapped in on different factors. For this reason, the number of items was reduced from 21 to 18 (Table 4).

Results of Reliability Tests of the Scale

As a result of the Cronbach's alpha internal consistency analysis that was carried out, the Cronbach's alpha coefficients of the dimensions of the Fear of Getting Pregnant Scale were found as .91 for "Physical reasons", .89 for "Psychological reasons", and .90 for "Social reasons", whereas the Cronbach's alpha coefficient of the total scale was .95. Hence, it was concluded that the scale was highly reliable (Table 4).

For the split-half reliability testing of the scale, the 18 items in the scale were divided into two halves, odd numbered items in one half and even numbered items in the other. The relationship between the results on the two sets of items was statistically highly significant (r=.93) (Table 5). Accordingly, the split-half reliability test of the scale revealed that it was highly reliable.

To measure the consistency of the scale over time, the scale was reapplied to 129 of all participants 4 weeks later. According to the results, there was a strong and statistically significant agreement between the test and retest results in both the scale total scores and the dimension scores. According to the intraclass correlation coefficients that were calculated, the items in the dimensions of the scale and the total scale were coherent with each other (p<.05). The rate of agreement between the test and retest was 99.5% for the physical reasons dimension, 99.8% for the psychological reasons dimension, 99.6% for the social reasons dimension, and 99.8% for the total Fear of Getting Pregnant Scale, which revealed very high agreement (Table 6).

Table 4. *Factor loads of scale items, scale dimensions, and Cronbach's Alpha*

	Factor 1	Factor 2	Factor 3
Item 18	.83		
Item 20	.81		
Item 17	.76		
Item 19	.73		
Item 21	.67		
Item 22	.57		
Item 10	.52		
Item 14		.74	
Item 15		.73	
Item 13		.73	
Item 12		.64	
Item 11		.60	
Item 16		.59	
Item 1			.87
Item 2			.87
Item 6			.72
Item 3			.65
Item 4			.62
	Item number	**Cronbach's Alpha**	
Fear of Getting Pregnant	18	.95	
Physical reasons	5	.91	
Psychological reasons	6	.89	
Social reasons	7	.90	

Table 5. *Results of Split-Half and Test-Retest Reliability Tests*

		Half 2		
Half 1	r*	.93**		
	p	.000		
	Intraclass Correlation Coefficient (ICC)	**95% Reliability Interval**		**p**
		Lower Limit	**Upper Limit**	
Fear of Getting Pregnant	.99	.99	.99	**.000****
Physical reasons	.99	.99	.99	**.000****
Psychological reasons	.99	.99	.99	**.000****
Social reasons	.99	.99	.99	**.000****

**r: Pearson's Correlation, **p< .001*

4. DISCUSSION

In this study, it was aimed to develop a measurement instrument to determine women's fears of getting pregnant and contribute this instrument to the relevant literature.

In studies on scale development, it is stated that an item pool should be created at least two to four times the number of items to be obtained or aimed to be obtained for a Likert type scale (16). In line with the determined purpose, a 22-item question pool was created and the pool of questions was sent to a group of 14 experts consisting of midwives and nurse academicians, and their opinions were received. Inter-expert agreement was evaluated with the Lawshe technique. According to the Lawshe technique, the number of experts should be at least 5 and at most 40. Experts were asked to rate the items as "necessary", "useful but insufficient" and "unnecessary". The CVR value is accepted as a minimum of .51 at the α=.05 significance level for 14 experts. The items below this value were removed, and the items that received a regulation proposal were rearranged and the item pool consisting of 22 questions was transformed into a candidate scale with 21 questions. The content validity index (CVI) value for the 21-item candidate scale was found to be .83. The minimum accepted value for the content validity index is .80 (17). According to this result, it can be said that the remaining 21 items express the area to be measured well.

Reliability is related to the consistency between the answers given by individuals to each test item, and how accurately a test or scale measures the feature it intends to measure. Validity is explained as the degree to which a scale measures what is intended to be measured, or the measurement instrument's suitability for the feature to be measured, and whether the measurement data really reflect the feature to be measured. First, KMO and Bartlett's tests were conducted to understand whether the scale was suitable for factor analysis. In this context, the KMO test measurement result should be .50 or above, and the result of the Bartlett's test of sphericity should be statistically significant (a result of .90 ≤ KMO ≥ .80 is interpreted as good) (18). In this study, the result of the KMO test was found to be .92, and the result of the Bartlett's test of sphericity was significant ($p<.05$) (Table 2). Hence, the sample and data of this study were adequate and suitable for factor analysis. Considering similar scales in the literature, the KMO statistic of the Fear of Childbirth and the Postpartum Period Scale was found to be .86 (7), the KMO statistic of the Women Childbirth Fear-Prior to Pregnancy Scale was determined as .90 (19), and the KMO statistic of the Childbirth Fear Scale for women of fertile age was found to be .88 (20). It is seen that the KMO value of the Fear of Getting Pregnant Scale was higher than those of similar scales.

Factor analysis is one of the widely used multivariate statistical techniques that transform many interrelated variables into a smaller number of independent factors. As a result of the EFA performed on the Fear of Getting Pregnant Scale, it was concluded that the scale had 18 items and three factors. The "Social reasons" dimension explained 25.85% of the total variance, the "Psychological reasons" dimension explained 22.28% of the total variance, and the "Physical reasons" dimension explained 20.64% of the total variance in scale scores. Together, the three dimensions of the scale explained 67.78% of the total variance in scale scores (Table 3). A criterion for factor analysis is that the rate of the total variance explained by the factors of a construct is desired to exceed 50%, because factors that do not collectively explain at least half of the total variance in the results of a construct may not be representative of the entire construct to be examined (21). These results showed that the scale had a high level of validity, while a three-factor construct was obtained as a result of the factor analysis. Like the Fear of Getting Pregnant Scale, the Childbirth Fear Scale for women of fertile age has three dimensions, namely fear of pregnancy, childbirth, and motherhood roles, not meeting physical social needs, and fear of pregnancy and childbirth problems, and its factors were determined to explain 51.93% of the total variance in scale scores (20). It is seen that the Fear of Childbirth and the Postpartum Period Scale has a structure with 10 factors, and physical, social, and psychological dimensions are also included among these factors (7). These results showed that the dimensions of the scale that was developed in this study are similar to those in existing scales.

In scale development studies, there is a common view that the factor load value of each item should be at least .30. Items with factor loads below this value are recommended to be eliminated. Other load value thresholds have been reported as .32, .40, and.45. Regardless of its sign, a load value of .60 or above is defined as high, and a load value between .30 and .59 is defined as medium (18). Among the items included in the dimensions of the Fear of Getting Pregnant Scale, there was no item with a factor load value below .40 (Table 4). If an item has a sufficiently high load value in multiple factors, the difference between these values is checked. This difference should be at least .10. If the difference is smaller than .10, the item is considered to be an overlapping item, and it is removed (21). Items 5, 8, and 9 in the Fear of Getting Pregnant Scale were excluded from the analysis because they were overlapping items. Therefore, the number of items in the scale was reduced from 21 to 18 (Table 4).

The Cronbach's alpha coefficient is frequently used to calculate the reliability of a Likert-type scale based on total scores. If this coefficient is high, this means that the items in the examined scale are consistent with each other and with the scale as a whole to measure the intended variable (13). As a result of the Cronbach's alpha internal consistency analysis that was performed to test the reliability of the Fear of Getting Pregnant Scale in this study, the Cronbach's alpha coefficients of the dimensions of the scale were found as .91 for "Physical reasons", .89 for "psychological reasons", and .90 for "social reasons", whereas the Cronbach's alpha coefficient of the total scale was .95 (Table 4). These values were higher than the acceptable value of .60, and they showed that the scale had a high level of reliability (8). Regarding similar scales in the literature, it was found that the Cronbach's alpha values of the dimensions of the Fear of

Childbirth and the Postpartum Period Scale ranged between .92 and .66, and the Cronbach's alpha coefficient of the total scale was .95 (7). The Cronbach's alpha value of the Women Childbirth Fear-Prior to Pregnancy Scale was found to be .89 (19). It was determined that the Cronbach's alpha values of the dimensions of the Childbirth Fear Scale for women of fertile age were between .75 and .88, and the Cronbach's alpha coefficient of the total scale was .86 (20). According to these results, the dimensions of the Fear of Getting Pregnant Scale and the entire scale were more reliable than similar scales in the literature.

Moreover, the split-half reliability test of the Fear of Getting Pregnant Scale revealed a positive correlation between the results of the oddly numbered items and the results of the evenly numbered items in the scale (r=.93). Accordingly, the scale was found to be highly reliable (Table 5).

The test-retest reliability analysis method is the application of a measurement instrument to the same group of participants twice under the same conditions and within a certain time interval. The correlation coefficient of the measurement values obtained from the two applications is the reliability coefficient of the scale. The most critical aspect of this type of approach is that the time interval between two measurements should be adjusted well. A time interval that is too short causes an artificially increased reliability criterion to emerge as it makes it easier to recall responses, and an interval that is too long makes it difficult to interpret the reliability criterion as it may make it impossible to provide the same conditions for two measurements in cases where some changes may occur in the measured property For a scale to be considered time-invariant, the correlation between the results of the two implementations (test and retest) must be at least .70 (8,14,16). In this study, 129 of the participants in the sample completed the Fear of Getting Pregnant Scale again 4 weeks later, and the correlation coefficient between the implementations was calculated as .99. This showed that the scale had high test-retest reliability (Table 5).

5. CONCLUSION

Among scales in the relevant literature, it is seen that existing scales measure the fear of childbirth and the attitude of women in the pre-pregnancy period or the early postpartum period. The Fear of Getting Pregnant scale was developed with the thought that there is a need for a measurement instrument that assesses women's physical, social, and psychological fears of becoming pregnant in the period before pregnancy. The reliability coefficients of the Fear of Getting Pregnant Scale showed that it is a scale that measures the fear of getting pregnant in women who are sexually active, have not had tubal ligation, are not infertile, are not pregnant, and are not in menopause. The Fear of Getting Pregnant Scale is the first scale developed on this subject. The widespread usage of the scale by adapting it to different languages and cultures will make a significant contribution to the literature. This scale, which was developed, validated and found reliable in this study, can be easily applied by health professionals, especially nurses and midwives.

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Acquisition of data for the study: NAD, KDB
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Clinical and Experimental Health Sciences

Cellular, Behavioral, and Locomotor Effects of Oral Nicotine in Male Rats with Bilateral Lesions in the Ventrolateral Striatum Induced with 6-OHDA

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ABSTRACT

Objective: Parkinson's disease is a progressive neurodegenerative disease having a spectrum of non-motor to motor symptoms. Unrelated to motor symptoms of sensory, autonomic, and neuropsychiatric symptoms often appear early in the course of the disease. It is a remarkable observation that patients in the premotor phase can easily quit smoking without help. This study was intended to investigate the interrelation between nicotine and the partial loss of dopaminergic innervation in the ventrolateral striatum induced by 6-OHDA.

Methods: We used an experimental premotor parkinsonism model. The oral nicotine preference of rats was investigated with the two-bottle free choice method. The behaviors related to locomotor activity and emotional state were evaluated with a locomotor activity test, elevated plus maze, and forced swimming test. Histopathological evaluation was performed in the striatum by staining techniques using hematoxylin+eosin (H&E) and immunohistochemistry markers (caspase-3, and MAP-2).

Results: Bilateral 6-OHDA lesions did not lead to a significant alteration in the total locomotor activity or nicotine preference. Nicotine increased horizontal but decreased vertical movements in addition to increasing anxiolytic but also depressive effects in the OHDA lesion group. The number of apoptotic cells was significantly lower in the lesion group receiving nicotine compared to those not receiving nicotine.

Conclusion: Our experimental study points to the role of oral nicotine in male rats with bilateral striatal 6-OHDA lesions in the ventrolateral striatum. Further studies are needed to understand the relationship between loss of dopaminergic innervation in the striatum and nicotine consumption.

Keywords: Nicotine, Parkinson's Disease, 6-OHDA, Ventrolateral Striatum, Experimental.

1. INTRODUCTION

Parkinson's disease (PD), a neurodegenerative disorder, is characterized by motor symptoms resulting from the progressive loss of nigrostriatal dopaminergic neurons. It has been reported that motor symptoms appear with the loss of approximately 30% of dopaminergic neurons in the substantia nigra or 50% of dopaminergic terminals in the striatum (1). In the preclinical phase of PD, nonspecific findings including autonomic dysregulation, sleep disorders, depression, and anxiety are observed (2). Moreover, it has been indicated that smoking cessation seen in the preclinical phase might be an early non-motor sign of PD (3,4). The relationship between nicotine and PD has been known for the last half-century, and the prevalence of PD in smokers is approximately 50% lower than in non-smokers (5). Chuanga (2019) stated that the ease of smoking cessation may occur as a result of the loss of nicotinic responses that occur at the prodromal stage long before the diagnosis of PD (6).

Nicotine has a general protective effect against nigrostriatal degeneration, modulates dopamine release via nAChRs on dopaminergic terminals (7), and decreases L-dopa-induced dyskinesias (8). On the other hand, the possible impact of nicotine on other motor and nonmotor symptoms is still debated. The current study aimed to examine the relationship between striatal dopamine loss and nicotine in rats with the bilateral striatal 6-OHDA lesion based on nicotine consumption, emotional behavior, locomotor activity, and histopathological findings.

2. MATERIAL AND METHODS

2.1. Animals and Experimental Procedure

This study was approved by University Animal Research Ethics Committee (HAYDEK 9/3-2009, Kocaeli University,

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Turkey) and adhered to the principles of the Declaration of Helsinki. The directives of the Animal Research Ethics Regulation in Turkey (2011/28141) and "Europe Communities Council (2010/63/EU)" were abided by throughout the study.

We tested 35 male Wistar, albino rats aged 6-12 months. Each subject was housed individually and had ad-lib access to a standardized ration. They were left in 12 hours light 12 hours dark periods, in 21-24 ^{0}C temperatures, and with a relative humidity of 50-60%.

We divided the animals into three groups; the first group (6 – OHDA lesion + nicotine solution; n=15) (6-OHDA+NW), the second group (Sham lesion + nicotine solution; n=10) (SHAM+NW), and the third group 6-OHDA lesion + tap water; n= 10) (6-OHDA+TW). Subject numbers were preserved in the tests including water consumption, locomotor activity, forced swimming test, and elevated plus maze.

NW and TW were given to the first two groups for three weeks before surgery and for four weeks after the surgery by "two bottles free choice method" (9). During this period, rats in the 6-OHDA+TW group consumed only TW. Water consumption of the subjects was measured after 16:00 once every two days and fresh water bottles were prepared after each measurement. Standardized bottles and droppers were provided to each subject and an equal amount of nicotine solution (NW) and tap water (TW) was filled in each bottle. After 7 weeks of the monitoring period, animals were subjected to locomotor activity, elevated plus maze (EPM), and forced swimming tests (FST). On the first day, locomotor activity and EPM tests were performed, respectively. FST was applied over the next 2 days. During the behavioral tests, nicotine consumption continued in the first two groups. Following behavioral tests, anesthetized animals were perfused transcardially with saline and 4% formaldehyde. Brains were removed and kept in a fixative for histological processing. The chronological order of the experimental procedures is illustrated by the timeline diagram (Figure 1).

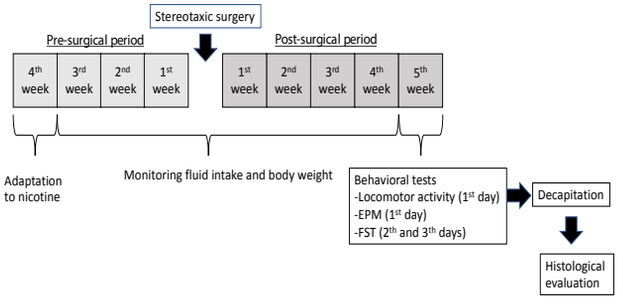

Figure 1. *Illustration of the experimental procedures*

2.2. Preparation of Oral Nicotinic Solution and Oral Nicotine Preference

The subjects in the 6-OHDA+NW and SHAM+NW groups were initially given nicotine (5 micrograms/ml) in water with non-caloric saccharin (4 mg/ml) to suppress the bitter taste of nicotine for a week. After this one-week-long adaptation period, the rats voluntarily consumed fluid from two bottles in their home cages, one with nicotine solution and the other with tap water.

For 3 weeks prior to the stereotaxic surgery, the saccharin dose was reduced to 4 mg/ml, 2 mg/ml, and 1 mg/ml in both NW and TW at one-week intervals, keeping nicotine at a constant dose of 5 microgram/ml. A fixed dose of 1 mg/ml saccharin was kept in both NW and TW from this point onward until the end of the experiment. Rats in the third group were given only tap water with reduced saccharin. Rats were weighted on a weekly basis. The starting and end weights of the bottles with NW and TW were measured separately. The sum of the two was calculated as the total water consumption. The weekly amount of fluid consumption was normalized to 300 g body weight. Nicotine preference was considered as the percentage of NW consumption to total water consumption.

2.3. Neurosurgery

For neurotoxic/sham lesions, stereotaxic surgery was performed in the rats under intraperitoneal ketamine (100 mg/kg) and xylazine (10 mg/kg) anesthesia. To create a bilateral striatal lesion, 2.5 µl of 6-OHDA at the concentration of 4.8 µg/µl dissolved in saline containing 0.1% ascorbic acid was injected into each ventrolateral region of the dorsal striatum (VLS) at the coordinates (AP +1.1, ML ± 3.2, DV 7.2). The internal cannula was introduced according to the rat brain atlas (10). Injections were performed using a 30-gauge cannula attached to the polyethylene tubing connected to a 10 µl Hamilton syringe and controlled by a micro infusion pump set to 0.5 µl/min infusion rate. The cannula was kept inside for two minutes for sufficient diffusion of 6-OHDA, following every infusion. The sham lesion was created using the same procedure as bilateral lesion groups, using an equal volume of the vehicle instead of 6-OHDA.

2.4. Behavioral Tests

Locomotor Activity

The locomotor activity apparatus (May 9803 Activity Monitor, Commat) had a white square plexiglass floor (40cmx40cm) and translucent plexiglass walls with 35cm height surrounding the exterior of this floor. Subjects were acclaimed in the test room for 30 minutes before being placed in the center of the open field. The test lasted for 10 mins. Horizontal, ambulatory, stereotypical, and vertical movements of each subject were recorded. The open field was cleaned with 70% ethanol after each subject and the new subject was placed in the system.

Elevated Plus Maze Test (EPM)

EPM is formed by placing two 10 cm wide platforms made of plexiglass in a "+" shape resulting in four arms perpendicular to each other and a center of 10cmx10cm area. The length of each arm is 50 cm and the maze is placed on 50cm high legs. The long sides of the two open arms are bordered by a 10 cm high white plexiglass and its tip is open. The two closed arms are surrounded on three sides by black plexiglass at a height of 40 cm. At the beginning of testing, each rat was placed on the central platform facing an open arm. The arm that the rat touched with four paws was considered an arm entry. Time spent on open arms (OET), time spent on enclosed arms (CET), open arm entry number (OEN), and enclosed arm entry number (CEN) were recorded. The percentages of the spent time and the number of entrances to the open/closed area were calculated.

Forced Swimming Test

The forced swimming test was performed in a 20 cm diameter, 60 cm height plexiglass cylinder filled with 25 ^{0}C water up to 50 cm height. Each rat was left in the water-filled cylinder twice. They were tested for 15 minutes on the first day, and 5 minutes on the second day. Each rat was kept in a cage covered with a paper towel and heated with a radiant heater for 10 minutes to dry and rest. All procedures were recorded with a video camera. Rats that moved enough to keep their head still above the water and that floated motionlessly were considered immobile (11). All tests were performed before 12:00 a.m. to avoid possible circadian effects on performance.

2.5. Histological Staining

The fixed brain of each rat was embedded in paraffin, and processedfor immunohistochemical and HE staining. Coronal sections of 5 µm were selected at levels between AP 2.28 mm and −0.12 mm area (10). For each animal, three tissue sections were examined. The sections were investigated by caspase-3 (1:1000, CPP32 Ab-4 rabbit polyclonal antibody, biomarkers) and microtubule-associated protein 2 (1:1000, MAP2, mouse monoclonal SMI-52, ab28032, Abcam). primary antibodies using the HRP and ABC staining kits (KP-50AR, Diagnostic Biosystems and sc-2017, Santa Cruz Biotechnology). Sections were visualized by ABC chromogen and mounted for analysis. The coverslips were visualized using the Leica DM2500 microscope with the Leica DFC295 HD camera system at 40x objective. The total number of cells and the caspase-3 labeled cells in the striatum were counted in four randomly chosen square areas (97 x 97 µm) randomly selected from each sample. For this analysis, seven animals were randomly selected by the researcher blinded to the group assignments. For semi-quantitative analysis of MAP-2 staining results, three sections were selected from the striatum of each rat. Staining intensity was graded as follows: 0: no staining, 1: weak; 2: moderate; and 3: intense (12).

2.6. Data Analysis and Statistics

All subjective scorings were performed by a researcher, who was blind to the group assignment of the rats. Results were expressed as mean ± standard error (SEM). Statistical significance levels of data were evaluated with the "GraphPad Prism-8" statistics program. One-way analysis of variance (ANOVA) was used for all behavioral tests and the cell counts. Nicotine preference, NW, TW, and total water consumption were analyzed with two-way ANOVA. Post hoc analysis was performed with Tukey test. Values were considered to be significant at $p<0.05$.

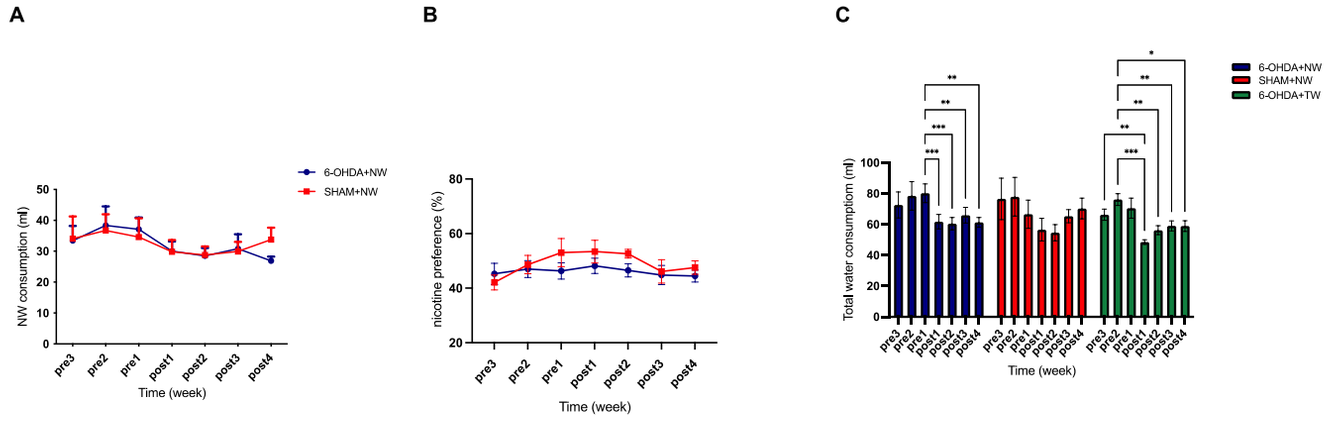

Figure 2. *Nicotine and total water consumption and nicotine preference of the groups*
*NW consumption (A) and preference (B) was not different between the groups and time points. Total water consumption (C) was lower post-lesion than in the pre-lesion period in both groups of 6-OHDA lesions. Total water consumption was lower after lesion in both groups with 6-OHDA lesions. * p <0.05, ** p <0.01, *** p <0.001*

Table 1. *Descriptive statistics. Mean ± SEM for nicotine and total water consumption, and nicotine preference.*

Weeks	pre3	pre2	pre1	post1	post2	post3	post4	Groups
Nicotine water consumption (ml)	33,4 ± 4,8	38,4 ± 6,2	37,1 ± 3,8	30,0 ± 3,1	28,5 ± 2,6	30,8 ± 4,6	26,9 ± 1,4	6-OHDA+NW
	34,1 ± 7,2	36,71 ± 5,2	34,6 ± 6,0	29,8 ± 3,8	28,8 ± 2,8	29,9 ± 3,1	33,8 ± 3,9	SHAM+NW
Nicotine preference (%)	45,3 ± 3,9	47 ± 3,1	46,3 ± 3	48,2 ± 2,8	46,5 ± 2,4	44,8 ± 3,5	44,5 ± 2,2	6-OHDA+NW
	42,1 ± 2,7	48,7 ± 3,4	53 ± 5,2	53,4 ± 4,2	52,6 ± 1,6	46,2 ± 4,3	47,6 ± 2,4	SHAM+NW
Total water consumption (ml)	72,6 ± 8,4	78,5 ± 9,2	80,2 ± 6,1	61,8 ± 4,7	60,5 ± 4,0	66,0 ± 5,1	61,3 ± 3,2	6-OHDA+NW
	76,6 ± 13,4	77,9 ± 12,5	66,6 ± 9,1	56,6 ± 7,3	54,6 ± 5,3	65,3 ± 4,3	70,3 ± 6,8	SHAM+NW
	66,3 ± 3,7	76,1 ± 3,8	70,6 ± 6,5	48,6 ± 1,5	56,2 ± 2,9	59,0 ± 3,3	59,0 ± 3,5	6-OHDA +TW

3. RESULTS

3.1. Temporal Distribution of Nicotine Water and Total Water Consumption

There was no significant effect of "group" and "time" on nicotine preferences (Figures 2A and 2B). All groups exhibited a decrease in consumption of NW and TW in the first week after the operation, which was attributed to the change in post-operative general condition. Two-way analysis of variance showed that water consumption changed significantly over time (F (1.883.60.27) = 12,13; p <0.0001). Total water consumption in the 6-OHDA lesioned rats was overall significantly lower during the post-lesion period than before the lesion irrespective of the experimental group (NW or TW). Tukey analysis showed that in the 6-OHDA+NW group, total water consumption was significantly lower at the 1st, 2nd, 3rd, and 4th weeks after the lesion (p = 0.0002, 0.0001, 0.0023, 0.0093, respectively). In the 6-OHDA+TW group, there was a significant difference between the before and after weeks of the lesion: pre-lesion 3rd week vs. post-lesion1st week (p=0.0066) and pre-lesion 2nd week vs. post-lesion1st, 2nd, 3rd, and 4th weeks (p = 0.0002, 0.0019, 0.0068, 0.0162, respectively) (Figure 2C). NW consumption, TW consumption and nicotine preference results were given in Table 1.

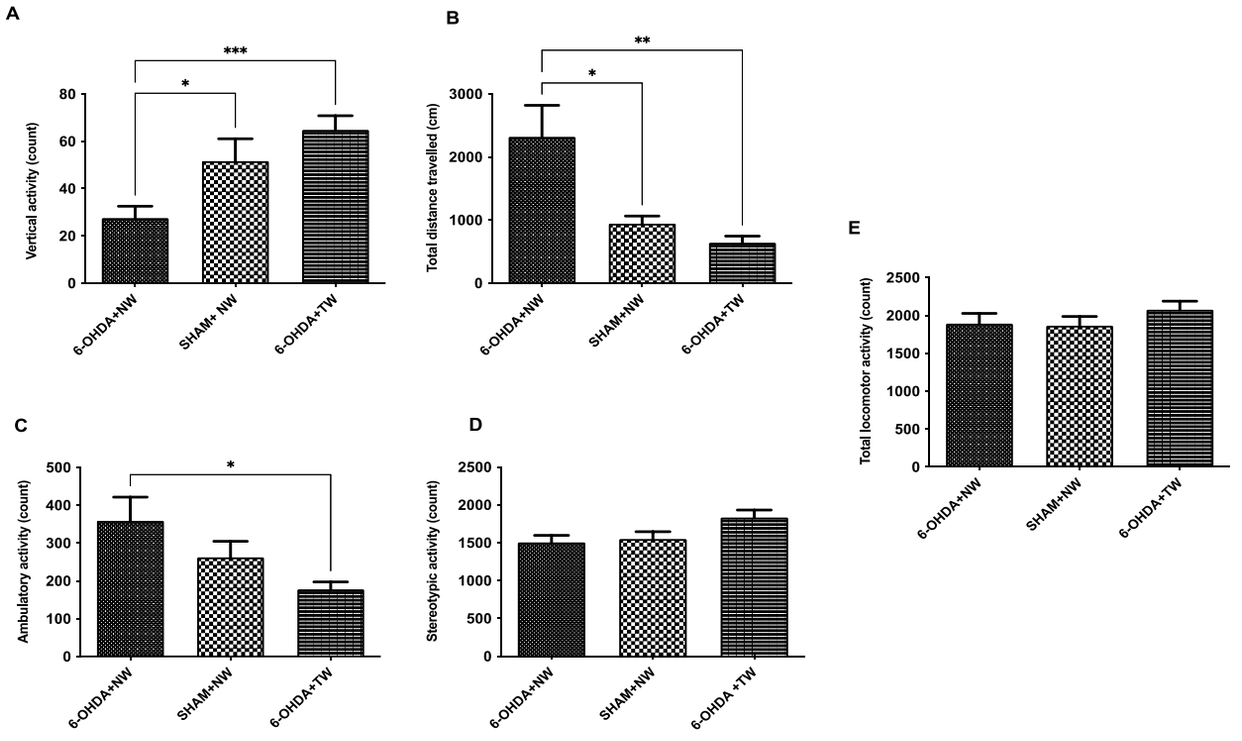

Figure 3. *Subtypes of locomotor activity of the groups*

Vertical movement (A) was lower and total distance traveled (B) was higher in the 6-OHDA+NW group compared to the other groups. Ambulatory action (C) was higher at 6-OHDA + NW compared to 6-OHDA+TW. Stereotypic (D) and total locomotor activity (E) was not different between the groups.

** p <0.05, ** p <0.01, *** p <0.005.*

3.2. Locomotor Activity

A significant overall difference was detected between the three groups in terms of vertical activity ($F(2,32) = 8.66$, $p=0.0010$); and distance traveled ($F(2,32) = 6.04$, $p=0.0060$) (Figure 3A and 3B). There was a trend for a difference between the groups in terms of ambulatory movement ($F(2,32) = 3.171$; $p=0.055$) (Figure 3C). Vertical movements were significantly lower in the 6-OHDA+NW compared to the 6-OHDA+TW ($p=0.0009$) and SHAM+NW ($p=0.0372$) groups (Figure 3A). The total distance traveled was significantly higher in the 6-OHDA+NW group compared to the Sham+NW ($p=0.0376$) and 6-OHDA+TW ($p=0.0094$) groups (Figure 3B). Contrary to the vertical movements, the number of ambulatory movements was significantly higher in the 6-OHDA+NW compared 6-OHDA+TW group ($p=0.0463$) (Figure 3C). These results showed that nicotine had an opposite effect on horizontal compared to vertical movements. There was no significant difference between the groups in terms of stereotypical ($F(2,32) = 3.18$, $p=0.055$), and total locomotor activity ($F(2,32) = 0.6920$, $p=0.5079$) (Figure 3D and 3E). Locomotor activity results (mean ± SEM) were given in Table 2.

Table 2. *Descriptive statistics. Mean ± SEM for the results of locomotor activity and emotional tests*

BEHAVIORAL TESTS	6-OHDA+NW	SHAM+NW	6-OHDA +TW
Ambulatory activity (count)	*359.1 ± 62.5*	*262.4 ± 42.5*	*177.7 ± 19.5*
Vertical activity (count)	*27.53 ± 5.0*	*51.6 ± 9.5*	*64,9 ± 5.9*
Total distance travelled (cm)	*2322 ± 497.8*	*942.5 ± 122.1*	*641.1 ± 106.0*
Stereotypic activity (count)	*1506 ± 93.6*	*1552 ± 94.4*	*1834 ± 98.7*
Total locomotor activity (count)	*1892 ± 136.7*	*1866 ± 121.5*	*2077 ± 112.5*
Time spent of open arm (%)	*33.62 ± 7.9*	*17.7 ± 4.5*	*10.33 ± 3.9*
Duration of immobility (sec)	*77.71 ± 10.1*	*37.8 ± 10.7*	*14.3 ± 3.2*

3.3. Anxiety and Depression-like Behavior

Figure 3 shows the performance of rats in different groups in EPM and FST. The percentage of time spent in open and closed arms also differed significantly between the three groups ($F(2,32) = 3.47$, $p=0.0431$ – Figure 4A). Post-hoc analysis revealed that the 6-OHDA+NW group spent more time in open arms ($p=0.0437$) and less time in closed arms ($p=0.0422$) than rats in the 6-OHDA+TW group. A significant difference in immobility time in FST was detected between the three groups ($F(2,31) = 12.87$, $p<0.0001$). The immobility time in the 6-OHDA+NW group was higher than in the SHAM+NW ($p=0.0109$) and the 6-OHDA+TW ($p<0.0001$) groups. The 6-OHDA+TW and the SHAM+NW groups had similar immobility times ($P=0.2233$) (Figure 4B). Anxiety and depression scores of the groups (mean ± SEM) were given in Table 2.

3.4. Histological and Immunohistochemical Results

The total number of cells was counted in the striatum with the H&E staining. The total number of cells differed between the groups, ($F(2,177) = 34.27$, $p<0.0001$); it was significantly lower in the 6-OHDA+TW group compared to the 6-OHDA+NW ($p=0.0049$) and SHAM+NW ($p<0.0001$) groups, and also in the 6-OHDA+NW group compared to the SHAM+NW group ($p<0.0001$) (Figure 5A). In the H&E staining, the morphologic changes induced in cells of the 6-OHDA+NW group were similar to those observed in cells of the SHAM+NW group. In the 6-OHDA+TW group, pathological changes including apoptotic bodies and cell shrinkage were observed in the cells in the striatum regardless of neurons and glia (Figure 5B).

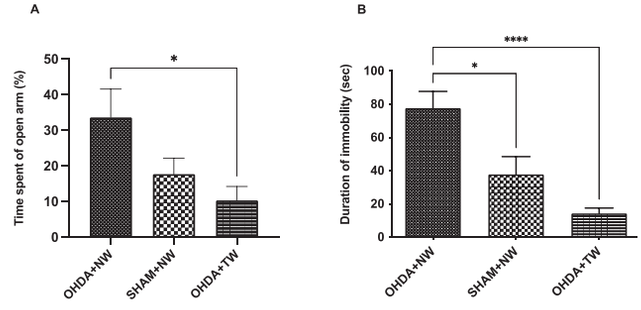

Figure 4. *Anxiety and depression-like behavior scores of groups in the plus maze and forced swimming tests*
*In the 6-OHDA+NW group, the percentage of time spent was higher in open arms (A) compared to the 6-OHDA+TW group. In the forced swimming test, immobility time was higher in the 6-OHDA+NW group than in other groups (B). * p <0.05, **** p <0.0001.*

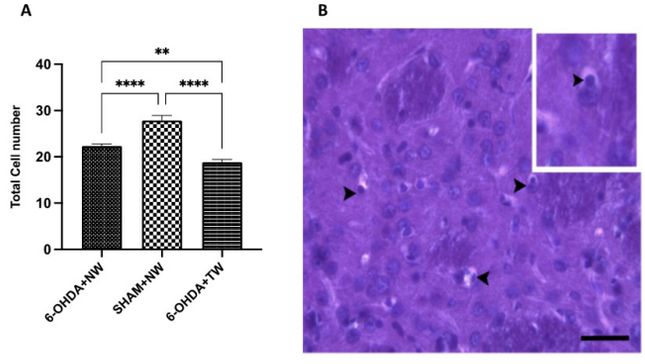

Figure 5. *Total cell numbers and H&E staining in the striatum*
*The figures are showing the number of total cells (A) and morphology of cells (B) in the striatum (6-OHDA+TW group). The majority of the cells exhibited the dark cell degenerative changes (arrowheads). These cells showed the pyknotic nucleus and shrunken cytoplasm. Inset shows dark cell. H&E staining; scale bar 20 µm.** p<0.01 ****p<0.0001*

The number of caspase-3 labeled cells in the striatum was also counted and compared to determine the degree of apoptosis. The total amount of caspase-positive apoptotic cells differed between the groups, ($F(2,177)= 149.0$, $p<0.0001$); it was significantly lower in the 6-OHDA+NW group compared to the 6-OHDA+TW ($p<0.0001$), and in the

SHAM+NW group compared to the 6-OHDA+TW ($p<0.0001$) and 6-OHDA+NW ($p<0.0001$) groups (Figure 6A).

Figure 6 (B, C, D) shows caspase-3 labeled cells in the striatum for all groups; 6-OHDA+NW (B), SHAM+NW (C), and 6-OHDA+TW (D).

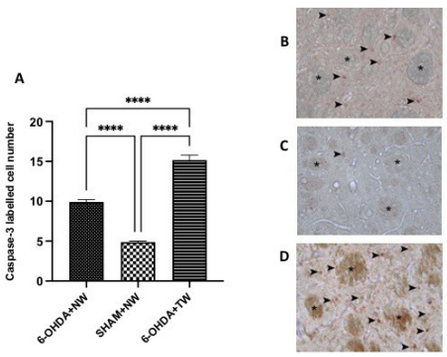

Figure 6. *Apoptotic cell numbers and caspase-3 immunopositive cells in the striatum*
*The figures are showing (A) the number of caspase-3 positive apoptotic cells, and representative images showing the caspase-3 labeled cells in the striatum in the 6-OHDA+NW (B), SHAM+NW (C), and 6-OHDA+TW (D) groups in the striatum. ** p<0.01 ****p<0.0001 Arrowheads, the caspase-3 labeled cells, and asterisks, the fiber bundles*

The 6-OHDA+NW exhibited moderate MAP-2 staining (Figure 7A). The SHAM+NW group showed strong staining while the 6-OHDA+TW group showed weak staining with the MAP-2 (a dendrite-specific marker for the neurons) (Figure 7B-C). The staining of the MAP-2 positive neurites in the striatal neurons was decreased in the 6-OHDA+TW lesion group (Figure 7C).

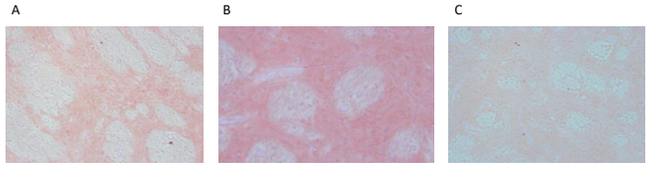

Figure 7. *MAP-2 immunostaining*
Representative images showing the MAP-2 staining in the striatum in the 6-OHDA+NW (A), SHAM+NW (B), and 6-OHDA+TW (C) groups.

4. DISCUSSION

Although nicotine is known to regulate dopamine release in the brain and upregulate specific nAChRs, there is not sufficient data regarding the reduced/stopped nicotine intake in preclinical PD and the potential role of dopaminergic loss in the basal ganglia circuit in this tendency. The current work is the first study that tested the effect of the reduced dopaminergic innervation of VLS on nicotine preference. This study also focuses on the behavioral and emotional effects of nicotine under conditions of denervation of the dopaminergic system in the VLS (13). Our results showed that bilateral striatal lesions did not lead to a significant alteration in total locomotor activity and nicotine consumption/preference. In the 6-OHDA+TW lesion group, nicotine increased the horizontal movement frequency (ambulatory activity and total distance) but decreased the vertical movement frequency. Nicotine also decreased anxiety-like behaviors but increased depression-like behaviors.

More specifically, VLS lesions reduced total water consumption but did not alter nicotine consumption/preference. Previous studies have shown that the VLS contributes to orofacial and forelimb movements (including licking, the facial expression of emotion, and reaching), goal-directed behavior, and reward circuitry (14) with a nonlinear relationship between lesion size and functional impairment (15). The fact that a significant decrease in total water consumption did not generalize to nicotine-water preference in the lesion group may indicate that the lesion does not affect VLS-related motor functions and reward mechanisms in the same way. Longer-term experimental studies using different routes of administration would help clarify the relationship between dopamine depletion in the subfields of the striatum and nicotine preference. Additionally, the wide age range of the animals per group, which is one of the limitations of the study, may have caused higher variability in the data. Future studies should also consider testing older rats to increase the validity of the model.

Total locomotor activity or its subcomponents are affected by motor, sensory and emotional factors (16). In the current study, the total locomotor activity did not differ between the groups, while there were differences in the subcomponent that can be classified as vertical and horizontal (17). In terms of total activity, the absence of a significant difference between the lesion and sham groups can be interpreted as the bilateral lesion of the VLS does not cause evident motor dysfunction. The significant effect of nicotine on horizontal and vertical movements only in the lesion group provides indirect evidence that nicotinic receptors of the cholinergic system are an active contributor to the mentioned motor activities in addition to the mesostriatal dopaminergic system. Previous studies show that nicotine may affect locomotor activity differently depending on the variables such as dose, duration, and internal and external preconditions (18,19). Therefore, the loss of dopaminergic innervation of the striatum might be one of the factors determining the effects of nicotine on locomotor activity patterns, so the VLS seems to be a candidate for one of the functional areas underlying the effects of nicotine. An increase in ambulatory movement induced by nicotine is a common finding, albeit a decrease in vertical movement has been reported at only high doses (20). At this point, it is important to distinguish the nature of the vertical movement. The vertical movement has been considered exploratory (21) as well as stereotypical (22) differing depending on whether the actions are goal-directed or not (23). Thus, these results can be explained in terms of the suppression of complex stereotypical movements as much as the reduction of exploratory behavior by nicotine in rats with VLS lesions, which requires further studies.

The relationship between smoking and neuropsychiatric disorders including depression and anxiety disorder has been known for a long time. Inconsistency of the results of both clinical and preclinical studies has directed the studies to investigate the factors regarding the emotional effects of nicotine. It has been reported that basal conditions arising from age, gender, and genetic structure are among the determining factors. In our study, the use of nicotine in animals with lesions significantly increased the immobility period in FST and duration in the open arm in EPM compared to nicotine use alone or the presence of lesion alone. These results suggest that the VLS might be an area that mediates the emotional effects of nicotine, as also suggested by locomotor activity results. Although depression is often associated with anxiety disorders in clinical practice, these emotional states/behaviors may be independent of each other (24). It should be kept in mind that the period of inactivity, which is typically used as a proxy for hopelessness in FST, may also be affected by factors independent of the presumed hopelessness state. For example, it has been suggested that immobility in FST may also interact with low-level anxiety (24).

The neuroprotective effect of nicotine has been demonstrated in different models generated with the administration of neurotoxic agents, including 6-OHDA (20,25,26,27). One of the limitations of this study is that tyrosine hydroxylase expression per se was not examined and thus striatal dopaminergic innervation could not be evaluated. However, the findings obtained with H&E, caspase-3, and MAP-2 staining have shown that nicotine prevents 6-OHDA-induced striatal cell loss.

In H&E staining, the lowest and highest cell counts were observed in the 6-OHDA+TW and sham+NW groups, respectively. In parallel, caspase-3 immunoreactivity, which reflects apoptotic cell death, is significantly reduced with nicotine use in groups with 6-OHDA lesions. Striatal dopamine denervation results in a significant loss of dendritic spines on medium spiny projection neurons in both animal models of parkinsonism and Parkinson's disease (28,29). Since Parkinson's disease affected the neuronal cytoskeleton, we also studied morphological changes through immunostaining of the dendrite-specific marker MAP-2 in the rat striatum. MAP-2 is found extensively in the somatodendritic areas of neurons, therefore, it is considered a neuron-specific protein (30). The results of the semi-quantitative assessment of MAP-2 immunoreactivity in the striatum (i.e., lower in the 6-OHDA+TW group compared to other groups) suggest that cell loss also includes neurons. Considering that the neuron types in the striatum are GABAergic projection neurons (medium-sized spiny neurons) accounting for 95% of striatal neurons and GABAergic/cholinergic interneurons accounting for 2-3% (31), the probability of loss in these neuron types is quite high. Studies using more specific markers will further elucidate the specific effects at the neuronal level.

5. CONCLUSION

In conclusion, the results of this preliminary study show that the bilateral VLS lesion with 6-OHDA does not affect nicotine preference, nicotine prevents non-dopaminergic neuron loss due to 6-OHDA, and its effects on locomotor activity pattern and emotional behaviors occur only under the lesion condition. The scope of the interpretation of the study results would have increased substantially if there was a full control group (e.g. sham and no nicotine). These results suggested that the behavioral effects of nicotine in animals with lesions, including emotional and motor aspects, may be related to the widespread distribution of nicotinic receptors as well as the predominance of reciprocal connections between anatomically and functionally separated regions in the striatum. The characterization of striatal cell loss caused by 6-OHDA and its prevention by nicotine as well as an explanation of the interaction, if any, between locomotor activity patterns and emotional responses require further studies which include the control group.

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Author Contribution: Research idea: P.I.
Design of the study: A.K.
Acquisition of data for the study: E.S.D.
Analysis of data for the study: A.K.
Interpretation of data for the study: E.S.D.
Drafting the manuscript: E.S.D.
Revising it critically for important intellectual content: A.K.
Final approval of the version to be published: A.K.

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Clinical and Experimental Health Sciences

The Effect of Post-Operative Sexual Counseling Carried out with PLISSIT Model on Sexual Function and Sexual Satisfaction in Gynecologic Cancers

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ABSTRACT

Objective: This study aims to determine the effect of sexual counseling on the sexual functions and sexual satisfaction of women who underwent surgical treatment due to gynecologic cancer.

Methods: The study sample consisted of 60 women (experimental group *n* = 30, control group *n* = 30) with ovarian, endometrial, and cervical cancer. The women in the experimental group received sexual counseling according to PLISSIT, while the women in the control group were not given sexual counseling but were monitored through routine follow-up. The Female Sexual Function Index (FSFI) and the Sexual Satisfaction Scale for Women (SSS-W) were used for the first and last evaluations of the groups.

Results: The mean age of the women in the experimental group was 51.87 ± 8.89, while it was 50.47 ± 9.43 in the control group. There was no significant difference between the two groups in terms of sexual function and sexual satisfaction levels in the first evaluation (p>.05), whereas there was a significant difference between the two groups in the final evaluation after the sexual counseling provided to the experimental group (p < .001). When the first and final evaluations of the women were considered, it was observed that 33.3% of the women in the experimental group had adequate sexual functioning in the final evaluation.

Conclusion: The sexual counseling carried out using the PLISSIT model for women who were treated for gynecologic cancer positively affected their sexual function and sexual satisfaction levels.

Keywords: Cancer, gynecologic surgery, sexuality, sex counseling, sexual dysfunction

1. INTRODUCTION

Gynecological cancers are malignant tumors that occur in female genital organs and have an adverse effect on women's quality of life (1). Gynecologic cancer symptoms—such as vaginal bleeding, weakness, stomach pain, and postcoital bleeding—can negatively affect the pre-treatment sexual health of women. Furthermore, physical symptoms such as post-treatment vaginal shortness, reduced vaginal elasticity, reduced vaginal lubrication, vaginal stenosis, clitoridectomy, pelvic nerve injury, fistulas, weakness, diarrhea, sleep withdrawal, infertility, and postcoital bleeding negatively affect the sexual health of affected women (2). Female reproductive organs are symbols of productivity, sexuality, and motherhood for women; accordingly, the loss of these organs can be harmful to the body image of the affected woman and can cause a decrease in self-esteem (3). Surgical treatment, radiotherapy, or chemotherapy applied in gynecological cancers negatively impact the affected woman's reproductive capacity and body image (1-3). The aim of surgical treatment, which is a possible cancer treatment option, involves the excision of the cancerous tissue, adjacent tissues, and nearby lymph nodes. In those cases in which cancer does not spread, surgery may be the only method of treatment (4).

Sexuality can be negatively affected by gynecological cancer diagnosis and treatment. Surgical procedures—such as the removal of the uterus and ovaries or the removal of the vulva tissue—can negatively influence the body image, self-esteem, and sexual lives of women (5). The removal of the upper part of the vagina after radical hysterectomy can cause sensory loss and dyspareunia due to nerve damage (6). Uterine contractions associated with orgasm often do not occur after total hysterectomy. The Ssar tissue caused by surgery can prevent the vagina from expanding (7). The incision and nerve tissue damage caused by surgery may induce sexual reluctance and pain. The excision of the vagina or cervix leads to sexual arousal disorders (1, 6, 7). In addition to gynecological cancer treatment, the woman who has undergone surgery tries to regain her female identity, values, priorities, and her responsibilities as a sexual partner

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(2). Therefore, support systems and consultancy services play important roles in eliminating anxiety and concerns as part of such a process (4, 8).

The PLISSIT model, one of the methods of incorporating the subject of sexuality into practice, is a widely used and easy-to-apply model. The PLISSIT model is a conceptual scheme for approaching the individual's current problems. With a four-level approach to the problem of each individual to evaluate sexuality, the P-LI-SS-IT model utilizes open-ended questions (4). The model entails cooperation with the individual, supports the patient's beliefs and value system, and adheres to the rules of understanding and respecting their decisions. Each phase of this model provides guidance for intervention and assessment for nurses with different levels of education. The phases of the model consist of P-Permission, LI-Limited Information, SS-Spesific Suggestion, and IT-Intensive Therapy (4, 6, 9).

Providing sexual counseling for women who underwent surgical treatment due to gynecologic cancer and their partners during this process is an important factor that improves these women's quality of life (9). In the first counseling session, which is the most important step of sexual counseling, using models on sexual functions can be useful for the evaluation of sexual life (10). When evaluating a patient, a sexual consultant should approach the individual with a holistic perspective. Issues such as honesty, privacy, and confidentiality also need to be prioritized. Information shared by clients should be listened to sensitively, and interviews with clients should be conducted using a professional manner (3, 10). Individual and relational issues must also be prioritized when handling the client's sexual problems. The goal of the treatment is to increase the quality of the client's sexual life. In addition, systemic homework concerning sexual intimacy and fantasies may be assigned during the interviews (8). In the literature, the number of studies evaluating the results of sexual counseling applied to gynecological cancer patients is limited. With this study, the importance of sexual counseling applied to gynecological cancer patients is emphasized, and health professionals are aimed to be guided about sexual counseling.

1.1. Aim of the study

This study aims to determine the effect of sexual counseling carried out with the PLISSIT model on the sexual functions and sexual satisfaction of women who underwent surgical treatment due to gynecologic cancer.

Research Hypotheses

H_1: Sexual counseling contributes to the improvement of sexual functions.

H_2: Sexual counseling contributes to an increase in sexual satisfaction.

2. METHODS

2.1. Design

This is a randomized controlled single blind experimental study.

2.2. Participants/Sampling

The study was conducted in the Gynecological Oncology Outpatient Clinic of a university hospital in Istanbul from March 2015 to March 2017. The study sample included women who had undergone surgery after having been diagnosed with ovarian, endometrial, or cervical cancers and who met the inclusion criteria. The study sample size for this research was calculated using the G*Power 3.1 power analysis program. In the G*Power analysis, calculations were made based on Nho's study results related to Female Sexual Function Index mean values (9). In the statistical analysis carried out using the results of the current study, the alpha (α) reliability coefficient and power were determined as .05 and 80%, respectively. As a result of the analysis, it was ascertained that 28 women for the experimental group and 25 women for the control group should be sampled. Considering possible losses during the study process, it was decided that the two study groups should include 30 participants.

The study sample comprised 18–65-year old women who underwent a surgery due to a diagnosis of endometrial, ovarian, and cervical cancer, who had completed at least one month after the post-operative coitus permission had been given, who were in the post-operative fourth month, and who had had experienced a regular sex life before their surgery. Women who were receiving chemotherapy, radiotherapy, brachytherapy, or chemoradiotherapy, who were diagnosed with gynecolocial cancers other than endometrial, ovarian, and cervical cancer ones, who had stage IV cancer, who had undergone additional operations such as colostomy or urostomy, who were sexually inactive, and whose partners had sexual dysfunction were excluded from the current study.

2.3. Randomization

The women were assigned to the experimental and control groups using numbers obtained from the website 'random.org.' The numbers were written individually—in accordance with the table of random numbers—and put in sealed envelopes to ensure blinding. The envelopes were administered by a secretary who was not related to the study to the women who were accepted to the outpatient clinic by appointment and who met the inclusion criteria after which they were directed to the researcher. The researcher, who knew which group the numbers were in, opened the envelope and carried out the research steps based on the group to which the women were assigned. Appointments were given to the participants so that they did not interact with each other. The interviews were held in a private room.

2.4. Data Collection Tools

2.4.1. Patient identification form

This form was prepared by the researchers and comprised 13 questions on participants' sociodemographic characteristics, general health history, and gynecologic cancer treatment.

2.4.2. Sexual history questionnaire

This questionnaire was prepared by the researchers to determine women's sexual health, sexual life characteristics, and sexual problems.

2.4.3. Female Sexual Function Index (FSFI)

This index was developed by Rosen et al. in 2000 to evaluate female sexual functions and consists of 19 items (11). The Turkish validity and reliability analysis of the scale was conducted by Oksuz and Malhan (2005), and the Cronbach's alpha coefficient of the scale was determined as .95, while the test–re-test reliability was determined as .75–.95 (12). The FSFI evaluates sexual functions or problems experienced within last four weeks. The index includes six subscales: desire, arousal, lubrication, orgasm, satisfaction, and pain. Each of the subscales are scored from one to six points, and the total score possible ranges from 2 to 36. Higher scores indicate more sufficient sexual functions (11). An FSFI total score of 26.55 or less signifies sexual dysfunction in women (13). In this study, the internal consistency coefficients of the measurements obtained from the FSFI ranged from .91 to .99 in the subscales, and the coefficient was α = .99 for the total scale.

2.4.4. Sexual Satisfaction Scale for Women (SSS-W)

The SSS-W was developed by Meston and Trampnell in 2005 and includes 30 questions (14). The Turkish validity and reliability analysis of the scale was conducted by Abali and Aslan (15). This five-point Likert-type scale is composed of five subscales: satisfaction, communication, compatibility, anxiety regarding the relationship, and personal anxiety. Each subscale is scored from 6 to 30 points. The total score of the scale is calculated using the satisfaction + communication + compatibility + (relational anxiety + personal anxiety/2) formula. The total score possible on this scale ranges from 30 to 150 points, and it has no breakpoint. Higher scores indicate higher sexual satisfaction levels (14). In this study, the internal consistency coefficients of the measurements obtained from the SSS-W ranged from .66 to .95 for the subscales and α = .91 for the total scale.

2.5. Ethical Considerations

The ethical approval for this study was obtained from Istanbul Medipol University Clinical Research Ethics Committee (number: 108400987-77, date: 12/02/2015). Before this study was carried out, written permission was obtained from the faculty management. Additionally, written consent was obtained from all individuals to document their agreement to participate in this study. While the study was being conducted, considerable attention was paid to ensure that the women's hospital procedures were not hindered. The study was performed in accordance with the "Ethical principles for medical research involving human subjects" of the Helsinki Declaration.

2.6. Data Collection

In the health institution where the study was conducted, sexual intercourse prohibition is imposed on patients who have undergone gynecological oncological surgical treatment until their first control visit. To collect the data, a total of 75 women, who had undergone surgical treatment and were diagnosed with endometrial, ovarian, and cervical cancer, were included in the study. Two of these women were referred to the Department of Psycho-Oncology, Istanbul University, Faculty of Medicine because they had previous sexual trauma. Eight women were excluded from the sample due to the initiation of chemotherapy, brachytherapy, radiotherapy, or chemoradiotherapy after surgery. Five women did not want to continue participating in the study. In accordance with the sample selection criteria, a total of 60 women were included in the sample for the experiment (30 women) and control (30 women) groups. The data collection tools were applied during the first evaluation and the last evaluation, which was carried out after 16 weeks. All interviews and sexual counseling sessions performed with the experimental and control groups were completed in a pre-determined special room through face-to-face interview sessions, each of which lasted 45 minutes. Interviews with the participants in the experimental group were carried out outside of the routine examination hours to prevent the groups from interacting with one another. The data from the experimental and control groups were collected by the same researcher. In addition, the sexual counseling interviews with the experimental group were made by the researcher who received Sexual Therapy Training.

2.7. Interventions and Procedures:

The interviews were conducted five times with the experimental group and twice (first and last interview) with the control group. In the first interview, "the Patient identification form, Sexual history questionnaire, FSFI, and SSS-W" were applied to all women. After the first interview, three more interviews were held for sexual counseling sessions with the experimental group. In the second interview, the 'Permission' phase of the PLISSIT model was completed by allowing the woman to express her feelings openly. An interval of one week was given between the second and third interviews with the experimental group. During the third interview, the women were informed about the effects of cancer and treatment on sexual functions and sexual health. At this stage, the women were given homework and special suggestions. The fourth interview was applied two weeks after the third interview for the implementation of

homework and special suggestions in the third interview, and the last step of the sexual counseling session was completed in this interview.

In studies conducted in the literature to determine the effectiveness of sexual counseling, patients were re-evaluated 4 months after counseling (9, 16). In line with the literature, 4 months after the first interview, the FSFI and SSS-W were re-administered to the experimental and control groups (last interview), with each session lasting an average of 45 minutes.

2.8. Analysis

Cronbach's alpha internal consistency coefficients were calculated to evaluate the reliability of the scales used in this study. Descriptive statistics (numbers, percentages, means, and standard deviations) were used to analyze the patients' sociodemographic characteristics and sexual history data. Independent *t*-test was used to compare the experimental and control group results that were obtained from the measurement tools. In this study, the statistical significance level was determined to be $p < .05$ at a 95% confidence interval.

3. RESULTS

In the study, the mean age of the experimental group (EG) and control group (CG) (EG: 51.87 ± 8.89; CG: 50.47 ± 9.43 years), the mean age of their partners (EG: 55.63 ± 9.66; CG: 55.40 ± 10.26 years), the number of their deliveries (EG: 2.46 ± 1.14; CG: 2.97 ± 1.23), and the mean duration of their marriages (EG: 30.73 ± 11.61; CG: 29.77 ± 11.60 years) were similar. According to the results, no statistically significant difference was found between the groups in terms of the type of cancer (EG: 66.7% with endometrial cancer, 20% with ovarian cancer, and 13.3% with cervical cancer; CG: 50% with endometrial cancer, 23.3% with ovarian cancer, and 26.7% with cervical cancer) ($p > 0.05$). Additionally, bilateral salpingo-oophorectomy (EG: 90%; CG: 80%) was applied to the majority of women ($p > 0.05$).

The current study found that the women in the experimental group and control group experienced lack of sexual desire (EG: 83.3%; CG: 90%), delayed arousal (EG: 43.3%; CG: 23.3%), and vaginal dryness (EG: 86.7%; CG: 90%). Almost half (43.3%) of the women in both groups stated that they felt pain during sexual intercourse. In addition, the majority of the women (75%) in both groups stated that they could not achieve orgasm (EG:73.3%; CG: 76.7%), and that they experienced sexual dissatisfaction (EG:83.3%; CG: 90%) (Table 1).

Table 1. *Characteristics of the sexual lives of the groups after surgical treatment*

	Groups	All Groups	Experimental Group (n=30)		Control Group (n=30)			
		%	n	%	n	%	X^2	p
Desire	Normal	13.3	5	16.7	3	10	0.577	.353[f]
	Lack of desire	86.7	25	83.3	27	90		
Arousal	Delayed	58.3	13	43.3	7	23.3	7.560	.023*
	Normal	25	3	10	12	40		
Vaginal Dryness	Reduced lubrication	75	26	86.7	27	90		
	Normal	11.7	4	13.3	3	10		
Problem in Sexuality	Painful sexual intercourse	43.3	14	46.7	14	46.7	1.646	.439
	Contraction in the vagina	41.7	11	36.7	14	46.7		
	Normal	58.3	5	16.7	2	6.7		
Orgasm	Yes	25	8	26.7	7	23.3	0.317	.573
	No	75	22	73.3	23	76.7		
Satisfaction	Normal	13.3	5	16.7	3	10	0.577	.448
	Insufficient	86.7	25	83.3	27	90		

**p< .05; f=Fisher's Exact Test; X2= Pearson Chi-Square Test*

Table 2. *Female sexual function index scores in the first and last evaluation*

FSFI	First evaluation				Last evaluation			
	Experimental Group (n=30)	Control Group (n=30)			Experimental Group (n=30)	Control Group (n=30)		
	Mean±SD	Mean±SD	t	p	Mean±SD	Mean±SD	t	p
Desire	1.22±0.11	1.36±0.63	1.201	.239	3.52±0.96	2.18±1.00	5.301	.000*
Arousal	0.0±0.0	0.24±0.93	1.418	.167	3.70±1.08	2.50±1.18	4.102	.000*
Lubrication	0.0±0.0	0.26±1.07	1.337	.192	3.42±1.07	1.92±1.26	4.959	.000*
Orgasm	0.0±0.0	0.31±1.18	1.426	.164	3.89±1.03	2.41±1.33	4.829	.000*
Satisfaction	0.80±0.0	1.07±1.02	1.439	.161	4.63±1.24	2.71±1.14	6.228	.000*
Pain	0.0±0.0	0.23±0.94	1.324	.196	3.52±1.10	1.77±1.39	5.385	.000*
Total Score	2.02±0.11	3.46±5.63	1.400	.172	22.68±6.14	13.49±6.97	5.417	.000*

**p< .001; t=Independent Samples t test*

In the first evaluation, no statistically significant difference was found between the FSFI scores of the groups ($p > .05$). However, there was an increase in both groups' FSFI scores in the last evaluation, and the increase in the experimental group was highly statistically significant compared to the control group ($p < .001$). Considering the FSFI cut-off point as 26.55, 33.3% of the women in the experimental group had sufficient sexual function based on the last evaluations (Table 2).

In the first evaluation, the sexual satisfaction levels of women in both groups were found to be similar ($p > .05$), with the exception of the Anxiety–Personal subscale ($p < .05$). However, in the last evaluation, the sexual satisfaction level of the women in the experimental group was higher than those in the control group, and this difference was statistically highly significant ($p < .001$) (Table 3).

Table 3. *Sexual satisfaction scale for women scores in the first and last evaluation*

SSS-W	First evaluation				Last evaluation			
	Experimental Group (n=30)	Control Group (n=30)			Experimental Group (n=30)	Control Group (n=30)		
	Mean±SD	Mean±SD	t	p	Mean±SD	Mean±SD	t	p
Satisfaction	12.50±2.27	13.37±2.76	1.328	.189	21.60±2.63	14.53±3.84	8.313	.000**
Communication	18.57±4.57	19.43±4.42	0.746	.458	23.37±1.43	20.23±3.77	4.262	.000**
Compatibility	20.03±3.34	19.03±3.99	1.053	.296	23.20±1.06	20.17±3.24	4.874	.000**
Anxiety-Relational	13.87±2.46	14.17±2.38	0.480	.633	22.00±2.17	15.23±3.86	8.379	.000**
Anxiety-Personal	15.00±2.26	16.40±2.31	2.371	.021*	24.50±0.57	16.97±3.36	12.114	.000**
Total Score	79.97±9.97	82.40±12.0	0.854	.397	114.67±6.21	87.13±15.52	9.022	.000**

**p< .05; **p< .001 t=Independent Samples t test*

Table 4. *Comparison of groups' sexual functions in the first and last evaluation*

Sexual functions	Frequence	Groups				X^2	p
		Experimental (n=30)		Control (n=30)			
		n	%	n	%		
Frequency of Sexual Intercourse in the First Evaluation	Several times in a week	8	26.7	6	20.0	0.373	.542
	Every other week or less	22	73.3	24	80.0		
Frequency of Sexual Intercourse in the Last Evaluation	Several times in a week	30	100.0	14	46.7	21.818	.000***[f]
	Every other week or less	0	0.0	16	53.3		
Duration of Sexual Intercourse in the First Evaluation	10 minutes or less	14	46.7	12	40.0	0.271	.602
	11 minutes and above	16	53.3	18	60.0		
Duration of Sexual Intercourse in the Last Evaluation	10 minutes or less	0	0.0	21	70.0	32.308	.000***
	11 minutes and above	30	100.0	9	30.0		
Intimacy with Partner in the First Evaluation	Good level	21	70.0	27	90.0	3.750	.052[f]
	Insufficient	9	30.0	3	10.0		
Intimacy with Partner in the Last Evaluation	Good level	30	100.0	12	40.0	25.714	.000***[f]
	Insufficient	0	0.0	18	60.0		

****p< .001; f=Fisher's Exact Test*

Table 4 shows the comparison of the sexual function characteristics of both groups in the first and last evaluation. In the first evaluation, no statistically significant difference was found between the groups in terms of the frequency of sexual intercourse ($p > .05$); however, in the last evaluation, a highly statistically significant difference was determined between the two groups ($p < .001$).

4. DISCUSSION

This study shows the effect of sexual counseling, carried out using the PLISSIT model, on female sexual function and satisfaction in women treated for gynecologic cancers. The results of this study are important as they contribute to the literature on sexual counseling in gynecologic cancers by providing evidence through a prospective randomized controlled research design.

Kennedy et al. (2015) carried out a study with 499 women with cancer to evaluate their sexual function and activity, and they found that 40.9% had endometrial cancer, 15.1% had ovarian cancer, and 15.1% had cervical cancer (17). Another study carried out with 181 gynecologic cancer patients to determine the psychometric validity of the FSFI revealed that 45.5% of the participants had endometrial cancer, 22.7% had ovarian cancer, and 27.3% had cervical cancer (16). In the current study, which was conducted in line with the literature, it was determined that 58.3% of participants had endometrial cancer, 21.7% had ovarian cancer, and 20% had cervical cancer.

The literature has shown that potential contributors to the worsening of the psychosexual health among gynecological cancer patients include physical changes in the vaginal regions, cancer adjuvant therapy, the development of a cancer-related pain, and depressive symptoms (1, 3, 4, 9, 10). The presence of any of these risk factors may be indicative of underlying sexual dysfunction. In this study, it was found that 86.7% experienced lack of sexual desire, 58.3% of the participants experienced delayed arousal, 75% experienced reduced lubrication, 43.3% experienced painful sexual intercourse, 75% experienced difficulty having an orgasm, and 86.7% experienced insufficient sexual pleasure (Table 1). When the literature is examined, some studies have arrived at similar results (3, 9, 17, 18).

Health professionals can provide effective and comprehensive care to gynecological cancer patients and their families if they fully understand the physical, emotional, social, and spiritual experiences of these women. The current study applied sexual counseling sessions based on the PLISSIT model after gynecologic surgery, and the study participants were evaluated with the FSFI and SSS-W both before and after the counseling sessions. Similar to the findings from the literature, this study showed that there was an increase in the sexual function levels (Table 2) of women who received post-operative sexual counseling. In agreement with previous studies in the literature, it was observed in this study that the level of sexual satisfaction of the women who were given sexual counseling in the experimental group increased significantly after the counseling according to the findings of the first and the final evaluation (Table 3). When the literature is examined, the results of randomized controlled studies show that there was no statistically significant difference between the two groups in terms of baseline sexual function, but after sexual counseling, it was significantly higher in the experimental group than the control group after intervention (7, 19, 20). The results of the current study are in compliance with the literature.

Sexual counseling is an activity that is important in maintaining both the overall and the sexual quality of life for many couples. Sexual counseling is recognized as an important aspect of care by the World Health Organization, and efforts are in progress to better understand the elements, implementation, and outcomes for sexual counseling as delivered by health care providers. In this study, sexual counseling was planned based on the PLISSIT model in order to reduce the sexual problems of the participants and to improve their sexual problem-solving skills. Sexual counseling was given to each patient in the experimental group through individual face-to-face interviews, and the sexual satisfaction levels of the women participating in the study were also examined. As a result of the study, it was determined that the frequency and duration of sexual intercourse increased in the experimental group compared to the control group. In addition, it was observed that the experimental group had better intimacy with their partners (Table 4). The results of the study are in parallel with the literature (21-23).

Strengths of the Study

- The study used a randomized controlled single blind experimental research design.
- The study utilized a method that is used in consulting work.
- Educational material was developed and used in the study.
- The study was conducted in a tertiary hospital, which accepted the highest number of gynecological patients of all hospitals in Turkey.

Study Limitations

- Partners of the participants were excluded from the study.
- Longer term results of sexual counseling were not evaluated.
- Cases directed to the expert therapist were not followed-up.

5. CONCLUSION

Sexual counseling carried out using the PLISSIT model for women being treated for gynecologic cancer significantly positively affected their sexual function and sexual satisfaction levels. Compared to the women in the control group, a positive change was seen among the participants in the experimental group who had undergone sexual counseling in regard to all stages of sexual functions, sexual satisfaction, frequency and duration of sexual intercourse, and intimacy with their partners. According to FSFI total cut-off points, although sexual dysfunction continued in both groups, it was eliminated in one-third of the women in the experimental group. It is recommended that future studies in the field include partners in counseling sessions, use different models, and carry out long-term follow-ups.

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Clinical and Experimental Health Sciences

Dental age estimation with special emphasis on age limits of 12/15 and 18 years: Detailed analysis according to governing law

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ABSTRACT

Objective: The aim of this study is to investigate the potential of Demirjian method in estimation of age groups with limits of 12, 15, and 18 years, according to ages of legal responsibilities.

Methods: The panoramic radiographs of the study population aged between 6 to 22 were assessed for third molar (3M) mineralization with Demirjian method with four subgroups. Group 1 consisted of individuals aged between 6 to and 12 years of age, Group 2 were aged between 12 to 15 (Group 2, ≥12, <15), Group 3 were aged between 15-18 years (Group 3, ≥15, <18) and Group 4 were aged over-18s (Group 4, ≥18). Chronological age, developmental stages of 3Ms, differences between bilateral 3M stages and their relations between age groups were evaluated.

Results: Regarding all 3M mineralization evaluations, stages 0 and A for Group 1; stages C and D for Group 2; stages E and F for Group 3; stage H for Group 4 was found to be high in percent ($p<.05$). Regarding the bilateral evaluations, the most variations were in readings of stages B, C, E and G as two stages below and one stage above the concordance.

Conclusion: Use of Demirjian method facilitated discrimination of specific age groups with 12, 15, and 18 age thresholds in a sample of a young Turkish subpopulation from the Northwest Anatolia. Regarding the staging assessment in Demirjian method, independent evaluation of each side must be considered for bilateral 3Ms.

Keywords: Age estimation, demirjian method, legal responsibility, governing law

1.INTRODUCTION

Amongst the dental age estimation methods, Demirjian's method is of particular interest and is widely applied in forensic studies (1). Using panoramic radiographs, this reliable and convenient system evaluates crown and root formation with a total maturity score which is converted into an estimated dental age (2). Considering the development of teeth, third molar mineralization has a unique advantage over the others, since its development begins at 5 and completes between 18 to 25 years of age (3). Due to this relatively prolonged process, the third molar (3M) is often assessed for estimation of chronological age especially for the late adolescence period (4). On the other hand, studies report geographic variations may result in overestimation of dental age in relation to the chronological age (5). Therefore, it was suggested to develop different estimation calculations based on local population characteristics (6).

With a special emphasis on the estimation of juvenile and adult status, most age estimation studies focus on the 18-year-old threshold. This discrimination is also important for the juvenile sub-groups as the definition child changes to adult. In Turkey, children under the age of 12 are exempt from criminal liability whereas children among 12 to 15 years and 15 to 18 years have different procedures according to the Turkish Penal Code (7). These age groups are defined due to the individual's capability to comprehend the legal meaning, to appreciate the result of the act and to control behaviors in respective of act. In addition to criminal liability, those age limits are also important in various legal regulations such as the identification age of the victim, or social events like marriage (8). Therefore, particularly for juveniles devoid of identification documents, age estimation is required for proceedings of legal procedures. Most of the age limits are set in European countries between 10 and 16 years. For example, in Switzerland, England and Wales children can be held liable for criminal offences from the age of 10. The minimum age in Austria, Spain, Hungary, Bulgaria, and Germany is 14 years of age. Like Turkey, Belgium, Netherlands and Ireland have a minimum age of 12 (9). Considering the majority of dental age estimation studies are interested in discrimination of adult and juvenile, there is a need of a detailed analysis of those above-mentioned age limit groups from a forensic, medicolegal point of view.

To the best of our knowledge, there are only a few dental age estimation studies evaluating those legally relevant specific

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age groups. Therefore, the aim of this study is to investigate the potential of Demirjian method in discrimination of groups with age limits of 12, 15, and 18 years in a sample of a young Turkish subpopulation from the Northwest Anatolia.

2. METHODS

2.1. Case Selection

The study protocol was carried out according to the principles described in the Declaration of Helsinki, including all amendments and revisions. The Ethics Committee of Bolu Abant Izzet Baysal University approved this retrospective study (approvel date 04.01.2022 and number 2021/312). The panoramic radiographs (OPGs) of patients were referred to the of Bolu Abant Izzet Baysal University, Faculty of Dentistry between 2015 and 2021 were retrospectively evaluated for bilateral mandibular 3M mineralization. OPGs were acquired using Sorodex Cranex Novus (Tuusula, Finland) which was operated at 60-70 kVp and 8-10 mA. Patients with any systemic disease that would affect mineralization process, patients with evidence of any pathological entities and dental anomalies associated with the 3M and patients with trauma and surgical operation history associated were excluded from the study. OPG images with poor quality were also excluded.

2.2. Study Group Formation

Regarding the mineralization process of the mandibular 3M, the minimum and maximum age limit of the study group was set as 6 to 22 years (10). Regarding the specific age limits, four subgroups were formed. Group 1 (n=139) consisted of individuals aged between 6 to and 12 years of age (Group 1, <12) whereas individuals of Group 2 (n=120) were aged between 12 to 15 (Group 2, ≥12, <15), individuals of Group 3 (n=126) were aged between 15-18 years (Group 3, ≥15, <18) and individuals of Group 4 (n=124) were aged over-18s (Group 4, ≥18). Chronological ages were calculated by subtracting the date of birth of each individual from the date of panoramic radiograph. Demographic data of each case were recorded.

2.3. Scoring and Data Analysis

All the OPGs were anonymized as numbers, adjusted, and exported as noncompressed tagged image file format (*tiff) for observer evaluation. The images did not contain any demographic data. A blind observer rated all images in a random order during evaluation (F.A.K.) All the left mandibular 3Ms and all the right mandibular 3Ms were evaluated in separate sessions. 102 images were reevaluated after a one-month interval in order to assess the intraobserver reliability.

All mandibular molars were rated with Demirjian's method (Figure 1) with an additional stage referring to the radiolucent bud formation of the 3M pointing the beginning of calcification.

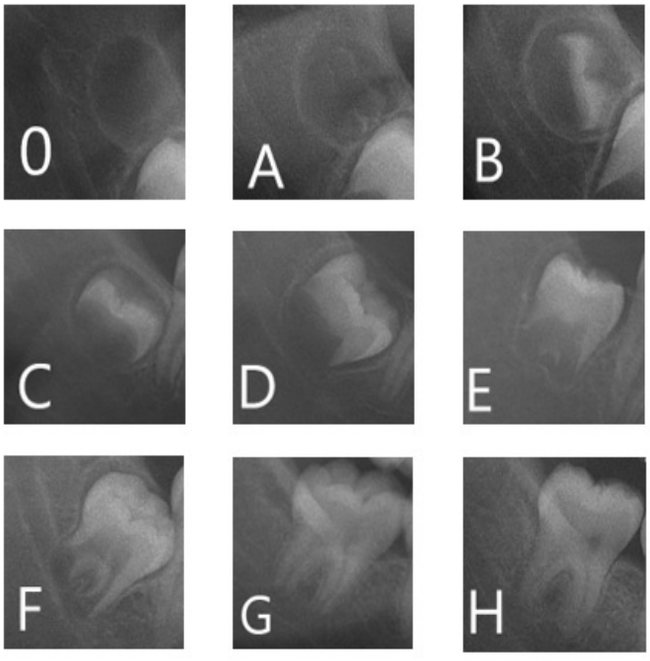

Figure 1. *Mineralization stages of mandibular third molar in cropped panoramic radiograph images. A) Stage 0: Radiolucent bud exists without any calcification. B) Stage A: Mineralization starts in cusp tips with single calcified points. C) Stage B: Fused mineralized points are recognizable. D) Stage C: Dentin accumulation starts after completion of enamel formation. E) Stage D: Crown formation is completed to the level of cementoenamel junction. F) Stage E: Formation of the root bifurcation starts. The root length remains shorter than the crown height. G) Stage F: The root length is equal to or greater than the crown height. Apical end is open with funnel shaped endings. H) Stage G: The root length is greater than the crown height. The dentin in the walls of root canal is parallel. I) Stage H: The apical ends of the roots are completely closed.*

2.4. Statistical analysis

Descriptive statistics for each variable data were calculated. Chronological age, developmental stages of teeth 38 and 48 and relations between age groups were evaluated by Pearson chi-square analysis. Data analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS, version 23 for Windows, Armonk, NY: IBM Corp). Statistical significance was set at $p < .05$. The intra-observer reliability was assessed by kappa values.

3.RESULTS

The study group consisted of 208 males (40.9%) and 301 females (59.1%) with a mean age of 14.34 ± 4.25. A total of 509 OPG images were examined with 509 lower right and 509 lower left mandibular 3Ms. The intra-observer reliability was found to be almost perfect with a kappa value of .966 ($p<.001$).

The developmental stages of the study group and descriptive statistics of chronological ages according to sex were given in Table 1.

Table 1. *The developmental stages of the study group and descriptive statistics of chronological ages according to sex*

		Left Mandibular Third Molar								*Right Mandibular Third Molar*							
							Percentiles								*Percentiles*		
Stage	Sex	N	Mean	SD	Min	Max	*25th*	*Median*	*75th*	N	Mean	SD	Min	Max	*25th*	*Median*	*75th*
0	M	18	8.00	1.495	6	12	7.0	8.0	8.2	13	7.54	.776	6	9	7.0	8.0	8.0
	F	14	7.50	.760	7	9	7.0	7.0	8.0	13	7.46	.660	7	9	7.0	7.0	8.0
A	M	18	9.11	1.410	7	12	8.0	9.0	10.0	20	8.65	1.226	7	12	8.0	8.5	9.0
	F	29	8.86	1.505	6	12	8.0	9.0	10.0	26	8.62	1.416	6	12	7.6	8.5	10.0
B	M	39	10.46	1.570	8	14	9.0	10.0	12.0	39	10.49	1.537	8	14	9.0	10.0	12.0
	F	35	10.29	1.673	8	14	9.0	10.0	11.0	38	10.34	1.849	8	16	9.0	10.0	11.3
C	M	23	12.35	1.071	10	14	12.0	12.0	13.0	24	12.08	.881	10	14	12.0	12.0	13.0
	F	33	13.24	1.601	10	16	12.0	13.0	14.5	34	13.06	1.613	10	17	12.0	13.0	14.0
D	M	9	13.56	2.128	11	17	12.0	13.0	15.5	9	13.56	1.509	12	17	12.5	13.0	14.0
	F	30	14.23	1.633	11	18	13.0	14.0	15.0	28	14.11	1.449	11	18	13.0	14.0	15.0
E	M	24	15.21	1.793	12	19	14.0	15.0	17.0	24	15.21	1.641	13	18	14.0	15.0	17.0
	F	58	15.34	1.743	12	19	14.0	15.0	17.0	53	15.21	1.758	12	20	14.0	15.0	16.0
F	M	19	16.58	1.071	14	18	16.0	16.0	18.0	21	16.43	1.502	12	19	16.0	16.0	17.5
	F	28	16.50	2.269	14	22	15.0	16.0	17.8	37	16.46	1.773	14	21	15.0	16.0	18.0
G	M	24	18.29	1.601	15	22	17.0	18.5	19.0	24	18.38	1.689	15	22	17.0	18.5	19.0
	F	45	18.31	2.109	15	22	17.0	18.0	20.0	45	18.51	2.191	15	22	17.0	19.0	20.0
H	M	34	20.44	1.211	17	22	19.8	21.0	21.0	34	20.38	1.231	17	22	19.0	20.5	21.0
	F	29	20.66	1.344	18	22	20.0	21.0	22.0	27	20.74	1.289	18	22	20.0	21.0	22.0

M: Male; F: Female; N: Number of individuals; SD: Standard Deviation; Min: Minimum; Max: Maximum, 25th: 75th

Distribution of number of individuals for each age group according to sex and developmental stage is presented in Table 2 for left mandibular 3M and in Table 3 for right mandibular 3M. For both tables, it was observed that in terms of number and percentage, distribution of age groups in developmental stages varied significantly for each sex and for all individuals regardless of sex (p<.001).

Stage distributions in age groups according to Table 2 were as follows; Group 1: stages 0, A and B were high in percent; stages E, F, G and H were not present. Group 2: stages C and D were high in percent; stages G and H were not present. Group 3: stages E and F were high in percent; stages 0, A, B and C were not present. Group 4: stage H was high in percent; stages 0, A, B, C and D were not present. Above presented distributions were same for all groups for both males and females, except Group 2 and 4 for females. The differences from the above distributions were stage 0 was also not present in Group 2 and stage D existed in Group 4. The absent stages for all age groups of left mandibular 3Ms were as follows; Group 1: stages E, F, G, H were not present. Group 2: stages G, H were not present. Group 3: stages 0, A, B were not present. Group 4: stages 0, A, B and C were not present.

According to Table 3, stages 0 and A for Group 1, stages C and D for Group 2, stage E for Group 3 and stages F and H Group 4 were found to be statistically high in percent for both males and females. The absent stages according to sex were as; Group 1: stages D, E, F, G and H were not present in males whereas stages E, F, G, H were not present in females. Group 2: stages 0, G, H were not present in both males and females. Group 3: stages 0, A, B and C were not present in males whereas stages 0, A, H were not present in females. Group 4: stages 0, A, B, C and D were not present in males whereas stages 0, A, B, C were not present in females. The absent stages for all age groups of right mandibular 3Ms were as follows; Group 1: stages E, F, G, H were not present. Group 2: stages 0, G, H were not present. Group 3: stages 0, A, H were not present. Group 4: stages 0, A, B and C were not present.

Table 4 presents distribution of number of individuals for each age group according to sex and developmental stage for both right and left mandibular 3Ms. The statistically high stages according to sex were as; Group 1: stages 0 and A were high for both in males and females. Group 2: stages C and D were high for both in males and females. Group 3: stages E and F were high for both in males and females. Group 1: stage H was high for males whereas stages G and H were high for females. The absent stages according to sex were as; Group 1: stages E, F, G and H were not present in both males and females. Group 2: stages G, H were not present in males whereas stages 0, G and H were not present in females. Group 3: stages 0, A, B, C and H were not present in males whereas stages 0, A, H were not present in females. Group 4: stages 0, A, B, C and D were not present in males whereas stages 0, A, B, C were not present in females. For all individuals of the study group for both mandibular 3Ms; stages 0 and A for Group 1; stages C, D in Group 2; stages E, F in Group 3; stage H in Group 4 were found to be significantly higher in percent. stages E, F, G, H were not present for Group 1 and stages G, H for Group 2, stages 0, A for Group 3 and stages 0, A, B and C were not present in Group 4 (Figure 2).

Table 5 shows the bilateral mandibular 3M presentation of developmental stages compliance. Number of matching stages were in the majority for every stage group. But there were also some unmatching for every developmental stage in both males and females, except for stage 0 of males. In this group, there was a full compliance of developmental stages.

Table 2. *Left mandibular third molar specific distribution of number of individuals for each age group according to sex and developmental stage*

	Stage	Group 1		Group 2		Group 3		Group 4		Total
		N	%	N	%	N	%	N	%	N
Male	0	17	94.4[a]	1	5.6[c]					18
	A	16	88.9[a]	2	11.1[c]					18
	B	28	71.8[a]	11	28.2[b]					39
	C	4	17.4[b]	19	82.6[a]					23
	D	1	11.1[b]	6	66.7[a]	2	22.2[b]			9
	E			10	41.7[b]	12	50.0[a]	2	8.3[d]	24
	F			1	5.3[c]	13	68.4[a]	5	26.3[c]	19
	G					9	37.5[b]	15	62.5[b]	24
	H					1	2.9[c]	33	97.1[a]	34
Female	0	14	100.0[a]							14
	A	27	93.1[a]	2	6.9[c]					29
	B	27	77.1[a]	8	22.9[b]					35
	C	3	9.1[b]	22	66.7[a]	8	24.2[b]			33
	D	2	6.7[b]	16	53.3[a]	11	36.7[b]	1	3.3[d]	30
	E			18	31.0[b]	36	62.1[a]	4	6.9[d]	58
	F			4	14.3[bc]	17	60.7[a]	7	25.0[c]	28
	G					17	37.8[b]	28	62.2[b]	45
	H							29	100.0[a]	29
Total	0	31	96.9[a]	1	3.1[c]					32
	A	43	91.5[a]	4	8.5[c]					47
	B	55	74.3[b]	19	25.7[b]					74
	C	7	12.5[d]	41	73.2[a]	8	14.3[c]			56
	D	3	7.7[d]	22	56.4[a]	13	33.3[b]	1	2.6[d]	39
	E			28	34.1[b]	48	58.5[a]	6	7.3[d]	82
	F			5	10.6[c]	30	63.8[a]	12	25.5[c]	47
	G					26	37.7[b]	43	62.3[b]	69
	H					1	1.6[c]	62	98.4[a]	63

N*: Number of individuals;* ***Letters (a, b, c, d)****; If the percentages of the stages given separately for each gender and age group have completely different letters, the stages in question are significantly different. For example, the stage with the letter a differs significantly from the stage with the letter b, c, d.*

Table 3. *Right mandibular third molar specific distribution of number of individuals for each age group according to sex and developmental stage*

	Stage	Group 1		Group 2		Group 3		Group 4		Total
		N	%	N	%	N	%	N	%	N
Male	0	13	100.0[a]							13
	A	19	95.0[a]	1	5.0[c]					20
	B	29	74.4[b]	10	2.6[b]					39
	C	5	20.8[b]	19	79.2[a]					24
	D			8	88.9[a]	1	11.1[c]			9
	E			10	41.7[b]	12	50.0[ab]	2	8.3[d]	24
	F			2	9.5[c]	14	66.7[a]	5	23.8[c]	21
	G					9	37.5[b]	15	62.5[b]	24
	H					1	2.9[c]	33	97.1[a]	34
Female	0	13	100.0[a]							13
	A	25	96.2[a]	1	3.8[c]					26
	B	29	76.3[b]	8	21.1[b]	1	2.6[c]			38
	C	5	14.7[c]	22	64.7[a]	7	20.6[b]			34
	D	1	3.6[c]	17	60.7[a]	9	32.1[b]	1	3.6[d]	28
	E			18	34.0[b]	32	60.4[a]	3	5.7[d]	53
	F			4	10.8[c]	23	62.2[a]	10	27.0[c]	37
	G					17	37.8[b]	28	62.2[b]	45
	H							27	100.0[a]	27
Total	0	26	100.0[a]							26
	A	44	95.7[a]	2	4.3[c]					46
	B	58	75.3[b]	18	23.4[b]	1	1.3[c]			77
	C	10	17.2[c]	41	70.7[a]	7	12.1[c]			58
	D	1	2.7[c]	25	67.6[a]	10	27.0[b]	1	2.7[d]	37
	E			28	36.4[b]	44	57.1[a]	5	6.5[d]	77
	F			6	10.3[c]	37	63.8[a]	15	25.9[c]	58
	G					26	37.7[b]	43	62.3[b]	69

N*: Number of individuals;* ***Letters (a, b, c, d)****; If the percentages of the stages given separately for each gender and age group have completely different letters, the stages in question are significantly different. For example, the stage with the letter a differs significantly from the stage with the letter b.*

Table 4. *Distribution of each age group according to sex and developmental stage for both right and left mandibular third molars*

		Group 1		Group 2		Group 3		Group 4		*Total*
	Stage	N	%	N	%	N	%	N	%	N
Male	0	30	96,8[a]	1	3,2[d]					31
	A	35	92,1[a]	3	7,9[d]					38
	B	57	73,1[b]	21	26,9[c]					78
	C	9	19,1[c]	38	80,9[a]					47
	D	1	5,6[d]	14	77,8[a]	3	16,7[c]			18
	E			20	41,7[b]	24	50,0[a]	4	8,3[d]	48
	F			3	7,5[d]	27	67,5[a]	10	25,0[c]	40
	G					18	37,5[ab]	30	62,5[b]	48
	H					2	2,9[d]	66	97,1[a]	68
Female	0	27	100,0[a]							27
	A	52	94,5[a]	3	5,5[c]					55
	B	56	76,7[b]	16	21,9[b]	1	1,4[c]			73
	C	8	11,9[c]	44	65,7[a]	15	22,4[b]			67
	D	3	5,2[c]	33	56,9[a]	20	34,5[b]	2	3,4[c]	58
	E			36	32,4[b]	68	61,3[a]	7	6,3[c]	111
	F			8	12,3[c]	40	61,5[a]	17	26,2[b]	65
	G					34	37,8[b]	56	62,2[a]	90
	H							56	100,0[a]	56
Total	0	57	98,3[a]	1	1,7[c]					58
	A	87	93,5[a]	6	6,5[c]					93
	B	113	74,8[b]	37	24,5[b]	1	0,7[c]			151
	C	17	14,9[c]	82	71,9[a]	15	13,2[c]			114
	D	4	5,3[c]	47	61,8[a]	23	30,3[b]	2	2,6[d]	76
	E			56	35,2[b]	92	57,9[a]	11	6,9[d]	159
	F			11	10,5[c]	67	63,8[a]	27	25,7[c]	105
	G					52	37,7[b]	86	62,3[b]	138
	H					2	1,6[c]	122	98,4[a]	124

N: *Number of individuals;* ***Letters (a, b, c, d)****; If the percentages of the stages given separately for each gender and age group have completely different letters, the stages in question are significantly different. For example, the stage with the letter a differs significantly from the stage with the letter b.*

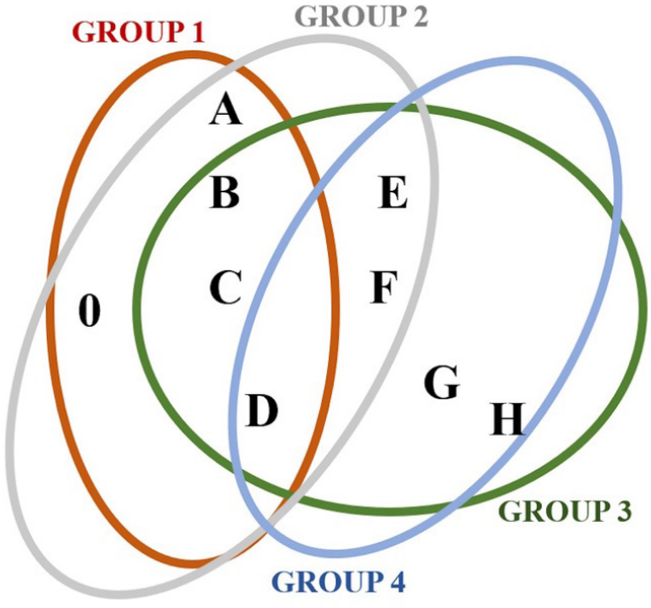

Figure 2. *Expression of Demirjian stages of third molar development from 0 to H in sets of specific age groups investigated in this present study. Red set refers to Group 1, gray set refers to Group 2, green set refers to Group 3 and blue set refers to Group 4.*

Table 5. *Presentation of developmental stages compliance between right and left mandibular third molar*

			LEFT third molar									
			0	A	B	C	D	E	F	G	H	Total
Male	RIGHT third molar	0	13	0	0	0	0	0	0	0	0	13
		A	3	15	2	0	0	0	0	0	0	20
		B	2	3	32	2	0	0	0	0	0	39
		C	0	0	5	18	1	0	0	0	0	24
		D	0	0	0	3	6	0	0	0	0	9
		E	0	0	0	0	2	21	1	0	0	24
		F	0	0	0	0	0	3	18	0	0	21
		G	0	0	0	0	0	0	0	23	1	24
		H	0	0	0	0	0	0	0	1	33	34
	Total		18	18	39	23	9	24	19	24	34	208
			0	A	B	C	D	E	F	G	H	Total
Female	RIGHT third molar	0	9	4	0	0	0	0	0	0	0	13
		A	5	19	2	0	0	0	0	0	0	26
		B	0	4	31	3	0	0	0	0	0	38
		C	0	2	2	24	6	0	0	0	0	34
		D	0	0	0	3	19	6	0	0	0	28
		E	0	0	0	3	5	41	4	0	0	53
		F	0	0	0	0	0	10	21	6	0	37
		G	0	0	0	0	0	1	3	38	3	45
		H	0	0	0	0	0	0	0	1	26	27
	Total		14	29	35	33	30	58	28	45	29	301
			0	A	B	C	D	E	F	G	H	Total
TOTAL	RIGHT third molar	0	22	4	0	0	0	0	0	0	0	26
		A	8	34	4	0	0	0	0	0	0	46
		B	2	7	63	5	0	0	0	0	0	77
		C	0	2	7	42	7	0	0	0	0	58
		D	0	0	0	6	25	6	0	0	0	37
		E	0	0	0	3	7	62	5	0	0	77
		F	0	0	0	0	0	13	39	6	0	58
		G	0	0	0	0	0	1	3	61	4	69
		H	0	0	0	0	0	0	0	2	59	61
	Total		32	47	74	56	39	82	47	69	63	509

4.DISCUSSION

The present study specifically evaluated the potential Demirjian's method for identification of an individual who has attained medicolegally significant ages of 12, 15 and 18 years in a Turkish subpopulation. Those three age limits are defined by Turkish Penal Code and children under the age of 12 have no legal responsibility. Any person who has not reached the age of 18 is a minor and if a minor is older than 12, but younger than 15, evaluation of the ability to appreciate the legal meaning and capability to control behavior is required. There are also different regulations concerning individuals older than 15 but younger than 18 years in Turkish Penal Code. This is also similar in Andorra, Belgium, Hungary, Ireland, Netherlands, San Marino, and Scotland where children can be held criminally liable from the age of 12. Another relevant threshold, age of 15 is also critical in Czech Republic, Iceland, Norway, Slovakia, and Sweden (9). Therefore, the age limits of 12, 15 and 18 years have legal significance both in Turkey and in some European countries as well. Regarding these specific thresholds, four groups were formed in our study investigating individuals under the age of 12, aged between 12 to 15, 15 to 18 and aged over 18 years.

Considering 3M mineralization profile of 509 individuals presented in this study, crypt formation (stage 0) started at age of 6 in males and 7 for females for both sides of the mandible. This is in accordance with the previous findings of other studies conducted in Turkish population who reported that reported that the crypt formation at the mandibular 3M at the age of 7 (10,11). Our results for the average age for closure of the root apex (stage H) was between 20.38 to 20.44 for males and 20.66 to 20.74 for females, in accordance with Orhan et al. who found this average as 20.1 years (10). As suggested by Lewis and Senn, ancestral population specificity is an important criterion for an accurate and reliable age estimation (4). Moreover, Orhan et al. reported that in Turkish population all stages of 3M development occurred at an earlier age than the Japanese, South African, German, and Spanish populations (10). Furthermore, the results of the age estimation studies conducted in the same population may also differ. These differences were attributed not only to geographic and ethnic variations, but also to methodology and dissimilarity of observers as well (12).

Regarding our results on the specific age groups with legal significance, probability of stages 0 and A were found to be higher than stage B in Group 1 with a statistical significance. Only one mandibular 3M (1.7%) with stage 0 was observed in Group 2. Therefore, an individual with stage 0 was high likely to be under the age of 12 and in Group 1. This is in accordance with Orhan et al. who reported that crypt formation was not observed after 10 and 11 years, for males and for females respectively (10). Additionally, in the present study root formation (stages E, F, G, H) was not observed in individuals under age 12 as well. Considering Group 2, probability of stages C and D were found to be higher with a statistical significance. Kasper et al. also suggested that an individual with a mandibular 3M presenting stage B or above should be greater than 12 years of age (13). In Group 2, stages G and H were not observed whereas only 11 teeth presented stage F (10.5%). Regarding Group 3, probability of stage E and F were found to be higher with a statistical significance, which may indicate that an individual with these stages is high likely to be older than age 15. Additionally, in males, all mineralization processes regarding crown development of 3M were completed and stages 0, A, B and C was not observed in this group. For females, the crown development seemed to continue as the stages B, C were observed in individuals between 15 and 18 years. This finding is in accordance with the findings of previous studies reporting that 3M of males matured earlier than those of females (3, 13, 14).

As development of stage H is related to the chronologic age of 18, this stage was found to be statistically high in Group 4,

in accordance with the results of previous studies (10, 12, 15, 16). For the individuals of 18 and over, only 2 mandibular 3M (2.6%) presented stage D and the rest were stage E and above. Various studies conducted in different populations related the absence of stages from A to E with the prediction of age 18 (10, 12, 14-16). In the present study, stages 0, A, B, C were not observed in Group 4. Regarding minimum ages, Kanchan et al. (17) reported that individuals with stage G and H were over 18 years of age in Indian population. However, in the present study, the minimum age for stage G was 15 for males and females, which was in accordance with Cantekin et al. (11) who also investigated 3M mineralization in Turkish population and reported this age as 15.3 for males and 15.1 for females, pointing out the population specific variations.

Another important consideration of the present study was differences in the right and left readings. Regarding the results of 3M mineralization for males; D, E stages were reached earlier, and stage F was reached later on the left side than the right side. Interestingly, the scores were not the same for right and left readings for "all" stages as presented in Table 5 with the most variation in readings of stages B, C, E and G as two stages below and one stage above the concordance. Such variations were also reported by Ashifa et al. (3) and Kasper et al. (13) who both recommended independent evaluation of both sides in staging 3M mineralization. Therefore, considering aforementioned age limits in various penal codes and the absence of some stages in some age groups, we also recommend evaluation of every single tooth for age estimation.

Similar to our approach, Kanchan et al. also investigated the potential of Demirjian method to provide cut – off points to age of 16 and 18, which have a legal significance in Indian governing law (17). They have concluded that Demirjian's stages of third molar maturation can be used to ascertain whether an individual has attained those medicolegally significant ages. Regarding the results of our study, we also recommend use of Demirjian method in assessment of groups investigating specific ages with legal significance. Considering the previous studies with additional skeletal indicators such as spheno-occipital synchondrosis and medial clavicle with 3M mineralization evaluation (18, 19), use of multifactorial approach can also be suggested for the enhanced analysis of those specific age groups for future studies.

5.CONCLUSION

The present investigation provides representative data regarding the discrimination of specific groups with age thresholds of 12, 15, and 18 used by Turkish and various European penal codes. Our results indicate that independent evaluation of both sides and consideration of sexual dimorphism are important in estimating age from the 3M mineralization. Considering growing diversity and the foreign-born population in various countries, collaborated age estimation studies may reveal more specific data for 3M development differences which can help ethnicity-specific evaluation of medicolegally relevant subadult age groups according to governing law.

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Design of the study: SB, FAK
Acquisition of data for the study: SB, FAK,
Analysis of data for the study: AS, HA
Interpretation of data for the study: SB, AS, FAK
Drafting the manuscript: SB, AS, FA K
Revising it critically for important intellectual content: AS
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Clinical and Experimental Health Sciences

Turkish Adaptation of Patient Nurse Trust Scale: A Validity and Reliability Study

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ABSTRACT

Objective: This study aims to adapt the Patient-Nurse Trust Scale to Turkish and perform validity and reliability analyses.

Methods: This study has been conducted as methodological. It was conducted between February 2021 and June 2021 in a training and research hospital in Istanbul, Turkey. The study was completed with 311 participants. Introductory Information Form, Patient-Nurse Trust Scale, and Trust in Nurses Scale were used for data collection. In addition to descriptive statistics, language validity, content validity, construct validity, criterion-related validity, discrimination, internal consistency reliability, two-half test reliability, and item analysis methods were used to determine the scale's psychometric properties.

Results: As a result of factor analysis, it was determined that the scale showed a single factor structure, and explained 66.63% of the total variance. Item factor load values were found to vary between .74 and .88. The ratio of the chi-square value to the degrees of freedom (397.496/112) was found to be 3.549. It was found that RMSEA= .09, GFI= .86, IFI= .93, NFI= .91, CFI= .93, and RFI= .87. It was found that the correlations of all items varied between .71 and .87. The Chronbach's alpha value for the whole scale was calculated as .97. As a result of parallel test analysis, it was determined that there was a significant positive correlation between both scales (r= .301; p= .000).

Conclusion: The exploratory factor analysis and confirmatory factor analysis results of the Turkish version of the scale are acceptable, and their reliability indexes are high.

Keywords: Trust, communication, patient-nurse relationship, validity, reliability.

1. INTRODUCTION

Nurses are expected to care for patients who have difficulties in meeting their self-care needs. Virginia Henderson emphasized that nurses performed uniquely in helping individuals recover and prepare for a peaceful death. This unique performance includes the development of a special care relationship between the patient and the nurse (1-3). Nurses are the health care providers closest to patients. Individuals have no choice but to rely on nurses, especially when they are critically ill. Therefore, "trust" is necessary to establish and maintain a professional caring relationship (1,3,4).

There are many definitions of trust. It is generally defined as the feeling of belief and attachment without fear, hesitation, and doubt, confidence It is emphasized that everything important for people happens in an environment of trust, and in this direction, "trust" is a basic requirement for humanity (1). Trust has the potential to give meaning to life by instilling faith and hope in people (5,6). Trusting another means opening up to an action and expecting the other to act according to their own wishes, interests, or will. The concept of trust in nursing research is widely discussed in patient-nurse relationships (3).

Effective patient-nurse communication has a great role in providing effective and successful nursing care. This communication is based on trust is very important in starting and maintaining a healthy patient-nurse relationship (5-7). Lack of communication can result in a lack of trust in the patient–nurse relationship (8,9). On the other hand, the patient-nurse relationship, which is established without developing a sense of trust, may affect communication negatively. This situation may prevent nurses from providing high-quality and patient-centered care to their patients (6,10,11). Carter argued that trust is even more fundamental than the duties of benevolence, righteousness, and harmlessness and that without trust, no one would have a

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reason to undertake these duties (2). On the other hand, it was emphasized that trust is a moral imperative to establish a professional care relationship and achieve desired patient outcomes (1,3).

Studies have demonstrated the importance of the concept of trust in providing positive patient outcomes in the patient-nurse relationship (12). It was stated that when the patient trusts the nurse, he feels physically and emotionally safe and sees himself as an active member of the care team (13,14). In the study of Kim et al. (2012), it was revealed that a high trust relationship reduces depression in individuals with chronic diseases (15).

In order to develop trust in the patient-nurse relationship, the nurse should understand the patient's needs well and provide humane care in line with their needs. In addition, allocating enough time for care, meeting the need for information, and creating a safe environment for the patient while giving care contribute to the development of trust in the patient-nurse relationship. Another important behavior that fosters this feeling is that nurses take on the role of patient advocate when necessary (1,2).

A measurement tool that will measure the trust between the patient and the nurse will guide the strategies that can improve this sense of trust. However, It was found in the Turkish literature only the Trust in Nurses Scale that was developed by Radwin and Cabral (2010) and adapted into Turkish (16,17). This scale was developed and tested only for cancer patients (16). It is thought to be necessary to develop a valid and reliable measurement tool that can accurately measure the patient-nurse trust relationship that can be applied in all patient groups. Accordingly, this study aims to adapt the Patient-Nurse Trust Scale into Turkish and perform validity and reliability analyses.

2. METHODS

2.1. Ethical Considerations

Ethics committee approval was obtained from Marmara University Faculty of Medicine Ethics Committee (date: 05.02.2021; no: 09.2021.204). Institutional permission was obtained from the İstanbul Health Directorate. Consent of the participants to participate in the study was obtained. Permission was obtained from Zha to adapt the Patient-Nurse Confidence Scale. Permission was obtained from Yücel to use the Trust in Nurses Scale.

2.2. Study design and setting

This study has been conducted as methodological. It was conducted between February 2021 and June 2021 in a training and research hospital in Istanbul, Turkey.

2.3. Sample size and participants

The study population consisted of patients who were hospitalized in inpatient clinics, excluding intensive care units, in a Training and Research Hospital. The sample has consisted of patients who met the inclusion criteria.

In the validity and reliability phase of scale development studies, in order to apply factor analysis to a data set, the amount of data should be at least five times the number of questions, and as this ratio increases, the analysis quality also increases. In addition, Comrey defines the sample size as 50 very poor, 100 poor, 200 moderate, 300 good, 500 very good, and 1000 excellent (18-20). Accordingly, the number of samples was determined as 380, 20 times as much as the original scale consisted of 19 items. The study was completed with 311 participants in line with the inclusion criteria (being between the ages of 18-85, being literate) and exclusion criteria (having a mental illness, hearing, and visual impairment).

2.4. Data Collection Tools

Introductory Information Form, Patient-Nurse Trust Scale, and Trust in Nurses Scale were used for data collection.

2.4.1. Information Form

This form prepared by the researchers was composed of five questions including socio-demographic variables.

2.4.2. Patient-Nurse Trust Scale (PNTS)

The scale was developed by Zha et al. (2020). The scale, scored in a four-point Likert format (1 = Strongly Disagree, 2 = Disagree, 3 = Agree, 4 = Strongly Agree), consists of 19 items. The score that can be obtained from the scale is between 19 and 76, and a higher score represents more trust between the patient and the nurse. The Cronbach's alpha value of the single factor scale is .95 (6).

2.4.3. Trust in Nurses Scale (TNS):

For the parallel test method, the TNS developed by Radwin and Cabral (2010) and adapted to Turkish by Ay and Yücel (2013) was used (16,17). The scale is unidimensional and contains five items and is scored as never (1), rarely (2), sometimes (3), often (4), usually (5), always (6) on a 6-point Likert scale. The highest score that can be obtained from the scale is 30, the lowest score is 5. A high score on the scale indicates a high level of trust in nurses. In Radwin and Cabral's (2010) study, the Cronbach alpha value of the scale was found to be .81 (16). The Cronbach alpha value of the Turkish version of the scale is .95 (17). In this study, the Cronbach alpha value of the scale was found to be .80.

2.5. Data Analysis

Study data were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 25.0 and Amos 22.0 program. Kolmogorov-Smirnov test was used to test whether the data set exhibits a normal distribution and it was seen that the

data set did not exhibit a normal distribution. In addition to descriptive statistics, language validity, content validity, construct validity, criterion-related validity, discrimination, internal consistency reliability, two-half test reliability (equivalent halves) and item analysis methods were used to determine the psychometric properties of the scale. Construct validity was tested with Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA). While evaluating the CFA fit indices, CFI (Comparative Fit Index), GFI (Goodness of Fit Index), IFI (Incremental Fit Index), NFI (Normed Fit Index), RFI (Relative Fit Index, RMSEA, Root Mean Square Error of Approximation) values were used.

3. RESULTS

The mean age of the participants was 49.01 (Sd=13.46), 44.4% were female, 55.6% were male, and the majority (55.9%) were primary school graduates. 83.9% of the participants who were hospitalized for an average of 6.53 (Sd=5.51) days stated that they had been hospitalized before. It was determined that the previous hospitalizations were 3.31 (Sd=2.50) times on average. When the participants were asked to rate their satisfaction with the care they received during their hospitalization on a scale ranging from 1 to 10, it was seen that their satisfaction with the care was 8.62 (Sd=1.81) on average. When the participants were asked to rate their trust in the nurses/nurses they care for on a scale ranging from 1 to 10, it was determined that the mean value was 8.54 (Sd=1.88) (Table 1).

Table 1. *Socio-demographic data of the participants (n=311)*

Results	Min-Max	Ort (Sd)	N	%
Age	18-65	49.01 (13.46)		
Gender				
Female			138	44.4
Male			173	55.6
Education				
Primary education			174	55.9
High school			55	17.7
University and above			82	26.4
Length of hospital stay (days)	1-43	6.53 (5.51)		
Prior hospitalization				
Yes			261	83.9
No			50	16.1
How many hospitalizations have you had before*	1-20	3.31 (2.50)		
How long is your hospital stay (days)	1-43	6.53 (5.51)		
Nursing care satisfaction	1-10	8.62 (1.81)		
Their trust in the nurses/ nurses they care for	1-10	8.54 (1.88)		

**Evaluation was made on those who answered "yes" to the previous question.*

3.1. Validity Analysis

3.1.1. Language Validity

For the language validity of the scale, the original scale was first translated into Turkish by five people who were fluent in both English and Turkish languages. Then, the best expressions were selected among all the translations by the researchers. It was translated into English again by three experts who are fluent in both languages and different from the first translation group. English translations were compared with the original scale. After the necessary arrangements, the Turkish form was created.

3.1.2. Content Validity

To assess the content validity, the opinions obtained from 15 experts were analyzed with the Davis technique (20). In this technique, experts assess the scale items with a four-point rating system. The content validity rate (CVR) is calculated for each item and is obtained by dividing the number of the items with 3 or 4 points on the expert forms by the total number of experts. The content validity index (CVI) is obtained by calculating the mean CVRs. It is recommended that the CVI be above 0.80 and the items with a CVR below .80 be eliminated (21). In the analysis results, the items' CVRs were found to range from .73 to 1, and the CVI was observed to be .91.

3.1.3. Face Validity

The face validity of the scale was evaluated with data obtained from 20 patients. During this pilot study, the researchers interviewed the participants face-to-face to assess whether any item was understood at the first reading, and how long it took to respond. For face validity, it was seen that the participants found the scale to be good in general and stated that the items were understandable. It was also stated that approximately 15-20 minutes were needed to complete the scale.

3.1.4. Construct Validity

The factor analysis of the scale was carried out with exploratory and confirmatory factor analyses. The factor analysis was deemed interpretable after the analysis of KMO and Bartlett's test results. The KMO and Bartlett's test values were found to be 0.94 and .000, respectively. As a result of EFA, it was determined that the scale showed a single factor structure, and the single factor structure explained 66.63% of the total variance (Table 2). The scree pilot plot also confirmed the single-factor structure of the scale (Figure 1). Item factor load values were found to vary between .74 and .88 (Table 2). According to the CFA, it was determined that the Structural Equation Modeling Results of the scale were significant at the p=.000 level and that the 19 items and one dimension forming the scale were related to the scale structure. The model has been improved. While making the improvement,

the variables that reduced the fit were determined, and new covariances were created for those with high covariance among the residual values. It is shown in Table 3 that the values accepted for the fit indices are provided in the later renewed fit index calculations. The ratio of the chi-square value to the degrees of freedom (397.496/112) was found to be 3.549. When the other fit indices were examined, it was found that RMSEA = .09, NFI = .91, RFI= .87, GFI =. 86, and CFI = .93. The model with standardized parameter estimates or the factors and items of the scale is presented in Figure 2.

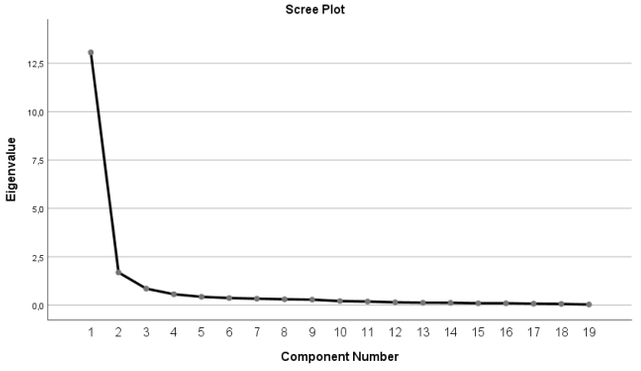

Figure 1. *Scree pilot graph*

Table 2. *Factor analysis results of the Patient-Nurse Trust Scale (n=311)*

Items	Item loads	Item-total correlation	Lower %27* – Upper%27*	
			t	p**
Item 11	.88	.87	-15.672	.000
Item 12	.87	.86	-15.093	.000
Item 17	.85	.82	-13.251	.000
Item 7	.84	.82	-13.937	.000
Item 5	.85	.82	-16.813	.000
Item 3	.84	.81	-14.638	.000
Item 13	.83	.81	-14.136	.000
Item 15	.83	.81	-13.010	.000
Item 18	.83	.81	-13.416	.000
Item 10	.82	.80	-15.006	.000
Item 19	.82	.80	-13.675	.000
Item 2	.81	.79	-11.755	.000
Item 8	.81	.78	-11.258	.000
Item 1	.80	.77	-11.053	.000
Item 6	.79	.76	-15.087	.000
Item 16	.79	.76	-12.821	.000
Item 9	.78	.75	-11.755	.000
Item 4	.74	.72	-14.001	.000
Item 14	.74	.71	-13.948	.000
Total variance explained		%66.63		
Cronbach's Alpha		.97		
Spearman-Brown		.94		
Guttman		.94		

*N=311;*n1=n2=84; **p<.001*

3.2. Reliability Analysis

In the item total item residual analysis performed for the reliability analysis of the scale, it was found that the correlations of all items varried between .71 and .87 (Table 2).

To determine the distinctiveness of the items in the scale, the raw scores obtained from the scale were ranked from largest to smallest, and the mean scores of the groups in the lower 27% and upper 27% were compared with the independent group t-test. As a result of the comparison, it was observed that there was a statistically significant difference between the averages of the lower and upper group item scores (p= .000).

Cronbach's alpha coefficient was calculated for the whole scale and sub-dimensions for internal consistency. The Chronbach's alpha value for the whole scale was calculated as .97. The spearman-Brown coefficient was .94 due to the two-half reliability analysis; The Guttman coefficient was found to be .94 (Table 2). When the item score averages of the lower 27% and upper 27% slices were compared, it was observed that there was a significant difference (p= .000) (Table 2).

To determine the consistency coefficients in the context of the analysis of the reliability of the scale, the parallel test method was applied. As seen in Table 4, as a result of Spearmen's correlation analysis, it was determined that there was a significant positive correlation between both scales (r= .301; p= .000).

Table 3. *Fit indexes as a result of confirmatory factor analysis (n=311)*

	Fit Indexes	Acceptable Fit Indexes	Good Fit Indexes
χ2/df	3.549	3≤χ2/df≤5	0≤χ2/df≤3
RMSEA	.09	0.06≤RMSEA≤1.0	.0≤RMSEA≤.05
GFI	.86	≥.90	≥.80
IFI	.93	≥.95	≥.85
CFI	.93	≥.95	≥.85
NFI	.91	≥.95	≥.80
RFI	.87	≥.95	≥.85
χ2 = 397.496, df=112, p=.000*			

*CFI, Comparative Fit Index; GFI, Goodness of Fit Index; IFI, Incremental Fit Inde; NFI, Normed Fit Index; RFI, Relative Fit Index; RMSEA, Root Mean Square Error of Approximation. *p<.05*

Table 4. *Reliability analysis results of the Patient-Nurse Trust Scale (n=311)*

	Parallel testing	
	r	p
Patient-Nurse Trust Scale	.372	.000
Scale of Trust to Nurses		
Spearmen correlation test was used; p<.001		

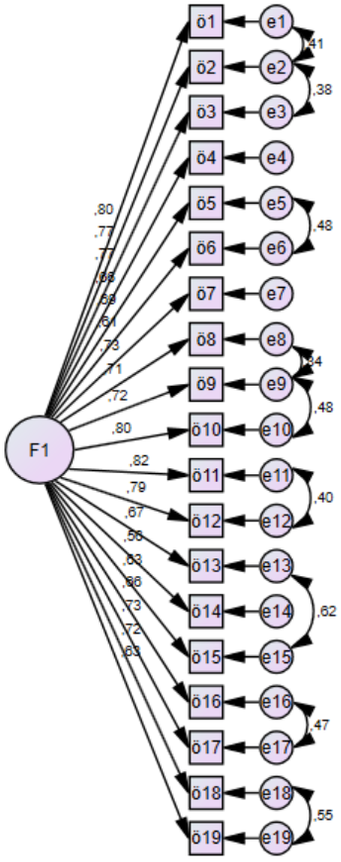

Figure 2. *Patient-Nurse Trust Scale CFA results*

4. DISCUSSION

In order to evaluate the content validity of the PNTS, the opinions of 15 experts were analyzed with the Devis technique. It is recommended that the CVI be above .80 (20,21). As a result of the analysis, the CVI was found to be .91. This finding showed that the content validity of the scale was good. In order to apply factor analysis to a data group, the data must be suitable for factor analysis and the sample must be sufficient (22).

When the results of Bartlet Sphericity Test and Kaiser-Meyer Olkin (KMO) Test conducted for this purpose are examined; It was determined that the Bartlet Test of Sphericity value was significant (p= .000) and the KMO sample fit coefficient was .94. KMO value between .80 and .90 and a significant Bartlet Test of Sphericity indicate that the sample is suitable for EFA (18). Accordingly, it has been seen that the data set is sufficient and suitable for EFA. The construct validity of the PNTS was tested using exploratory factor analysis. EFA is a method for determining the number of factors under which the items in a measurement instrument can be gathered and/or what kind of relationship there is among the factors. In other words, exploratory factor analysis shows how many sub-dimensions the scale consists of and which items these sub-dimensions consist of (20,22).

The EFA showed that one-factor structure explained 66.6% of the total variance. It was stated that the single-factor structure in the original scale explained 53.2% of the total variance. It was seen that the total variance explained in the Turkish version of the scale was higher. The total variance explained in the single factor scales should be over 30% (18,21). Hence, with all things considered, it may be stated that the percentage of the variance explained by the scale was very high and sufficient.

The scree plot graph also confirmed that the scale exhibited a single factor structure. Considering that the interval between two points in the plot is considered to be one factor, and the distances between the points after the first factor were negligible and very similar (20), it was determined that a single-factor structure was suitable for the scale. It is noteworthy that a single-factor structure may provide advantages for users in terms of implementation and assessment using this scale. In multi-factor scales, analyzes (reliability indexes, comparison tests, etc.) are performed separately for each sub-factor. On the other hand, in single factor scales, these analyzes are carried out for the whole of the scale at once. These advantages provide convenience to researchers.

The load value in factor analysis is the critical value used to determine whether an item should be included in the dimension where it is defined. An item is usually expected to have a load value of .45 or higher (18,20). The minimum required value for the item-total test correlation to be sufficient is specified as 0.30 (20,21). The item-total test correlation values of the remaining items vary between .74 and .88. This finding is an important finding in terms of the construct validity of the scale and shows that the items that make up the scale accurately measure the concept that is intended to be measured. It was observed that the item factor load values of the original scale ranged from .64 to .84. In most of the scale adaptation studies, it is seen that the intelligibility of the items is affected by cultural and linguistic differences, and therefore, factor loadings are lower than the original values. However, in this study, it was observed that most item loads in the Turkish version of the scale were higher than the original scale. This finding is important for the validity of the scale.

CFA results were analyzed to determine whether the original scale was validated in Turkish patients. It is stated that GFI and IFI indices above .85 and NFI and CFI indices above .80 reflect good fit (22). The findings show that the Turkish version of the scale has good fit values for the GFI, CFI, NFI and IFI indices. RMSEA value below .06 reflects good fit, while a value below .10 indicates an acceptable level of fit (22,23). It was seen that the RMSEA index for this scale was .09 and it had acceptable fit criteria. A ratio of chi-square value to degrees of freedom below three indicates a good fit; it is stated that a score below five reflects acceptable fit (21-23). When the CFA results were examined, the ratio of the chi-square value to the degrees of freedom was found to be 3.08 (p= .000). This value below five reflects an acceptable

level of compliance (22). After reviewing the goodness-of-fit indices obtained from confirmatory factor analysis, the model is considered suitable.

Internal consistency and reliability coefficients were found to over .97. Cronbach's alpha reliability coefficient is an ideal method for determining internal consistency in Likert-type scales, and it shows the agreement of the items in the scale with each other (18). Split-half tests determine reliability by dividing the test into two equal parts where the relationship between the two parts is calculated using the Spearman-Brown correlation coefficient. It is expected that this relationship will be significant and high. In scale development and adaptation processes, reliability coefficients of .70 and higher are considered to have sufficient reliability (18,20,22). In this study, Spearman-Brown and Guttman reliability coefficients were found to be .94 for the Turkish version of the scale. Accordingly, because the Cronbach's alpha, Spearman-Brown, and Guttman values were all .70 or higher for the entirety and sub-dimensions, this scale has sufficient internal consistency and satisfies the split-half reliability criteria.

In determining the parallel form reliability, the correlation between the points obtained from two-scale tools is looked at by implementing a different scale tool that has the same qualities to the same individuals at the same time. The Trust in Nurses scale, whose validity and reliability have been proven in the Turkish language, was referred for the parallel form reliability. A correlation value between .70 and 1.00 reflects a high-level correlation, while a value between .30 and .70 demonstrates a mid-level correlation (22). A positive significant correlation was found between the The Trust in Nurses scale and the Patient-Nurse Trust Scale (r= .372; p= .000). This result is important in terms of the reliability of the scale.

5. CONCLUSION

The results obtained from the study have shown that the exploratory factor analysis and confirmatory factor analysis results of the Turkish version of the Patient-Nurse Trust Scale are acceptable, and its reliability indexes are high. In this respect, it can be said that the Single-factor and 19-item Patient-Nurse Trust Scale is a valid and reliable measurement tool that can accurately measure the level of trust patients have in their caregivers.

Trust is an important part of the patient-nurse relationship. A trusting relationship must be established and maintained to achieve positive patient outcomes. All clinician nurses, can use the Patient-Nurse Trust Scale to determine the confidence level of their patients. The scale will also guide nurses, nurse managers, and nurse educators in the development of strategies that can improve trust between patient-nurses. On the other hand, it can be suggested that the Patient-Nurse Trust Scale be used in large samples containing different patient groups. and the nurse.

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Author Contribution:

Research idea: GKO

Design of the study: GKO, DCP

Acquisition of data for the study: GKO, DCP, FA

Analysis of data for the study: GKO, DCP

Interpretation of data for the study: GKO, DCP, FA

Drafting the manuscript: GKO, DCP, FA

Revising it critically for important intellectual content: GKO, DCP, FA

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Clinical and Experimental Health Sciences

Optical Properties of Newly Developed Monolithic CAD/CAM Materials After Aging

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ABSTRACT

Objective: With the widespread use of CAD/CAM (computer aided design and manufacture) systems in dentistry, many restorative materials have been produced. In our study, we aimed to evaluate the change in optical properties of newly developed translucent monolithic zirconia (TMZ) (Cercon HT Dentsply, Sirona, USA), zirconia-reinforced lithium silicate (ZLS) (Celtra Duo, Dentsply, Germany) and lithium disilicate (LS2) (IPS e.max CAD, Ivoclar Vivadent, Liechtenstein) materials with aging.

Methods:10 discs of 12mm diameter and 1.2 mm thickness were produced from high translucent A2 color of each material. The aging process was applied in an autoclave under 134ºC, 0.2MPa pressure. For optical evaluation, L*, a*, b* values of the samples were measured by spectrophotometry before aging, after 3 hours and 6 hours aging. ΔE00 values and translucency parameters (TP) were calculated. The data were evaluated statistically.

Results: In the present study, all the materials had undergone color change as a result of aging, but this change was within acceptable limits (ΔE00 <1.8). The ΔE00 value of the ZLS was above the perceptibility threshold (ΔE00 >0.8). There was a decrease in the translucency of all materials used in the study, but this decrease was not statistically significant.

Conclusion: In the light of the findings obtained from this in vitro study, aging did not cause color and translucency changes in TMZ, ZLS, LS2 monolithic CAD/CAM materials.

Keywords: CAD/CAM, zirconia, translucency, CIE Lab, optic

1. INTRODUCTION

With the increase in aesthetic expectations of patients and the use of CAD/CAM (computer aided design and manufacture) technologies in dentistry, many new restorative materials with superior properties in terms of biocompatibility, aesthetics and function have been produced (1).

Lithium disilicate reinforced glass-ceramic (LS_2) restorations are preferred especially in anterior restorations due to their optical properties, however the most important shortcoming of these restorations is their low fracture resistance. In 2005, precrystalline IPS e.max CAD blocks containing 40% lithium metasilicate ($Li_2Si_2O_3$) and lithium disilicate ($Li_2Si_2O_5$) crystal cores were produced. Blocks with an initial blue color have a medium hardness and strength (130MPa), so they are easier to mill (2). After milling, the restoration is heated to 850°C, during this process flexural strength increases to 262±88MPa and restoration changes to the selected tooth color (3). Crystallized material contains approximately 1.5mm in size fine grainy needle-shaped lithium disilicate crystals integrated into a glass matrix at a rate of 70% by volume (4).

Zirconia is one of the materials with superior biological and mechanical properties, which contains 3 different crystal forms; monoclinic, tetragonal and cubic (5). Zirconia is a 'metastable' material that can transform from the tetragonal phase to the monoclinic phase under certain conditions. As a result of mechanical forces such as sandblasting, abrasion and heat treatments, some of the tetragonal particles turn into monoclinic particles that are larger in volume (6). This increse in volume between the monolithic crystals causes the particles to separate from the surface. (7). As a result of this separation, the surface roughness increases and microcracks are formed (8). Kobayashi et al. observed that spontaneous transformations from tetragonal phase to monoclinic phase

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occur in zirconia exposed to high humidity environment and low temperature. This phenomenon is known as 'Low temperature degradation (LTD)' or 'Hydrothermal degradation' (9). Although LTD often occurs at 200-400°C, prolonged exposure of the material to heat and moisture in the oral cavity can also cause LTD (10).

Due to zirconia's opaque appearance, it must be veneered with feldspathic porcelain to provide an acceptable aesthetic. This layered structure combines the strength of zirconia with the aesthetics of ceramic (11). However, due to ceramic chipping in veneered zirconia systems (12), more translucent monolithic zirconia (TMZ) restorations have been developed by modifying the microstructure (13). Increasing the yttria concentration is the most preferred method used for this purpose. In this way, the cubic phase amount and translucency of the material are increased. The increase in yttria content causes an increase in the amount of optically isotropic cubic phase and hence its translucency (14). A yttria content of 5% moles is defined as 'high translucent zirconia' and 8% moles as 'ultratranslucent zirconia' (15).

Zirconia-reinforced lithium silicate glass ceramics (ZLS) are new materials that can be used with CAD/CAM technology produced to combine the positive mechanical properties of zirconia with the aesthetic appearance of glass ceramics. It is obtained by strengthening the glass phase with 10% by weight of ZrO_2. After crystallization, lithium metasilicate and lithium disilicate crystals exist as a binary microstructure in the glassy phase containing 10% zirconium oxide. The crystals are 0.5-0.7 µm in size and are 4-8 times smaller in size than lithium disilicate crystals (16).

The aim of this study was to evaluate the effect of artificial aging on color and translucency of newly developed TMZ, ZLS and LS_2 CAD/CAM materials.

The null hypothesis was that no significant differences would be found in the color and transluceny of monolithic CAD/CAM materials with increasing aging time.

2. METHODS

According to the results of the power analysis performed to determine the number of samples required for this study, at least 8 samples should be taken for each of the groups with 95% confidence and 95.6% test power.

Three types of ceramic materials were used in this study; translucent monolithic zirconia (TMZ) (Cercon HT, Dentsply, Sirona, USA), zirconia reinforced lithium silicate (ZLS) (Celtra Duo, Dentsply, Hanau-Wolfgang, Germany) and lithium disilicate (LS_2) (IPS emax CAD, Ivoclar Vivadent, Schaan, Leichtenstein) (Table 1).

Table 1. *Materials used in the study and manufacturer*

	Material Type	Composition	Manufacturer	Lot No
IPS emax CAD	Lithium disilicate	%57-80 SiO_2, %11-19 Li_2O, K_2O_3, P_2O_5, ZrO_2, Al_2O_3	Ivoclar Vivadent, Schaan, Leichtenstein	Y18855 Y33214 X42738
Celtra Duo	Zirconia reinforced lithium silicate	%58 SiO_2, %18 Li_2O, %10 ZrO_2, P_2O_5, Al_2O_3	Dentsply,Hanau-Wolfgang,Germany	16002157 16004027
Cercon HT	Translucent zirconia	Zirkonyum oksit, %5 litrium oksit, hafnium oksit <%3,Al_2O_3,SiO_2<%1	Dentsply, Sirona, USA	18033377 18034109

10 disc shaped specimens (12X1.2 mm) from HT (high translucent), A2 discs and blocks of materials were prepared for each group with CAD/CAM technology. For LS_2 and ZLS discs, partially crystallized blocks were milled to cylindrical form using Cerec system (InLab MC X5 Sirona, Bensheim, Germany). Then the cylinders were sliced into discs with a low-speed water-cooled diamond saw to the designed thickness (IsoMet 1000, Buehler, Illinois, USA). After milling, the specimens were crystallized according to the manufacturer's instructions. For TMZ, specimens with the final diameter of 12 mm and the final thickness of 1.2 mm were milled (InLab MC X5 Sirona, Bensheim, Germany) and sintered in a sintering oven (MIHM-VOGT GmbH & Co. KG, Stutensee-Blankenloch, Germany) according to the manufacturer's instructions. All sample sizes were checked with a digital caliper (Insize Mini Digital Caliper Series 1111, China). Finally one side of the discs were polished with coarse, medium coarse and super fine grit ceramic polishing rubbers (Diapol HP,Eve, Ernst Vetter GmbH, Germany) and polishing paste (Renfert Polish all in one Diamond Polish, Renfert GMBH, Hilzingen, Germany).

The specimens were artificially aged in an autoclave (Goldberg, Eryiğit Otoklav A.Ş., Türkiye) at 134 °C, under 0.2 MPa for 3 and 6 hours according to ISO standard 13356 (17).

According to the CIE Lab color system developed by the Commission Internationale de l'Eclairage, international color commission; each color is expressed in terms of three components; referred to by the abbreviations L^*(brightness), a^*(red-green), and b^*(yellow-blue) (18). The vertical axis L represents the brightness or lightness coordinates of

the object between white and black, the horizontal axis a represents the chroma coordinates of the object between red and green, the horizontal axis b represents the chroma coordinates of the object between yellow and blue. The intersection of these three coordinates gives the value of that color (19). The amount of color change (ΔE_{00}) that occurs in any object after a certain period of time or as a result of an applied treatment can be calculated using L^*, a^* and b^* values.

For optical evaluation, measurements were made on the polished surfaces of the samples on white (L=92,98, a=-1,42, b=4,34) and black (L=26,38, a= 0,24, b= – 0,08) backgrounds with a spectrophotometer (CM-26d, Konica Minolta, Tokyo, Japan) before aging (baseline), after aging for 3 hours and after aging for 6 hours. L^*, a^* and b^* values were obtained. The color change (DE_{00}) of the samples was calculated with the CIEDE2000 equation. In this study, the CIEDE (1:1:1) system, in which kL, kC and kH parametric values were taken as '1', was used.

$$DE_{00}=[(DL'/k_LS_L)^2 + (DC'/k_CS_C)^2+ (DH'/k_HS_H)^2 +R_T (DC'/k_CS_C)(DH'/k_HS_H)]^{1/2}$$

In the CIE Lab system, the translucency value of an object is expressed by the translucency parameter (TP)(20). Translucency parameters were calculated with the following formula using the color difference of L^*, a^* and b^* values measured from samples on black and white backgrounds.

$$TP=[(L_{B^*} – L_{W^*})^2 + (a_{B^*} – a_{W^*})^2+ (b_{B^*} – b_{W^*})^2]^{1/2}$$

For statistical analysis the data were expressed as mean and standard deviation. The distribution normality of the variables were tested with Kolmogorov-Smirnov test. According to Kolmogorov Smirnov test, the data were not normally distributed so non-parametric tests were used for analyses. For all tests, SPSS 27.0 Statistical Software Package (IBM Corporation,New York,USA) was used and the level of significance was set at p<0.05. Kruskal-Wallis and Mann-Whitney U tests were used in the analysis of quantitative independent data, Friedman test and Wilcoxon test were used in the analysis of dependent quantitative data.

3. RESULTS

The means and the standard deviations of the L^*, a^*, b^* values are shown in Tables 2,3 and 4. No significant difference was observed between the baseline, after 3 and 6 hours of aging L^* and b^* values in TMZ, ZLS and LS_2 groups (Table 2,Table 4). In the TMZ group, no significant difference was observed between the baseline and after 3 and 6 hours of aging a^* values. In the ZLS group, 6 hours aging a^* value was significantly higher than the 3 hours aging and baseline a^* values. No significant difference was observed between the baseline and 3 hours of aging a^* values. In the LS_2 group, the 6 hours of aging a^* value was significantly higher than the baseline a^* value but 3 hours of aging a^* value did not differ significantly from baseline and 6 hours of aging a^* value (Table 3).

When we compared the ΔE_{00} values of the materials at different aging intervals; ΔE_{00} values of all groups were below acceptability threshold after aging of 3 hours and 6 hours ($\Delta E_{00} < 1.8$). Only the ΔE_{00} values of ZLS were above the perceptability threshold ($\Delta E_{00} > 0.8$). There was no significant difference between the baseline-3hours, baseline-6hours and 3 hours-6 hours ΔE_{00} values of all materials (p>0.05) (Table 5).

When we compared the TP values between groups; baseline, 3 hours and 6 hours of aging TP values were significantly higher in the LS_2 group than in the TMZ and ZLS groups before and after aging. The TP values of the ZLS group were also significantly higher than the TMZ group. No significant difference was observed between the baseline, 3 hours and 6 hours of aging TP values of TMZ, ZLS and LS_2 groups (p>0.05) (Table 6).

Table 2. *L* values of materials according to different aging times*

		Min-Max	Median	Mean ± SD	p
TMZ	Baseline L	76,1-77,2	76,5	76,5 ± 0,4	0,452 F
	3 hours L	76,3-77,2	76,8	76,4 ± 0,2	
	6 hours L	76,5-77,3	76,8	76,8 ± 0,3	
ZLS	Baseline L	72,4-74,7	73,5	73,5 ± 0,7	0,273 F
	3 hours L	72,1-74,4	73,4	73,4 ± 0,7	
	6 hours L	72,0-74,1	73,0	73,0 ± 0,6	
LS2	Baseline L	74,4-75,6	74,9	75,0 ± 0,4	0,061 F
	3 hours L	73,8-75,6	74,6	74,7 ± 0,5	
	6 hours L	73,3-76,3	74,2	74,3 ± 0,9	

[F] *Friedman*

Table 3. *a* values of materials according to different aging times*

		Min-Max	Median	Mean± SD	p
TMZ	Baseline a	2,66-3,30	2,93	2,96 ± 0,19	0,452 F
	3 hours a	2,70- 3,19	2,90	2,93 ± 0,14	
	6 hours a	2,84- 3,37	2,95	2,99 ± 0,16	
ZLS	Baseline a	0,69-1,82	1,53	1,42 ± 0,32	0,003 F
	3 hours a	1,41-1,96	1,74	1,73 ± 0,17	
	6 hours a	1,72-2,17	1,90	1,91 ± 0,15	
LS2	Baseline a	0,30- 0 53	0,38	0,40 ± 0,08	0,045 F
	3 hours a	0,10- 0,69	0,51	0,46 ± 0,17	
	6 hours a	0,39- 0,71	0,54	0,55 ± 0,13	

[F] *Friedman*

Table 4. *b* values of materials according to different aging times*

		Min-Max	Median	Mean± SD	p
TMZ	Baseline b	15,7-17,2	16,4	16,4± 0,4	0,067 F
	3 hours b	15,4-17,2	15,9	16,0 ± 0,5	
	6 hours b	15,7-16,8	15,9	16,0 ± 0,3	
ZLS	Baseline b	14,1-16,2	15,3	15,3 ± 0,6	0,150 F
	3 hours b	15,2-16,0	16,0	15,8 ± 0,3	
	6 hours b	15,0-16,3	15,7	15,7 ± 0,5	
LS2	Baseline b	13,4-14,1	14,0	13,9 ± 0,2	0,082 F
	3 hours b	13,5-14,5	14,3	14,2 ± 0,3	
	6 hours b	13,8-14,6	14,0	14,2 ± 0,3	

[F] *Friedman*

Table 5. *The ΔE_{00} values of the materials at different aging times*

		Min-Max	Median	Mean ± sd	p
TMZ	B- 3h	0,12- 0,99	0,56	0,51 ± 0,27	0,741 F
	B-6h	0,17- 1,07	0,55	0,57 ± 0,27	
	3h-6h	0,20- 1,03	0,31	0,44 ± 0,28	
ZLS	B- 3h	0,30- 1,82	0,86	0,95 ± 0,54	0,497 F
	B-6h	0,27- 2,29	0,69	0,89 ± 0,61	
	3h-6h	0,25-1,86	0,73	0,81 ± 0,46	
LS2	B- 3h	0,11-1,15	0,60	0,61 ± 0,31	0,741 F
	B-6h	0,21-1,51	0,62	0,68 ± 0,38	
	3h-6h	0,11- 1,47	0,83	0,83 ± 0,44	

[F] *Friedman*

Table 6. *TP values of materials at the end of different aging times*

		Min-Max	Median	Mean ± sd	p
TMZ	Baseline TP	6,9- 7,8	7,3	7,3 ± 0,3	0,273 F
	3 hours TP	7,2- 7,7	7,5	7,4 ± 0,2	
	6 hours TP	7,2- 7,5	7,3	7,3 ± 0,1	
ZLS	Baseline TP	14,3- 16,7	16,3	16,0 ± 0,7	0,150 F
	3 hours TP	14,4- 17,0	15,8	15,9 ± 0,8	
	6 hours TP	14,6- 16,6	15,5	15,5 ± 0,7	
LS2	Baseline TP	15,6- 17,0	16,4	16,4 ± 0,4	0, 301 F
	3 hours TP	15,2- 17,0	16,4	16,3 ± 0,5	
	6 hours TP	15,3- 18,0	16,0	16,3 ± 0,8	

[F] *Friedman*

4. DISCUSSION

The null hypothesis that aging would not affect the color and translucency of monolithic CAD/CAM materials (TMZ, ZLS and LS_2) used in the present study was accepted.

The thickness of the material used in monolithic restorations effects the optical and mechanical properties (21). Kanchanavasita et al. reported that material thickness has a significant effect on translucency, and translucency increases with decrease in thickness (22). For all-ceramic restorations, a thickness of 1-1.5mm is generally required (23). In our study the samples were prepared in a thickness of 1.2 mm in order to be similar to the crown thicknesses used in the clinic.

In addition to thickness, surface finishing processes are also effective in the translucency of ceramics (24). It has been reported that in glazed monolithic zirconia, the glaze layer wears off over time and the restoration causes wear on the opposing tooth or restoration (25). For this reason, it has been stated that polishing is a more suitable surface finishing process than glazing for zirconia restorations (26). Likewise, polishing the ZLS and LS_2 restoration surfaces is reported to be sufficient in terms of wear and plaque retention (27). In this study, mechanical polishing was applied to one surface of each sample in order to ensure standardization between the different materials used.

Materials to be used in restorative dentistry age by exposure to temperature changes, chewing forces and moisture in the oral environment, so it is very important for these materials to be aesthetically and mechanically stable as well as biocompatibility. There are many aging methods that can simulate long-term clinical conditions in a short time. One of this methods is accelerated aging in autoclave (17). Aging in an autoclave at 134°C for 1 hour is an effective method for predicting the long-term performance of materials since it is equivalent to 3-4 years of in vivo use (28). Therefore, in our study, autoclave aging was applied for 3 hours and 6 hours, reflecting the clinical use of approximately 10-20 years.

For long-term clinical success of aesthetic restorations, the color must be stable, but the color and translucency of dental ceramics is affected by hydrothermal aging (29,30). The amount of color change is interpreted according to two different threshold values: the color change value that can be noticed by 50% of the observers is defined as the 'perceptibility threshold' and the acceptable color change by 50% of the observers is defined as the 'acceptability threshold' value. Paravina et al. reported the perceptability threshold as 0.8 and the acceptability threshold as 1.8 for ΔE_{00} (31).

There are various studies evaluating the color change of all ceramics after aging. Different outcomes were reported in these studies, resulting in L^*, a^*, b^* values that increased or decreased and ΔE_{00} values that exceeded or did not exceed the acceptability threshold (32,33,34). The materials used in the studies, the aging protocols, the various color measurement devices and the accepted threshold values could all be contributing factors to the wide range of results. In our study, after 3 hours and 6 hours of aging, L^*, a^*, b^* values were affected. In general, translucent zirconia samples became lighter, more reddish, and more bluish, while ZLS and LS_2 samples became darker, more reddish and more yellowish. Zhang et al. reported in their meta-analysis study that aging for more than 20 hours caused color change in translucent zirconias above the acceptability threshold (35). Similarly, in this study, aging period was less than 20 hours; color changes in all groups were within the clinically acceptable range. However, ΔE_{00} values of ZLS samples were above the perceptability threshold. According to Gonuldas et al. thermal conditions may cause pigment destruction in dental ceramics, resulting in color instability (36).

An aesthetic restoration depends not only on the color match but also on the harmony of translucency (37). Translucency is a substance's ability to reflect some light while also transmitting some of it (38). A fully opaque material's TP value is zero. As the translucency of the material increases, the TP value also increases (20).

The TP value of LS_2 was found to be higher than TMZ which is consistent with the studies of Nassary Zadeh and Harada. (39,40). However, unlike the studies of Sen and Us, LS_2 baseline TP values were significantly higher than ZLS baseline TP values. The literature contains a wide range of results from studies on the effect of aging on translucency (33,41,42,43). According to the findings of the meta-analysis study of Zhang et al., there is a significant change in TP values when the aging time in autoclave exceeds 20 hours (35). In the present study consistent with this literature, aging for 3 hours and 6 hours caused a decrease in TP values of translucent zirconia samples, but this change was not statistically significant.

Since there is no study in the literature in which ZLS is aged in an autoclave, we compared our data with studies using similar thermal aging methods. Alp et al. subjected the ZLS and LS_2 samples to 5000 thermal cycles with coffee. They reported that LS_2 was more translucent than ZLS before and after the thermal cycle, and the thermal cycle reduced the translucency of both materials (44). Porojan et al. applied 10000 thermal cycles to ZLS and LS_2 samples. They reported that aging caused a significant decrease in TP in all samples (45). In our study, unlike these studies, aging caused a slight decrease in TP values of ZLS and LS_2 samples, however, this change was not significant. The reason why our findings were different from literature may be the different aging methods applied.

Tong et al. reported that porosity is one of the factors affecting the translucency of ceramics (46). During clinical use, a dissolution occurs in glass ceramics. The difference between the dissolution rates of the crystal and glass phases causes a rough surface to form. In zirconia ceramics, on the other hand, surface roughness may occur with the change of the volume of the crystals in the phase change regions and affect the translucency (6,29). Pereira et al. state that a smoother surface reduces hydrothermal aging by decreasing the areas that interact with water (47). In the present study, mechanical polishing was applied to TMZ, ZLS and LS_2 samples, and it was determined that there was no significant change in translucency as a result of aging, and the color difference remained at a clinically acceptable level. Based on this result, it can be concluded that the mechanical polishing of zirconia and glass ceramic materials is effective in protecting the materials from the negative effects of hydrothermal aging.

5. CONCLUSION

All the materials used in this study have undergone color change as a result of aging, but this change was within acceptable limits. Only the ΔE_{00} value of ZLS was above the perceptability threshold. There was no statistically significant difference in the amount of color change between aged TMZ, ZLS and LS_2 samples. After aging the highest TP value was found in the LS_2 group, and the lowest TP value was found in the TMZ group. The difference between groups was significant. There was a decrease in the translucency of all materials used in the study, but this decrease was not statistically significant.

In the light of the findings obtained from this in vitro study, translucent zirconia, zirconica reinforced lithium silicate and lithium disilicate monolithic ceramic materials that were used in this study were found to be optically sufficient for approximately 15 years of clinical use. However, further clinical studies are needed to support the results of our study.

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Clinical and Experimental Health Sciences

Validity and Reliability of the Turkish Version of the Postoperative Fatigue Scale

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ABSTRACT

Objective: Postoperative fatigue is an undesired and discouraging symptom that many patients experience after the surgery operation. Good assessment is essential to detect and manage this symptom. There is no specific Turkish validity and reliability measurement tool to assess postoperative fatigue. In this study, it was conducted to adapt the Postoperative Fatigue Scale (PO-FS) to Turkish in order to evaluate postoperative fatigue.

Methods: Methodological study method was applied. This study was conducted with a total of 276 patients. The data of the study were collected using the personal information form, PO-FS and Visual Analog Scale-Fatigue in April-July 2019.

Results: PO-FS sub-scales fatigue, vigor, and daily life activities have Cronbach's α coefficient of 0.873, 0.898, and 0.815, respectively. The factorial analysis revealed that three factors explain 76.344% of the total variance. These findings suggest that Turkish version of PO-FS is a valid and reliable scale.

Conclusion: PO-FS's Turkish translation is valid and can be reliably used for determining the postoperative fatigue of patients.

Keywords: Postoperative fatigue, reliability, validity

1. INTRODUCTION

Fatigue is a subjective sense of discomfort but it objectively causes the loss of ability to participate in daily life activities or normal activities (1). The term "postoperative fatigue" is defined as a discouraging symptom that may have an unpleasant effect on the patient's quality of life and it may last days after the surgery (2). After the surgery, the patients tend to experience postoperative fatigue (POF) that may last 2-4 weeks (3). POF generally affects the healthy individuals having a low level of or no fatigue in the beginning but it is directly related to surgical procedures and perioperative interventions (4,5). Delaying the mobilization, fatigue distorts the muscular function, delays healing, and increases the risk of severe complications such as pneumonia and deep vein thrombosis (6). Furthermore, fatigue may cause an individual to have various severe psychological problems such as anxiety, fear, sensuality, discomfort, sleeplessness, depression, and self-depreciation (3). It rarely threatens life and is thought to be an inevitable result of the surgery but the cumulative effect of fatigue and relevant shekels may significantly decrease the quality of life of patients and it may delay return to normal activities including working (6).

Professional healthcare team, especially the recommendations and evaluations of nurses play a significant role in patients' effective struggle with fatigue. Besides determining the time of fatigue, it is very important to determine the factors that might affect the fatigue such as surgical procedure, medications, rest, nutrition, culture, environment, psychological status, and hunger in assessing the fatigue (7). Multidimensional assessment instruments are used in POF evaluations (4).

Although there is no globally accepted standard measurement method for fatigue, various measurement instruments have been developed for assessing the fatigue. Ideally, the assessment should be performed making use of patient's own statements (8). In the literature, it is stated that analog

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or digital scales (Brief Fatigue Inventory) as well as more complex multidimensional scales (Piper Fatigue Self-Report Scale, Visual Analog Scale for Fatigue) are used to evaluate fatigue (9). However, POF assessment is made using the fatigue scale or the Quality of Life (QoL) scales that assess fatigue in the sub-dimension (4). Fatigue assessment tools are also discussed in studies evaluating fatigue in various diseases (10). According to a recent POF (4) review, there are two scales that can assess POF and they are; Fatigue Questionnaire (FQ) by Chalder et al. (11) and Identity Consequence Fatigue Scale (ICFS) by Paddison et al. (12). Nøstdahl et al. (2016) developed the 10-item postoperative fatigue scale of the ICFS to be practical in clinical use and to minimize patient burden (5). Although there are fatigue scales, which assess the severity of patients' fatigue and reliability and validity of which have been tested in Turkish population (13,14), there is no specific assessment tool to assess the postoperative fatigue of individual. For this purpose, a practical postoperative fatigue scale was developed by Nøstdahl et al. (2016) to evaluate the postoperative fatigue status of patients (5).

This study, it was aimed to test the validity and reliability of "Identity-Consequence Fatigue Scale" (ICFS), which has been developed by Nøstdahl et al. (5), in Turkish population.

Research questions;

Is PO-FS a valid measurement tool in Turkish society?

Is PO-FS a reliable measurement tool in Turkish society?

2. METHODS

2.1. Design

The present study employs descriptive and methodological design. Before the study, an e-mail was sent to Torkjell Nøstdahl, one of the developers of scale, for obtaining the written approval and a briefing on and assessments about the scale were obtained. Before the study, the approval was obtained from Aksaray University Human Research Ethics Committee (date 26.09.2018; protocol no:2018/183) and from the institution. Participation in the study was the verbal consents of patients were obtained after informing them about the study.

2.2. Participants

The present study was carried out on the patients, who have undergone surgery between April and July 2019 in surgical departments of a training and research hospital (orthopedics, neurosurgery, general surgery, plastic surgery, otolaryngology, cardiovascular surgeon, and urology). The inclusion criteria for this study; (1) age of ≥18 years, (2) being on minimum 3rd postoperative day, (3) being able to communicate in Turkish language, (4) having no psychiatric or cognitive disorder, (5) having no history of severe auditory deficiency reported in clinical records, (6) operation under general anesthesia and being classified in Group 1 or Group 2 according to American Society of Anesthesiologists (ASA) classification. The study was completed with a total of 276 patients.

2.3. Data Collection Tools

"14-Item Introductory Information Form" containing items about age, gender, marital status, previous surgeries, hospital experience, type and duration of surgery, and "Postoperative Fatigue Scale (PO-FS)" and "Visual Analog Scale (VAS)" were used.

Postoperative Fatigue Scale (PO-FS): Postoperative fatigue scale was developed by Nøstdahl et al. in 2016 (5) as the 10-item short form of perioperative fatigue scale developed by Paddison et al. (2006) (12). PO-FS was divided into 10 items and 3 subscales measuring three dimensions of postoperative fatigue. The subscales are fatigue (Items 2, 4, 5, and 6), vigor (Items 1, 3, 7), and daily life activities (Items 8, 9, and 10). Each item is scored between 0 and 5 points. Cronbach's α coefficients were found to be 0.90 for fatigue, 0.84 for vigor, and 0.73 for daily activity (5).

Visual Analog Scale (VAS): Visual Analog Scale is a scale developed by Price et al. (15). VAS was used in many studies for subjectively assessing the severity of pain and it was proven to be valid and reliable. The VAS was used to assess fatigue. The scale is with evaluates fatigue on a 10-cm ruler between "0 = not fatigue" and "10 = higher the fatigue." (16).

2.4. Data Collection

The data collection was performed with patients by the researcher in surgical clinics 72 hours after the surgery. Patients answered the items of Postoperative Fatigue Scale in approx. 12 minutes. The application of all the questionnaire forms took approx. 15 minutes.

2.5. Data Analysis

The adaptation steps of the scale into Turkish were carried out in accordance with the literature on this subject (17-20). The coding and statistical analyzes of the data were performed using Statistical Package for the Social Sciences for Windows (SPSS) and Analysis of Moment Structures (Amos) statistical package programs. Exploratory factor analysis and confirmatory factor analysis were used for the validity and reliability of the scale, Pearson correlation technique was used to determine the item-total score correlation, and Cronbach's reliability coefficient analysis was used to determine the internal consistency of the scale. Before the factor analysis, Kaiser–Meyer–Olkin (KMO) and Barlet tests were used for determining the sample sufficiency and suitability for factor analysis.

2.5.1. Content validity: Content validity is an indicator of how well the items of a survey reflect the intended concept. In the literature, it is stated that the indicating consensus among experts is 0.80 of content validity value (18).

2.5.2. Construct validity: Construct validity the Spearman coefficient was used to measure the strength and direction

of the monotonic relationship between two variables. Correlation coefficients > 0.5 indicate strong correlation, 0.3–0.5 moderate, and <0.3 weak correlation (19). Construct validity can be measured by hypothesis testing and structural validity (17). Construct validity was assessed by performing hypothesis testing against VAS-fatigue scores in the questionnaire using a Spearman's rank correlation. The hypothesis in this study was that there would be a strong correlation between PO-FS sub-dimensions and VAS-fatigue, as the two scales measure similar constructs. Structural validity was evaluated by exploratory factor analysis in the postoperative period 276 patients.

2.5.3. Internal consistency: Internal consistency was calculated Cronbach's alpha to determine internal consistency. Cronbach's α values 0.70 or more were regarded as acceptable (21).

2.5.4. Test-retest measurement: Test-retest measurement is a method used to examine the temporal stability and result consistency of a measurement tool in different time intervals (22). In the literature, it is stated that the minimum score of acceptable test-retest reliability is 0.70 (23).

3. RESULTS

The mean age of 276 patients (157 [% 56.9] female, 119 [% 43.1] male) participating in the study was found to be 53.59 ± 17.52 years. The demographic characteristics and the types of operations are presented in Table 1.

In Table 1, it is stated that the mean score of PO-FS's vigor subscale was 58.40±19.91, that of fatigue subscale was 42.68±20.47, and that of daily activity subscale was 27.19±27.52.

3.1. Content Validity

An important stage of the study process is language validation. Translating a scale into another language may change the nature of the scale due to differences in expression. Careful evaluation of the scale items is important in adapting the scale to a new culture (20,24). The three methods used to translate the original scale into the target language are one-way, group and reverse translation. The most widely used method to ensure intercultural equality among these methods is the "reverse translation" method (24). In this study, the reverse translation method was used. It was translated from English to Turkish by the researchers to test the validity of the adaptation of the PO-FS to Turkish culture. After reviewing the translated forms, the final form of questionnaire was obtained. Then, the translated form was translated to English by 2 linguists having command of both languages. It was also translated by another linguist from English to Turkish. It was determined that the meanings of the items did not change between the original scale and its Turkish translation. Finally, the Turkish grammar control of the scale was performed by a Turkish language specialist.

Table 1. *Socio-demographic characteristics of participants (N=276)*

Characteristics		
Age (Mean±SD) (Min-Max)	53.59±17.52 (18-96)	
Duration surgery;hour (Min-Max)	1.58±0.88 (0.30-5.0)	
Subscales of the Questionnaire		
Vigor	58.40±19.91 (0-100)	
Fatigue	42.68±20.47 (0-100)	
Daily activities	27.19±27.52 (0-100)	
	N	**(%)**
Gender		
Female	157	56.9
Male	119	43.1
Marital status		
Married	222	80.4
Single	54	19.6
Education status		
Not literate	72	26.1
Literate	34	12.3
Primary education	95	34.4
High school	26	9.4
University	49	17.8
Occupation		
Not working	185	67.0
Worker	50	18.1
Officer	12	4.3
Self-Employment	11	4.0
Retired	18	6.6
Chronic disease		
Yes	124	44.9
No	152	55.1
Use drugs		
Yes	135	48.9
No	141	51.1
Previous surgery		
Yes	143	51.8
No	133	48.2
Surgery performend		
Nose Surgery	10	3.6
Tonsillectomy	5	1.8
Prosthetic Surgery	67	24.3
Other Oprtopedic Surgeries	16	5.8
Plastic Surgery Operations	10	3.6
Breast Surgery Mastectomy	1	0.4
Obesity Surgery	12	4.3
Other General Surgery Operations	40	14.5
Coronary Artery Bypass Graft Surgery	4	1.4
Other Cardiovascular Surgery Operations	9	3.3
Brain Surgery Medium Group Surgeries	67	24.3
Urology Medium Group Operations	20	7.2
Urology Minor Operations	15	5.5
The ASA score		
Group 1	176	63.8
Group 2	100	36.2
Total	**276**	**100.0**

ASA. American Society of Anesthesiolgist; SD. standard deviation

The content validity index was used for validating the linguistic and cultural equivalency of the items and content values by making use of quantitative values, as well as accurately assessing the opinions of experts. The opinions of 7 experts were obtained in total. In parallel with the expert opinions, no items were removed from the questionnaire. The understandability was tested by applying the questionnaire to 15 patients that were not involved in the present study. It was determined in the preliminary application group that the statements in the questionnaire were understandable.

Table 2. *Total item correlations and cronbach's a coefficients of the questionnaire*

Items	Average of scale if item is removed	Variance of scale if the item is removed	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha If Item Deleted
1.	17.86	62.00	0.740	0.654	0.903
2.	18.83	59.52	0.753	0.613	0.902
3.	17.88	61.81	0.733	0.675	0.904
4.	18.43	60.89	0.748	0.677	0.903
5.	18.49	61.85	0.706	0.575	0.905
6.	18.74	60.04	0.690	0.510	0.906
7.	17.79	60.64	0.752	0.709	0.902
8.	19.57	63.50	0.577	0.441	0.912
9.	19.53	63.98	0.566	0.492	0.913
10.	19.45	61.34	0.616	0.571	0.911

3.2. Internal consistency

Scale's total correlation scores, and Alpha values are presented in Table 2. PO-FS Turkish Form's total item correlation scores ranged from 0.566 to 0.753 points. Cronbach's coefficient was found to be 0.862 for the whole scale, 0.873 for the fatigue, 0.898 for the vigor and 0.815 for the daily activity subscale (Table 3).

Table 3. *Factor structure and explotary variance values of the scale*

Factors	Items	Cronbach alpha	Factors Loading
Factor 1	4. I have been feeling fatigued	0.873	0.791
	5. Physically. I have felt tired		0.766
	6. I have had to restrict how much I try and do in a day		0.701
	2. I have been feeling worn out		0.699
Factor 2	3. I have been feeling vigorous	0.898	0.806
	7. I have been feeling lively		0.805
	1. I have been feeling energetic		0.798
Factor 3	8. Read a newspaper/book or watch TV	0.815	0.748
	9. Dress		0.826
	10.Visit or socialize with family and friends		0.842
Total Cronbach alpha		0.862	
Total Variance	**%** 76.344		

3.3. Exploratory factor analysis

Analysis, KMO and Bartlett tests were applied before factor analysis to evaluate sampling adequacy and factor suitability. The KMO value was found to be 0.908. This value shows its suitability for the analysis of the principal components. Thus, the result of Barlett's sphericity test was found to be statistically significant. The result of the test shows that the data are interrelated and suitable for factor analysis.

As a result of exploratory factor analysis (EFA), the three-dimensional structure of the scale was obtained. The factor loads were found to range between 0.798 and 0.806 for vigor subscale, 0.699 and 0.791 for fatigue dimension, and 0.748 and 0.842 for daily activity dimension. Moreover, it was determined that the scale was explaining 76.344% of the total variance (Table 3).

The three-dimensional structure of the scale was confirmed using the Confirmatory Factor Analysis (CFA). The factor loads were found to range between 0.84 and 0.88 for vigor dimension, 0.73 and 0.86 for fatigue dimension, and 0.70 and 0.86 daily life dimension. As a result of CFA, the result of the goodness of fit of scale; index values X^2 / standard deviation = 2.117, Goodness of Fit Index (GFI) = 0.955, Adjusted Goodness of Fit Index (AGFI) = 0.923, Comparative Fit Index (CFI) = 0.979, Root Mean Square Error of Approximation (RMSEA) = 0.064.

Figure 1 shows that the factor loadings of PO-FS vary between 0.70 and 0.88. As a result of the scale's test-retest analysis, it was determined that there was a positive correlation between the first and second applications of the scale (r = 0.973, p = 0.01).

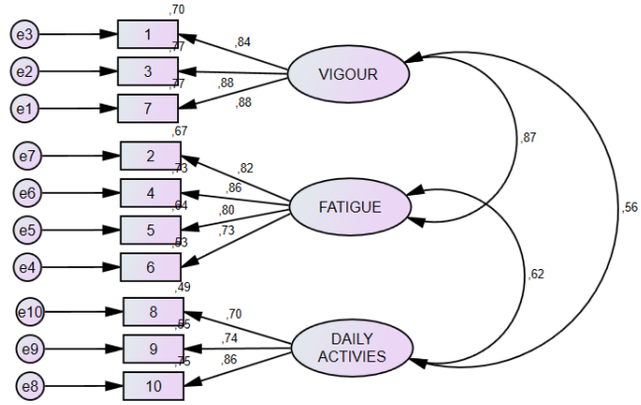

Figure 1. *The path diagram for Postoperative Fatigue Scale Turkish version.*

3.4. Correlation between PO-FS and VAS-Fatigue

To test concurrent validity, the scale is applied concurrently with another previously validated scale that examines the same or related construct. This shows how useful it is to predict a measure such as predictive validity. As post-operative fatigue status may differ between patients,

the VAS-Fatigue was used as a second scale to assess the reliability of the PO-FS. As a result of the analysis, a positive correlation was found between the mean scores of VAS-Fatigue and the mean scores of all PO-FS subscales (Table 4).

Table 4. *Parallel forms equivalence results*

Subscales of the Questionnaire		VAS Fatigue
Vigor	r	0.573
	p	0.01
Fatigue	r	0.772
	p	0.01
Daily activities	r	0.362
	p	0.01

PO-FS Postoperative Fatigue Scale; VAS Visual Analog Scale

4. DISCUSSION

Postoperative fatigue is one of the negative events after major and minor surgical operations[6]. Although there are scales measuring the fatigue severity of the patients in Turkish population (13,14), there is no specific assessment tool to assess the postoperative fatigue level of an individual. Therefore, this study was conducted to test the validity and reliability of the Turkish version of the PO-FS.

In order for an assessment tool to be considered sufficient, Cronbach's coefficient should be as close to 1 as possible (19,25,26) or the values equal to or higher than 0.7 were accepted to indicate a good reliability (27). In the present study, Cronbach's coefficient was found to be 0.86 for PO-FS in total, 0.89 for vigor subscale, 0.87 for fatigue subscale, and 0.81 for daily activity subscale (Table 3). As a result of the reliability analysis, the alpha coefficients were found to be higher than 0.80 for each of the subscales. It suggests that the scale is reliable (27). Nøstdahl et al. tested PO-FS by applying to the patients before and after the surgery (5). For the postoperative application of PO-FS, the Cronbach's coefficients were found to be 0.84 for vigor subscale, 0.90 for fatigue subscale, and 0.73 for daily activity subscale.

In this study, factor loads of all items ranged from 0.69 to 0.84 (Table 3) and between 0.54 and 0.96 in the study carried out by Nøstdahl et al. (5). These results show that the items of PO-FS have a high level of factor loads.

In the present study carried out on the adaptation of PO-FS to Turkish, 76.34% of the total variation was explained. The same value was 74.7% in the study of Nøstdahl et al. (2016) (5). In addition, the results of the explained variance ratio show that the PO-FS consists of 3 subscales and the factor load is sufficient as in the original form of the scale. Index values X^2 / standard deviation = 2.117, GFI = 0.955, AGFI = 0.923, CFI = 0.979, RMSEA = 0.064. When the goodness of fit indices of the model are examined, it is seen that the value of X2 /df is 2.117. Models where this value is <2 for the normal value and <5 for the acceptable value are considered good models (28). On the other hand, the GFI value, which is an important indicator of model fit and expected to show a value of .90 for an acceptable model (29), was found to be .95 in this study. In validity and reliability studies, RMSEA values between 0.050 and 0.080 are acceptable. Currently, the values obtained in our study include acceptable goodness-of-fit values (28,29). It was determined as a result of EFA that the goodness of fit was achieved. The relevant fit index values show that the form is acceptable (30).

A positive correlation was found between the two scales in comparison with the VAS-Fatigue scale to test the stability of the PO-FS (Table 4). Nøstdahl et al. (2016) (5) also used second form for reliability method with 31-item ICFS and, when compared to the original 31-item scale, they found that 98% of the change in total fatigue score between preoperative and postoperative periods was maintained. Thus, these results show that 10-item Short Form PO-FS is a valid and reliable instrument to use in researches.

This study had some limitations. In this study, sample included of a single research hospital in a city in Turkey. Further studies are needed with operation patients hospitalized in different hospitals in different geographic regions of Turkey.

5. CONCLUSION

PO-FS can be used for Turkish culture because it was translated to Turkish language using the content reliability and inter-observer reliability criteria and no difference was found between the experts' opinions on the items of PO-FS. PO-FS's Turkish form's total item correlation scores range between 0.566 and 0.753. From this aspect, the Turkish form's total item correlation values were found to be at the reliability level. The results of reliability analysis showed that the alpha coefficient of each dimension was higher than 0.80. In conclusion, PO-FS can be used for assessing the postoperative fatigue level of patients after a surgical intervention.

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Clinical and Experimental Health Sciences

Hyaluronic Acid-Curcumin Complex Triggers Apoptotic Pathway in Breast Cancer Cells via CD44 Receptors

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ABSTRACT

Objective: Curcumin (CUR) was modified with hyaluronic acid (HA) to increase its water solubility and bioavailability. Our aim was to increase the uptake of CUR into the cells that express CD44 receptors and to compare the cellular effects in two different human breast carcinoma cells, MCF-7 and MDA-MB-231.

Methods: Hyaluronic acid-curcumin complex (HA-CUR) was synthesized and characterized. MCF-7 and MDA-MB-231 cells were grown under appropriate conditions and the effect of CUR and HA-CUR on cell viability was determined. Apoptosis levels of cells after treatment with CUR and HA-CUR were also measured. CD44 receptor levels of both cells were compared and then apoptosis levels were measured in MDA-MB-231 cells after saturation of CD 44 receptors with HA. In both cells expression of caspase-9 and PARP was analyzed to confirm apoptosis.

Results: In MCF-7 cells, the percentage apoptosis level of the CUR group was slightly lower than the HA-CUR group. In MDA-MB-231 cells, no statistically significant difference was found in the CUR group compared to the control group, but the apoptosis level of the HA-CUR group was higher than the control group. CD44 receptor levels were higher in MDA-MB-231 cells compared to MCF-7 cells. Blocking the CD44 receptors reversed the apoptotic effect of HA-CUR in MDA-MB-231 cells. Both CUR and HA-CUR had apoptotic effects in MCF-7 and MDA-MB-231 cells.

Conclusion: Conjugation of CUR with HA, which is specific for CD44 receptors, aids in its entry to target cells making it a powerful agent for targeted cancer therapy.

Keywords: Hyaluronic acid, Curcumin, MCF-7, MDA-MB-231, CD44 receptor.

1. INTRODUCTION

Curcumin (CUR) is a yellow pigment of the spice turmeric (*Curcuma longa*) which is chemically known as diferuloylmethane. It exhibits different pharmacological activities including those against oxidation, infection, atherosclerosis, and various cancers (1). At the molecular level, CUR has anti-inflammatory activity through the suppression of numerous cell-signaling pathways. However, properties such as lack of water solubility, poor stability, and low absorption rates have limited the clinical application of CUR (2).

Hyaluronic acid (HA), also known as hyaluronan, is a negatively charged water-soluble natural chain polysaccharide. It can interact specifically with CD44 receptors that are over-expressed in some cancer cells suggesting its use as an effective anti-cancer agent (3). HA has been used to modify CUR via covalent bonding and the amphiphilic polymer obtained by combining HA and CUR will self-assemble into nanoparticles in aqueous media (4). HA-specific receptor CD44 can be expressed on the surface of different cancer cells (5, 6).

In this study, we have modified CUR with HA in order to increase its water solubility and bioavailability. Our aim was to increase the uptake of CUR into the cells that express CD44 receptors and to compare the cellular effects in two different human breast carcinoma cells, MCF-7 and MDA-MB-231.

2. MATERIALS AND METHODS

Hyaluronic acid (HA) was purchased from Contipro Inc. (Dolni Dobrouc, Czech Republic). Curcumin (CUR, Sigma Cat. No.: C1386), 4-Dimethylaminopyridine (DMAP), N,N′-Dicyclohexylcarbodiimide (DCC), Dimethyl sulfoxide (DMSO) and Pefabloc were purchased from Sigma (Darmstadt, Germany). All reagents were used without further purification and were of HPLC or analytical grade. ApopNexin Annexin V-FITC apoptosis detection kit was from Merck

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Millipore (Darmstadt, Germany). Anti-PARP, anti-Caspase-9 and anti-IgG antibodies were purchased from Cell Signaling Technology (Boston, MA, USA).

2.1. Synthesis and Characterization of HA-CUR

HA-CUR was obtained as described by Manju and Sereenivasan (7). Figure 1 summarizes the process. Firstly, 80 mg of HA was dissolved in 8 mL of 1:1 H_2O/DMSO mixture and then 10 mg of DCC and 4 mg of DMAP were added. The solution was stirred for 1 h to activate the carboxylic group of HA. Then, 375 mg of CUR was dissolved in 5 mL of DMSO and slowly added to the above solution under nitrogen and the mixture was stirred well at 60–65°C for 6 h. The resultant solution was dialyzed using 3.500 Da MWCO dialysis kit (Sigma, PURX35005) against DMSO for 1 day and then against ultra-pure water for 3 days. Finally, HA-CUR was lyophilized and kept under refrigeration. Zeta potential, size distribution and polydispersity index (PDI) of HA-CUR were determined at 25°C using Zetasizer Nano ZS90 (Malvern Instruments, Worcestershire, UK). The concentration of CUR in HA-CUR was determined by spectrophotometric measurement. A stock solution of 1.0 mg/mL CUR was prepared in DMSO. From this solution, working standards were obtained by diluting 0.04, 0.08, 0.12, 0.24, 0.48, and 0.72 mL with 10 mL of DMSO. Maximum absorbance of CUR over the wavelength range 300-700 nm was observed at 440 nm. Absorbances measured at this wavelength were used to construct a calibration curve. Then 10 mg of HA-CUR was dissolved in 10 mL of PBS and its absorbance at 440 nm was used to calculate the CUR content.

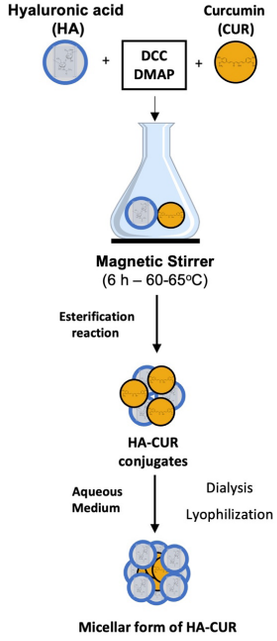


Figure 1. *Summary of the process used to obtain HA-CUR.*

2.2. Cell Culture

Breast cancer cell lines, MCF-7 (ATCC®; HTB22™) and MDA-MB-231 (ATCC®; HTB26™) were cultured in RPMI-1640 and minimum essential medium (DMEM), supplemented with 1% glutamine, penicillin (10,000 U/mL), streptomycin (10 mg/mL), and 10% fetal bovine serum (FBS). Cells were maintained at 37°C in a humidified atmosphere containing 5% CO_2.

2.3. Measurement of Cell Viability

The stable tetrazolium salt of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was used to determine cell viability (8). MTT assay is a quantitative and sensitive method which measures the growth rate of cells. Cells were seeded into 96-well plates (6,500 cells/well) containing 100 µL of medium/well and incubated at 37°C to adhere. A medium containing 0.1% DMSO with cells was used as a control. The next day, CUR and HA-CUR were applied (0, 2.5, 5, 15, 20, 30, 40, 50 µg/mL). The effects on cell viability were determined at the end of 24 and 48 h by adding 10 µL of MTT solution. Cells were further incubated at 37°C for 3 h and their absorbance was measured at 570 nm. The absorbance is directly proportional to the number of viable cells.

2.4. CD44 Surface Receptors

The amount of CD44 receptors on the surface of MCF-7 and MDA-MB-231 cells was determined by indirect staining. Three tubes were prepared for each measurement and 200,000 cells/well were added to each tube. The first tube was used to locate the cells in the FSC-SSC panel and was not stained. The second tube was stained with the secondary antibody and used for non-specific binding. CD44 was determined by adding the first and second antibodies to the third tube. The tubes were incubated for 15 min at room temperature after adding 5 µL of the first antibody. Then 5 µL of FITC-labeled secondary antibody was added, the tubes were further incubated at room temperature in the dark for 10 min and analyzed by flow cytometry (BD Bioscience, FACSCalibur, CA, USA).

2.5. Detection of Apoptosis

ApopNexin FITC Apoptosis Detection Kit was used for detection of apoptosis after CUR and HA-CUR administration. MCF-7 and MDA-MB-231 cells were seeded in 6-well plates (200,000 cells/well), then CUR and/or HA-CUR (15 µg/mL) were added. After 48 h, cells were removed from the plates and suspended in 5 mL tubes containing the Annexin V binding buffer. Then 5 µL Annexin V and 10 µL PI solutions were added to 100 µL of cell suspension. Cells were gently vortexed and incubated for 15 min at room temperature in the dark. Finally, 400 µL of Annexin V binding buffer was added to each tube and flow cytometric analysis was performed. In each trial 10,000 cells were counted and run

in 3 replicates. Results were evaluated using the CellQuest program (Becton Dickinson, FACSCalibur, USA).

In MDA-MB-231 cells, apoptosis detection was also performed after saturating the CD44 receptors. For this purpose, cells were seeded in 6-well plates (200,000 cells/well) and left to adhere for 24 h. Then HA that was used for conjugation was added to saturate the CD44 receptors (10 µg/mL in fresh medium). The medium containing HA was removed after 24 h and refreshed with CUR and/or HA-CUR containing medium. Cells were further incubated for 48 h before detection of apoptosis as described above.

2.6. Western Blot Analysis

Western blot analysis of caspase-9 and poly (ADP-ribose) polymerase (PARP) expression was performed as described earlier in (8). Cells were seeded in 60 cm culture dishes ($2x10^5$ cells) and their protein was extracted with the lysis buffer. Protein concentration was determined with BCA Protein Assay kit (Pierce Chemical, USA) and approximately 40 µg of total protein was loaded to each well. Detection was performed using the West Pico chemiluminescent substrate kit (Thermo Scientific, USA) and the ChemiDoc MP System (Bio-Rad, USA).

2.7. Statistics

Statistical analysis was performed using GraphPad Prism 7.0 (San Diego, CA, USA). All results represent the mean ± SD of three independent experiments. Significance was tested using either a two-tailed Student's t-test or one-way ANOVA.

3. RESULTS

Maximum absorbance of curcumin was at 440 nm. Absorbances were measured at this wavelength and the standard curve of curcumin was obtained (y=0.001x + 0.0131, R^2=0.9994). Then 10 mg of HA-CUR was dissolved in 10 ml of PBS and its absorbance was measured. The amount of curcumin contained in HA-CUR was calculated using the standard curve and found to be half of the CUR added. The size distribution and zeta potential of HA-CUR were measured. The mean zeta potential, the mean intensity value and polydispersity index (PDI) were – 14.11 mV, 434.33 and 0.761 (n=3), respectively.

3.1. Cell Viability

MCF-7 and MDA MB-231 cells were grown as described in methods. The effect of CUR and HA-CUR on cell viability was investigated in a dose and time-dependent manner (Figure 2). In MCF-7 cells, at 15 µg/ml dosage and after 24 h, cell viability was 75.85% in the CUR treated group, while it was 68.77% in the HA-CUR group. After 48 h, these values were 94.07% and 91.94%, respectively. In MDA-MB-231 cells, at 15 µg/ml dosage and after 24 h, cell viability was 64.90% in the CUR treated group, while it was 17.83% in the HA-CUR group. After 48 h, these values were found to be 56.17% and 41.08%, respectively.

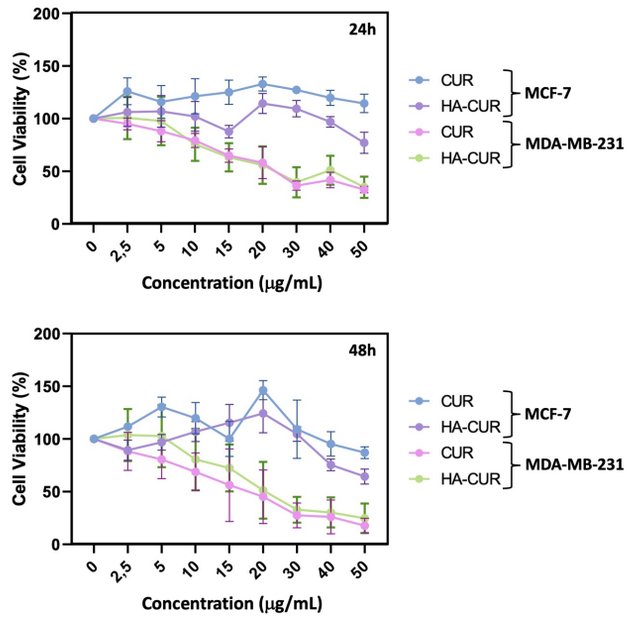


Figure 2. *Effect of CUR and HA-CUR on cell viability in MCF-7 and MDA-MB-231 cells: A) 24 h; B) 48 h. Values are expressed as the mean ± SD of three determinations.*

3.2. CD44 Receptor Levels of MCF-7 and MDA MB-231 Cells

MCF-7 and MDA MB-231 cells were stained with FITC-labeled anti-CD44 antibody and analyzed by flow cytometry (Figure 3). CD44 receptor levels were approximately 6 times higher in MDA-MB-231 cells (917.56%) compared to MCF-7 cells (152.52%).

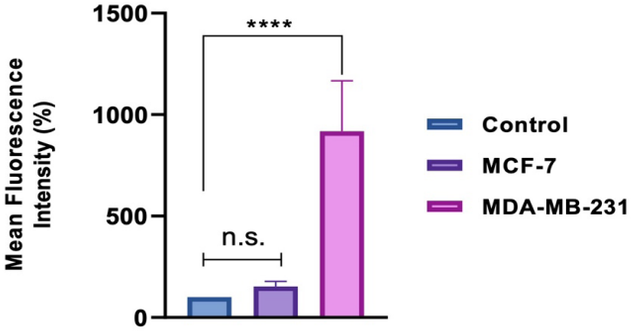


Figure 3. *CD44 surface receptor levels of MCF-7 and MDA-MB-231 cells. Values are expressed as mean ± SD of three determinations. ****p<0.0001. One-way ANOVA with Tukey multiple comparisons test was used.*

3.3. Effect of CUR and HA-CUR on Apoptosis of MCF-7 and MDA MB-231 Cells

The apoptotic effect of CUR and HA-CUR at 15 µg/ml dosage and after 48 h is shown in Figure 4. In MCF-7 cells, percentage apoptosis level of the CUR group was slightly lower than HA-CUR group (11.93 vs 17.63). There was no statistical difference between control and other groups. In MDA-MB-231 cells, no statistically significant difference was found in the CUR group compared to the control group (10.02 vs 14.27). The apoptosis level of the HA-CUR group was approximately 2.5-times higher than the control group (34.47 vs 14.27).

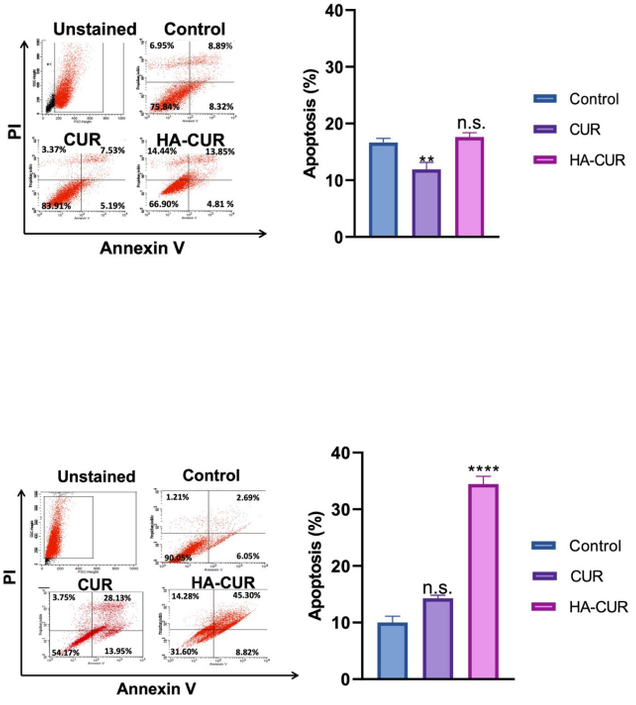


Figure 4. *Percentage apoptosis levels of A) MCF-7 cells and B) MDA-MB-231 cells after treatment with CUR and HA-CUR. Representative images and quantitative results of analysis are given. Cells were classified as live cells (Annexin V-, PI-), apoptotic cells (Annexin V+, PI – and Annexin +, PI+), and necrotic cells (Annexin V-, PI+). Values are expressed as mean ± SD of three determinations. **p<0.01; ****p<0.0001; n.s. p>0.05 vs control. One-way ANOVA with ordinary multiple comparisons test was used.*

3.4. Saturation of CD44 Receptors in MDA-MB-231 Cells

Figure 5 shows the results of CD44 receptor saturation in MDA-MB-231 cells. The percentage apoptosis of non-saturated control group (Control-NS) was 6.91% and that of saturated control group (Control-S) was 12.18%. There was a slight difference between these two groups (p=0.012). There was no statistically significant difference between the apoptosis levels of Control-S and HA-CUR-S (p=0.933). But apoptosis level of HA-CUR-S (24.07%) was significantly higher (p=0.0052) than that of HA-CUR-NS (13.00%).

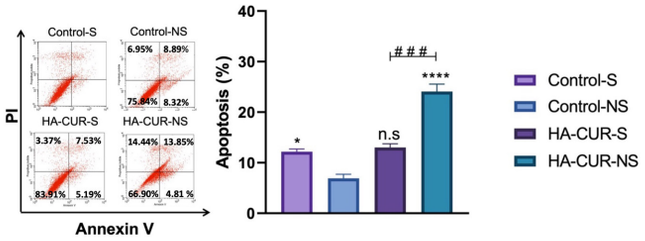
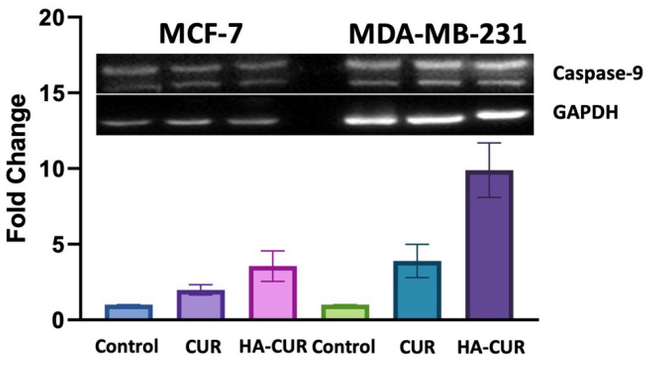


Figure 5. *Analysis of apoptosis in MDA-MB-231 cells before and after saturating the CD44 receptors.* Positive control cells were incubated with HA whereas negative control cells were not. *p<0.05; *****p<0.0001; vs control-NS*
n.s. p>0.05 vs control. ### p<0.001; HA-CUR-NS vs HA-CUR-S. One-way ANOVA with TUKEY multiple comparisons test was used.

3.5. Western Blot Assay

The results of Western blot analysis are shown in Figure 6. Cleavage of caspase-9 confirmed apoptosis in both cancer cell lines. Caspase-9 was cleaved from 35 kDa to 37 kDa when the cells were exposed to CUR. In MCF-7 cells, caspase-9 expression was increased 1.98 fold in the CUR group compared to control group. It was also increased 3.55 fold in the HA-CUR group. In MDA-MB-231 cells, the fold values of the same groups were determined as 3.88 and 9.88, respectively. Treatment with CUR upregulated cleaved caspase-9 in both cell lines compared to controls, confirming our apoptosis results. Up-regulation was approximately 3 times higher than MCF-7 cells in MDA-MB-231 cells. PARP expression was 0.324 fold lower than the control group in MCF-7 cells with HA-CUR application. PARP expression was 1.38 fold higher in the CUR group while it was 2.49 fold higher in the HA-CUR group compared to the control group in MDA-MB-231 cells.



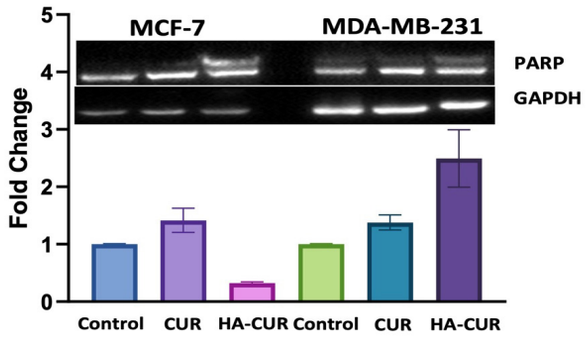


Figure 6. *Western blot analysis of caspase-9 and PARP protein expression after CUR and HA-CUR treatment in MCF-7 and MDA-MB-231 cells.* Band intensity was analyzed by densitometry. Fold changes of protein expression levels were calculated after bands were normalized to GAPDH.

4. DISCUSSION

Curcumin has been widely investigated as a drug candidate against various cancers. However, the molecule has poor bioavailability and stability in aqueous media at neutral pH values. In this study, we have conjugated CUR with HA to improve its water solubility and bioavailability. HA was chosen considering its affinity towards the cell-specific surface marker CD44. The conjugate (HA-CUR) was found to carry a net negative charge showing that HA molecules conveniently covered CUR. HA-CUR also formed micelles in aqueous media due to its amphiphilic character. Particle size distribution and polydispersity index determined by light scattering were found to be compatible with previous reports (7).

Anti-proliferative, anti-angiogenesis and anti-metastatic effects of CUR on cancer cells are gained by targeting signaling molecules such as growth factors, cytokines, transcription factors and genes modulating cellular proliferation and apoptosis (9). Hu et al. (10) reported that CUR is more active on breast cancer cells that are ER+, such as MCF-7 with regards to the ER – cells, such as MDA-MB-231. CUR induces apoptosis by regulating the expression of apoptosis related proteins in cancer cells (11, 12). In our study, the effect of CUR and HA-CUR on cell viability was determined in MCF-7 and MDA-MB-231 cells. In previous studies it was observed that CUR decreased the viability of K562 cells after 48 h (13). Similar studies exist in the literature reporting changes after 48 h in MCF-7 and MDA-MB-231 and cells (14). Therefore, we decided to use 15 µg/ml dosage and 48 h to further determine the apoptotic effects of CUR and HA-CUR. In MCF-7 cells, percentage apoptosis level of the CUR group was slightly lower than HA-CUR group and there was no statistical difference between control and other groups. In MDA-MB-231 cells, no statistically significant difference was found in the CUR group compared to the control group but the apoptosis level of the HA-CUR group was 2.5-times higher than the control group.

Yang, et al. (15) suggested that the apoptotic effect of CUR would increase when it enters the cell by receptor-dependent endocytosis. We have determined that CD44 receptor levels were 6 times higher in MDA-MB-231 cells compared to MCF-7 cells. In a previous study (16), the effects of receptors on metastasis was evaluated by comparing luminal breast lines in terms of CD44 and CD24 receptor amounts. Similar to our results, CD44 receptor levels were higher in MDA-MB-231 cells compared to MCF-7 cells suggesting that the metastatic ability of the cells decreased via this receptor. In order to validate the role of CD44 receptors on the apoptotic effects of CUR and HA-CUR, we have first saturated the receptors on MDA-MB-231 cells with HA and apoptosis measurements were then repeated. We observed that blocking the CD44 receptors reversed the apoptotic effect, suggesting the increased apoptosis levels in MDA-MB-231cells with unblocked receptors were related to the facilitated entry of HA-CUR through receptor-mediated endocytosis. HA induced apoptosis in all groups where CD-44 receptors were blocked. This finding is in accordance with previous reports showing that saturating CD44 receptors with low molecular weight HA can induce apoptotic pathways (17, 18).

Western blot experiments were conducted to confirm our apoptosis results. When the cells were exposed to CUR, Caspase-9 was cleaved from 35 kDa to 37 kDa. Treatment with CUR up-regulated cleaved caspase-9 in both cell lines. Up-regulation was 3 times higher in MDA-MB-231 cells. Hu et al. (10) reported that CUR inhibits Akt/mTOR phosphorylation pathway and suppresses expression of BCL2, an anti-apoptotic protein, and induces expression of BAX, an apoptotic protein that cleaves caspase-3. CUR also elevates Bax and p21 and decreases Bcl2 and p53 and NF-κBp65 levels in MDA-MB-231 cells (19). Increasing Bax/Bcl-2 ratio also results in the inhibition of cancer cell proliferation (20). All of these changes are clearly related to increased apoptosis levels we have observed after CUR treatment.

5. CONCLUSION

We have observed that both CUR and HA-CUR induced apoptosis in breast cancer cells (MCF-7 and MDA-MB-231). The effect was more pronounced in MDA-MB-231 cells which also had higher levels of CD44 receptors. Covering CUR molecules with HA, which is specific for CD44 receptors, aids their entry to target cells. Also, conjugating CUR with HA makes the molecule much more stable, increasing its apoptotic effect.

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Author Contribution:
Research idea: ZMO, ASY
Design of the study: ZMO, AMYG, ASY
Acquisition of data for the study: ZMO, GB, AMYG
Analysis of data for the study: ZMO, GB, AMYG

Interpretation of data for the study: All authors
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Clinical and Experimental Health Sciences

Phytochemical, Pharmacological, and Toxicological Studies on *Peganum harmala* L.: An Overview of the Last Decade

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ABSTRACT

Objective: Plants have been used to treat ailments since the dawn of humanity. The use of medicinal plants for various purposes such as preventing diseases, treating diseases and supporting medical treatment is increasing day by day. On the other hand, medicinal plants are important sources of raw materials for the pharmaceutical industry. It has been demonstrated that *Peganum harmala* L. and the phytochemicals it contains have a wide variety of pharmacological activities. *P. harmala* and its active ingredients can be an important resource for the pharmaceutical industry. In this review, the phytochemistry, pharmacological effects, clinical studies, and toxicity of *P. harmala* are discussed under the current information.

Methods: Studies on *P. harmala* were searched using Pubmed, Scopus, Science Direct databases, and Google Scholar search engine. As a result of the searches, 96 articles were included in the study.

Results: The main group of secondary metabolites responsible for the biological activities of *P. harmala* is alkaloids. The plant and its isolated secondary plant compounds have been shown to have many pharmacological actions, counting antiamnestic, anticancer, antidepressant, antiinflammatory, cardiovascular, gastroprotective, hepatoprotective, nephroprotective, and vasodilator activities. Studies evaluating the plant's clinical effects have been carried out in recent years. However, it has been recorded in the literature that the use of *P. harmala* causes poisoning with symptoms such as neurosensory symptoms, visual hallucination, bradycardia, hypotension, agitation, tremor, ataxia, and vomiting.

Conclusion: Considering the pharmacological effects, the number of studies on the efficacy and safety of *P. harmala* and its secondary metabolites should be increased.

Keywords: *Peganum harmala*, alkaloid, β-carboline, antidepressant, anticancer, toxicity

1. INTRODUCTION

Peganum harmala L. (family Nitriaceae) is known in Iran as "Espand," in North Africa as "Harmel," in the United States as "African rue," "Mexican rue," or "Turkish rue," and in Türkiye as "üzerlik," "lezik," "ülerzik," and "uzarih". It is a herbaceous suffrutescent perennial that is common around the world, particularly in North Africa, the Middle East, Türkiye, Pakistan, India, Iran, Kazakhstan, Mexico, and South America (1). The stem is erect, glabrous, and can grow up to 70 cm. Leaves are 3-5 cm long, alternate, with small and lower stipules, that are multiply split into linear, lanceolate, or narrowly elliptic segments usually with three parts at the base. The flowers are sessile and often located opposite the leaves. Sepals are linear, green, similar to leaf segments, usually irregularly segmented, and have a very small epicalyx. Petals are white, elliptical, 10-13(-19) mm long, and usually slightly exceeding the sepals. The flowering period in Türkiye is May-July. The fruit is a short-stalked, broadly obovoid or spherical, 8x8 mm, locicid capsule (2).

For generations, the plant has been utilized in folk medicine for therapeutic purposes. The seeds are used in Pakistan in powder form and internally to treat asthma, colic, and jaundice, to reduce malaria fever, and as an antihelminthic. The decoction prepared from the seeds is used to increase breast milk, for abortion, as a stimulant, and to treat laryngitis (3). In India, seeds cooked in sesame oil are dripped into the ear and used to relieve earache (4). In Türkiye, the seeds are used as an anthelmintic, menstrual remedy, to treat hemorrhoids, stimulate the nervous system, and relieve abdominal pain. The powdered seeds are used externally to treat eczema and hemorrhoids (5,6,7). It is known that the aerial parts and the seeds of the plant are used as an infusion, decoction, and powder for the treatment of diabetes and hypertension in northern Algeria (8). In Kyrgyzstan, the decoction prepared from the roots is used in washing and

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bathing to cleanse infected skin areas (9). In Iran, fruits in the form of powder and decoction are used to treat toothache, gynecological infections, and menstrual cramps (10). In Pakistan, incense made by mixing and burning the leaves of *Skimmea laureola* is used to drive away evil and against the evil eye (11). The seeds of *P. harmala* are used instead of *Banisteriopsis caapi* in the preparation of Ayahuasca, which is consumed as a hallucinogenic beverage by tribes in the Amazon. For this reason, the plant is known as an analogue of Ayahuasca Tea (12).

P. harmala contains mainly alkaloids, fatty acids, triterpenoids, anthraquinones, flavonoids, phenolic acids, and essential oils. Studies have shown that ethanolic, methanolic, and aqueous extracts prepared from seeds, and the alkaloid fraction obtained from these extract have a wide range of pharmacological effects, including antiinflammatory, antimicrobial, antidepressant, antitumoral, analgesic, antihypertensive, hypoglycemic, gastroprotective, and neuroprotective effects (1,13,14).

Göbel isolated harmaline, a *β*-carboline alkaloid, from the seeds and roots of *P. harmala* in 1841. The evaluation of the efficacy of harmaline and other *β*-carboline alkaloids and their synthetic derivatives in chronic diseases such as cancer, Alzheimer's disease, Parkinson's disease, diabetes, and hypertension has been the subject of many studies (13). Studies on the isolation of alkaloids from *P. harmala*, elucidation of the structures of isolated compounds, and determination of their pharmacological activities have continued since 1841 until today. In recent years, the number of clinical studies investigating the efficacy of *P. harmala* in humans has increased. However, case reports have indicated that toxic effects occur when the plant is used concomitantly with conventional drugs or taken in high doses.

In the literature, there are comprehensive review studies on the phytochemistry, biological effects, and toxicity of the genus *Peganum*. These studies did not focus directly on the *P. harmala* species, but also covered other *Peganum* species (1,13). When the previous studies on *P. harmala* were examined, it was seen that the number of comprehensive studies was limited and current data as well as the results of clinical investigations were lacking. In this review, the phytochemistry, pharmacological effects, clinical studies, interactions with herbal products/conventional drugs, and toxicity of *P. harmala* are discussed in accordance with current information. Pubmed, Scopus, Science Direct, and Google Scholar databases were used to search for studies concerning *P. harmala*. The following keyword combinations were used for the search: "phytochemistry" or "chemical compound" or "pharmacological effects" or "biological effects" or "clinical trials" or "drug interaction" or "interaction with herbal products" or "toxicity" or "case report" and "*Peganum harmala*". The current data between the years 2010-2021 are discussed in the review. Since the number of available studies evaluating the toxic effects of the plant is limited, the literature was searched without specifying the time interval only for this part of the manuscript. The references listed in the chosen publications were searched for additional reports which were not included in the databases. For studies with similar results, the most recent was examined. A total of 96 accessible articles whose language was English were included in the study.

2. PHYTOCHEMISTRY

The most important group of secondary metabolites responsible for the biological effects of *P. harmala* is the alkaloids. In the studies, the seeds of the plant were found to have high alkaloid content (2-7.7%). Various alkaloid groups with *β*-carboline, quinazoline, and indole structures were identified in the seeds. In addition to alkaloids, *P. harmala* also contains fatty acids, triterpenoids, anthraquinones, flavonoids, phenolic acids, and other phytochemicals (13). The secondary metabolite groups and chemical compounds contained in the plant, the plant parts from which these compounds are extracted, and the solvent/solvent systems used in the extraction are listed in Table 1.

Different parts of *P. harmala* were found to contain essential oil. The chemical composition of the essential oils may vary due to differences in the geographical region, harvesting time, stage, drying method, and essential oil extraction procedures. The results of the studies in which the essential oil composition of *P. harmala* was investigated are shown in Table 2.

3. PHARMACOLOGICAL EFFECTS

3.1. Antiamnesic Activity and Effect on Alzheimer's Disease

Liu *et al*. investigated the *in vivo* acetylcholinesterase (AChE) inhibitory activity of ethanol extract (EXT_E), alkaloid fraction (ALK) and flavonoid fraction (FLA) prepared from the aerial parts of *P. harmala*. Mice were treated with the EXT_E at doses of 183, 550, and 1650 mg/kg with the ALK and FLA at doses of 10, 30, and 90 mg/kg. All treatments were administered orally in a single dose. As a result, AChE activity was significantly decreased and acetylcholine content was significantly increased in the cortex and hippocampus of mice in the EXT_E and ALK groups (at all doses, $p<0.05$). There was no significant change in the FLA group. In the continuation of the study, the effect of EXT_E and ALK on scopolamine-induced memory deficits was investigated using the Morris water maze (MWM) tasks. In this phase of the study, EXT_E (at doses of 183, 550, and 1650 mg/kg) and ALK (at doses of 10, 30, and 90 mg/kg) were administered by oral gavage for 1 week. The scopolamine-induced reduction in swimming time within the target zone and reduction in the number of crossings in the platform were significantly reversed by EXT_E and ALK ($p<0.05$ for EXT_E at 550, 1650 mg/kg and ALK at 30, 90 mg/kg). AChE activity and protein expression were significantly reduced and acetylcholine content was significantly increased (at all doses, $p<0.05$). There was no significant change in choline acetyltransferase (ChAT) activity, ChAT protein expression, and choline content (41). The results of another *in vivo* study showed that administration of deoxyvasicine (DVAS; at doses of 5, 15, and 45 mg/kg, 7 days, orally) improved learning and memory deficits in the MWM test in male C57BL/6J mice. DVAS

reduced AChE levels (at all doses, $p<0.05$) in the hippocampus and cortex. Treatment with DVAS significantly increased ChAT levels in the hippocampus at three doses administered (at all doses, $p<0.01$). However, only the 45 mg/kg dose of DVAS was significantly effective in increasing ChAT levels in the cortex ($p<0.05$). It ameliorated scopolamine-induced neuronal damage by increasing hippocampal brain-derived neurotrophic factor levels (at all doses, $p<0.05$). It decreased neuroinflammation by suppressing tumor necrosis factor-α (TNF-α) levels (at all doses, $p<0.01$) and oxidative stress by increasing glutathione peroxidase (GSH-px) levels and activity (at all doses $p<0.01$). DVAS also affected neurotransmitter levels by increasing levels of acetylcholine, 5-hydroxytryptamine, and γ-aminobutyric acid, and decreasing levels of 5-hydroxy indole-3-acetic acid and glutamic acid (42).

The effect of a methanol extract prepared from the seeds of *P. harmala* (approximately 14% and 21% (w/w) harmine and harmaline content, respectively) on learning and memory problems in a rat model of Alzheimer's-like pathology induced by aluminum chloride ($AlCl_3$) was evaluated. The extract was administered orally at a dose of 187.5 mg/kg for 4 weeks, beginning 2 weeks after exposure to $AlCl_3$. It increased hippocampal levels of insulin, glucagon-like peptide-1 (GLP-1), phosphorylated Akt at serine 473 (pS473-Akt), and glucose transporter type 4 (GLUT 4). It reduced the level of insulin receptor substrate-1 phosphorylation at serine 307 (pS307-IRS-1), beta-amyloid(Aβ)42, augmented pS9-glycogen synthase kinase-3β (pS9-GSK-3β) and phosphorylated tau (*p*-tau) in the hippocampus. The increased nuclear factor erythroid 2-related factor 2 (Nrf 2) and improved hippocampal oxidative stress markers. As a result, it was found that the extract attenuated $AlCl_3$-induced cognitive impairment by affecting the indicated biochemical parameters and signaling pathways (43).

3.2. Antibacterial Activity

The antibacterial effect of the harmala alkaloid-rich fraction contained in chitosan-coated poly(lactic-co-glycolic acid) nanoparticles (H/CS/PLGA NP) on *Staphylococcus aureus* and *Escherichia coli* was studied by the broth macro dilution method. H/CS/PLGA NP showed high antibacterial activity against *S. aureus* and *E. coli* with minimum inhibitory concentration (MIC) values of 0.125 and 0.06 mg/mL, respectively (MIC value of 0.5 mg/mL for the harmala alkaloid-rich fraction only; 0.18 mg/mL MIC value for the chitosan/PLGA-coated blank) (44).

3.3. Antidepressant Activity

Herraiz *et al*. investigated the effects of acidic methanolic extracts from the leaves, stems, seeds, and roots of *P. harmala* on monoamine oxidase-A (MAO-A). Seed and root extracts strongly inhibited MAO-A with IC_{50} values of 27.6±1.3 and 159.3±17.5 µg/L, respectively. Stem and leaf extracts inhibited MAO-A by 50% and 40%, respectively, at a concentration of 2.5 mg/mL. Although the stem and leaf extracts are considered MAO-A inhibitors, their effect was shown to be lower than that of the seed and root extracts. As a result of the quantitative studies, it was found that MAO-A inhibition of the seed extract was dependent on harmaline and harmine content, while the root extract was dependent only on harmine. Stem and leaf extracts showed lower inhibitory activity at lower harmine content. In the continuation of the study, kinetic studies were performed with the seed extract. The seed extract competitively and reversibly inhibited MAO-A. It showed no significant inhibitory effect on MAO-B with an IC_{50} value of 416 µg/L. As a result, the extract inhibited MAO-A more selectively than MAO-B (12). In another study, peganin, deoxypeganin, and peganin glucoside isolated from seeds were found to weakly and insignificantly inhibit the isoenzyme MAO-A, but not the isoenzyme MAO-B. As a result of the study, quinazoline alkaloids were not accepted as MAO inhibitors. MAO-A inhibition was associated only with the content of β-carboline alkaloids (23).

Sassoui *et al*. reported that an ethanol extract of *P. harmala* seeds (at doses of 100 and 300 mg/kg, single dose, orally) significantly reduced immobility time in the forced swimming test in Wistar rats. In addition, the extract decreased the level of serum adrenocorticotropic hormone and the defecation rate. According to these results, the extract was found to have an antidepressant effect, and the highest effect was observed in rats treated with a dose of 300 mg/kg (45).

3.4. Antiinflammatory Activity

Bensalem *et al*. tested the inhibitory effect of ethanol extracts from different parts of *P. harmala* and the β-carboline alkaloids on the enzyme myeloperoxidase (MPO), which plays a role in inflammation, using the taurine-chloramine assay. The extract prepared from the seed and aerial parts strongly inhibited MPO activity at a concentration of 20 µg/mL, by 97±5% and 43±4%, respectively. The root extract showed a low inhibitory effect of 15±6%. Harmine, harmaline, and harmane showed significant inhibition of MPO with IC_{50} values of 0.26, 0.08, and 0.72 µM, respectively. Harmaline was found to have the highest inhibitory activity and this effect was higher than that of 5-fluorotryptamine (IC_{50}:200 nM). In molecular docking studies, the alkaloids were found to have a high affinity for the active site of MPO. The ΔG values for harmine, harmaline, and harmane were - 4.4, - 6.1, and - 3.1 kcal/mol, respectively (46).

Methanol extract of *P. harmala* whole plant (at a dose of 200 mg/kg, *i.p*.) inhibited carrageenan-induced paw edema in Wistar albino mice by 75.14% ($p<0.001$) in 3 hours (100 mg/kg body weight indomethacin, 86.1%) (47). In another study, it was found that the cream formulation prepared with 20% *P. harmala* seed oil significantly inhibited the inflammation induced by carrageenan by 60.4% (1% diclofenac: 45.65%) (30). The effect of a methanol extract from the leaves of *P. harmala* was studied in the polyarthritic rat model induced by Complete Freund's Adjuvant (CFA). The extract was administered orally to the rats at doses of 200, 400, and

600 mg/kg/day for 21 days. CFA-induced paw edema was suppressed by 19.3±1.27% by the extract at a dose of 600 mg/kg (for 200, 400 mg/kg extracts, 5 mg/kg diclofenac sodium 14.56%±1.99%, 16.82%±3.21%, 16.80±2.73%, respectively). Treatment with the extract decreased the levels of C-reactive protein (CRP), rheumatoid factor, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). The extract ameliorated oxidative damage in polyarthritic rats by increasing the levels of superoxide dismutase (SOD), reducing glutathione (GSH), and catalase (CAT). It suppressed the levels of malondialdehyde (MDA), prostaglandin-E_2 (PGE_2), and TNF-α. In addition, the study evaluated the effect of the extract on hematological parameters. While the extract increased the number of red blood cells (RBCs), it decreased the number of white blood cells (WBCs) and platelets. It had no effect on hemoglobin levels. All effects were dose-dependent, with the highest effect observed in rats given 600 mg/kg of the extract (48). Wang *et al*. investigated the osteoclastogenic effects of harmine in the titanium-induced periprosthetic osteolysis model. Male C57BL/J6 mice were administered low (5 mg/kg/day) or high (10 mg/kg/day) doses of harmin emulsion intragastrically for 2 weeks. Both doses significantly increased bone mineral density (BMD) and bone volume/tissue volume (BV/TV), while reducing porosity area and the number of pores. It decreased interleukin (IL)-1β, TNF-α, and IL-6 levels at both doses. It suppressed inflammation by shifting macrophage polarization from M1 (pro-inflammatory phenotype ($(F4/80^+/iNOS^+)$) to M2 (anti-inflammatory phenotype ($(F4/80^+/Arg\text{-}1^+)$). Harmine was shown to reduce inflammation in periprosthetic osteolysis by suppressing c-Jun N-terminal kinase activation (49).

3.5. Antitussive, Expectorant, and Bronchodilator Activities

Liu *et al*. investigated the antitussive effects of methanol extracts (EXT_M), ALK, and FLA prepared from the aerial parts of *P. harmala* in ammonia liquor-, capsaicin-, and citric acid-induced cough models in mice and guinea pigs. Mice were treated with EXT_M at doses of 183, 550, and 1650 mg/kg and with ALK and FLA at doses of 10, 30, and 90 mg/kg (single oral administration). In all three models, EXT_M and ALK suppressed cough frequency and prolonged cough delay. FLA had no effect on cough frequency and latent period. The results showed that high-dose EXTM (1650 mg/kg) and ALK (90 mg/kg) had as good a pharmacological effect as codeine phosphate (30 mg/kg). To determine the mucolytic effect of EXT_M, ALK, and FLA, the phenol red secretion assay was performed in mice. EXT_M increased phenol red secretion by 0.64-, 1.08-, and 1.29-fold (p<0.05) at doses of 183, 550, and 1650 mg/kg, respectively. ALK increased phenol red secretion by 0.63-, 0.96-, and 1.06-fold (p<0.05) at doses of 10, 30, and 90 mg/kg. FLA had no effect on the amount of phenol red secretion. High-dose EXT_M and ALK were shown to have a higher expectorant effect than the standard drug ammonium chloride (1500 mg/kg dose). The bronchodilator effect was evaluated by acetylcholine chloride and histamine-induced bronchoconstriction test. EXT_M showed a bronchodilator effect by prolonging the pre-convulsive time by 67.34%, 101.96%, and 138.00% at doses of 183, 550, and 1650 mg/kg, respectively. ALK prolonged the pre-convulsive time by 55.47%, 97.74%, and 126.77% at doses of 10, 30, and 90 mg/kg, respectively. For FLA administered at doses of 10, 30, and 90 mg/kg, the values were 84.69%, 95.94%, and 154.52%, respectively. The standard drug aminophylline at a dose of 50 mg/kg prolonged the pre-convulsive time by 162.28% (50).

3.6. Antiviral Activity

Benzekri *et al*. tested the anti-HSV2 activity of sixteen extracts of seeds, stems, leaves, and flowers of *P. harmala* using hexane, dichloromethane, ethyl acetate, and methanol in the plaque reduction assay. As a result, the methanolic extract of seeds was the only extract that showed anti-HSV2 activity (selectivity index (SI): 13.19, IC_{50}: 161 µg/mL). The extract showed antiviral activity by exhibiting virucidal effects on both virus entry and release of the newly formed virions. Continuing the study, the active component of the extract was isolated and defined as harmine. It showed a synergistic effect with a combination index of 0.5 when co-administered with aciclovir (51). In another study, the antiviral activity of ethanolic extract and total alkaloid fraction from *P. harmala* seeds against influenza A/Puerto Rico/8/34 (H1N1; PR8) virus was investigated using Madin Darby canine kidney epithelial cell line. The total alkaloid fraction (IC_{50}: 5.8 µg/mL, SI: 23.1) had higher antiviral activity than the crude extract (IC_{50}: 9.87 µg/mL, SI: 12.45). The extract inhibited viral RNA replication as well as polymerase activity. However, the extract did not cause hemagglutination inhibition and did not exhibit virucidal activity (52).

3.7. Cardiovascular Activity

Keihanian *et al*. studied the effect of an ethanol extract from the seeds of *P. harmala* in the treatment of chronic heart failure in an isoproterenol-induced rat model. The extract was administered intraperitoneally to Wistar rats at a dose of 100 mg/kg/day for 30 days. The extract improved ejection fraction by 26.08% (p<0.01). Left ventricular end-diastolic diameter was significantly decreased in the *P. harmala* treated group. The extract decreased the levels of N-terminal proatrial natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), creatine kinase myocardial band (CK-MB), and angiotensin-converting enzyme (ACE) in serum (53). Huang *et al*. studied the therapeutic effect of harmine on cardiac hypertrophy in a spontaneous hypertension rat model. Wistar-Kyoto rats were treated with 0.05% harmine (at a dosage of approximately 50 mg/kg/day) added to the diet for 12 weeks. Harmine was shown to ameliorate cardiac hypertrophy caused by pressure overload. On the other hand, harmine had no effect on blood pressure. Harmine significantly increased left ventricular systolic inner diameter (LVID) and significantly decreased interventricular septal thickness in diastole (IVSd), left ventricular posterior wall end-diastolic thickness (LVPWd), left ventricular mass index (LVMI), ejection fraction (EF), and fractional shortening (FS). Harmine upregulated the fetal genes β-myosin heavy chain

(*β*-MHC), B-type natriuretic peptide (BNP), NT-proBNP, and atrial natriuretic factor (ANF). Harmine decreased the expression of structure - and function-related proteins such as NFAT-activated mediators, myocyte-specific enhancer factor 2C (Mef2C), and sarcoplasmic/reticular Ca^{2+}-ATPase 2A (SERCA2A). In the continuation of the study, the mechanisms underlying the attenuating effect of harmine on cardiac hypertrophy were investigated. Harmine decreased the mRNA levels of inflammatory mediators such as IL-1*β*, IL-6, IL-10, and TNF-*α*. It suppressed the mRNA levels of macrophage maker (Emr1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in cardiac tissue. It decreased the mRNA levels of chemokines (CCL2, CXCL1) and chemokine receptor-2, a chemoattractant for inflammatory cells. In conclusion, harmine was found to inhibit the activation of the nuclear factor kappa B (NF-κB) signaling pathway and suppress the expression of proinflammatory cytokines in the heart (54).

3.8. Effect on Cancer

The cytotoxic, antiproliferative, and antiangiogenic effects of the hydroalcoholic extract prepared from *P. harmala* seed on human umbilical vein endothelial cells (HUVEC) at different concentrations were studied *in vitro*. The cytotoxic concentration of the extract was determined to be 150 µg/mL. The extract strongly inhibited the proliferation of HUVEC (IC_{50}: approximately 85 µg/mL) such a dose-dependent manner. It showed a partial antiangiogenic effect at concentrations of 40 and 80 µg/mL. At higher concentrations (100 and 120 µg/mL), it inhibited the production of endothelial tubular formations and suppressed endothelial cell branching. In addition, the extract reduced vascular endothelial growth factor secretion in HUVEC (55).

The anticancer activities of many compounds, mainly alkaloids, isolated from *P. harmala* are being studied and attempts are being made to elucidate their mechanisms of action. The effect of harmine 24, 36, and 48 h incubation at concentrations of 2, 4, 8, 16, 32, and 64 *µ*g/mL on the TPC-1 line was investigated by 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay. The IC_{50} values of harmine against TPC-1 cells at 24, 36, and 48 hours were 16.57 ± 1.4, 9.48 ± 1.1, and 5.51 ± 0.7 µg/mL, respectively. Harmine suppressed TPC-1 cell proliferation significantly in a concentration- and time-dependent manner. Harmine treatment resulted in a dose-dependent increase in Bax expression and a decrease in Bcl-2 expression. Consequently, it was found to exhibit apoptotic effects by significantly reducing the Bcl-2/Bax ratio. It also induced caspase-3 activity, which plays a role in apoptosis. In addition, it suppressed TPC-1 cell invasion and migration in a dose-dependent manner (56). Hamsa *et al*. studied the effect of harmine on metastatic lung tumors using three different methods, including concurrent, prophylactic, and after-tumor development administrations. Harmine inhibited tumor nodules at rates of 83.6%, 68.4%, and 51.6% in the concurrent, prophylactic, and post-tumor administration models, respectively. The survival rate of metastatic rats in these three models improved significantly after harmine administration by 172.54%, 147.18%, and 120.76%, respectively. Harmine administration decreased the concentration of biochemical parameters in the lungs, such as collagen, hydroxyproline, hexosamine, and uronic acid, which were elevated in metastatic tumors. It suppressed the levels of proinflammatory cytokines such as IL-1*β*, IL-6, TNF-*α*, and granulocyte-macrophage colony-stimulating factor (GM-CSF). It downregulated the expression of several pro-metastatic genes such as extracellular signal[en] regulated kinase (ERK)-1, ERK-2, VEGF, metalloproteinase (MMP)-2, and MMP-9 while upregulating the expression of anti-metastatic genes such as nm23, tissue inhibitor of metalloproteinase (TIMP)-1, and TIMP-2 (57). Peganumine A was reported to be moderately cytotoxic in MCF-7 (IC_{50}: 38.5 µM), PC-3 (IC_{50}: 40.2 µM), and HepG2 (IC_{50}: 55.4 µM) cell lines. This compound showed selective effects in HL-60 cells with an IC_{50} value of 5.58 µM. In another study, pegaharmaline A (IC_{50}: 9.4 µM) and pegaharmaline B (IC_{50}: 13.6 µM) were found to have significant cytotoxic effects in HL-60 cells. In HL-60 cells, peganumaline B (IC_{50}: 21.54 µM), peganumaline F (IC_{50}: 24.55 µM), and pegaharmine E (IC_{50}: 25.07 µM) showed moderate cytotoxic effects (17,18,28). Wang *et al*. found that harmalacidine had potent cytotoxic activity on U937 with an IC_{50} value of 3.1±0.2 µmol/L. Harmalacidine was found to act on mitochondrial and protein tyrosine kinase signaling pathways (PTKs-Ras/Raf/ERK) (27).

3.9. Effect on Parkinson's Disease

Yalçın *et al*. reported that *P. harmala* seed methanol extract exhibited an inhibitory effect (IC_{50}: 1.09±0.33 µg/mL) on catechol-*O*-methyltransferase (COMT). Analysis of the extract revealed that the main alkaloid contained therein is harmaline. Later in the investigation, the alkaloid responsible for the inhibitory effect was determined using harmaline and harmalol standards. Harmaline (IC_{50}: 0.98±0.12 µg/mL) strongly inhibited COMT. This effect was higher than that of harmalol (IC_{50}: 3.59±0.37 µg/mL) (58).

The effect of *P. harmala* seed aqueous extract (10 mg/kg, *i.p*.) on 6-hydroxydopamine-induced Parkinson's disease symptoms and markers of oxidative stress was studied in Wistar rats. The extract improved muscle stiffness in Murprogo's test and apomorphine-induced one-direction rotation behavior in the rotation test. Markers of oxidative stress, such as lipid peroxidation and protein oxidation, were found to be significantly lower in the brains of rats treated with the extract. In addition, the extract inhibited ACE activity in the brain. The histological study, it prevented the degeneration of dopaminergic neurons. These results show that the extract can effectively reduce the symptoms of Parkinson's disease and the markers of oxidative stress (59).

Table 1. *Chemical compounds contained in P. harmala*

	Compound/Compounds	Plant Parts	Extract Type	References
	Alkaloids			
β-carboline alkaloids	Harmaline	S	$HClO_4$:MeOH (1:1)	(12)
		AP	MeOH:H_20 (7:3)	(15)
	Harmine	S, R, St, L	$HClO_4$:MeOH (1:1)	(12)
		S	85% EtOH	(16)
		AP	MeOH:H_20 (7:3)	(15)
	Harmalol	S, R	$HClO_4$:MeOH (1:1)	(12)
		S	85% EtOH	(16)
	Harmol	S	85% EtOH	(16)
		R, St	$HClO_4$:MeOH (1:1)	(12)
	Tetrahydroharmine	S	$HClO_4$:MeOH (1:1); 85% EtOH	(12, 16)
	Harmane, 3-hydroxylated harmine, 1-hydroxy-7-methoxy-*β*-carboline, acetylnorharmine, harmic acid methy ester, harmaline, harmalanine, harmine *N*-oxide, 2-aldehyde-tetrahydroharmine	S	85% EtOH	(16)
	Pegaharmalines A and B	S	-	(17)
	Peganumine A	S	95% EtOH	(18)
	Peganumines B, C, F, G, H	S	85% EtOH	(19)
	Pegaharmines A–D	S	95% EtOH	(20)
	Pegaharmines F–K	S	95% EtOH and 75% EtOH	(21)
	Pegaharines A–G	S	95% EtOH	(22)
Quinazoline alkaloids	Peganine (vasicine)	S	$HClO_4$:MeOH (1:1); 85% EtOH; 95% EtOH; 70% aqueous MeOH	(16,23-25)
		Fr, Fl, St R	$HClO_4$:MeOH (1:1)	(23)
		AP	MeOH:H_20 (7:3)	(15)
	Deoxypeganine (deoxyvasicine)	S	$HClO_4$:MeOH (1:1); 85% EtOH	(16, 23)
		Fr, Fl, St	$HClO_4$:MeOH (1:1)	(23)
	Peganine *β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside (peganine glucoside)	S	$HClO_4$:MeOH (1:1)	(23)
	Vasicinone	S	85% EtOH; 95% EtOH; 70% aqueous MeOH	(16, 24, 25)
	Deoxyvasicinone	S	85% EtOH; 95% EtOH; 70% aqueous MeOH	(16, 24, 25)
	(*S*) vasicinone-1-*O*-*β*-D-glucopyranoside	S	70% aqueous MeOH; 95% EtOH	(24,25)
	(*R*) vasicinone-1-*O*-*β*-D-glucopyranoside	S	70% aqueous MeOH	(25)
	(*S*) and (*R*)-vasicinone *β*-D-glucopyranosyl-(1→6)-*β*-D-glucopyranoside, quinanolin-4(3H)-one, methyl 3-(4-oxoquinazolin-3(4H)-yl) propanoate, vasicinolone, 1-(2-aminobenzyl)-3-hydroxypyrrolidine-2-one, (*S*) – 1-(2-aminobenzyl)-3-hydroxypyrrolidin-2-one *β*-D-glucopyranosyl-(1 → 6)-*β*-D-glucopyranoside, (*R*)-1-(2-aminobenzyl)-3-hydroxypyrrolidin-2-one *β*-D-glucopyranosyl-(1 → 6)-*β*-D-glucopyranoside	S	95% EtOH	(24)
	2-carboxyl-3,4-dihydroquinazoline	S	85% EtOH	(16)
	Pegamine	S	85% EtOH; 95% EtOH	(16,24)
	Peganumines D and E	S	85% EtOH	(19)
β-Carboline-quinazoline dimers	Pegaharmols A and B	R	95% EtOH	(26)
Indole alkaloids	2-(indol-3-yl)ethyl-*β*-D-glucopyranoside, 2-(indol-3-yl)ethyl-α-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside, (*S*)-3-hydroxy-3-(*N*-acetyl-2-aminoethyl)-6-methoxyindol-2-one	S	70% aqueous MeOH	(27)
	6-methoxyindoline	S	85% EtOH	(16)
	(±)-peganines A–B; (±)-peganumalines A-E, peganumaline F	S	95% EtOH and 75% EtOH	(21,28)

Thiazole derivatives alkaloids	Peganumals A–B	S	95% EtOH and 75% EtOH	(21)
Fatty acids				
Saturated fatty acids	Tetradecanoic, pentadecanoic, tridecanoic, hexadecanoic, heptadecanoic and octadecanoic acids	WP	*n*-hexane	(29)
	Palmitic, stearic, arachidic, behenic and tetracosanoic (lignoceric) acids	S(oil)	*n*-hexane	(30,31)
Saturated fatty acid derivatives	12-methyl tetradecanoic, 5,9,13-trimethyl tetradecanoic, 2-methyl octadecanoic acids	WP	*n*-hexane	(29)
Unsaturated fatty acids	(*E*)-9-dodecenoic, (*Z*)-9-hexadecenoic, (*Z,Z*)-9,12-octadecadienoic and (*Z,Z,Z*)-9,12,15-octadecatrienoic acids	WP	*n*-hexane	(29)
	Linoleic, oleic, palmitoleic, linolenic, gadoleic, erucic, and vaccenic acids	S (oil)	*n*-hexane	(30, 31)
Triterpenoids				
Lupane type triterpenoids	3α-acetoxy-14α-hydroxy-lup-20(29)-en-11-oxo-28-oic acid methyl ester, 3*β*-acetoxy-27-(4-hydroxy-3-methoxy-*E*-cinnamoyloxy) lup-en-28-oic acid methyl ester and 3*β*-acetoxy-27-hydroxy-lup-20(29) – en-28-oic acid	S	70% EtOH	(32)
Oleanane type triterpenoids	3α-acetoxy-27-hydroxy-olean-12-en-11-oxo-28-oic acid methyl ester, 3α-hydroxy-olean-27-(4-hydroxy-3-methoxy-*E*-cinnamoyloxy)-12-en-28-oic acid methyl ester, 3α-acetoxy-27-hydroxyolean-12-en-28-oic acid	S	70% EtOH	(32)
Pentacyclic triterpenoids	3α-acetoxy oleanolic acid, urs-12-ene-28-carboxy-3α-tetradecanoate, methyl-lup-20 (29)-en-3-on-28-oate, betulonic acid, lup-20 (29)-en-3-on-28-oic acid, 3-oxo-27-hydroxylup-20 (29) – en-28-acid methyl ester, 3-oxo-27-hydroxylup-20(29)-en-28-oic acid, 3α-acetoxy-27-hydroxylup-20 (29)-en-28-oic acid methyl ester, 3*β*-acetoxy-27-hydroxylup-20(29)-en-28-oic acid methyl ester, 3α,27-dihydroxylup-20(29)-en-28-oic acid methyl ester	S	70% EtOH	(32)
Anthraquinone				
Anthraquinones	Peganone 1 (3,6-dihydroxy-8-methoxy-2-methyl anthraquinone), Peganone 2 (8-hydroxy-7-methoxy-2-methyl anthraquinone)	S	EtOH	(13)
Flavonoids				
Flavone glycosides	Peganetin, deacetylpeganetin	AP	MeOH:$H_2$0 (7:3)	(15)
	Acacetin-7-*O*-rhamnoside	AP	MeOH	(13)
	Acacetin-7-*O*-[6''-*O*-glucosyl-2''-*O*-(3'''-acetylramnosyl) glycoside	AP	MeOH	(13)
	Acacetin-7-*O*-(2''''-*O*-rhamnosyl-2''-*O* glucosylglucoside)	AP	MeOH	(13)
	Glycoflavone 2''-*O*-rhamnosyl-2''-*O*-glucosylcytoside	AP	MeOH	(13)
	Cynaroside (Luteolin 7-glucoside)	L	MeOH	(33)
Flavonol glycosides	Rutin	S	MeOH	(34)
Flavanols	Catechin	S	MeOH	(34)
Flavanones	Hesperetin	S	MeOH	(34)
Phenolic acids				
Hydroxycinnamic acid derivative phenolic acids	*p*-coumaric acid, chlorogenic acid	S	MeOH	(34)
	Hydrocaffeic, caffeic, rosmarinic acids	L	MeOH	(33)
Hydroxybenzoic acid derivative phenolic acids	Protocatechuic acid	L	MeOH	(33)

S: Seed, AP: Aerial part, R: Root, St: Stem, L: Leaf, Fr: Fruit, Fl: Flower, WP: Whole plant, HClO4: perchloric acid, EtOH: ethanol, MeOH: metanol

Table 2. *Composition of essential oil samples obtained from P. harmala*

Location	Part of the plant used	Essential oil extraction method	Major Compounds	References
Egypt	Aerial part	Hydrodistillation	1-hexyl-2-nitrocyclohexane (9.07%), *Z*-2-octadecen-1-ol (8.13%), 3,5,24-trimethyltetracontane (7.84%)	(35)
Pakistan	Aerial part	-	Camphor (28,244%), capillin (13,176%)	(36)
China	Aerial part	Hydrodistillation	Limonene (14.5%), thymol (%11.5)	(37)
Persia	Fruit	Hydrodistillation	α-pinene (72.6%), trans-verbenol (3.9%), sabinene (2.6%)	(38)
Algeria	Seed	Hydrodistillation	Eugenol (17.5%), thymol (7%), α-isomethyl-(*E*)-ionol (7%), dihydro carveol acetate (6.2%)	(39)
Egypt	Seed	Hydrodistillation	Eugenol (17.2%), *n*-tetradecanol (12.3%), dodecanoic acid (5.9%)	(39)
Libya	Seed	Hydrodistillation	Eugenol (17.8%), *n*-tetradecanol (11.3%), β-acorenolo (% 7.4)	(39)
Morocco	Seed	Hydrodistillation	Eugenol (13.2%), *n*-tetradecanol (11.1%), bakerol (7.5%)	(39)
Tunisia	Seed	Hydrodistillation	Eugenol (69.2%), (*E*)-anethole (6.9%)	(39)
Iran	Seed	HS-SPME	2,3-dimethyl benzofuran (28.32%), cis-linalool oxide (7.46%), [2E] – decenal (6.57%)	(40)

Table 3. *Cases of poisoning due to P. harmala*

Patient's History	Part of the Plant Used, How to Use and Amount of Usage	Reason for Use	Clinical Findings	Reference
76 F, Parkinson's disease. History of use of levodopa/benserazide, rasagiline, and long-acting carbidopa levodopa	100 g of seed infusion, orally	Unspecified	Pulse ↑(120 beats/min), tachycardia, BP ↑ (165/90 mmHg), GCS 15/15; serotonergic syndrome	(88)
20 F, pregnancy history	A handful of seeds, orally	To induce abortion	Bradycardia at 45 pulse/minute then a tachycardia at 132 pulse/minute, LFTs ↑, kidney function tests ↑, troponine and creatine phosphokinaseMB ↑	(89)
31 F, pregnancy history	1 cup (~ 50g) of powdered seeds drunk with water	To induce abortion	Leukocytosis	(90)
58 F, 15 years of Type 2 DM patient, history of metformin and glibenclamide use	Boiled herb seeds, orally, 250 mL (one glass)	Regulation of blood sugar	Pulse ↑(120 beats/min), tachycardia, BG (250 mg/dl) ↑, HbA1c ↑ (>8), LFTs ↑, LDH↑, WBC ↑, PT and aPTT ↑, GCS 14/15	(91)
54 F, history of HT and atenolol use	Mixture of water, sugar and seeds, oral, 50 g	Treatment of chronic constipation	Pulse ↑(105 beats/min), tachycardia, BP ↑ (160/90 mmHg)	(92)
24 F, 22 weeks of pregnancy history	Seed. The use and amount of the seeds are not specified.	To induce abortion	Respiratory rate (30/min) ↑, LFTs ↑, Troponin ↑, Creatine phosphokinase –MB ↑, GCS 12/15 (Kidney failure, liver damage, fetal death)	(93)
45 F	Seeds mixed with a spoonful of honey, orally, 50 g	Treatment of hypermenorrhea	BP↓ (90/60 mmHg)	(94)
41 F	100 g of seed infusion, orally	To reduce anxiety	BP↑ (138/103 mmHg), Pulse ↑ (110 beats/min), Respiratory rate ↑ (30/min), GCS 8 BG↑ (225 mg/dL)	(95)
35 M	150 g of seed, orally	Unspecified	BP↓ (80/40 mmHg), Pulse ↑ (100 beats/min), mild anemia (Hb of 12.9 g/dl)	(96)

F: female, BP: Blood pressure, GCS: Glasgow coma scale, LFTs: Liver function tests, DM: diabetes mellitus, BG: Blood Glucose, HbA1c: glycosylated hemoglobin, LDH: lactate dehydrogenase, PT: prothrombin time, aPTT: Activated Partial Thromboplastin Time, HT: Hypertension, M: male

3.10. Gastroprotective Activity

Singh *et al*. investigated the gastroprotective effect of peganine hydrochloride which was purified from *P. harmala* seed ethanolic extract, in Sprague-Dawley rats using models of cold-induced stress (CRU), aspirin (AS), alcohol (AL), and pyloric ligation (PL) that caused the gastric ulcer. Peganine (20 mg/kg, single dose, oral) provided 50.0% (p<0.05), 89.41% (p<0.001), 58.50%, and 62.50% (p<0.01) protection in CRU, AL, AS and PL models, respectively (omeprazole at a dose of 10 mg/kg: 77.4%, 49.97% and 69.42% in CRU, AS, PL models. 500 mg/kg sucralfate: 62.5% in AL model). It reduced free acidity by 33.38% (p<0.01), total acidity by 38.09% (p<0.01), and increased mucin secretion by 67.91% (p<0.01) in the PL model. *In vitro* studies showed that the antisecretory mechanism of action of peganine (1-100 µg/mL at different concentrations) was related to its inhibition of H^+K^+ ATPase activity. Peganine inhibited the proton pump (IC_{50}: 73.47 µg/mL). The results support that peganin has remarkable gastroprotective activity in rats (60).

3.11. Nephroprotective Activity

Niu *et al*. studied the effect of harmine on lipopolysaccharide-induced acute kidney injury in male Kunming mice. Harmine was administered intragastrically at a dose of 25 or 50 mg/kg for five days. Harmine decreased blood urea nitrogen (BUN) and creatinine levels in a dose-dependent manner. At the 50 mg/kg dose, it significantly suppressed the increase in serum cystatin C levels. It decreased the dose-dependent formation of MDA and MPO and increased the activities of SOD and GSH. Harmine suppressed Toll-like receptor 4 (TLR4) expression and phosphorylation of NF-κB p65 and inhibitor of κBα. In addition, harmine inhibited the expression of NLRP3, caspase-1, and IL-1*β*. Harmine ameliorates acute kidney injury by blocking TLR4-NF-κB and NLRP3 signaling pathways (61).

3.12. Others

Results of other studies revealed that *P. harmala* extracts and isolated secondary metabolites exhibited antidiabetic, diuretic, vasorelaxant, antiparasitic, acaricidal, hepatoprotective, and wound healing activities (62-69).

4. CLINICAL STUDIES

In a double-blind, controlled, randomized clinical trial, the efficacy of *P. harmala* seed oil (standardized with 0.0025% harmaline and 0.057% harmine) was evaluated in patients with knee osteoarthritis. Four drops of the *Peganum* oil or the control group (olive oil) were applied to the knees three times a day for four weeks. The Visual Analog Scale (VAS) was used at weeks 0 and 4 to determine the patients' pain relief. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used to determine improvement in pain, stiffness, and functional symptoms. When scores were compared from VAS, pain decreased significantly in both groups (p<0.05). In the group of patients receiving *Peganum* oil, a decrease of 52.56% was observed (Control group: 17%). Except for stiffness, the WOMAC variables were significantly decreased (p<0.001). Based on the WOMAC results, it was found that pain decreased by 37.89% in the *Peganum* oil group. (Control group: 16.41) Pain and functional limitations decreased significantly in the *Peganum* group compared to the control group after 4 weeks (p<0.001). On physical examination, knee tenderness was found at baseline in both groups, but tenderness decreased significantly after 4 weeks of treatment (p<0.001) (70).

Hafshejani *et al*. conducted a randomized controlled clinical trial to evaluate the efficacy of *P. harmala* in female patients (n=100) diagnosed with osteoporosis. During the study, female patients received medical treatments, including calcium D (500 mg) twice daily and Osteofos® (70 mg, alendronic acid) twice weekly. In addition to medical treatment, patients in the treatment group received capsules of *P. harmala* seed (500 mg) twice daily for three months. It was reported that the mean BMD of the femur and spine significantly improved in the treatment group (p<0.001). BMD changes in the femur (-0.37) and spinal cord (-0.44) were higher in the treatment group than in the control group (BMD changes in the control group for the femur and spinal cord were - 0.24 and - 0.22 p<0.001, respectively) (71).

A clinical investigation was conducted on 90 patients who were diagnosed with benign prostatic hyperplasia (BPH) using the International Prostate Symptom Score (IPSS). The patients were separated into three groups. The first group received 1 g of *P. harmala* seed oral capsules, the second group received tamsulosin with 1 g of *P. harmala* seed oral capsules, and the third group received tamsulosin alone. The established treatment regimen was applied for four weeks. As a result, the difference in IPSS mean scores before and after treatment was determined to be significant (p=0.001). The lowest IPSS score was calculated in the group of receiving capsules with *P. harmala* and tamsulosin simultaneously (12.0±4.4 points). The highest score was calculated in the group receiving only tamsulosin (16.5±3.7 points). A significant reduction in urine frequency in urinary frequency (p=0.002), nocturia (p=0.001), and intermittent voiding (p=0.002) were observed in all three groups before and after the intervention. Finally, it was discovered that oral administration of *P. harmala* seeds may be effective in lowering urinary symptoms in BPH patients and that the combination with tamsulosin may be more effective in relieving urinary symptoms compared to the other groups (72).

In a randomized clinical trial, 80 patients with renal and ureteral stones of 4 to 10 mm were given capsules of tamsulosin (0.4 mg/day) or *P. harmala* (50 mg/kg/day) for two weeks. Stone size was significantly reduced after treatment in both groups. The mean stone size decreased from 13.31±7.16 mm to 4.07±3.66 mm in the group receiving *P. harmala* (tamsulosin: decrease from 10.79±4.82 mm to 5.15±3.63 mm). In terms of stone size, there has been no statistical variance (p=0.21). The number of stones

decreased, with no significant difference between groups. A more significant decrease in pain scores was observed in the group receiving *P. harmala* (p=0.002). The efficacy of the treatment was more than 75% in both groups. The results of the study showed that *P. harmala* was as effective as tamsulosin. In addition, *P. harmala* was reported to be more effective in relieving pain than tamsulosin (73).

Within a random, double-blind, placebo-controlled clinical study of 61 patients with gastroesophageal malignancy, groups were separated to control and treatment. All groups continued to receive the chemotherapeutic agents 5-fluorouracil, uracil, and cisplatin throughout the study. The treatment group, in addition to their own medications, received the drug Spinal-Z (containing a mixture of *P. harmala* seed methanolic extracts and *Dracocephalum kotschyi* Boiss leaves) at a dose of 600 mg/m^2/day for 6 months. Complaints like abdominal pain (p=0.004), anorexia (p<0.001), and constipation (p=0.01) decreased in the group receiving Spinal Z compared to pretreatment. Compared to the control group, complaints of abdominal pain, heartburn, constipation, and vomiting decreased significantly in the treatment group (74).

4. TOXICITY

In vitro and *in vivo* studies were conducted to evaluate the toxicity of *P. harmala* and its secondary metabolites, mainly alkaloids. Apart from cytotoxicity studies, studies on healthy cells are given in this section.

The cytotoxic effect of *P. harmala* hydroalcoholic seed extract (10%) on L929 fibroblast cells was tested in the MTT method. Cell viability decreased as the incubation period increased. After 1, 24, and 72 hours of incubation, the percentages of cell viability were confirmed to be 94%, 69%, and 51%, respectively. In the study, it was revealed that the cytotoxic effect was lower when compared to 5.25% sodium hypochlorite (75). The toxic selectivity of indole alkaloids isolated from the plant against human embryonic kidney cells (HEK-293) was evaluated. Indole alkaloids showed a very low toxic effect in HEK-293 cells (IC_{50} values above 200 µmol/L) when compared to human leukemia cell lines (27).

Studies in the literature have shown that *β*-carboline alkaloids have genotoxic, mutagenic, and cytotoxic properties. Genotoxic effects of harman and harmine (20, 40, 80 µg/mL) on V79 Chinese hamster lung fibroblast cells were investigated by single-cell gel electrophoresis test (Comet assay). In comparison to the control groups, both alkaloids increased the frequency of abnormal cells and induced DNA damage at all concentrations. It has been stated that harman and harmine have genotoxic effects on V79 cells and this effect is associated with the induction of DNA strand breaks (76). In another study, yeast *Saccharomyces cerevisiae* was incubated with harman and harmine at concentrations of 100, 200, 300, and 400 µg/L. Both alkaloids caused DNA damage by causing single and/or double-strand breaks in DNA. Harmine was found to be more cytotoxic than harman in haploid and diploid cells (77).

Acute Toxicity: Benbott *et al*. reported that *intraperitoneal* (*i.p.*) administration of an alkaloid extract prepared from the seeds was moderately toxic to Wistar albino rats with an LD_{50} of 350 mg/kg body weight. Clinical changes such as convulsions, agitation, tachycardia, dyspnea, somnolence, decreased locomotor activity, and anorexia were observed in the animals (78). The *intramuscular (i.m.)* administration of an aqueous extract of *P. harmala* to rats resulted in an LD_{50} value of 420 mg/kg (79). In another study, when the aqueous extract was given orally in an acute dose, the LD_{50} value was discovered to be 2.70±0.05 g/kg (80).

Subacute Toxicity: The total alkaloid extract from the seeds of *P. harmala* was administered orally to rats for 28 days at doses of 15, 45, and 150 mg/kg/day. The extract was found to be safe at doses of 15 and 45 mg/kg/day. In the first three days of the study, tremors occurred 15 minutes after administration in rats receiving the extract at a dose of 150 mg/kg and continued for 4 hours. The extract's no observed adverse effect level (NOAEL) was revealed to be 45 mg/kg/day (81).

Chronic Toxicity: Oral administration of *P. harmala* aqueous extract to rats at doses of 1, 1.35, and 2 g/kg 6 times a week for 3 months raised transaminase levels. In the histological examination, rats administered the extract at a dose of 2 g/kg showed signs of liver degeneration and spongiform changes in the central nervous system (80).

Genotoxicity: Abderrahman *et al*. investigated the cytological effect of the alkaloid extract from the seeds of *P. harmala* (12.5, 25, 50, and 100 mg/kg body weight, *i.p*., single dose) by calculating the mitotic index values in bone marrow cells of mice. While the mitotic index significantly decreased from 4.45 to 3.31 in the extract-treated group, the mitodepression index increased. Cytogenetic studies showed that the extract caused a significant increase in the percentage of chromosomal aberrations and induced sister chromatid exchange. These results indicate that the extract may have genotoxic effects (82).

Reproductive Toxicity: It was demonstrated that methanol extracts of *P. harmala* prepared at different doses (2, 2.5, and 3 g/kg/day) significantly prolonged the duration of the estrus phase and estrus cycle in female rats. The number of live offspring was reduced and the number of resorbed fetuses was raised when methanol extracts were administered at doses of 2.5 and 3.5 g/kg/day. It did not affect the reproductive rate, number of live offspring, number of resorbed fetuses, and implantation sites when administered at a dose of 2.0 g/kg/day (83). The effect of hydroalcoholic extract prepared from *P. harmala* seeds on the spontaneous rhythmic contraction of the isolated rat uterus was tested. It has been determined that the extract at concentrations of 12.5 and 50 µg/mL produces uterotonic effects in the presence of KCl in a calcium-free solution (84).

P. harmala aqueous extract has been shown to significantly reduce the weight of reproductive organs like the testis, epididymis, seminal vesicle, ventral prostate, and vas

deferens when given to adult male albino rats for 60 days at a dose of 300 mg/kg. The extract decreased sperm motility and density in the cauda epididymis and testicular ducts. In seminiferous tubules, it diminished spermatogenesis activity. In the continuation of the study, the serum hormonal levels of the rats were measured at 300 mg/kg dose. It has been found that the aqueous extract causes levels of testosterone and follicle-stimulating hormone to decline. It was observed that the extract reduced the number of female rats fertilized with male rats, the implantation site, and the number of viable fetuses (85).

Human Toxicity

In the literature, there are case reports of adverse effects resulting from the concomitant use of drugs or other herbal products with *P. harmala*. A 42-year-old male patient who has a mood disorder and has been taking *P. harmala* (dose unknown) for the treatment of hemorrhoids was the subject of one such case report. The patient had a history of taking quetiapine 1000 mg/day and fluoxetine 40 mg/day. The patient, who presented to the emergency department with complaints of nausea, vomiting, sweating, and tremors, was noted to have visual hallucinations, confusion, agitation, and hyperactive delirium. The patient was diagnosed with serotonin syndrome associated with the concomitant use of fluoxetine and *P. harmala* (86). Liu *et al*. reported dimethyltryptamine (DMT) poisoning in two individuals who ingested an herbal stew of *P. harmala* seeds with MAO inhibitor effect and *Acacia* tree bark containing DMT. Biochemical and toxicological analyzes of a 22-year-old male patient who reported to the emergency department with complaints of restlessness and confusion revealed a serious increase in myoglobin levels (5252 ng/mL). The patient's serum and urine showed 25 and 1206 ng/mL DMT and 3.3 and 1564 ng/mL harmaline, respectively. Another male patient, 24, was admitted to the hospital with symptoms of impulsive mood changes and violent behavior. On analysis, myoglobin level was found to be elevated similar to the other case (381 ng/mL). While 478 ng/mL DMT and 1230 ng/mL harmaline were detected in the urine, the presence of the two compounds in the serum could not be determined (87).

There are many cases of poisoning associated with uncontrolled and unconscious consumption of *P. harmala*. Neurological, gastrointestinal, and cardiovascular symptoms accounted for 34.4%, 31.9%, and 15.8% of the cases of poisoning, respectively. Following the consumption of *P. harmala* seeds, patients apply to the clinic with complaints such as visual and auditory hallucinations, locomotor ataxia, nausea, vomiting, confusion, and agitation (88-96). Some cases of poisoning by *P. harmala* are listed in Table 3.

5. CONCLUSIONS

The use of plants for various purposes such as curing diseases, preventing diseases, and improving general health is as old as the history of mankind. Today, research on medicinal plants continues and activity studies are being conducted by isolating compounds that can guide the development of new conventional medicines from medicinal plants. In this review, botanical characteristics, traditional uses, chemical composition, pharmacological effects, toxicity, interactions with drugs and other herbal products, and cases of human toxicity of *P. harmala* were studied based on scientific data.

P. harmala contains alkaloids (*β*-carboline, quinazoline, *β*-carboline-quinazoline dimers, indole, and thiazole), anthraquinones, phenolic acids (hydroxycinnamic acid and hydroxybenzoic acid derivatives), flavonoids (flavone glycoside, flavonol, flavonol glycoside, and flavanones), triterpenoids (lupane, oleanane, and pentacyclic) and fatty acids. It has been shown that the essential oils obtained by hydrodistillation from different parts of the plant contain compounds such as camphor, eugenol, *n*-tetradecanol, *α*-pinene, thymol, and limonene. The main secondary metabolite group responsible for the pharmacological effects of the herb are alkaloids in the structure of *β*-carboline and quinazoline. The plant and its alkaloids have shown anti amnestic, anticancer, antidepressant, antiinflammatory, cardiovascular, gastroprotective, hepatoprotective, nephroprotective, and vasodilator activities in preclinical studies. These effects reveal that the plant *P. harmala* can be an important resource in the pharmaceutical industry for the development of new drugs for the treatment of various diseases. In recent years, investigations examining the efficacy of the herb on humans have also been published. As a result of clinical studies, positive results have been obtained by using *P. harmala* in addition to medical treatment for diseases such as osteoporosis and BPH. In addition, it is noteworthy that it reduces the side effects caused by drugs used in the treatment of gastroesophageal malignancy. For these reasons, clinical studies are needed especially on the metabolites of *P. harmala* in areas where preclinical studies are concentrated and positive results are obtained. The therapeutic mechanisms of action of *P. harmala* and its secondary metabolites should be clarified and the pharmacological effects determined by preclinical studies should be supported by clinical studies.

In vitro and *in vivo* studies have revealed that various extracts of *P. harmala* and *β*-carboline alkaloids have cytotoxic, genotoxic, mutagenic, cytotoxic, and reproductive toxicity. However, cases of poisoning, manifested by symptoms such as neurosensory symptoms, visual hallucination, bradycardia, hypotension, agitation, tremor, ataxia, and vomiting, associated with the use of *P. harmala* in humans have been recorded. Considering these, preclinical and clinical data on the safety of the plant and its isolated compounds need to be increased.

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Clinical and Experimental Health Sciences

The Effect of the COVID-19 Pandemic on the Surgery Process

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ABSTRACT

With this review, it was aimed to discuss the effect of the COVID-19 pandemic on the process before, during and after surgery. Studies that were accessed using the keywords "COVID-19", "perioperative" and "surgery" in Pubmed and Science Direct and Turkish databases were discussed. The measures taken with the declaration of the pandemic also affected surgical practices, and postponing elective cases other than emergency and cancer surgery was one of the common measures implemented in many countries. In addition to all these measures and recommendations, the fact that the operating room environment has some unique risk factors draws attention to the process before, during and after the surgery. Guidelines for the measures to be taken in the national and international arena are published in order to plan the workforce of health professionals and to use limited health care resources effectively, as well as to prevent the spread of COVID-19. These measures and recommendations are shaped according to the statistical fluctuation in the number of infected cases and health care resources in countries, and policies and procedures regarding the preoperative, intraoperative and postoperative period are updated. It is extremely important to follow the current literature in order to protect both patients and healthcare professionals involved in the surgical process and to prevent cross-contamination against the COVID-19 virus.

Keywords: COVID-19, Pandemic, Surgery Process, Perioperative

1. INTRODUCTION

With the first case seen at the end of 2019, the COVID-19 virus (SARS-CoV-2) spread rapidly all over the world and was declared a pandemic by the World Health Organization on March 11, 2020 (1). The COVID-19 virus has turned into a global public health problem that increases morbidity and mortality by affecting infected individuals in different ways, from symptoms such as cough, fever, fatigue, loss of smell and taste, to pneumonia, acute respiratory distress syndrome and multi-organ failure (2).

The transmission of the COVID-19 virus through droplets and contact brought practices such as hand hygiene, masks, social distance and social isolation (3). In addition, after the declaration of COVID-19 as a pandemic, various measures were taken in many countries in order to effectively plan healthcare resources and the workforce of healthcare professionals and to meet the increasing demand. These measures also affected surgical practices and included the postponement of elective cases other than emergency and cancer surgery (4).

In addition to all these precautions and recommendations, the operating room environment has some unique risk factors, which also draws attention to the operation process. Aerosol formation increases as a result of conditions such as gases used during intubation, extubation, laparoscopic procedures in surgical procedures, contact with body fluids in open surgery, or increased surgical smoke in the use of electrocautery (5,6). Aerosol formation also increases the risk of being infected with COVID-19 for surgical team members and patients (7). Another risk factor that increases the risk of transmission of COVID-19 is the possibility of air and surface contamination. Studies have reported that the half-life of the COVID-19 virus in ambient air is between 1.1-1.2 hours and it can remain contagious for up to 3 hours. In addition, it is stated that the virus remains alive on tools made of steel for about 48 hours. Accordingly, the use of steel in many instruments in the operating room may increase the risk factors for being infected with COVID-19 (8).

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In accordance with the dynamic nature of the COVID-19 Pandemic, the measures taken during the process have also changed. Many national and international guidelines for returning to elective surgery have been published. According to these guidelines, the decrease in the incidence of COVID-19 and the incidence of new cases in the last 14 days at the provincial level should be taken into account. In order for elective surgery to start again, a committee consisting of administrative and health managers should be formed and plans should be made by this committee. The workforce of surgical team members should be planned against the risk of a new COVID-19 wave. Adequacy of resources such as intensive care unit and service bed capacity, personal protective equipment adequacy, and the number of ventilators should be evaluated (9,10).

These measures and recommendations are shaped according to the statistical fluctuation in the number of infected cases and health care resources in countries, and policies and procedures related to the pre, during and post-operative period are updated (9,10).

1.1. Aim of the Review

In this review, it was aimed to discuss the effect of the COVID-19 pandemic on the process before, during and after the surgery.

2. PERIOD BEFORE THE SURGERY

2.1. Preoperative Patient Evaluation

Health professionals who take part in the preparation of the patient before the operation should use personal protective equipment, attention to hand hygiene and social distance rules (11). Before the pre-operative evaluation of the patient, nurses and doctors should collect their hair, wear a hospital gown, and tuck the trouser legs of the clothing into boots that fully cover the ankles, without holes and, if possible, sterilizable. Then, a bonnet, gloves, apron, FFP2(N95) mask, goggles or face-protecting transparent visor and a second layer of outer gloves that completely cover the hair are put on (12). All patients undergoing surgery should be evaluated in three groups based on the likelihood of having COVID-19 infection (ie, uninfected, asymptomatic, and symptomatic people). Before the operation, the general condition of the patient, the presence of active or recent respiratory or gastrointestinal symptoms, symptoms such as anosmia, fever, and a history of recent travel to an endemic country in the last 14 days or contact with a person at risk of contracting COVID-19 infection should be questioned. In cases requiring emergency surgery where the nasopharyngeal PCR test result cannot be expected, patients should be assumed to be infected with COVID-19 and should be approached similarly to infected patients (13,14). Thoracic computed tomography (CT) can be considered as an alternative to waiting for the PCR test result to determine the characteristic appearance of the lung, especially for patients with COVID-19 symptoms in emergency surgery (14). In these patients, all pre-, intra-, and post-operative precautions should be considered until the diagnosis is confirmed or the patient is discharged (13). Patients diagnosed with or suspected of COVID-19 should be taken to a separate area from patients who have proven to be negative for COVID-19, different predetermined routes should be used during in-hospital transfers, and if possible, they should be admitted to a single room to prevent cross-infection (11,13,15). It is recommended to clarify the patient's status of being infected with COVID-19 by obtaining a nasopharyngeal PCR sample 48-72 hours before surgeries other than emergency surgeries in a previously designated isolated area of the hospital (10,14,16).

The use of telemedicine methods in the pre-operative evaluation of patients will become widespread, allowing patients to spend less time in the hospital and determining the surgical priority (11,17). In addition, in order to protect both the patient and the healthcare professionals, the patient and, if any, the patient's relatives, from the moment they arrive at the healthcare institution, use personal protective equipment, primarily a mask (14). Many institutions have restricted visitors due to the pandemic. When a companion is required, the patient's relatives should be questioned in terms of COVID-19 findings and education should be given on ways to prevent them (10).

Patients who are scheduled for surgery should be questioned if they have three doses of COVID-19 vaccine before surgery, with the last dose at least 2 weeks before the surgery. Completion of vaccine doses as soon as possible should be encouraged during the confirmation of vaccination status and decision-making for surgery. Considering the high level of transmission of the Omicron variant despite vaccination, it is recommended to continue with the existing measures to reduce the risk of patients becoming infected with COVID-19 before, during and after the surgery (11).

While making the decision for surgery of patients diagnosed with COVID-19, surgical indications should be comprehensively evaluated with multidisciplinary cooperation before surgery. It is known in studies that the rate of pulmonary complications and mortality increases in COVID-19 positive individuals. Each patient should be evaluated individually according to the profit-loss balance, and the option of postponing the surgery for at least 7 weeks should be considered (18). This assessment should include the risk of mortality and complications, if possible with a validated risk scoring system, such as the patient's age, comorbid diseases, time of infection with COVID-19 and ongoing COVID-19 symptoms, surgical risk factors, and risk of progression of the condition requiring surgical indication. In addition, patients should be evaluated in terms of modifiable risk factors such as nutrition, exercise and smoking cessation before surgery. These patients should be evaluated in terms of regional or local anesthesia rather than general anesthesia (11).

2.2. Arrangement of the Operating Room

For cases diagnosed or suspected of COVID-19, the operating room should be selected in an area with separate access to the operating room and relatively isolated from other operating rooms. During the pandemic, it should be planned to use the same operating room and anesthesia device for COVID-19 patients (19). Signs should be placed on the door of the operating room in a clearly visible way against entering without a COVID-19 warning and personal protective equipment (15). Operating room equipment such as anesthesia monitors, computers, electrosurgical instruments, and ultrasonography device surfaces should be wrapped in plastic sheathing to reduce the risk of contamination and facilitate cleaning (14,20,21).

2.3. Preparation of the Surgical Team

Health workers; In addition to patients, their families and other hospital personnel, they are also in contact with day surgery of elective patients, so they are more likely to cause cross-infection. Therefore, daily assessment of health status of health professionals and recording of body temperature should be put into practice (22). Any healthcare professional should be questioned in terms of a history of increased body temperature, cough, cold, body aches, diarrhea, fatigue, contact with a COVID-19 patient without the use of Personal Protective Equipment (PPE), and isolated and investigated for the possibility of contracting the disease (10,22). N95/FFP2 or N99/FFP3 mask with high protection to the surgical team, safety glasses, clear face visor, durable liquid-proof gown, double-layer gloves (first should be washed with a layer of alcohol or virucidal agent), training should be given on the wearing and removal of personal protective equipment such as non-perforated shoes that cover the whole foot, or sterile rubber boots (15). Moreover, surgical team members should protect devices such as cell phones or pagers in a plastic sheath (14). In addition, health professionals who have just joined the surgical team should receive training (10). Two different areas should be designated close to the operating room for them to put on and take off the equipment. Informative articles such as posters explaining the correct wearing and removal procedures of personal protective equipment should be posted in these areas (22). Meeting of the surgical team before the operation seems to be effective in evaluating the current situation and ensuring effective cooperation during the operation process (23).

2.4. Patient Transfer to the Operating Room

The patient diagnosed with COVID-19 or suspected of being infected is transferred directly to the operating room after the surgical team is notified, as the surgical team and the necessary materials in the operating room are ready (24). Every non-intubated patient should wear a surgical mask, gloves, disposable cap and shoe cover during transfer If possible, hand hygiene should be provided before transfer (15). The transfer of the patient to the operating room is provided by the shortest route, away from common areas and with the least human traffic, taking into account the physical conditions of the hospital (19). Transfer personnel should receive training on the use of personal protective equipment. The patient should come from the clinic to the operating room with nurses and transfer personnel wearing personal protective equipment, and a minimum number of personnel changes should be made in this process. The patient should enter and exit the operating room as quickly as possible. If inter-hospital patient transfer or transfer from other buildings within the hospital is required, a special vehicle should be used. It is important that the driver and the patient are in different parts of the vehicle and that they use personal protective equipment. The elevators used in the transfer of the patient should be cleaned and disinfected at regular intervals and in case of any unexpected contamination during the transfer (15). Items related to COVID-19 should be added to the Safe Surgery Checklist, or A surgical checklist specific to COVID-19 should also be established (25).

3. SURGERY PERIOD

3.1. Admission of the Patient to the Operating Room

The patient is taken to the operating table after being greeted by the anesthesiologist and circulating nurse in the operating room. The stretcher on which the patient comes to the operating room is disinfected. If the planned surgical procedure does not require general anesthesia and the clinical situation permits, patients should continue to wear protective masks throughout the procedure (15). Keeping the patient's documents and records outside the operating room may reduce the possibility of contamination (6,20,26).

3.2. Arrangement of the Operating Room

If a patient has been diagnosed with COVID-19 or is highly suspected of being infected with COVID-19, surgery should be performed in a negative pressure operating room (27). Providing at least 25 air changes per hour is considered sufficient to effectively reduce the viral load in the operating room. Doors should be kept closed during surgery (6,20). Before the operation, only the necessary materials and equipment should be brought to the operating room. Once surgery has begun, every effort should be made to use the materials available in the room to minimize the risk of infection and to minimize personnel entering and leaving the operating room (15). Caution should be exercised in aerosol-generating applications, it is recommended to operate devices such as electrocautery at the lowest power and to use surgical smoke evacuation devices (13,26). Alcohol-containing solutions should always be available for hand hygiene (15).

3.3. Surgical Team and Anesthesia

After the surgical team member enters the operating room, they should not leave the operating room until the surgery is

completed and should not re-enter, if possible, after leaving the operating room (15). A heat and moisture exchange filter should be installed at the expiration outlet of the anesthesia device in the breathing circuit, and soda-lime and this filter should be replaced after each operation (6,19,28). The anesthesiologist should place all necessary medications and equipment on a tray prior to surgery. The anesthesia medicine cart should be located in the corridor in front of the operating room. In case of need for additional medication, hand hygiene should be provided and gloves should be changed before contacting the anesthetic medicine car. A staff waiting in the operating room or a second circulating nurse may be assigned to provide supplies. The healthcare professional assigned for the supply of materials should wear personal protective equipment when entering the corridor where the operating room is located (19). When communicating with these personnel, it is recommended to use a pager or telephone to avoid cross-contamination (24). During the anesthesia induction and intubation procedure, no one from the surgical team other than the anesthesia team should be present in the operating room. An experienced member of the anesthesia team should perform the intubation procedure (26). During anesthesia induction and patient awakening, surgical team members within 2 meters of the patient should use personal protective equipment and, if possible, a Powered Air Purifying Respirator (PAPR). All procedures, from the induction of anesthesia to the patient's awakening and transfer to the ward or intensive care unit, should be performed in a single operating room, if possible (19). Just like the surgical team, the anesthesia team should wear double gloves and the outer gloves should be removed after intubation (21). After the anesthesia application, the surgical team should come to the operating room to position the patient, wearing non-sterile personal protective equipment. Then, removing the non-sterile gown and gloves in the operating room, and putting on the personal protective equipment such as surgical hand washing, sterile gloves, sterile surgical gown and second layer of sterile surgical gloves, the operating room should be re-entered (15,29). In these cases, it is recommended to form a separate team with more experience (30).

4. PERIOD AFTER THE SURGERY

If a patient diagnosed with COVID-19 is to be transferred directly to the intensive care unit, a dedicated transport ventilator should be used. To reduce aerosol risks, gas flow should be turned off and the endotracheal tube should be clamped with forceps when switching from an operating room ventilator to a portable device (15). Intensive care personnel should use personal protective equipment and, if possible, PAPR during transport (19). The route used should be disinfected while transferring from the operating room to the intensive care unit or surgical service after the surgery (15). Samples taken from a patient diagnosed with COVID-19 during surgery should be placed in double bags and labeled as 2019 nCoV and handled as infectious samples in the pathology laboratory (13,22,31). During the transfer of the patient from the operating room, the responsible healthcare professional should wear personal protective equipment different from those worn in the operating room (15).

Surgical team members should remove the upper glove, durable waterproof apron and shoe cover and throw them in the biological waste bin to provide hand hygiene. Then, the face visor and gloves should be removed and hand hygiene should be ensured, and the N95 mask should be removed last. Surgical team members should take a shower after each operation (20).

A minimum of one hour is scheduled between surgery of elective patients to allow operating room personnel to provide patient transfer, to operate through decontamination of all surfaces in the operating room, screens, cables, monitors, and anesthesia equipment (19). After the patient leaves the operating room, all disposable materials should be thrown into biological waste bags, even if they are not used. Disposable materials must be closed and sealed in the operating room before being transported to the waste management predetermined waste collection area. When waste bins are damaged, they must be replaced immediately. Personnel involved in closing and transporting waste bins should wear personal protective equipment and should be removed immediately afterwards. Likewise, textile products such as sheets and pillows should be chosen for single use if possible. Non-disposable laundry (pillow, pillowcases, crossbars, etc.) should be thrown directly into special collection boxes and the boxes should be closed and sealed before being sent for sterilization (15). Decontamination, disinfection and sterilization processes should begin for reusable instruments. Instruments that are visibly contaminated with blood and body fluids should be cleaned in a designated area before disinfection (28). Surgical instruments should be labeled as COVID-19 and delivered to the sterilization unit in double-layer medical waste bags and closed boxes. In addition, the sterilization unit should be informed (32,33). It is recommended that all surfaces in the operating room be sprayed with a quaternary ammonium chloride compound and wiped with a dry cloth after 1-3 minutes (34).

Surface disinfection of floors, walls and medical devices in the operating room where COVID-19 cases are accepted should take at least 30 minutes and a disinfectant containing 1000mg/L chlorine should be used. This process should be applied 3 times a day and should be repeated in case of contamination. Surface cleaning should be done from the clean area to the dirty area, and the cloth used for cleaning different areas should be renewed. Reusable surgical instruments exposed to patient body fluids; If there is no visible contamination in the disinfectant containing 1000mg/L chlorine; If there is visible contamination, it should be kept in disinfectant containing 5000mg/L chlorine for at least 30 minutes, after drying, the devices should be completely closed, packaged and sent to the sterilization center (35). After cases of COVID-19, hydrogen peroxide vapor or ultraviolet-C rays should be used for cleaning the operating room (19,34,35).

A record should be kept of the surgical team involved in procedures involving potentially infected patients (15).

5. POSTOPERATIVE PATIENT CARE

To minimize the risk of post-operative contamination and limit it to a single operating room, patients with a diagnosis of COVID-19 should not be brought to the Post-Anesthesia Care Unit (PACU) (20,34). While the patients diagnosed with COVID-19 are transferred to the previously determined COVID-19 services in line with the physical facilities of the hospital after the surgery; negative patients can be transferred to the standard surgical service (24). Negative patients also require daily assessment of body temperature and respiratory symptoms. Any patient with a new-onset fever or cough should be isolated and thoroughly investigated to rule out COVID-19 infection. Patients with a suspected or confirmed diagnosis of COVID-19 should be isolated in a negative pressure single room. Personal protective equipment should be used in all interventions such as postoperative patient care, medications, and wound treatment (13,22,31). In addition, the post-operative administration of COVID-19 treatment to infected patients is controversial, but multidisciplinary follow-up by anesthesiologists and pulmonologists is required due to the prevalence of postoperative pulmonary complications in these patients (12). Moreover, it is thought that the positive results of ERAS protocols, such as less postoperative complications, shorter hospital stay and lower cost, will have positive effects for patients undergoing surgery in the COVID-19 Pandemic (15,36).

6. CONCLUSION

In this review, national and international publications regarding the pre, during and post-operative period with the declaration of the COVID-19 pandemic were reviewed. The surgical process, by its nature, consists of a complex chain of events that are stressful and require attention. By adding the risk of an infectious disease to this chain; A multidisciplinary cooperation is required from the pre-operative preparation of the patient to the discharge. These measures and recommendations are shaped according to the statistical fluctuation in the number of infected cases and health care resources in countries, and policies and procedures regarding the preoperative, intraoperative and postoperative period are updated. It is extremely important to follow the current literature in order to protect both patients and healthcare professionals involved in the surgical process and to prevent cross-contamination against the COVID-19 virus.

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Clinical and Experimental Health Sciences

Nanoparticles and Their Application in Prosthetic Dentistry

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ABSTRACT

In recent years, nanoparticles produced with nanotechnology have been widely used in many fields of medicine and dentistry such as prosthetic dental treatment. The advanced properties of nanoparticles such as biocompatibility, durability, solubility, large surface area, high stability, and thermal conductivity facilitate the development of dental materials. Compared to the traditional materials used, they can offer useful features, such as better diagnosis, treatment plans, improvement, and protection of oral health. Therefore, a better understanding of nanotechnology and nanoparticles is essential to appreciate how these materials can be utilised in our daily practice. This review provides an overview of nanoparticles and their applications in dentistry.

Keywords: Nanoparticles, nanomaterials, prosthodontics, denture bases, implantology.

1. INTRODUCTION

The term “nano” describes the research and development of science at the atomic or molecular level, leading to fields such as nanotechnology or nanoscience (1). Nanotechnology is defined as the manipulation of matter in sizes ranging from 1 to 100 nanometers (nm), while a nm is a unit of billionth (10-9 meters) meter in length, denoting dimensions of a matter at the atomic scale (2). Nanomaterials are defined as materials consisting of 50 % or more particles having a size between 1nm-100nm by The European Commission (3).

Nanoparticles can have different morphologies such as prisms, rods, cubes, spheres, and different structures and forms such as nanocrystals, nanocoatings, nanotubes, and nanofibers (4). Nanotechnology and nanoparticles can be used in various medical fields such as pharmacological research, clinical diagnosis, support of the immune system, cryogenic storage of biological tissues, detection of proteins, investigation of DNA structure, and tissue engineering (1). The change in the mechanical, optical, chemical, and electrical characteristics of nanoparticles has led to developments in nanomaterials and biotechnology, and it has increased their use in various industrial sectors, medicine, and dentistry (2,5).

Most of the research in dentistry is conducted to develop materials that are biocompatible and can withstand the hard conditions of the oral environment. The use of nanoparticles in dentistry is increasing rapidly due to physicochemical and biological characteristics such as biocompatibility, durability, solubility, large surface area, high stability, and thermal conductivity. However, some nanoparticles have disadvantages and limitations such as toxicity and limited availability besides their numerous advantages (4).

Although there are many synthesis methods such as mechanochemical processing, sol-gel, thermal decomposition, ionic-liquid route, hydrothermal synthesis, spray pyrolysis, and emulsion precipitation in the synthesis of nanoparticles, the most frequently used methods in dentistry are sol-gel method and hydrothermal synthesis method (4,6,7).

Sol-Gel Synthesis Method: It is difficult to control the structure during the production of nanoparticles. In the sol-gel synthesis method, nanoparticles can be obtained in desired sizes homogeneously and in different structures such as nanofibers, nanowires, nanotubes, flakes, flowers, and stars (8).

Sol is defined as a stable colloidal suspension of solid particles in a liquid, while gel is defined as a stably expanding, porous, three-dimensional, and semi-solid mesh. Particle characteristics and phase structure can be changed by using the two most common precursor groups: metal alkoxides and

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metallic salts. The most common nanoparticles for dental materials are metal oxides (7,9,10).

Nanoparticles such as silica (SiO2) and zirconium (ZrO2) produced by the sol-gel method are used in many fields such as nanofill composites, glass ionomers, and adhesives (11). Although the advantages of the sol-gel synthesis method can be counted as providing high purity and homogeneous dispersion nanoparticle synthesis, being easy and commercialized, longer synthesis times, and low sintering capacity can be counted as the disadvantages (7). Shukale and Seal (12), successfully synthesized nanocrystalline ZrO2 nanoparticles which contain 100% tetragonal phase, by the sol-gel method.

Hydrothermal Synthesis Method: The hydrothermal method is an ideal technique to synthesize various nanomaterials with high purity and controlled microstructure (6). It is an advanced technology for the preparation of nanocrystal by a chemical reaction in an aqueous solution under high temperature and pressure. The hydrothermal synthesis method has many advantages such as high purity, various crystal shapes, homogeneous distribution, saving time, and providing controllable size particle synthesis; against these advantages excess equipment and high heat requirement are considered disadvantages (7).

Taguchi et al. (13) synthesized ZrO2 nanoparticles by hydrothermal method and found that the products synthesized at temperatures above 300°C contained the mixtures of tetragonal and monoclinic phases, while the products synthesized at 200°C showed an amorphous phase. Arantes et al. (14) synthesized ZrO (NO3) 2.H2O and ZrOCl2. 8H2O aqueous solutions by hydrothermal treatment at 110°C for 24 hours and obtained pure nanocrystalline stable monoclinic zirconia colloids.

1.1. Dentistry and Nanoparticles

The use of nanoparticles in dentistry is rapidly increasing due to their physicochemical and biological properties such as biocompatibility, durability, resolution, high stability and thermal conductivity. The use of nanoparticles is promising because they are materials that can help prevent or eliminate oral problems such as dental caries, periodontal disease, peri-implantitis, oral candidiasis, and shorten the treatment period (4). Hydroxyapatite (HA), SiO2, Carbon (C), Titanium dioxide (TiO2), and ZrO2 are some of the nanoparticles used in dentistry (5).

In dentistry, nanotechnology has started with the addition of nanoparticles to filling materials, and nanoparticles are used in the production of bone graft materials, endodontic antimicrobial irrigation agents, sealer materials, remineralization agents, orthodontic wires and brackets, dental implants, dental prosthesis materials, anti-sensitivity and whitening agents, tooth enamel polishing agents, and anti-caries agents (5,15).

1.1.1. Nanoparticles in surgical treatments

Nanotechnology and nanoparticles are used in many areas of surgery such as improving implant surface properties, increasing osteointegration, tissue compatibility and biocompatibility, production of bone grafts, and in the diagnosis and treatment of oral cancers.

1.1.1.1. Use in implant treatments

Dental implants can be coated with various nanoparticles using nanotechnology. The surface of the implant plays a critical role in ensuring biocompatibility and osteointegration in implant supported prostheses, which is the gold standard treatment option for tooth loss. Coating the implants with pharmacological nanoparticles such as nano TiO2, HA, calcium phosphate (Ca3(PO4)2), calcium silicate (Ca2O4Si), C and bisphosphonates induces cell differentiation, and proliferation and can provide a suitable environment for early and long-term bone formation by increasing vascularity in cortical bone (16).

Due to its similarity to the inorganic components of bone, nano-HA is the most preferred nanocoating for dental implants. Implants with nano-HA surface showed better osteointegration, bone formation, and better bone-implant interaction (17,18). Yang et al. (19) evaluated the effects of titanium implants coated with nano-HA on osseointegration after 6 and 12 weeks of placement and showed that HA nanoparticles increased osteointegration.

Copper, bismuth and silver (Ag) nanoparticles with antibacterial properties are used for the prevention and treatment of periimplantitis. TiO2 nanoparticles significantly reduce microbial adhesion, roughness, and chemical weathering on implants, significantly reducing the number of bacteria attached to the implant surface (5).

1.1.1.2. Use in graft materials

Bone is a natural nanostructure composed of organic compounds reinforced with inorganic structure. Bone grafts are materials that mimic natural bone. Nanocrystals containing calcium as in bones and collagen particles mimicking soft tissues around bones can be used as bone-like nanoproducts. The mixture of nanocrystalline calcium sulfate particles and calcium sulfate hemihydrate powder is one of the graft materials produced with nanotechnology (20).

1.1.1.3. Use in diagnosis and treatment of oral cancers

The very small size of the nanoparticles allows them to pass through the kidneys, be carried into the tumors through the vessels, and collected in the tumors. Therefore, in cancer treatment, multifunctional nanoparticles like cadmium selenide can be produced that will detect, image, and treat tumors (21).

Magnetic, colloidal gold, and ceramic nanoparticles have been used in new and effective drug systems developed with

nonatechnology to eliminate the disadvantages of existing cancer treatment techniques (22).

1.1.2. Nanoparticules in endodontic treatments

In endodontic treatments, nanoparticles are used as antimicrobial agents to reduce the disadvantages of traditional antibacterial agents. Nanoparticles can also be used by adding them to sealers, canal filling material, intracanal medicaments and irrigation solutions (23).

1.1.2.1. Use in irrigation solutions

Nanoparticles can be added to traditional irrigation solutions such as chlorhexidine (CHX), sodium hypochlorite (NaOCl), and chitosan in order to reduce their cytotoxic effects on the surrounding bone and soft tissues (23). Ag and chitosan nanoparticles are frequently used because of their rapid bactericidal effect, biocompatibility, low toxicity, and long-term antibacterial activity (23,24) It has been shown that Ag nanoparticles provide superior antibacterial effect compared to 2.5% NaOCl (25).

1.1.2.2. Use in intra-canal medications

Intracanal medicaments function as anti-inflammatory and antibacterial agents that can be used between appointments (23). While calcium hydroxide paste is commonly used, the addition of Ag nanoparticles (20 nm) to calcium hydroxide can increase the antibacterial effect of the material (25).

1.1.2.3. Use in canal filling materials

Gutta percha, Ag tips, and resilon are commonly used obturation materials for root canal filling. The addition of bismuth oxide, niobium oxide, and ZrO2 nanoparticles into the canal filling materials provides a radiopacifying effect and facilitates treatment follow-up on the radiograph (7).

Ca2O4Si nanoparticles ranging in size from 80 to 100 nm are viscous, antibacterial stimulating bone formation, and are used in the apical third of root canals (26). To improve the properties of endodontic pastes, nanoparticles such as chitosan and zinc oxide (ZnO) can be used to prevent bacterial penetration (4,27).

1.1.3. Nanoparticles In Restorative Treatments

Nanotechnologies can be used for the production of dental composites (nano-composites), glass ionomer cements (nano-ionomers), and materials that regenerate dental tissues.

Ultra-dispersed supramolecular nanoparticles with sizes between 10 micrometer (µm) and 1000 µm can prevent the caries formation process by providing remineralization of the teeth by adding them to toothpaste and mouthwash (28).

1.1.3.1. Use in glass ionomer cements

Conventional and resin-modified glass ionomer cements have disadvantages such as poor aesthetics, mechanical properties, and bond strength, as well as beneficial properties such as releasing fluoride and remineralizing tooth structure in the oral environment. Chitosan, HA, fluorapatite, TiO2, SiO2, and ZrO2 nanoparticles can be added to glass ionomer in order to improve its aesthetic properties (29). Resin-modified glass ionomers containing fluoroaluminosilicate nanoparticles are widely used in clinical practice. In a new nanomaterial, 15% SiO2 nanofillers in 40 nm size were added to the ionomer, and better wear resistance and a reduction in curing time were observed (30). The addition of nano-HA (100–150 nm) to resin-modified glass ionomers increased the bond strength to tooth structure (31).

Kumar et al. (32) showed that the addition of 10% by weight chitosan nanoparticles to the glass ionomer cement increased the resistance of the material and the fluoride release, while İbrahim et al. (33) showed that the addition of TiO2 nanoparticles showed antimicrobial activity with biofilm inhibition and improved some physical properties.

1.1.3.2. Use in dental composites

The use of nanoparticles has increased to improve the physical and aesthetic properties of dental composites and to overcome problems such as polymerization shrinkage, wear resistance, and microhardness.

The most widely used resin nanocomposites are nano-hybrid and nano-filled composites containing fillers in varying proportions (1-100 nm, 20-600 nm) (2,29). Nanofillers mainly contain particles of 1 to 100 nm in size, while nano-hybrids consist of larger particles ranging from 0.4 to 5 µm. Resin-based composites contain glass fillers of barium, zirconium, strontium, or ytterbium. These amorphous particles are usually 400 nm-1µm or larger in size (15,34).

The addition of SiO2 nanoparticles into composite materials increases wear resistance in posterior applications, while SiO2-HA-based nanoparticles relieve dental sensitivity and reduce enamel decalcification (5,35).

1.1.4. Nanoparticles in orthodontic treatments

Roughness, surface free energy, and friction force properties play an important role in orthodontic brackets and archwires. Nanoparticles can be added to the materials in order to improve the mechanical and physical properties of the materials used in orthodontics (1).

Katz et al. (36) reported that orthodontic braces coated with tungsten disulfide nanoparticles reduce the friction force that occurs during orthodontic movements. Cao et al. (37) showed that brackets coated with nitrogen-doped TiO2 nanoparticles were effective in preventing enamel demineralization and gingivitis in patients.

1.1.5. Nanoparticles in prothetic treatments

Nanotechnology is able to develop newer materials with better properties in prosthetic treatments. Nanoparticles such as SiO2, TiO2, Ag, and ZrO2 are used to improve the properties of materials such as resin-containing denture base materials, dental composites, dental impression materials, bonding cements, tissue shapers, dental implants, dental ceramics, and maxillofacial prostheses (5).

1.1.5.1. Use in acrylic resins

Due to its biocompatibility, aesthetics, and stability in the oral environment, ease of repair, tasteless and odorless, high polishability, low cost, and removable dentures are generally made with traditional heat-polymerized polymethylmethacrylate (PMMA) material. However, it has poor mechanical properties such as low bending and impact strength, fracture and fatigue resistance, and insufficient surface hardness, allowing microbial adhesion.

In order to improve the physicochemical properties of the material, zirconium oxide, TiO2, aluminum, and SiO2 nanoparticles are added to PMMA. With the addition of ZrO2 nanoparticles, the dimensional accuracy and tensile strength of the material can be increased significantly, and it can also reduce the adhesion of candida to the surface. However, as the nano-ZrO2 concentration increases, the translucency of PMMA may decrease (4,38).

Gad et al. (39,40), in their studies, achieved an increase in the bending strength of the denture base in repairs made by adding different sizes and different amounts of nano-ZrO2 into auto-polymerizing acrylic. In Ashour and Ebrahim's study (41), it has been shown that the addition of 5-15 nm ZrO2 nanoparticles to PMMA increases its mechanical properties.

TiO2, ZnO, and Ag nanoparticles can be added to PMMA due to their antimicrobial properties and prevent prosthetic stomatitis (4,42–44). Karci et al. (45) showed that SiO2 nanoparticle groups had lower flexural strength compared to TiO2 and aluminum nanoparticle-added groups.

The addition of C nanoparticles to heat-polymerized acrylic reduces polymerization shrinkage and improves mechanical properties. Cooper et al. (46) showed that the addition of a small number of C nanotubes will significantly increase the impact strength of PMMA.

1.1.5.2. Use in dental composites

Synthetic resins are widely used because they are insoluble, aesthetic, insensitive to dehydration, easy to manipulate, and inexpensive. Nano-fillers of 1-100 nm are added to the resin matrix to produce nanocomposites. There are two types of nanoparticles used; nanomers and nanoclusters (47). The nanomers are monodispersed, and non-clustered SiO2 particles. Nanocluster fillers are 2-20 nm in size (47,48).

Nanocomposites can be divided into subgroups as nanofill composites, nanohybrid composites, TiO2 added resin-based composites, alumina (Al2O3) nanoparticle composites, Ca3(PO4)2 and calcium fluoride (CaF2) nanoparticle-based nanocomposites, and ormosers (organically modified ceramics) with fillers in the range of 1-100 nm (47–49).

1.1.5.3. Use in dental adhesives

It is common to use polymerizable silane-treated filler particles to increase the strength of dental adhesives that provide material interdental adhesion-cohesion. Because adhesives are not very viscous, filler particles have a tendency to settle during storage. To overcome this disadvantage, SiO2 and ZrO2 nanoparticles of 5-7 nm are added to the adhesives. These particles are so small that they cannot be seen with the naked eye and are not affected by gravity, and stable suspensions can be obtained without a reduction in bond strength (50). With the addition of nanoadhesives, bond strength to enamel and dentin can be increased, and a longer shelf life can be achieved. By adding nanoparticles such as ZrO2, radiopacity can be gained (47).

1.1.5.4. Use in composite dentures

In removable dentures, teeth made of materials such as porcelain and acrylic are used, but acrylic teeth wear over time. Nanocomposite dentures contain homogeneously dispersed nanofillers and polymethyl methacrylate. They show high durability and polishability, increased shear strength, superior aesthetics and higher wear resistance (51).

Abbas and Sakr (52) compared the wear rate between nanocomposite and acrylic dental materials containing 75 nm SiO2 nanoparticles and showed that nano-composite dentures have higher but similar wear resistance than PMMA dentures.

1.1.5.5. Use in tissue conditioners

Tissue conditioners are widely used to heal tissues in removable prostheses. These materials degenerate over time and become susceptible to colonization by microorganisms. The addition of Ag nanoparticles to tissue conditioners provides antimicrobial properties against S.aureus, S.mutans, and C.albicans (48,49). Nam (53), after an incubation period of 24 hours and 72 hours in tissue conditioners supplemented with Ag nanoparticles, S.aureus, S.mutans, and C.albicans showed that it exhibited antimicrobial properties against albicans.

1.1.5.6. Use in soft lining material

Soft prosthetic lining material is used to reduce the forces transmitted to the supporting tissues and to prevent trauma. Soft linings can cause differentiation of material structure due to high humidity and high temperature under the dentures. This causes an increase in pathological microorganisms. It has been shown that the addition of TiO2, chlorhexidine, or Ag nanoparticles in high concentrations into the soft lining material has antimicrobial activity against candida species and

is effective in preventing denture stomatitis (42,54). Garner et al. (55) showed that the addition of CHX nanoparticles to dental silicones prevented denture stomatitis by providing an antifungal effect against C.albicans, which plays a role in oral fungal infections in removable dentures.

1.1.5.7. Use in dental cements

By adding nanoparticles to dental bonding cements, properties of cements such as fracture toughness, bending strength, compressive strength and antibacterial activity have been improved. It is very important for dental cements to show antibacterial properties, and Ag nanoparticles have been added to dental cements for this purpose. Resin composite cement containing Ag nanoparticles has been shown to have a long-term antibacterial effect against S.mutans and has good mechanical properties (48).

It has been found that nanoparticle-added dental cements provide a significant increase in bond strength compared to conventional cements and have very good bonding to dentin tubules and reduce polymerization shrinkage (56). In Karimi et al. (57)'s study, ZnO and MgO nanoparticles were added to improve the compressive and tensile strength of zinc polycarboxylate cement, and they showed excellent physical and mechanical strength compared to conventional zinc polycarboxylate cements.

The addition of nano-HA/fluorapatite and TiO2 particles to glass ionomer cements significantly increased compressive, tensile, and biaxial flexural strengths compared to conventional glass ionomer cements (58,59).

1.1.5.8. Use in impression materials

An ideal impression material should be biocompatible, have a suitable density but a fluidity to give details, be hydrophilic, provide dimensional stability, and have elasticity. In order to provide these properties and to improve the physical and mechanical properties of the impression materials, nanoparticles can be added.

The addition of nanoparticles to polyvinylsiloxanes, which are impression materials, improves their hydrophilic properties, fluidity, and clarity compared to conventional polyvinylsiloxanes (60). It exhibits high tear resistance, resistance to degradation and increased fluidity. The slip-cast feature and heat resistance reduce the errors caused by movements during impression (20).

The antimicrobial properties of impression materials such as alginate can prevent cross-infections. Nano-Ag particles can be added to impression materials due to their antibacterial properties (61). Omidkhoda et al. (61) showed that the addition of Ag nanoparticles at 500 ppm and 1000 ppm concentrations to the alginate material reduced the growth of E.coli, S.aureus, and C.albicans on the alginate surface, but did not completely prevent it.

1.1.5.9. Use in maxillofacial prosthesis

Maxillofacial prostheses are made of various artificial materials such as silicone, polyvinyl chloride, polymethyl methacrylate, polyurethanes, and chlorinated polyethylene. In addition to the positive features such as acceptable tear, tensile, high mechanical strength, and ease of production, silicones have negative features such as discoloration, deterioration of their physical and mechanical properties, and repair difficulties. In addition, it has disadvantages such as short usage time and contamination. In order to overcome these problems, better strength and flexibility can be achieved by adding many nanoparticles to it.

Due to its antibacterial properties, Ag nanoparticles were added to the materials and it was observed that it prevented C. albicans from adhering to the surface of these prostheses (62).

Silicone elastomers are very sensitive to tearing due to the mobility of facial structures such as the eyes, mouth, and nose. The addition of nano-sized Ti, Zn or Ce oxides in concentrations of 2.0-2.5% by weight increases the tear and tensile strength and stretching percentage to have certain flexibility for ideal facial prostheses (63,64).

Polymer molecules are more sensitive to ultraviolet (UV) light, and when exposed, it degrades and causes the molecules to break into smaller pieces and changes the shape of the molecule. Nano-sized ZnO, TiO2 and cerium dioxide (CeO2) are mainly used as UV shields (63).

Pigments are added to the silicone elastomer material to color the maxillofacial prosthesis material (65). Han Y. et al. (66) studied the color stability of pigmented maxillofacial silicone elastomer, nano – TiO2, ZnO, and CeO2 were used as opacifiers for the silicone elastomer, and TiO2 and CeO2 caused the least color change.

1.1.5.10. Use in dental ceramics

In prosthetic dentistry, ceramics have become increasingly common in restorative materials due to their aesthetic properties, chemical stability, biocompatibility, low plaque accumulation, low thermal conductivity, and radioactivity compared to metal alloys (67,68).

Dental ceramics are obtained by mixing kaolin, quartz, and feldspar at high temperatures (69). Apart from these three main substances, various color pigments, intermediate oxides, glass modifiers, opacity, and gloss additives can be added to their structures (70).

During the last 20 years, studies have focused on the strengthening of dental ceramics by modifying their microstructure, and different ceramic materials have been produced by adding particles of different sizes to the material content. Particles of nano-size have been used to develop ceramics in recent years.

The composition, microstructure and properties of ceramics determine various ceramic classifications and clinical indications. Ceramics vary in production techniques,

infrastructure, microstructure, etc. classified in many different ways. Gracis et al. (71) according to their structural characteristics, dental ceramics and ceramic-like materials are divided into three main groups as glass matrix ceramics, resin matrix ceramics, and polycrystalline ceramics.

- Glass Matrix Ceramics; It contains glass phase, nonmetallic, and inorganic ceramic materials. It is divided into subgroups as feldspathic, synthetic, and glass infiltrated ceramics.
- Feldspathic ceramics is a traditional ceramic group consisting of feldspar, quartz, and kaolin. They are the most translucent and aesthetic materials and have disadvantages such as low flexural strengths, and brittleness.
- Synthetic ceramics are grouped under three headings: leucite-based, lithium disilicate-based, and fluoropatite-based (71).

Zirconia reinforced lithium silicate ceramics (ZLS); are obtained by adding approximately 10% by weight of zirconia to glass-ceramics. Crystal particles (0.6-0.8 µm) in ZLS ceramics are significantly smaller than crystal particles (2.5 µm) in conventional lithium disilicate glass ceramics, but larger than particle sizes in nanoceramics (72).

- Glass Infiltrated Ceramics; are possible to divide glass infiltrated ceramics into 3 groups as alumina, alumina and magnesium, and alumina and zirconia.
- Resin Matrix Ceramics; are mainly polymer matrix materials with durable inorganic content such as glasses, porcelains, ceramics and glass ceramics. Resin nanoceramics are divided into subgroups as glass-ceramics in the resin matrix and zirconia-silica ceramics in the resin matrix.
- Resin Nanoceramics are ceramic materials containing nanoparticles to improve the deficiencies of dental ceramics. Atoms added to a nanoscale structure can cause different changes in physical properties. While the material is mechanically weakened or strengthened, another property may change completely and different physical properties may emerge. Nanoceramics have been shown to be more durable and have higher wear resistance than restorations made from conventional ceramics, acrylic materials, and microfilled composites. Many nanoceramics have higher hardness and strength than conventional materials (49,73,74).

One of the materials in this group is a material consisting of 80% of its weight in a resin matrix by adding nanoceramic particles. The nanoceramic, that is, the inorganic part, forms SiO_2 nanoparticles with a diameter of 20 nm, ZrO_2 nanoparticles with a diameter of 4-11 nm, and $SiO_2 – ZrO_2$ nanoclusters that fill the gaps between the filler (71).

In another nanoceramic material produced by nanotechnology, 20 nm SiO_2 and 300 nm barium glass fillers constitute 71% of the inorganic part by weight. Having a dentin-like modulus of elasticity and high-stress absorption without deterioration, it is one of the most recommended materials to produce crowns on implants (69,75,76).

- Resin matrix glass-ceramics are ideal restorative materials formed by combining composites with elastic modulus close to dentin and feldspathic ceramics with elastic modulus close to the enamel. Its contents are 86% by weight of feldspathic ceramic enriched with aluminum oxide, while the organic matrix is composed of UDMA and TEGDMA monomers (76).
- Resin Matrix Zirconia-Silica Ceramics consists of 85% inorganic and 15% organic matrix consisting of different monomers. This material is the first resin composite material shaped by Computer Aided Design/Computer Aided Manufacturing(CAD/CAM), consisting of 85% by weight $ZrO_2 – SiO_2$ ceramic particles. $ZrO_2 – SiO_2$ filler particles are synthesized by the sol-gel synthesis method with a spherical shape and average particle size of 0.6 µm (77).
- Polycrystalline Ceramics are nonmetallic, inorganic ceramic materials and do not contain any glass phase. They are divided into the following subgroups; alumina, stabilized zirconia, zirconia reinforced alumina and alumina reinforced zirconia ceramics.
- Alumina ceramics contain high purity Al_2O_3 in amounts reaching 99.5%. It is produced with CAD/CAM system to be used as core material.
- Zirconia Reinforced Alumina and Alumina Reinforced Zirconia Ceramics contain alumina and zirconia in micro or nano scales. Zirconia-reinforced alumina (ZTA, zirconia-toughened alumina) and alumina-reinforced zirconia (ATZ, alumina-toughened zirconia) ceramics have been developed because zirconia is generally partially stabilized in the tetragonal phase, and alumina has a durable structure. It is recommended that ZTA contains at least 50% alumina, and ATZ contains at least 50% zirconia (71).
- Stabilized Zirconia Ceramic is one of the most preferred ceramic metals in recent years due to its high mechanical strength. It can be found in nature in the forms of ZrO_2 and zirconium silicate ($ZrSiO_4$). Pure zirconia exists in three crystalline phases. It exists in the monoclinic (m) phase at room temperature, in the tetragonal phase (t) above ~1170°C, and in the cubic (c) phase above ~2370°C (78). When unstabilized zirconia is heated above the phase transition temperature and cooled at room temperature, its crystal structure changes from the tetragonal phase to the monoclinic phase. Zirconia does not have sufficient mechanical strength in the monoclinic phase, so stabilizing oxides such as Calcium Oxide (CaO), Magnesium Oxide (MgO) and Yttrium Oxide (Y_2O_3) are added to its composition in order to keep it partially stabilized in the tetragonal phase at room temperature (79,80).

First-generation Zirconia Polycrystals (3Y-TZP) stabilized with 3 mol% yttria show very good mechanical strength. Phase transformation from tetragonal to monoclinic in the material

provides high mechanical strength due to volume increase in crystals (79–81).

First-generation zirconia has high opacity due to its 0.25% aluminum oxide content by weight (78,82). This material can be used both as a substructure and as a two-layer (83,84). For the monolithic use of zirconia, the number of Al2O3 grains has been reduced, the particle size has been reduced, the sintering temperature has been increased compared to the first generation, and this material is called second-generation zirconia, but the strength and light transmittance were not found sufficient (78,85).

Third-generation yttria partially stabilized or fully stabilized zirconia polycrystals (Y-PSZ, Y-FSZ) produced to obtain more aesthetic and translucent monolithic restorations have been introduced. Due to the higher Y2O3 stabilizer content (approximately 5-9.3 moles by weight) compared to the first and second generation, it is not only metastable in the tetragonal phase but also contains a cubic phase ratio of up to 53% (85,86). However, while the increase in the cubic phase is an advantage as it increases the translucency, it is a disadvantage that it causes a decrease in the tetragonal-monoclinic phase transformation ratio formed by stress in zirconia. Because by reducing the hardness of the material, it causes a decrease in strength and a decrease in its mechanical properties (78,86,87).

In a few studies conducted in recent years, it has been tried to increase the strength of the material by eliminating the negative effects of the mechanical surface treatments applied to the crowns with nanoparticle coating methods on monolithic crowns. For production and harmonization with CAD/CAM systems, etching, finishing, and polishing operations are required (88,89).

The applied surface treatments can cause topographic changes, damage, and t-m phase transformation in dental zirconia (84). In the case of cracks in the material due to mechanical, physical, and chemical stimuli, the phase of the crystals around the crack changes from tetragonal to monoclinic and causes a 3-4% volume increase in the crystals. This increase in volume can provide high mechanical strength to the material by forming a compressive stress layer that absorbs energy and stops crack formation and propagation. However, the increase in stimuli can also create a negative effect by causing excessive cracks and a decrease in the strength of the material (79–81). Compared to the first and second generations, the third generation zirconias, which contain up to 53% cubic phase ratio, have lower hardness and strength than the previous generations due to the reduction of the tetragonal-monoclinic phase transformation ratio that occurs with stress in the zirconia (86).

1.1.5.11. Use in dental glaze material

Dental glaze application is applied to provide aesthetics in ceramic restorations and to smooth rough surfaces (90). In various articles, the changes in the physical and mechanical properties of ceramics by adding various nanoparticles into the glaze material were investigated.

Venkatesh et al. (91) added the nano-ZrO2 particles synthesized using the sol-gel method into the glaze at different rates and showed that the increase in the nano-ZrO2 content directly increased the wear resistance of the material. Moosa et al. (92) applied a glaze containing nano-Al2O3 with 13nm particle size at different rates on zirconia restorations and determined that it was effective in increasing the resistance of the restoration.

In order to increase the strength and mechanical properties of zirconia material, the idea of coating the material with nanoparticles has been studied by several researchers.

Okada et al. (93) researched on the durability of Y-TZP material coated with 21 nm monoclinic phase ZrO2 nanoparticles obtained by hydrothermal method. They stated that due to the smaller thermal expansion coefficient of the mZrO2 coating layer compared to the Y-TZP material, compression stresses occur after thermal heat treatment, and this increases the mechanical strength of zirconia.

Uno et al. (79) applied a solution containing SiO2 and m ZrO2 nanoparticles obtained by hydrothermal method to translucent Y-PSZ material at different rates and temperatures; its mechanical properties were investigated, and they showed that the flexural strength of the coated samples at 10/1 mZrO2/SiO2 ratio and heat treatment at 1500°C increased significantly compared to other samples and sintered Y-PSZ. It was determined that the flexural strength increased significantly compared to the control group.

In Fujii et al. (94)'s study to increase the mechanical strength of the highly translucent Y-PSZ material with a yttria content of 5 mol%, 20-50 nm nano-ZrO2 particles in monoclinic phase were used as coating material. Heat-treated samples showed a significant increase in mechanical strength compared to the control group.

2. CONCLUSION

In the fields of dentistry and prosthetic dentistry, nanotechnology is frequently used in the production of new materials that will increase the potential applications and benefits compared to the traditional materials used. This technology increases the quality of dental biomaterials and produces materials with much better properties. It offers useful features for better diagnosis, treatment plans, and the improvement and protection of oral health. Due to their superior physical, mechanical, chemical, and biological properties, nanomaterials have recently gained importance in many dentistry fields, especially prosthetic treatments. However, in vitro studies on the use of different nanoparticles in dental materials, their safety, effectiveness, and applicability are not sufficient. More studies and data are needed on the use of nanoparticles in the dental field.

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