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ABOUT

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The journal was published under the name MUSBED until April 22, 2016.

The target audience of the journal includes specialists and medical professionals working in all disciplines of health sciences. The journal is the official publication of Marmara University, Institute of Health Sciences and it is published four times a year in March, June, September, and December. The journal publishes content in English. The journal publishes clinical and experimental research articles, review articles, case reports, letters to the editor, and editorial comments prepared in accordance with ethical guidelines in all disciplines of health sciences.

Aim & Scope

The aim of the journal is to contribute to the literature by publishing clinical and experimental research articles, case reports, letters to the editor, and and editorial comments prepared in accordance with the ethical guidelines in all disciplines of health sciences. The target audience of the journal includes specialists and medical professionals working in all disciplines of health sciences.

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Testing Positive for Covid-19, Signs and Symptoms, Treatment, and Covid-19-Related Anxiety: A Case of Factory Workers

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ABSTRACT

Objective: This paper investigated the incidence of COVID-19 contraction, signs and symptoms, treatment, pandemic-related anxiety, and related factors in factory workers.

Methods: This was a descriptive study conducted in a factory operating in the textile industry. No sampling was performed. The sample consisted of 287 volunteers. Data were collected using a sociodemographic characteristics questionnaire and the Coronavirus Anxiety Scale Short Form.

Results: Less than half the participants tested positive for COVID-19 (41.1%). They were treated at home (68.6%) or in a hospital (19.5%). The most common symptoms were fatigue, joint pain, change in the sense of taste, and headache. The mean duration of home and hospital treatment was 7.00±0.00 and 12.49±6.14, respectively. Participants had a mean anxiety scale score of 7.65±3.71. Less than half the participants (31%) had high COVID-19 anxiety levels. The incidence of COVID-19 infection and anxiety was higher in participants who were on medication for chronic illnesses. Age and BMI were correlated with hospitalization for COVID-19.

Conclusions: The incidence of COVID-19 infection is high among factory workers. Therefore, authorities should consider them a priority group for vaccination and provide them with training on COVID-19 risk factors and preventive measures.

Keywords: COVID-19, anxiety, risk factor, chronic illness

1. INTRODUCTION

Novel coronavirus disease (COVID-19) broke out in Wuhan/China at the end of 2019 and has been classified as a pandemic by the World Health Organization (WHO). Turkey announced its first confirmed case of COVID-19 on March 11, 2020 (1). The COVID-19 virus is transmitted through respiratory droplets and contact routes and survives on surfaces for several hours. Individuals can be infected by touching those surfaces and then touching their face (e.g., eyes, nose, mouth) (2, 3). All countries have taken numerous measures to prevent the spread of the virus (4). The Turkish Ministry of Health has introduced numerous rules and regulations to workplaces. Employers have to train employees about what the COVID-19 is and how it spread, how it is related to dietary habits, individual measures for infection control, and disinfection and sterilization rules. The preventive measures that should be enforced in workplaces are reducing the number of workers in shifts, ensuring the minimum distance between workers, setting different break times, using personal protective equipment (PPE), and informing all workers on hygiene protocols (2).

The COVID-19 pandemic has had an unprecedented impact on virtually every aspect of life (4). The clinical features of COVID-19 vary from an asymptomatic state to mild flu-like illness, severe pneumonia, multiorgan dysfunction, or even death (5, 6). The severity of COVID-19 symptoms depends on numerous risk factors (old age, gender, etc.) and underlying comorbidities (hypertension, diabetes, obesity, chronic lung diseases, heart, liver and kidney diseases, tumors, etc.) (7, 8).

The pandemic takes a greater toll on workers because they are more likely to contract the virus by having close contact with the infected and pass it on to others (9). Moreover, those infected may have no symptoms yet still be able to transmit infection (10). People have been experiencing mental problems since the onset of the pandemic because they fear getting infected or have a hard time complying with preventive measures (11). The pandemic has caused

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high levels of anxiety because it has exacerbated access to food and healthcare services, put a strain on people's mental health, and made them worried about getting infected and becoming severely ill (12).

Nurses should be effective consultants and educators and play an active role in informing all segments of society on infectious diseases, risk factors, and ways of protection (13). We should determine the incidence of COVID-19 infection among factory workers and analyze the situation based on their sociodemographic characteristics, Body Mass Indices (BMI), habits, chronic illnesses, anxiety levels, and factors affecting the course of the infection. This information can help nurses update their knowledge for patient/public education and identify the general situation of workers and related factors more easily. Therefore, this paper investigated the incidence of COVID-19 infection, signs and symptoms, treatment, pandemic-related anxiety, and related factors in factory workers.

2. METHODS

This was a descriptive and correlational study.

2.1. Research Questions

- Is the incidence of COVID-19 infection in factory workers the same as that in the general population?
- What are the signs and symptoms of COVID-19 among factory workers?
- What levels of anxiety do factory workers have?
- What factors affect the incidence of COVID-19 infection among factory workers?
- What factors affect the treatment for COVID-19 in factory workers?
- What factors affect the levels of anxiety in factory workers?

2.2. Research Setting

The study was conducted in a textile factory in Seydişehir/Beyşehir/Konya. The factory was the research site of choice because it has been up and running since the onset of the pandemic.

2.3. Population

The study population consisted of 441 workers with at least six months of work experience since the onset of the pandemic. Workplace physician and workplace nurse are available at the factory. Doctors and nurses carry out routine follow-up of employees within the scope of occupational health and safety.

2.4. Sample

Louvardi et al. reported higher levels of stress in patients with chronic illnesses than in those without chronic illnesses since the onset of the pandemic ($p<.05$). We used Louvardi et al.'s results to calculate the ideal sample size. We performed a power analysis (GPower) to determine the appropriate sample size. The result showed that a sample size of 246 would be large enough to detect significant differences. We increased the number by 15% to avoid missing data (14). The power analysis yielded that a sample size of 283 would be large enough to detect significant differences (power of 80%, $\alpha= 0.05$, effect size = 0.80). Therefore, the sample consisted of 283 factory workers who agreed to participate in the study.

2.5. Data Collection Tools

Data were collected using a sociodemographic characteristics questionnaire and the Coronavirus Anxiety Scale (CAS) Short Form.

2.5.1. Sociodemographic Characteristics Questionnaire.

The sociodemographic characteristics questionnaire was based on a literature review conducted by the researchers (7, 8, 15-18). The questionnaire consisted of 17 items on sociodemographic characteristics, tobacco and alcohol use, chronic illness, exposure to COVID-19, and signs/symptoms and treatment (for those who tested positive for COVID-19). The items on signs/symptoms also assessed their severity. The items are rated "mild," "moderate," and "severe." Body weight and body height were classified according to the adult BMI classification by the World Health Organization (WHO).

2.5.2. Coronavirus Anxiety Scale (CAS) Short Form.

The Coronavirus Anxiety Scale (CAS)-Short Form was developed by Lee and adapted to Turkish by Biçer et al.. The instrument consists of five items scored on a five-point Likert-type scale ("0 = Not at all," "1 = Rare, less than a day or two," "2 = Several days," "3 = More than seven days," "4 = Nearly every day over the last two weeks"). The original scale has a Cronbach's alpha of 0.93, while the Turkish version has a Cronbach's alpha of 0.83. The total scale score ranges from 0 to 20. A score higher than nine indicates high anxiety (19). The scale had a Cronbach's alpha of 0.87 in this study.

2.6. Variables

The dependent variables were "testing positive for COVID-19," "signs/symptoms," "treatment type," and "COVID-19 anxiety level." The independent variables were "age," "gender," "BMI," "work experience," "alcohol and tobacco use," "chronic illness," and "being on medication."

Data Collection

The data were collected face-to-face in the factory between April 15 and May 15, 2021. Necessary measures were taken before the interviews.

2.8. Ethical Considerations

The study was approved by the ethics committee of Necmettin Erbakan University Health Sciences Scientific Research Ethics Committee (No: 07.04.2021-9/12) and the Turkish Ministry of Health (Serap Batı-2021-03-02T00_44_01). Verbal consent was obtained from the factory management. Informed consent was obtained from participants before data collection. Permission was obtained from the developer of the Coronavirus Anxiety Scale. The research was conducted according to the ethical principles outlined by the Declaration of Helsinki. The research was applied and reported according to STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology) (20).

2.9. Limitations

The study had two limitations. First, the results were sample-specific. Second, the research was conducted during the pandemic. The third limitation is that the data are collected with the self-notifications of the employees.

2.10. Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS, v. 22.0) at a confidence interval of 95% and a significance level of.05. Percentage, mean, and standard deviation were used for the descriptive data. The Kolmogorov-Smirnov test was used for normality testing. The categorical data (sociodemographic data, habits, testing positive for COVID-19, and treatment types) were analyzed using the Chi-Square test. The Mann-Whitney U test was used for pairwise group comparisons. The Kruskal Wallis test was used to compare more than two groups. A Tamhane test (posthoc) was used to determine the source of significant differences.

3. RESULTS

Table 1 shows the participants' sociodemographic and individual characteristics. The majority of the participants were men (61.7%) and younger than 40 (67.2%). Participants had a mean age of 35.65±9.08 and a mean BMI of 26.53±8.03. The majority of the participants had less than five years of work experience (62.3%) and worked 45 hours a week (61.7%).

Less than half the participants used tobacco (44.3%) and alcohol (13.9%). A quarter of the participants had a chronic illness (23%); hypertension (34.8%), allergic asthma (19.7%), diabetes mellitus (DM) (9.1%), and chronic obstructive pulmonary disease (COPD) (7.6%). Less than half the participants tested positive for COVID-19 (41.1%). Participants infected with COVID-19 were treated at home (68.6%) (HomT group) or in a hospital (19.5%) (HosT group) or did not receive any treatment (NoT group) (11.9%). The HomT and HosT groups had a mean 7.00±0.00 and 12.49±6.14 days of treatment, respectively. Three HosT participants (13%) were admitted to intensive care units (Table 2).

Table 1. *Sociodemographic Characteristics*

	n	%
Gender		
Woman	110	38.3
Man	177	61.7
Total	287	100.0
Work experience (year)		
<1	48	16.7
1-5	131	45.6
6-10	67	23.3
11-15	26	9.2
≥16	15	5.2
Total	287	100.0
Working hours per week		
45	177	61.7
>45	110	38.3
Total	287	100.0
Age (year)	35.65±9.08	
BMI (kg/m^2)	26.53±8.03	

Participants had a mean CAS score of 7.65±3.71. Three out of ten participants had high anxiety (Table 2).

Table 3 shows the most common signs/symptoms in participants diagnosed with COVID-19. The most common symptoms were fatigue, joint pain, change in the sense of taste, and headache. Eighty-two participants had fatigue: severe (57.32%), moderate (40.24%), or mild (2.44%). Eighty-two participants had joint pain: severe (62.20%), moderate (29.27%), or mild (8.54%). Eighty-two participants experienced a change in their sense of taste: severe (54.88%), moderate (32.93%), or mild (12.20%). Eighty-one participants had a headache: severe (35.80%), moderate (50.62%), or mild (13.58%). The least common symptoms were itching, change in mucous, and dizziness.

Table 4 shows the factors affecting the incidence of COVID-19 diagnosis. There was a correlation between work experience and COVID-19 infection (p=.023). Participants with 1-5 years of work experience were diagnosed with COVID-19 more than others. Participants who were on medication were diagnosed with COVID-19 more than those who were not. Participants with chronic illnesses were diagnosed with COVID-19 more than those with no chronic illness (p<.05) (Table 4).

Being on medication affected the type of treatment (p<.05). Hospitalization was more common in participants who were on medication than in those who were not. Age also affected the type of treatment (p<.05). The mean age of the HosT

group was higher than that of the HomT group (p<.05) (Table 5).

Body Mass Index also affected the type of treatment (p<.05). The HosT group had a higher mean BMI than the HomT and NoT groups (p.001; p<.001) (Table 5).

There was a correlation between work experience and COVID-19 anxiety levels (p<.05). Participants with 1-5 years of work experience had higher levels of anxiety than others. Participants with chronic illnesses had higher levels of anxiety than those with no chronic illness (p<.05). Participants who were on medication had higher anxiety levels than those who were not (p<.05) (Table 6).

Table 2. *Habits and Diseases*

	n	%
Chronic illness		
Yes	66	23.0
No	242	77.0
Total	287	100.0
Chronic illness type[1]		
Hypertension (HT)	23	34.8
Allergic Asthma	13	19.7
Diabetes Mellitus (DM)	6	9.1
Chronic Obstructive Pulmonary Disease (COPD)	5	7.6
Rheumatoid Arthritis (RA)	3	4.5
Depression	3	4.5
Others	13	19.7
total	66	100.0
Medication use		
Yes	70	24.4
No	217	75.6
Total	287	100.0
Testing positive for COVID-19		
Yes	118	41.1
No	169	58.9
Total	287	100.0
Treatment		
None (NoT group)	14	11.9
Home treatment with medication (HomT group)	81	68.6
Hospitalization (HosT group)[2]	23	19.5
Total	118	100.0
Anxiety levels[3]		
Normal (<9 points)	198	69.0
High (≥9 points)	89	31.0
Total	118	100.0
Treatment duration (day)		
HomT	7.00±0.00	
HosT	12.49±6.14	

[1]From highest to lowest incidence. Diseases stated less than three times were grouped under "Others."
[2]Three HosT participants (13%) were admitted to intensive care units
[3]Mean Coronavirus Anxiety Scale (CAS) Score: 7.65±3.71

Table 3. *COVID-19 signs/symptoms*

	Mild n (%)*	Moderate n (%)*	Severe n (%)*	Total n (%)**
Fatigue	2 (2.44)	33 (40.24)	47 (57.32)	82 (100.00)
Joint pain	7 (8.54)	24 (29.27)	51 (62.20)	82 (100.00)
Change in the sense of taste	10 (12.20)	27 (32.93)	45 (54.88)	82 (100.00)
Headache	11 (13.58)	41 (50.62)	29 (35.80)	81 (100.00)
Fever	21 (29.17)	30 (41.67)	21 (29.17)	72 (100.00)
Change/loss in appetite	18 (29.51)	21 (34.43)	22 (36.07)	61 (100.00)
Cough	14 (24.56)	17 (29.82)	26 (45.61)	57 (100.00)
Sore throat	9 (17.31)	21 (40.38)	22 (42.31)	52 (100.00)
Diarrhea	14 (34.15)	17 (41.46)	10 (24.39)	41 (100.00)
Running nose	16 (39.02)	17 (41.46)	8 (19.51)	41 (100.00)
Nausea	15 (39.47)	12 (31.58)	11 (28.95)	38 (100.00)
Stomachache	10 (27.03)	12 (32.43)	15 (40.54)	37 (100.00)
Dizziness	11 (30.56)	14 (38.89)	11 (30.56)	36 (100.00)
Change in Mucous	7 (23.33)	14 (46.67)	9 (30.00)	30 (100.00)
Itching	18(66.67)	6 (22.22)	3 (11.11)	27 (100.00)

** Row percentage*
***From highest to lowest*

Table 4. *Factors affecting COVID-19 diagnosis*

	Testing positive for COVID-19		
	Yes* n(%)	No* n(%)	Total*
Work experience (year)			
<1	16 (5.6)	32 (11.1)	48 (16.7)
1-5	55 (19.2)	76 (26.5)	131 (45.6)
6-10	22 (7.7)	45 (15.7)	67 (23.3)
11-15	14 (4.9)	12 (4.2)	26 (9.1)
≥16	11 (3.8)	4 (1.4)	15 (5.2)
Total	118 (41.1)	169 (58.9)	287 (100.0)
	$\chi2$ =11.31, p**=.023		
Chronic illness			
Var Türkçe yazım düzeltilmeli	35 (12.2)	31 (10.8)	66 (23.0)
Yok	83 (28.9)	138(48.1)	221 (77.0)
Total	118 (41.1)	169 (58.9)	287 (100.0)
	χ^2 = 5.03, p**=.025		
Medication use			
Yes	38 (13.2)	32(11.1)	70 (24.4)
No	80 (27.9)	137 (47.7)	217 (75.6)
Total	118 (41.1)	169 (58.9)	287 (100.0)

**Total percentages ** Chi-square test*

Table 5. *Factors affecting treatment type*

	Treatment Type			
	NoT*	**HomT***	**HosT***	**Total***
Medication use				
Yes	7 (5.9)	20 (16.9)	11 (9.3)	38 (32.2)
No	7 (5.9)	61 (51.7)	12 (10.2)	80 (67.8)
Total	14 (11.9)	81 (68.6)	23 (19.5)	118(100.0)
	χ^2 = 6.70, p**=.035			
Age				
	[1] 62.68 [2] 52.62 [3] 81.78	KW=13.18 p=.001	2-3: p***=.001	
BMI				
	[1] 57.43 [2] 55.41 [3] 75.15	KW=6.02 p=.049	1-3: p***<.001 2-3: p***<.001	

Total percentages ** Chi-square test KW: Kruskal Wallis test * binary comparison p-value (Post-hoc Tamhane's Test)*

Table 6. *Anxiety levels and related factors*

	Anxiety		
	Normal *	**High ***	**Total***
Work experience (year)			
<1	37 (12.9))	11 (3.8)	48 (16.7)
1-5	80 (27.9)	51 (17.8)	131 (45.6)
6-10	50 (17.4)	17 (5.9)	67 (23.3)
11-15	17 (5.9)	9 (3.1)	26 (9.1)
≥16	14 (4.9)	1 (0.3)	15 (5.2)
Total	198 (69.0)	89 (31.0)	287 (100.0)
	χ2 =10.62, p**=.031		
Chronic illness			
Yes	34 (11.8)	32 (11.1)	66 (23.0)
No	164 (57.1)	57 (19.9)	221 (77.0)
Total	198 (69.0)	89 (31.0)	287 (100.0)
	χ^2 = 5.03, p**=.025		
Medication use			
Yes	38 (13.2)	32(11.1)	70 (24.4)
No	160 (55.7)	57 (19.9)	217 (75.6)
Total	198 (69.0)	89 (31.0)	287 (100.0)
	χ^2 = 9.35, p**=.002		

**Total percentages ** Chi-square test*

4. DISCUSSION

COVID-19 is a global threat to public health. As of 26.04.2021, the number of confirmed COVID-19 cases is 147.538.302, corresponding to 18.83% of the world's population (21). According to the Turkish Ministry of Health (2021), the number of COVID-19 tests is 46.153.151, and the number of confirmed cases is 4.667.281. In other words, ten percent of the tests come out positive, corresponding to six percent of the national population. Our results showed that 41.1% of the participants had been tested positive for COVID-19, which is twice as much as the global rate (18.82%) and four times as much as the national rate (10.11%). According to the Turkish Ministry of Health (2021) data, our research site was in a "very high-risk" city. Our result shows a trend similar to what is reported in "very high-risk" regions of Turkey. Factory workers are considered a high-risk group that has been adversely affected by the pandemic. They have faced various problems, such as layoffs, unpaid leave, fewer working hours, and lower wages (22). Our result is not surprising because our participants were blue-collar workers who had to keep working during the pandemic to provide for themselves and their families. It is also because they had difficulty affording hygiene products and PPE due to financial problems and had low awareness of the seriousness of the health risks, and therefore, paid little attention to preventive measures.

Although COVID-19 is similar to seasonal influenza, it typically presents with much more severe symptoms. The most common symptom in our participants was joint pain (62.5%). People diagnosed with COVID-19 also experience chest and stomachache (23) and myalgia (56.6%), and general fatigue (56.6%) (24). However, research shows that the most common symptom of COVID-19 is headaches. For example, Lan et al. reported severe headaches in four out of ten COVID-19 patients. Toptan et al. also found that seven out of ten COVID-19 patients suffered from headaches for up to three days since their diagnosis (25). However, they stated that headache was more prevalent in women, which might be related to migraines. Lippi et al. conducted a literature review and concluded that headache was an important symptom in COVID-19 patients because people with a headache were more likely to test positive for COVID-19 (OR: 95%) (26). Pain causes different problems, especially fatigue. Menni et al. focused on the symptoms of COVID-19 and conducted a survey with 2.618.862 people in England and the USA (17). They determined that almost three out of ten people in the England group and more than two out of ten people in the USA group experienced fatigue. What is more, Townsend et al. argue that fatigue is observed in half of the COVID-19 patients even ten weeks after treatment and that it can even turn into permanent fatigue. Another symptom of COVID-19 is the loss/change in the sense of smell and taste (27). Menni et al. reported a loss/change in the sense of smell and taste in almost seven out of ten COVID-19 patients (17). Lan et al. looked into post-COVID symptoms in 592 healthcare professionals and reported the loss/change in the sense of smell and taste in 15.7% of the participants. Menni et al. also found that more than six out of ten COVID-19 patients (n=13.863) experienced a loss in their sense of smell and taste. Anyone with the symptoms of COVID-19 should self-isolate to prevent the spread of the infection (17, 23, 24). The least common symptoms in our participants were joint pain, headache, fatigue, and change in the sense of taste. Some of the symptoms of COVID-19 are similar to those of the common cold. Therefore, anyone showing those symptoms should self-quarantine until their tests come back.

First, the World Health Organization and then the health ministers of all countries have drawn up treatment

guidelines. There are three treatment options: (1) at home with no medication, (2) at home with medication and (3) admission to a hospital. According to WHO (2020), elderly and obese individuals and those on medication for chronic illnesses may experience more problems during recovery and may need inpatient treatment. Demirel Kaya et al. reported that Turkish patients treated on standard protocols had a mean age of 61±16 years and that 65% had at least one chronic illness for which they took medication. High BMI increases the likelihood of lung infections in that population (28). Individuals with obesity are twice as likely to develop pulmonary diseases and almost three times as likely to need hospitalization as non-obese people. They stay in the hospital almost four times longer and have a higher mortality rate than non-obese people (16). The BMI ≥ 28 kg/m^2 and diabetes are independent risk factors for severe illness in patients with COVID-19 (29). Individuals with obesity are 2.7 to 3.3 times more likely to develop type 1 diabetes, hypertension, and high triglycerides (30). Obesity also increases the severity of COVID-19 and the risk of mortality (15). Our HosT group consisted of older adults who were on medication for chronic illnesses. This result shows that age, chronic illnesses, and regular medication use are also risk factors for more severe COVID-19 in young adults who work during the pandemic.

Participants experienced stress because young adults and workers are also at risk of contracting the coronavirus. Moghanibashi-Mansourieh reported severe (9.3%) and very severe (9.8%) anxiety in the Iranian population. He also found that women and people aged 21-40 years experienced higher levels of anxiety (31). Özdin and Bayrak Özdin also determined that anxiety was more common in women than in men, in people aged 18-49 years than in those older than 50, and in people with chronic illnesses than in those without chronic illnesses (32). Shangguan et al. also reported a positive correlation between chronic illnesses and anxiety. People experience anxiety during the pandemic because they think their lives will be adversely affected by COVID-19 (67.7%) (33). They are also afraid of contracting the virus (44.8%) and infecting their loved ones (78.3%) and facing financial problems (47.3%). People with health problems experience great anxiety about the pandemic and constantly think about the virus (p<.001). Elderly individuals also spend a great deal of time thinking about the pandemic (p<.001) (34). It was announced by the World Health Organization that men over the age of 60 and people who take regular medications have a higher risk of COVID-19 infection (4). We also found that participants who were on medication for chronic illnesses had higher levels of anxiety. This is probably because campaigns on COVID-19 raised their awareness of the seriousness of the situation, resulting in increased levels of anxiety. The pandemic has taken its toll on some sectors, and people working in those sectors have faced unemployment and economic difficulties, exacerbating their already-existing problems (22). Our participants were blue-collar workers who had to work to provide for their families during the pandemic. They had high anxiety levels probably because they experienced economic difficulties and had to work during the pandemic and also because they were at risk of contracting the virus and transmitting it to their loved ones.

5. CONCLUSION

At the time when the data were collected, the vaccination of all individuals had not yet been completed, only the vaccination of risky groups was continuing. The rate of COVID-19 infection was significantly higher among our participants than at the global and national levels. The most common symptoms were joint pain, fatigue, change in the sense of taste, and headache. The HosT group consisted mainly of people with chronic illnesses, those who were on medication, and those with high BMI. Participants had high anxiety levels affected by working hours, chronic illnesses, and regular medication use. However, participants' habits did not affect the rate of COVID-19 diagnosis, types of treatment, and anxiety levels.

Authorities should provide workers in the manufacturing industry with training on COVID-19 risk factors and preventive measures and consider them a priority group for vaccination, regardless of age, chronic illnesses, and medication use. The workplace nurse and physician should continue the training and follow-up of employees in this context.

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Clinical and Experimental Health Sciences

Measures Taken by Nurses to Protect Themselves from the Covid-19 Virus and Methods They Use to Cope with Stress

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ABSTRACT

Objective: In the present study, the aim was to determine the measures taken by nurses to protect themselves from the COVID-19, and methods they use to cope with stress.

Methods: This descriptive and cross-sectional study was carried out with 237 nurses working in Manisa City Hospital, located in Manisa, between August 2020 and March 2021. Data were collected with the Nurse Information Form, the Perceived Stress Scale, and the Ways of Coping with Stress Questionnaire. In the analysis of the data, numbers, percentage distribution, Mann Whitney u test, Kruskal Wallis test and Spearman correlation analysis were used.

Results: Protective equipment used most by the nurses while they gave care to patients with COVID-19 were gloves (96.6%), masks (95.3%) and N95 masks (90.7%). Among the issues that caused the nurses to have stress most were the fear of transmitting viruses to their families or immediate circles, and experiencing physical or psychological disorders. The mean score the nurses obtained from the overall Perceived Stress Scale was 30.36±5.63. The mean scores the nurses obtained from the sub-dimensions of the Ways of Coping with Stress Questionnaire were as follows: Self-confident approach sub-dimension: 19.83±3.44, optimistic approach sub-dimension: 13.99±2.37, desperate approach sub-dimension: 18.23±4.15, submissive approach sub-dimension: 12.89±2.98 and seeking social support sub-dimension: 10.83±1.97.

Conclusion: In our study, the majority of the nurses felt stressed during the COVID-19 pandemic. They were not competent enough to use the methods of coping with stress. Health institutions should reduce the stress on nurses and provide support to motivate them to work keenly.

Keywords: Nurse, preventive measure, COVID-19, stress, coping with stress, prevention.

1. INTRODUCTION

The COVID-19 pandemic has led to not only a nationwide both also a global crisis. Health professionals can work earnestly if their physical and mental health is good, and it should be kept in mind that success in crisis management depends on people's being healthy and working efficiently (1-3). Pandemic is a cause of physical illnesses, mental trauma and risk of death for citizens, administrators and healthcare professionals across the country. Therefore, the main goal of crisis management during the Covid-19 pandemic should be not only to protect public health and to treat patients, but also to protect the physical and mental health of health personnel fighting the disease on the front line (3-7). Healthcare personnel responsible for admitting patients with COVID-19 to hospital and caring for them have been exposed to various personal and organizational stresses that negatively affect their health and job satisfaction (8,9). Therefore, recognizing stress factors and providing periodic training will be an effective step towards prevention, treatment and stress reduction (10-12). Given the fact that nearly half of the health personnel experienced burnout, emotional fatigue or work-related stress before the Covid-19 pandemic, it is not surprising that most of them experienced depression, severe anxiety, sleep problems, psychological stress and burnout during the pandemic (5,7,13,14).

It is important to focus on the problems experienced by healthcare professionals in order to protect and control their mental health. In line with the identified problems, the support provided by taking into account the needs of healthcare professionals will protect their mental gpandemic and providing appropriate support in the light of these findings will protect their mental and physical health. Thus, the quality of health care will improve. Protecting the mental health of healthcare professionals is important for controlling the long-term health of both society and healthcare professionals.

The present study was conducted to determine the measures taken by nurses to protect themselves from the Corona virus, and methods they used to cope with stress.

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2. METHODS

Before the study was conducted ethical approval from the Manisa Celal Bayar University, Faculty of Medicine, Health Sciences Ethics Committee (date: July 22, 2020, number: 20.478.486/470) and the institutional permission from the chief of the hospital where the study was to be conducted were obtained. The participants gave their written consent after they were informed about the content and purpose of the study by the researcher. Then, the participants volunteering to participate in the study responded the online survey form.

This descriptive and cross-sectional study was carried out with nurses working in Manisa City Hospital between August 2020 and March 2021. Nurses working in the Manisa City Hospital affiliated to the Manisa Provincial Health Directorate (N: 520) comprised the study population. The sample size of the study was calculated as 221 nurses using the Epi Info statistical package program (margin of error: 5%, design effect: 1.0, confidence interval: 95%). However, considering the possibility of losses during the study, it was decided to include 237 nurses.

The study data were collected using the Nurse Information Form, the Perceived Stress Scale, and the Ways of Coping with Stress Questionnaire.

2.1. Data Collection Tools

2.1.1. Nurse Information Form

The researcher explained the content and purpose of the study to the participants, and collected the data from the volunteer participants online. The form is used to question nurses' demographic, occupational and Covid-19-related characteristics.

2.1.2. Perceived Stress Scale

The scale was developed by Cohen et al. (15). Erci adapted the scale into Turkish in 2006 after conducting its validity and reliability study (16). The scale consists of 10 items. Responses given to the items are rated on a 5-point Likert type scale ranging from 1 to 5. The score for the overall Perceived Stress Scale is the sum of the scores of the 10 items. The lowest and highest possible scores to be obtained from the scale are 10 and 50 respectively. Participants who score ≥30 are considered to have stress (16).

2.1.3. Ways of Coping with Stress Questionnaire

The scale developed by Folkman and Lazarus (1980) was adapted into Turkish by Hisli Şahin and Durak, after conducting its validity and reliability study (17). The 30-item scale has the following five sub-dimensions: 1 – Self-confident approach, 2 – Optimistic approach, 3 – Desperate approach, 4 – submissive approach and 5 – Searching for social support approach. The 1st and 9th items in the searching for social support approach sub-dimension of the scale are reverse scored. Scores for each sub-dimension are calculated separately. The increase in the scores obtained from the self-confident approach, optimistic approach and seeking social support approach sub-dimensions indicate that the person copes with stress effectively whereas the increase in the scores obtained from the desperate approach and submissive approach sub-dimensions indicate that the person uses ineffective methods in coping with stress.

2.2. Statistical Analysis

The data were analyzed using the SPSS (Statistical Package for Social Science) 26.0 package program. In the analysis of the data, numbers, percentage distribution and descriptive statistics were used to define the demographic characteristics, the Kolmogorov Smirnov normality test was used to determine whether the data were normally distributed, and the Mann Whitney U test, Kruskall Wallis test and Spearman correlation analysis were used for the data that were not normally distributed. p values less than 0.05 were accepted as the level of statistical significance.

3. RESULTS

Of the nurses, 61.2% were under the age of 31, 78.9% were women, 58.2% were single, 89.5% had a bachelor's degree and above, 64.1% had an income equal to expenses, 57.8% worked in the profession for less than 8 years, 69.2% worked in the hospital for less than 3 years, and 39.2% worked in the intensive care unit (Table 1).

Of the participating nurses, 73.4% had to buy protective equipment with their own means during the COVID-19 process, 85.2% felt stressed due to COVID-19, 62.9% thought they were not competent enough to use the methods of coping with stress during the COVID-19 pandemic, 62.9% were perceived as a source of infection by their neighbors because they worked in the hospital during the COVID-19 pandemic, 95.8% felt stressed due to fear of being infected with corona virus in the working environment and transmitting it to family members or close friends, 58.6% did not consider leaving their job due to the COVID-19 pandemic, 54.4% experienced physical or psychological disorders due to stress during the COVID-19 pandemic, and 26.9% reported that the situation that caused anxiety and fear most was the possibility of transmitting the corona virus to their families (Table 2).

The protective equipment worn by the nurses giving care to patients with COVID-19 were mostly gloves (96.6%) and masks (95.3%). The analysis of the relationship between the nurses' sociodemographic characteristics and their perceived stress levels revealed that the only significant relationship was between their perceived stress levels and the sex variable. The mean score the female nurses obtained from the Perceived Stress Scale was higher than was that of the male nurses ($p<0.05$).

Table 1. *Sociodemographic/professional characteristics of the nurses (n=237)*

Variables	n	%
Age *31.38±7.96 (min-max: 22.00-59.00) years		
<31 years	145	61.2
≥31 years	92	38.8
Sex		
Women	187	78.9
Men	50	21.1
Marital status		
Single	138	58.2
Married	99	41.8
Educational status		
Vocational Health High School + Associate Degree	25	10.5
Bachelor's degree and above	212	89.5
Income status		
Income less than expenses	61	25.7
Income equal to expenses	152	64.1
Income more than expenses	24	10.1
Length of service in the profession *8.53±8.88 (min-max: 0.17-39.00) years	137	57.8
<8 years	100	42.2
≥8 years		
Length of service in the hospital *3.76±5.61 (min-max: 0.08-30.00) years	164	69.2
<3 years	73	30.8
≥3 years		
Clinic worked in		
Emergency	24	10.1
Intensive care unit	93	39.2
Surgical or internal services	50	21.1
Specialized units (operating rooms, dialysis unit etc.)	39	16.5
Other (outpatient clinic, electrocardiogram. blood collection etc.)	31	13.1

** mean ± standard deviation*

While the mean score the participating nurses obtained from the Perceived Stress Scale was 30.36±5.63, the mean scores they obtained from the sub-dimensions of the Ways of Coping with Stress Questionnaire were as follows: Self-confident approach sub-dimension: 19.83±3.44, optimistic approach sub-dimension: 13.99±2.37, desperate approach sub-dimension: 18.23±4.15, submissive approach sub-dimension: 12.89±2.98 and seeking social support sub-dimension: 10.83±1.97 (Tablo 3).

The analysis of the correlations between the mean scores the nurses obtained from the Perceived Stress Scale and the sub-dimensions of the Ways of Coping with Stress Questionnaire revealed that there was a very weak positive correlation between the Perceived Stress Scale and the Desperate Approach and Submissive Approach sub-dimensions (r_s: 0.194, p=0.003; r_s: 0.134, p=0.039 respectively) and that there was no significant correlation between the Perceived Stress Scale and the Self-Confident Approach, Optimistic Approach, and Searching for Social Support Approach sub-dimensions (p>0.05) (Table 4).

Table 2. *Stress sources of nurses in the covid-19 pandemic (n=237)*

Variables	n	%
The need to buy protective equipment with his or her own means during the Covid-19 pandemic	174	73.4
Yes	63	26.6
No		
Feeling stressed due to Covid-19		
Yes	202	85.2
No	35	14.8
Feeling inadequate in using methods of coping with stress during the Covid-19 pandemic	149	62.9
Yes	88	37.1
No		
Being perceived as a source of infection by neighbors because of working in the hospital during the Covid-19 pandemic	149	62.9
Yes	88	37.1
No		
Feeling stressed due to fear of being infected with corona virus in the working environment and transmitting it to family members or close friends	227	95.8
Yes	10	4.2
No		
Considering quitting the job due to the Covid-19 pandemic	139	58.6
Never	81	34.2
Sometimes	17	7.2
Often		
Experiencing stress-induced physical or psychological disorders during the Covid-19 pandemic	129	54.4
Yes	108	45.6
No		
Variables		
Factors causing anxiety and fear due to the Covid-19 epidemic (n=791) *	**n**	**%**
The risk of transmission of the Corona virus	179	22.6
Fear of death	63	8.0
The risk of transmission of the Corona virus	213	26.9
Fear of transmitting Corona virus to the family members	42	5.3
Not being able to help patients diagnosed with Covid-19 positive	126	15.9
Loss of a family member	162	20.5
Not being able to be with the family members when they need help Others	6	0.8

**Multiple response number percentage distribution*

Table 3. *Distribution of the mean scores the participating nurses obtained from the perceived stress scale, and the ways of coping with stress questionnaire (n=237)*

Scales	Mean±SD	Median (IQR*)	Min-Max
Perceived Stress Scale	30.36±5.63	31.00 (4.50)	12.00-50.00
Sub-dimensions of the Ways of Coping with Stress Questionnaire			
Self-Confident Approach	19.83±3.44	21.00 (3.00)	7.00-28.00
Optimistic Approach	13.99±2.37	15.00 (2.00)	5.00-20.00
Desperate Approach	18.23±4.15	18.00 (5.00)	8.00-31.00
Submissive Approach	12.89±2.98	13.00 (4.00)	6.00-22.00
Seeking Social Support	10.83±1.97	11.00 (2.00)	4.00-16.00

**IQR: Interquartile Range*

Table 4. *Correlations between the mean scores the nurses obtained from the perceived stress scale and sub-dimensions of the ways of coping with stress questionnaire scores (n=237)*

	Perceived Stress Scale
Self-confident approach	r_s: 0.079 p=0.226
Optimistic approach	r_s: 0.021 p=0.752
Desperate approach	r_s: 0.194 p=0.003**
Submissive approach	r_s: 0.134 p=0.039*
Searching for social support approach	r_s: 0.110 p=0.091

**p<0.05, **p<0.01, rs: Spearman Correlation Analysis*

4. DISCUSSION

The results of our study demonstrated that the majority of the participating nurses (85%) felt stressed during the COVID-19 pandemic. In several studies, causes of distress among health workers have been stated as follows: Vulnerability, loss of control about their own health, the spread of the virus, the health of their families and people in their immediate environment, changes in the working environment, concerns about isolation, contagiousness of the COVID-19 and relationship between the COVID-19 and high morbidity rate. Among other factors causing healthcare workers to experience pressure and anxiety are material shortages and the increase in the COVID-19 cases (18). In Lai et al.'s study, most of the participants worked in tertiary hospitals. In Jackson et al.'s study, nurses, women, and front-line workers in Wuhan were determined to have more severe symptoms during all the measurements. In the same study, it was concluded that women and those having a moderate-level task experienced depression, anxiety, and distress more severely (2). In some studies, a significant portion of the participants suffered from anxiety, depression, and insomnia symptoms, and more than 70% of them had psychological distress (18,19). A study conducted in Austria examined therapists' stress levels and fears of contracting COVID-19. In a study conducted in Austria, therapists' stress levels and fears of contracting COVID-19 were investigated. The findings of this study demonstrated that there was a positive relationship between their fear of contracting COVID-19 infection and stress levels (20). The results of aforementioned studies were consistent with our results. When an individual feels threatened, his or her nervous system activates the organism for an emergency and responds to the emergency by secreting some stress hormones, which prepares the individual to escape from danger.

In the present study, protective measures taken by nurses most while giving care to patients with COVID-19 were wearing gloves, masks and N95 masks. Of the participating nurses, 73.4% had to buy protective equipment with their own means during the COVID-19 process. In Tayyip and Alsolaminin's study, in which stress and fear experienced by nurses working in a state hospital during the COVID-19 pandemic in Saudi Arabia were investigated, the participants stated that they were at a high risk of being infected in their workplace, and therefore they experienced a lot of stress at work and were afraid of getting sick (21). They also had a high level of fear of transmitting COVID-19 to their family members, friends and colleagues (21). Rahman et al. emphasized that the nurses in their case study were worried about transmitting the disease to their families because its risk of person-to-person transmission was high, and they experienced mental stress because insufficient personal protective equipment increased the potential for transmission, and because they were isolated in the workplace and were assigned to high-risk positions. Nurses' working for hours and hours continuously pushed their limits (6). In El-Hage et al.'s study, health workers had problems such as lack of personal protective equipment, lack of communication, lack of care materials, disruption of daily family and social life during the COVID-19 pandemic. Other problems were lack of support, fear of infecting a loved one, isolation or social stigma, job stress and insecurity. Therefore, the risk of anxiety, depression, exhaustion, addiction and post-traumatic stress disorder was high among health workers (5). In Rolling et al.'s study conducted at Strasbourg University Hospital, among the risk factors stated by the health workers were unfamiliarity with the virus, infection risk, high morbidity and mortality rates, perception that protective equipment was inadequate, and unpredictability (22). In Arnetz et al.'s study, nurses' perceptions of COVID-19-related stress were investigated under the following six main themes: Fear of exposure to COVID-19 and getting sick; fear of transmitting the virus to others; restrictions such as social distancing and business closures due to the pandemic; infection, illness and death of patients, co-workers or loved ones; feelings of inadequacy and desperation, especially in relation to the condition and treatment of their patients; and work-related problems such as relationships with colleagues, perceived workplace administrative failures, and lack of material and training (23). The results of the aforementioned study are consistent with the results of our study.

In the present study, the analysis of the correlations between the mean scores the nurses obtained from the Perceived Stress Scale and the sub-dimensions of the Ways of Coping with Stress Questionnaire scores revealed that there was a very weak positive correlation between the Perceived Stress Scale and the Desperate Approach and Submissive Approach sub-dimensions. This suggests that they were not competent enough in using the methods of coping with stress. In Klaid et al.'s study conducted in Saudi Arabia, providing personal protective equipment, wearing protective equipment while treating everyone who presented to the hospital, and providing sufficient information to prevent infection were regarded as factors that could be used in coping with COVID-19 (24).

5. CONCLUSION

In our study, health institutions should reduce the stress on nurses and provide support to motivate them to work keenly. During the pandemic, in the field of health, the aim should be to improve nurses' coping skills and resilience, and to reduce their burnout levels and risk of developing mental health problems. In addition, the health workers' basic physical needs such as safety (access to personal protective equipment), food and water, rest and sleep must be met. Healthcare workers' right to take breaks and to spare time for themselves should be ensured. Quality communication should be ensured with all personnel, and they should be informed accurately.

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Clinical and Experimental Health Sciences

The Reliability, Validity and Cross-Cultural Adaptation of Turkish Version of Jefferson Scale of Empathy for Health Professions Students

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ABSTRACT

Objective: The study is aimed to study for the reliability, validity, and cross-cultural adaptation of the Turkish version of the Jefferson Scale of Empathy for undergraduate health profession students (JSE-HPS).

Methods: Cultural adaptation of JSE-HPS was carried out in 5 stages according to the protocol of Beaton et al.JSE-HPS was administered to students who educated in the departments of Physiotherapy and Rehabilitation, Nursing and Health Management. The reliability of JSE-HPS was evaluated by internal consistency and test-retest analysis using Cronbach's alpha and intraclass correlation coefficient (ICC), respectively. Criterion validity assessed by comparing the scores of JSE-HPS and Emphatic Tendency Scale (ETS). An analysis of construct validity was carried out by exploratory and confirmatory factor analysis.

Results: The exploratory factor analysis revealed the presence of three factors that explain 44.68% of the total variance and that correspond to the dimensions of the original scale. Following factor structures were obtained as "Perspective taking", "Compassionate care" and "Standing in patient's shoes". Turkish version of JSE-HPS total score were significantly correlated with the ETS total score (r=0.187, p=.005). The Cronbach's Alpha internal consistency coefficient was found α = .793. The test-retest reliability coefficient was 0.86. The confirmatory factor analysis verified a good fit of the model (χ2/df = 1.776).

Conclusion: The Turkish version of JSE-HPS is a valid and reliable scale for evaluating empathy levels of undergraduate health professions students.

Keywords: Empathy, health professions students, Jefferson scale of empathy, empathic tendency scale

1. INTRODUCTION

Empathy, which can be briefly defined as understanding and feeling of one's thoughts upon experiences (1). It has been gaining importance in health care since Hojat et al., thoroughly described its core features such as cognitive part of empathy which is directly related to being able to understand experiences, concerns, and perspectives of the patient regarding patient care (2).

A great majority of the literature has been focusing on the aspect of physician and health care provider yet recently establishing or measuring empathy has been performed with the undergraduate students (3). There are a lot of studies showed that improved empathy levels in health professionals not only ensure patient compliance and satisfaction but also enhance the quality of the initial diagnosis (4, 5). Hojat et al.' also contributed that increased empathy has been found to affect better clinical outcomes when compared to ones that have lower empathy (2). Gained efficient clinical outcomes with improved empathy have not been only shown for physicians but also were shown in nurses who work with cancer patients (6).

Since empathy and its related dimensions are important to integrate a better skill to provide in health care, measuring empathy gained attention (7). Hogan's Empathy Scale (8), Empathic Tendency Scale (9), and Empathic Skill Scale (10) are tools that are often used to assess empathy yet these might have some lacks concerning measure specific subgroups. The Jefferson Scale of Empathy (JSE) was developed by Hojat et al., to measure empathy in physicians (2). JSE has three versions for Medical students (JSE-S), Health Professions (JSE-HP), Health Professions students (JSE-HPS) (2,11). Some studies used JSE in different profession cohorts such as nursing (7) and dentistry (12).

Due to the importance of empathy among health professionals has been understood, establishing the measure of empathy among undergraduate health profession students attract attention. JSE has 20 items that cover some parameters such

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as physician's view from patient, understanding, feeling, and thinking experiences of patients (3). As a previously mentioned, other tools that assess empathy cannot be modifiable for some subgroups, thereby JSE-HPS seems to be convenient to adapt to empathetic studies involving healthcare students (3,11).

Since there might be lacking of some tools which assess empathy directly such as Empathic Tendency Scale and Empathic Skill Scale in Turkish language, yet these were discussed as cannot be quite modifiable to some specific sub-groups such as health profession students (7). Although JSE-S and JSE-HP have Turkish versions, no instrument developed specifically health professions students such as JSE-HPS for evaluating empathy in Turkish language (13,14). As indicated before, JSE-HPS is a quite proper tool to adapt some specific subgroups due to items are easily modifiable. In addition, there is an emerging need for empathy assessment tool especially for undergraduate students in health sciences who are directly linked to patients one by one in Turkish language.

Thus, this study is aimed to study for the reliability, validity, and cross-cultural adaptation of the Turkish version of the Jefferson Scale of Empathy for undergraduate health profession students.

2.METHODS

2.1. Study Design

The research is a methodological study.

2.2. Study Setting and Sample

The study was conducted in a Faculty of Health Sciences in Izmir, Turkey between February 2020, and April 2020. All students who educated in the departments of Physiotherapy and Rehabilitation, Nursing and Health Management were asked to participate in this study (N=430). The students were informed about the research and their written informed consent was obtained. The research was started with 228 students who can be reached and agreed to participate in the research. This study was approved by local Ethics Committee (Reference number= 07/2020) and registered in the Clinical Trial Register (ref: NCT04422834). The inclusion criteria were set as being volunteer to participate and currently studying as a student in Faculty of Health Sciences.

2.3. Measurement

The data were gathered by using the sociodemographic form, JSE-HPS and Empathic Tendency Scale (ETS). Sociodemographic form consists of four questions about the age, gender, department and class of the students.

Jefferson Scale of Empathy for Health Professions Students: It was originally developed by Hojat et al. intended to measure empathy levels for health professional students. The JSE-HPS consists of a total 20-items each scored by seven-point Likert Scale as 1: "Strongly disagree" through 7: "Strongly agree". Ten out of 20 items are scored directly according to the Likert weights while the other half are reversely scored. The minimum and maximum scores for JSE-HPS can be reached to 20 and 140, respectively. The higher scores indicate better empathic aspect or vice versa. The reliability coefficient of JSE-HPS was found to be 0.78 (2).

Emphatic Tendency Scale: It was originally developed by Dokmen et al. specifically intends to measure the attitude of people's skill of empathy. Turkish validation and reliability study were also conducted in which internal reliability of the tool was found as 0.82 according to the Cronbach's alpha value. ETS has 20 items and each have 5-point Likert type feature where 1 through 5 equals to "Completely contradictory, Quite contradictory, Undecided, Quite proper, Completely proper", respectively. Each item of the tool consists of ideas regarding the behaviors which can be faced in daily life. One is required to fill each item by filling the one of the numbers from 1 through 5 by simply indicating how much they agree in the related idea. Since there are negative items in the scale, the relevant items were converted into positive items. Negative items are "3, 6, 7, 8, 11, 12, 13, 15". The minimum and maximum scores can be taken from the tool are 20 and 100, respectively. Higher scores indicate better empathic attitude or vice versa (9).

2.4. Translation and Cross-cultural Adaptation

Cultural adaptation of JSE-HPS was carried out in 5 stages according to the protocol of Beaton et al (15). At the first stage, original scale was translated separately into Turkish by a committee of three health professionals whose native language is Turkish. At the second stage, the same committee contributed to one integrated draft from three separately translated form of the tool to establish the most appropriate terms in the translated final version at the end of this stage. At the third stage, back translation in which two native English speakers who were out of the topic translated this scale back to English was perform. At the fourth stage, the expert committee studied the final draft to harmonize culturally to minimize differences between the original and translated version. At the fifth stage, a pilot study was carried out in 30 students by applying the Turkish version of the translated scale. After the pilot study, it was reported that the statement of "to stand in their patients' shoes" in the Item 9: "Health care providers should try to stand in their patients' shoes when providing care to them" was not understood by students. For this reason, this statement was changed to "to put themselves in their patients' place" for better understanding in Turkish culture. Since the whole scale was accepted as easily understandable and convenient with the Turkish language according to the pilot study results, the final version of the scale was established. The Turkish translation of the JSE-HPS was copyrighted by © Thomas Jefferson University, 2001. All rights reserved.

2.5. Reliability

The reliability of the JSE-HPS was evaluated by internal consistency and test-retest analysis. Cronbach's alpha was computed to assess the internal consistency of scale. Cronbach's Alpha coefficient ranges from "0" to "1" and approaching "1" shows that the scale items are consistent with each other (16). Test-retest reliability was done by re-applying the JSE-HPS after seven days. It was calculated by using the intraclass correlation coefficient (ICC) (17).

2.6. Validity

Criterion validity was assessed with by comparing JSE-HPS scores and ETS scores. Pearson's correlation coefficient was used to quantify the magnitude of the correlation. It was categorized as poor (<0.40), fair to good (0.40–0.75), and excellent (>0.75).

Construct validity was evaluated by factorial analysis. Exploratory factor analysis was used to reduce data to a smaller set of summary variables. In confirmatory factor analysis, it was determined whether the factor structure assessed by exploratory factor analysis was confirmed for the Turkish sample (17).

2.7. Statistical Analysis

Statistical significance level was set as $p \leq 0.05$ and all statistical analyses were performed using PASW software (SPSS, version 21). Demographic characteristics of students were shown according to variable types. Cronbach's alpha coefficient was calculated to assess the internal consistency of the scale. The test-retest reliability of total score and each item was investigated via ICC and Kappa coefficient, respectively. Criterion validity was assessed by Pearson's correlation coefficient. Keiser-Meyer-Olkin (KMO) and Bartlett's sphericity test was conducted to investigate whether the scale was appropriate for factor analysis. Exploratory and confirmatory factor analysis were performed to assess the construct validity according to Eigen values.

3.RESULTS

430 students were informed about participating the study, however 228 students accepted to participate at baseline. 61 students did not attend test-retest analysis; therefore, this study was completed with 167 students. Students' mean age was 19.82 ± 1.03 year and 68.8% of the participants were females. According to departments, the distribution of the total sample was as follows: 39.5% nursing, 40.3% physiotherapy and rehabilitation, and 20.2% health management. A total of 53.9% of the students were in their first year of education while the rest of them were in the second grade.

Validity

Construct Validity

The KMO test which was performed to determine the compatibility of the data obtained with the 20 item – scale for factor analysis was found to be 0.78. Varimax rotation procedure was performed to analyze the principal components of the factors and factor loads were obtained. Three items (items 5, 12 and 18) in which factor loads below 0.30 were excluded from the scale. After elimination of items, KMO value was found as 0.82 and Bartlett's test of sphericity resulted as $\chi^2 = 917.382$, $p < 0.001$.

Explanatory factor analysis showed that JSE-HPS Turkish version includes three factors at which Eigenvalues of them were found to above one: Factor 1 (Items: 2,4,9,10,13,15,16,17,20), Factor 2 (Items: 1,7,8,11,14,19) and Factor 3 (Items: 3,6). These factors were identified as "Perspective taking" (PT), "Compassionate care" (CC) and "Standing in patient's shoes" (SPS), respectively. Factors 1, 2 and 3 were found to be able to explain total variances as follows: 27.45%, 9.43% and 7.81%, respectively. These factors explain 44.68% of total variance. Factor loading are shown in Table 1.

Table 2 presents the goodness of fit indexes of the three factors model consisting of 17 items. Accordingly, the ratio of chi square degrees of freedom was $\chi^2/df = 1.776$; Root Mean Square Error of Approximation (RMSEA) was 0.058 and Comparative Fit Index (CFI) was 0.889. Figure 1 presents the confirmatory factor analysis diagram of the model.

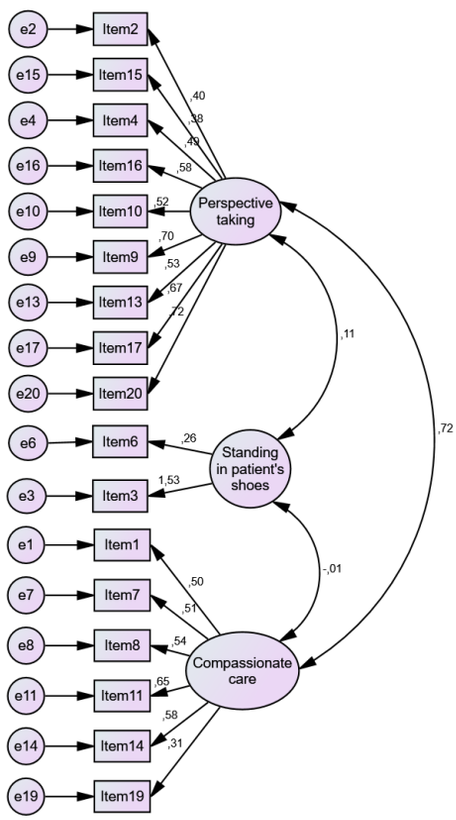

Figure 1. *ConfirmatoryFactor Analysis Diagram of JSE-HPS.*

Table 1. *Factor loadings of items of the Turkish version of JSE-HPS*

Items	Sub-dimensions		
	1. PT	2. CC	3. SPS
2.Patients feel better when their health care providers understand their feelings.	0.45		
4.Understanding body language is as important as verbal communication in health care provider – patient relationships.	0.51		
9.Health care providers should try to stand in their patients' shoes when providing care to them.	0.64		
10. Patients value a health care provider's understanding of their feelings; this has a therapeutic effect.	0.57		
13. Healthcare providers should try to understand what is in the minds of patients by paying attention to non-verbal cues and body language.	0.66		
15. Empathy is a therapeutic skill without which a health care provider's success is limited	0.49		
16. Healthcareproviders' understanding of theemotionalstatus of their patients and their families, is an important component of the healthcare provider – patient relationship.	0.57		
17. Healthcare providers should try to think like to care better for their patients.	0.76		
20.I believe that empathy is an important factor in patients' treatment.	0.66		
1.Health care providers' understanding of their patients' and their families' feelings does not influence medical or surgical treatment.		0.65	
7.Attention to patients' emotions is not important in patient interview.		0.54	
8.Attentiveness to patients' personal experiences does not influence treatment outcomes.		0.69	
11. Patients can be curedonly by targeted treatment; therefore, health care providers' emotional ties with their patients do not have a significant influence in treatment outcomes.		0.56	
14.I believe that emotion has no place in the treatment of medical illness.		0.69	
19.I do not enjoy reading non-medical literature or the arts.		0.4	
3.It is difficult for a health care provider to view things from patients' perspectives.			0.76
6. Because each person is different, it is difficult to see events from the patients' perspective.			0.8
Eigenvalue variance	1.6	4.67	1.33
Explained variance	9.43%	27.45%	7.806%
Total variance	44.68%		

PT= Perspective taking,CC= Compassionate care SPS= Standing in patient's shoes

Table 2. *Item-total correlation coefficient of the JSE-HPS*

	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
Item 20	0.603	0.771
Item 9	0.587	0.768
Item 11	0.54	0773
Item 16	0.513	0.776
Item 17	0.508	0.773
Item 10	0.46	0.781
Item 13	0.448	0.778
Item 7	0.442	0.78
Item 14	0.417	0.78
Item 4	0.415	0.783
Item 8	0.406	0.781
Item 15	0.337	0.787
Item 1	0.336	0.79
Item 2	0.333	0.787
Item 19	0.237	0.792
Item 6	0.148	0.802
Item 3	0.143	0.803

Criterion Validity

Concurrent validity results showed that the Turkish version of JSE-HPS total score (r=.187, p=.005) and CC (r=.151, p=.023) and SPS (r=.158, p=.017) subscale scores were significantly correlated with the ETS total score except for PT subscale score.

The Floor-Ceiling Effect

The floor-ceiling effect was calculated for the first measurement of the items in JSE-HPS. The probability of students to answer as "Strongly agree = 7" for ceiling effect in " Item 13" and "Item 20" was higher compared to other items. The probability of answering "Strongly disagree = 1" for floor effect in "Item 2" and "Item 7" was much higher compared to other items.

Reliability

Internal Consistency / Item-total Correlation

The Cronbach's Alpha internal consistency coefficient obtained from the JSE-HPS scoring system was found α = .793. Cronbach's alpha internal consistency coefficients were found for factors PT, CC and SPS as follows: α = .78, α = .67 and α = .58, respectively. Item-total correlation coefficients were ranged between r = .143 (Item 6) and r = .603 (Item 20) (Table 2). The total scale mean score was found as 96.21 ± 10.71, and the mean scores of the sub-factors PT, CC and

SPS were found as 53.32 ± 6.51, 35.23 ± 5.14 and 7.68 ± 2.63, respectively.

Test-retest Analysis

The scale was implemented by 167 students after seven days to examine the consistency of the scale over time. The test-retest reliability coefficient was found to 0.86 for the whole scale and 0.81, 0.86 and 1 for the subscales, respectively (p <.001) (Table 3). According to the Intraclass correlation coefficient (ICC) values, it was determined that the scale has "good to excellent" test-retest results.

Table 3. *Reliability of Turkish version of JSE-HPS*

JSE-HPS subdimensions	ICC (95% CI)	p
Perspective taking (PT)	0.86 (0.81-0.89)	<.001
Compassionate care (CC)	0.81 (0.74-0.86)	<.001
Standing in patient's shoes (SPS)	1	<.001
Total	0.86 (0.83-0.91)	<.001

JSE-HPS=Jefferson Scale of Empathy-HealthProfessionsStudents; ICC= Intraclass correlation coefficient

4. DISCUSSION

This is the first study of Turkish validation of the JSE-HPS with undergraduate health professions students educating departments of physiotherapy and rehabilitation, nursing, and health management. According to the results, Turkish version of the JSE-HPS is a reliable, valid, and appropriate scale to evaluate empathy among health professions students demonstrated satisfactory psychometric properties which was consistent with the original version (18).

Since the importance of empathy and its related aspects in terms of health care has been understood well, the need of measuring empathy not only objectively but also holistically arise (19). The "Jefferson Scale of Empathy", which was developed by Hojat et al, has been the most frequently used scale globally according to the numbers which show translated a total of 39 languages along with the confirmed psychometric properties in several languages in different World regions (2,11,19). When compared to the translated ones, the Turkish version is also compatible in terms of obtained factors, explained cumulative variance, and overall reliability and validity scores. "Perspective Taking", "Compassionate care" and "Standing in Patient's shoes" are factors that are the same with Brazilian, Japan, Iranian, and Mexican versions of JSE-HPS (20-22)

Considering the overall scores obtained from Brazilian, Iranian, and Japan versions, the overall score of the Turkish version of JSE-HPS was found to be relatively lower.The reason for lower scores of JSE-HPS might be multi-dimensional such as the difference in cultural characteristics and some intrinsic and extrinsic factors (20-22). On the other hand, relatively lower scores might be attributable to a few factors related to sample characteristics such as half of them were 1st grade of students and arbitrary filling of the questionnaire might also contribute.

The exploratory factor analysis of the Turkish version of JSE-HPS showed a moderate to good compatibility with the findings obtained JSE translation studies in the literature by expressing the main three factors such as "Perspective Taking", "Compassionate Care" and "Standing in the patient's shoes", respectively. The factor structure was same as the original JSE-HPS scale (11). As a result of the fit index values revealed in the confirmatory factor analysis of the scale, it was found that the three-factor model fit the data well. Similarly, a three-factor structure was found in the results of other studies published except for Williams et al. (7,13,23-27). A total of 45% cumulative variance was reported by Paro et al, likewise the same range was obtained in our study (20). "Compassionate Care" was found the main factor according to the contributed variance in the Brazilian version of JSE-HPS, however; "Perspective Taking" was found the main contributing factor not only in the Japan version but also in the Turkish version. This main difference can be attributed to the cultural diversities between Eastern and Western countries. However, Item 5 "*A health care provider's sense of humor contributes to a better clinical outcome*", in the PT factor;Item 12 "*Asking patients about what is happening in their personal lives is not helpful in understanding their physical complaints*" and Item 18 "*Health care providers should not allow themselves to be influenced by strong personal bonds between their patients families*" in the CC factor were extracted due to the lower factor loadings below 0.30. Similar results were produced in the literature. For example, Williams et al.[3]reported that three items (Item 2, Item 5 and Item 18) were removed from the scale. However, in some studies (25-27) it was concluded that the 20-item scale was valid and reliable similar to the original scale. The main reason for removing three items could be related to translation or cultural differences. Different sense of humor of health care providers, different requests of patients to describe their daily lives and strong personal bonds between Turkish population and Western cultures are very common. This situation could be the reason of lower factor loading for Item 5 "*A health care provider's sense of humor contributes to a better clinical outcome*". In eastern cultures asking one's situation not only in the clinical base but also personally is accepted as respectful and sincere behavior therefore Item 12 "*Asking patients about what is happening in their personal lives is not helpful in understanding their physical complaints*" might have created confusion. In addition, since the holistic approach to the patient is not in the foreground in the education of the students in health management department, they may have thought that the private lives of the patients are not related to their physical complaints.

Item 18 "*Health care providers should not allow themselves to be influenced by strong personal bonds between their patients families*" was removed from the scale in most validity and reliability studies (3, 7, 13, 20, 21, 23, 28). It may be related to translation or cultural differences. Participants' perception of the importance of strong personal ties between patients and families due to their different sociocultural structure may differ. Again, the meaning of these items may differ in

situations where the patients' family members should be included in making decisions about the patient. Especially strong personal ties between Turkish family members may have also led to this result.

The floor and ceiling effect, which can be analyzed by a cumulative rate of "Strongly agree" and "Strongly disagree" in item-based, Item13 *"Health care providers should try to understand what is in the minds of patients by paying attention to non-verbal cues and body language."*and Item 20*"I believe that empathy is an important factor in patients' treatment."*showed ceiling effect while Item 2*"Patients feel better when their health care providers understand their feelings."* and Item 7*"Attention to patients' emotions is not important in patient interview."* showed floor effect. In our opinion, the floor effect of item 2 in the Turkish version of JSE-HPS can be attributed to some cultural patient characteristics in Turkish people by thinking that the patients might exaggerate their condition. However, the floor effect in item 7 is a relatively expected result due to great majority of participants were nursing and physiotherapy students who may think that the anamnesis is very important in both patient care and rehabilitation.

The reliability of the Turkish version of JSE-HPS was found around 0.80 which is accepted as a good result and coherent with other JSE-HPS studies along with the factors' scores (20-22, 29) according to the Cronbach's alpha value. The Cronbach's alpha value in the Spanish, Korean, Italian Chinese and Australian versions of JSE-HPS was 0.83, 0.87, 0.78, 0.93 and 0.75, respectively (3, 23, 25, 27, 28). The test re-test analysis which focuses on consistency over time of the Turkish version of the JSE-HPS was found excellent according to the ICC value even it was completed with a 27% attrition rate. This value shows that the scale scores are constant with respect to time.

Turkish version of JSE-HPS is a valid tool for evaluating empathy since the correlations between the scales show moderate effect sizes. Although there is a relatively lacking in different JSE-HPS studies, we also analyzed the criterion-related validity by the Turkish version of the ETS (9), and found good to excellent correlations not only for the total score but also for each factor except for perspective taking.

Item total correlation is the correlation between a single item and the total of items. For internal consistency, the item-total score correlation of each item is expected to be at least r = 0.20. However, the decision to remove items below this value is made by evaluating the effect of the item on the Cronbach's alpha coefficient. In this study, it was decided to keep these items in the scale since there was no significant difference in the Cronbach's alpha value when Item 3 (0.143) and Item 6 (0.148) with low item-total correlations were excluded, and these items theoretically measure empathy. The item-total correlations range varies in different studies in literature as 0.11 to 0.46,[7] 0.34 to 0.64[23] and, 0.17 to 0.63[25].

There are some strengths and limitations of this study. Analyzing criterion-related validity with ETS along with EFA within construct validity might be accepted as a strength. Also, applying the Turkish version of JSE-HPS to different health professions students is another strength of our study. The following issues can be assigned as limitations: This study was performed in a certain socio-demographic region and only in one university. Also, it was conducted on undergraduate students studying in departments of physiotherapy and rehabilitation, nursing, and health management. JSE-HPS has been developed on all healthcare professions students. Therefore, it may be suggested to carry out validity and reliability studies with a sample different undergraduate (midwifery, nutrition and dietetics, language and speech therapist, paramedic, etc.) and graduate students. Another limitation is relatively higher attrition rate in test re-test period. However, our results are consistent and can be crosschecked with other JSE-HPS translation and validation studies.

5. CONCLUSION

Evaluating the empathy levels of health professions students during their education is important in terms of gaining empathy skills. JSE-HPS is a specific scale that evaluates the empathy level of health professions students. The results of the study determined that the Turkish version of JSE-HPS is a valid and reliable scale for evaluating undergraduate health professions students' empathy level.It was concluded that the Turkish version of JSE-HPS has satisfactory psychometric properties as a measure of empathy in Turkish health professions students and can be used to identify important factors in empathy education. Since JSE-HPS is about the empathy level, the relationship of the scale with variables such as communication, self-sensitivity, problem solving, and emotional intelligence related to the concept of empathy can be examined in further studies.

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This study was approved by Ethics Committee of İzmir Bakircay University Non-invasive Clinical Research Ethics Committee (Approval date: 07/02/2020; protocol number: 07)

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Author Contributions:

Research idea: EGİ, KÖ, AT, YB

Design of the study: EGİ, KÖ, AT, YB

Acquisition of data for the study: EGİ, KÖ, AT

Analysis of data for the study: AT

Interpretation of data for the study: EGİ, KÖ, AT, YB

Drafting the manuscript: EGİ, KÖ, AT, YB

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Clinical and Experimental Health Sciences

The Effect of Preventive Nursing Interventions on Reduction of Obesity Risk University Students: A Randomized Controlled Trial

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ABSTRACT

Objective: The aim of the study was to assess the effect of an obesity prevention program to decrease obesity risk on university students at risk.

Methods: This is a parallel-group randomized controlled trial that is suitable for the Consolidated Standards of Reporting Trials (CONSORT) statement. The study was carried out at a University in Turkey. The study participants were 70 students (experiments 35 and control 35). The obesity prevention program, which includes education and practices about eating habits and physical activity, and motivational messages, was implemented for 11 weeks. Nutrition training attitude score, exercise nutrition behavior score and exercise benefit/barrier score, body mass index, waist size ratio, and body fat percentage are the outcomes of the research.

Dependent samples t-test, independent t-test, and intention to treat (ITT) were used for data analysis.

Results: The difference between the experimental group and the control group was statistically significant in attitude and behavior of nutrition exercise ($p<.05$). The difference between the experimental and control groups was significant in terms of scores on the exercise benefit/barrier scale ($p<.05$) but not significant on anthropometric measures. In the experimental group, the pre-test and the post-test differed in body mass index (BMI) and it was found that BMI was reduced after the obesity prevention program ($p<0.05$).

Conclusions: This study is important to reduce obesity risk among university students.

Keywords: Nursing, Nutrition, Obesity, Exercise, Randomized Controlled Trials, University Students

1. INTRODUCTION

Obesity is defined as an abnormal or excessive accumulation of fat in the body, leading to poor health (1). It has been reported that globally, 1.9 billion adults aged 18 years and over are overweight; of these, over 60 million are obese. Among adults aged 18 years and over, 39% are overweight and 13% suffer from obesity. Globally, 41 million children under the age of 5, and 340 million children and adolescents aged 5-19 years are overweight or obese (2), and the prevalence of obesity in OECD countries is 22.6% (3). The prevalence of obesity in Turkey is similar to those reported in developed Western countries (4, 5). In a study conducted in 22 countries, it is stated that the prevalence of obesity or overweight in university students is 22% (24.7% male and 19.3% female) (6).

The sooner obesity begins, the higher the risk of disease will be. Overweight and obese children are more likely to become obese in adulthood and to develop non-communicable diseases at an earlier age (7). Obesity is a disease that should be treated, as it leads to many health problems (8). Studies conducted have shown that interventions made for obesity treatment are long-continued, and these interventions have a limited effect on the decrease in body weight (9-11). To prevent obesity-accompanying diseases and the attendant financial burden that incurs due to treatment costs, it is highly important to develop various protective measures for people at risk of obesity before the occurrence of obesity (12-14). Therefore, obesity which is an economic effect on health systems and the individual should be prevented first, and then if necessary, treatment should be provided (8). Obesity can be prevented through healthy dietary habits augmented by physical activity (15). Current studies conducted generally focus on therapeutic interventions for people with obesity (9-11). However, there is a need to carry out more studies that examine the effects of the interventions applied to risk groups for obesity and the effects of these interventions on reducing the risk of obesity. It is more important to focus on preventing obesity rather than on treating obesity. The risk of

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obesity can be reduced by providing education on effective and sustainable eating habits to be followed at every stage of life, encouraging adolescents to exercise, and explaining the importance of physical activity (8, 16).

In the studies, it is seen that physical activity and nutrition are generally considered separate interventions, and obese individuals are included in the studies (9, 10). For this reason, the fact that the study was conducted in a group at risk of obesity and that it included interventions related to nutrition and physical activity, as well as the inclusion of individual and group activities in the program, differ from other studies.

Study Hypotheses

H1: The nutrition-exercise attitude scores of the university students receiving the obesity prevention program increase positively compared to the control group.

H2: The exercise benefits scores, of the university students receiving the obesity prevention program increase positively compared to the control group.

H3: The exercise barrier scores, of the university students receiving the obesity prevention program, decrease positively compared to the control group.

H4: The BMI of the university students receiving the obesity prevention program, decrease compared to the control group.

H5: The waist/hip ratio of the university students receiving obesity prevention program, decrease compared to the control group.

H6: The body fat percentages, of the university students receiving the obesity prevention program, decrease compared to the control group.

2. METHODS

2.1. Study Design

This study is a randomized, controlled trial using two parallel-group as an experimental and a control group in a pretest-posttest design. Reporting adhered to the CONSORT extension for parallel-group randomized controlled trials (17). This study is registered at ClinicalTrials.gov (ref. no: NCT03115229).

2.2. Study Setting and Participants

The study was conducted on 152 university students who were at risk of obesity and were studying in the Health Management Department at a University, in the 2015-2016 academic year in Turkey. The researchers performed a risk screening, to determine the reference population. As a result of the survey conducted with 152 students, this study determined that 29 students did not fall under any of the obesity risk groups. The exclusion criteria were applied to 123 students who were determined to be at risk for obesity. From these exclusion criteria results, the population for the randomized controlled trial ended up being 103 students who were between the ages of 19 and 24 and at risk of obesity.

Inclusion criteria; This study considered three key criteria to determine the risk of obesity; Pre-obesity (BMI: 24.9-29.9) (18) or Unhealthy nutritional habits (Global Status Report on Noncommunicable Diseases/GSRN 2010), or Physical inactivity (19).

Exclusion criteria; BMI less than 18.5 and greater than 29.9, under 19 or over 24 years old, regular drug use, any pre-existing health condition, and being pregnant.

2.3. Sample Size

The sample size of this randomized controlled trial was determined through power analysis, conducted using GPower 3.1 software (20). The study of Yurt and Yıldız, found the Nutrition-exercise attitude scale mean score and standard deviation value of the pre-test: 45.96 ± 6.45; post-test: 51.75 ± 6.67. The calculation was made considering this means score, and the minimum sample size was found to be 35 students should be included in both groups with 95% power and 95% confidence interval, 0.05 α error probability, and 0.8 effect size.

This study selected 70 students, from among the determined 103 students to be in the at-risk group, to form the study group by using a simple random numbers table. A total of 70 students, randomly selected, were randomly assigned to the control and experimental groups so that each group would have 35 students.

2.4. Randomization

This study used random stratification (by sex) to ensure randomization. After stratification, block randomization was performed. To ensure equal distribution in terms of gender in each group, this study created two strata: male and female. In the randomization stage, randomization was performed by a statistician, not the researcher, to prevent subjectivity and to conceal randomization. Shortly before beginning interventions, the researchers were informed about the groups that had been randomized. The experimental and control groups had several characteristics in common (Figure 1).

2.5. Data Collection and Tools

Study data were collected in two different rooms of the fitness center. Students' body fat percentage and waist/hip circumference were measured, and their BMI values were calculated. The researchers performed pre-and post-test measurements on students in the morning hours when the students were hungry, and with them in minimal clothing. For body fat percentage measurements, this study used the Tanita BC 418 brand weighing instrument. Then students

were administered questionnaires and scales assessing cognitive and behavioral variables. All data were collected by two researchers (one was a doctoral student in community health nursing and the other, a trainer who graduated from the Faculty of Sport Sciences) other than the researcher who conducted this study. In the RCT, the researchers were not blind to the intervention group or the person performing the intervention; however, data collectors, statisticians, and reporters were blind to these matters.

The primary outcomes were: nutrition–exercise attitude, exercise-nutrition behavior, and exercise benefit/barriers score. The secondary outcomes were: body mass index, waist-to-hip ratio, and body fat percentage. Before starting the interventions, this study performed anthropometric measurements of the participants (BMI, waist/hip ratio, and body fat percentage) and administered the measurement instruments.

2.5.1. Information Form

This form included questions on the sociodemographic characteristics and health status of the participants.

2.5.2. Nutrition-Exercise Attitude Scale

This scale was developed by Yurt, Save (21) to determine attitudes about nutrition and exercise. It is a 5-point Likert-type and one-dimensional scale consisting of 13 items. The Cronbach's Alpha of the scale was found to be 0.74. The lowest score that can be obtained from the scale is 13 and the highest score is 65. A high total score from the scale indicates a positive attitude toward nutrition and exercise.

2.5.3. Nutrition-Exercise Behavior Scale

Yurt, Save (21) developed this scale to determine behaviors about nutrition. It is a 5-point Likert-type scale consisting of 45 items and its Cronbach's Alpha value is 0.85. Items 7, 8, 9, 10, 11, 12, 14, 15, 17, 18, 20, 22, 30, 31, 32, 34, 35, 36, 37, 38, 39, 42, 43 were scored in the opposite direction. The scale consists of 4 sub-dimensions; Psychological Dependent Eating Behavior (PDEA), Healthy Nutrition-Exercise Behavior (HNEB), Unhealthy Nutrition-Exercise Behavior (UNEB), and Meal Pattern (MP). PDEA, score distribution is between 11-55. A low score indicates the absence of PDEA. HNEB, score distribution is between 14-70. A high score indicates healthy nutrition-exercise behavior. UNEB score distribution is between 14-70. A low score indicates the absence of unhealthy nutrition-exercise behavior. MP, score distribution is between 6-30. A high score indicates a good meal pattern.

2.5.4. Exercise Benefits/barriers Scale:

The Turkish adaptation of the scale developed by Sechrist, Walker (22) was made by Ortabag, Ceylan (23). This scale has two sub-dimensions Exercise Benefits Scale (EBES) and the Exercise Barriers Scale (EBAS). The Cronbach Alpha value is 0.87. EBAS items 4, 6, 9, 12, 14, 16, 19, 21, 24, 28, 33, 37, 40, and 42, EBES items 1, 2, 3, 5, 7, 8, 10, 11, 13, 15, 17, 18, 20, 22, 23, 25, 26, 27, 29, 30, 31, 32, 34, 35, 36, 38, 39, 41 and 43. The lowest score that can be obtained from the scale is 43 and the highest score is 172. The higher the score, the more the individual believes in the benefits of exercise. When the EBES is used alone, the score range is 29-116. The higher the score, the more positive believes in the benefits of exercise. When the EBAS is used alone, the score range is 14-56. The higher the score, the greater the perception of barriers to exercise (23).

2.6. Overview of the Intervention

Experimental group: The interventions were performed for the experimental group for 11 weeks. The interventions performed for the experimental group were divided into three categories as follows; Interventions for nutritional habits; including group training, individual interventions, and group events. Group training; during the first three weeks, training which included four sessions of 45 minutes about causes of obesity, right and wrong eating habits, and healthy cooking techniques were provided to students in the experiment by the researcher. Individual interventions: Every week, the researchers asked each student in the experimental group about their food consumption, using the "24-hour Recall Method". Nutritional counseling was given individually. Group events; to increase fruit/vegetable consumption and to improve the motivation of students towards healthy nutrition salad competitions were organized within the kitchen competition in the faculty. Interventions for physical activity; group training, group exercises, individual interventions, and group events were applied for 8 weeks. Interventions were performed via social media; throughout 11 weeks, almost 100 WhatsApp and short text messages were sent to the students. See this study protocol for detailed information (24).

Control group: Since there is no health promotion program for students on campus, the students in this group continued their routine practices.

The following precautions were taken to avoid contamination in the study. Experimental and control group students were asked not to talk to each other about education. The training of the experimental group was given outside the lesson hours, without the knowledge of the control group. Students were informed about keeping the interventions related to exercise confidential.

2.7. Ethical Consideration

Permission was obtained from the Ethics Committee at a University (decision number: 2015/75). The participants were informed about the research purposes and benefits/risks of intervention and procedures. Written informed consent was obtained from all the participants.

2.8. Statistical Analyses

A dependent samples t-test was performed to evaluate the pre-and post-test results of the groups, and an independent samples t-test was used to evaluate the difference between the control and experimental groups. The similarity of control variables between the groups was analyzed with the Chi-square test. The obtained data were tested at the p<.05 significance level and bidirectionally. Intention to treat (ITT) analysis was performed in the evaluation of the data. In addition, effect size (d) and confidence interval were calculated. The collected study data were analyzed by computer using SPSS 20.0 statistical analysis software by a statistician.

3. RESULTS

There was no statistically significant difference between the experimental and control groups in terms of sociodemographic characteristics (p>.05) (Table 1).

In examining the post-test scores of the groups, as shown in Table 2, it was found that there was a statistical difference between the Nutrition-Exercise Attitude Scale (NEAS) post-test scores of the experimental and control groups, with the scores of the experimental group being positively higher compared to those of the control group (p<.05), and the effect size was at a high level.

It was determined that the PDEA score of the control group increased statistically significantly in the post-test compared to the pretest (p<.05). Psychological dependent eating habits of this control group caused their behavior to be adversely affected. The inter-group comparison showed that the Healthy Nutrition-Exercise Behavior (HNEB) scores of the experimental group after the application of the nursing interventions increased compared to those of the control group, which was an indication that the nursing interventions were effective (p<.05), and the effect size was at a high level. It was determined that the UNEB scores of the experimental group decreased significantly after the experiment compared to the pre-experiment, and the unhealthy nutrition and exercise behavior changed positively (p<.05), and the effect size was found to be high. This comparison also showed that the experimental group had higher scores on the post-test Meal Pattern (MP) than those of the control and that the meal pattern positively changed in the experimental group (p<.05). The effect size was also found to be high (Table 3).

The results indicated that the experimental group had higher scores on the Exercise Benefits/Barriers Scale's Total Score (EBBS) for the post-test than those of the control group and the attitudes of the experimental group participants towards the benefits of exercise were shown to have changed positively (p<.05), with the effect size being at a high level. The fact that the experimental group had higher scores on the EBES for the post-test than those of the control group indicates that the nursing interventions had a positive effect on the attitudes of the experimental group participants towards the benefits of exercise (p<.05), and the effect size was high. The inter-group comparison determined that the experimental group had lower scores on the post-test EBAS than those of the control group, which indicated that the nursing interventions reduced the barriers to exercise and had a positive effect (p<.05), with the effect size being at a high level (Table 4).

According to Table 5, no statistically significant difference was found between the experimental and control groups in terms of BMI, waist/hip measurements, and body fat percentage means (p>.05). However, there was a significant change in BMI in the experimental group pre-test and post-test (p<.05).

Interventions carried out within this study had no negative effects and no participants were harmed during the study.

Table 1. *Distribution of similarities in socio-demographic and health characteristics of students in the experimental and control groups*

Variable	Experimental (n: 35)		Control (n: 35)		X^2	p
	n	%	n	%		
Gender						
Female	26	74,3	26	74,3	0,000	1,000
Male	9	25,7	9	25,7		
Grade						
1. Grade	11	31,4	10	28,6	4,667	0.097
2. Grade	14	40	7	20,0		
3. Grade	10	28,6	18	51,4		
Perceived Economic Status						
Good	6	17,1	5	14,3	0,108	0.743
Moderate	29	82,9	30	85,7		
Presence of obesity in first-degree relatives						
Yes	8	22,9	11	31,4	0,650	0.420
No	27	77,1	24	68,6		

X^2: Chi-square test.

Table 2. *Means of pre-test and post-test of nutrition-exercise attitude scale (NEAS) scores measure for experimental and control groups*

Groups		Pre-Test	Post-Test	Comparison Pre-Test/Post-Test		Effect Size (%95 CI)
		Mean±SD	Mean±SD	t[a]	*p	d
Experimental (n:35)		39.86±1.35	51.80±0.89	-9.208	.000	0.982 (0.991 – 0.964)
Control (n:35)		41.11±1.14	42.86±0.89	-1.745	.090	
Comparison Groups	t[b]	-0.711	7.111			
	*p	0.479	0.000			
Effect Size (%95 CI)	d		0.980 (0.968 – 0.988)			

**p<0.001*

Notes: t[a] = dependent samples t-test, t[b]= independent sample t-test, SD = Standard Deviation.

Table 3. *Means of pre-test and post-test of nutrition-exercise behavior scale (nebs) scores measure for experimental and control groups*

Nutrition-Exercise Behavior Scale's (NEBS) sub-dimensions means		Pre-Test	Post-Test	Comparison Pre-Test/ Post-Test		Effect Size (%95 CI)
		Mean±SD	Mean±SD	t[a]	*p	d
Psychological Dependent Eating Behavior (PDEA)						
Experimental (n:35)		28.14±1.12	27.37±1.07	0.760	.43	0.331 (-0.003 – 0.598)
Control (n:35)		26.63±0.86	29.29±1.02	-2.558	.015	
Comparison Groups	t[b]	1.074	-1.296			
	p	0.287	0.199			
Effect Size (%95 CI)	d		0.675 (0.785 – – 0.523)			
Healthy Nutrition-Exercise Behavior (HNEB)						
Experimental (n:35)		40.09±1.47	52.51±1.15	-8.866	.0000	0.978 (0.989 – 0.956)
Control (n:35)		41.86±1.18	42.71±1.13	-0.683	.499	
Comparison Groups	t[b]	-0.937	6.078			
	*p	0.352	0.000			
Effect Size (%95 CI)	d		0.974(0.958 – 0.984)			
Unhealthy Nutrition-Exercise Behavior (UNEB)						
Experimental (n:35)		39.17±1.12	36.09±0.93	3.702	.001	0.831 (0.688 – 0.912)
Control (n:35)		36.97±1.16	37.29±1.09	-0.332	.742	
Comparison Groups	t[b]	1.360	-0.839			
	p	0.178	0.404			
Effect Size (%95 CI)	d		-0.510 (-0.665 – – 0.312)			
Meal Pattern (MP)						
Experimental (n:35)		19.83±0.56	22.83±0. 55	-5.074	.0000	0.938 (0.969 – 0.880)
Control (n:35)		21.03±0.73	20.29±0.87	1.552	.130	
Comparison Groups	t[b]	-1.310	2.471			
	p	0.194	0.016			
Effect Size (%95 CI)	d		0.867 (0.794 – 0.915)			

**p<0.001*

Notes: t[a] = dependent samples t-test, t[b]= independent sample t-test, SD = Standard Deviation.

Table 4. *Means of pre-test and post-test of exercise benefit /barriers scale total and subscale scores measure for experimental and control groups*

The exercise benefit /barriers scale		Pre-Test	Post-Test	Comparison Pre-Test/Post-Test		Effect Size (%95 CI)
Exercise Benefits/Bariers Scale's Total Score (EBBS)		**Mean±SD**	**Mean±SD**	**t[a]**	***p**	**d**
Experimental (n:35)		120.57±1.86	129.40±1.59	-3.615	.001	0.930 (0.964 – 0.865)
Control (n:35)		121.08±1.92	121.80±2.16	-0.339	.737	
Comparison Groups	**t[b]**	-0.192	2.824			
	p	0.848	0.006			
Effect Size (%95 CI)	**d**		0.894 (0.834 – 0.933)			
Exercise Benefits Scale (EBES)						
Experimental (n:35)		90.66±2.17	103.00±1.84	-4.655	.000	0.950 (0.975 – 0.902)
Control (n:35)		90.03±2.00	91.08±2.20	-0.563	.577	
Comparison Groups	**t[b]**	0.213	4.150			
	***p**	0.832	0.000			
Effect Size (%95 CI)	**d**		0.946 (0.914 – 0.966)			
Exercise Barriers Scale (EBAS)						
Experimental (n:35)		29.91±0.84	26.40±0.89	4.191	.000	0.896 (0.802 – 0.947)
Control (n:35)		31.05±0.84	30.71±0.92	0.493	.625	
Comparison Groups	**t[b]**	-0.961	-3.355			
	p	0.340	0.001			
Effect Size (%95 CI)	**d**		0.921 (0.950 – 0.875)			

**p<0.001*

Notes: t[a] = dependent samples t-test, t[b]= independent sample t-test SD = Standard Deviation.

Table 5. *Means of pre-test and post-test of some anthropometric measurements (BMI, waist/hip measurements, and body fat percentage) scores measure for experimental and control groups*

Anthropometric measurement		Pre-Test	Post-Test	Comparison Pre-Test/Post-Test		Effect Size (%95 CI)
		Mean±SD	**Mean±SD**	**t[a]**	**p**	**d**
BMI						
Experimental (n:35)		22.56±0.37	22.30±0.31	2.185	.036	0.352 (0.021 – 0.613)
Control (n:35)		22.54±0.48	22.67±0.47	-1.539	.133	
Comparison Groups	**t[b]**	0.038	-0.651			
	p	0.970	0.517			
Effect Size (%95 CI)	**d**		0.418 (0.595 – 0.203)			
Waist/hip measurements						
Experimental (n:35)		0.79±0.01	0.78±0.01	1.327	.193	0.465 (0.156 – 0.691)
Control (n:35)		0.79±0.01	0.79±0.01	0.601	.522	
Comparison Groups	**t[b]**	-0.333	0.698			
	p	0.741	0.487			
Effect Size (%95 CI)	**d**		-0.429 (-0.603 – – 0.216)			
Body fat percentage						
Experimental (n:35)		23.80±1.37	23.56±1.33	0.649	.520	0.091 (-0.250 – 0.412)
Control (n:35)		23.04±1.18	22.89 ±1.21	0.323	.729	
Comparison Groups	**t[b]**	0.420	0.370			
	p	0.676	0.713			
Effect Size (%95 CI)	**d**		– 0.253 (0.019 – 0.461)			

Notes: t[a] = dependent samples t-test, t[b]= independent sample t-test, SD = Standard Deviation.

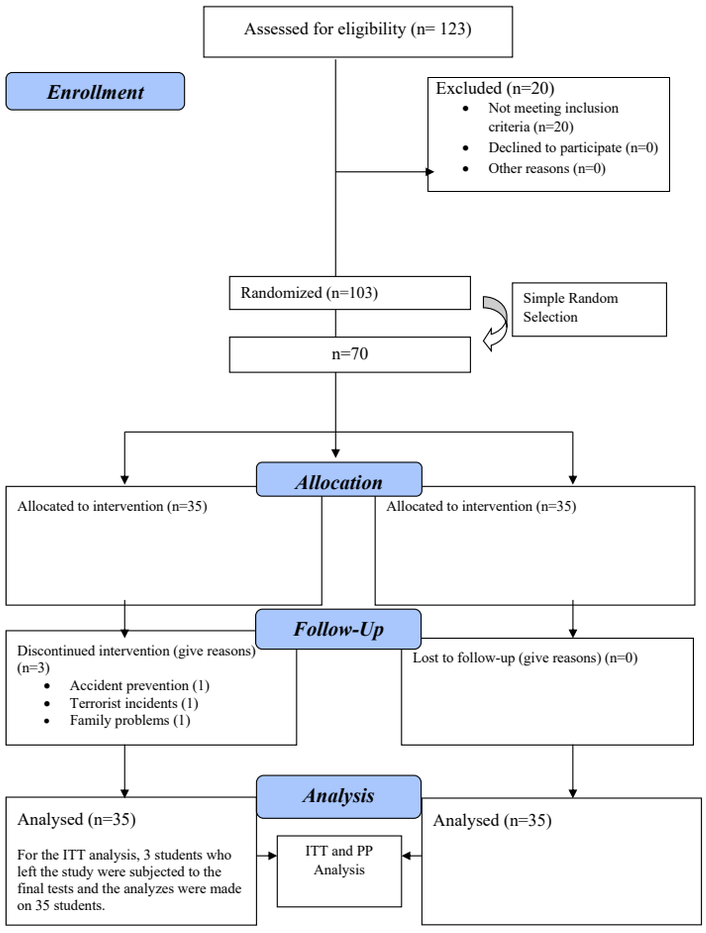

Figure 1. *CONSORT flow diagram of this study.*

4. DISCUSSION

Study results on the application of preventive nursing interventions, which included healthy nutrition and physical activity training, practices, and motivational messages sent via social media, showed that the students' attitudes towards nutrition and exercise had changed positively, as determined by the post-test scores, and that the effect size was at a high level, according to inter-group comparisons. Studies conducted have revealed that training programs and practices on nutrition attitude were effective in reducing obesity risk (25, 26).

According to the inter-group comparison, the experimental group had higher scores on healthy nutrition/exercise behavior and MP in the post-test than those of the control group, which shows that during the 11-week-intervention, the healthy nutrition behavior and meal pattern of the experimental group positively changed, with the effect size being high and confidence intervals being close. In addition, it was observed that unhealthy nutrition and exercise behavior in the experimental group decreased after the interventions and changed positively. It was further observed that the nursing interventions, which included the four basic nursing interventions of the Omaha System (Health education-counseling-guidance, Treatment, and procedure, Case management, Surveillance) (27) had positive effects on nutrition, exercise, and meal patterns of the students. From these results, it was demonstrated that providing training programs on nutrition and physical activity and culinary practices, conducting weekly personal counseling sessions, assessing nutritional status using the 24-hour recall method, and sending motivational messages via social media, all had positive effects on the nutrition-exercise behaviors of the students. It has been reported that promoting healthy lifestyles to prevent obesity is highly important in terms of public health (28). An intervention study conducted with female university students between the ages of 18 and 26 revealed that the interventions applied to the experimental group resulted in a considerable decrease in caloric intake and carbohydrate consumption, as well as an improvement in their nutrition behavior (29). A systematic review study conducted on training programs provided to address the nutritional habits of computer-based obesity determined that computer-based programs positively changed nutritional habits and physical activity (30). An intervention study designed to prevent obesity in adolescents through an Internet program found a significant difference in healthy nutrition behaviors and physical activity and reported

that school-based programs were suitable for adolescents in terms of preventing obesity and developing healthy behaviors (25). The results reported in another intervention study support the findings of the present study showing that the interventions made were effective in improving healthy nutrition-exercise attitude and behavior (31-36). The relevant literature shows that the training programs and practices developed on healthy nutrition and exercise had significant effects on forming healthy lifestyles and especially on developing healthy nutrition behaviors and attitudes. The present study results are in line with those presented in the literature. It is believed that nursing interventions performed to improve attitudes on nutrition and exercise and attendant behaviors lead to a decrease in the risks of nutrition and physical activity for students.

In the pretest-posttest comparison of the students in the control group, at the end of the 11-week period, it was determined that the psychological dependent eating behaviors of the students changed negatively and the effect size was high in the negative direction. Psychological dependent eating behavior has a characteristic that changes over time. This situation suggests that the eating behaviors of the students who did not receive intervention during these periods may be negatively affected since the post-test measurements are close to the final exam week of the students.

Compared to the control group, the attitudes of the experimental group on the benefits of exercise positively changed on the post-test; this change suggests that the interventions were highly effective in the experimental group, and the confidence interval was close. Post-test comparisons between groups showed that the nursing interventions made for the experimental group reduced the barriers to exercise and provided positive changes; the effect size was high, and the confidence intervals were close. In this context, it is believed that the training programs on physical activity, weekly physical activities, trekking, cycling events, and pedometer usage all had positive effects on the attitudes of students toward the benefits of exercise. An intervention study conducted with adolescents revealed that physical activity practices improved the educational skills of students and motivated them to continue school sports (37). According to another intervention study involving a control group and experimental group, the diet was shown to result in a decrease in body weight for the experimental group, while combined treatments (i.e. diet and physical activity) were found to have similar results for the experimental and control group in the short term, in the long-term, when diet and physical activity were combined, there was a greater sustained decrease in body weight. It was determined that programs which are based only on physical activity are less effective in obesity prevention than combined treatments, which include both nutrition and physical activity (11). The literature review showed that healthy nutrition and regular physical activity have significant effects on obesity prevention. To get a person to start exercising, the person must believe in the benefits of exercise and that perceived barriers to physical activity be reduced. Intervention studies have emphasized that the combined practices involving both physical activity and nutrition are more effective in obesity prevention (11, 38, 39). Furthermore, it is believed that interventions are effective in helping individuals to understand the benefits of exercise and to realize barriers to physical activity.

The present study found no statistical difference in the post-test between the experimental and control groups in terms of BMI, waist/hip ratio, and body fat percentage. Hebden, Chey (10) stated that interventions that last four or more months provide a greater decrease in body weight and that the effect of interventions carried out for less time and involving multiple lifestyle changes on the control of body weight had no definitive impacts on young adults. A study stated that BMI, a low-fat mass percent, and lower fat mass are associated with low dietary energy density. In future study may provide low dietary energy density for decrease BMI, waist/hip ratio, and body fat percentage (40). Additional experimental studies that carry out interventions for longer periods to decrease anthropometric measurements would be beneficial. Considering that the main purpose of the present study was to reduce the risks associated with obesity, it can be argued that the 11-week intervention study was successful in doing this; however, no change was found in the anthropometric measurements of the participants.

There were two main limitations to this study. First, the students in the experimental and control groups were taking courses in the same classroom at the university and living in the same dormitory, and therefore, it is possible that their daily interaction mutually impacted their behavior and attitudes. Moreover, this study was limited to 11 weeks due to the academic calendar of the students.

5. CONCLUSION

At the end of this study, it was concluded that the preventive nursing interventions involving multiple actions for obesity prevention that were applied to university students in a planned way, positively benefit the students' nutrition-exercise attitudes and behavior and improves their perceptions of the benefits of exercise, the results of which reduce the risk of obesity. The present study revealed the importance of nursing interventions in taking preventive measures for obesity in university students.

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Acquisition of data for the study: TO
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Clinical and Experimental Health Sciences

Enhanced Enzyme Inhibitory Effects of the Nanohybrid Eggplant Extract: An Unusual Pharmaceutical Form for Medicinal Plant

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ABSTRACT

Objective: Recently, biosynthesis/synthesis of nanoflowers has become very attractive for chemical and pharmaceutical sciences, and enhanced enzyme activities. Various plant extracts and their active compounds are effectively used as organic component for novel nanoflowers synthesis. *Solanum melongena* L., commonly known as eggplant in English, a vegetable and medicinal plant belongs to Solanaceae family has several advantages in materials synthesis due to cheap and obtained easily. The aim of this study is to compare the enzyme ((alpha-glucosidase (AGase), alpha-amylase (AAase), tyrosinase (Tyr), acetylcholinesterase (AChE) and butyryl cholinesterase (BChE)) inhibitory effects of the eggplant' calyx extract and its Solanum-inorganic hybrid nanoflower (Sm-ihNFs) via *in vitro* experimental methods.

Methods: The hybrid nanoflower was formed (NF) with organic molecules, eggplant extract (Sm), and inorganic compounds, copper to enhance the catalytic activities. The inhibition capacities of the eggplant extract, and its hybrid nanoflower were evaluated on selected enzymes (AGase, AAase, Tyr, AChE and BChE) which play significant roles physiologically by *in vitro* tests in this study.

Results: According to inhibition percentages and IC_{50} values, Sm-ihNFs showed higher inhibitory activities on enzymes other than ache than the plain crude plant extract. Among all the enzymes that were studied, Sm-ihNFs demonstrated significantly higher alpha-glucosidase and alpha-amylase inhibition activities compared to acarbose. And when compared to galantamine hydrobromide Sm-ihNFs showed higher enzyme inhibition and significant IC_{50} value.

Conclusion: It was thought that Sm-ihNFs prepared from eggplant extract may have promising potential for antidiabetic drug formulations in the future. The hybrid nanoflowers will be promising and guide for the future work in terms of pharmaceutical and cosmeceutical industry.

Keywords: *Solanum melongena*; nanoflower; alpha-glucosidase amylase; tyrosinase; cholinesterases

1. INTRODUCTION

Solanum melongena L. (Solanaceae), commonly known as eggplant, is one of the most consumed, economically valuable vegetables in most of the world (1). The aerial parts of the plant are rich in alkaloids and saponins, phenolics (2,3). Dönmez et al. examined whether methanolic eggplant extract has antihemorrhoidal and antioxidant activities on rats or not. They have used eggplant calyx for preparing the extract. As a result of the study, it has been shown that the extract has high biological activity (3). Medicinal features such as analgesic, antifungal, antiasthmatic, antidiabetic, antihemorrhoidal, antiinflammatory, antipyretic, antioxidant, antiplatelet, hypocholesterolemic, hypolipidemic, hypotensive, and spasmogenic activities of the plant have been scientifically proven (4-19). Umamageswari and Maniyar demonstrated that eggplant leaf extract has antiinflammatory activity, which is related to many enzymes (20). Previously, Kwon et al. had evaluated just α-amylase (AAase), α-glucosidase (AGase) and angiotensin I-converting enzyme (ACE) inhibitory activities of eggplant extract to investigate a potential drug for type 2 diabetes and hypertension (21).

In recent years, innovative ideas on the development of biomaterials using herbal extracts have been putting forward and many plant-derived nanostructures and nanoparticles are tried to be developed with different methods (22). Hybrid nanoflower is a novel nano-bio agent formed with organic and inorganic compounds, moreover, creating hybrid nanoflowers using plant extracts and their constituents, which is green chemistry, became attractive yet convenient (23-29). It has been reported so far that nanoflowers obtained

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using plant extract exhibit improved biological activity. The organic-inorganic hybrid nanoflower (TF-Cu^{2+} hNF) was obtained using *Trigonella foenum-graecum* L. extracts with copper ions. The TF-Cu^{2+} hNF exhibited enhanced antibacterial activity against *Enterococcus faecium, E. faecalis, Staphylococcus aureus, Bacillus cereus, Salmonella typhi* and *Escherichia coli* except against *Pseudomonas aeruginosa* and *Haemophilus influenza* (30). The TF-Cu^{2+} hNFs and free TF extracts were also reported to show no antifungal activity at the same research. The synthesis of *Viburnum opulus* (European cranberry bush) extract based Cu^{2+} hybrid nano forms called "snowballs" and their effective catalytic and antimicrobial features compared to free European cranberry bush extracts were reported (31). They suggested that biologic activities may follow a fenton-like pathway. Baldemir and coworkers reported the synthesis and characterization method for hybrid nanoflower with using green tea extract and copper ion. Baldemir and coworkers reported the synthesis and characterization method for hybrid nanoflower with using *Camellia sinensis* (L.) Kuntze extract and copper ion (32). They also demonstrated enhanced antimicrobial and catalytic activities of nanoflowers. In the last nanoflower study using curcumin extract, the effect of reaction time and curcumin concentrations on nanoflower's morphology was reported (33).

Solanum melongena plant extracts with their rich alkaloid, saponin and phenolic constituents can be used in hybrid nanoflower synthesis. However, no study was recorded on enzymes inhibitory activities of calyx and the nanoflower form of the extract to this point. In addition to antidiabetic enzyme activities, it was aimed to evaluate anticholinesterase and tyrosinase enzyme inhibition activities in this article. In this study, which allows comparison of antidiabetic activity, the anticholinesterase and tyrosinase enzyme inhibition activities of calyxes were examined for the first time. For this; the hybrid nanoflowers using eggplant extract were obtained in optimum conditions, then characterized with several techniques such as Scanning Electron Microscope (SEM), Energy Dispersive X-Ray Analysis (EDX), Fourier Transform Infrared (FTIR) and X-Ray Diffraction (XRD). Then, some important enzyme inhibition activities such as alpha-glucosidase (AGase), alpha-amylase (AAase), tyrosinase (Tyr), acetylcholinesterase (AChE) and butyryl cholinesterase (BChE) of hybrid nanoflowers were investigated in comparison with the free extract. We suggested that enhanced enzymatic activities of nanoflowers may expand their uses a usual pharmaceutical form for an edible/medicinal plant.

2. METHODS

2.1. Preparation of the Extract

The cultured plant materials, which was founded in the Herbarium of Faculty of Pharmacy/Gazi University/Ankara/Turkey as authenticated voucher specimen (GUE 3500), were gathered during August-September 2016-2017 at the Central Anatolia of Turkey. Only the dark-green calyx of the mature eggplant fruit was separated and dried in shade, then ground to powder, extracted with methanol by maceration. The yield of the extract was calculated as 11.4 percent.

2.2. Synthesis of Hybrid Nanoflowers (Sm-ihnfs)

Sm-ihNFs was synthesized following modified reported method (31, 34). The calyx methanolic extract with concentrations from 0.02 to 0.2 mg mL^{-1} was separately added into the mixture containing 50 mL of 10 mM PBS (pH7.4) and 0.8 mM Cu^{2+} ion. The occurring blueish-green precipitates, washed with water, and centrifuged at 5000 rpm for 10 min. The washing process was repeated 3 times and the final product was dried at 50°C for further characterizations and enzyme assays. Sm-ihNFs was characterized by using the morphologies of the synthesized Sm-ihNFs were examined by using Scanning Electron Microscopy (ZEISS EVO-LS10). The chemical and crystal structures of the Sm-ihNFs were characterized using Fourier Transform Infrared spectroscopy (Perkin Elmer 400, Spectrometer Spotlight 400 Imaging System) and X-Ray Diffraction (Bruker, AXS D8 Advance Model) analysis, respectively. The elemental analysis of the Sm-ihNFs was performed by energy dispersive X-ray (ZEISS EVO-LS10) analysis.

2.3. Enzyme inhibition activity

Alpha-glucosidase inhibition (35): The inhibition method of α-glucosidase was followed according to Kumar et al. Acarbose was utilized as reference. The test solution (25 µL) was diluted with a PBS which added to α-glucosidase (25 µL, 0.5 U/mL). After the 10 minutes incubation at 25ºC, 25 µL of 0.5 mM PNPG was added to each well then, the mixture was further waited for 30 minutes at 37ºC. At the end of the incubation term, sodium carbonate (0.2 M, 100 µL) was joined to put an end to the reaction and the absorbances were read at 405 nm. All concentrations were carried out in triplicate to obtain an accurate statistical analysis.

Alpha-amylase inhibition (36): The inhibition method of *α*-alpha-amylase was followed by Kumar et al. While acarbose was a positive control, PBS (pH 6.9, 0.02 M, PBS) was a negative control in place of the specimen. Each specimen was conducted in triplicate with diverse concentrations. The reaction mix containing 50 µL of test solution was diluted with buffer, 25 µL of enzyme (5000 µg/mL, *α*-amylase) and incubated for about 10 minutes at 25ºC. Then 50 µL of freshly prepared 0.5 % starch solution (w/v) was annexed to each well as a substrate and incubated for a further 10 minutes at 25ºC. Incubation period was followed by addition of 1 % 3,5-dinitrosalicylic acid (DNS, 100 µL) coloring reagent and heated in a water bath for 10 minutes. The absorbances were read at 540 nm.

Tyrosinase enzyme inhibition (37): Tyrosinase inhibition was detected by the improved dopa chrome method. L-DOPA was used as substrate. A part of the plant extracts and their nanoflowers, under the optimal conditions, diffused in DMSO

(PBS, 6.8 pH, 80 µL), 40 µL of L-DOPA, and 40 µL tyrosinase enzymes were added into each well. Analysis was performed in a microplate by using ELISA plate reader and absorbances were measured at 475 nm. Results were evaluated by comparing with the DMSO and α-kojic acid.

The AChE and BChE inhibition (38,39): The acetylcholinesterase/butyryl cholinesterase inhibition assay was evaluated by Ellman colorimetric method as described by Öztürk. 150 µL of 0.1 M PBS (pH=8.0), 10 µL of test solutions in MeOH: DMSO (4k: 1k, v/v) with different concentrations and 20 µL of 0.1 U/mL enzyme solution (acetylcholinesterase-butyryl cholinesterase was obtained from equine serum) were incubate for 15 minutes at 25°C. 10 µL of a solution of 0.2 mM (acetylcholine/butyryl thiocholine) and 10 µL of 0.5 mM DTNB were mixed and the absorbances of the mix were measured at 412 nm. Galantamine hydrobromide (Sigma-Aldrich, Germany) was used as a positive control.

2.4. Statistical analysis

The differences in values between the reference and test groups were compared by using GraphPad Prism Software (8.3 Version, La Jolla/CA/USA) in statistical analysis. The results are expressed as the mean ± standard error means (S.E.M.). When one-way ANOVA with Tukey Multiple Comparison Test was used, p-values of less than 0.05 were considered statistically significant.

3. RESULTS

3.1. Synthesis of Hybrid Nanoflowers (Sm-Ihnf)

Sm-ihNFs was synthesized using calyx extract of the plant in phosphate buffered saline and Cu (II) ion for 3 days of incubation. The extract contains diverse types of phytochemicals, such as alkaloids, saponosides, flavonoids that comprise important elements such as N, O and S atoms, which can form complexes with Cu (II) ions due to their strong affinity. In the synthesis of Sm-ihNFs, the most significant interaction is the coordination chemistry between Cu (II) ions and some molecules, mostly alkaloids containing N atom, which allows the formation of the hybrid structures with flower-like shapes under definite circumstances.

Formation of hybrid nanoflower consists of three consecutive steps as nucleation, growth, and completion. Nucleation occurs formation of the key nanocrystals of copper phosphate from Cu (II) and phosphate ions interactions. The reaction with primary nanocrystals and the biomolecules leads to the formation of the petals of flowers-like shapes during growth. As a result of penetration of petal-like structures, hybrid nanoflower formation occurs.

Concentration of organic component is one of the most essential parameters that influence the morphology and the structure of organic-inorganic hybrid nanoflowers. Consequently, effect of the concentrations of the extract on the morphology of Sm-ihNFs was investigated applying SEM analysis (Fig.1). The most uniform morphology of hybrid nanoflowers was obtained as the optimum condition. The average size of nanoflowers was 5-6 µm.

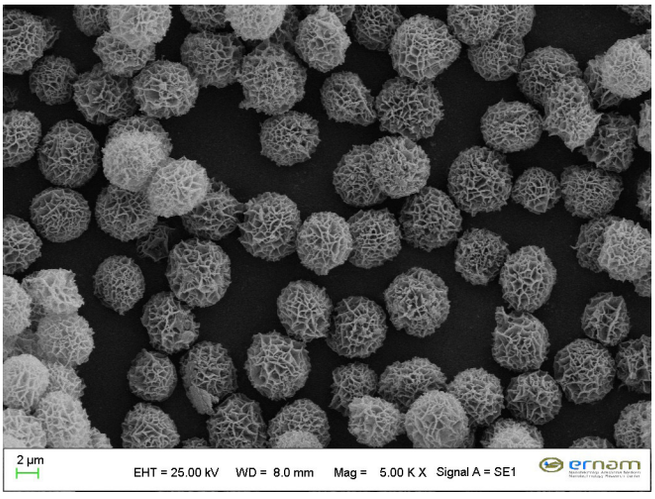

Figure 1. *Scanning electron microscopic images of hybrid nanoflowers formed with 0.1 mg mL-1 extract of S. melongena*

The elemental analysis of the synthesized Sm-ihNFs was performed by EDX (Fig.2). The EDX spectrum was revealed presence of major elements such as C, N, O, P, and Cu in the structure. The copper metal can be evaluated as a major skeleton of the hybrid nanoflower.

The functional groups in the structure of organic compounds, whether the two compounds are the same, the state of the bonds in the structure, the binding sites and whether the structure is aromatic or aliphatic were determined with the FTIR analysis, (Fig.3). The bending and stretching bonds in the free plant extract were characteristically also detected in the hybrid structure.

The measurement of particle sizes, phase equilibria and crystal structure of Sm-ihNFs were investigated by XRD (Fig.4). The all diffraction peaks of $Cu_3(PO_4)_2.3H_2O$ were matched well with the JCPDS card (022-0548).

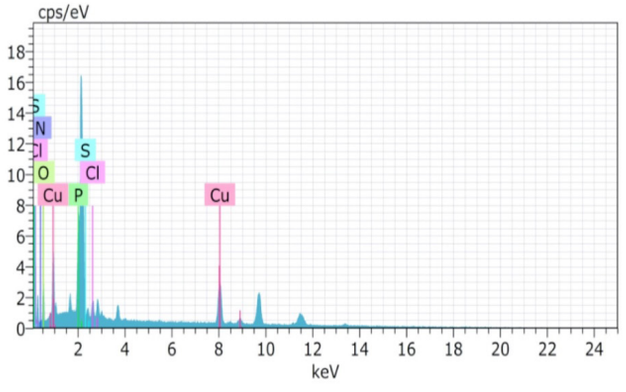

Figure 2. *EDX spectra of hybrid nanoflowers formed with 0.1 mg mL-1 extract of S. melongena*

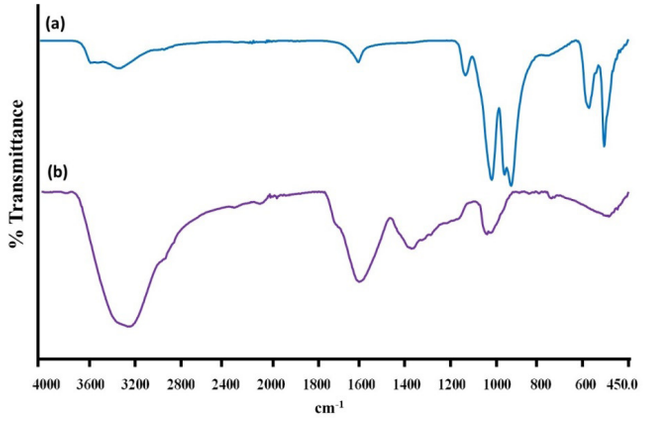

Figure 3. *FT-IR spectrums of (a) hybrid nanoflowers formed with 0.1 mg mL-1 extract of S. melongena and (b) the plant extract*

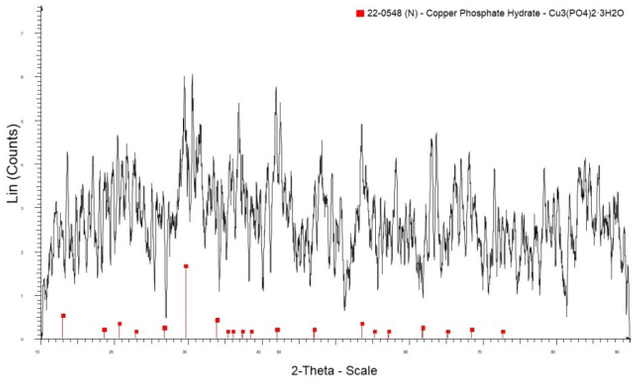

Figure 4. *XRD spectra of hybrid nanoflowers formed with 0.1 mg mL-1 extract of S. melongena*

Table 1. *Anticholinesterase activity (Inhibition % ± S.E.M.& IC_{50} value) of eggplant extract and Sm-ihNFs*

Samples	Anticholinesterase activity			
	AChE		BChE	
	Inhibition % #	IC_{50} (ppm)	Inhibition % #	IC_{50} (ppm)
Sm	70.12 ± 0.15***	17.09 ± 1.36**	75.76 ± 0.65**	28.29 ± 4.30**
Sm-ihNFs	13.83 ± 1.93***	321.46 ± 6.31***	85.12 ± 1.87*	32.76 ± 8,90**
Galantamine hydrobromide	92.23 ± 0.65***	2.31 ± 0.19**	81.82 ± 0.56*	3.01 ± 0.22*

 # Inhibition % ± S.E.M. at 0.2 mg mL^{-1} concentrations
**p<.5, **p<.05, ***p<.005, ANOVA test*

Table 2. *Antidiabetic activity (Inhibition % ± S.E.M.& IC_{50} value) of eggplant extract and Sm-ihNFs*

Samples	Antidiabetic activity			
	a-glucosidase		*a*-amylase	
	Inhibition % #	IC_{50} (ppm)	Inhibition % #	IC_{50} (ppm)
Sm	46.67 ± 4.64*	212.33 ± 17.19***	42.05 ± 5.42**	213.80 ± 21.68***
Sm-ihNFs	82.77 ± 1.31***	31.95 ± 6.72**	83.06 ± 2.92***	27.81 ± 15.21**
Acarbose	57.74 ± 0.83*	59.27 ± 15.09*	58.40 ± 0.61*	38.46 ± 11.73**

 # Inhibition % ± S.E.M. at 0.2 mg mL^{-1} concentrations
**p<.5, **p<.05, ***p<.005, ANOVA test*

Table 3. *Tyrosinase enzyme inhibition (Inhibition % ± S.E.M.& IC_{50} value) of eggplant extract and Sm-ihNFs*

Samples	Tyrosinase inhibition activity	
	Inhibition % #	IC_{50} (ppm)
Sm	4.59 ± 3.53*	704.56 ± 39.23***
Sm-ihNFs	16.43 ± 0.31**	423.80 ± 2.02**
Kojic acid	24.23 ± 5.52**	371.80 ± 36.80**

 # Inhibition % ± S.E.M. at 0.2 mg mL^{-1} concentrations
**p<.5, **p<.05, ***p<.005, ANOVA test*

3.2. Enzyme inhibitions

According to average cholinesterases inhibition ± standard error means (S.E.M.) values were given in Table 1, the BChE activity of nanoflower was higher than the galantamine hydrobromide, whereas the AChE inhibition activity was higher in the plain extract.

According to average of the *a*-glucosidase and *a*-amylase inhibition ± standard error mean (S.E.M.) inhibition values

were given in Table 2, the enzyme inhibition of the samples was elevated compared to the reference acarbose.

Average Tyr inhibition ± standard error means (S.E.M.) were demonstrated by the calculation of absorbance of the plain extract and its hybrid nanoflowers against blank sample. According to inhibition values given in Table 3, the results showed that the enzyme inhibition of the samples was low compared to kojic acid.

4. DISCUSSION

The prevalence of chronic and metabolic disorders continues to increase in humans around the world. The tendency to herbal resources has risen for the purpose of prevention or treatment of diseases (40). Today, many scientists have focused on the integration of natural resources and technological developments. In our study, nanoflower-plant hybridization studies were carried out to increase the biological activity potential of plants. One of the most important reasons for using *Solanum melongena* (eggplant) in this study was limited pharmacological studies on it despite its economically valuable. The present study demonstrated the green synthesis, characterization, and activity of the organic-inorganic hybrid Sm-ihNFs enzymes inhibitors. This easy to apply and one-step immobilization withstand the relation reactions between amine groups in the character strength of enzymes and cupric phosphate nanoflowers. Three consecutive steps were conducted for forming the nanoflower-like structure. First step was nucleation and formation of primary nano crystals. Second step was arranging crystals, and last step was formation of nanoflowers (23).

The results were promising that the hybrid nanostructures were synthesized demonstrated appealing blooming structures as 5-6 µm size. Likewise, characterization of the Sm-ihNFs was successfully completed by using different techniques (SEM, EDX, FTIR, and XRD). In a period of approximately 30-35 years, pharmacological and phytochemical studies on *Solanum species* have gained importance. At least 65 species (including *S. aculeastrum, S. aethiopicum, S. americanum S. anguivi, S. cathayanum, S. capsicoides, S. diphyllum, S. muricatum, S. nigrum, S. septemlobum, S. sessiliflorum*, *S. spirale, S. surattense, S. torvum S. tuberosum, S. violaceum,* and *S. xanthocarpum*) have been studied on scientific platform. The most antioxidants and anticancer activities of *Solanum species* have been demonstrated by scientists. The responsible compounds of pharmacological activities, such as antibacterial, anticancer, anticonvulsant, antidiabetic, anti-fungal, anti-inflammatory, antileishmanial, antioxidants, antitumor, and spasmolytic, of *Solanum* species have been attributed to steroidal alkaloids (41-43). There have been some publications related to the subject of this manuscript despite the small number of pharmacological studies on eggplant. One of these studies was conducted by Kwon and coworkers. They indicated that eggplants have radical scavenging-linked antioxidant activity and α-glucosidase inhibitory effect due to rich phenolic compounds (10). That result supported our study, moreover, the hybrid nanoflower exhibited higher effective *a*-glucosidase and *a*-amylase enzymes activities than the plain plant extract. In another *in vitro* study, calystegines, a tropane alkaloid derivative in eggplant, showed glycosidases inhibitory activity (44). Consequently, the hybrid nano-flower might contain the N including alkaloid structure, therefore.

In a poster presentation presented by Ketprayoon and Chaicharoenpong, while *S melongena*'s methanolic fruit extract showed low tyrosinase inhibitor activity, tyrosinase inhibitor activity of *S melongena*'s aqueous fruit extract could not be determined (45). Although no significant activity was observed in both the calyx extracts and the hybrid nanoflower, higher effective tyrosinase inhibitor activity was determined in the hybrid nanoflower in our study. In another study, the ethanolic eggplant peels extract have showed the skin protecting (46). There is a need for evaluation of different eggplant parts and their various extracts.

The cholinesterase inhibitors are still the most important clinical strategy to manage Alzheimer's disease. In this study, while Sm-ihNF showed BChE enzyme inhibitory effect, it was not very successful on AChE enzyme inhibition. However, this is, to the best of our knowledge, the first report of the analysis of both acetyl and butyryl choline esterase enzymes inhibition activities of eggplant. It is thought that *Solanum* glycoalkaloids may be the compounds responsible for anticholinesterase activities (47).

5. CONCLUSION

The enzyme inhibition tests have been used for getting an idea about several different illness due to their activity and specificity performance. Although there are many enzyme inhibition studies on plants, studies on nano technological-chemical studies for increasing activity based on natural sources are limited. With the studies shown in this text, a novel and elegant immobilization approach was used to form nanoflower-like structures from enzymes exhibiting highly enhanced catalytical activity and stability. The nanoflower's large surface area, limited the mass-transfer, and nanoscale-related enzyme cooperation are potential causes in enzyme inhibition tests and biological activity studies. The synthesis of protein-inorganic hybrid nanoflower containing plant extracts is an important factor considering its suitability for commercial applications in pharmacy and cosmetics.

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Peer-review: *Externally peer-reviewed.*
Author Contributions:
Research idea: UKC.

Design of the study: NÖ.
Acquisition of data for the study: CA.
Analysis of data for the study: CD.
Interpretation of data for the study: NE.
Drafting the manuscript: CD.
Revising it critically for important intellectual content: UKC.
Final approval of the version to be published: CD.

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Clinical and Experimental Health Sciences

Does Chitosan Introduce Protection Against Methotrexate-Induced Hepatorenal Injury in Rats?

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ABSTRACT

Objective: Chitosan possesses antioxidant properties and exhibits anti-inflammatory characteristics. The objective of the investigation was to assess the effectiveness of chitosan in protecting against hepatorenal injury induced by methotrexate (MTX), a medication utilized for immunosuppression and chemotherapy.

Methods: Wistar albino rats were allocated into 3 different groups, each consisting of six animals (n=6). The control group received saline for 5 days (i.p.), the MTX group was administrated a single dose MTX (60 mg/kg, i.p.) along with saline for four days (i.p.), while MTX+Chitosan group received a single dose of MTX (60 mg/kg, i.p.) followed by Chitosan administration (200 mg/kg, i.p.) for four days. On the sixth day, the animals were decapitated, and blood and tissue samples were collected. BUN, creatinine and tissue inhibitors of metalloproteinase-1 (TIMP-1) levels and activities of AST, ALT, ALP, LDH, matrix metalloproteinases (MMP-3, MMP-8, MMP-9) activities were quantified in the blood. The liver and kidney were evaluated for caspase-3 and-9 through western blotting, while structural damage was examined using light microscopy.

Results: In the MTX administered group, blood and tissues values except for all TIMP-1 statistically increased when compared to the control group, while activity of TIMP-1 decreased significantly. The Chitosan-treated MTX group had comparable values to the control group.

Conclusion: Based on its influence on metalloproteinases and caspases, our findings lead to the conclusion that Chitosan offers a protective effect against liver and kidney damage induced by MTX.

Keywords: Caspase, Chitosan, Methotrexate, MMP, TIMP-1

1. INTRODUCTION

Methotrexate (MTX) is an inhibitor of dihydrofolate reductase (DHFR) that is involved in the treatment protocols of cancer and autoimmune disorders. It has been shown to cause hepatorenal damage via different oxidative and inflammatory mechanisms (1–3).

Matrix metalloproteinases (MMP) activation has been associated with inflammation, angiogenesis, embryogenesis, and apoptosis. Furthermore, it augments caspase (Casp) activity, impacts hemodynamic parameters, and induces hepatorenal damage during MTX administration (4, 5). MMPs, which are proteolytic enzymes integral to the extracellular matrix, perform crucial functions in a range of biological processes, encompassing inflammation and tissue repair. Tissue inhibitors (TIMPs) naturally inhibit MMPs by effectively regulating their activity. TIMPs bind to MMPs in a unidirectional manner, exerting inhibitory effects. Consequently, the balance between MMP and TIMP levels becomes a critical determinant of MMPs' efficacy in maintaining tissue homeostasis (6, 7). Caspases serve as the principal executors of apoptosis, and numerous studies have demonstrated their involvement in MTX-induced tissue injuries, including oral and hepatorenal tissues (8, 9).

Chitosan, utilized in diverse medical applications, has demonstrated protective effects attributed to its antioxidant and anti-inflammatory properties in numerous studies on inflammation and toxicity (10–12). While investigations have explored the protective effects of various antioxidant and anti-inflammatory drugs against MTX toxicity, the issue of hepatorenal damage remains significant in MTX administration (10–12). However, as of now, there is no evidence to suggest the efficacy of chitosan in ameliorating drug-induced hepatorenal injury, which limits its use as a treatment option in methotrexate therapy (9, 13).

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In the present study, we utilized MTX to induce liver and kidney damage in order to examine the effect of chitosan on MTX-induced hepatorenal injury. Rats were chosen as the experimental model to assess the potential protective efficacy of chitosan against MTX-induced hepatorenal injury. Based on these considerations, the aim of our study was to assess the protective effects of chitosan against MTX-induced hepatorenal injury by examining MMPs, caspases, and conducting a histopathological examination.

2. METHODS

According to the 1964 Helsinki Declaration's guiding principles, this study was carried out. The Local Animal Experiments Ethics Committee of the Near East University was authorized to approve the study protocol (Decision no: 2020/111). The experiment was carried out in a single center as a single-blind, randomized, controlled study. A total of eighteen Wistar albino rats, including both males and females, were allocated into three groups (n=6). The rats were housed following standard laboratory conditions. The control group was administered oral saline exclusively for a duration of 5 days. Conversely, the MTX group received an intraperitoneal dose of 60 mg/kg MTX on day 1, followed by intraperitoneal administration of saline for the subsequent 4 days (14). The MTX + Chitosan group, on the other hand, received a single intraperitoneal dose of 60 mg/kg MTX, followed by four days of oral gavage with 200 mg/kg Chitosan (15, 16). Following the sacrifice of the animals on day 6, blood and tissue samples (liver and kidney) were collected from each subject. Low molecular weight chitosan (50-190 kDa) was used in this study because it has been shown to significantly decrease tumor growth, whilst high molecular weight has not been shown to have any effect. Chitosan has a deacetylation level of 75-85%, making it suitable for use in biomedicine including tissue regeneration, inflammation, and cancer therapy (17, 18).

2.1. Biochemical Assays

Biochemical indicators including alanine transaminase (ALT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine were measured and evaluated using commercially available test kits (Mindray, Shenzen, China). Specific enzyme immunoassay test kits designed for rats were utilized to determine the activity levels of MMPs (MMP-3, MMP-8, and MMP-9) and TIMP-1 levels (MMP-3 E-EL-R0619, MMP-9 E-EL-R302 from Elabscience, Wuhan, China; MMP-8 ELR-MMP8 and TIMP-1 ELR-TIMP-1 from RayBiotech Life Inc., Norcross, GA, USA).

2.2. Histopathologic Evaluation

Structural damage to tissues was evaluated under the light microscope. Formalin solution (10%) was used for the fixation of liver and kidney tissues. The 4 µm thick slices cut from paraffin blocks obtained during standard histological tissue processing. Routine staining with hematoxylin and eosin was conducted on these slices. Subsequently, the sections were examined using a light microscope.

2.3. Western blotting

Each group's dissected tissues were homogenized before being centrifuged at 2000g for 10 min. According to the Lowry method, the quantity of protein in each sample was 50 µg. The samples were then loaded onto SDS (12%) PAGE gels. Samples were separated according to their protein weights and transferred to the nitrocellulose membranes (Schleicher and Schuell, 0.45 m, Germany for 75 min at 90 V) and incubated with primary antibodies [caspase-3 (casp-3; sc-56053) and caspase-9 (casp-9; sc-56076) 1:200 dilution, at +4° C], while all membranes were standardised with β-actin (1:100; sc-130657) and analysed with a free program for densitometric analysis (www.totallab.com).

2.4. Statistical Analysis

The statistical analysis was performed using Prism 7.0 software (GraphPad, CA, USA). Significances among sample means were assessed using the TUKEY's test following a one-way analysis of variance (ANOVA). A significance level of $p<0.05$ was employed to determine statistical significance.

3. RESULTS

Administration of MTX resulted in elevated levels of biochemical indicators, including AST, ALT, LDH, BUN, and creatinine, compared to the control group. However, after treatment with Chitosan, a significant reduction in the changes of these biochemical parameters was observed compared to the group that received MTX ($p<0.05$; $p<0.01$) (Table 1).

Table 1. *Serum a) AST and b) ALT c) BUN, d) Creatinine and e) LDH activities of all groups (n=6) in hepatorenal damage induced by MTX in rats.*

	Control	MTX	MTX-Chitosan
AST (U/L)	103.4 ± 16.1	199.1 ± 16.6 **	129.9 ± 12.5 +
ALT (U/L)	44.3 ± 4.8	89.5 ± 8.9 **	58.5 ± 9.6 +
LDH (U/L)	871 ± 44	1389 ± 130 **	977 ± 54 +
BUN (U/L)	16.80 ± 1.68	25.70 ± 2.67 *	17.64 ± 1.59 +
Creatinine (U/L))	0.62 ± 0.03	1.16 ± 0.12 **	0.69 ± 0.11 ++

** p<0.05, ** p<0.01 compared to control group; + p<0.05 ++ p<0.01 compared to MTX group.*

Significant increases in the activities of MMP-3, MMP-8, and MMP-9 were observed in the MTX group, along with a notable decrease in TIMP-1 activity compared to the control group. However, in the MTX + Chitosan group, these parameters exhibited a significant decrease compared to the MTX group ($p<0.05$, $p<0.01$), reaching values comparable to those of the control group (Table 2).

Table 2. *Serum a) MMP-3, b) MMP-8 c) MMP-9 and d) TIMP-1 activities of all groups (n=6) in hepatorenal damage induced by MTX in rats.*

	Control	MTX	MTX-Chitosan
MMP-3 (ng/ml)	10.04 ± 0.33	16.17 ± 2.03 *	11.01 ± 0.72 +
MMP-8 (pg/ml)	10.39 ± 0.49	15.23 ± 1.16 **	11.28 ± 0.81 +
MMP-9 (ng/ml)	35.70 ± 3.12	70.83 ± 5.04 ****	41.34 ± 4.25 +++
TIMP-1 (ng/ml)	1.14 ± 0.08	0.62 ± 0.06 **	1.07 ± 0.08 ++

** p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001 compared to control group; + p<0.05 ++ p<0.01 +++ p<0.001 compared to MTX group.*

The impact of Chitosan treatment on tissue levels of caspase-3 (casp-3) and caspase-9 (casp-9) was evaluated using the Western Blotting method (Figure 1). In the MTX group, both kidney and liver tissues exhibited statistically higher levels of casp-3 expression compared to the control group (p<0.001 and p<0.01, respectively). However, the administration of chitosan significantly reduced casp-3 expression in both liver and kidney tissues of the MTX + Chitosan group in comparison to the MTX group (p<0.001 for liver, p<0.05 for kidney; Figure 2A and 2B). Furthermore, casp-9 expression demonstrated a significant increase in the liver and renal tissues of the MTX group compared to the control group (p<0.01 for both tissues). Nonetheless, treatment with Chitosan led to a significant reduction in casp-9 expression in both liver (p<0.01, Figure 2C) and kidney tissues (p<0.05, Figure 2D).

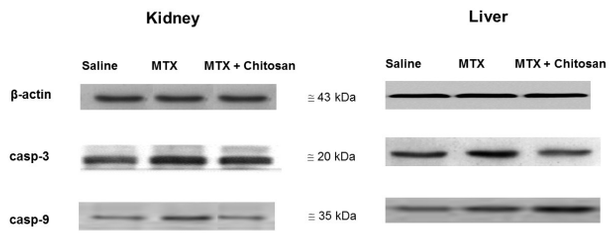

Figure 1. *Representative membrane images showing the protein levels of β-actin, casp-3, and casp-9 in kidney and liver tissues of Chitosan treatment in the methotrexate-induced rat hepatorenal model.*

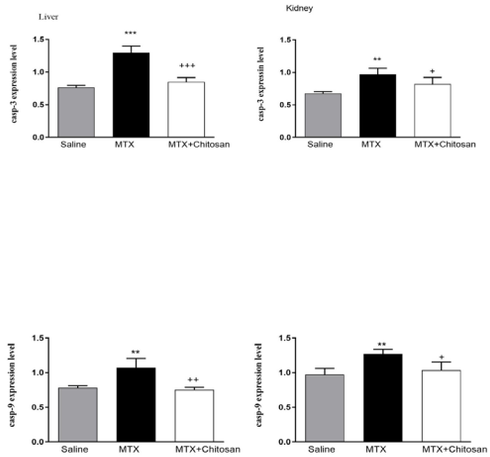

Figure 2. *Protein levels of caspase-3 and caspase-9 in kidney and liver tissues in the MTX-induced rat hepatorenal model. ** p<0.01, *** p<0.001 compared to control group, + p<0.05 ++ p<0.01, +++ p<0.01 compared to MTX group.*

Histological examination revealed necrotic spots with inflammatory cells in the MTX group's liver tissue (Figure 3B). MTX + Chitosan treatment, on the other hand, resulted in decreased neutrophil infiltration, with no evident necrotic spots (Figure 3C). Microscopic examination of the kidney showed fibrotic changes with neutrophil infiltration in the renal cortex, tubules, Bowman's capsule, proximal and distal tubules in the MTX group. However, no significant neutrophil infiltration and structural alterations were detected in the nephron cells of MTX+Chitosan group (Figure 4).

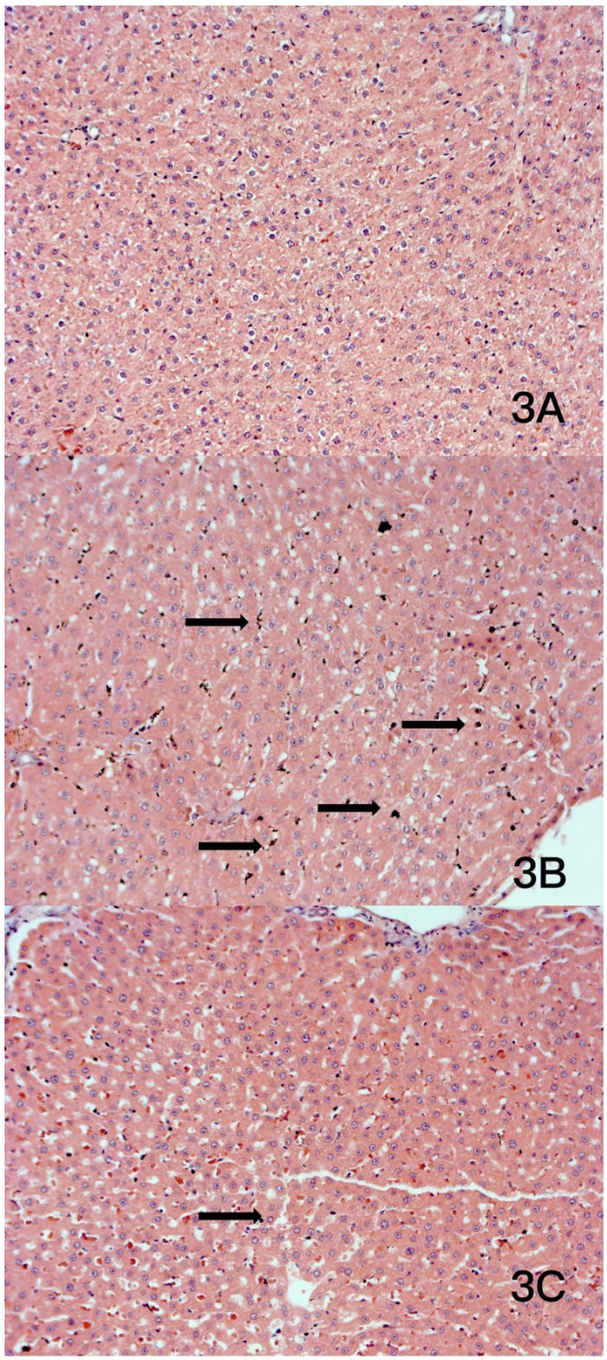

Figure 3. *Histopathological evaluation of liver tissues. 3A: Normal integrity of liver in Control group; 3B Severe inflammatory cell infiltrations (arrow) were detected in MTX group; 3C: Mild inflammatory cells were observed (arrow) in MTX+Chitosan group.*

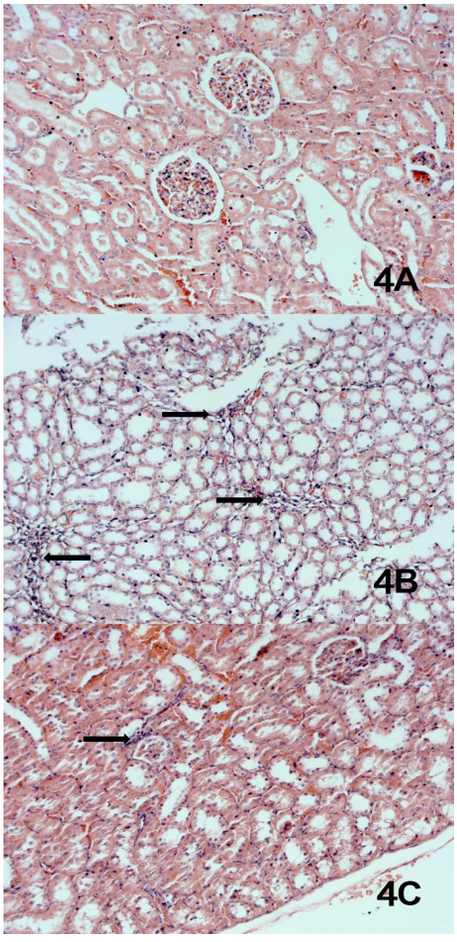

Figure 4. *Histopathological assessment of kidney tissues. 4A: Normal structure of kidney in Control group; 4B: Fibrosis and moderately inflammatory cell infiltrations (arrow) were detected in MTX group; 4C: Mild inflammatory cells were observed (arrow) and fibrosis is absent in MTX+Chitosan group.*

4. DISCUSSION

Several studies have established that chitosan, a biopolymer that is compatible with tissues, has anti-inflammatory and antioxidant properties, and it is also utilized in the production of different of pharmaceutical preparations (19, 20). In this study, the effects of methotrexate on ALT, AST, BUN, serum MMPs, creatinine, caspase and LDH activity, inflammation, and the protective impact of chitosan were examined by histopathological evaluation of the structural damages.

Different chemotherapy agents have been reported to increase ALT, AST, BUN, and creatinine levels, as well as LDH activation, all of which are important enzymes for assessing liver and kidney function (21, 22). Methotrexate (MTX), a known hepatorenal toxicant, has been associated with elevations in serum levels of AST, ALT, BUN, creatinine, and the activation of LDH. Furthermore, MTX is used to induce tissue damage in experimental studies (10, 11). In this study, we observed that chitosan altered the MTX-induced increase in serum ALT, AST, BUN, and creatinine levels. The study results are consistent with those of earlier researches that reported that chitosan can modulate AST, ALT, BUN, creatinine levels, and LDH activity, especially in inflammatory conditions (19, 23, 24).

MMPs, that provide normal maintenance of the normal physiological process, considered as an important marker during tissue damage or diseases (25). They are considered as proteolytic enzymes that infiltrate neutrophils, especially in the inflammatory process. The role of MMPs in the formation of hepatorenal damage due to inflammation or various agents has also been demonstrated (26, 27). The studies on the effects of MTX on MMPs are still controversial (28–30). It has been suggested that MTX exerts a protective effect by decreasing the MMPs activity, which is increased during rheumatoid arthritis. MTX has also been shown to increase MMPs activity in cancer patients. In our study, MTX treatment increased MMP activity while decreasing TIPM-1 activity. Although this does not explain how MTX causes hepatorenal injury, the heterogeneity in MMP activation suggests that MMPs may contribute to MTX-induced hepatorenal injury. In our study, chitosan treatment decreased the activity of MMP-3, MMP-8, MMP-9, and TIMP-1 to levels that were close to that of the control group. The effects of chitosan on MMP activities have been investigated in several studies, and results from these studies are consistent with our findings (31, 32).

In addition, MTX treatment is known to trigger apoptosis by increasing caspase activity. The activation of caspase 3 and 9 is an essential factor in the emergence of MTX-induced liver and kidney injury (33, 34). Studies on Chitosan have revealed that it has antiapoptotic effects (35, 36). In our study, hepatorenal injury following MTX administration was significantly decreased by chitosan administration in accordance with the literature (9).

MTX has been shown to induce structural damage in the liver and renal tissues. Previous studies reported the existence of widespread neutrophil infiltration and tissue necrosis (11, 12). The current study showed that administration of MTX induced damage to both liver and kidney tissues. Histopathological examination confirmed the presence of structural damage in the liver and kidney tissues caused by MTX treatment. These histopathological findings are in line with previous studies (37, 38), and the damage regressed following Chitosan treatment. Thus, the cytoprotective agent, chitosan, has been demonstrated to reduce MTX-induced hepatorenal injury in the presented study.

Similar to other animal experiments, this study possesses several limitations that can influence future research directions. Subsequent investigations should independently validate the involvement of proteolytic and apoptotic enzymes in MTX-induced hepatorenal toxicity and ascertain whether chitosan's protective effect operates via modulation of these enzymes. As this study was conducted on rats, it highlights the necessity for clinical trials to evaluate the efficacy of chitosan as a therapeutic intervention. Histopathological findings play a crucial role in assessing the extent of structural damage. The parameters we assessed contribute to providing an integrative picture of chitosan's impact on MTX-mediated hepatorenal

injury. Further analysis is imperative to elucidate the potential intricate mechanisms underlying this effect.

5. CONCLUSION

Based on the study findings, it was observed that chitosan exhibited no cytotoxic effects. Instead, it demonstrated a structural and functional protective role against MTX-induced hepatorenal toxicity. This protective effect was attributed to its modulation of proteolytic and apoptotic enzymes. MTX, commonly administered for autoimmune conditions like rheumatoid arthritis and cancer, significantly impacts liver and kidney tissues in a detrimental manner. Hence, our findings propose an alternative approach to MTX therapy, emphasizing the potential of chitosan as a therapeutic intervention.

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

Ethics Committee Approval: *This study was approved by the Animal Experiments Local Ethics Committee of Near East University (Approval date: 17.04.2020; number: 2020/111).*

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Author Contributions:

Research idea: AOS, KB
Design of the study: AOS, KB, SS
Acquisition of data for the study: SS, HO, AA
Analysis of data for the study: SS, HO, AA
Interpretation of data for the study: AOS, SS, KB
Drafting the manuscript: AOS, KB
Revising it critically for important intellectual content: AOS, KB, SS, HO, AA
Final approval of the version to be published: AOS, KB, SS, HO, AA

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Clinical and Experimental Health Sciences

Influence of Low-Temperature Degradation on Phase Transformation and Biaxial Flexural Strength on Different High-Translucent 4Y-PSZ, 5Y-PSZ, 6Y-PSZ Monolithic Zirconia

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ABSTRACT

Objective: This study aimed to investigate the effect of low-temperature degradation (LTD) in phase transformation and biaxial flexural strength of high-translucent yttria partially stabilized zirconia (Y-PSZ) and yttria tetragonal zirconia polycrystalline (3-YTZP).

Methods: A total of 120 new high-translucent 3-YTZP (NMS) and Y – PSZ (KST, KUT, NQ3MS) zirconia disc specimens were manufactured according to ISO 6872 for biaxial flexural strength (14 mm., 1.2 ± 0.02 mm). The specimens from each type of material were divided into 3 subgroups (n:30) according to the LTD in an autoclave at 134 C0 at 2 bar (n:10) (at 5, 20 hour (h)). Specimens without LTD served as the control. Data of the monoclinic phase changes (Xm) and flexural strength were analyzed using two-way ANOVA followed by post hoc MannWhitney U test. Weibull statistics were used to analyze strength reliability.

Results: LTD increased the monoclinic content significantly for NMS and slightly for the KST group. A monoclinic phase was not detected for KUT and NQ3MS groups. The biaxial flexural strength of the NMS group was affected significantly and decreased with an increase in the 20 h aging. For flexural strength values, there was no significant difference in aging times for each of the KST, KUT, and NQ3MS groups. Weibull analysis showed the highest characteristic strength for NMS (1412.9), KST (750.1), NQ3MS(790.5) and KUT (615.2) groups. The Weibull modulus (m) increased in the NMS, KUT, and NQ3MS groups compared with the control group and decreased in the KST group.

Conclusion: LTD caused a significant decrease in the biaxial flexural strength results of the NMS group but did not significantly affect the KST, KUT, and NQ3MS groups' values.

Keywords: High-translucent zirconia, Low-temperature degradation, Phase transformation, Biaxial flexural strength

1. INTRODUCTION

Y-TZP is the most widely used material in the construction of all-porcelain syetems (1,2). Zirconia is a material consisting of 3 different phases.: monoclinic (m), tetragonal (t), and cubic (c)(3). The m phase is a stable phase at low temperatures up to 1170°C and with the increase transforms into a tetragonal phase (4,5) and then at 2370°C into a cubic phase (5). The transformation from the tetragonal phase to the monoclinic phase (t→m) occurs during cooling below about 970°C and 3%-4% volumetric increase forms in the material, that creates compressive stresses (3,4). Thereby, the crack tip closes and more crack propagation is prevented (4). In addition to the positive effect on the crack tip, the t→m transformation decreases mechanical stability (6,7). 3Y-TZP zirconia used in prosthetic dentistry, which is an opaque material and has limited translucency, often contains 3 mol% yttria as a stabilizing element (2,4,8,9). Recently, highly-translucent Y-TZP ceramics have become popular for making monolithic restorations. New methods have been used to improve the translucency of traditional 3Y-TZP zirconia, including increasing the yttria content. Decreasing the addition of alumina from 0.25% to 0.1% can increase translucency, and adding 0.2 mol% La_2O_3 to Y-TZP changes the sintering time and temperature and reduces the grain size. Thus, it also effectively eliminates light scattering and can improve transparency (2,8,10,11).

Another disadvantage of 3Y-TZP restoration is that Y-TZP undergoes a negative phase transformation known as LTD (12,13). In the presence of water at low temperatures, a t→m phase transformation occurs. Thereby, the transformation progresses from the surface to the interior of the material (12,13). LTD causes surface roughness and followed by microcracking (14,15) and negatively affects the mechanical properties of Y-TZP (14-17). The sensitivity of Y-TZP to LTD

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depends on several factors. The transformation is slowed with decreasing grain size and increasing in the stabilizer content (18-21). Also, the rate of phase transformation increases with increased temperature and aging time (14,16,17). However, it may be the surface treatments can induce residual stress and the cubic phase acts as the nucleation site for the t→m transformation (22, 23).

0.25% by mass of alumina (Al_2O_3) was added to the first generation 3Y-TZP to facilitate sintering. However, these zirconia show high opacity due to the birefringence feature of their non-cubic phases (24). Thereby, the Y-PSZ was produced by increasing the yttria content and applying an isotropic cubic phase to tetragonal zirconia (24, 25). The alumina concentration of second-generation PSZ has been reduced and porosity formation has been prevented by sintering at higher temperatures (26). PSZ contains nanosized tetragonal or monoclinic particles in a cubic matrix (27).

Fully stabilized zirconia (FSZ) was introduced and controversially compared to the first and second generations, including a cubic phase ratio of up to 53% in their microstructure. Cubic crystals show a larger volume than tetragonal crystals and so light scatters less severely and makes it more translucent (1, 28). For developing translucent zirconia, the ratio of the cubic phase has increased.

The LTD process of zirconia is multifactorial. T→m transformation is largely related to the presence of water or water vapor in the environment, the affinity of the material, the shape, size, and location of the particles, and the stabilizer content (29). After LTD, zirconia material exhibits different mechanical behavior according to the depth of the 't-m phase transformation layer at different degrees depending on its structural content (30). An increase in the amount of monoclinic phase was determined because of the LTD of zirconia at low temperatures (31, 32). The high monoclinic phase amount decreases the flexural strength of the material (33). The null hypothesis is that LTD in newly high-translucent zirconia does not affect the phase transformation and biaxial flexural strength of the material. The aim of this study was to determine the effect of LTD on phase changes and biaxial flexural strength in newly developed high-translucent zirconia and to compare it with high-translucent 3Y-TZP zirconia.

2. METHODS

2.1. Preparation of specimens

Three new high-translucent Y-PSZ; and one 3Y-TZP disc were used and the compositions of the monolithic materials are presented in Table 1. A total of 120 high-translucent zirconia disc specimens were prepared from pre-sintered blocks with a final size of 14.0 mm and 1.2±0.2 mm in thickness, after sintering in accordance with ISO 6872(34). Presinterized disks were shaped by milling using the unit of CAD/CAM system (imes-score 250'i, Onex Dental, Ankara, Turkey). The specimens were obtained in 20%-25% enlarged sizes to compensate for the sintering shrinkage of the system and were sintered (Tabeo – 1/S/Zircon-100, MIHMVOGT GmbH & Co. KG, Stutensee, Germany) according to manufacturer specifications (Table 2). The specimens were finished with silicon carbide paper (800 and 1200 grit) after sintering under water cooling. One surface of all specimens was performed by the same person using diamond medium-grained bur and then fine-grained bur for 30 seconds, (Diacera Medium, Diacera Fine, G&Z Instrumente GmbH, Lustenau, Austria) with a micromotor at 10000 rpm with water cooling.

Table 1. *Materials and their composition used in this study.*

Material	Manufacturer	Composition	Batch Nummer
Katana Zirconia UTML **KUT** (5Y-PSZ)	Kuraray Noritake Dental Inc., Miyoshi, Japonya	ZrO_2 + HfO_2 %87-92 (Y_2O_3) %8-11 Diğer oksitler %0-2	DOZBT
Katana Zirconia STML **KST (**4Y-PSZ)	Kuraray Noritake Dental Inc., Miyoshi, Japonya	ZrO2 + HfO_2 %88-93 (Y_2O_3) %7-10 Diğer oksitler %0-2	EAUWN
Nacera Pearl Q^3MS **NQ^3MS** (6Y-PSZ)	Doceram Medical Ceramics GmbH, Dortmund, Almanya	Yitriya-stabilize %40 tetragonal, %60 cubic zirkonya polikristal (%6 mol Y_2O_3)	5057862
Nacera Pearl MS **NMS** (3Y-TZP)	Doceram Medical Ceramics GmbH, Dortmund, Almanya	ZrO_2 +HfO_2 + Y_2O_3> %99, Y_2O_3 %4,5-%6	5146158

Table 2.*Sintering parameters used in this study.*

GENERAL SINTERING PROGRAM	KST / KUT	NQ^3MS / NMS
High temperature	1550°C / 2822 ° F	1500°C
Time	2 hour	2 hour
Temperature increase rate	10°C / 18°F minute	8° C / minute
Temperature decrease rate	– 10°C / – 18°F minute	– 8° C / minute

Nacera Pearl Multi Shade (NMS), Nacera Pearl Q3 (NQ^3MS), Katana UTML (KUT), Katana STML (KST)

2.2. Low-Temperature Aging

LTD was performed according to the ISO 13356 standard in an autoclave (Eryiğit Steam Sterilizer, Eryiğit Medical Devices Inc., Ankara, Turkey) at 134 C^0 at 2 bar (n:10) over a period of 5, and 20 h. Specimens without LTD served as the control (Figure 1).

The polished surfaces of the samples in the non-aged group were evaluated as the control group. The specimens were placed on an autoclave tray in a pressure chamber at 134 C^0 under 2 bar for up 5 and 20 h for the phase transformation.

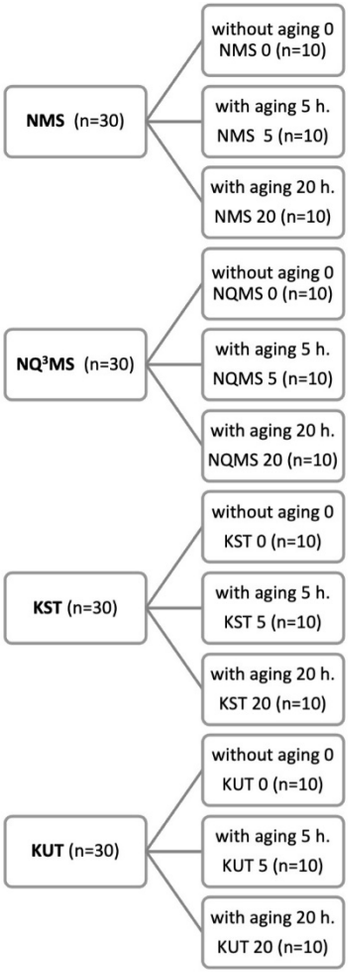

Figure 1. *Schematic represantation of the study design*

2.3. X-Ray Diffraction (XRD) Analysis

Randomly selected specimens from each material were examined to determine the crystalline phases by X-ray diffractometer device (Bruker D8 ADVANCE, Bruker Turkey Ltd.Şti, Ankara, Turkey). X-ray diffraction (XRD) data were collected using a 2θ diffractometer and using CuK α radiation (30mA and 40kV). Spectra were collected in the 2θ with a range of 2040^{0}at a step interval of 1^0/min. and a step size of 0.020. The monoclinic phase fraction (Xm) and peak intensities of 28 and 30 degrees were analyzed with processing software ORIGIN 2021. The amount of monoclinic phase fraction (Xm) was calculated using the Garvie and Nicholson methodology (35); Equation:

$$X_M = \frac{I_{M(111)} + I_{M(111^-)}}{I_{M(111)} + I_{M(111^-)} + I_T}$$

Xm = the overall intensity ratio of the monoclinic phase

Im1 $(111)_m$ =the intensity of the monolinic peak at 28.2^0

Im2 $(111)_m$ =the intensity of the monolinic peak at 31.5^0

It $(101)_t$ =the intensity of the tetragonal peak at 30.2^0

2.4. Biaxial Flexural Test

Biaxial flexural strength of high-translucent zirconia specimens was performed in a piston-on three ball test using a testing machine (Lloyd Instruments, Ametek Inc, Florida, USA). Discshaped specimens of different Y-PSZ and 3Y-TZP materials were positioned with the treated surface on three supporting balls (3.2 mm. in diameter, seperate on a support circle with a diameter of 10 mm) in a triangular position. An sticking plaster was placed on the compression side of the specimens for uniform load distribution. All disk-shaped zirconia specimens were loaded with a flat punch at a crosshead speed of 0.5 mm/min until failure. The results of the biaxial flexural strength were determined using the equation in accordance with ISO 6872; Q =-0.2387 P (X – Y) /d2

Q: the flexural strength at fracture

P: the total load causing fracture (N)

X = (1+ v) ln (r2/r3)2 + [(1-v) /2] (r2/r3)2 Y

= (1+ v) [1 + ln (r1/r3)2] + (1-v) (r1/r3)2 v:

Poisson's ratio of 0.3 for zirconia

2.5. Statistical Analysis

The conformity of continuous variables to normal distribution was tested with the Shapiro Wilk test. Biaxial flexural strength test data were analyzed using two-way ANOVA (Multivariate General Linear model, Two-way ANOVA) the effect of independent variables on two dependent variables, followed by post hoc Mann–Whitney U test. Correlation analysis of two independent and non-normally distributed variables was performed using Spearman's rho correlation analysis. The significance level was determined as 0.05. Comparative analysis were performed using the SPSS v24 Program (IBM Ltd, Armonk, NY, USA). Weibull analysis was performed using the Minitab (Microsoft Ltd, New Mexico, USA) program and analyzed the variability of flexural strength.

3. RESULTS

The relative amount of monoclinic phase of three different Y-PSZ and one 3Y-TZP were determined by different aging times by XRD analysis.

3.1. XRD Analysis

LTD affected the monoclinic phase results differently in terms of different yttria contents in the microstructure of the investigated materials. The XRD diffraction patterns of the experimental groups are shown in Figures 2a,b and 3a,b. XRD results for control group specimens revealed that only the tetragonal phase and monoclinic phases were not detected. LTD increased the monoclinic content significantly for the NMS group between aging times but slightly increased for the KST group ($p<.05$). The monoclinic phase was not detected for KUT and NQ^{3}MS groups and no significant difference was found between aging times. The materials were compared in terms of Xm values according to LTD and the results are shown in Table 3 and in Figure 4.

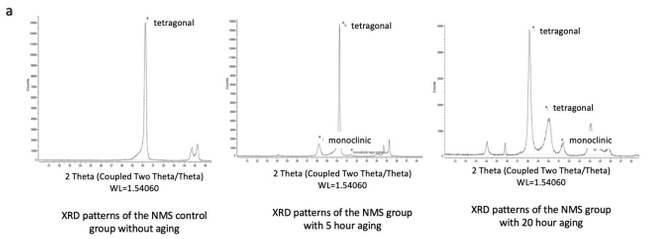

Figure 2a. *X-ray diffraction patterns of the NMS group after LTD with aging times.*

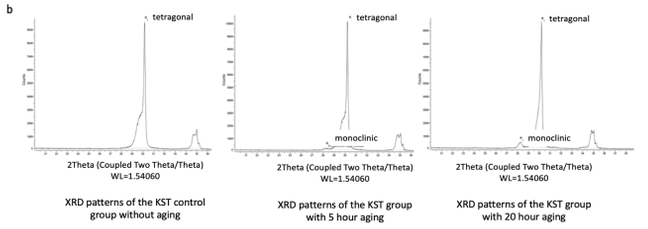

Figure 2b. *X-ray diffraction patterns of the KST group after LTD with aging times.*

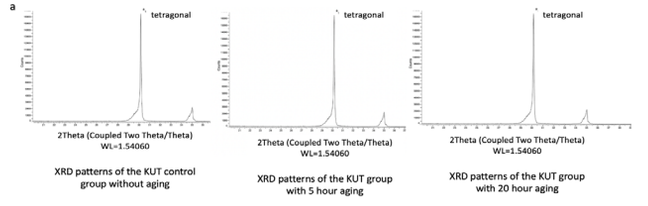

Figure 3a. *X-ray diffraction patterns of the KUT group after LTD with aging times.*

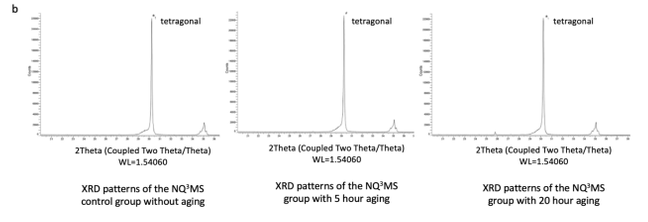

Figure 3b. *X-ray diffraction patterns of the NQ3MS group after LTD with aging times.*

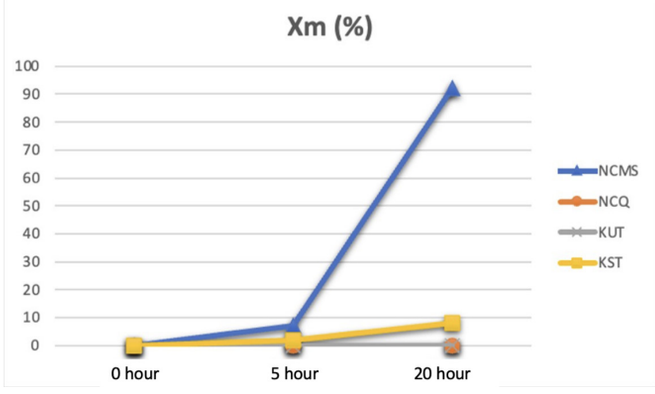

Figure 4. *Mean monoclinic phase fraction Xm (%) of the investigated materials after LTD.*

Table 3. *Summary of m-phase fraction (Xm in%) of the investigated materials*

m-phase Xm (%)							
Groups	**LTD**	**Mean**	**SD**	**Min.**	**Max.**	**χ^2**	**p***
NMS	0 hour 5 hour 20 hour	0 [a] 7 [b] 92 [c]	0 5 1	0 0 92	0 16 93	19.538	<.001
KST	0 hour 5 hour 20 hour	0 [a] 2 [b] 8 [c]	0 0 2	0 2 5	0 3 9	20.000	<.001
KUT	0 hour 5 hour 20 hour	0 [a,b] 0 [a,c] 0 [b,c]	0 0 1	0 0 0	0 0 2	4.000	.126
NQ^{3}MS	0 hour 5 hour 20 hour	0 0 0	0 0 0	0 0 0	0 0 0	–	–

There is no statistically significant difference between Kruskal Wallis test heat treatment measurements, Mann-Whitney U test: posthoc pairwise comparisons, and mean Xm (%) values of groups with common lowercase letters. Nacera Pearl Multi Shade (NMS), Nacera Pearl Q3 (NQ^{3}MS), Katana UTML (KUT), Katana STML (KST), low-temperature degradation (LTD), standard deviation (SD).

3.2. Biaxial Flexural Strength

The comparisons of the materials in terms of flexural strength values according to the LTD are shown in Table 4. LTD affected the biaxial flexural results differ in terms of different yttria contents in the microstructure of the materials. LTD resulted in a significant decrease in flexural strength values of the NMS group. The biaxial flexural strength values of the NMS group (1344.2) was significantly decreased with an increase in the 20 h aging time (1091.8 MPa). The flexural strength values of KST (4Y-PSZ), KUT (5Y-PSZ), and NQ^{3}MS (6Y-PSZ) were not significantly affected by LTD. For strength values, there was no significant difference in aging times for each of the three KST (728.9, 696.4, 640.4), KUT (554.1, 557.6, 566.4), and NQ^{3}MS (665.9, 733.1, 717.7 MPa) Y-PSZ groups. Mean biaxial flexural strength values of different Y-PSZ and 3-YTZP materials after LTD are shown in Figure 5.

Table 4. *Mean values and standart deviatioans (SD) of the biaxial flexural strength (MPa)*

Flexural Strength (MPa)							
Groups	**LTD**	**Mean**	**SD**	**Min.**	**Max.**	**χ^2**	**p***
NMS	0 hour 5 hour 20 hour	1344.2 [a] 1248.3 [a] 1091.8 [b]	154.2 66.8 97.7	1161.4 1158 946.3	1672.5 1340.6 1239.6	11.400	<.001
KST	0 hour 5 hour 20 hour	728.9 [a,b] 696.4 [a,c] 640.4 [b,c]	48.7 114.5 75.6	642.8 532.9 538.8	792.7 856.7 755.3	5.600	.072
KUT	0 hour 5 hour 20 hour	554.1 [a,b] 557.6 [a,c] 566.4 [b,c]	146.7 156.3 81.1	398.7 406.6 432.5	853.4 794 730.2	0.600	.814
NQ^{3}MS	0 hour 5 hour 20 hour	665.9 [a,b] 733.1 [a,c] 717.7 [b,c]	92.1 142.1 62.9	486.9 547.4 604.9	756.9 1001 823.4	4.200	.514

There is no statistically significant difference between Kruskal Wallis test heat treatment measurements, Mann-Whitney U test: posthoc pairwise comparisons, and mean flexural strength (MPa) values of groups with common lowercase letters. Nacera Pearl Multi Shade (NMS), Nacera Pearl Q3 (NQ^{3}MS), Katana UTML (KUT), Katana STML (KST), low-temperature degradation (LTD), standard deviation (SD).

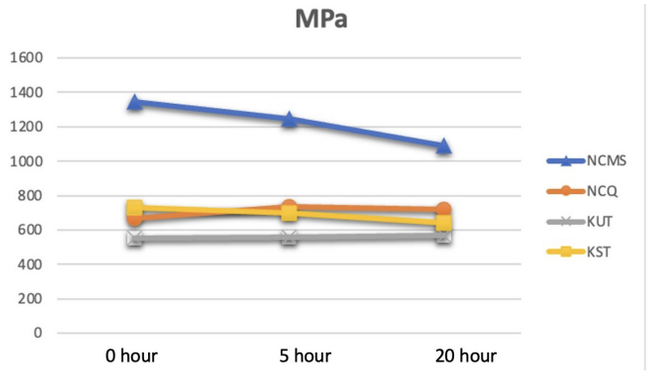

Figure 5. *Mean biaxial flexural strength values and standart deviatioans (SD)(MPa) of the investigated materials after LTD.*

3.3. Weibull Analysis

The Weibull statistical analysis is presented in Table 5 and Figures 6a,b and 7a,b. Weibull analysis showed the highest characteristic strength for NMS 1412.9 and KST 750.1 in the control group and for NQ³MS 790.5 and KUT 615.2 MPa in the 5 h aging group. The Weibull modulus (m) of NMS, KST, KUT, and NQ³MS was between 8.8–13.3, 18.8–9.4, 4.1–9.4, 10.5–13.2 respectively. While m values increased in the NMS, KUT, and NQ³MS groups, they decreased in the KST group. There was no statistically significant difference between the characteristic strength values of the KUT and NQ³MS groups.

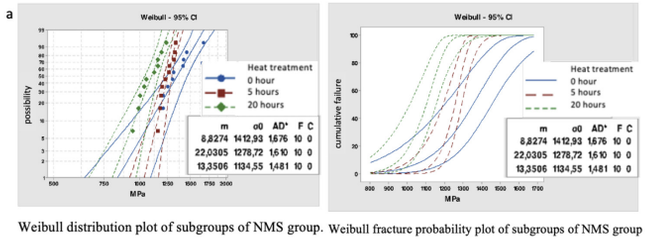

Figure 6a. *Weibull distribution and fracture probability plots of NMS group after LTD.*

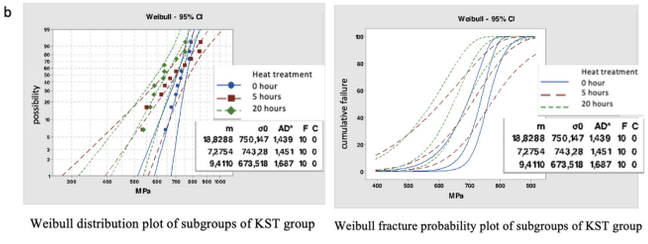

Figure 6b. *Weibull distribution and fracture probability plots of KST group after LTD.*

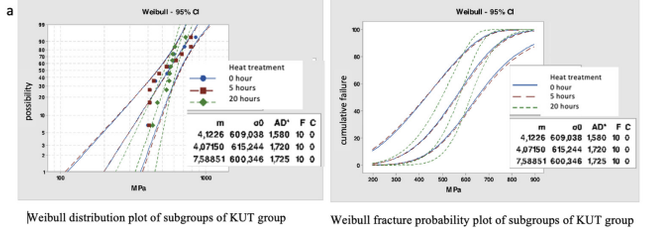

Figure 7a. *Weibull distribution and fracture probability plots of KUT group after LTD.*

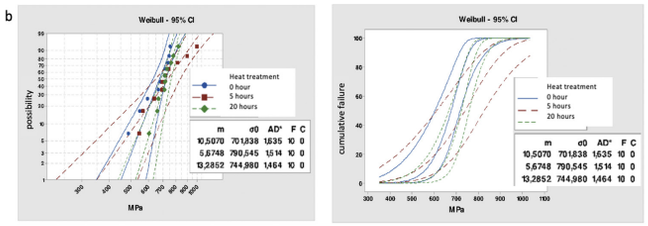

Figure 7b. *Weibull distribution and fracture probability plots of NQ3MS group after LTD.*

Table 5*. Biaxial flexural strengths (SD), and Weibull parameters of the investigated materials with the Weibull statistical method*

Groups	NMS		NQ³MS		KUT		KST	
LTD	m	σ_0	m	σ_0	m	σ_0	m	σ_0
0 hour	8.82[a]	1412.9[a]	10.50[a]	701.8[a,b]	4.123[a,b]	609.0[a,b]	18.829[a]	750.1[a]
5 hour	22.03[b]	1278.7[b]	5.675[b]	790.5[a,c]	7.275[a,c]	615.2[a,c]	7.275[b]	743.3[b]
20 hour	13.35[c]	1134.6[c]	13.285[c]	745.0[b,c]	9.411[b,c]	600.3[b,c]	9.411[c]	673.5[c]

There is no statistically significant difference between the values of groups with common lowercase letters in the same column. Nacera Pearl Multi Shade (NMS), Nacera Pearl Q3 (NQ³MS), Katana UTML (KUT), Katana STML (KST), characteristic strength (σ_0), weibull modulus (m), low-temperature degradation (LTD).

4. DISCUSSION

The null hypothesis of this research is that the LTD in new high-translucent monolithic zirconia systems does not affect the monoclinic phase change and the biaxial flexural strength of the investigated materials. High-translucent NMS and KST materials were affected by LTD in terms of phase transformation, while high-translucent KUT, and NQ³MS materials did not show phase changes after LTD. The flexural strength values of the NMS group were affected by LTD, but the KST, KUT, and NQ³MS groups were not affected. The null hypothesis was partially rejected.

The high yttria and cubic phase content of the materials used in the study have many advantages. KUT is known as ultra-translucent zirconia (36) and 8%-11% of its content is Y_2O_3(37). Kwon et al. reported that this ultra-translucent material can therefore be used for restorations in the anterior region and is a wear-resistant material (38). KST is referred to as super translucent zirconia (36). This material, which contains 7%-10% Y_2O_3, provides light transmittance similar to that of natural teeth. According to the manufacturer's information, both KUT and KST can be used in single-tooth restorations, and up to three unit bridges (37). NQ³MS, contains 40% tetragonal and 60% cubic zirconia and 6 mol% Y_2O_3 according to the manufacturer's information. NQ³MS is an ultra-high translucent zirconia (6Y-PSZ) and indicated for monolithic single crowns and restorations of up to three units (39). Studies have shown that these materials with high yttria content do not undergo t→m phase transformation due to their good stabilization (25, 37, 40, 41). The absence of this transformation also protects zirconia from the negative effects. Zang et al. concluded that the material did not undergo a t-m transformation, and thus its transparency increased,

but its strength decreased (8). However, the study results suggest that nanocrystalline zirconia potentially exhibit both desirable translucency and mechanical properties (1, 2, 8).

The LTD of zirconia materials is applied under laboratory conditions to evaluate their effectiveness and predict their long-term behavior. Studies using an autoclave as hydrothermal aging at 134 °C, 2 bar pressure for 20 h have shown that 20 h in the autoclave supports an extensive t→m phase transformation (13, 42)**.** Pereira et al. investigated the effects of LTD on Y-TZP and evaluated the behavior of the material to be used in the clinical setting according to the ISO 13356. It is also reported that aging in an autoclave at 134 °C, 2 bar for 5 h sufficiently ensures that the m phase content is not more than 25% (43). Zhuang et al. reported that the 20 h LTD would correspond to 30 to 80 years at body temperature (44). In this study, LTD was applied to the samples in an autoclave for 5 and 20 h to examine the flexural strength effects. Pereira et al.(45) investigated the effects of LTD using diamond burs and found an Xm value of 53.33% for the control group after 20 h with Y-TZP samples. It is thought that the reason why the relative monoclinic phase amounts of the NMS group (93%) were higher in this study, especially for the 20 h group, is that the Y-TZP blocks used in their study contain Al_2O_3. The NMS group used in this study does not contain Al_2O_3 order to increase translucency. For the KST, KUT, and NQ^{3}MS groups with high yttria content was no monoclinic phase transformation was observed in the non-aged, 5, and 20 h aging groups. The high resistance of these materials to aging may be related to the higher stabilizer content (4%,5%, and 6 mol%) and thus the elimination of the phase transformation mechanism. Additionally, many cubic crystals in their microstructure may have eliminated the phase transformation (25, 36).

Kou et al.(46) evaluated the effect of LTD on two different high-translucent (DD cubeX2 and Prettau Anterior) zirconia on phase transformation and flexural strength and found that after 10 h of LTD, DD cubeX2 showed a significant reduction in flexural strength, but Prettau Anterior showed no significant difference increase in flexural strength. The phase composition for both unaged and aged specimens of both DD cubeX2 and the Prettau Anterior constitute 99% cubic or tetragonal zirconia.

Pereira et al.(36) assessed different high-translucent zirconia (Katana ML/HT, STML, UTML) after 20 h of LTD. They reported that LTD increased the monoclinic content for ML/HT and did not affect STML and UTML, similar to the KUT and NQ^{3}MS groups in this study after 20 h. Also, Pereira et al. added that aging for 20 h did not affect the characteristic strength of KST and KUT. The flexural strengths of the new KST, KUT, and NQ^{3}MS groups were significantly lower than those of the NMS group. The NMS group (1344.2) significantly decreased only with an increase in the 20 h aging time (1091.8). However, the strength values of KST, KUT, and NQ^{3}MS were not significantly affected by LTD. Kwon (38), Pereira (36), and Reyes (47) similarly stated in their previous studies that high-translucent zirconia has lower flexural strength than 3Y-TZP. It is thought that KST, KUT, and NQ^{3}MS with higher stabilizer (Y_2O_3) content have lower results due to the disappearance of the transformation mechanism and because a large amount of cubic phase increases translucency but decreases mechanical strength.

Flinn et al.(48) evaluate the effect of LTD behavior on the strength values of 4 different translucent zirconia (BruxZir, Prettau, Katana ML, and Katana HT13) and reported that after aging for 200 h, the monoclinic phase increased to 76.1% for Prettau, 76% for BruxZir, 35.8% for Katana HT13, 33.2% for Katana ML. They concluded that the flexural strength values of BruxZir and Prettau decreased significantly during the aging period, but no statistically significant change in Katana ML and Katana HT13 zirconia. For both Prettau (8.27% Y_2O_3) and BruxZir (9.75% Y_2O_3) zirconia materials, the monoclinic phase amount was more than 50% after 200 h of aging. In this study, the monoclinic phase of the NMS zirconia after 20 h aging was 92%. The mean flexural strength values of Prettau and BruxZir decreased with an increase in the monoclinic phase and are similar in terms of the decrease in the strength values of the NMS zirconia after 20 h aging. The Katana ML (10.95% Y2O3) and Katana HT13(10.91% Y_2O_3) zirconia with higher yttria content exhibited less LTD.

Harada et al.(49) investigated the effect of LTD for 50 h on the phase change and flexural strength of 5YZ and 3YZ and reported that 5YZ was found to be more resistant to LTD than 3YZ. After 50 h of LTD, no significant changes in the characteristic strengths of 5YZ and 3YZ were observed similarly to this study for the KUT and NQ^{3}MS groups. The reason for this is thought to be the longer aging period applied by Harada et al.

Pittayachawan et al.(7) reported that the Weibull analysis used commonly statistical methods to examine the strength reliability and variability because of defects in the material. They also added that some studies have also expressed m values of some ceramics in the range of 5–15.

In their study, the Weibull modulus was determined as 9.3–12.9 for Lava (Y-TZP) zirconia.

In this study, the Weibull modulus of the NMS group, with lower yttria content, determined, was higher than the Weibull modulus of high-translucent PSZ. Weibull analysis showed the highest characteristic strength for NMS(1412.9) and KST(750.1) on the control and for NQ^{3}MS (790.5) and KUT (6152) in the 5 h group. Weibull modulus (m) of NMS, KST, KUT, and NQ^{3}MS were between 8.8–13.3, 18.8–9.4, 4.1–9.4, 10.5–13.2 respectively. Weibull m values increased in the NMS, KUT, and NQ^{3}MS groups, but decreased in the KST group. The Weibull modulus results in this study are in the range of 5–15 and acceptable for dental ceramics. Zhang et al.(10) investigated two different PSZ with different mol% yttria contents and found that 5YSZ showed lower strength and with lower Weibull modulus. A similar weibull modulus result was found in this study only for the KST group.

Nakamura et al.(50), examined the effects of the LTD for 10 and 100 h on the phase transformation and strength

properties of colored and non-colored 3Y-TZP zirconia. They reported that the LTD affected the strength values of non-colored 3Y-TZP but unaffected colored 3Y-TZP. In their study, the flexural strength results increased after 10 h but decreased after 100 h of the LTD. Similar to this study, for the NMS group, the strength values significantly decreased with an increase in the 20 h aging. The m value of the non-aged NMS group in this study was 8.8–13.3 and similar results (8.3-10.8) were reported by Nakamura et al. for non-aged 3Y-TZP. Pereira et al. reported that the Weibull modulus increased with the characteristic strength of Y-TZP specimens after 20 h of aging (36). In contrast to Pereira et al., in this study, the m value increased for the NMS, KUT, and NQ^{3}MS groups, and the characteristic strength of the KST and NMS groups decreased significantly.

This in vitro study evaluated the long-term use of new high-translucent monolithic zirconia restorations. LTD caused a significant decrease in the biaxial flexural strength results only for the NMS group but did not significantly affect the KST, KUT, and NQ^{3}MS groups with higher yttria content. It was seen that the presence of the cubic phase in high-translucent materials has two advantages: increased translucency and low resistance to temperature degradation. The flexural strength results of the high-translucent zirconia tested in this study were the minimum accepted value for class 5 restorations in fixed prostheses according to ISO 6872 and were more than 500 MPa.

For high-translucent 3 Y-TZP, it was determined that the tetragonal phase could transform into the monoclinic phase in a humid environment without mechanical stress. This probably caused microcracks and reduced mechanical strength.

The present study has some limitations. Clinical oral conditions can not be simulated. The LTD test is applied to in vitro conditions, in order to evaluate their effectiveness and long-term behavior because of the time-consuming and difficult experiment. Before the LTD process, one surface of all samples was polished by the same person with one type of zirconia polishing set for standardization. This study performed only an in vitro static test. Another limitation of this study was that the effect of different surface treatments and high-translucent zirconia with different yttria contents was not investigated. High-translucent zirconia materials obtained from only two manufacturers were evaluated. The effect of LTD on different surface treatments and high-translucent materials with different yttria contents can be used for future studies. It may be important to conduct in vitro experiments with dynamic loading to evaluate the effect of mechanical forces in the oral environment.

5. CONCLUSION

With the limitations of this study, the following conclusions were made:

1. LTD increased the monoclinic phase significantly for NMS and slightly in the KST group, but no monoclinic phase was detected in the KUT and NQ^{3}MS groups.
2. LTD resulted in a significant decrease in flexural strength values of the NMS group but did not significantly affect the values of the KST, KUT, and NQ^{3}MS groups.
3. Weibull analysis showed the highest characteristic strength for NMS and KST on the control, and KUT, NQ^{3}MS on the 5 h aging. Weibull m values increased in the NMS, KUT, and NQ^{3}MS groups, but decreased in the KST group.
4. The flexural strength values of the NMS (3Y-TZP) group caused a significant decrease after 20 h, but no significant changes were measured in the KST (4Y-PSZ), KUT (5YPSZ), and NQ^{3}MS(6Y-PSZ) groups.

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Clinical and Experimental Health Sciences

Non-medical Use of Prescription Psychostimulants and Academic Performance in Medical Students

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ABSTRACT

Objective: It is well-known that healthy medical students use psychostimulants to improve their cognitive functions and reduce their need for sleep. The main motivation behind this cognitive enhancement is to increase academic performance. However, the literature is not clear enough to support this situation.

Methods: This cross-sectional study was conducted through an online questionnaire, with 585 students participating. The grade point average number was used to assess the student' academic performance. Additionally, a self-evaluation scale was employed to assess levels of pharmaceutical knowledge, study performance, academic success, academic anxiety, and study habits.

Results: Out of 585 healthy students surveyed, 40 (7.3%) stated that using psychostimulants to enhance their academic performance. However, there was no significant difference in grade point average scores and perceived academic success levels between users and non-users. Nevertheless, most of the users reported benefiting from taking psychostimulant drugs. Risk factors for non-medical use of prescription psychostimulants included high levels of pharmacology knowledge, smoking, and poor academic performance.

Conclusion: Although the non-medical use of prescription psychostimulants did not appear to significantly impact academic performance, most students reported positive subjective experiences, which could have a motivational effect. Therefore, it is crucial to conduct more in-depth investigations into the benefits and side effects of psychostimulants in healthy young individuals and provide them with up-to-date information on this issue

Keywords: Psychostimulant, academic performance, medical student, methylphenidate

1. INTRODUCTION

Prescription medications such as methylphenidate, modafinil, amphetamine, and atomoxetine are used to treat attention deficit hyperactivity disorder (ADHD), narcolepsy, etc. These psychologically active substances work on various molecular targets in the brain and can alter mood, behavior, and consciousness (1). However, recent data suggests that healthy individuals are increasingly interested in using these drugs to enhance their cognitive performance (2). Cognitive enhancement is the name given to methods that aim to improve cognitive capacities like memory or attention in healthy people (3).

Medical students are one of the most significant healthy populations who prefer to use psychostimulants (4-6). Several studies have reported that the incidence of psychostimulant usage among medical students in different countries ranges from 8 to 19 percent (7, 8). Medical education is a demanding and competitive field, and the high probability of psychostimulant use among medical students may be related to this competitive nature (9). Recent findings suggest that high levels of stress related to concerns for academic success and feeling under pressure are related to increased psychostimulant use among medical students (10). The primary rationale for using these drugs is to enhance cognitive performance, such as attention, memory, and concentration, and to gain an advantage in overcoming challenging tasks in medical school. It's reported in the literature that one of the most important motivations for the use of psychostimulants is to improve academic performance (11, 12).

The aim of this study is to investigate the non-medical use of psychostimulants (NMUPS) in medical students. The primary research topic of our study is to question the relationship between academic performance and NMUPS.

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2. METHODS

2.1. Participants and Procedure

This cross-sectional study involved undergraduate medical students from different cities in Turkey, who were selected through a non-probabilistic snowball sampling method. An online questionnaire was conducted, which was distributed to medical student groups in various faculties and university medical students through social media platforms (WhatsApp, Facebook, and e-mail) in February – March 2020. The sample size has been made considering a 5% margin error and a 95% confidence level with a 50% response rate. It is determined that a minimum of 246 participants should be included. A total of 660 students participated in the questionnaire, but 75 participants who provided incomplete or inappropriate responses were excluded from the study. Additionally, 35 medical students who reported being diagnosed with narcolepsy or ADHD were also excluded (see Figure 1). The participants provided their informed consent, and the Ethics Committee of Bezmialem Vakif University approved the study (approval number 03.02.2020-03/50).

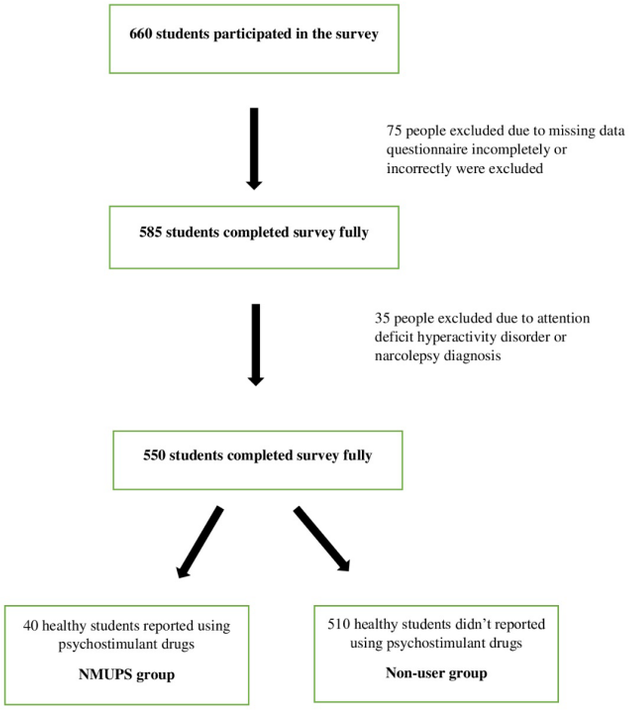

Figure 1. *Study Flowchart*
NMUPS: Non-medical Use of Prescription Psychostimulant

2.2. Online Questionnaire

The Google Forms platform was utilized to create and distribute a structured questionnaire. Prior literature was examined and used to develop the questionnaire, which was then reviewed by a panel of four experts. In a pilot study with 20 students, the clarity of the questionnaire items was assessed, and based on their feedback, the questions were revised. The data collected during the pilot study were not included in the statistical analysis.

The questionnaire consisted of 37 questions, which were divided into seven sections: demographic information, medical history, patterns of psychostimulant use and experiences, self-evaluation of academic success, anxiety levels, study performance, and sleep quality. In the self-evaluation section, people were asked to evaluate themselves between 1-5 points on a Likert scale. Participants were asked to report their Grade Points Average (GPA) as an indicator of academic success. In the questionnaire, participants were asked whether they had previously been diagnosed with ADHD or narcolepsy. Participants who declared a diagnosis of ADHD or narcolepsy were excluded from the final analysis.

At the beginning of the online questionnaire, the concept of Non-Medical Use of Prescription Stimulants (NMUPS) was explained thoroughly to the participants. They were informed that the use of psychostimulants for medical diagnosis was not considered NMUPS and was not intended for academic purposes.

2.3. Statistical Analysis

IBM software (SPSS 26.0 for Windows; IBM Corp, Armonk, NY) was used for statistical analyses. Descriptive statistics were calculated, Pearson chi-square analyses and Fisher's exact test were used between groups for categorical comparisons. The distribution of normality was assessed by the Kolmogorov-Smirnov test. The use of the Mann-Whitney U test to compare age differences across groups was made. The level of significance was set at ≤ 0.05. The parameters that had the greatest impact on NMUPS were determined using binary logistic regression with the entry method. Applying logistic regression and correlation, the hypothesis is tested. Variables with significant differences were included in the regression model after univariate analyses.

3. RESULTS

A total of 585 students completed the questionnaire, with 35 individuals (5.9%) who had a diagnosis of ADHD or narcolepsy being excluded. Of the 585 participants, 356 (64.7%) were female, and the mean age was 23.32 (SD 4.38) years. In terms of academic status, 225 students (40.9%) were in the basic medical sciences term (years 1-3), 218 students (39.6%) were in the clinical term, and 106 students (19.2%) were graduate students (either in residency or preparing for the residency exam).

The NMUPS group consisted of 40 healthy students who reported using psychostimulants to enhance their academic performance without a diagnosis. The prevalence of NMUPS was found to be 7.3% among the participants. There was no significant difference in gender or academic status between users and non-users. However, age (p=.01), smoking (p<.001), and alcohol use (p<.05) showed significant differences between the two groups (Table-1).

Table 1. *Characteristics of the medical students who were non-medical users of psychostimulant (n = 40) and non-user (n = 510)*

	User n (%)	Non-user n (%)	p
Gender			0.759
Female	25 (4.5)	331 (60.2)	
Male	15 (2.7)	179 (32.5)	
Age (mean ± SD)	24.55 ± 3.35	23.23 ± 4.44	**.001***
Semester			.055
1-3	11 (2)	214 (39)	
4-6	16 (2.9)	202 (36.8)	
Graduate/Resident	13 (2.4)	93 (16.9)	
Grade Points Average (0-4)			.959
<2.5	7 (1.3)	82 (14.9)	
2.5-3	15 (2.7)	188 (34.2)	
>3	18 (3.3)	240 (43.6)	
Smoking			**<.001 ****
Yes	17 (3.1)	23 (4.2)	
No	59 (10.7)	451 (82)	
Alcohol			**.03 ****
Yes	12 (2.2)	84 (15.3)	
No	28 (5.1)	426 (77.5)	
Herbal Product /Supplement use			.069
Yes	10 (1.8)	73 (13.3)	
No	30 (5.5)	437 (79.5)	

** The Mann Whitney U test, **Chi-Squa*

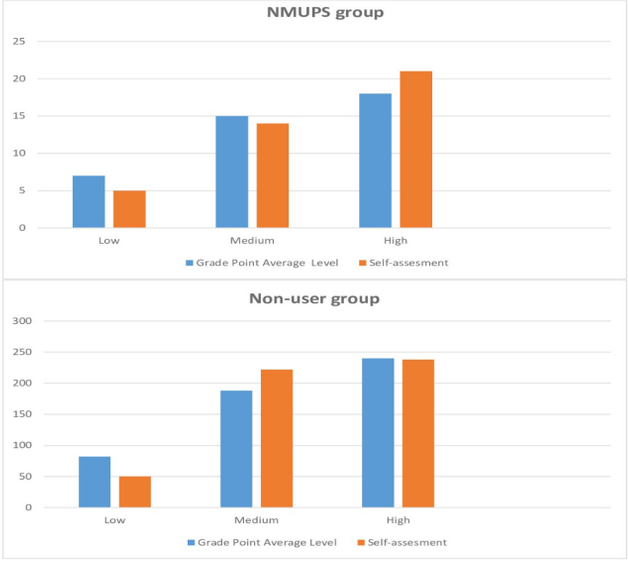

Figure 2. *Evaluation of academic success in NMUPS and non-user groups.*
NMUPS: Non-medical Use of Prescription Psychostimulant

We employed both subjective and objective criteria to assess academic success. The objective criterion was the GPA score, which reflects the student's performance on medical school exams. The subjective criterion was based on the students' self-assessment of their success. However, we did not observe a significant difference between the user and non-user students in terms of their GPA scores or perceived academic success levels (p>.05), as depicted in Figure 2. Furthermore, there was no significant difference between the groups in terms of self-assessment of academic anxiety and sleep quality (p>.05). However, there was a statistically significant difference between the groups in terms of study performance levels (p<.05) and pharmacological knowledge levels (p<.05).

We aimed to identify the patterns of NMUPS in medical students, and therefore, we investigated the frequency, duration, and timing of psychostimulant use, among other factors. Out of the participants, 21 (52.5%) reported using psychostimulants several times in their life, while 4 (10%) used them several times a month, 2 (5%) used them several times a week, 5 (12.5%) used them once a day, and 8 (2%) used them regularly during exam periods.

The purposes of the students to use psychostimulants were as follows; to enhance cognitive function (n: 29, 72.5%), to provide alertness (n:18, 45%), motivation (n:13,32.5%), request to try (n: 7,17.5%), to reduce anxiety (n: 6, 15%). Most of the users (n: 34, 85%) stated that they benefited from psychostimulant drugs. The positive experiences of the students related to using psychostimulants were as follows; Cognitive functions (attention, memory) increased in 23 (57.5%) students, 20 (50%) students became better focused, 10 (25%) students increased their motivation, 14 (35%) students' need for sleep decreased. The side effects reported were palpitation, insomnia, anxiety, tremor, gastrointestinal problems, and headache, respectively. 9 students (22.5%) reported no side effects related to psychostimulants.

Of the 510 students not using psychostimulants, 200 (39.2%) cited concerns regarding addiction and side effects as the reason. 68 (13.3%) students reported that consuming coffee/tea was sufficient for their study needs and did not require psychostimulants. Additionally, 76 (14.9%) students believed that psychostimulants would not be effective in enhancing cognition in healthy individuals.

A binomial logistic regression was performed to identify risk factors associated with the use of psychostimulants. The constructed binary logistic regression model was tested using the Omnibus Tests of Model Coefficients, and it was determined statistically significant. (p<.001). The model achieved a success rate of 92.7 percent. The model explained 14.4% (Nagelkerke R2) of the variance in NMUPS. Based on the regression analysis, smoking, increased knowledge of pharmacology, and study performance were identified as risk factors (Table 2).

Table 2. *Risk factors associated with a non-medical user of psychostimulant in medical students (user vs non-user)*

Predictor				95%Confidence Interval	
	B	OR	p	Lower	Upper
Smoking	-1.693	**0.184**	**<.001**	0.078	0.433
Alcohol	0.294	1.341	.534	0.532	3.381
Pharmacological Knowledge	-0.594	**0.552**	**.007**	0.359	0.849
Study Performance	3.810	45.160	.083	0.948	2.394
Age	-0.20	0.980	.554	0.916	1.048

4. DISCUSSION

This study has investigated the effects of psychostimulants on academic performance. Socio-demographic, health status, lifestyle characteristics, and prevalence of the users were obtained. The results indicate that the prevalence of NMUPS among undergraduate Turkish medical students was 7.3%.

This study found that the use of NMUPS did not have a significant effect on academic performance, as there was no significant difference between users and non-users in terms of objective (GPA score) and subjective (self-report) evaluation of academic performance. Contrary to our finding some studies have reported an impact of NMUPS on school performance (1, 13). Similar findings emphasized that the expectation of academic benefits from psychostimulants is likely illusory (12). A previous study reported short-term improvement in alertness and energy levels, rather than long-term academic benefits (14). Thus, there is controversy surrounding the use of psychostimulants to enhance cognitive function, and the evidence for their effectiveness in individuals without ADHD is not conclusive. Based on a meta-analysis of several randomized controlled trials, some positive effects on long-term memory consolidation were found with the use of psychostimulants for cognitive enhancement. However, there were no significant effects observed on attention, cognitive control, mood, or executive functions (15, 16). A study showed that psychostimulant use reduces the magnitude of neurochemical regional activation of the brain during a task (17). The study concluded that methylphenidate restricted the use of attention resources in the healthy human brain to achieve similar performance levels in a task. While this may be beneficial for individuals with ADHD, it could be harmful for those whose brain activity is already optimally focused.

Academic achievement did not appear to be related to non-medical use of prescription stimulants (NMUPS), although it is noteworthy that the majority of students reported having favorable subjective experiences with these drugs. Psychostimulants affected self-assessment of cognitive enhancement. It can strengthen the idea that psychostimulants have a motivational component in addition to their sole therapeutic actions (18). This motivation mainly depends on an expectation of cognitive enhancement. In the field of education, the motivation concept has become an important topic, and the term 'motivation' can be defined as the reasoning for an action or behavior in a particular way. There are different motivations that shape students' behavior. A similar study highlighted the significant disparity between subjective experiences and the acquired objective academic outcomes (19). A qualitative interview with university students suggested that the effects of NMUPS that help individuals are not as purely cognitive as often seems to be assumed. The student claimed that these drugs served as an emotional coping strategy for dealing with loss of fun, confidence, and interest (20).

In our research, we found that knowledge level about psychostimulants is a risk factor for NMUPS. However, psychostimulants can be addictive, and their long-term effects on healthy individuals are not well known. These drugs are highly addictive and have the potential to cause cardiovascular, neurological, and psychiatric complications (21, 22). So why do hardworking students use them more? We believe that there is a lack of information or misinformation about NMUPS. While the cognitive effects of these drugs are often emphasized, their side effects are often ignored. According to in-depth interviews with university students, the majority of users perceive psychostimulants as generally safe substances (23). Risks of NMUPS are well explained, but poorly evaluated by users (2).

According to our findings in terms of GPA, there was no statistically significant difference, in academic success, academic anxiety perception, and sleep quality between the user and non-user students. However, the differences between users and non-users were age, smoking, alcohol, study performance, and knowledge level. According to the present literature, users were more likely to use cigarettes and alcohol, had different normative values, and had a lower risk perception. (24, 25). Therefore, we suggest that this issue should be discussed together with addiction and health risk perception beyond academic success and cognition.

The small number of participants using NMUPS in our study can be considered a limitation in terms of generalizability. Although our questionnaire was only sent to medical school students and their university groups, the use of an online questionnaire is a limitation of the research, and the data collected in this study is based on self-report of the participants, which may introduce selection bias. Also, we collected GPA scores, ADHD or narcolepsy diagnoses, and other relevant information from self-reports provided by the individuals themselves. However, this aspect presents a limitation in our research. Also, the standardization of GPA scores of students from different universities may not be provided. There may be differences between the difficulty levels of exam of the different universites. But we ignored this situation as there is a standard educational curriculum within the same country.

5. CONCLUSION

The use of psychostimulants for academic and cognitive-enhancing purposes is a controversial issue. We could not find a statistically relevant relationship between academic performance and NMPSU in healthy medical students. It was remarkable that most of the students had positive subjective experiences as opposed to objective data. Neuroimaging research to explore the impact of NMPUS on the brains of healthy young individuals, as well as future studies delving into its psychosocial effects, could offer more comprehensive insights into these matters. Giving greater emphasis to the side effects and addictive potential of psychostimulant drugs in pharmacology education among medical school students might act as a deterrent against the off-label use of such drugs by young individuals.

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Design of the study: BSS, MYB, OB
Acquisition of data for the study: BSS, MYB, OB
Analysis of data for the study: BSS, MYB
Interpretation of data for the study: BSS, MYB
Drafting the manuscript: BSS, MYB
Revising it critically for important intellectual content: BSS, MYB
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Clinical and Experimental Health Sciences

Health Promotion Model-Based Health Education Program in Acute Coronary Syndrome Patient: An Experimental Study

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ABSTRACT

Objective: This study was conducted to examine the effect of a Health Promotion Model-based health education program on increasing the health-promoting behaviors of acute coronary syndrome patients.

Methods: This is an experimental study that used a pretest-posttest design with a control group. The sample consisted of 101 patients hospitalized with the diagnosis of acute coronary syndrome in Turkey. The data were collected by using a Patient Monitoring Form and the Health Promoting Lifestyle Profile-II. While the patients in the control group received routine procedures, the patients in the experimental group were included in the health education program.

Results: The health promoting-behaviors of the control group were found to be higher than those of the experimental group in the first follow-up ($p<0.001$). In the last follow-up, on the other hand, it was found that the experimental group's health-promoting behaviors and smoking cessation rate were higher than the control group. Additionally, the experimental group's LDL levels, rehospitalization rates and percutaneous coronary intervention rates were found to be lower than the control group ($p <0.05$).

Conclusion: The Health Promotion Model-based health education program was found to be an effective method in increasing health-promoting behaviors and smoking cessation rates, and controlling LDL levels in acute coronary syndrome patients. It had a positive effect on reducing the rate of rehospitalization and percutaneous coronary intervention.

Keywords: Acute coronary syndrome, health-promoting behaviors, patient education, secondary protection.

1. INTRODUCTION

Cardiovascular diseases (CVD) are the leading causes of mortality/morbidity in developed and developing countries (1,2). It has been reported that recurrent coronary events increase mortality in individuals surviving ACS and put a great burden on the country's economy (3). In the guidelines of the European Society of Cardiology on ACS treatment, secondary protection for individuals with ACS is strongly recommended. The guidelines recommend increasing health-promotion behaviors (HPB) (1,2). HPB include health-related behaviors such as health responsibility, physical activity, nutrition, spiritual growth, interpersonal relationships, stress management and smoking cessation (4,5). The most important factors that affect HPB are known to include lack of knowledge (6,7). In previous studies conducted on this topic, it has been found that individuals with ACS have low knowledge levels and attention about HPB and smoking cessation (8). As to be understood from these results, it occurs to us as an important necessity to conduct educational interventions to increase HPB in patients with ACS. However, as a result of the literature review, it was seen that there are a limited number of intervention studies on these topics (9-11).

Education is an important and effective method used in meeting the information needs of patients and developing behavioral change (12,13). Brown et al. (14) reported that educational interventions are beneficial for patients, but more research is needed to determine the most effective and appropriate format, duration, timing and methods of education. Anderson et al. (15) recommended comparing the effectiveness of different methods and approaches to present educational content. Undoubtedly, providing education to protect and promote the health of the individual, family and society and to prevent illness is one of the primary roles of nursing. However, patient education is not just a technical application and a simple presentation. It is also a set of goals and values. It has own philosophy and the goal is to change behavior. In order to develop behavior change, a systematic and planned application is required. Because different factors

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cause different behaviors and attitudes to emerge. In order to know these factors and to plan initiatives in this direction, health protection and improvement behaviors of individuals are explained with models (5,16). Models/theories, which are an important component of the scientific knowledge content of nursing, are used as guides in patient education as well as in every stage of nursing (17). Nola Pender's Health Promotion Model is one of the widely used models to explain health protection and promotion behaviors. The model is not aimed at preventing any disease or disability, but it aims to improve health, or in other words, to increase the general health and well-being of the individual (Figure 1) (5). It has been reported that trainings prepared on the basis of Health Promotion Model in various chronic diseases are effective in improving health behaviors. Ersin and Bahar (18), in their study where they examined the effect of patient education based on Health Promotion Model on early detection behaviors of breast and cervical cancer, reported that patients developed positive behavioral changes after the education. Çövener (16), in his study to standardize diabetes education, created a Type I diabetes management model based on the Health Promotion Model.

This study aimed to examine the effects of a Health Promotion Model-based health education program on increasing the health-promoting behaviors of acute coronary syndrome patients.

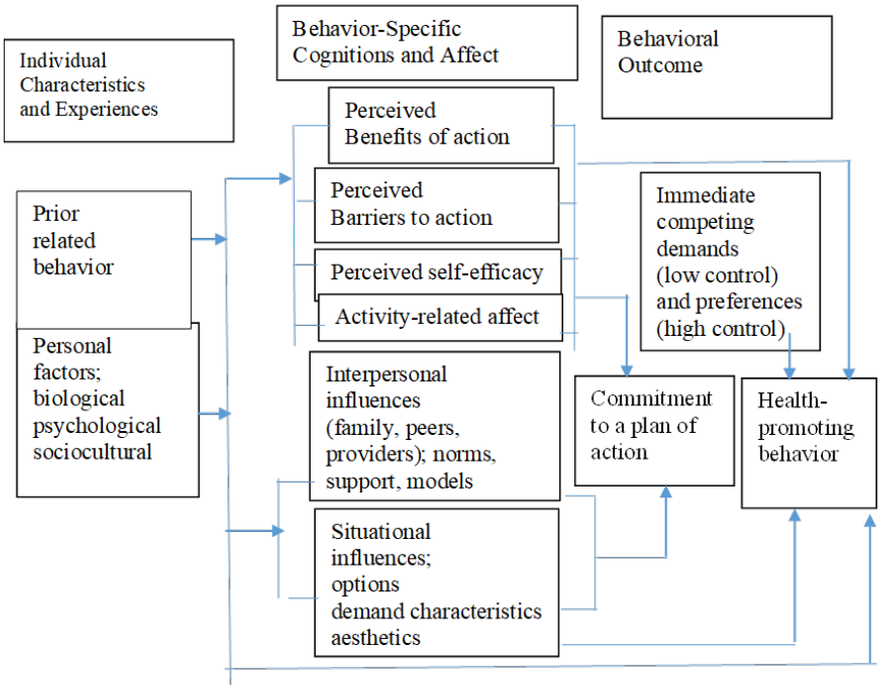

Figure 1. *Basic of Nola J. Pender's Health Promotion Model*

2. METHODS

2.1. Ethical considerations

Ethics committee approval and institutional permission were obtained respectively from Ethics Committee (09.2018.362) and the institution where the study was carried out. The participants were informed by the researcher about the purpose of the research, and their written consent was obtained. In the implementation of the study, the researchers adhered to the World Medical Association (WMA) – Ethical Principles for Medical Research Involving Human Subjects. Due to the nature of the study, it was impossible for the participants to be blind. Blind analysis was used in this study.

2.2. Design

This experimental study used a pretest-posttest design with a control group. The patients in the control group (CG) received routine hospital procedures, whereas the patients in the experimental group (EG) was included in a health education program based on the Health Promotion Model.

2.3. Population and Sample

The population of the research consisted of patients who were hospitalized in the cardiology department of a university hospital for treatment purposes between 07 August 2018 and 30 May 2019. Patients who did not have a history of CVD or a disease that would impede walking or lead to audio, visual or comprehension problems, had one of the diagnostic criteria of ACS, were aged between 18 and 79 years and

could speak and understand Turkish well were included in the study. According to the study by Eshah (11), considering the effect size of 0.5, in a 90% confidence interval and with a 90% test power, the sample size was estimated to be 32 individuals in each group. However, considering that there would be losses, the sample size was kept larger, including 60 in each group, were enrolled in the study. The data of CG and EG were collected at separate times to prevent patients from communicating with each other about the education program. In order to standardize environmental factors. Which group would gather first was determined by drawing lots. According to the result of the draw, the data of the control group were collected first.

The targeted number of patients was reached between 07 August – 15 October 2018 in the CG and between 18 March – 30 May 2019 in the EG. As a result of data losses, the data of 101 patients in total, 52 in EG and 49 in CG, were included in the analysis (Figure 2).

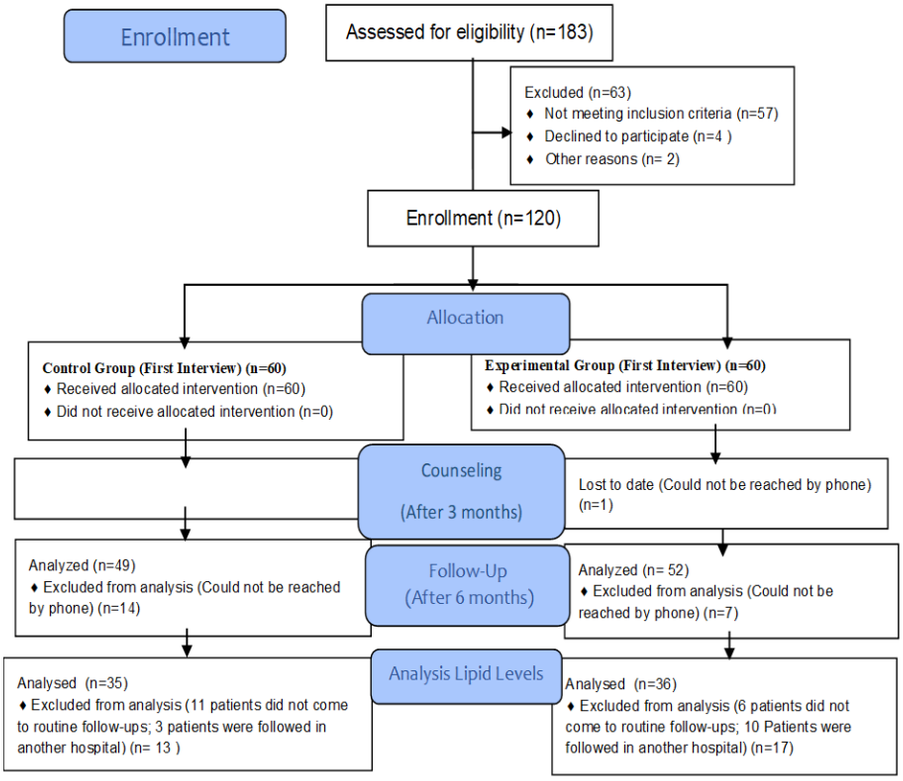

Figure 2. *Study Sampling*

2.4. Data Collection

2.4.1. Patient Follow-Up Form

This form was prepared by the researcher in line with the literature review (1,2,5), information and observations of the researcher. The form consisted of 27 questions regarding socio-demographic characteristics, habits (smoking, alcohol), previous medical history, and current health status (blood pressure, blood pressure, blood sugar level, blood lipid levels, etc.).

The data in the patient follow-up form were filled in by interviewing the patients face to face, examining their files, and obtaining blood results from the hospital system.

2.4.2. Health-Promoting Lifestyle Profile-II (HPLP-II)

This scale was created by Walker and et al. (19) on the basis of the Health Promotion Model and measures HPB which is related to a healthy lifestyle. The HPLP-II tool consists of 52 HPB items that are categorized into six subscales: health responsibility, nutrition, spiritual growth, interpersonal relationships, physical activity and stress management. It is a 4-point Likert-type scale that is used to measure each behavior, and the total score of HPLP-II ranges from 52 to 208. While a minimum of 9 and a maximum of 36 points are obtained from the sub-dimensions of health responsibility, nutrition, spiritual growth, and interpersonal relations, a minimum of 8 and a maximum of 32 points are obtained from the sub-dimensions of physical activity and stress management. A high score on the scale indicates a high level of healthy promation behaviors. In the Turkish reliability

and validity study of the scale, its Cronbach's alpha value was reported as 0.92 (20). In this study, it is found that the Cronbach's alpha coefficient of the scale as 0.91.

2.5. Implementation

In the first interviews of both groups, the data of the first follow-up were collected using the Patient Follow-Up Form and HPLP-II in the cardiology clinic. If the patient from whom the first follow-up data were collected was in EG, they were given the Education Program and the Education Manual. In CG, on the other hand, no intervention was made during the research period other than the routine hospital protocols (discharge and medication use training).

The patients in EG were called for counseling interviews three months after the first interview. In these interviews, it was aimed to direct the patient to health-promoting behaviors and provide reminding information.

The patients in both groups were called six months after the first interview and the last follow-up data were collected.

2.6. Implementing the Health Education Program

The health education program was developed on the basis of the Health Promotion Model to promote health and the guidelines of the European Society of Cardiology on ACS treatment, secondary protection for individuals with ACS (1,2,5). A training manual was prepared to increase the memorability of the information given in education. The Education Program and the Education Manual, which were prepared in draft form supported with various images, tables and figures, were submitted to three nurses, who are professors in nursing, and one professor of medicine in the cardiology branch. After making necessary arrangements in line with the feedback that was received from these experts, the Education Program and the Education Manual were finalized.

The patient, who was included in EG, and whose general health status was stable, was invited to the meeting room for the education (in the presence of a relative for each patient). The Education Program that was prepared as a PowerPoint file was presented to the patient. The education sessions were held with a minimum of 2 (one patient and one relative) and a maximum of 10 (5 patients and 5 relatives) persons. The Education Program was completed in two sessions, each session lasting 30 minutes. A 30-minute break was given between the sessions. To ensure the consistency of the education program, all sessions were held by the same researcher. A checklist was also utilized to ensure that all components of the program were provided for every patient. The checklist consisted of 9 items: meeting, sharing the purpose and content of the education, discussing the blood lipid level, blood sugar values, blood pressure level of the patients, education presentation, teaching pulse counting, calculating the body mass index, and receiving feedback. The subject content of the Education Program was given below.

Subject Content of Education

Content	Subtitles
What is Cardiovascular Disease (Coronary Artery Disease)?	
What is a Heart Attack (Myocardial Infarction)?	
What is Coronary Angiography?	
What is the Structure of Blood Vessels?	
How Are Plaques Formed?	- The Effect of Blood Lipid Levels - Damaged Blood Vessel Wall
What Are the Risk Factors Causing Cardiovascular Disease?	- Uncontrollable Risk Factors - Controllable Risk Factors
How Do We Control Risk Factors?	- Nutrition - Physical Activity - Maintaining a Healthy Body Weight - Quitting alcohol and cigarettes - Medication use - Stress management - Health responsibility

The Health Education Program was carried out in line with the components of the Health Promotion Model as follows.

2.6.1. Individual Characteristics and Experiences

While filling the data collection tools, the patients' personal characteristics, attitudes towards health-promoting behaviors and their familial and environmental status regarding the disease were questioned. In line with the information that was obtained, the patients' information needs were identified, and the Education Program was provided, and these points were emphasized.

2.6.2. Behavior-Specific Cognitions and Affect

Perceived Benefits of Action: The positive outcomes that will occur from health-promoting behaviors and the influences of these outcomes on the quality of life were explained, and it was aimed to enhance beliefs in the benefits of behaviors.

Perceived Barriers to Action: It was aimed to increase beliefs in the negative effects of unhealthy behaviors on the human body by describing the pathophysiology of atherosclerosis and risk factors causing atherosclerosis. Possible obstacles to the performance and adoption of behaviors and how these obstacles could be overcome were discussed. The points to be considered while displaying behaviors (e.g., exercise, nutrition) were emphasized.

Perceived Self-Efficacy: The patients were supported in making the decision to start health-promoting behaviors, and their target dates were determined. The functional ability to enhance self-efficacy was taught. The talk test was recommended for a safe exercise. The Body Mass Index (BMI) was calculated over the index table, and radial pulse and blood pressure were measured.

Activity-Related Affect: Subjective positive or negative feelings that occur before, during and following behaviors were discussed. Factors leading to negative feelings were debated.

Interpersonal Influences: The family member responsible for the individual's care was encouraged to participate in the Education Program. The expectations of family members from the individual and the expectations of the individual from family members were questioned.

Situational Influences: The patients were reminded to make these behaviors permanent by benefitting from the fact that hospitals support health-promoting behaviors (e.g., no smoking, cardiac diets at meals, regular administration of medicines).

2.6.3. Behavioral Outcomes

In the last 10 minutes of the education process, the patients were allowed to ask what they wondered about, and a discussion was held. The patient's priorities were discussed. For each patient, their goals and the dates by which they thought of reaching these goals were determined together with the patient and given to the patient in writing. The achievement of the goals determined in the counseling interviews was questioned. While the positive responses were supported by using behavior-promoting words, feedback was given to change risky behaviors. Behavioral outcome was measured six months after the Education Program using HPLP-II.

2.7. Data Analysis

Descriptive statistical methods (percentage, mean, standard deviation) were used while analyzing the data obtained in the study. Pearson's Chi-squared test was used for the relationships between the categorical variables between two groups. While making comparisons between the groups, Independent-Samples t-Test was used for the parametric data, and Mann-Whitney U-test was used for the non-parametric data. Wilcoxon signed-rank test was used since the data did not show a normal distribution in the intragroup comparisons.

Table 1. *Comparison of groups in terms of demographic characteristics*

		EG (52) n (%)	CG (49) n (%)	Test statistics	p
Sex	**Female**	7(13.5%)	6(12.2%)	0.033*	1.000
	Male	45(86.5%)	43(87.8%)		
Age (Mean ±SD)		56.92±10.49	52.59±8.04	-2.316**	0.023
BMI (Median) (IQR)		27.71(25.73-32.37)	27.10(25.04-30.64)	1104***	0.248
Education level	**Illiterate**	8(15.4%)	5(10.2%)	9.152*	0.057
	Primary	28(53.8%)	27(55.1%)		
	Secondary	6(11.5%)	0(0.0%)		
	High School	7(13.5%)	9(18.4%)		
	Graduate	3(5.8%)	8(16.3%)		
Marital status	**Married**	47(90.4%)	42(85.7%)	0.526*	0.547
	Single	5(9.6%)	7(14.3%)		
Employment status	**Employed**	26(50.0%)	31(63.3%)	1.806*	0.229
	Unemployed	26(50.0%)	18(36.7%)		
Monthly household income (TL)	**<2000**	18(34.6%)	15(30.6%)	0.279*	0.087
	2000-5000	28(53.8%)	27(55.1%)		
	>5000	6(11.5%)	7(14.3%)		
Systemic disease	**None**	17(32.7%)	20(40.8%)	1.511*	0.680
	HT	13(25.0%)	12(24.5%)		
	DM	10(19.2%)	10(20.4%)		
	HT+DM	12(23.1%)	7(14.3%)		
Smoking status	**Yes**	24(46.2%)	32(65.3%)	3.746*	0.072
	No	28(53.8%)	17(34.7%)		
Clinical type of ACS	**NSTEMI**	21(40.4%)	21(42.9%)	3.557*	0.169
	STEMI	31(59.6%)	25(51.0%)		
	UA	0(0.0%)	3(6.1%)		
Intervention	**Stent**	25(48.1%)	27(55.1%)	2.014*	0.365
	Stent+ Balloon angioplasty	21(40.4%)	20(40.6%)		
	Balloon angioplasty	6(11.5%)	2(4.1%)		
Medical therapy	**S+A+B**	25(48.1%)	28(57.1%)	1.342	0.511
	S+A + P	18(34.6%)	16(32.7%)		
	S+A + E	9(17.3%)	5(10.2%)		
Atorvastatin mg (Median) (IQR)		40(20-80)	40(20-80)	1124.5	0.721

**Pearson's Chi-squared **Independent-Samples t-Test ***Mann Whitney U*
A: Acetylsalicylic acid B: Brilinta E: Effient P: Plavix S: Statin-class lipid-lowering

3. RESULTS

When the groups were compared in terms of their demographic characteristics that could affect the results of the research, the mean age of EG was found to be higher than CG ($p<0.05$), but there was no significant difference between the groups in terms of the other characteristics ($p>0.05$) (Table 1).

In the comparison of the groups' overall HPLP-II scores, it was found that the scores of CG were significantly higher than those of EG in the first follow-up ($p<0.001$), and the scores of EG were significantly higher than those of CG in the last follow-up ($p<0.001$). In the intragroup comparisons, it was observed that the last follow-up scores of EG increased significantly in comparison to the group's first follow-up scores ($p<0.001$), while no significant difference was found between the two follow-up scores of CG ($p>0.05$) (Table 2).

When the groups were compared in terms of their HPLP-II subscale scores, all subscale scores of CG were found to be higher than those of EG in the first follow-up. It was seen that all subscale scores of EG increased in the last follow-up in comparison to the first follow-up and became higher than those in CG ($p<0.05$). In terms of CG, it was found that, from the first follow-up to the last follow-up, the nutrition subscale scores significantly increased, while the interpersonal relationships subscale scores significantly decreased ($p<0.05$) (Table 2).

When the groups were compared in terms of their first and last follow-up blood lipid levels the last follow-up LDL values, a 55-unit decrease and a 24-unit decrease was found in EG and CG, respectively. When the difference of the LDL reduction values between the two groups was analyzed, the LDL reduction value of EG was found to be significantly higher than that of CG ($p<0.01$) (Table 3).

According to the comparison between the groups, the smoking rate of EG was found to be significantly lower than that of CG in the last follow-up ($p<0.05$) (Table 4).

In the comparison of the groups in terms of their rehospitalization and PCI application status, the rehospitalization and unplanned PCI application rates after ACS were found to be significantly lower in EG than CG ($p<0.01$) ($p<0.05$) (Table 4).

Table 2. *Comparison of groups in terms of scores obtained from HPLP-II*

		EG (n=52) Median(IQR)	CG (n=49) Median(IQR)	Score range of the scale	U	p
HPLP-II Overall	**First follow-up**	108(99-123)	125(111-138)	52-208	658.5	0.001
	Last follow-up	152(139-163)	126(117-136)		278.5	0.001
	Z	-5.906	-0.116			
	p	0.001	0.907			
HPLP-II Subscales						
Health Responsibility	**First follow-up**	17(13-20)	21(19-24)	9-36	611.0	0.001
	Last follow-up	24(22-27)	22(20-24)		780.0	0.001
	Z	-6.173	-1.471			
	p	<0.001	0.141			
Physical Activity	**First follow-up**	10(9-12)	11(9-16)	8-32	986.0	0.048
	Last follow-up	22(17-25)	11(10-15)		286.0	0.001
	Z	-6.173	-0.850			
	p	0.001	0.395			
Nutrition	**First follow-up**	19(17-22)	21(18-24)	9-36	944.5	0.025
	Last follow-up	30(28-33)	23(20-27)		207.5	0.001
	Z	-6.151	-2.158			
	p	0.001	0.031			
Spiritual Growth	**First follow-up**	23(21-25)	27(25-30)	9-36	647.5	0.001
	Last follow-up	27(25-29)	26(24-27)		858.5	0.010
	Z	-5.069	-1.502			
	p	0.001	0.133			
Interpersonal Relationships	**First follow-up**	22(19-25)	26(22-30)	9-36	731.5	0.001
	Last follow-up	26(24-29)	24(21-26)		858.5	0.010
	Z	-4.942	-1.973			
	p	0.001	0.048			
Stress Management	**First follow-up**	17(15-21)	19(16-21)	8-32	1064	0.152
	Last follow-up	23(21-25)	19(19-22)		560.0	0.001
	Z	-5.858	-2.102			
	p	0.001	0.056			

IQR=interquartile range *U= Mann-Whitney U test* *Z= Wilcoxon signed-rank test*

Table 3. *Comparison of groups in terms of blood lipid levels*

		EG (35) Median(IQR)	CG (36) Median(IQR)	U	P
HDL (mg/dl)	**First follow-up**	35.0(34-43)	40.0 (34-45)	411.0	0.241
	Last follow-up	40.0(34-42)	39.0(35-44)	459.0	0.610
	Z	-1.047	-0.472		
	p	0.295	0.637		
LDL (mg/dl)	**First follow-up**	125.0(115-163)	109.5(93-138)	309.0	0.010
	Last follow-up	70.0(58-108)	85.0(66-118)	399.5	0.003
	Z	-4.223	-2.940		
	p	0.001	0.003		
Triglyceride (mg/dl)	**First follow-up**	187.0(143-221)	135.0(100-211)	359.5	0.061
	Last follow-up	126.0(88-181)	119.5(73-175)	464.5	0.665
	Z	-3.116	-1.627		
	p	0.002	0.104		
T-Cholesterol (mg/dl)	**First follow-up**	191.0(180-231)	183.0(156-215)	395.5	0.167
	Last follow-up	135.0(117-171)	137.5(124-191)	437.0	0.417
	Z	-4.115	-2.843		
	p	0.001	0.004		

IQR=interquartile range U= Mann-Whitney U test Z= Wilcoxon signed-rank test

Table 4. *Comparison of groups in terms of smoking status and rehospitalization and percutaneous coronary intervention*

			EG (52) n(%)	CG (49) n(%)	X^2	p
Smoking Status	**First Follow-up**	**Yes**	24(46.2%)	32(65.3%)	3.746	0.072
		No	28(53.8%)	17(34.7%)		
	Last Follow-up	**Yes**	13(25.0%)	22(44.9%)	4.411	0.040
		No	39(75.0%)	27(55.1%)		
Unplanned Rehospitalization after ACS		**Yes**	1(1.9)	9(18.4%)	7.647	0.007
		No	51 (98.1%)	40(81.6%)		
Unplanned PCI after ACS		**Yes**	1(1.9%)	7(14.3%)	5.287	0.028
		No	51(98.1%)	42(85.7%)		

X^2 =Pearson Chi-Squared

4. DISCUSSION

4.1. Discussion of the Results on the Health-Promoting Lifestyle Profile-II

While HPB are of vital importance for patients with ACS, in this study, it is found that in the first follow-up that the HPLP-II total scores and responsibility, physical activity, nutrition and stress management subscale scores of both groups were close to the lowest score. Besides, the scores of EG were lower than those of CG. As to be understood from these results, unfortunately, HPB were not on the desired level in the individuals with ACS. The fact that the HPB levels of EG were lower than CG was thought to be associated with age. As highlighted in the Health Promotion Model, with aging, cognitive processes, some dimensions of memory and all functions of the body begin to regress (21). Starting from this point, the necessity of planning interventions to control risk factors after a potentially mortal disease such as ACS, especially in elderly individuals, and to increase HPB has to be emphasized.

In the last follow-up carried out to measure the effectiveness of the Health Education Program towards promoting health, it was observed that EG's HPLP-II scores increased and became higher than those of CG, and these scores of EG were very close to the highest score that could be obtained in the scale. In the analysis of the groups in terms of the HPLP-II subscales, it was seen that all subscale scores of EG increased in the last follow-up, and these last follow-up scores were very close to the highest possible score. These data were evaluated as important findings showing the effectiveness of the education program implemented for increasing health-promoting behaviors, although the mean age of EG was high. Previous studies have reported that there is a positive relationship between the level of knowledge and health responsibility, healthy nutrition (22), physical activity and believing in the benefit of activity, knowing about safe exercise methods, low perception of illness (2), future expectations and spiritual development (23). These findings supported the results of EG in this study. Only nutritional behaviors increased in CG in this study. Nutrition is an issue that healthcare professionals and the media highlight. As a result, patients may easily access information on this topic. It

was thought that there was an increase in healthy nutrition in CG as a result of meeting the information needs of the patients, even if this increase was insufficient. Based on this, the effect of accessing information on behavioral change became clearer. Another important finding obtained from the data of CG was that interpersonal relationships were negatively affected after ACS. When social support systems are inadequate for individuals who encounter a potentially mortal disease, patients may experience anger towards their relatives (5,23). It was thought that this situation negatively affected the interpersonal relationships of the patients included in this study.

4.2. Discussion of the Results on Blood Lipid Levels

The most significant parameter of dyslipidemia treatment is LDL. The level of LDL is desired to be below 70 mg/dL in high-risk patients (2). In this study, the LDL values of both groups were above the target value in the first follow-up. However, in the last follow-up, the decrease in the LDL value of EG was higher than the decrease in the value of CG, where the LDL value of EG reached the target value. Based on these results, it was concluded that the Health Education Program lowered LDL levels by increasing HPB. These results were important in terms of pioneering interventions to be performed in addition to medical treatment.

4.3. Discussion of the Results on Smoking Status, Rehospitalization and Percutaneous Coronary Intervention

Comparing the groups in terms of smoking status, based on the first follow-up data, the smoking rates of both groups were high. Raising the awareness of patients on this issue and guiding them to quit smoking is important in the treatment process.

Based on the last follow-up data, the smoking rate of EG decreased and became lower than that of CG. Smoking cessation contributes positively to the health status by increasing both the self-confidence and physical activity capacity of the individual (1). In their meta-analysis, Suissa et al. (24) reported that individual and telephone-based counseling programs are efficacious for smoking cessation in CVD patients, and their results showed similarity to those in this study. It was concluded that the Health Education Program was an effective method in reducing rates.

Rehospitalization after ACS and application of percutaneous coronary intervention (PCI) are indicators of poor prognosis. The rates of rehospitalization of ACS patients in the first year were reported as 12.2% (readmission or PCI) (25). In this study, the rate of rehospitalization and application of unplanned PCI in EG was found to be significantly lower than that in CG. Yudi et al. (25) reported that the female sex, diagnosis of diabetes, history of coronary bypass surgery or PCI, low ejection fraction, cardiac failure and obstructive sleep apnea are independent predictors of readmissions. In addition to independent predictors, HPB was reported to have significant effects on recurrent coronary events (7,26). In this study, while the LDL levels of the patients in EG were lower than those of the patients in CG, the HPB and cigarette cessation rates of the former were higher than the latter. Besides, patients with a history of CVD were excluded from the study. None of the patients had obstructive sleep apnea, and the majority of the patients were male. As a result, the sample did not include many factors that could have been identified as primary predictors. In this sense, the groups were similar, and based on the low rate of rehospitalization in EG, it was concluded that the Health Education Program on promoting health had a positive effect on reducing the rates of rehospitalization and PCI.

4.4. Limitations

The findings of this study are limited to the data obtained from the data collection tools “Patient Follow-Up Form”, “BMCS”, “GSES” and “HPLP-II”.

5. CONCLUSION

The Health Education Program, which was modelled on the basis of the Health Promotion Model, was found to be an effective method for ACS patients in terms of increasing their health-promoting behaviors and smoking cessation rates, and controlling their LDL levels. Moreover, it was concluded that the program had a positive effect on reducing the rehospitalization and PCI rates.

Based on these results, we recommend applying training and education programs aimed at increasing health-promoting behaviors for patients after ACS routinely, using behavioral models in planning training and education programs, evaluating the effectiveness of such training or education through counseling interviews, questioning health-promoting behaviors in interviews and motivating patients on this issue.

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Author Contributions:
Research idea: AKŞ, SEA
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Acquisition of data for the study: AKŞ, HB
Analysis of data for the study: AKŞ,
Interpretation of data for the study: AKŞ
Drafting the manuscript: AKŞ, SEA
Revising it critically for important intellectual content: ŞEA, BM
Final approval of the version to be published: ŞEA, BM

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Clinical and Experimental Health Sciences

Development of Hypoglycemia Management Scale for Teachers

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ABSTRACT

Objective: Hypoglycemia which is an acute complication of diabetes is an absolutely serious and may possibly develop at any moment. Each of the schools do not have a nurse to intervene in emergency. Thus, the responsibility for such emergency situations put on the shoulders of teachers. The objective of this research was to develop and test the psychometric properties of Hypoglycaemia Management Scale for Teachers.

Methods: It was a scale development study with a methodological design. 400 teachers of primary, secondary and high schools were included in the study. The item pool was 30. The scale was presented to 5 of the experts and after the content validity the draft scale was 31 items. Data collected between the dates 6th Feb to 11th March 2020. Teachers filled the data collection tools by themselves. Factor analyses, item-total correlation, split-half reliability, test-retest reliability was tested for psychometric properties.

Results: The scale had 11 items and 2 subscales named "Hypoglycemia Knowledge" included some hypoglycemia-related expressions and "Hypoglycemia Management" included some expressions related with the practices to be followed in hypoglycemia situations.

Conclusion: A reliable and valid scale was developed to measure hypoglycemia management of teachers. It may be used in practice to assess hypoglycemia management of teachers in school setting.

Keywords: Scale development, hypoglycemia management, teacher, school, type 1 diabetes.

1. INTRODUCTION

Type 1 diabetes is a chronic disease occurring at every period of life but in childhood and adolescence with the highest incidence. People with type 1 diabetes need daily insulin treatment and regular blood glucose follow-up in order to control blood glucose level (1). Clinical symptoms were observed after the 80%-90% destruction of beta cells in pancreas (2).

According to 2017 data of International Diabetes Federation, approximately 7,5 million people have type 1 diabetes in the World and this number is estimated to reach 9,5 million by the year 2045 (3). Nearly 10% of the people with diabetes have type 1 diabetes (1). According to Diabetes Atlas 2017, the number of children and adolescences between the ages of 0-19 with type 1 diabetes were 25.669 in Turkey (3). In recent years, an increase was detected in type 1 diabetes incidence around the World and in our country as well. Type 1 diabetes incidence under 19 years in our country was reported as 10,7/100000 and prevalence as 0.75/1000 (3). Type 1 diabetes mostly develops in youth less than 15 years of age (4).

Hypoglycemia is the most frequently observed acute complication of type 1 diabetes and defined as reducing blood glucose level. The symptoms appear when the blood glucose level reduce under 70 mg/dl. Among the common reasons of hypoglycemia are rapid development of the child, malnutrition, excessive exercises, getting too much insulin, wrong insulin injection technique and skipping a meal. Hypoglycemia begins with such symptoms as anger, fatigue, dizziness, sweating and shivering. Change in behaviors is the very first symptom for majority of children (4).

It has been estimated that around 20.000 students with diabetes are available according to "Students with Diabetes Instruction" announced by Ministry of Education in 2013 (5). This number is considered to increase due to rising prevalence (4).

Adolescences with a chronic disease like type 1 diabetes attach importance academic success as well as social life and struggle to manage their conditions (6,7). However, school management, school/pediatric nurse, classmates, canteen personnel, school bus drivers should be aware of the condition of the child and be informed in advance to support the child with type 1 diabetes (7).

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Pediatric/school nurses have a crucial role by encouraging the child to overcome with his/her condition to develop their health by providing care and education (8). However, each of the schools do not have a nurse to intervene in emergency. Thus, the responsibility for such emergency situations put on the shoulders of teachers. So, teachers should be able to provide emergency care to students with chronic diseases (9-11). However, the study by Clay et al. demonstrated that teachers did not always have appropriate knowledge to meet the needs of those children (12). Even though "Diabetes Education Programme in Schools" started with the protocol signed by Ministry of Education, Ministry of Health and Pediatric Endocrinology (6) approximately 40% of teachers do not have enough knowledge about hypoglycemia which is the most serious complication of type 1 diabetes (13).

Hypoglycemia which is an acute complication of diabetes is an absolutely serious and may possibly develop at any moment. Although some kind of scales are available in literature for health care providers or parents, not any scales assessing the hypoglycemia management exist for teachers in literature may not be found.

The purpose of this study was that developing a reliable and valid tool measuring the hypoglycemia management of teachers.

2. METHODS

2.1. Research Questions

Q1. Is "hypoglycemia management scale for teachers" a reliable scale?

Q2. Is "hypoglycemia management scale for teachers" a valid scale?

2.2. Design

The study was conducted methodologically. The instrument was developed in 3 phases. First items were generated and then content and face validity tested in second phase. In third phase other psychometric properties such as construct validity, internal consistency reliability, item to total correlation, split-half reliability and test-retest reliability was tested.

2.3. Participants

It was stated in literature that a scale should have 5-10 times more sample than item total number in order to ensure reliability and validity (14-16). Our draft scale included 31 items. So that the number of teachers included in the sample were planned to be 155-310. The study was completed with 400 volunteer primary, secondary and high school teachers. The inclusion criteria were; working as a teacher in schools where the study was conducted, being volunteer to participate in the study and not having diabetes.

2.4. Data Collection Tools

***Socio-demographic Characteristics Form*:** It was prepared by the researchers and included sociodemographic variables such as gender, characteristics students, etc.

Hypoglycemia Management Scale for Teachers (HMST)

Establishing item pool: In the development process of HMST item pool was established primarily. Researchers determined 30 items. The scale was designed in five-likert type as "1=Strongly disagree", "2=Disagree", "3=Undecided", "4=Agree" and "5=Strongly Agree". The scale was read and filled individually.

Content Validity: One of the reasonable ways to test the content validity is to get the view of an expert. The scale was presented to 5 of the experts to assess its comprehensibility. Experts' team consisted of clinicians working on diabetes and academician nurses. In order to ensure both cultural and linguistic equivalence and prove content validity with numerical values, Content Validity Index – CVI was utilized as an assessment measurement (17). Experts were scored each of the item 1-4 according to Davis method (18). The scores meant as follows: 1 = not appropriate; 2= the item should be re-designed to be appropriate; 3= appropriate but still needs minor changes; 4= very appropriate. The scores of each expert was evaluated and the items with 1 and 2 scores were removed from the scale and re-designed accordingly. When the 80% of the items were assessed as 3-4 scores, CVI score of the scale was determined as 0,80. Having a CVI score above 0,80 demonstrates an appropriate content validity (17). In addition; 1 item was added to the scale on demand of the experts and the content validity of the scale was accomplished with 31 items in total.

Face Validity: Literature suggests on development of a scale that the draft scale should be tested in a sample group with similar features (17,19). Following the accomplishment of content validity, 31 of the teachers were held a pre-implementation to evaluate face validity and to perform necessary changes on data collection tools and the 31 itemed form was implemented accordingly.

2.5. Data Collection

The study was conducted at primary, secondary and high schools between the dates of 6th Feb,2020 and 11th March,2020. Data collected with Socio-demographic Characteristics Form and Hypoglycemia Management Scale for Teachers were asked to fill in the data collection tools by themselves. Researchers accompanied to the teachers during data collection in order to prevent data loss. Duration of data collection lasted approximately 10-15 minutes.

2.6. Analysis of Data

The data were analysed by using NCSS (Number Cruncher Statistical System) 2007 software programme (Licence No:1675948377483; Serial No: N7H5-J8E5-D4G2-H5L6-W2R7). Views of the experts

were assessed through Content Validity Index. Factor analysis was performed to ensure construct validity. As for validity analysis of the scale, internal consistency (Cronbach's Alpha Coefficient), item-total score validity, test-retest validity and Split-Half validity scores were calculated. In order to calculate socio-demographic data, descriptive statistical analysis (mean, standard deviation, percentage) were performed.

2.7. Ethical Considerations

Ethical committee permission was obtained from the Ethical Committee of Non-Interventional Clinical Studies of Health Sciences Faculty University, Türkiye. (Permission no: 14.11.2019/137). Moreover, following to providing essential information to the participants, an informed consent form was asked from the volunteers.

3. RESULTS

3.1. Socio-demographic Characteristics of Teachers

Of the 73.8% of teachers had no student with type 1 diabetes before and 71% of them have not taken any diabetes education. Detailed socio-demographic data of teachers were presented at Table 1.

Table 1. *The distribution of socio-demographic characteristics of teachers (n=400)*

	n	%
Gender		
Female	285	71.25
Male	115	28.75
Education		
Primary	136	34
Secondary	124	31
High school	140	35
Any students with type-1 diabetes at school?		
Yes	174	43.5
No	226	56.5
Any students with type-1 diabetes in class?		
Yes	43	10.8
No	357	89.3
Have you ever had a student with type-1 diabetes?		
Yes	105	26.3
No	295	73.8
Have you ever encountered with hypoglycemia?		
Yes	95	23.8
No	305	76.3
Have you ever taken diabetes education?		
Yes	116	29
No	284	71

3.2. Content Validity

A consensus was generated among expert views for HMST according to Kendall's W concordance analysis performed to ensure content validity (Kendall's W_a=.32, df=29, p>.05). Content Validity Index analysed through expert views according to Davis (18) method was identified as.975.

3.3. Construct Validity

Exploratory Factor analysis was implemented to identify factor structure of the scale. In order to determine the compatibility of the data to factor analysis, Kaiser-Meyer-Olkin (KMO) and Bartlett's test of sphericity were implemented. Kaiser-Meyer-Olkin (KMO) value of HMST was found .838. On the other hand, Bartlett's test of sphericity score was found statistically significant (c^2=934,446 df=55 p<.001).

In factor analysis varimax rotation technique was used. As the result of factor analysis 13 items taking load from more than one factor and having a difference more than .10 between loads were removed from the scale. The scale has a two-factor structure. Two factor structure explains 45.20% of the total variant of scale. "Scree plot" graphic demonstrates the factor structure of the scale (Figure 1).

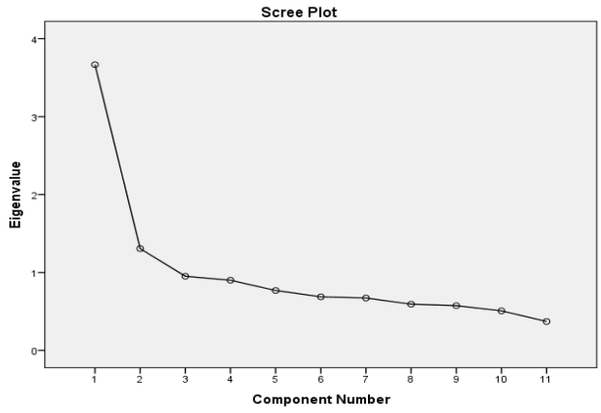

Figure 1. *Scree Plot Graphic of HMST*

Factor 1: Items 1-2-3-4-5-7 were gathered under factor 1. Those items includes essential information about hypoglycemia that is an acute complication of Type 1 diabetes. Thus, the factor was named as "Hypoglycemia Knowledge"

Factor 2: Items 6-8-9-10-11 were placed under factor 2. Those items includes certain expressions about teachers' practises in hypoglycemia condition. Thus the factor was named as "hypoglycemia management".

When the factor loads of items were examined, item loads were identified between .49 and .77. The findings obtained from exploratory factor analysis were presented at Table 2.

Table 2. *Hypoglycemia management scale for eachers and characteristics of sub-groups (n=400)*

Factors	Factor load	Item total correlation values
Factor 1 (Hypoglycemia Knowledge)		
1. Blood glucose level at 70 mg/dl or less is defined as hypoglycemia	0.66	0.55
2. Loss of the consciousness and seizure are among the symptoms of hypoglycemia.	0.72	0.45
3. I would think hypogelycemis might develop if I notice shivering in my student with type-1 diabetes.	0.77	0.54
4. In hypoglycemia situation form y student with type-1 diabetes. the very first thing I should do is to provide carbohydrate (sugar. fruit juice.honey etc.) if he/she is concious.	0.71	0.54
5. I encourage my student with type-1 diabetes measuring the blood-glucose in P.E lessons.	0.60	0.49
7. Hypoglysemis is not a severe condition.	0.49	0.32
Factor 2 (Hypoglycemia management)		
6. I measure the blood-glucose with glucometer if necessary	0.57	0.27
8. I am able to recognize hypoglycemia in my student with type-1 diabetes.	0.68	0.49
9. I always have sugar and fruit juice in my class.	0.67	0.35
10. If I have to administer glucon to my student with type-1 diabetes. I take him/her side-lying position after the administration.	0.62	0.36
11. I inform other students about the hypoglycemia in case of emergency situations when I am not with them (breaks).	0.52	0.48

3.4. Reliability

Item total correlation of HMST ranged between .27 and .55 (Table 2). 7 of the items were removed from the scale since their correlation coefficient calculated via item total correlation were beneath .30 and exploratory factor analysis was implemented again to get the final shape of the factor structures (Table 2). 6th item was decided to remain in the scale because its item total score correlation was 0.27 but its factor load was .57. Cronbach's alpha coefficient of the scale was found .777.

Spearman Brown and Guttman Split Half coefficients calculated for split-half reliability of the scale and it was presented at Table 3.

Table 3. *Cronbach's alpha and split-half reliability results of hypoglycemia management scale for teachers*

Sub-scales (n=400)	Items	Cronbach's Alpha Coefficient	Split-half Reliability	
			Spearman-Brown Coefficient	Guttman Split-half Coefficient
Hypoglycemia knowledge	6	.720	.702	.700
Hypoglycemia management	5	.601		
Total scale	11	.777		

Test-retest reliability results were presented at Table 4. According to ICC analysis: 85.4% of fit was found between first and last measurements of "Hypoglycemia Knowledge" sub-group (factor 1); 86.5% of fit between first and last measurements of "Hypoglycemia Management" sub-group and 86.3% of fit in total score were determined.

Table 4. *Test-retest results of hypoglycemia management scale for teachers*

Sub-scales (n=112)	First measurement Mean ± SD	Second measurement Mean ± SD	ICC (%95 CI)	*p*
Hypoglycemia Knowledge	22.72 ± 3.44	23.22 ± 3.24	0.854	*.000**
Hypoglycemia management	17.33 ± 3.27	17.53 ± 3.09	0.865	*.000**
Total scale	40.62 ± 5.59	43.65 ± 5.07	0.863	*.000**

† *ICC: Intraclass Correlation Coefficient * p<.001*
‡. *CI: Confidence interval*
§ *SD: Standart deviation*

3.5. Scoring of Hypoglycaemia Management Scale for Teachers

The scale had a five-likert type and included 11 items and two sub-dimensions. The first factor included 6 items. The minimum score of this factor was 6 and the maximum one was 30. Increasing score for this factor meant high level of hypoglycemia knowledge. The 7th item in the factor should be scored reversely. The second factor consisted of 5 items. The minimum score was 5 and the maximum one was 25. High scores in this factor meant positive attitudes towards hypoglycemia management.

Minimum score for the scale was 11 and the maximum one was 55. High scores stood for high level of hypoglycemia management.

4. DISCUSSION

Scale development study was begun with the scanning of related literature. The scanning of the literature demonstrated that even though some hypoglycemia related scales were available for health care providers and parents, not any scale existed to assess hypoglycemia management of teachers. Hypoglycemia which is a complication of diabetes is a rather serious and fast developing condition. School administration, nurse, teachers, classmates, canteen personnel and school bus drivers should be aware of the chronic conditions the child has experienced. However, teachers are the front-line supporters for children with chronic conditions just like type 1 diabetes (11). It is highly crucial that teachers should have enough knowledge and experience to meet the needs of children with type 1 diabetes specifically in hypoglycemia situation. This scale would enable to measure hypoglycemia management of teachers.

A newly developed scale should fulfill two important factors: reliability and validity. Validity refers to how accurately a method measures what it is intended to measure. So, a scale can be considered valid if it measures the intended features without interfering with any other features. A valid scale requires to be reliable. Reliability refers to consistency among the responses to each of the items (17). At present study content and construct validity were utilized to test the validity of the scale.

4.1. Content Validity

Content validity refers to the degree to which an assessment instrument is relevant to, and representative of, the targeted construct it is designed to measure (17, 20). In order to ensure content validity Kendall's W concordance analysis was performed and not any significant difference was detected among the views of experts. Such a result is the indicator of items' comprehensibility by the experts. The scale is a comprehensible tool to assess hypoglycemia management of teachers.

4.2. Construct Validity

Construct validity refers to how well a test or tool measures the construct that it was designed to measure. Factor analysis is one of the methods to examine construct validity (16, 17). Explanatory factor analysis-EFA is the technique used to determine the number of sub-dimensions and the relations between them (16, 17, 19, 21). Explanatory factor analysis-EFA is used to test construct validity of scales. However, prior to implementation of Explanatory factor analysis-EFA, Kaiser-Meyer-Olkin (KMO) test was utilized to test the appropriacy of number of sample and Bartlett's test of sphericity to identify the appropriacy of relations between variables (14). Kaiser-Meyer-Olkin (KMO) is an index comparing the size of observed correlation coefficients with partial correlation coefficients. Kaiser-Meyer-Olkin (KMO) value ranges between 0 and 1. Kaiser-Meyer-Olkin (KMO) value is .80 or above meritorious, .70 or above middling, .60 or above mediocre, .50 or above miserable, and below .50, unacceptable. As for Bartlett's test of sphericity, having p value smaller than .05 means that the correlation between variables is sufficient for a factor analysis (14). At present study, Kaiser-Meyer-Olkin (KMO) value was found.838 and p value of Bartlett's test of sphericity was found p<.001 and significant showing that the sample was sufficient for factor analysis and correlation matrix of the items is appropriate to fulfill factor analysis respectively.

In explanatory factor analysis, it was paid a special attention that eigenvalue of items should be 1.00 at least, item factor load value .30 the least, and .10 the least for items with sufficient factor load between two factors (14, 22). As the result of analyses, the number of factors were determined as two. "Screeplot" graphic presented the factorial structure of the scale (figure 1).

According to "Scree plot" graphic, by taking into consideration that the distance between two points is accepted as a factor and the distance following the second factor both small and similar (14), it was approved as two-factor scale. Literature suggests that factor loads should not be less than .30. Factor loads' being ±.70 and above are considered indicative of well-defined structure, ± .50 or greater are considered practically significant, in the range of ±. 30 to ±. 40 are considered to meet the minimal level for interpretation of structure and less than ± .10 can be considered equivalent to zero for purposes of assessing simple structure (14). At present study, it was detected that factor loads were rather high (Table 2) and it explained factorial structure of the scale.

4.3. Reliability

Reliability studies refer the extent to which an experiment, test, or measuring procedure yields the same results on repeated trial. It measures the stability of a test over time. Although a valid test is always reliable, a reliable test is not always valid (19).

The reliability of HMST was tested via internal consistency, item total correlation, split-half method and test-retest reliability analysis. Internal consistency reflects the extent to which items within an instrument measure various aspects of the same characteristic or construct (17). The most frequently used method to test internal consistency is Cronbach's alpha reliability and represented with alpha value. When the Cronbach's alpha value was found .00<α <.40, it represents an unreliable scale; .40<α <.60 lower reliability; .60<α <.80 rather reliable and .80<α <1.00 high level reliability (23). The Cronbach's alpha value of our scale was found .777 showing that the scale is rather reliable (Tablo 3).

Item total correlation explains the relation between the scores obtained from items and total score of the test. Higher item correlation means the items exemplify similar behaviours and high level of internal consistency as well. Literature suggests on this issue that item total score correlation's being .30 and above represents that items distinguish the participants well (24, 25); .20-.30 can remain in the test if necessary; .20 and less means that those items should be removed (26). At present study, even though item total score correlation of the 6th item was .27, it was decided to remain in the test since its factor load was .57 (Table 2).

Another way to test the reliability is the split-half method. Split-half method refers to splitting a body of supposedly homogeneous data into two halves and calculating the results separately for each to assess their reliability by using Spearman-Brown formula and Guttmann split-half formula (27). Reaching a value of .70 and above represents a reliable measurement for the scale (26). In our study, Spearman Brown split-half correlation was found 0,702 and Guttman Split-half coefficient was calculated as .70 (Table 3). Reliability coefficient obtained in this study demonstrated that it was a reliable scale.

According to test-retest result performed to test the reliability of the scale, a positive high level relation was identified for the overall scale (r=.863; p<.01) and it was determined as .865 for hypoglycemia knowledge sub-dimension and .865 for hypoglycemia management sub-dimension (Table 4). Test-retest method, used to measure scale's do not change in time, is expected to have a value over .70 (26). When those values are taken into account, this scale has an appropriate reliability to be implemented.

Completion of the study with more participants (n=400) than expected is the strength of our study. The limitation is that psychometric properties only tested on Turkish culture and language. Completion of the study with more participants (n=400) than expected is the strength of our study. Concurrent validity would not be able to test due to absence of a similar scale is the limit of the study.

5. CONCLUSION

It was observed in terms of reliability and validity tests that the proofs are rather strong related with psychometric aspects of the tool. In this study, a scale was developed to measure hypoglycemia management of teachers with an acceptable evidence of reliability and validity. It is considered to be a reference on the issue since not any similar studies exist in literature.

Strong and weak sides of teachers on hypoglycemia management can be identified with HMST. This scale is absolutely essential to determine hypoglycemia management skills of teachers in emergency situations of children with type 1 diabetes especially when there is no school nurse. Hypoglycaemia Management Scale for Teachers can also help diabetes nurses to identify teachers' ability on hypoglycaemia management and, plan and perform education for teachers to improve effective hypoglycaemia management in school settings.

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Research idea: ÇÇÖ
Design of the study: ÇÇÖ
Acquisition of data for the study: RNA, ASB, FÇ
Analysis of data for the study: ÇÇÖ
Interpretation of data for the study: ÇÇÖ
Drafting the manuscript: ÇÇÖ, RNA, ASB, FÇ
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Clinical and Experimental Health Sciences

Artifacts Caused by Orthodontic Appliances on Magnetic Resonance Imaging: Awareness and Knowledge Level of Maxillofacial Radiologists and Orthodontists

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ABSTRACT

Objective: Artifacts caused by orthodontic appliances on Magnetic Resonance Imaging (MRI) can affect the image quality and make diagnosis difficult. The debate is ongoing on whether orthodontic appliances should be removed to eliminate these problems. This study aimed to evaluate the awareness and knowledge level of dentists working in maxillofacial radiology and orthodontics about this subject through a questionnaire.

Methods: The questionnaire consisted of 20 items and four parts: A) Personal information, B) Awareness level about the artifacts and complications caused by orthodontic appliances on MRI, C) Knowledge level about the factors related to artifacts and complications caused by orthodontic appliances on MRI, and D) Preventive approaches. The questionnaire was prepared on Google Forms and sent to potential participants via e-mail. The Chi-square ($\chi 2$) test was used for the statistical analysis of the variables.

Results: Most participants were aware of the artifacts caused by orthodontic appliances on MRI (90.8%) (93.5% of maxillofacial radiologists and 88.5% of orthodontists) and thought that material type influenced the artifact formation (98.1%) (100% of maxillofacial radiologists and 96.3% of orthodontists). The percentage of participants with 1-5 years of experience who were aware of artifacts was less than those with more experience ($p = .033$). The percentage of orthodontists who referred patients for orthodontic appliance removal was higher than maxillofacial radiologists who requested the orthodontic appliance removal (93.5%>15%).

Conclusion: Simultaneously increasing demands for both orthodontic treatment and MRI in the society cause concerns about the MRI image quality due to artifacts on images of the head and neck region. The main output of this study is that dentists working in orthodontics and maxillofacial radiology have a high awareness and knowledge about the artifacts and complications caused by orthodontic appliances on MRI.

Keywords: Magnetic resonance imaging, artifacts, orthodontic appliances

1. INTRODUCTION

Magnetic Resonance Imaging (MRI) is a radiological diagnostic technique that uses radiofrequency energy instead of ionizing radiation, particularly in the evaluation of soft tissue lesions (1). On MRI, the artifact is defined as the distortion of signal intensity or voids unrelated to any identifiable anatomical basis in the resultant image (2). MRI artifacts include motion, saturation, chemical, and metal artifacts (2). Metallic objects in the patient's body can produce local inhomogeneities into the main magnetic field that cause artifacts on MRI (3). The factors affecting the severity of the artifact depend on the object's magnetic susceptibility (paramagnetic, diamagnetic, and ferromagnetic), spatial orientation, size (length and diameter), homogeneity, amount (number), and shape. Besides these, the distance between the Region of Interest (ROI) and the object, echo time, pulse sequence, magnetic field strength, imaging plane, and image resolution also have effects (3-7). Additionally, metallic objects can cause complications such as heating and movement during the Magnetic Resonance (MR) scan (8-11). Various strategies have offered to reduce the metal artifacts and complications, but it is impossible to completely overcome them (12).

MRI of the head and neck region is becoming commonly used for investigating oral and maxillofacial pathological lesions, temporomandibular joint disorders, in addition to other conditions (13). Dental implants, prostheses, and orthodontic appliances (e.g., fixed or removable orthodontic and maxillofacial orthopedic appliances) located in the oral cavity can cause artifacts on the MRI of these regions (14). The poor-quality images may lead to misdiagnosis or mismanagement of an ongoing treatment process (2). In conventional orthodontic treatment, two different types of archwires [Stainless Steel (SS) and Nickel-Titanium (Ni-Ti)] are usually attached to the SS brackets which are bonded to the teeth. Therefore, these metallic orthodontic appliances have a high potential to cause

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complications such as heating and movement during the MR scanning and artifacts on images (11). In recent years, among the general population, MRI referrals (15) and orthodontic treatments (16) have increased independently of each other. As a result, radiologists frequently request orthodontists to remove fixed metal orthodontic appliances, particularly before the head and neck region MRI (17). Although the responsibility for evaluating these risks lies primarily with the radiologist, they often do not have comprehensive knowledge about the magnetic susceptibility of the material of the orthodontic appliances. Consulting an orthodontist may often remain unsatisfactory due to similar lack of awareness and knowledge (18). In the past, although several studies have investigated the effects of the artifacts and complications caused by orthodontic appliances on MRI, the results are unclear because of the variety of materials of devices and examined regions (1,9,10,18-28). However, today, increasing data on the orthodontic appliance and MRI relationship leads to more precise judgments on the subject (13).

Removing and rebonding the orthodontic appliance during the ongoing orthodontic treatment process is time-consuming, costly, and laborious for the patient and orthodontist; also, it can damage the tooth enamel and affect the course of the treatment negatively (29). In studies examining the effect of orthodontic appliances that cause artifacts on image quality, the fact that the orthodontic appliance is close to the ROI and contains steel was shown as the reason for its removal (17,30). In contrast, according to the study that focused on the size of the artifact, it was related to the magnetic properties of the MRI device and the material type of orthodontic appliance (18). The decision to remove fixed orthodontic appliances before MRI creates a process that is affected by many factors and can cause many disadvantages, depending on the case. Orthodontists must decide between avoiding image artifacts and not affect the prognosis of ongoing orthodontic treatment. Maxillofacial and medical radiologists also experience the same difficulty in deciding which orthodontic appliance to request removal according to the ROI and its material type.

This study aimed to evaluate the level of awareness and knowledge of dentists working in orthodontics and maxillofacial radiology about artifacts and complications that orthodontic appliances may cause on MRI. The hypothesis of this study was "there was no difference between the awareness and knowledge level of dentists working in maxillofacial radiology and orthodontics about the artifacts caused by orthodontic appliances on MRI."

2. METHODS

This study was approved by the Gazi University Ethics Committee (date: 10/07/2020, number: 06), and all stages of the study were conducted in accordance with the Declaration of Helsinki. For this study, a special questionnaire was set up to investigate the level of awareness and knowledge about the MRI artifacts caused by orthodontic appliances. The questionnaire was designed to be responded to by dentists who were specialists or continuing their specialty training in orthodontics or maxillofacial radiology. Initially, the questionnaire was set up by an orthodontist and two maxillofacial radiologists with at least 15 years of professional experience, and the first version included 21 questions. It was then evaluated by an orthodontist and a medical radiologist who were blind to previous procedures, and a question was removed in line with their recommendations. Additionally, a face-to-face pre-test was conducted with five maxillofacial radiologists and five orthodontists; incomprehensible, misunderstood, or guiding questions were determined, and then the questionnaire was rearranged in line with these criticisms. After these stages, the questionnaire was carefully checked by the authors to ensure it did not contain any questions that contradicted each other or misdirected the participants.

The last version of the questionnaire consisted of 20 items and four parts: A) Personal information, B) Awareness level of dentists about the artifacts and complications caused by orthodontic appliances on MRI, C) Knowledge level of dentists about the factors related to artifacts and complications caused by orthodontic appliances on MRI, and D) Preventive approaches (Table 1). The questionnaire was prepared on Google Forms (Alphabet, Mountain View, California). It was sent via e-mail to the members of the Turkish Association of Orthodontists and the Turkish Society of Oral Diagnosis and Maxillofacial Radiology with permission. The members of these associations consist of specialists and those who continue their specialization training in dentistry faculties cross Turkey. The questionnaire was prepared in Turkish, then translated into English during the writing process. It was applied to 229 participants between August 08 and September 29, 2020.

2.1. Data Analysis

While determining the study's sample size, the G-Power analysis 3.1.0 package program was used. In the analysis, the power of the test was 0.80, $\alpha = 0.05$, and the effect size was 0.3. For the participant groups, a total of at least 204 volunteers, including 102 maxillofacial radiologists and 102 orthodontists, were planned to participate in the questionnaire.

The IBM SPSS package program (version 25) (SPSS Inc., Chicago, IL) was used for summarizing and analyzing the data. First, the numbers and percentages of the participants were listed according to their answers to the questionnaire. Then the necessary statistical analysis was made using the Chi-square (χ^2) test for the relationship between the two variables. Less than 0.05 as the *p*-value was taken as statistically significant.

3. RESULTS

A total of 229 dentists, 107 (46.7%) working in maxillofacial radiology and 122 (53.3%) in orthodontics, participated in this study. Table 1 shows the distribution of the responses given by the participants in numbers and percentages on the original questionnaire used in the study.

The relationship between the participants' awareness of the artifacts caused by orthodontic appliances on MRI

and their personal information is presented in Table 2. Regarding the awareness of artifacts, although the percentage of maxillofacial radiologists is higher than that of orthodontists and lecturers have a higher percentage than those in other titles, the differences were not statistically significant (p = 0.197, p = 0.637). However, regarding professional experience, the percentage of participants who were aware of the artifacts with 1-5 years of experience was less than the more experienced participants, and the difference was statistically significant (p = 0.033).

The relationship between the participant's awareness of the effect of orthodontic appliance material type on the artifact formation on MRI and the personal information of the participants is shown in Table 3. There was no statistically significant difference between being aware of the effect of the orthodontic appliance material type on the artifact formation on MRI and the specialty area (p = 0.052), title (p = 0.157), and professional experience (p = 0.188).

Table 4 shows the distribution of the participants from two different specialty areas who can encounter MRI artifacts caused by orthodontic appliances in clinical practice according to title and professional experience. In the orthodontic area, the percentage of research assistants with 1-5 years of experience referred patients for orthodontic appliance removal before MRI was lower than the more experienced specialists and lecturers, and the difference was statistically significant (p = 0.000, p = 0.001). Whereas, in maxillofacial radiology, the percentage of the requests for the removal of the orthodontic appliance from a patient under an orthodontic treatment before MRI did not make a statistically significant difference according to the title (p = 0.152) and professional experience (p = 0.109).

Table 1. *Distribution of the participants according to the questionnaire form and their responses, N (%) (N = 229)*

A) Personal information				
1. Age	Min; 25 Max; 64 Mean ± standard deviation; 34.6 ± 8.3			
				N (%)
2. Gender	Female			161 (70.3)
	Male			68 (29.7)
3. Specialty area	Maxillofacial radiology			107 (46.7)
	Orthodontics			122 (53.3)
4. Title	Research assistant			69 (30.1)
	Specialist dentist			76 (33.2)
	Lecturer			84 (36.7)
5. Professional experience	1-5 years			102 (44.5)
	6-10 years			54 (23.6)
	10+ years			73 (31.9)
B) Awareness level about the artifacts and complications caused by orthodontic appliances on MRI		**Specialty area**		**Total**
		Maxillofacial radiology	**Orthodontics**	
		N (%)	**N (%)**	
6. Are you aware of the artifacts that can be caused by fixed/removable orthodontic appliances on MRI?	Yes	100 (93.5)	108 (88.5)	208 (90.8)
	No	7 (6.5)	14 (11.5)	21 (9.2)
7. What complications do you know about orthodontic appliances other than artifacts on MRI? [Φ]	Soft and hard tissue injury due to the movement of the appliances (projectile effect)	72 (72.0)	75 (69.4)	147 (70.7)
	Soft and hard tissues thermal injury due to heating of appliances	82 (82.0)	73 (67.6)	155 (74.5)
	Orthodontic treatment failure due to bending of the archwire or unwanted tooth movements	61 (61.0)	46 (42.6)	107 (51.4)
8. Does the material type of the orthodontic appliance influence the artifact on MRI?	Yes	100 (100.0)	104 (96.3)	204 (98.1)
	No	0 (0.0)	4 (3.7)	4 (1.9)
9. Can the material selection of the orthodontic appliances be determined according to the patient's medical history and potential MRI needs?	Yes	85 (85.0)	94 (87.6)	179 (86.1)
	No	15 (15.0)	14 (13.0)	29 (13.9)
10. As a dentist working in orthodontics, have you had a patient who was referred for the removal of the brackets or any orthodontic appliance before MRI?	Yes	-	101 (93.5)	101 (93.5)
	No	-	7 (6.5)	7 (6.5)
11. As a dentist working in maxillofacial radiology, have you requested that a patient's bracket or any orthodontic appliance be removed before MRI?	Yes	15 (15.0)	-	15 (15)
	No	85 (85.0)	-	85 (85)

12. Who should make the final decision whether to remove any orthodontic appliance before MRI? Φ	Orthodontist	70 (70.0)	71 (65.7)	141 (67.8)
	Maxillofacial radiologist	86 (86.0)	67 (62.0)	153 (73.6)
	Medical radiologist	74 (74.0)	93 (86.1)	167 (80.3)
C) Knowledge level about the factors related to artifacts and complications caused by orthodontic appliances on MRI				
13. What are the effects of the artifact of orthodontic appliances on MRI? Φ	Only image quality is affected (minimal distortion)	67 (67.0)	74 (68.5)	141 (67.8)
	Diagnosis is also affected	96 (96.0)	92 (85.2)	188 (90.4)
14. In which region or regions do orthodontic appliances cause artifacts mostly on MRI? Φ	Brain	40 (40.0)	62 (57.4)	102 (49)
	TMJ	69 (69.0)	76 (70.4)	145 (69.7)
	Neck	45 (45.0)	71 (65.7)	116 (55.8)
	Maxillofacial	95 (95.0)	100 (92.6)	195 (93.8)
	Whole body	1 (1.0)	2 (1.9)	3 (1.4)
	In similar severity in every part of the body	1 (1.0)	0 (0.0)	1 (0.5)
15. Which of them influences the occurrence of artifacts or complications on MRI? Φ	Magnetic main field strength (1.5T, 3T, etc.)	94 (94.0)	70 (64.8)	164 (78.8)
	MR pulse sequence (Spin echo, Gradient echo, etc.)	59 (59.0)	26 (24.1)	85 (40.9)
	Weight of the MR images (T1, T2, etc.)	49 (49.0)	17 (15.7)	66 (31.7)
	Size of the FOV	46 (46.0)	28 (25.9)	74 (35.6)
	Thickness of the section	29 (29.0)	20 (18.5)	49 (23.6)
	Section plane	36 (36.0)	24 (22.2)	60 (28.8)
	Orthodontic appliance size	83 (83.0)	70 (64.8)	153 (73.6)
	Orthodontic appliance shape	53 (53.0)	29 (26.9)	82 (39.4)
	Material composition of the orthodontic appliance	92 (92.0)	84 (77.8)	176 (84.6)
	Magnetic susceptibility of the orthodontic appliance material	91 (91.0)	75 (69.4)	166 (79.8)
	Orientation of the orthodontic appliance	43 (43.0)	18 (16.7)	61 (29.3)
	Distance of the orthodontic appliance to the ROI	80 (80.0)	87 (80.6)	167 (80.3)
16. If you believe the material effect, what do you think is the least effective in artifact formation? Φ	Stainless steel	7 (7.0)	6 (5.6)	13 (6.3)
	Titanium	32 (32.0)	24 (22.2)	56 (26.9)
	Ceramic	50 (50.0)	81 (75.0)	131 (63.0)
	Stainless steel + Ceramic	5 (5.0)	2 (1.9)	7 (3.4)
	Nickel free stainless steel	4 (4.0)	6 (5.6)	10 (4.8)
	Nickel-titanium	11 (11.0)	16 (14.8)	27 (13.0)
	Chromium-cobalt	6 (6.0)	6 (5.6)	12 (5.8)
	Plastic	82 (82.0)	88 (81.5)	170 (81.7)
D) Preventive approaches				
17. What should be done to avoid artifacts and complications arising on MRI associated with orthodontic appliances? Φ	Removal of archwires	69 (69.0)	83 (76.9)	152 (73.1)
	Removal of retainers	38 (38.0)	41 (38.0)	79 (38)
	Removal of removable appliances	93 (93.0)	98 (90.7)	191 (91.8)
	Removal all types of brackets	9 (9.0)	25 (23.1)	34 (16.3)
	Removal stainless steel brackets only	59 (59.0)	68 (63.0)	127 (61.1)
	Checking the fixation of the fixed appliances attachments	56 (56.0)	38 (35.2)	94 (45.2)
18. What is your approach to your patients who will apply for the removal fixed orthodontic appliance or for consultation? Φ	Confirm the removal	15 (15.0)	32 (29.6)	47 (22.6)
	Tell the removal is unnecessary	12 (12.0)	9 (8.3)	21 (10.1)
	Decide according to the closeness of the ROI to the orthodontic appliance	74 (74.0)	89 (82.4)	163 (78.4)
	Confirm the MRI after necessary security measures have been taken for the orthodontic aspect	72 (72.0)	57 (52.8)	129 (62)
	Reconsider the MRI indication	25 (25.0)	36 (33.3)	61 (29.3)
19. What is the most important disadvantage of the bracket removal process to avoid artifact on MRI? Φ	Waste of time both for patient and dentist	77 (77.0)	104 (96.3)	181 (87)
	Financial loss	54 (54.0)	99 (91.7)	153 (73.6)
	Effect the prognosis of orthodontic treatment	62 (62.0)	80 (74.1)	142 (68.3)
	Damage of the dental tissues	73 (73.0)	60 (55.6)	133 (63.9)

20. What could be the forward-looking strategies to avoid MRI artifacts caused by orthodontic appliances? Φ	Using small-sized brackets with less magnetic susceptibility material (MR-safe)	89 (89.0)	90 (83.3)	179 (86.1)
	Shortening the scan time	32 (32.0)	28 (25.9)	60 (28.8)
	Scanning in lower magnetic strength	37 (37.0)	44 (40.7)	81 (38.9)
	Making the material selection of the orthodontic appliance according to the MRI potential in the light of the patient's medical history	81 (81.0)	91 (84.3)	172 (82.7)
	Using an artifact reduction software	81 (81.0)	74 (68.5)	155 (74.5)

Φ; Multiple-choice question

Abbreviations: MRI; Magnetic Resonance Imaging, TMJ; Temporomandibular Joint, MR; Magnetic Resonance FOV; Field of View, ROI; Region of Interest

Table 2. *Statistical analysis of the relationship between the participants' awareness of the artifacts that orthodontic appliances may cause on MRI and their personal information, N (%) (N = 229) (6th Question)*

Variables		Are you aware of the artifacts that can be caused by fixed/removable orthodontic appliances on MRI?				
		Yes	No	Total	x^2	*p*-value
		N (%)	N (%)	N (%)		
Specialty area	Maxillofacial radiology	100 (93.5)	7 (6.5)	107 (100)	1.666	0.197
	Orthodontics	108 (88.5)	14 (11.5)	122 (100)		
Title	Research assistant	61 (88.4)	8 (11.6)	69 (100)	0.901	0.637
	Specialist dentist	69 (90.8)	7 (9.2)	76 (100)		
	Lecturer	78 (92.9)	6 (7.1)	84 (100)		
Professional experience	1-5 years	87 (85.3)	15 (14.7)	102 (100)	6.844	0.033*
	6-10 years	51 (94.4)	3 (5.6)	54 (100)		
	10+ years	70 (95.9)	3 (4.1)	73 (100)		

**; The Chi-square statistic is significant at the 0.05 level*

Abbreviation: MRI; Magnetic Resonance Imaging

Table 3. *Statistical analysis of the relationship between the participants' awareness about the effect of the orthodontic appliance material type on artifact formation and their personal information, N (%) (N = 208) (8th Question)*

Variables		Does the material type of the orthodontic appliance influence the artifact on MRI				
		Yes	No	Total	x^2	*p*-value
		N (%)	N (%)	N (%)		
Specialty area	Maxillofacial radiology	100 (100)	0 (0)	100 (100)	3.776	0.052
	Orthodontics	104 (96.3)	4 (3.7)	108 (100)		
Title	Research assistant	60 (98.4)	1 (1.6)	61 (100)	3.706	0.157
	Specialist dentist	66 (95.7)	3 (4.3)	69 (100)		
	Lecturer	78 (100)	0 (0)	78 (100)		
Professional experience	1-5 years	86 (98.9)	1 (1.1)	87 (100)	3.348	0.188
	6-10 years	51 (100)	0 (0)	51 (100)		
	10+ years	67 (95.7)	3 (4.3)	70 (100)		

The Chi-square statistic is significant at the 0.05 level

Abbreviation: MRI; Magnetic Resonance Imaging

Table 4. *Statistical analysis of the clinical approaches of dentists from two different specialties to the orthodontic appliance-MRI artifact relationship according to title and professional experience, N (%) (N = 208) (10th and 11th Questions)*

Variables			Title			Professional experience		
			Research assistant	Specialist dentist	Lecturer	1-5 years	6-10 years	10+ years
As a dentist working in orthodontics, have you had a patient who was referred for the removal of the brackets or any orthodontic appliance before MRI?	**Yes**	**N (%)**	19 (73.1)	56 (100)	26 (100)	32 (82.1)	24 (100)	45 (100)
	No	**N (%)**	7 (26.9)	0 (0)	0 (0)	7 (17.9)	0 (0)	0 (0)
	Total	**N (%)**	26 (100)	56 (100)	26 (100)	39 (100)	24 (100)	45 (100)
	x^2		23.607			13.243		
	***p*-value**		0.000*			0.001*		

As a dentist working in maxillofacial radiology, have you requested that a patient's brackets or any orthodontic appliance be removed before MRI?	**Yes**	**N (%)**	2 (5.7)	3 (23.1)	10 (19.2)	5 (10.4)	3 (11.1)	7 (28)
	No	**N (%)**	33 (94.3)	10 (76.9)	42 (80.8)	43 (89.6)	24 (88.9)	18 (72)
	Total	**N (%)**	35 (100)	13 (100)	52 (100)	48 (100)	27 (100)	25 (100)
	x^2		3.762			4.425		
	***p*-value**		0.152			0.109		

**; The Chi-square statistic is significant at the 0.05 level*
Abbreviation: MRI; Magnetic Resonance Imaging

4. DISCUSSION

In the literature, the artifacts and complications caused by orthodontic appliances on MRI were investigated in many studies (1,9,10,18-28). To the best of our knowledge, there is no published article evaluating the level of awareness and/or knowledge about factors that caused artifacts of dentists who had to decide whether to remove these appliances. This study was conducted to reflect the approach of dentists working in maxillofacial radiology and orthodontics to the artifacts and complications that orthodontic appliances may cause on MRI and the difficulties in deciding on the removal. The hypothesis of this study was supported as there was no difference between the awareness and knowledge level of dentists working in maxillofacial radiology and orthodontics about the artifacts caused by orthodontic appliances on MRI.

4.1. Level of Awareness About the Artifacts and Complications

Metal objects in the body, including the orthodontic appliances, cause artifacts on MRI (18). In this study, most participants were aware of the orthodontic appliance-related artifacts on MRI (90.8%). When it was scoped in more detailed regarding specialty area, title, and professional experience, the maxillofacial radiologists, lecturers, and 10+ years of experience participants' awareness level was higher. However, only for professional experience, the difference was statistically significant. If participants were unaware of metal artifacts on MRI (6th question), they were forced to stop answering the questionnaire.

In addition to artifacts, there are other complications that metallic objects may cause during the MR scanning. The strong magnetic field of the MR system causes the sudden movement of ferromagnetic objects with great force (known as the projectile effect) (31). Even though it is claimed otherwise (31-33), the generated force cannot exceed the 60 N threshold required to deboned the fixed orthodontic appliances (9-11,34), but this may pose a risk, especially in patients with an insufficient bracket-tooth attachment (30). Another complication is the possible thermal damage of the oral cavity tissues caused by orthodontic appliances exposed to radiofrequency (8,21,35,36). However, depending on the manufacturer, the increase in temperature is between 0.2 and 3.04°C, which has a negligible effect (11,25). Despite reports of previous studies and manufacturers' assurances on these issues, most participants believed that the risk of thermal injury and motion injury was high. However, just half of the participants believed that orthodontic treatment could fail because of the bending of the archwire or unwanted tooth movements.

It has been stated that the material type influences the artifact (14). In this study, in line with this previous finding, most participants (98.1%) thought that the material type influenced artifact formation. Participants' specialty area, title, and professional experience did not change their approach to this subject.

Orthodontists may prefer non-metal appliances like ceramic brackets to SS brackets for patients who require periodic MRI evaluations (18). Since the patient's health history cannot always guide to possible MRI requirements, it would be reasonable to choose the type of SS that causes less artifact on MRI (37). In this study, most participants stated that it would be a reasonable method to make the material selection of orthodontic appliances according to the medical history and potential MRI needs of the patient.

Since this study interested the orthodontic appliances that cause artifacts on MRI, the addressees of the subjects as dentists would naturally be those working in maxillofacial radiology and orthodontics. However, responses to the 10th and 11th questions showed that the percentage of encountering this subject in orthodontics (referred patients for removal) was higher than in maxillofacial radiology (requested for removal) (93.5% >15%). Because of the relatively limited use of MRI in maxillofacial radiology, dental radiological examination of patients with orthodontic appliances is usually completed without problems such as artifacts or complications. According to the participant's responses to the 12th question, the final decision on removing the appliance should be made by medical radiologists rather than orthodontists and maxillofacial radiologists. This result showed that those who referred patients to orthodontists for removing the appliances might have be mostly medical radiologists.

4.2. Level of Knowledge About the Factors Caused Artifacts and Complications

According to the orthodontic appliance type, material type, or ROI, the artifacts could affect the image quality, which makes the diagnosis difficult or impossible (2,17,22,28,30,37-39). The images of regions close to orthodontic appliances are more affected (30). Depending on the appliance and material type, the artifacts could be observed in the oral cavity, Temporomandibular Joint (TMJ), brain, posterior cerebral

fossa, cervical vertebrae, cervical region, and paranasal sinuses. However, since the artifacts caused by orthodontic appliances are localized in the oral cavity, the diagnostic quality of other head and neck regions with more routine MRI indications is not affected much (17,27,30). In another study, the regions with severe artifacts caused by SS appliances were reported as the hard palate, tongue base, mandible body, globes, frontal lobes, and nasopharynx (37). In this study, the percentage of participants who thought the diagnosis would be affected was higher than those who believed only the image quality would be affected (90.4%>67.8%). The participants stated that orthodontic appliance artifacts could be observed mainly in the maxillofacial region, in line with the studies in the literature (93.8%) (17,27,30,37).

The factors influencing metal-related artifact's production on MRI can be classified as object-related, parameter-related, and sequence-related (5). If the orthodontic appliance material composition is rich in ferromagnetic metal, which has high magnetic susceptibilities, the artifact size will be larger than paramagnetic and diamagnetic substances (14). The severity of the artifact increases in the presence of larger-sized and round-shaped metal objects (3,7,18). The T2-weighted images are more susceptible than the T1-weighted images due to longer echo times (19,30). The faster gradient-echo sequence leads to larger artifacts than the spin-echo sequence (40). It has been reported that the low magnetic field strength (e.g., 1.5 T vs. 3 T), small Field of View (FOV), thin slice, to locate the long axis of the object parallel to the axis of the main magnetic field, and more distance to the ROI will decrease the metal artifacts (18,30,37,41). Furthermore, while metallic object-induced artifacts can completely obscure the region of interest in one section plane, they may cause fewer effects on another plane (20). In this study, the participants thought that the material composition of the orthodontic appliance (84.6%), the distance of the orthodontic appliance to the region to be examined (80.3%), and the magnetic susceptibility of the orthodontic appliance material (79.8%), respectively, were the most influential factors on artifacts formation. The thickness of the section (23.6%), the section plane (28.8%), and the orientation of the orthodontic appliance (29.3%) were thought to be the least influential factors on artifacts formation.

The orthodontic appliances may contain ferromagnetic metals such as Chromium (Cr)-Cobalt (Co), and Ni-Cr that interfere with magnetic fields and cause artifacts on MRI (14,20,42). In fixed orthodontic treatment, Ni-Ti and SS archwires are used with SS brackets (SS composed of Ni (8%-12%), Cr (17%-22%), and variable amounts of other metals) (43). Some researchers stated that the material proportions in the metals used are also effective in forming of artifacts (37). Several studies revealed that SS brackets cause greater artifacts than plastic, ceramic, and titanium brackets with a metal slot leading to MRI non-interpretability (17,22,23,28,37). In addition to studies that reported that titanium, often considered MR compatible, produces artifacts (4,20,38), some studies also stated that titanium only causes minor artifacts (6,14,17). These different results can be explained by the different amounts of titanium used because it has been claimed that smaller amounts cause more minor artifacts (17,44). Therefore, unlike other materials, we cannot speak of a consensus on the effect of titanium artifact formation. Most of the participants considered plastic and ceramic as less effective materials in the construction of MRI artifacts. In line with the literature's confusion, there was no dominant opinion about titanium among the participants in this study.

4.3. Preventive Approaches

Because of possible artifacts and complications that orthodontic appliances may cause, the number of patients applying to dentists working in maxillofacial radiology and orthodontics is increasing day by day. Although many studies have investigated whether orthodontic appliances should be removed before MRI, the issue remains unclear (1,10,17,19,23,24,37). Before the removal or non-removal decision, the following three risky situations should be considered; high-frequency-induced heating of the appliance, movement of the appliance caused by the main field, and artifact formation, which might restrict the diagnosis (18). In the studies conducted, it was emphasized that the decision should generally be made according to the material type of the appliances (1,17,20,45), the region to be examined (1,20), and the type of the appliances (17,23,45). Especially in cases where oral cavity and brain examination will be performed, removal the appliances containing SS material has been recommended, which can be removed relatively easily. In contrast, studies indicated that all orthodontic appliances may remain in the mouth without materials discrimination during MRI (26) or that SS brackets do not always need to be removed if the brain and TMJ regions are to be examined (27). The stability of orthodontic instruments, such as ligament wires, archwires, brackets, bands, and tubes that are decided to remain in the patient's mouth, should be carefully checked (24). It was stated that loose orthodontic appliances pose a significant danger to the patient, so the attachment of all banded and bonded components should be checked or passively ligated with elastomeric chains for added safety (24,30). Additionally, all removable metallic appliances must be removed, as their removal will not cause any difficulties or additional costs (10,30). In this study, for preventing MRI artifacts and complications, the removal of removable appliances had the highest rate (91.8%), while the removal of archwires was also very popular (73.1%). In another question that inquired what should be considered when making the removal decision, most participants stated that the distance of the orthodontic appliance to the ROI was the most important factor (78.1%).

The removal of orthodontic appliances, especially SS brackets, before MRI is a problematic procedure in many aspects. In fact, it can be time-consuming, costly, and uncomfortable for both the patient and orthodontist (46). Moreover, this procedure could damage the enamel structure, prolong the treatment period and influence the prognosis of treatment (47). In line

with this information, the study participants also highlighted the waste of time for both patients and orthodontists, and financial loss is an important disadvantage.

Strategies to reduce metal artifacts on MRI can be listed as follows; 1) using small-sized brackets that have less magnetic susceptibility material, 2) using SE sequence instead of GE sequence, 3) shortening the scan time, 4) scanning in lower magnetic field strength, 5) making the material selection of the orthodontic appliance according to the MRI potential in light of the patient's medical history, and 6) using an artifact reduction software (5,18,26,48,49). The dentists who participated in this study thought the ideal way to reduce the artifacts was to use small-sized brackets with less magnetic susceptibility material.

Increasing demands for both orthodontic treatment and MR in society force orthodontists to be more conscious about the types of appliances they use. The difficulty of removing fixed orthodontic appliances necessitates orthodontists to choose them by considering the possible future medical needs of their patients as well as orthodontic treatment. The prominent solutions of the participants in this study to avoid artifacts and other complications of orthodontic appliances were to act with the consideration about the potential use of MRI for medically specific patients and to use MRI-safe materials. Future studies may provide more detailed data on the frequency of dentists' encounters with orthodontic cases of dentists and the problems they experience.

A limitation of this study was that the questionnaire was conducted in a single country and online with the participation of a limited number of orthodontists and maxillofacial radiologists. Different results may be obtained when applied to more participants in other countries. Another limitation is that medical radiologists request an MRI of the head and neck region more than maxillofacial radiologists. Similar questionnaires that medical radiologists will include can be applied in future studies.

5. CONCLUSIONS

The results of this study demonstrate that dentists working in orthodontics and maxillofacial radiology have a high level of awareness and knowledge about the artifacts and complications caused by orthodontic appliances on MRI. The levels of the participants with less professional experience in both specialty areas were lower. The number of referrals for the removal of the orthodontic appliances to orthodontics was higher compared with the number of requests for the removal from maxillofacial radiology. Using small-sized brackets with less magnetic susceptibility material was considered the ideal way to reduce the number of artifacts on MRI.

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Clinical and Experimental Health Sciences

The Relationship Between the Mentorship Skills and Professional Attitudes of Preceptor Nurses: A Multi-Centre Study

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ABSTRACT

Objective: The research was conducted to determine to evaluate the mentoring skills of the preceptor nurses, their professional attitudes and the relationship between mentorship skills and professional attitudes.

Method: The study was conducted with all preceptor nurses who guided newly hired nurses (n: 245) that were employed at two university hospitals, two research, and training hospitals, and two private hospitals under the Turkish Ministry of Health. The data were collected between 1 August and 30 October 2017. The research was conducted with a descriptive and relationship-seeking design. The data were collected by using Nurse Information Form, the Mentorship Scale, and the Vocational Professional Attitude Inventory. Frequencies, percentages, means, standard deviations, ANOVA, t-test, Kruskal Wallis tests were used to analyze the data, while Cronbach's alpha coefficient and Pearson analyses were used for reliability analysis.

Results: This research determined that 80.8% stated that they voluntarily worked as preceptor nurses, 58.8% said they attended training programs on the preceptor, and 84.1% expressed their relationship with the nurse they supervised as a teacher-student relationship. The participants had high mentorship skills (4.27±0.43) and high vocational professional attitudes (147.42±9.56). As the mentorship skills of the participants increased, it was observed that their vocational professional attitudes also significantly increased (p<.001).

Conclusion: The preceptor nurses who participated in this study had high levels of mentorship skills. The participants also had high levels of vocational professional attitudes. As the mentorship skills of the participants increased, their vocational professional attitudes also increased significantly.

Keywords: Mentoring; preceptorship; nurse clinicians; attitude; nurses

1. INTRODUCTION

Mentorship is one of the most significant methods/approaches that are used to ensure that students especially nurses who are newly hired, use the theoretical knowledge required by the profession in application areas, gain skills, improve their professional capabilities, and form positive attitudes towards the profession (1).

According to Crisp and Cruz (2009), mentoring; is a development process in which one person (mentor) shares his knowledge and experience and supports the development of the other (mentee). The main purpose; is to enable the individual to develop in line with his/her personal and professional development goals (1). Mentorship is a process of personal and professional development and learning that covers processes of supervision, guidance, coaching, facilitation, assessment, and monitoring through sharing knowledge, skills, and experiences based on mutual trust and volunteerism toward the personal and vocational development goals of the individual. Mentorship is a trusting relationship between a novice and a professional (1-3).

Mentorship in nursing is an effective and significant method of socialization for the occupational adaptation and development of the mentee (student, hired nurse, etc.) (4). The mentee needs to provide safe and high-quality care, show professional development, and achieve adaptation to the profession (5). Mentoring in nursing is also the most common and preferred learning approach in which the mentor (clinical guide nurse) helps the mentee acquire clinical skills and contribute to their learning in the clinical field. Among the many factors that impact the teaching-learning process and the professional socialization of undergraduate nursing students and newly hired nurses in clinical learning environments, the role and responsibility of a clinical mentor (preceptor) are considered crucial (6). In the mentoring process in nursing, the relationship between mentor and mentee is not accidental and spontaneous. On the contrary, this relationship has a two-way sharing; new knowledge is built by sharing knowledge and experiences, so an individual and collaborative process can be mentioned. Dickson et al. it

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is emphasized that when nurses start working in the clinical field without going through any mentoring process, their perception of nursing as a profession is negatively affected (7). In the mentoring process in nursing, the mentor primarily needs to share his knowledge, skills, and experiences with the mentees, review their performance, guide them in line with their abilities and talents, interpret their strengths and needs to be developed, offer suggestions about opportunities and threats, support them psychologically and motivate them, etc. must-have features. Mentors with these characteristics have important roles not only in gaining professional skills, but also in developing critical thinking skills, supporting their adaptation to the profession, and improving their ability to cope with problems/events (8-10). Preceptors have experienced nurses who work with novice nurses and nurse students to facilitate and expand their clinical education by sharing experiences in patient care and with technology (3). Preceptorship is important for both healthcare organizations and education to enhance students' and newly hired nurses' clinical competencies, professional growth, and commitment to the nursing profession and organizational environments (11). Preceptorship is also the most prevalent and preferred learning approach where the mentor (preceptor nurse) supports the mentee to gain clinical skills in the clinical environment and contributes to their learning (12). The new skills nurses acquire through mentoring, preceptors, and debriefing in the residency program can be effective in producing an environment within which new nurses can experience a positive transition to practice (3). In this process, preceptors also play important roles in facilitating development, experience, and provision of support in the achievement of open, honest, and sensitive communication by understanding the perceptions of the mentee and helping the mentee adapt to the job and progress in their professional path (11). Mentors with these characteristics have significant roles in not only the mentee's acquisition of professional skills but also their development of critical thinking skills, supporting them in their occupational adaptation, and improving their skills of coping with problems (13).

In the mentorship process, mentees are individuals who aim to be successful, need to gain institutional culture and institutional commitment, and need to have a professional approach to reach their career goals. In this sense, in addition to the supportive, helpful, and professional approaches of mentors, their possession of professional attitudes also allows the vocational attitudes of their mentees to develop in a positive direction (14). There is empirical evidence that support from mentors in clinical practice is essential for nursing students' professional attitude, and positive mentor experiences enhance students' motivation to remain in the nursing profession (15). Vocational professional attitudes are important in terms of the formation of the standards of nursing and the provision of qualified nursing care (16). In addition to increasing the quality of care, the establishment of professional attitudes among mentors is also important in terms of making a professional contribution and increasing the status of the profession (17). However, preceptors' mentorship skills, competencies, and professional attitudes require qualifications or training that are poorly defined across organizational and educational settings (11). A robust assessment of preceptor nurses' current and required competencies as mentors is crucial for the development of high-quality mentorship training and delivery for enhancing newly hired nurses' learning in clinical practice. For these reasons, it is important to determine the mentorship skills and professional attitudes of preceptor nurses, discuss the aspects that need to be improved, and conduct studies in this direction. Studies on clinical mentoring are limited. There is no study regarding "Mentorship skills and professional attitudes of preceptor nurses: A Multi-Centre Study". We believe that this study will be beneficial to nurses and other researchers. Also, we believe that this study will guide manager nurses in the process of determining and developing preceptor nurses. It was aimed to evaluate the mentoring skills of the preceptor nurses, their professional attitudes the relationship between mentorship skills and professional attitudes, and their views on the mentoring process.

For this purpose, answers were sought to the following questions:

1. What are the views of preceptor nurses on the process of mentorship?
2. What is the level of mentoring skills of the preceptor nurses?
3. How are the vocational professional attitudes of preceptor nurses?
4. Is there a relationship between the mentorship skills and vocational professional attitudes of preceptor nurses?
5. Is there a difference between the mentoring process and the mentoring scale total-sub-size and VPAI total mean scores of preceptor nurses?

2. METHODS

2.1. Ethics Approval

Ethics committee approval was received on 03.05.2017 and number 166985 from the Istanbul University Cerrahpaşa Medical Faculty Clinical Studies Ethics Committee. After explaining the study's objective and the data collection process, verbal consent was obtained from the preceptor nurses who voluntarily agreed to participate.

2.2. Sample

The study population consisted of preceptor nurses (n: 526) employed in three university hospitals, two research and training hospitals and five private hospitals of the Turkish Ministry of Health in Istanbul and Kocaeli provinces in Turkey. It was aimed to reach the entire population of the study, but three of the private hospitals and one university hospitals that were approached for the study did not provide permission. The research was carried out in 6 hospitals in Turkey. The data were collected from 245 preceptor nurses between 1 August – 30 October 2017. The data were collected by face-to-face interview method after explaining the purpose of the research to the preceptor nurses, how the data collection process would be done and how long it would take. No time limit was set during the collection of data, and filling out the forms took

an average of 7-8 minutes. The research was conducted with a descriptive, and correlational research design.

2.3. Instruments

The data were collected through an Information Form, the Mentorship Scale, and the Vocational Professional Attitude Inventory (VPAI).

Information Form: The form contained 15 questions to determine the sociodemographic and professional characteristics of preceptor nurses and their statuses of participation in scientific activities inside and outside the institution.

Mentorship Scale: The scale developed by Noe (18) was tested for validity and reliability in Turkish by Özkalp et al (19). The 30-item scale consists of six dimensions coaching, taking a role model, self-expression and visibility, counselling, acceptance and approval, and friendship. The response options for the 5-point Likert-type scale areas. The minimum possible score in the inventory is 30, while the maximum is 150. Higher scores on the scale indicate that the mentorship skills of the participant increase in a positive direction. The Cronbach's alpha value of the scale has been reported as .96 for the total scale (18). In this study, Cronbach's alpha value of the scale was found as .94 for the total scale, coaching .88; role modeling .77; self-expression and making visible .87; counseling .74; acceptance and approval .79 and friendship .66.

Vocational Professional Attitude Inventory (VPAI): The inventory was developed by Erbil and Bakır (16) and consists of 32 items. The inventory consists of questions about attitudes such as vocational training and development, interpersonal relations, and approach to problems and is one-dimensional. The response options for the 5-point Likert-type inventory areas. The minimum possible score in the inventory is 32, while the maximum is 160. Higher scores in the inventory indicate increased levels of vocational professionalism in the participant. The total scale Cronbach's alpha value of the inventory was reported as .89 (16). In this study, the Cronbach's alpha value of the inventory was calculated as .89.

2.4. Data Analysis

The data were analyzed by using the SPSS 22 software for Windows. The data were analyzed by using: frequencies, percentages, means, and standard deviations, t-tests, Spearman's tests. The relationship between the mean Mentorship Scale and dimension scores and the mean VPAI scores of the participants was analyzed by Spearman's test. The statistical significance level was accepted as $p< .05$ in the analyses (95% confidence interval).

3. RESULTS

3.1. Socio-demographic and professional characteristics of preceptor nurses

The preceptor nurse's mean age was 36.44±6.85. 95.5% of the participants were women. Of the participants, 48.6% had undergraduate degrees, while 33.5% had postgraduate degrees. Of the participants, 40.4% worked at specialized units such as operating rooms and intensive care units, while 22.9% worked at internal medicine units. 39.2% were service head nurses, and 33.1% were service nurses, whereas they had been working as nurses for a mean time of 15.13±7.29 years.

3.2. Preceptor nurses' views on the guiding process

Of the participants, 80.8% stated that they worked as preceptor nurses voluntarily, and 58.8% said they had attended a training program on preceptors. 44.9% of the participants stated that they had been working as preceptor nurses at their institution for 2-4 years (mean: 4.32±3.63 years), 42.9% guided for one month or shorter, and 36.3% guided for three months or longer (mean: 1.93±0.89 months) Of the participants 66.1% stated that they worked with the nurse they guided only in the daytime shift, 84.1% define this relationship mostly as a relationship of teacher-student, 39.6% defined their relationship as a friendship and 23.3% explained it as a master-apprentice relationship (Table1).

Table 1. *Views of the participants on the process of preceptorship (N=245)*

Views of the participants on the process of preceptorship		n (%)
Status of working as preceptor nurses voluntarily	Yes	**198(80.8)**
	No	47(19.2)
Status of having attended a training program on preceptorship	Yes	**144(58.8)**
	No	101(41.2)
Time of working as preceptor nurses at the institution	≤1 year	51(20.8)
	2-4 years	**110(44.9)**
	≥5 years	84(34.3)
Time of preceptorship (months)	≤1 month	**105(42.9)**
	2 months	51(20.8)
	≥3 months	89(36.3)
Status of working together with preceptor nurses and a newly hired nurse	Only in the daytime shift	**162(66.1)**
	In all shifts	46(18.8)
	Mostly	26(10.6)
	Rarely	10(4.1)
	Other	1(0.4)
The status of the preceptor nurse in terms of their definition of their relationship with the newly hired nurse*	Teacher-student	**206(84.1)**
	Friend	97(39.6)
	Master-apprentice	57(23.3)
	Older sister/brother-younger sibling	51(20.8)
	Superior-subordinate/ Director-officer	24(9.8)
	Parent-offspring	3(1.2)
	Other	5(2.0)

**Multiple options were marked.*

3.3. Mentoring skills and vocational professional attitudes of preceptor nurses

The Mentorship Scale's mean score was 4.27±0.43. Coaching's mean score was 4.34±0.55. Taking a Role Model's mean score was 4.02±0.54. Self-expression and Visibility's mean score was 4.18±0.62. Counseling's mean score was 4.47±0.44. Acceptance

and Approval's mean score was 4.57±0.50. Friendship's mean score was 4.07±0.65. The minimum and maximum scores of the participants in VPAI were respectively 111 and 160, while their mean score was found as 147.42±9.56 (Table 2).

Table 2. *Mentorship Scale and VPAI total and dimension mean scores and standard deviations of the preceptor nurses (N= 245)*

Mentorship Scale	Number of Items	Minimum	Maximum	Mean (SD)
Coaching	5	1.60	5.00	4.34±0.55
Taking a role model	5	2.20	5.00	4.02±0.54
Self-expression and visibility	5	1.80	5.00	4.18±0.62
Counselling	9	2.20	5.00	4.47±0.44
Acceptance and approval	3	2.67	5.00	4.57±0.50
Friendship	3	2.00	5.00	4.07±0.65
TOTAL	**30**	**2.13**	**5.00**	**4.27±0.43**
VPAI* TOTAL	**Number of Items**	**Minimum**	**Maximum**	**Mean (SD)**
	32	**111**	**160**	**147.42±9.56**

**VPAI: Vocational Professional Attitude Inventory*

3.4. Relationship between mentoring skills and vocational professional attitude of preceptor nurses

The relationship between the Mentorship Scale total and dimension mean scores and the VPAI mean scores of the participants were found to be positively significant (p<.001), but this relationship was on a weak level (r=.39). The relationship was weak in the total Mentorship Scale (r=.39) and the dimension of coaching (r=.40), weak in the dimensions of taking a role model (r=.235), counseling (r=.29), friendship (r=.28), and very weak in the dimension of acceptance and approval (r=.19) (Table 3). For the "r" value, the results were considered to indicate 0.00-0.25: very weak, 0.26-0.49: weak, 0.50-0.69: medium, 0.70-0.89: high, 0.90-1.00: very high relationships (20).

Table 3. *Comparison of the preceptor nurses' views on the mentoring process and the total and sub-dimension mean scores of the mentoring scale*

Preceptor nurses' views		Mentoring Scale total and sub-dimensios						
		Coaching	Taking a role model	Self – expression and visibility	Counselling	Acceptance and Approval	Friendship	TOTAL
Status of working as preceptor nurses voluntarily	Yes	4.37±,51	4.07±.52	4.20±.60	4.50±.41	4.59±.49	4.09±.62	4.30±.40
	No	4.21±.6	3.81±.57	4,04±.70	4.34±.53	4.51±.57	3.97±.75	4.14±.53
		t: 1.842 p: .067	**t: 2.999 p: .003**	t:1.654 p: .099	**t:2.364 p: .019**	t:.940 p: .347	t:1.137 p: .257	**t: 2.444 p: .015**
Status of having attended a training program on preceptorship	**Yes**	4.43±.48	4.11±.49	4.24±.59	4.54±.38	4.64±.46	4.14±.65	4.34±.38
	No	4.21±.61	3.90±.58	4.08±.66	3.38±.49	4.48±.55	3.97±.63	4.17±.48
		t:3.175 p: .002	**t: 2.981 p: .003**	**t:1.990 p: .048**	**t: 2.864 p: .005**	**t:2.309 p: .022**	**t: 2.060 p: .040**	**t:3.219 p: .001**
Time of preceptorship (months)	≤1 month[a]	4.32±.60	3.95±.56	4.18±.64	4.46±.48	4.56±.54	3.93±.70	4.24±.47
	2 months[b]	4.11±.49	3.96±.57	4.08±.59	4.30±43	4.42±53	3.91±.57	4.12±39
	≥3 months[c]	4.49±.46	4.15±.48	4.22±.62	4.59±35	4.67±42	4.32±.54	4.39±37
		F:8.436 p: .0001 b< a, c	**F:3.907 p: .021 a<c**	F: .854 p: .427	**F:7. 579 p: .001 b<c**	**F:3.989 p: .020 b<c**	**F: 11.372 p: .0001 b<c**	**F:7.270 p: .001 a, b<c**
Status preceptor nurse and the supervised nurse working together	In all shifts	4.50± .52	4.02± .55	4.24± .67	4.63± .38	4.66± .44	4.38 ± .55	4.41± .38
	Other	**4.30± .59**	4.02± .53	4.16± .61	4.43± .44	4.55± .52	4.00± .65	4.24± .44
		t=2.206 p=.028	t=.842 p= .400	t=.748 p= .455	**t=2.801 p= .005**	t=1.296 p= .196	**t=3.682 p= .000**	**t=2.370 p= .019**

p<.05¸p<.01, ***p<.001*

3.5. Preceptor nurses' mentoring process, mentoring scale total-sub-size and VPAI total mean scores of comparison

It was found that the volunteer preceptor nurses had statistically significantly higher scores on the Mentoring Scale total and role modeling (p< .005; t: 2.99), Counseling sub-dimension scores (p< .05; t:2.36), and VPAI total score (p< .05; t:1.99) compared to non-volunteers. It was found that the preceptor nurses participating in a guidance training program had statistically higher mean scores of the Mentorship Scale total and sub-dimension mean scores (p< .001; t: 3.22), and VPAI total scores (p< .05; t=2.33) than those who did not attend the training program.

The mean scores of Friendship (p< .0001; F: 11.37) Counseling (p< .001; F:7.57), Coaching (p< .001; F:8.43) sub-dimensions, acceptance and approval (p < .05; F:3.98), role modeling (p< .05; F:3.90) sub-dimension mean scores, and VPAI total scores (p> .05; F: 0.36) of nurses who guided for three months or more was found to be statistically higher than the mean scores of the nurses who guided for two months or less. The preceptor nurses who work with the novice nurses in all shifts, counseling (p<.05; t=2.80), friendship (p<.001; t=3.68) sub-dimension mean scores, Mentoring Scale total mean scores (p<.05; t=2.37), coaching (p< .05; t=2.20) sub-dimension mean scores, and VPAI total scores (p<.01; t=2.25) (Table 4) was found to be statistically higher than the mean scores of the preceptor nurses who do not work with novice nurses were statistically higher.

4. DISCUSSION

4.1. Socio-demographic and professional characteristics of preceptor nurses

This finding showed that the preceptor nurses who guided newly hired nurses in terms of achievement of their adaptation to the institution/unit/service they would start working at and preparation for the roles and responsibilities required by their jobs were qualified in terms of knowledge and skills. 63.3% of the participants worked at internal medicine units and specialized fields such as operating rooms and intensive care units. This finding may be interpreted as that newly hired nurses wanted to work in these fields first to gain professional knowledge and skills and prepare for the profession. This finding also makes one think that more preceptor nurses were employed at these specialized units as these units require more clinical guidance nursing.

4.2. Preceptor nurses' views on the guidance process

Muleya et al. stated that the willingness of the mentor is important for the mentee to be able to improve their knowledge, skills, and attitudes (14). Crisp and Cruz and Tenenbaum et al. reported that mentors need to share their knowledge, skills, and experiences based on mutual trust and volunteerism without hierarchy (22,23). This study determined that 80.8% of the participants worked as preceptor nurses voluntarily (Table 1). This finding may be interpreted as those preceptor nurses who do their jobs voluntarily will share more knowledge, skills, and experiences with novice nurses, and this will create a positive learning environment. Kurul (24) determined that the interactions of midwives who received mentorship training with students were strengthened, and their attitudes toward students increased in a positive direction. Of the participants, 58.8% had attended a training program on preceptorship (Table 1). This finding may be interpreted as that, with a guiding training program, preceptor nurses would be aware of their roles and responsibilities, improve their mentorship skills, and show a professional attitude toward nurses' who are newly hired, and therefore, the mentorship process will be affected positively.

McIntosh et al (15) stated that it is useful for nurses who have experience in the field they work in to take part in mentorship for the process to be more productive and effective, professional experience is a highly important factor in mentorship. It was determined that the participants had been working as preceptor nurses at their institution for a mean time of 4.32±3.63 years (Table 1). This finding, which was similar to those in previous studies, may be interpreted as those preceptor nurses who have been working at their institution for a long time may be qualified to both reflect the culture of the institution they work at onto newly hired nurses and help them utilize the mentorship process effectively.

While structured (formal) mentorship takes place within a certain time such as 6-12 months (25), in unstructured (informal) mentorship, this time is usually spread along a long process like 3-6 years (26). It was found that the participants guided newly hired nurses by a mean time of 1.93±0.89 months (Table 1). This finding may be interpreted as that the guiding process could not be properly structured, the guiding time was insufficient for newly hired nurses, and the guiding process should be structured in a way suitable for the time emphasized in the literature.

Lloyd et al (27) revealed that nursing students who worked on the same shift as their mentors spent more time on education activities regarding the clinical field in comparison to those who did not. It was determined that 66.1% of the participants worked together with the preceptor nurses who guided them only during the daytime shift (Table 1). This finding may be interpreted as that, due to the "duty to achieve adaptation of newly hired nurses to the service/unit" and as they worked in the daytime shift, clinical head nurses that constituted 39% of the sample had the newly hired nurses they supervised work in the daytime shift, too.

4.3. Mentoring skills and vocational professional attitudes of preceptor nurses

In their studies with instructors, Özkalp et al (19), Noe (18), and Altuntaş (28) reported high mentorship skills. It was determined that the mentorship skills (total scale and all dimension mean scores) of the participants were high (4.27±0.43) (Table 2). This finding may be interpreted as that the participants had mentorship skills such as displaying a positive point of view towards newly hired nurses in

the mentorship process, supporting their development, contributing to their career development, discussing their thoughts and feelings, giving them responsibility, and providing feedback for their development.

In the literature, the vocational professional attitudes of nurses have been mostly reported as medium-level (19,29,30) and high (16,17). The vocational professional attitudes of the participants were found to be high (147.42±9.56) (Table 2). This may be interpreted as that the participants had vocational professional attitudes such as paying importance to work discipline, having responsibility, finding patient safety important, working in collaboration with colleagues, and acting tolerantly towards them.

4.4. Relationship between mentoring skills and VPAI of preceptor nurses

Astrove (31) determined a positive relationship between the career development and learning outputs of newly hired employees and the professional attitudes of mentors. Altıok (32) reported that the mentorship role of preceptor nurses that play a role in training, especially newly graduated nurses is highly important, newly hired nurses expect approval from their mentors, and this support is effective on the vocational professional attitudes of nurses. Muleya et al. (14) revealed that mentees want to work with mentor nurses who display a professional attitude. Çelik (33) found that, in librarian training, as the professional attitudes of mentors increased, the effectiveness of the guiding process also increased by providing mentees with the opportunity for systematic learning and development. Lentz and Allen (34) concluded that professional attitude and organizational commitment have a positive relationship with mentorship. Wu et al (35) reported that the mentorship role of preceptor nurses that play a role in training distinctly newly-hired nurses is highly important, newly-hired nurses expect approval from their mentors, and this support is effective on the vocational professional attitudes of nurses. It was determined that, as the mentorship skills of the participants increased, their vocational professional attitudes also significantly ($p< .001$) (Table 2). This finding indicated that preceptor nurses who have supportive, helpful, and professional traits have positively developed vocational professional attitudes.

4.5. Preceptor nurses' views on the mentoring process and mentoring scale total-sub-size and VPAI comparison of total score averages

Astrove (31) found that volunteerism in the mentoring process is among the factors that directly affect the quality of the mentoring relationship. It was determined that preceptor nurses who voluntarily engaged in guidance nursing had a higher average role model and counseling sub-size scores than those who did not voluntarily engage in guidance nursing ($p<.05$) (Table 4). This finding can be interpreted as an increase in the mentoring skills of preceptor nurses who volunteer as guidance nurses in role modeling and counseling. Although no similar studies are measuring the professional attitude of clinical guidance nurses, studies are showing that the level of professional attitude of nurses who love and willingly perform their profession is higher (36). It was determined that preceptor nurses who voluntarily performed had a higher average score ($p< .05$) than those who did not (Table 4). This finding can be interpreted as the preceptor nurses who do their profession voluntarily, willingly, and fondly having higher professional attitudes.

In many studies in the literature, it has been pointed out that the competence required to provide mentoring service can only be gained after the mentoring training, and the training of mentor and mentee training is insufficient in less than three days (8,31,37). For an effective mentoring process to occur, structured mentor training programs for mentors and mentees must be implemented before the process begins, and activities related to the development of mentoring skills should be included in the content of the training programs. It was determined that the mentoring total scale of all sub-size score averages and VPAI total score averages of preceptor nurses participating in a guidance-related training program were higher than those who did not receive training ($p< .05$) (Table 4). Although no similar research has been found, Karadaş et al. (2018) (38) concluded that continuing education should be encouraged in maintaining the professionalism of nurses. This finding can be interpreted as training in guidance nursing has an important place in ensuring the professional development of preceptor nurses, developing professional attitudes, and ensuring the continuity of qualified nursing services.

Vatan (39) suggested that the 6-month mentoring process was found to be insufficient in her study and that the process should take longer. In the literature, it is stated that the mentoring process should take at least one year to be effective (40). In the research, preceptor nurses who guided for three months or more had higher mean scores on the Mentoring Scale ($p< .001$), coaching ($p< .001$), role modeling ($p< .05$), counseling ($p< .001$), acceptance and approval ($p< .05$), friendship ($p< .001$) sub-dimension scores (Table 4). This finding can be interpreted as the counseling period that should be carried out for a longer period to develop the guidance relationship between the preceptor nurse and the novice nurse. Vatan (39) showed that increasing the number of mentors' and mentees' interviews increases the effectiveness. Hayes (40) stated that for mentees to feel more competent in inpatient care, the mentor and mentee should work together in the same clinical environment. It was determined that preceptor nurses working with newly hired nurses in all shifts had a higher VPAI total score average, in the sub-dimension of coaching, counseling, and friendship scores were higher than those who worked with the newly hired nurses in other shifts ($p< .01$). This finding can be interpreted as the fact that the preceptor nurse spends more time on the counseling task by working with the novice nurse in all shifts, increasing professional attitude. The preceptor nurse who works with the newly hired nurse on all shifts devotes more time to them in the guidance process, strengthening the knowledge and skills of self and the novice nurse.

Limitations of the Study

For the study, applications were made to ten hospitals where preceptor nursing was applied in Istanbul and Kocaeli. Only six of the applicant hospitals gave the institution permission for research. The study is limited to the preceptor nurses employed at two private hospitals, two university hospitals, and two research and training hospitals in the provinces of Istanbul and Kocaeli in Turkey and the nurses' self-reports. It cannot be generalized to all preceptor nurses. The findings obtained from this study were collected with self-reported measurement tools based on participants' perceptions.

5. CONCLUSION

The preceptor nurses who participated in this study had high levels of mentorship skills. The participants also had high levels of vocational professional attitudes. As the mentorship skills of the participants increased, their vocational professional attitudes also increased significantly, but this relationship was weak level. It was found that the volunteer preceptor nurses had statistically significantly higher scores on the Mentoring Scale total and role modeling, counseling sub-dimension scores, and VPAI total score compared to non-volunteers.

It was found that the preceptor nurses participating in a guidance training program had statistically higher mean scores of the Mentorship Scale total and sub-dimension mean scores, and VPAI total scores than those who did not attend the training program. The mean scores of friendship, counseling, and coaching sub-dimensions, acceptance and approval, role modeling sub-dimension mean scores, and VPAI total scores of nurses who guided for three months or more were found to be statistically higher than the mean scores of the nurses who guided for two months or less.

The preceptor nurses who work with the novice nurses in all shifts, counseling, friendship sub-dimension mean scores, Mentoring Scale total mean scores coaching sub-dimension mean scores, and VPAI total scores were found to be statistically higher than the mean scores of the preceptor nurses who do not work with novice nurses were statistically higher.

It is recommended that;

- Structured Mentor Training Programs should be prepared to ensure that the mentoring process of preceptor nurses takes place effectively and efficiently, the outputs of these programs should be evaluated, and existing programs should be improved and structured.
- The preceptor nursing process should be structured for at least 3 months or longer.
- The labor planning of the preceptor nurse should be made by keeping the training process in mind until the orientation of the newly hired nurse ends, and the workload of the preceptor nurse in the mentorship process should be reduced,
- Preceptor nurses should be chosen from among nurses who volunteer to give training.
- The preceptor nurses should serve as guide nurses after receiving the preceptor training course.
- Preceptor nurses should work with newly hired nurses in all shifts day and night during the guidance process.
- Qualitative or quantitative/qualitative (mixed) quasi-experimental or action research should be carried out on structured preceptor nurse training and practices.

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Clinical and Experimental Health Sciences

Validity and Reliability of the Turkish Version of the Gastroesophageal Reflux Disease Quality of Life Questionnaire

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ABSTRACT

Objective: Gastroesophageal reflux is a disease that is common in society and affects quality of life. The aim of the present study was to test the validity and reliability of the Turkish version of the Gastroesophageal Reflux Disease Quality of Life scale.

Methods: A total of 161 patients with gastroesophageal reflux disease who applied to the gastroenterology outpatient department of a university hospital between July 2017 – October 2017 constituted the sample of this study. The study was a methodological and descriptive study. In the validity and reliability studies, the language validity, content validity, internal consistency (Cronbach's alpha reliability coefficient) and confirmatory factor analysis methods were used.

Results: The Cronbach's alpha reliability coefficient of the Gastroesophageal Reflux Disease Quality of Life scale was α = 0.885, while its content validity ranged between 0.84-0.92. According to confirmatory factor analysis, the 4-factor structure of the scale, consisting of 16 items, generally had good fit.

Conclusion: The Turkish version of the Gastroesophageal Reflux Disease Quality of Life scale was found to be a valid and reliable scale that can be used to measure the quality of life of individuals diagnosed with gastroesophageal reflux disease.

Keywords: Gastroesophageal reflux; questionnaire; quality of life; reliability; validity; scale.

1. INTRODUCTION

Gastroesophageal reflux disease (GERD) is a prevalent disease of the upper gastrointestinal tract, typically characterized by heartburn and the escape of stomach contents into the esophagus. Recent studies indicated that the prevalence of GERD is 27.8% in North America, 25.9% in Europe, 7.8% in East Asia and 33.1% in the Middle East. In Turkey, the prevalence of GERD was determined to be 22.8%. Symptoms of the disease include pyrosis dysphagia, regurgitation, bitter water coming into the mouth, odynophagia, lump in the throat, laryngitis, asthma, coughing and chest pain unrelated to the heart (1-3). These symptoms can severely affect the daily lives of individuals with GERD (4). Furthermore, complications such as ulcers, strictures, bleeding, adenocarcinomas, vocal cord granulomas, laryngeal cancer, aspiration pneumonia, asthmatic bronchitis and Barrett's esophagus may develop in GERD patients (5). It was reported patients experience difficulty in moving, changes to their nutrition patterns, disruptions in their social relations and daily lives, and sleep deprivation as a result of their symptoms, severity of symptoms and complications that develop (4,6). Therefore, it is important to evaluate the quality of life of GERD patients.

It is indisputable that quality of life is evaluated in various disease cases. Studies conducted about quality of life provide the opportunity to determine how patients respond to diseases and solutions for problems that occur during treatment. When planning the development of a special care system regarding gastrointestinal disorders, the individuality of the disorders and quality of life should be taken into consideration (7). Although the evaluation of patients quality of life in assessing the effect of GERD symptoms on the health status of patients is increasingly considered as an indicator of medical outcome, the evaluation of patients quality of life in clinical studies is difficult due to the limited number of standard assessment tools specific to the disease (8). It is recommended that quality of life be evaluated with disease-specific quality of life scales in addition to general quality of life (9,10). Determining quality of life with a disease-specific scale is important for nurses in terms of evidence-based practice and decision making.

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Scales developed to assess the quality of life of people with gastrointestinal diseases include Quality of Life Reflux and Dyspepsia (QOLRAD), the Gastrointestinal Quality of Life Index (GIQLI), the Functional Digestive Disorders Quality of Life Questionnaire (FDDQL), the GERD Health-Related Quality of Life (GERD-HRQL), the Quality of Life After Anti-reflux Surgery (QOLARS) questionnaire and Gastroesophageal Reflux Disease Quality of Life Scale (GERD-QOL) (11). Of these scales, only QOLRAD was adapted into Turkish (12). GERD-HRQOL is used before and after anti-reflux surgery (11), which does not include all GER patients. GERD-QOL is a scale specific to GERD, which can be applied to patients diagnosed with reflux in any condition, with or without reflux surgery. GERD-QOL was chosen because there is no scale specific to GERD, which has validity and reliability in our country, and to contribute to the literature and make up for this deficiency. In this regard, this study aimed to determine the validity and reliability of the Turkish version of the Gastroesophageal Reflux Disease Quality of Life Scale (GERD-QOL), which is a disease-specific scale developed by Chan et al. (13).

2. METHODS

2.1. Type of Study and Ethical Aspect

The study was conducted methodologically. Prior to conducting the study, permission was obtained from the author who developed the GERD-QOL scale and the institution where the study was conducted. Finally, approval was obtained from the Medicine Faculty Ethics Committee (Ethics Committee Approval Number: 71522473 / 050.01.04 / 13-22.12.16). Before the patients were included in the study, the informed consent form was signed by the patients after the purpose of the study was verbally explained to them.

2.2. *Study Population and Selection Criteria*

The population of the study consisted of 1162 GERD patients who applied to the gastroenterology clinic. The sample of the study was composed of patients who were diagnosed with GERD by the physician at the clinic, agreed to participate in the study, met the inclusion criteria and had no communication issues. As scale validity-reliability studies require the sample size to be at least five times or ten times the number of items on the scale to be validated (14,15), a sample of 160 patients was determined to be sufficient for this particular scale containing 16 items. The study was eventually completed with 161 patients.

2.3. Design of Study

2.3.1. Gastroesophageal Reflux Disease Quality of Life Scale

The GERD-QOL scale developed by Chan et al (13) in 2009 consists of 16 items and four sub-dimensions, namely daily activity (DA) (Cronbach's alpha: 0.882), treatment effect (TE) (Cronbach's alpha: 0.771), diet (DI) (Cronbach's alpha: 0.644) and psychological well-being (PW) (Cronbach's alpha: ,0.771). Sleep, exercise, rest, work and social effects are evaluated in DA (items 2, 4, 5, 8, 10, 11, 12, 13), discomfort or side effects caused by medical treatment in TE (items 3, 7, 14), worries and anxieties of the patient in PW (items 15, 16) and diet in DI (items 1, 6, 9) (13). In the five-point Likert type scale, 4 points is given for "strongly disagree", 3 points for "partially disagree", 2 points for "neutral", 1 point for "partially agree" and 0 points for "strongly agree". Each item is based on the recollection of dominant reflux symptoms encountered in the last seven days. The scoring of a single sub-dimension is in the range of 0-100, while the total score for the four sub-dimensions varies between 0 and 400. The sub-dimension and total score calculations of the scale are given below. A low score obtained from the scale refers to poor quality of life. The higher the score, the less effect GERD has on the patient. In the calculation of the scores for the sub-dimensions, the points of the items are added together.

DA: (Q2+Q4+Q5+Q8+Q10+Q11+Q12+Q13)*100/32

TE: (Q3+Q7+Q14)*100/12

DI: (Q1+Q6+Q9)*100/12

PW: (Q15+Q16)*100/8

The total score for the scale is calculated by DA+TE+DI+PW/4.

The GERD-QOL scale was created for GERD patients to determine the effect on their quality of life of their symptoms in the last week. There is no time/hour interval recommended by the developers of the scale.

2.3.2. Study Location and Date of The Research

The study was carried out at the gastroenterology clinic of a university training and research hospital in Turkey between July 2017 and October 2017.

2.3.3. Data Collection

In the first stage of the data collection process, studies for language validity were carried out in order to adapt the GERD-QOL scale to Turkish and determine the validity and reliability of the scale. Before the study, permission was obtained from the author, the developer of the scale, via e-mail. The back translation method was used to translate the scale. Within this scope, the original scale was translated into Turkish separately by five experts who are fluent in both Turkish and English. The most appropriate expressions were selected and the Turkish version of the scale was created based on the adaptation of the translated scale to the original scale. For content validity, the scale was sent to 13 experts, who were asked to evaluate whether the Turkish translation of the scale was compatible with the original scale. The necessary changes were made in line with feedback and recommendations received and the Turkish version of the scale was finalized. Then, the Turkish scale was sent to two experts in the Turkish language field to be evaluated in terms of grammar and wording and the necessary changes were made in accordance with their recommendations. The scale was then translated back into

English by a foreign language lecturer, whose native tongue is Turkish and who did not know anything about the scale, without seeing the English format of the scale. The final version of the scale in English was sent back to the author who developed the scale for approval. After his suggestions, the necessary corrections were made again.

The content validity of a scale is important to determine whether the items in the original scale have the same meaning in the language and culture the scale is adapted to. In this study, the Davis technique was used, in which expert opinions are graded as (a) appropriate, (b) item should be slightly reviewed, (c) item should be seriously reviewed and (d) item is not suitable. In this technique, the number of experts who mark options (a) and (b) is divided by the total number of experts in order to calculate the content validity index (CVI). The value of 0.80 is accepted as the criterion without comparing the calculated value with any statistical criterion (16,17). The number of experts in this study to which the GERD-QOL scale was sent to was 13.

The primary purpose of confirmatory factor analysis (CFA) is to determine the ability of a previously defined factor to match the observed data set. Whether a measurement developed in the past is appropriate to be used in a different society is important when testing scales (18). In some cases, it may be sufficient to only perform confirmatory factor analysis in the adaptation of a scale from a foreign language into Turkish (19). In this study, the CFA method was used in the evaluation of the validity of the scale.

Reliability is an indicator of the stability of the scores obtained in repeated measurements under the same conditions with a measurement tool (20,21). Internal consistency is the calculation of the homogeneity of the questions for a criterion that are assumed to measure a certain area and whether the questions measure only the desired concept. One of the methods used to measure internal consistency is Cronbach's alpha coefficient (17,22). In this study, the Cronbach's alpha ($\alpha = 0.885$) coefficient was calculated in the reliability analysis of the GERD-QOL scale.

2.4. Data Analysis Process

This study was carried out with a total of 161 patients. The data were analyzed by transferring them to the Statistical Package for Social Sciences (SPSS) version 23 and SPSS Analysis of Moment Structures (AMOS) version 23 programs (IBM Corp.; Armonk, NY, USA). In the study; the back translation method was used to measure the language validity of the scale, expert opinions were obtained for content validity, Cronbach's alpha coefficient was calculated in order to determine the internal consistency. The CFA method was used to determine the validity of the scale.

3. RESULTS

In this study, 44% of the patients were between the ages of 20 and 40 years, 76.4% were married, 83.9% had a core family structure, 41.6% were primary school graduates, 65.7% were unemployed, 44.1% had an equal income-expense balance, 55.9% were smokers, and 93.2% did not consume alcohol. According to the body mass index (BMI) of the patients, 32.9% were overweight while 31.7% were obese. The duration to receive a reflux diagnosis was 61.61±74.78 months and, in addition to GERD, 51.6% of the patients had another disease diagnosed by a physician (data not shown in the Table).

3.1. Content Validity

The CVI values of the items were calculated by the 13 experts to range between 0.84 and 0.92. The Davis technique was applied to determine the content validity of the scale, after the language equivalence studies were completed. No item was removed from the scale as all values were 0.8 or higher. The arithmetic mean and standard deviation values for the items on the GERD-QOL scale are presented in Table 1.

Table 1. *GERD-QOL scale expression averages*

	Mean±SD	Min-Max
GERD-QOL 1	1.90±1.685	0.0 – 4.0
GERD-QOL 2	1.43±1.560	0.0 – 4.0
GERD-QOL 3	2.24±1.654	0.0 – 4.0
GERD-QOL 4	2.10±1.629	0.0 – 4.0
GERD-QOL 5	2.39±1.597	0.0 – 4.0
GERD-QOL 6	1.67±1.669	0.0 – 4.0
GERD-QOL 7	2.49±1.538	0.0 – 4.0
GERD-QOL 8	1.68±1.719	0.0 – 4.0
GERD-QOL 9	1.62±1.628	0.0 – 4.0
GERD-QOL 10	1.60±1.686	0.0 – 4.0
GERD-QOL 11	2.27±1.609	0.0 – 4.0
GERD-QOL 12	2.94±1.340	0.0 – 4.0
GERD-QOL 13	2.15±1.633	0.0 – 4.0
GERD-QOL 14	2.16±1.683	0.0 – 4.0
GERD-QOL 15	1.27±1.593	0.0 – 4.0
GERD-QOL 16	1.44±1.608	0.0 – 4.0

GERD-QOL: Gastroesophageal Reflux Disease Quality of Life Scale
Mean: Average, SD: Standard Deviation, Min: Minimum,
Max: Maximum

3.2. Construct Validity of the Gastroesophageal Reflux Disease Quality of Life Scale

3.2.1. Confirmatory Factor Analysis

Confirmatory factor analysis was performed with the IBM SPSS AMOS 22 program on the data set with 161 samples. In the first stage, the first-degree CFA model consisting of latent variables (4-factor dimension: DA, TE, DI, PW) and indicator variables (expressions forming the factors/dimensions) was created (Figure 1). In order to estimate the parameter values of the non-metric latent variables, the factor in one of the paths drawn from the latent variables to the indicator (observed) variables should be equal to 1 or a value (usually 1) should be assigned to the variance of the latent variable (23).

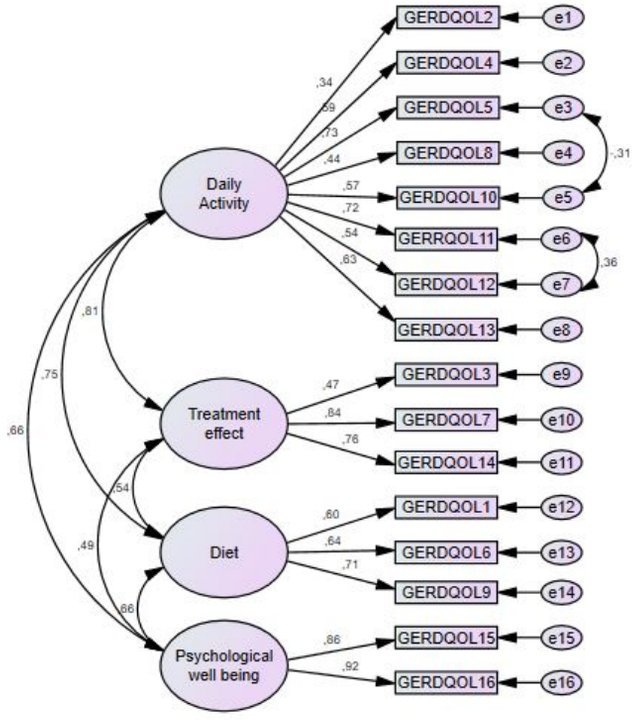

Figure 1. *1st Degree CFA model with 4 sub-dimensions*

In the second stage of the confirmatory factor analysis, the maximum likelihood method was applied, which provides reliable results even when the data is not normally distributed in estimating the model and used in structural equation models. By doing so, the aim was to estimate the variances of DA, TE, DI, and PW (latent variables), the regression coefficients for the paths drawn from the latent variables to the observed variables, and parameters including the errors of the observed variables. In order to improve the fit indexes, a bilateral relationship was established between the error terms of questions "GERD-QOL 5" and "GERD-QOL 10", "GERD-QOL 11" and "GERD-QOL 12" in the GERD-QOL scale, which had the highest modification index (fit index) values. However, a relational addition was made between the dimensions in order to determine the correlation expected between the dimensions. The relationship between the dimensions is shown in Figure 1.

In the final stage, the fit indexes were evaluated for the first-degree CFA model developed with four dimensions. Considering the results, it was determined that the four-factor structure of the GERDQOL scale consisting of 16 items fitted well in general.

Considering the fit values given in Table 2, the values for Chi-square/degree of Freedom (χ2/df), Incremental Fit Index (IFI), Comparative Fit Index (CFI), Root Mean Square Error of Approximation (RMSEA) and Standardized Root-Mean Square Residual (SRMR) were good, while the values of Turker-Lewis Index (TLI) were unacceptable (24–27). In general, it can be said that the GERD-QOL scale was acceptable in terms of goodness of fit index values.

Table 2. *Fit indexes of CFA model*

Index	GERD-QOL Fit Index	Good Fit	Acceptable Fit	Result
χ2/df	1.903	0 ≤ χ2 /df ≤ 3	3 <χ 2 /df ≤ 5	Good Fit
GFI	0.869	0.95 ≤ GFI ≤ 1	0.90 ≤ GFI<0.95	Unacceptable Fit
IFI	0.911	0.95 ≤ IFI ≤ 1	0.90 ≤ IFI <0.95	Acceptable Fit
TLI	0.886	0.95 ≤ TLI ≤1	0.90 ≤ TLI <0.95	Unacceptable Fit
CFI	0.909	0.95 ≤ CFI ≤ 1	0.90 ≤ CFI < 0.95	Good Fit
RMSEA	0.075	.00 ≤ RMSEA ≤ .05	0.05< RMSEA ≤ 0.08	Acceptable Fit
SRMR	0.0684	.00 ≤ SRMR ≤ .05	0.05< SRMR ≤ 0.10	Acceptable Fit

χ2/df= Chi-square/degree of Freedom; GFI= Goodnessof Fit Index; IFI= Incremental Fit Index; TLI= Turker-Lewis Index; |CFI= Comparative Fit İndex; RMSEA= Root Mean Square Error of Approximation; SRMR= Standardized Root-Mean Square Residual; GERD-QOL: Gastroesophageal Reflux Disease Quality of Life Scale

3.2.2. Reliability Analysis

In the internal consistency analysis performed to determine the reliability of the scale, Cronbach's alpha value was calculated. The Cronbach's alpha values for the sub-dimensions of the scale were between 0.694 and 0.882, while this value was found to be 0.885 for the entire scale (Table 3).

Table 3. *Reliability of the scale and its sub-dimensions*

		Questions	Item-Total Correlation	Cronbach's Alpha	
GERD-QOL Scale	Daily Activity Sub-Dimension	GERD-QOL 2	0.367	0.791	0.885
		GERD-QOL 4	0.553		
		GERD-QOL 5	0.618		
		GERD-QOL 8	0.429		
		GERD-QOL 10	0.517		
		GERD-QOL 11	0.632		
		GERD-QOL 12	0.484		
		GERD-QOL 13	0.557		
	Treatment Effect Sub-Dimension	GERD-QOL 3	0.417	0.724	
		GERD-QOL 7	0.601		
		GERD-QOL 14	0.570		
	Diet Sub-Dimension	GERD-QOL 1	0.479	0.694	
		GERD-QOL 6	0.497		
		GERD-QOL 9	0.601		
	Psychological Well-Being Sub-Dimension	GERD-QOL 15	0.606	0.882	
		GERD-QOL 16	0.647		

GERD-QOL: Gastroesophageal Reflux Disease Quality of Life Scale

4. DISCUSSION

When a scale is translated into another language, items should contain meaningful expressions in the language it is translated into. The items should be simple and easy to understand after translation. The use of terms and idioms that the target population will have difficulty in understanding

should be avoided. Three translation methods can be used in the adaptation of a scale into another language. These are back-translation, one-way translation and group translation(19,28). In this study, the back-translation method was used for the translation of the GERD-QOL scale into Turkish.

Validity is "*the ability to measure a characteristic that a measuring tool aims to measure accurately without involving any other characteristics".* As validity is required to be in line with the purpose of a scale, it can vary depending on the purpose, method of application, and the group to which it is applied. The level of validity is determined by calculating the validity coefficient, which has a value between – 1.0 and +1.0. The higher the correlation coefficient, the better the scale serves its purpose (17,20). There are many methods such as content validity, criterion validity and construct validity that can be used to ensure the validity of a scale. In this study, the content validity and construct validity (CFA) methods were used.

The values for all of the items in the GERD-QOL scale were above the standard CVI value of 0.8. Therefore, it can be said that content validity was achieved.

Construct validity is calculated in order to evaluate to what extent the items on the valid scale can measure the desired characteristic. There are four methods, namely factor analysis (explanatory and confirmatory), comparison of contrast or known groups, hypothesis testing, and multivariate-multi-method matrix approach, that can be used to determine construct validity (17,19,29). When developing a new scale, explanatory factor analysis should be performed before confirmatory factor analysis. Confirmatory factor analysis is sufficient when adapting a scale from a foreign language to Turkish (19). Thus, in this study, confirmatory factor analysis was performed.

According to the data in the literature, the $\chi 2/df$ value should be equal to or less than five to be acceptable. For a good fit, the RMSA value should be equal to or less than 0.08, the SRMR value should be less than 0.1, the CFI value should be equal to or greater than 0.9, the IFI value should be 0.9 and, the Goodness of Fit Index (GFI) and TLI values should be above 0.9 (18,19). In this study, the scale was acceptable as the calculated CFA sub-dimensions were within the value ranges proposed in the literature.

The GFI statistics in confirmatory factor analysis performed for the purpose of construct validity should be at the determined level to ensure the construct validity (19).

In accordance with the information in the literature and considering the goodness of fit data in this study, it was observed that the $\chi 2/df$, IFI, CFI, RMSEA and SRMR values were good, while the GFI and TLI values were not within the acceptable limits (Table 2). In accordance with the goodness of fit indexes, it was determined that the GERD-QOL scale was acceptable and its structure with four factors containing 16 items had good fit.

Reliability is "the degree in which a measuring instrument measures the variable it wants to measure with consistency or the degree of how free the measurement results are from errors" (17). In addition, it is the consistency of the measurement value calculated in the repeated measurements under the same conditions by using the same scale (20). A scale with either no reliability or low reliability is considered to have low scientific value (19).

Internal consistency is an indicator of the homogeneity of the questions in a scale and whether or not they measure the desired concept. The main view of internal consistency is the assumption that all scale items, that are autonomously developed to achieve a specific goal in a scale, are known and have equal weights (17).

Cronbach's alpha reliability coefficient is calculated to determine whether the items are reliable in measuring the same dimension (19,30). "It is a weighted standard change average calculated by dividing the sum of the variances of k items by the general variance in the scale"(17). As the Cronbach's alpha coefficient approaches 1, the internal consistency of the items is higher. Furthermore, a coefficient value between 0.6 and 0.7 indicates that the scale has sufficient reliability level, while a coefficient value between 0.7 and 0.9 indicates that it has a high level of reliability (17).

Implications for Clinical Practice, the Gastroesophageal Reflux (GER) is a chronic and recurrent disease(31). Lifestyle change has great importance in the management of chronic diseases. The care, training and consultancy services provided by healthcare professionals for chronic diseases that negatively affect quality of life are very important. It is important to choose appropriate tools that measure the health dimensions of patients' private life to evaluate health-related quality of life (32). The GERD-QOL scale is a scale specific to GERD. Using a scale with proven validity and reliability, it is possible to determine which dimension of quality of life is particularly affected in patients with GERD at the individual level. In line with the results obtained with this scale, the needs of the individuals will be determined, the right interventions can be made for these needs, and the quality of life of patients can be improved by increasing the quality of the care service provided. In addition, since the GERD-QOL scale is short (16 items), it will provide the advantage of easy application by nurses in the clinic. The scale is simple for patients to understand and does not contain medical terms. Patients can easily understand and answer the scale questions. This scale is a useful and extensive tool for nurses and another healthcare professionals to assess the quality of life of patients with GERD.

The limitations of the study can be listed as only covering GERD patients in the outpatient clinic, and not evaluating the presence of comorbidities and effect of disease severity on quality of life. It can also be said that collecting data through face-to-face interviews may have increased the clarity of some elements. Test-retest reliability could not be performed because GER-QOL had measured the last week.

5. CONCLUSIONS

In this study, the Cronbach's alpha reliability coefficients of the GERD-QOL scale and its sub-dimensions were calculated. According to the results obtained, the Cronbach's alpha values were found to be 0.885 for the entire scale and between 0.694 and 0.882 for the sub-dimensions. Based on these results, all the items in the scale measure the same characteristic. The characteristics measured by the GERD-QOL scale are homogeneous, and thus, the GERD-QOL scale is a reliable measurement tool.

When the results of the language equivalence, content validity, internal consistency (Cronbach's alpha reliability coefficient) and construct validity (CFA) are evaluated as a whole, it was concluded that the Turkish version of the GERD-QOL scale is a reliable and valid scale that can be used for patients with GERD.

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Design of the study: HS, ST
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Clinical and Experimental Health Sciences

Digital Evaluation of the Depth and Width of Upper and Lower Molar Cavity Preparations of Dental Students

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ABSTRACT

Objective: The aim of this study was to evaluate the mesial and distal seat widths and the buccal, lingual, and axial wall height values of cavity preparations by measuring them with the help of a digital scanner.

Methods: In this study, 70 randomly selected students of 140 tooth preparations (mandibular molar and a maxillary molar cavities) of phantom jaw models were evaluated. The prepared teeth were scanned with an intraoral scanner. The parameters used in the analysis were the depth values of the buccal and lingual (or palatal) wall depth, the mesial and distal axial wall height, and the mesial and distal seat width values. For main effects and interactions, two-way analysis of variance was used, and for multiple comparisons, Tukey's test was used ($p < .05$).

Results: No significant difference was found in the teeth according to cavity depth. However, a significant difference was found in the cavity regions' depths or widths. There was no difference between the total buccal (1.93 ± 0.01 mm) and lingual (1.91 ± 0.32 mm) depth values. There was no difference between the total mesial (1.51 ± 0.27 mm) and distal (1.41 ± 0.26 mm) seat width values. There was no difference between the total mesial (1.11 ± 0.35 mm) and distal (1.21 ± 0.27 mm) axial wall height values.

Conclusion: It was observed that the students had more difficulty in the distal region of the tooth than in the mesial region. Digital methods in preclinical education can provide objective results in the evaluation of cavity preparations.

Keywords: Digital dentistry, tooth preparation, cavity depth, operative dentistry

1. INTRODUCTION

In dental education, students are provided with preclinical practical applications to achieve and develop their basic dental skills (1). This process includes a series of progressive stages, starting with the theoretical course and then progressing to preclinical simulation through to the clinical phase process (2). Phantom jaw models used in preclinical applications provide the opportunity to learn appropriate ergonomic working conditions and to practice the appropriate use of hand tools, such as mirrors and probes (3). Before treating the real patient in the clinic, the student is taught in preclinical practical lessons, using artificial or extracted natural teeth. For this reason, it is desired that the preclinical education of dental students who will treat patients the clinics should already include individual patient care (1). One of the important components of preclinical dental education is restorative dentistry. The practice of restorative dentistry enables students to acquire and develop manual dexterity and learn about the clinical aspects of restoration of carious or defective teeth (4).

One of the most important skills for dentists is replacing the diseased tooth structure. This skill is the main focus of undergraduate operative dentistry courses. For this reason, among the main objectives of undergraduate operative dentistry education, the education of students on making cavity preparations in teeth is important (5). The restoration should protect the remaining tooth structure, as well as create the lost tooth structure. This varies depending on the type of restoration and the material. It is important to protect the existing tooth structure, not to remove the healthy tooth structure unnecessarily, to preserve the vitality of the pulp, and to ensure retention form (6). Before going to the clinic, preclinical practice laboratories offer dental students the opportunity to learn the basic skills of operative dentistry (2). Depth perception is an important requirement in dental practice, and it is necessary not only to perceive that surfaces are at different depths but also to accurately estimate the depth within a three-dimensional object (7).

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Digitization in dentistry is a popular and expanding field, especially for the computer-aided design or computer-aided manufacture of dental restorations and devices (8). In particular, the general trend in this regard has affected laboratory practices and clinical approaches, both in computer technology and developments in industrial fields. New digital techniques will require the development of new training methods and the implementation of existing treatment protocols. The high reliability of the evaluation process regarding the performance of dental students in terms of feedback on their mistakes is essential (9). Computer-based technologies offer an opportunity to increase quality management, not only related to standardized restoration production, but also to the optimization of clinical procedures. Computer-based software ensures high processing quality and efficiency. It analyzes the examined profile (region) by scanning the full 360-degree inspection area, thus providing a comprehensive evaluation. As the parameters examined are adjustable, the intended restoration design and restorative materials can be taken into account (10).

As a result of the evaluations, the examination of the cavity depth values prepared by the dental students and measurement with the help of digital software can provide more reliable results. Therefore, the aim of this study was to evaluate the cavity depth values and mesial and distal seat width values, as well as the buccal, lingual, and axial wall height values measured with the help of a digital scanner. The null hypotheses of this study were as follows: (1) There is no significant difference between the mesial and distal seat width values and the buccal, lingual, and axial wall height values of the different tooth regions. (2) There was no significant difference between the depth values examined for different teeth.

2. METHODS

In this study, cavity preparations prepared by second-year dental students in phantom jaw models under practical exam conditions were used. Ethical approval for the study was obtained from the Necmettin Erbakan University, Faculty of Dentistry, Non-Pharmaceutical and Medical Device Ethics Committee (24.11.2022/221). Attention was paid to ensuring that the phantom jaw models used by the dental students were standard and of the same brand (Fuji, Piramit Dental, Türkiye). Cavity preparations made in phantom jaw models of 70 dental students participating in the study were examined. A total of 140 phantom teeth with MOD cavities were examined (right mandibular first molar and left mandibular first molar). Then, the teeth were scanned with an intraoral scanner 3Shape TRIOS (Copenhagen K, Denmark). The digitized models were transferred to the 3Shape 3D Viewer (Copenhagen K, Denmark) program in Standard Tessellation Language (STL) format, and three-dimensional measurements were made (Figure 1). The parameters used in the analysis are the depth values of the buccal, lingual, or palatal walls, axial wall height, and mesial and distal gingival seat width values (Figure 2 and Figure 3). In line with these parameters, it was determined that the occlusal depth was 2 mm, the axial wall height was 1 mm, and the gingival seat widths were 1.5 mm (11). In addition, according to the prepared teeth, regions were classified as upper and lower molar teeth. Digital measurements of the cavity preparations were made by two observers independently of each other.

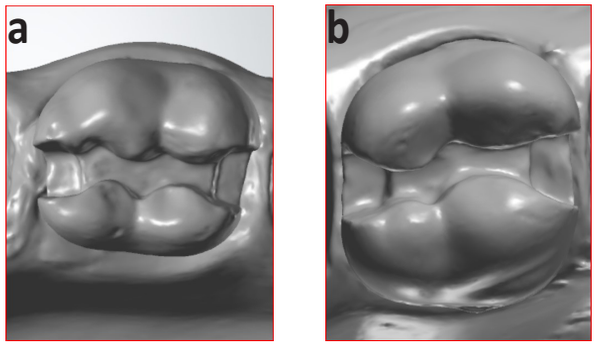

Figure 1. *a: Scanned sample lower molar tooth b: Scanned sample upper molar tooth*

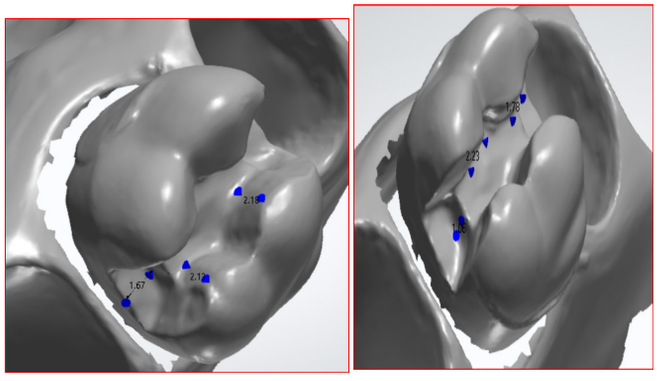

Figure 2. *Digital measurements of the sample upper molar teeth from different directions*

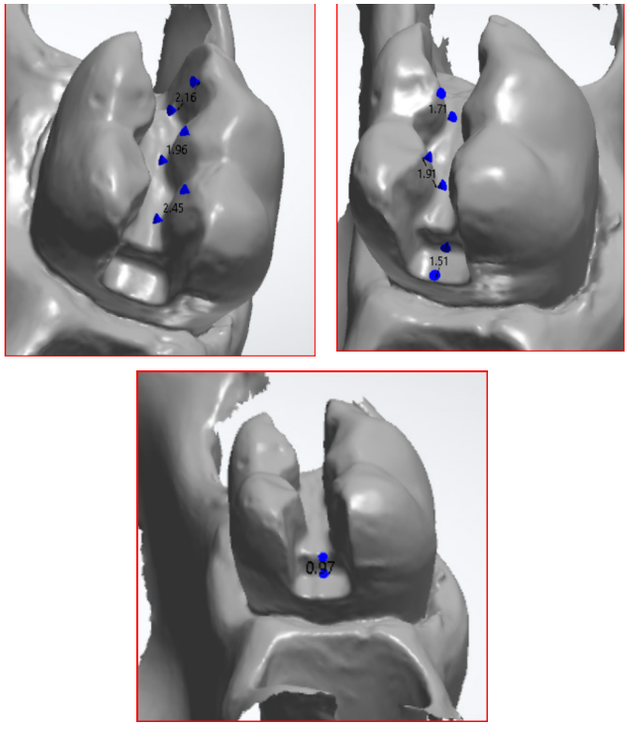

Figure 3. *Digital measurements of the sample lower molar teeth from different directions*

Statistical Analysis

The IBM SPSS Statistics for Windows (Version 23.0. Armonk, NY: USA) package program was used to perform the statistical analysis. Upon examination of the compliance of the data with the normal distribution, the decision was made by considering the Kolmogorov-Smirnov test, as well as the skewness and kurtosis values. The two-way analysis of variance was used for the depth or width of the interaction between the factors (region×tooth). If the interaction between region and tooth was not significant, the depth or width values of the analyzed variables on the main effects were evaluated by examining the total values (if the main effect was significant). The Bonferroni test was used to compare the main effects. Tukey's test was used for multiple comparisons. Partial eta squared (η^2) values are a statistical measure used to rank the effect of independent variables on dependent variables. The effect of region, tooth, and interactions on the dependent variable was also shown with partial eta squared. It was used to show the level of the main effect or the effect of the interaction on the dependent variable. The significance level of difference was set at $p < .05$.

3. RESULTS

The main effects and interactions of the investigated parameters are shown in Table 1. Descriptive values (mean ± standard deviation) are shown in Table 2. According to the two-way ANOVA results, no significant differences were found between the teeth according to the examined cavity depth or width ($p = .466$), although there was no difference between the lower and upper teeth (Table 2). However, it was determined that there were significant differences in the cavity regions according to the cavity depth or width ($p < .001$). There was no difference between the total buccal (1.93 ± 0.01 mm) and lingual (1.91 ± 0.32 mm) depth values ($p = .069$). There was also no difference between the total mesial (1.51 ± 0.27 mm) and distal (1.41 ± 0.26 mm) seat width values ($p = .069$). In addition, there were no differences between the total mesial (1.11 ± 0.35 mm) and distal (1.21 ± 0.27 mm) axial wall height values ($p = .086$).

When the agreement between the observers was examined without any discrimination, the ICC value was found to be 0.995 ($p < .001$). The correlation values obtained ranged between 0.991 and 0.998 when tooth separation was made, and the obtained values were statistically significant ($p < .001$). The correlation value was high and statistically significant, the analysis was performed by taking the average values of the observers' measurements (Table 3).

Table 1. *Two-way ANOVA results for parameters (main effects and interaction)*

Source	Type III Sum of Squares	df	Mean Square	F	p	Partial Eta Squared
region	0.048	1	0.048	0.533	.466	.001
tooth	81.947	5	16.389	183.345	< .001	.525
region × tooth	0.345	5	0.069	0.772	.570	.005

R Squared = .527 (Adjusted R Squared = .520)

Table 2. *Means and standard deviations for region and teeth. The total data in the column indicates the teeth, and the total data in the row indicates the region*

Region	36	16	Total
B	1.95 ± 0.25	1.90 ± 0.36	1.93 ± 0.31[a]
L	1.88 ± 0.23	1.93 ± 0.39	1.91 ± 0.32[a]
MB	1.49 ± 0.28	1.53 ± 0.26	1.51 ± 0.27[b]
MA	1.10 ± 0.36	1.13 ± 0.35	1.11 ± 0.35[c]
DB	1.42 ± 0.26	1.40 ± 0.25	1.41 ± 0.26[b]
DA	1.19 ± 0.24	1.23 ± 0.29	1.21 ± 0.27[c]
Total	1.50 ± 0.42[A]	1.52 ± 0.44[A]	1.51 ± 0.43

B:Buccal, L:Lingual, MB: Mesial gingival seat width, MA: Mesial axial wall height DB: Distal gingival seat width DA: Distal axial wall height
Different lower letters represent statistically significant differences in column. Different capital letters represent statistically significant differences in colum in row. There is no difference between the same letter.

Table 3. *ICC results*

	ICC (%95 CI)	p
36-B	0.992 (0.987 – 0.995)	<.001
36-L	0.991 (0.986 – 0.994)	<.001
36-MB	0.991 (0.985 – 0.994)	<.001
36-MA	0.997 (0.995 – 0.998)	<.001
36-DB	0.995 (0.991 – 0.997)	<.001
36-DA	0.995 (0.993 – 0.997)	<.001
16-B	0.944 (0.911 – 0.965)	<.001
16-L	0.998 (0.996 – 0.999)	<.001
16-MB	0.994 (0.991 – 0.997)	<.001
16-MA	0.995 (0.992 – 0.997)	<.001
16-DB	0.996 (0.993 – 0.997)	<.001
16-DA	0.998 (0.997 – 0.999)	<.001
Total	0.995 (0.994 – 0.995)	<.001

B:Buccal. L:Lingual. MB: Mesial gingival seat width. MA: Mesial axial wall height
DB: Distal gingival seat width DA: Distal axial wall height

4. DISCUSSION

In this study, the mesial and distal seat width, buccal and lingual depth, and mesial and distal axial wall heights of the lower and upper molar cavity preparations were prepared in a preclinical laboratory. The prepared teeth were measured and evaluated with the help of digital software. In this study, the evaluation of Class II cavity preparations was based on the parameters used in the previous study (11). The reasons for using these criteria for evaluation are based on their clinical significance.

Previous study should be stated that the use of amalgam in dental restorations is decreasing over the years amalgam's cost, durability and ease of manipulation have persuaded many dentists to continue to use it as their first choice for restoring posterior teeth (12). Amalgam restorations require mechanical retention, and therefore cavity design is essential for retention and resistance forms (11). Cavity forms prepared in the teeth include the preservation of the remaining tooth structure. However, with increasing cavity depth, the remaining dentin thickness may decrease,

resulting in approaching the pulp of the tooth (13). Therefore, accurate measurement of cavity depth is an important factor for evaluation. Preclinical dental education contributes greatly to the clinical practice of dental students. Preclinical laboratories in operative dentistry play an important role in the early development of psychomotor skills in dental students (11). With the increasing innovations in dentistry, it is necessary to train dental students to be fully equipped. Using approaches that help the students plan, analyze, and evaluate their work is an important part of learning (14). However, the performance results of preclinical applications cannot be directly correlated with clinical practice (15). The teeth used in this study consisted of plastic teeth used in phantom jaw models. Since this is not similar to the natural tooth structure, it cannot be attributed to the cavity depth to be created in the natural tooth, but it can provide an idea during the cavity preparation stage.

The null hypothesis of our study was that there is no significant difference between the buccal, lingual, and axial walls of the different tooth regions, the cavity depth values, and the mesial and distal seat width values, and it was rejected. Differences were detected in cavity preparations according to region. The buccal depth of the cavity was found to be closer when compared with the lingual depth of the cavity, which was measured at values closer to the cavity depth values. The fact that the students had a more comfortable viewing angle in the buccal region of the cavity in the phantom jaw model may have played a role in this situation. However, no feedback was received from the students in this study, which constitutes a limitation to the research. The fact that the mesial seat width and mesial axial height of the lower molar tooth were closer to the desired values than the distal seat width and distal axial height indicates that the students experience difficulty in the distal region (axial and gingival). This may be because they cannot fully apply indirect working principles yet. When the cavity depth or width of the lower and upper molars were evaluated (main effects), they were found to be similar. Based on these findings, our study's null hypothesis (2) was accepted. The prepared teeth were not found to be cavity depth or width significantly different, independent of the jaw.

Cavity preparation is an important skill for all dental students to acquire. Students may not understand the instructors' judgments and may think that bias exists (16). In dental education, cavity preparations are evaluated subjectively using the visual method. However, visual assessment cannot objectively inform students or evaluate the precise parameters of tooth structure removal to achieve optimal preparation (17). Evaluation of cavity preparation with digital devices may help students to be more objective in their feedback. In this study, as a result of the observers' evaluation of the values measured in the cavity, it was found that the interobserver agreement was high. With digital measurements, evaluation is possible and reliable under certain conditions (18). It has been suggested that digital working models offer advantages, such as storage feasibility, ease of retrieval of information, ease of transfer as needed, potentially equal or better diagnostic capabilities, and sending virtual images for reference or immediate consultation (19). Previous research has shown that digital measurements gave more accurate results than manual measurements because digital measurement shows a three-dimensional view, allowing for better positioning of reference points and involves measuring diameters and distances along selected planes (20). Therefore, three-dimensional digital scanning and measurement have been found to be reliable (6). In our study, three-dimensional digital scanning and measurement methods were used to achieve more reliable results and standardization. However, these systems may also have disadvantages, such as scanner-related design issues and the inability to measure certain regions exactly (16). In addition, a cavity preparation evaluation software system for dentistry was reported to be in development (21).

This study has some limitations. For example, clinical situations could not be simulated because students prepared artificial teeth in a preclinical laboratory. Clinical dentistry study is significantly more difficult than preclinical study due to changes in tongue and cheek factors, saliva, and patient-related factors. These factors that make clinical work difficult for dental students are absent from preclinical education. In addition, the shape of caries is most likely to determine the shape of the cavity in clinical conditions. Therefore, different teeth and different cavity preparations may also be investigated in future studies. If the same scanner model and certain standardizations are provided, a multicenter study can be done to express the importance of preclinical practice well. According to the findings from this study, although the results seem promising, several dental faculties in different cities can be included. In this study, student preparations were randomly selected while obtaining data, and it is not known how many points the included models received as a result of the evaluation. In addition, the students' scores and the digital assessments of the preparations can be compared in future studies.

5. CONCLUSION

As a result of the findings of this study, the cavity depth and seat width values of the teeth in cavity preparations were within acceptable limits. However, it was observed that the students had more difficulty in the distal region of the tooth than in the mesial region. More practical training is required with indirect working and working positions in dentistry education. The preparation of students with different teeth should be investigated in future studies. Digital methods in preclinical education can provide objective results in the evaluation of cavity preparations.

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Design of the study: M.F., H.Y.G.
Acquisition of data for the study: M.F., H.Y.G.
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Clinical and Experimental Health Sciences

The Effect of Structured Education on Nurses' Ventrogluteal Injection Knowledge and Skills

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ABSTRACT

Objective: For a safe intramuscular injection, it is essential to provide nurses with knowledge and skills for using the ventrogluteal site. This study was conducted to determine the effect of structured education on the knowledge and skills of nurses on ventrogluteal injection and their ventrogluteal site preference for intramuscular injection.

Methods: The study was carried out between February and December 2021. The sample consisted of 81 nurses. While training was given to the experimental group (n=46), no training was provided for the control group (n=35). The data were collected using the Information Form, Determination Form of First-Choice Site for Intramuscular Injection, Knowledge Level Form for Ventrogluteal Injection Administration, Ventrogluteal Injection Skill Checklist, and Observation Form for Determining the Choice Site for Intramuscular Injection.

Results: The experimental group's follow-up test rates of choosing the ventrogluteal site for intramuscular injection were found to be higher than those of the control group. Besides, In the follow-up data, the knowledge and skill scores of the experimental group for administering injections into the ventrogluteal site were found to be higher than those of the control group ($p<0.05$).

Conclusions: Structured education for intramuscular injection into the ventrogluteal site was an effective method to increase the nurses' knowledge and skills on ventrogluteal injection and the rate of use of the ventrogluteal site.

Keywords: Intramuscular injection, gluteal region, patient safety, education

1. INTRODUCTION

Intramuscular (IM) injection administrations were introduced in nursing practices in the early 1960s. Today, IM injections are among the most frequently administered nursing practices (1,2). Unsafe injection administrations cause severe complications and increase patient morbidity and mortality (3,4). Therefore, to define safe injection practices, nurses have investigated IM injection complications, preferred injection sites, procedures to reduce injection-related pain and injection techniques since the early 1970s (2). According to the results of previous studies, it is known that the most important determinant of a safe injection is selecting the injection site (5-7).

The site chosen for injection is required to be away from nerves, vessels and bone structures, the target muscle tissue is required to be of a thickness suitable for injection, and the subcutaneous tissue needs to be thin enough to allow access to the muscle tissue. Recent studies have reported that nurses select the dorsogluteal (DG) site as their first choice for IM injection (8-10). Nevertheless, it has been recommended to choose a site safer than the DG site for IM injection due to reasons such as that the anatomical structure of the sciatic nerve is different from what is known (the proximal part of the nerve lies closer to the head and is approximately in the midline of a line drawn in the ischial tuberosity with the great thoracic) (4), the majority of injections that are considered to be IM injections are actually made into the subcutaneous tissue (7), and the subcutaneous tissue is thick enough to prevent reaching the target muscle (6). As a result, the DG site is recommended to be avoided as the first choice (4,5,11). In the selection of the injection site, instead of DG, it is recommended to use the ventrogluteal (VG) site where large bony prominences are present, which is farther from the sciatic nerve (12), major blood vessels and where subcutaneous fat tissue is thinner (2,9). The usage rates of the VG site have been reported as 18% (13), 8.3% (9), and 7.4% (14,15) whereas the usage rates of the DG site have been reported as 64% (13), 85.4% (9) and 76.5% (14). As it may be understood from all these results, the DG site continues to be used as the first choice despite its high potential risk and the changing knowledge in the literature. The rates of using the VG site, which is a safe site, are quite low. Milutinovic et al. (9), and Arslan and Özden (13) concluded that nurses still prefer the DG site since they do not have sufficient knowledge regarding the individual elements of the application of IM injections into the ventrogluteal site, like locating the injection site by using

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the V method or the G method. It was reported that the majority of nurses gave wrong answers to statements about the choice of injection site (80%) (13), in which age groups the VG site should be used (84.1%) and what kind of drugs should be administered to which site (74.9%) (15), and the researchers concluded that nurses should be trained on this issue (13,15). Salami et al. (16) reported that 14.0% of drug administration errors due to route errors were made during intramuscular drug administration.

Considering all these data, for safe intramuscular injections within the scope of patient safety, it is an important requirement to meet nurses' knowledge and skill needs regarding the use of the VG site and increase the rate of using the VG site.

This study was carried out to determine the effect of structured education on the knowledge and skills of nurses on VG injection and their preference for the VG site for intramuscular injection.

2. METHODS

2.1. Ethics Approval

Ethics committee approval and institution approval was obtained (Decision no 09.2019.161, dated 09.2019). The participants were informed about the purpose of the study, and their written consent was obtained. In the implementation of the research process, the World Medical Association (WMA) – Ethical Principles for Medical Research Involving Human Subjects were adhered to.

2.2. Design, Sample, and Setting

This study was conducted using a pretest-posttest randomized-controlled trial design and was carried out between February and December 2021.

The population included nurses working in a private university hospital. The sample consisted of those among this population who met the inclusion criteria (having at least one year of experience working in clinics where adult patients are cared for) and agreed to participate. The required sample size for the study was calculated by performing a power analysis. Based on the study by Amanak (17), the sample size was calculated to be 30 individuals in each group considering the effect size of 0.4, a confidence interval of 95%, and a test power of 95%. Considering the possibility of data loss, each group was planned to consist of 60 people. To create the sample, clinics that provide care for adult patients were determined. For the homogeneous distribution of the internal and surgical clinics in the experimental and control groups, the clinics were divided into two groups surgical and internal clinics. Among these groups, the clinics to be included in the experimental and control groups were determined by the randomization method. To prevent interaction between the participants, it was ensured that all nurses in the same clinic were assigned to the same group. As a result, 60 nurses were assigned to the experimental group, and 52 nurses were assigned to the control group (Figure 1).

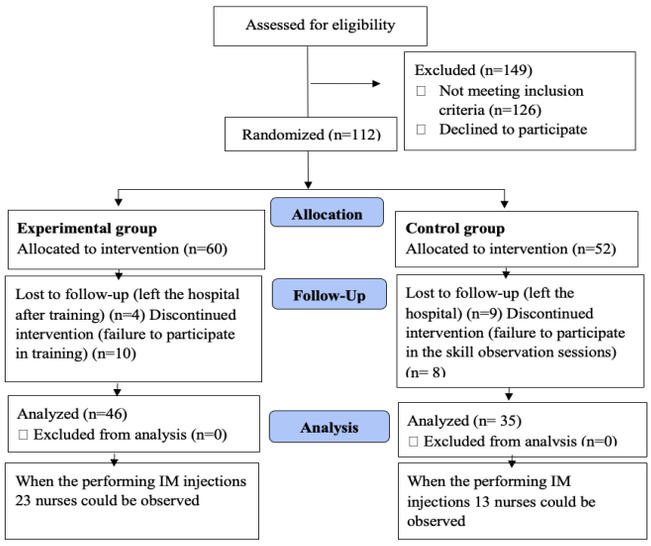

Figure 1. *CONSORT diagram of the study*

2.3. Study Questions

Does structured education on administering injections into the VG site increase the knowledge and skill levels of nurses for the use of the VG site?

Does structured education on administering injections into the VG site increase the use of the VG site?

2.4. Instruments

Data were obtained with an Information form, a Determination form of the first-choice site for IM injection, a Knowledge level form for VG injection administration, a VG injection skill checklist, and an Observation form for determining the choice site for IM injection.

Knowledge level forms for VG injection administration and VG injection skill checklist were submitted to three nurses, who are professors in nursing, and two clinical nurses in the hospital. After making necessary arrangements in line with the feedback that was received from these experts, the forms were finalized.

2.4.1. Information Form

The form consisted of six questions aiming to determine the demographic data of the participants.

2.4.2. Determination Form of First-Choice Site for IM Injection

The form consisted of seven questions aiming to determine the participants' use of the VG site and the sites they preferred in IM injection administration. In this form, there are questions about specifying the first preferred IM injection site and marking the first preferred site on a figure.

2.4.3. Knowledge Level Form for VG Injection Administration

This form, prepared to determine the participants' level of knowledge on VG injection, consisted of 28 statements that could be marked as "true" or "false." There were a total of 16 correct statements and 12 false statements. Each right answer was scored as 1 point, and each wrong answer was scored as 0 points, while the lowest and highest scores that could be obtained on the form were 0 and 28. The response time was 20 minutes. Form was prepared by reviewing the literature (10,14,18).

2.4.4. VG Injection Skill Checklist

The checklist consisted of 19 process steps aiming to evaluate the participants' ability to administer IM injection into the VG site. The lowest and highest scores that could be obtained on the checklist were 0 and 19. The form was prepared by reviewing the literature (10,14,18).

2.4.5. Observation Form for Determining The Choice Site for IM Injection

The form was prepared to determine the site chosen by the participants during their clinical applications of IM injection. In the form, the observer was asked to mark one of the two options; the nurse chose the VG region or not chose the VG region for IM injection.

2.5. Implementation

First interview the information form, the determination form of first-choice site for IM injection and the knowledge level form for VG injection administration were applied (pretest). One week after the first interview the participants who filled out the forms were invited for skill observations on scheduled dates. Skill observations were made in three sessions on three different days, with a maximum of 20 people per session. The participants were asked to administer an IM drug into the VG site on a manikin. In the meantime, they were evaluated with the VG injection skill checklist (pretest). The same researcher made all skill observations.

While collecting pretest data the participants were informed that they would be observed in the clinic during IM injection administrations in terms of selecting injection sites. However, they were not told when and by whom the observation would be made.

Following the pretest data collection, the participants included in the experimental group were given an invitation with the date and time they were going to attend the education program (two weeks after the first interview). The material of the education program was prepared in Microsoft PowerPoint and supported by images and videos taken by the researcher. The educational content covered the topics of IM injection, IM injection sites, selection of the VG site, administration method of injection into the VG site, and pre-and post-procedure evaluation methods in injection. In terms of the conformity of the education content, opinions were obtained from five experts in relevant fields. The education program was held on three different days, two sessions per day, for six sessions. A checklist was also used to ensure that all components of the education program were provided in each education session. Each participant in the experimental group attended the education program once. Each session included 10-12 participants, and it lasted 40 minutes in total. Following the education program, the knowledge level form for IM injection administration (posttest) was applied. Then, the participants were asked to perform injection administration into the VG site on a manikin. These injection administration practices of the participants were evaluated with the VG injection skill checklist (posttest).

The IM site selections of the participants in both groups were determined by observing them with the observation form for determining the choice site for IM injection four weeks after their first interview. It was aimed to observe each participant once while they were performing IM injections. For this purpose, observations were made by visiting clinics at three different treatment hours (single-blind). Since no drug required IM injection in the treatment of the patients of some participants, or the BMI of their patient was not suitable for injection into the VG site (3 patients in the experimental group and 2 patients in the control group, BMI>25 kg/m^2), only 23 nurses could be observed in the experimental group, and 13 nurses could be observed in the control group.

Sixteen weeks after the first interview, all participants were asked to fill the knowledge level form for IM injection administration into the VG Site (follow-up test) and the determination form of first-choice site for IM injection (follow-up test). Following the filling of the forms (after one week), the participants were invited for skill observations, and their IM injections administered into the VG site were evaluated using the VG injection skill checklist (follow-up test) (Figure 2.)

In the literature, it is reported that at least three weeks should pass for the development of behavior change after the education aimed at gaining skills. The time required to measure the permanence of knowledge has been reported as 3-6 months (19,20). For this purpose, in this study, IM injection skill was assessed four weeks after the education and knowledge of IM injection at VG Site sixteen weeks after the education.

After the data collection process was completed, training was given to the nurses in the control group in order to ensure equal opportunity.

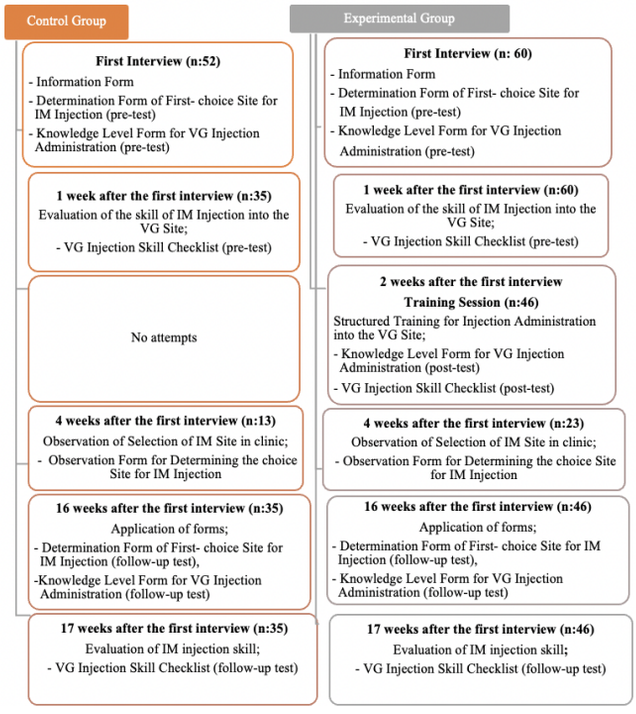

Figure 2. *Flowchart of the research*

2.6. Data Analysis

Descriptive statistical methods (percentage, mean, standard deviation) were used while analyzing the data obtained in the study. Pearson's Chi-Squared test was used for the categorical variables between the two groups. In the intergroup comparisons, the Mann-Whitney U test was used for the non-normally distributed data. Wilcoxon signed-rank test was used for the intragroup comparisons, and Friedman F-test for repeated measures was utilized for more than two groups.

2.7. Limitations

Besides, failure to observe all nurses in the groups during the clinical observation (since there was no IM injection in the treatment) is one of the limitations of this study.

3. RESULTS

Table 1 shows the demographic characteristics of the individuals participating in the study. When the experimental group and the control group were compared in terms of features that would affect the data of the study, no significant difference was found between the two groups (p>0.05) (Table 1).

Table 1. *Demographic characteristics of the groups*

Results		Experimental group (n:46)		Control group (n:35)		Test statistics	P
		n	(%)	n	(%)		
Age	**Mean (±SD)**	23.22(±4.23)		24.67(±1.90)		606.0*	**0.052**
Gender	Female	35	76.1	26	74.3	0.035**	**1.000**
	Male	11	23.9	9	25.7		
Educational Level	Medical-Vocational High School	16	34.8	12	34.3	0.513**	**0.329**
	Associate Degree	5	10.9	8	22.9		
	Undergraduate	24	52.2	13	37.1		
	Postgraduate	1	2.2	2	5.7		
Years of Work	0-1 year	17	37.0	15	42.8	0.415**	**0.813**
	2-5 years	13	28.2	10	28.6		
	Five and <5 years	16	34.8	10	28.6		
Field of Work	Surgical Units	22	71.0	12	46.2	3.617**	**0.070**
	Internal Units	9	29.0	14	53.8		
Status of Receiving Education for VG Injection	Yes	28	60.9	24	68.6	3.437**	**0.494**
	No	18	39.1	11	31.4		
***** How long ago was the education received?**	0-1 year	16	57.1	15	65.2	0.913	**0.613**
	1-2 years	5	17.9	2	8.7		
	Two and < 2 years	7	25.0	6	26.1		
Number of Injections per week Median (IQR)		10 (5-30)		8 (4-28)		348.50*	**0.572**

Notes: * *Mann-Whitney U,* ** Pearson's Chi-Squared, ****Those who had received education previously were analyzed.*
Abbreviations: VG: Ventrogluteal; *IQR: interquartile range*

The participants were evaluated in two ways: by asking participants to fill out the determination form of the first-choice site for IM injection and by making observations during IM injection with the observation form to determine the participants' site choice for IM injection. In line with the answers given to the form, in the pretest, it was found that 80.4% of the experimental group (n:37) and 88.6% of the control group (n:31) preferred the DG site as their first choice (p=0.539). In the follow-up test, it was determined that 82.6% of the experimental group (n=40) and 14.4% of the control group (n=5) preferred the VG site as their first choice (p=0.002). When the participants in the groups were observed in the clinic regarding the site they chose for IM injection, it was found that 87% (n: 20) of the 23 observed participants in the experimental group preferred the VG site. In comparison, 0% (n:0) of the 13 observed participants in the control group preferred the VG site (p=0.000) (Table 2).

Table 2. *Comparison of the groups in terms first-choice site for IM injection*

Results		Experimental group		Control group		Test statistics	P
		n:46	%	n:35	%		
First-Choice Site Pretest	VG	3	6.6	2	5.8	0.560	0.539
	DG	37	80.4	31	88.6		
	Deltoid	0	0	0	0		
	Femoral	4	8.7	1	2.8		
	Latero Femoral	2	4.3	1	2.8		
First-Choice Site Follow-up Test	VG	38	82.6	5	14.4	4.511	0.002
	DG	4	8.8	28	80.0		
	Deltoid	0	0	0	0		
	Femoral	2	4.3	1	2.8		
	Latero Femoral	2	4.3	1	2.8		
		N (23)	%	N (13)	%		
Clinical Observation	VG	20	87	0	0	25.435*	0.000
	DG	3	13	13	100		

Notes: ** Pearson's Chi-Squared*
Abbreviations: *VG, Ventrogluteal; DG, Dorsogluteal*

Comparing the groups in terms of their scores on the knowledge level form for VG injection administration, the experimental group's follow-up score was found to be higher than that of the control group (p=0.000). Besides, the follow-up knowledge level scores of the experimental group were higher than their posttest and the pretest scores, and their posttest scores were higher than their pretest scores (p=0.000). The follow-up test scores of the participants in the control group were found to be higher than their pretest scores (p=0.005) (Table 3).

Table 3. *Comparison of the groups in terms of scores of knowledge level for VG injection administration*

Results	Experimental group Median (IQR)	Control group Median (IQR)	Test statistics	P
Pretest (a)	19 (16-21)	19 (16-21)	760.0*	0.471
Posttest (b)	25 (25-27)			
Follow-up test (c)	26 (25-28)	21 (19-23)	0.000*	0.000
Test statistics	38.072**	-2.824***		
P	0.000	0.005		
Post hoc****	b>a, c>a, c>b			

Notes: ** Mann-Whitney U test ** Friedman F test *** Wilcoxon signed-rank test ****Wilcoxon signed-rank test – - – Bonferroni correction was made and considered as p=0.001 significant.*
Abbreviations: *IQR=interquartile range*

When the groups were compared in terms of their VG injection skill scores, the follow-up score of the experimental group was found to be significantly higher than that of the control group (p=0.000). The posttest score of the experimental group was found to be higher than their pretest score, and their follow-up test score was higher than their posttest and pretest scores (p=0.000) (Table 4).

Table 4. *Comparison of the groups in terms of VG injection skill scores*

Results	Experimental group Median (IQR)	Control Group Median (IQR)	Test statistics	P
Observation pretest (a)	10 (8-11)	10 (8-11)	795.50*	0.928
Observation posttest (b)	18 (8-20)			
Observation follow-up test (c)	19 (8-20)	8 (8-11)	242.00*	0.000
Test statistics	80.595**	-0.577***		
p	0.000	0.564		
Post hoc****	b>a, c>a, c>b			

Notes: ** Mann-Whitney U test ** Friedman F test *** Wilcoxon* signed-rank test **** Wilcoxon signed-rank test – - – Bonferroni correction was made and considered as p:0.001 significant.
Abbreviations: *IQR=interquartile range*

4. DISCUSSION

IM injection, one of the invasive procedures applied by nurses, has an essential place in treating patients. It is a safe way of administering drugs that are desired to be absorbed quickly (faster subcutaneously and orally, slower through the venous route) and has highly intense and irritating effects. However, the prerequisite for achieving the desired effect is that the administration should be made in the correct injection site, with the proper technique, into the right tissue (muscle) (2,9).

In the pretest data of this study, the majority of the participants in both groups stated that they chose the DG site as their first choice. The number of participants who stated that they preferred the VG site was very low in both groups (p=0.539) (Table 4). It was remarkable that although more than half of the participants were newly graduated and had received education to administer injections into the VG site in their undergraduate education, their usage rates of the VG site were low (Table 1). According to all these results, despite the knowledge gained in undergraduate education about the VG site, newly graduated nurses use traditional methods. It is believed that one of the reasons for this was the fact that although newly graduated nurses want to use the VG site in line with their education, they cannot find any opportunity. As stated in the literature, the rate of nurses using the VG site in clinics was found to be low due to the lack of sufficient knowledge about the use of the area, not having applied to this area before, and the area being close to the bones (8,9,15). In terms of patient safety, newly graduated nurses are not allowed to practice alone, and they are asked to perform all drug administrations under the guidance of a clinic nurse. It is possible that clinic nurses who did not have any knowledge about this issue might not have allowed newly graduated nurses to use the VG site. Thus, the knowledge and skills that are not used in the first years of the profession cannot turn into a settled behavior.

In the pretest, the knowledge and skill levels for injection into the VG site were intermediate in both groups (p>0.05) (Table 2-4). The knowledge and skill levels of the nurses were not sufficient for IM injection, which requires psychomotor skills and causes serious complications. Studies have reported that nurses have low levels of knowledge and skills to apply IM injection to the VG site and suggested planning structured education or in-service training initiatives on this topic (9,10,21). Our findings were compatible with the literature, and the necessity of attempts to increase the level of knowledge and skills about VG injection was revealed once again.

In the follow-up-test data, 16 weeks after the structured education program given to increase the nurses' use of the VG site, their knowledge and skill levels, it was determined that the majority of the experimental group chose the VG site, and the control group chose the DG site (observation form for determining the choice site for IM injection) (p<0.005). Moreover, the knowledge and skill levels of the experimental group for injection administration into the VG site were found to be significantly higher than those of the control group (p>0.05) (Table 3-4). In the intragroup comparisons, it was observed that the knowledge and skill level follow-up test scores of the experimental group were higher than their posttest scores, while their posttest scores were higher than their pretest scores, indicating improvement. In the control group, the knowledge level follow-up test scores were found to be higher than the pretest scores (p=0.05). However, no significant difference was found in the skill level scores of the control group (p=0.564) (Table 3-4). Based on these findings, it was thought that the education program contributed to the increase in the experimental group's rate of using the VG site and the increase in their knowledge and skill levels, and the participants' adoption of knowledge and skills regarding the practice of IM injection into the VG site (Table 2) provided the increase in the follow-up test. The increase in the posttest knowledge level of the control group was accepted as the pretest effect.

These results clearly showed that the education program increased the rates of using the VG site among the participants. In the education program, it was emphasized that in addition to the technique of administering an injection into the VG site, complications related to the use of the DG site, the advantages of using the VG site, and safe IM injection are the responsibilities of the nurse. The nurses were recommended to use the VG site for IM injections. Furthermore, factors such as the fact that the education program was conducted in a clinical setting, theoretical education was reinforced with demonstration, the participants had the opportunity to apply the information right after the education program were considered essential in the effectiveness of the education program that was provided. It was concluded that these initiatives provide positive results in increasing the effectiveness of education. In the literature, there are some studies about nurses' choices of site for IM injection (8,9,10,22), pain control (23) and needle length to be used (6), whereas studies examining skill levels are limited (16,24). In this study, the skill levels of the nurses were objectively observed and evaluated. This situation increases the reliability of this study's data collected and analysed. The results obtained on this topic are also important in terms of their contribution to the literature.

5. CONCLUSION

Although injection into the VG site is presented in the nursing literature and taught in nursing curricula, nurses continue to use the DG site for intramuscular injection. Based on the findings in this study, it was observed that the education program conducted in the experimental group was an effective method to increase nurses' knowledge and skill levels in administering injections into the VG site and their rates of VG site use. Both for patient safety and for nurses not to be confronted with the law, recommendations are; Organizing and implementing similar education programs must be done, the region selections of the nurses working in the clinic should be observed at regular intervals and regulatory initiatives should be planned in line with the findings and training on site selection and administration methods in IM injection should be repeated at regular intervals.

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Clinical and Experimental Health Sciences

The Relationship Between Hand Preference and Mandibular Asymmetry: A Preliminary Study

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ABSTRACT

Objective: The objective of this study was to evaluate the relationship between functional laterality (hand preference) and mandibular asymmetry in skeletal Class I, normodivergent patients.

Methods: 21 left-handed and 40 right-handed Class I normodivergent patients were included in the study. The hand preferences of the participants were determined by using the Oldfied hand preference questionnaire. Mandibular condylar height (CH), ramal height (RH), and total height (CH+RH) were measured on pretreatment panoramic radiographic images of the patients, and asymmetry values were obtained according to the formula of asymmetry indices. Data were analyzed with the Student's t-test and Pearson chi-square.

Results: Right and left CH values were greater in left-handed patients than in right-handed patients. Right and left RH and CH+RH values were greater in right-handed patients than in left-handed. However, there was no difference between the measurements ($p > .05$). There was no significant relationship between the functional values and hand-use preference ($p > .05$).

Conclusions: Hand use preference was not associated with condylar, ramal, and total mandibular asymmetry.

Keywords: Hand preference, facial asymmetry, functional laterality, malocclusion, panoramic radiographs, orthodontics

1. INTRODUCTION

Directional asymmetries are divergences of bilateral symmetry that appear by choice on the right or left side (1). The asymmetry of the skull is also reported to be directional and appears as larger left sphenoid, malar, and occipital bones compared to the right, while the parietal, temporal, and frontal bones differ in opposite and the internal length of the skull is smaller on the left than the right (2). Interestingly; directional craniofacial asymmetries have been related to cerebral asymmetries associated with functional lateralities (such as hand, foot, and eye preferences used in daily activities) (3,4). Hand preference is the most investigated type of functional laterality and is defined as the typical preference of one hand over the other in various tasks performed in daily life (5). While the left hemisphere of right-handed individuals is reported to be dominant, the right cortex of individuals with left-handedness is defined as the dominant hemisphere to a large extent (6). It has been suggested that the asymmetrical development of brain regions may be causing the asymmetric craniofacial structures (4) and the asymmetric craniofacial structures can be expected to be reflected in lower facial asymmetries or malocclusions (7). Hand use preference that was reported to be accompanied by cerebral asymmetries (6) was previously associated with facial asymmetry (4,8), unilateral Angle Class II malocclusions (9), hemifacial microsomia (10), and unilateral crossbites (11) Since mandibular asymmetry, which can naturally occur in most subjects (12) is reported to be the primary marker of facial asymmetry (13) it can be expected that functional laterality, handedness, may be associated with mandibular asymmetry.

Studies on this topic are quite old. The aim of the present study is to evaluate the relationship between the ramal, condylar, and total mandibular asymmetry and functional laterality (hand preference) in skeletal Class I, normodivergent patients and to present a current perspective.

2. METHODS

This study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine, Akdeniz University (Approval number: KAEK-450) before the commencement of the present study.

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2.1. Data Collection

Data were collected from the Akdeniz University, Faculty of Dentistry, Department of Orthodontics archives between 2012 and 2020. Pretreatment panoramic radiographs of 150 patients with no previous orthodontic treatment history, dental Class I molar relationships, ANB angle (0° ≤ ANB ≤ 5°; skeletal Class I relationship), normodivergant (28° ≤ SNGoGN ≤ 36°) vertical skeletal pattern, nonocclusions or posterior crossbites in transverse plane were evaluated (13).

The following radiologic inclusion criteria were used for digital panoramic radiographic images (DPRIs) of selected patients: *(1) the presence of normal coronoid processes and the condyle in DPRIs, (2) the presence of all teeth germs whether a third molar germ exists or not, (3) no acquired or developmental neuromuscular or craniofacial deformities and (4) no history of trauma.* DPRIs wherein temporomandibular joint pathology or craniofacial trauma was suspected, poor image quality with horizontal distortions, wherein anatomic landmarks for performing linear measurements were not visualized, were excluded. Considering the exclusion criteria, a total of 61 participants were included in the study.

The Oldfied hand-use preference questionnaire (14) modified by Geschwind and Behan (15) was transferred to the “Google Forms” (Google Inc., California, USA) website, and a special link for the survey was created. the created link was delivered to the participants via “WhatsApp” (Meta Inc, California, USA). The patients were informed about the questionnaire and the questionnaire was filled out voluntarily. At the top of the questionnaire, there was a statement that the participants participated in the study voluntarily.

This questionnaire consists of 10 questions (Figure 1). Response options were evaluated as “always with the right hand” (+ 10 points), “usually right hand” (+ 5 points), “with both hands” (0 points), “usually with left hand” (-5 points), and “always with the left hand” (-10 points). The results obtained as a result of scoring were evaluated according to the score of Geschwind and Behan (15-17) According to the score of Geschwind and Behan, the sum of the above scores determines the laterality score. The distribution of points is as follows: Strong right-hand users: +80 to +100 poiright-handright hand users: +20 to +75 points, both-handed: – 15 to +15 points, weak left-hand users: – 20 to – 75 points, anleft-handleft hand users: – 80 to – 100 points. In this study, individuals with a score of +20 to +100 were considered “right-handedness”, and individuals with a score of – 20 to – 100 were considered “left-handedness”. Both – handed (-15 to +15 points) participants and patients who incompletely filled out the hand-use preference questionnaire were not included in the study.

	always right	usually right	both hand	usually left	always left
Writing					
Painting					
Throwing					
Holding scissors					
Holding toothbrush					
Holding knife					
Holding spoon					
Holding handle for a shovel					
Striking a match					
Twisting off the lid of a jar					

Figure 1. *Ten questions of the Oldfied hand preference questionnaire which was modified by Geschwind and Behan (15)*

2.2. Mandibular Dimensions

DPRIs were gained with the same device (Planmeca ProMax; Planmeca Oy, 00880 Helsinki, Finland) by the same x-ray technician. All DPRIs were assessed using the same monitor by the same observer (H.T.A.) who has eight years of experience in oral radiology. Ten DPRIs were evaluated per day for preventing observer fatigue.

Anatomical points and lines were detected according to Habets et al. (18) (Figure 2) and linear measurements were measured on DPRIs on both the right and left sides:

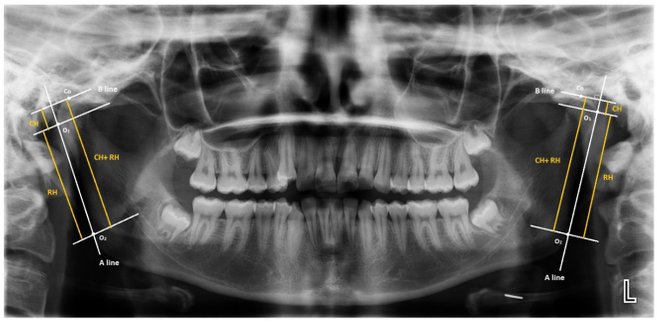

Figure 2. *Linear measurements on the panoramic radiographic image: Co: the most superior part of the condyle; O1 and O2: the most lateral points of the condyle; A line: a ramus tangent B line: a perpendicular line from Co to A line; CH: Condylar height; RH: Ramal height; CH+RH: Total height*

Condylar height (CH): measurement between Co and O1 points

Ramal height (RH): measurement between O1 and O2 points

Total height (CH+RH): measurement between Co and O2 points

All measurements were automatically calibrated by the Planmeca Romexis 4.0 software program, which was developed for the Planmeca ProMax machine (Planmeca Oy, 00880 Helsinki, Finland).

The asymmetry indices were obtained by the following formula:

Asymmetry Index (AI) = [(Right – Left)/(Right + Left)] × 100

The value obtained as a result of the formula was recorded as "asymmetry presence" if ≥ 3%, and as " asymmetry absence" if < 3%. If the measurements made on the left are greater than the right, negative values were obtained as a result of the formula, and in the presence of a negative value, it was accepted that the left side was more dominant than the right side.

After 4 weeks, all measurements were repeated for all patients, and intra-observer variability was assessed.

2.3. Statistical Analysis

Data were statistically analyzed by using IBM SPSS Statistics (version 23.0, IBM, Armonk, NY). Quantitative variables among the groups were compared using the student's t-test. Pearson chi-square test was used to analyze the difference between categorical variables. Intra-observer reliability for numerical data was assessed by the interclass correlation coefficient. Because the intra-observer reliability was high, initial measurements were used for analysis, and statistical significance was accepted at $p < .05$.

3. RESULTS

The correlation coefficient was high and it was above 0.90 in all measurements. A total of 61 participants, including 40 females (65.6%), and 21 males (34.4%) were included in the study. The mean age was 13.52 ± 3.1 years (the age range was between 10 and 25 years). There were 41 (67.2%) right-handedness participants and 20 (32.8%) left-handedness participants. No statistically significant relationship was found between hand use preference and gender and age ($p > .05$). 42 (68.9%) of the participants had condylar asymmetry, 23 (37.7%) had ramal asymmetry and 22 (36.1%) had total asymmetry. No statistically significant relationship was found between gender and condylar, ramal, and total asymmetry ($p > .05$). In addition, there was no significant relationship between age and condylar, ramal, and total asymmetry ($p > .05$). Table 1 presents the number of female and male patients according to right-handedness, left-handedness, condylar asymmetry, ramal asymmetry, and total asymmetry.

Table 2 presents the descriptive data of measurements for both sides, regardless of the hand-use preference. The differences between the right and left side measurements of the CH, RH, and CH+RH weren't significant ($t(120) = – .668$, $p > .05$ for CH, $t(120) = – .387$, $p > .05$ for RH, and $t(120) = – .498$, $p > .05$ for CH+RH).

Table 3 presents the comparison of the right and left side measurements according to hand preference. There was no significant difference between the right and left side measurements of the CH, RH, and CH+RH considering the hand use preference ($p > .05$)

Table 4 presents the comparison of all measurements in right-handedness and left-handedness. While right and left CH values were greater in left-handedness than right-handedness, right and left RH and CH+RH values were greater in right-handedness than left-handedness. However, there was no significant difference between the measurements ($p > .05$).

Table 5 presents the relationships between the hand use preference and AI values and AI measurements of the condyle, ramus, and condyle+ramus were not statistically affected by the hand use preference ($p > .05$).

Table 1 *Number of female and male patients*

Gender	Right handedness (n)	Left handedness (n)	CA presence (n)	CA absence (n)	RA presence (n)	RA absence (n)	TA presence (n)	TA absence (n)
Female	26 (%63,41)	14 (%70)	29(%69,05)	11(%57,89)	14(%60,87)	26(%68,42)	14(%63,64)	26(%66,67)
Male	15 (%36,59)	6 (%30)	13(%30,95)	8 (%42,11)	9 (%39,13)	12(%31,58)	8 (%36,36)	13(%33,33)
p	.611		.396		.547		.811	

n: number of patients; %: percentages; CA: condylar asymmetry, RA: ramal asymmetry; and TA: total asymmetry

Table 2 *The mean, standard deviation, minimum, maximum and p values of the condylar, ramal and condylar+ramal height measurement for the left and right sides*

Parameter	n	Mean (mm)	SD	min	max	t	p
right CH	61	8.22	2.09	4.1	14.9	-.668	.505
left CH	61	8.47	2.05	4.7	15.4		
right RH	61	59.48	9.07	41.7	79.1	-.387	.699
left RH	61	60.14	9.63	42.8	78.8		
right CH+RH	61	67.7	9.65	47.6	89.9	-.498	.620
left CH+RH	61	68.6	10.44	47.5	93.1		

CH: condylar height; RH: ramal height; CH+RH: total height; n: number of patients; mm: millimeter; SD: standard deviation; min: minimum; max: maximum

Table 3. *The comparison of the right and left side measurements according to hand preference*

	right handedness			
	right mean (mm) ± SD	left mean (mm) ± SD	t	p
CH	8.13 ± 1.75	8.24 ± 1.51	-.302	.764
RH	61.2 ± 7.78	61.78 ± 8.99	-.312	.756
CH+RH	69.33 ± 7.91	70.02 ± 9.53	-.355	.723
	left handedness			
CH	8.41 ± 2.7	8.95 ± 2.84	-.616	.541
RH	55.96 ± 10.62	56.77 ± 10.26	-.247	.806
CH+RH	64.36 ± 12.04	65.72 ± 11.84	-.359	.722

CH: condylar height; RH: ramal height; CH+RH: total height; mm: millimeter; SD: standard deviation

Table 4 *Comparison of all measurements in the right handedness and left handedness*

Parameter	Hand preference	n	Mean (mm)	SD	min	max	p
right CH	right hand	41	8.13	1.75	4.10	13	.636
	left hand	20	8.4	3.7	4.9	14.9	
left CH	right hand	41	8.24	1.52	5.1	11.6	.309
	left hand	20	8.95	2.84	4.7	15.4	
right RH	right hand	41	61.2	7.78	47.60	79.10	.059
	left hand	20	55.96	10.62	42.7	75	
left RH	right hand	41	61.78	8.99	44.16	78.80	.56
	left hand	20	56.78	10.26	42.8	77.7	
right CH+RH	right hand	41	69.33	7.91	53.6	87.80	.132
	left hand	20	64.36	12.04	47.6	89.9	
left CH+RH	right hand	41	70.02	9.53	52.61	87.3	.590
	left hand	20	65.71	11.84	47.5	93.10	

CH: condylar height; RH: ramal height; CH+RH: total height; n: number of patients; mm: millimeter; SD: standard deviation; min: minimum; max: maximum

Table 5 *The relationships between the AI values and the hand use preference*

parameter	groups	mean(%)	SD	min	max	t	p
condylar AI	right handedness	7.23	5.9	0.54	25.15		
	left handedness	6.59	5.4	0.59	20.51	-.407	.686
ramal AI	right handedness	2.88	2	0.07	7.9		
	left handedness	2.39	2.24	0.08	9.4	-.852	.397
total AI	right handedness	2.36	1.73	0.29	6.8		
	left handedness	2.65	2.46	0.11	10.15	.542	.590

AI: asymmetry index; SD: standart deviation; min: minimum; max: maximum

4. DISCUSSION

Although hundreds of behavioral asymmetries have been identified as a result of hemispheric asymmetry, the most obvious one is hand preference (7). Most of right-handers are reported to be right-eyed and right-footed and they have their skills represented in the left cerebral hemisphere, whereas left-handers have less anatomical symmetry in the brain (9). Since it has been reported that hand preference may be associated with cerebral asymmetries and therefore with craniofacial asymmetries (6), it has been claimed in some studies that there may be a relationship between handedness and orthodontic anomalies such as facial asymmetry (4,8) and unilateral Angle Class II malocclusions (9). Facial asymmetries and orthodontic malocclusions were also related to condylar and ramal mandibular asymmetries (19,20). In the present study, it was aimed to evaluate the relationship between the condylar and ramal mandibular asymmetries and functional laterality, and hand preference.

Some researchers have criticized the use of questionnaires because their results have been found conflicting compared with direct observations. On the other hand; observational evaluations have also been reported to be unclear because manual functions can be learned equally with both hands (21). It has been shown that the determination of the dominant hands of the individuals with only one action (such as writing or observation) does not generally reflect the result; it is stated that the correct result is reached with the hand preference questionnaires (22,23) The most frequently used Oldfied questionnaire was preferred in the current study because it is simple, easy to understand, and suitable for all ages and the reliability of the questionnaire has also been demonstrated (24-26). According to this questionnaire hand use preference is grouped in three ways: right-handedness, left-handedness, and ambidextrous. Ambidextrous participants were excluded from the current study to be able to avoid bias in the results.

Such a consistent and strong preference for behavior on one side is unique to humans, though hand preference has been observed in some other primates (27). The factors that determine hand-use preference may be genetic or environmental (28). It has been reported that 90% of human subjects consistently choose their right hand for dexterous duties (29). Similar to the study Tan, 67.2% of the participants in the present study were determined as right-handed and 32.8% were left-handed (17).

AI formula was used in studies in which mandibular vertical asymmetry was found to be related to different malocclusion types such as unilateral crossbites (19), Angle Class II malocclusions (30), and temporomandibular disorders (31-33). To eliminate the effect of the relationship between the malocclusions and mandibular asymmetry; skeletal Class I and normodivergent patients were included in the present study.

Facial asymmetry has been accepted as an inherently occurring phenomenon in most subjects (13). While many researchers reported that the right side of the face is more developed than the left side (34,35), there are also studies claiming the opposite (4,8). In the present study mean CH, RH, and CH+ RH values were higher on the left side than the right side but this difference was also not significant.

It was suggested that an asymmetric development of brain regions related to functional laterality may cause the

asymmetric development of facial regions (4). Smith reported that cognitive duties that involve one hemisphere more than the other may result in higher muscle size and activity, on the side of the face which is controlled by that hemisphere (35). Besides, right-handedness was associated with a greater ethmoid roof on the left side and a larger left side of the brain (4,8,36). Keleş et al concluded that facial areas on the left were significantly larger than those on the right in right-handers and the left-handers tended to have larger facial areas on the right (4). Parallel to that findings; the left facial region was found larger for right-handers than left-handers (8). Gary et al. investigated the frequency of left-handedness in patients with hemifacial microsomia in which the predominant side of involvement was right in 49 % (10). They reported that patients with hemifacial microsomia were more likely to be left-handed compared with the control group and also they concluded that hemifacial microsomia affects cerebral lateralization (10). According to all these findings, it is obvious that handedness is associated with facial asymmetry. The mandibular asymmetry which is maybe the primary reason for facial asymmetry (37) directly affects the facial appearance (38). In the present study, CH, RH, and CH+RH values measured on the left side were higher than on the right side on both right-handed and left-handed participants; but this result was not statistically significant for all parameters in both groups. Mandibular asymmetry indices were also statistically similar to right-handed and left-handed participants. This finding was parallel to Hujoel et al.'s study in which the authors concluded that lower face asymmetries were not associated with heritable features (1). Mandibular asymmetry can be caused by functional factors as well as morphological or genetic disorders (39-41). The asymmetric function and activity of the jaws may cause different development of the left and right parts of the mandible (20,42,43). Since malocclusions or functional disorders that may cause mandibular asymmetry were eliminated during the sample selection of the current study, it can be concluded that hand preference, which is a marker of functional laterality, alone did not affect mandibular asymmetry.

The current study has some limitations. First; the small left-handed sample size may be a limitation, but considering the finding that 90% of the society tends to be right-handed (44,45) the small number of left-handed participants in such retrospective evaluation is an expected situation. The method for determining the hand-use preference of the participants may be another limitation of the study. Although the questionnaires were accepted as reliable methods, their use with observational evaluations may yield more reliable results (23,24).

5. CONCLUSIONS

Condylar, ramal, and total mandibular height measurements for the left and right sides of the mandibula were similar in the skeletal Class 1, normodivergent study group. Hand use preference was not associated with condylar, ramal, and total mandibular asymmetry. Longer-term studies in which hand use preference and mandibular asymmetry were also observed clinically may support the results of the present study.

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Clinical and Experimental Health Sciences

Comparison of Two Body Wear Resistance of Novel Strength-Gradient Monolithic Zirconia with Two Different CAD/CAM Materials

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ABSTRACT

Objective: Novel strength-gradient monolithic zirconia is a developed material recently introduced to the market and its mechanical properties should be investigated in vitro. The aim of the study is to compare the wear rates of three different CAD/CAM materials with a chewing simulator after one year of dynamic loading.

Methods: 7x7x3 mm discs were prepared from lithium disilicate, strength-gradient monolithic zirconia, and zirconia-reinforced lithium silicate glass ceramic. Both groups were divided into two subgroups (n=12) as glazed and mechanically polished.

The samples were scanned with a laser scanner device (SD Mechatronic Laser Scanner LAS-20, Westerham, Germany) to determine the amount of wear. The samples were placed in a chewing simulator (SD Mechatronic Chewing Simulator CS-4.2, Westerham, Germany) for 240 000 cycles which is equivalent to 1 year of clinical use. After the dynamic loading in the chewing simulator, the samples were scanned again in the laser scanner, and the data was obtained. Kruskal Wallis test was used to analyze the data.

Results: The amount of wear of each material was found to be statistically significant ($p<.05$). No significant differences between the polished and glazed groups of Zir and LD were found but glazed CD was significantly more wear-resistant than polished CD ($P<.05$).

Conclusions: Wear is a phenomenon that can be affected by different factors such as microstructure and surface finishing of the materials. Wear resistance should be taken into consideration when choosing a material.

Keywords: Strength-gradient monolithic zirconia, zirconia-reinforced lithium silicate, lithium disilicate, wear

1. INTRODUCTION

Due to their advantageous qualities, computer-aided design and computer-aided manufacturing (CAD-CAM) materials are being utilized more frequently (1,3), as the demand for monolithic restorations has been rising (4-7). Due to its high flexural strength, excellent mechanical properties, and enhanced translucency, lithium disilicate glass-ceramic has gained popularity for all-ceramic restorations (2,8,9). Full ceramic restorations eliminate the majority of the complications occurred in first-generation zirconia restorations such as chipping of veneering porcelain, delamination, and fracture (2,5,10). In addition, the need for excessive tooth preparation was also eliminated due to decreased thickness of monolithic restorations. Lithium disilicate being the superior restorative material in the dental market, forced manufacturers to develop aesthetically pleasing CAD/CAM monolithic materials with similar indications and properties. These materials are strength-gradient zirconia and zirconia-reinforced lithium silicate ceramic (5).

Zirconia-reinforced lithium silicate ceramic (ZLS) had 10% dissolved zirconia embedded in a silica-based glass matrix to combine beneficial characteristics of zirconia and glass ceramic (8,9,11,12). Although ZLS does not require heat treatment for the crystallization of the material, it has been reported that fired ZLS has stronger flexural strength than milled ZLS (3,12).

Conventional dental zirconia (3Y-TZP; 3mol% Yttria-stabilized Tetragonal Zirconia Polycrystal) is not particularly translucent or aesthetically pleasing (10). Strategies such as reducing the amount of aluminum oxide (Al_2O_3), increasing the yttria content, and controlling the sintering temperature have been developed to improve its translucency (13-18). Currently, 3Y-, 4Y, and 5Y-TZP (%mol yttria-stabilized zirconia) zirconia grades are available for monolithic restorations. In general,

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the cubic content and translucency increase with increasing yttria content. However, this also results in a decrease in strength and toughness (14). Strength-gradient zirconia has been introduced to the market to further enhance the aesthetic qualities of zirconia restorations by integrating the beneficial properties of several zirconia grades. In the base layer of the material, which functions as a strong framework for the cervical part of the restoration, a stronger 3Y-TZP or 4Y-TZP is used. The more translucent 5Y-TZP is placed in the top layers, coinciding with the restoration's incisal or occlusal part (15). Even though these strength-gradient zirconia blanks are currently on the market, there is relatively limited scientific information on these materials.

The phenomenon of wear is a physiological process; any restoration material could influence the wear rate of the opposing teeth (4). Surface pretreatment is an important parameter affecting the wear resistance of a material (2,19). Typically, pretreatment consists of polishing and/or glazing to obtain a homogenous surface for both oral health and aesthetics (20). Polishing has become even more crucial as a result of the development of CAD/CAM technology, which has made it possible to provide restorations in just one appointment (5).

The aim of this study is to examine the in vitro two-body wear resistance of ceramic materials (strength-gradient zirconia, lithium-disilicate, zirconia-reinforced lithium silicate ceramic) after two different surface pretreatment procedures. The first hypothesis was that the wear resistance of the established materials would not be different when opposing monolithic zirconia; the second hypothesis was that different pretreatments would not influence the wear resistance of the materials.

2. METHODS

Three monolithic ceramics were examined: strength-gradient monolithic zirconia ([Zir], IPS e.max ZirCAD Prime, Ivoclar, Schaan, Liechtenstein), a lithium-disilicate ([LD], IPS e.max CAD, Ivoclar Vivadent, Schaan, Liechtenstein), and a zirconia-reinforced lithium silicate glass ceramic ([ZLS], Celtra Duo, Dentsply Sirona, Bensheim, Germany) listed in Table 1. For each material, a total of 24 disk-shaped samples (n = 24, N = 72) were manufactured.

Table 1. *Materials used in study*

Material	Classification	Composition	Manufacturer
IPS e.max CAD	Lithium disilicate ceramic	57%-80% SiO_2, 11%-19% Li_2O, 0%-13% K_2O, 0%-11% P_2O_5, 0%-8% ZrO_2, 0%-8% ZnO, 0%-5% Al_2O_3, 0%-5% MgO	Ivoclar Vivadent AG
IPS e.max ZirCAD Prime	Strenght-Gradient Monolithic Zirconia	Tetragonal polycrystalline zirconia with 3mol, 4mol, 5mol-%yttria	Ivoclar Vivadent AG
Celtra Duo	Zirconia-reinforced lithium silicate ceramic	Lithium silicate with 10% $Zr0_2$	Dentsply Sirona

2.1. Specimen Preparation

LD and CD blocks were cut into disks (7x7x3 mm) with a precision saw (IsoMet 1000; Buehler, IL, USA), polished with silicon abrasive papers (400-, 600-, 800-, 1200-grit papers; 3M, MN, USA) by a mechanical polishing machine (Presi Minitech, Eybens, France) at a constant speed of 300 rpm under water irrigation. LD samples were then crystallized (850◦C for 10 min at a heating rate of 30◦C/min) following the manufacturer's instructions in a ceramic oven (Programat P310; Ivoclar Vivadent, Schaan, Liechtenstein). The zirconia specimens were milled from disks and were sintered in a furnace (Mihm-Vogt HT, Mihm-Vogt & Co KB, Stutensee, Germany) for 2 hours at 1550 ^{0}C.

Specimens were then subdivided into two groups (n = 12 per subgroup) undergoing different pretreatments: 1) polishing (P), 2) glazing (G). LD and ZLS specimens were polished with a three-step polishing system (DIAPOL® RA, EVE Ernst Vetter GmbH, Keltern, Germany), and IPS e.max ZirCAD Prime specimens were polished with a two-step polishing system (DIACERA RA, EVE Ernst Vetter GmbH, Keltern, Germany). DIAPOL® RA and DIACERA RA polishing kits (EVE Ernst Vetter GmbH, Keltern, Germany) were used at a constant of 10 000 rpm for 30 seconds. The same operator carried out all the manual finishing and polishing procedures. The manufacturer's recommended glazing material was used on each ceramic and samples were fired in a ceramic oven (Programat P310, Ivoclar Vivadent, Schaan, Liechtenstein; Multimat Cube, Dentsply Sirona, Bensheim, Germany) respectively.

Seventy-two monolithic zirconia (GC Initial Monolithic Zirconia, GC, Leuven, Belgium) antagonists which are in a form of a rounded triangular prism with a round tip of 3 mm in diameter were designed (SolidWorks 3D CAD, SolidWorks Corporation, Waltham, MA, USA), milled (inLab MC X5, Dentsply Sirona, Bensheim, Germany), and sintered (Mihm-Vogt HT, Mihm-Vogt & Co KB, Stutensee, Germany) for 2 hours at 1550 ^{0}C. The antagonists were then polished in a mechanical polishing machine with silicon carbide abrasive papers (400-, 600-, 800-, 1200-grit papers; 3M, MN, USA) and DIACERA RA polishing kit (EVE Ernst Vetter GmbH, Keltern, Germany) respectively.

The specimens and the antagonists were placed in metal holders with an auto-polymerizing acrylic resin (Imicryl, Konya, Turkey) and stored in distilled water at 37 ^{0}C for 24 hours before testing.

2.2. Wear Evaluation

A dual-axis computer-controlled chewing simulator (CS-4.2, SD Mechatronik GmbH, Westerham, Germany) was used for the two-body wear simulation. The specimens were fixed to the lower rotating component of the machine, whereas the antagonists were fastened to the upper stationary part. The equivalent of 1 year in vivo which is a total number of 240 000 cycles was applied with a vertical load of 50 N, and a lateral movement of 0.6 mm with a frequency of 1.6 Hz. The wear procedure was performed in distilled water simultaneously thermocycling between 5 ^{0}C and 55 0C. The parameters used for the chewing simulation are presented in Table 2.

Table 2. *Settings of Parameters for the Wear Resistance Protocol*

Parameter	Value
Number of cycles	240 000
Load	50 N
Lateral movement	-0.6 mm
Descendent speed	30 mm/s
Lifting speed	55 mm/s
Feed speed	30 mm/s
Return speed	55 mm/s
Temperature	5 ^{0}-55 ^{0}C
Frequency	1,6 Hz

Each specimen was scanned with a three-dimensional (3D) laser scanner (LAS-20, SD Mechatronik GmbH, Westerham, Germany), antagonists were wetted with scan powder (Matte Spray, Creamagna Chemicals, İstanbul, Turkey) and scanned with a dental lab scanner (inEos X5, Dentsply Sirona, Bensheim, Germany) before and after undergoing the chewing test to acquire standard tessellation language (STL) files. Data were superimposed (Fig 1) to calculate the volumetric loss (mm^3) and wear depth (mm) of each specimen and the volumetric loss (mm^3) of their antagonists using a surface analysis program (Geomagic Control of 3D Systems, SD Mechatronik, Westerham, Germany).

2.3. Statistical Analysis

IBM Statistical Package for Social Sciences V23 software (IBM Corp, New York, USA) was used to complete the statistical analysis. Data's normality was determined by the Kolmogorov-Smirnov test. The correlation between volume loss (mm^3) and wear depth (mm) was analyzed by Kendall's Tau-b test. The wear data were evaluated using the Kruskal-Wallis and Mann-Whitney U test, with the statistical significance set at $p < .05$.

3. RESULTS

Table 3 shows every material and antagonist's mean values, standard deviations, and statistical results. Kruskal-Wallis confirmed statistically significant differences in volume loss and wear depths among all materials ($p < .05$) (Fig 2). The lowest mean volume loss (0.020±0.018 mm^3) was found for Z, followed by LD (0.060±0.036 mm^3). CD showed the highest mean volume loss of 0.066±0.041 mm^3. Kendall's Tau-b correlation test indicated a 90% positive correlation between volume loss and wear depth ($p < .01$). No significant difference was found between the antagonists' volume loss and wear depths ($p > .05$). No significant differences between the polished and glazed groups of Zir and LD were found however, glazed CD was significantly more wear-resistant than polished CD ($p < .05$).

Table 3. *Mean values (and Standard Deviations) for Volume Loss and Wear Depth*

Material	Volume Loss (mm^3)	Wear Depth (mm)	Antagonist Wear (mm^3)
ZirP	0.016 ± 0.012^a	0.003 ± 0.002^x	0.002^y
ZirG	0.025 ± 0.022^a	0.003 ± 0.002^x	0.003^y
LDP	0.072 ± 0.042^b	0.048 ± 0.029^y	0.002^y
LDG	0.049 ± 0.026^b	0.032 ± 0.024^y	0.003^y
CDP	0.082 ± 0.031^c	0.050 ± 0.025^z	0.002^y
CDG	0.050 ± 0.045^d	0.028 ± 0.029$^\alpha$	0.002^y

^{a} Same letters indicate no statistically significant differences for the same column (p = .05).

4. DISCUSSION

This study examined the wear resistance of CAD/CAM ceramic materials and zirconia antagonists. The effect of the material in terms of wear resistance was significant, therefore the first null hypothesis was rejected. The second null hypothesis was that surface pretreatment did not affect the materials' wear resistance. This hypothesis was partially accepted, except for CD group.

It is crucial for a restorative material to have similar mechanical properties to the enamel. An acceptable wear pattern of restorative materials should represent the physiological wear of natural teeth (3). Over the decade, many studies have compared the wear of lithium disilicate to the gold alloy which is known for its similar wear behavior to that of enamel (21). The wear resistance of lithium disilicate has also been compared with zirconia in the literature (3,22-25). Therefore, in this study the wear resistance of novel strength-gradient monolithic zirconia and zirconia-reinforced lithium silicate materials have been compared to lithium disilicate. In the present study, LD was more wear-resistant than CD with its antagonist as zirconia. Ozkir et al (22) and Matzinger et al (24) both found LD to be more wear-resistant which is consistent with the results of the present study. On the contrary, other studies have reported similar wear behaviors between LD and ZLS (1,4,5,26). Differences in results may be due to the mechanical differences between polished ZLS and glazed ZLS.

Lithium disilicate is a material that needs to be crystallized which increases the production time and cost of a restoration. In opposition to this, ZLS-based Celtra Duo was developed and advertised in the market as a material that does not need crystallization and can be mechanically polished and adhesively luted just after occlusal adjustment in the same session. Due to this benefit, CD is particularly well suited for the chairside fabrication of indirect restorations. However, Celtra Duo benefits from a glaze firing cycle because it enhances its aesthetics and increases its flexural strength from 210 MPa to 370 MPa (3). In two studies that investigated the wear resistance of CD both after grinding and after an additional glaze firing cycle for six months in vivo, glazed CD exhibited a wear resistance similar to LD and gold alloy whereas the wear resistance of ground CD was found to be statistically different from LD and gold (3,21). The present study also found that glazed CD was significantly more wear-resistant than polished CD. These findings suggest that the glaze firing cycle results in increased wear resistance of ZLS-based materials.

The majority of the studies that have examined the wear resistance of monolithic zirconia used 3Y-TZP. Few studies have investigated the wear behavior of 4Y-TZP and 5Y-TZP, however, there is limited information on the wear properties of strength-gradient zirconia in the literature. Regardless of their yttria content, fracture toughness, or strength, different generations of zirconia gave rise to minimal and comparable wear behaviors (10,27,28). Similarly, Zir exhibited significantly higher wear resistance as compared to other ceramic materials which complies with previous studies that reported consistent results on the high wear resistance of zirconia (2,10,29-31). Zir's strong wear resistance, similar to that of 3Y-TZP, suggests that microstructural differences between zirconia generations are likely to have little impact on wear behavior (32). However, differences in material properties, such as hardness, modulus of elasticity, or flexural strength play a role in the wear behavior of CAD/CAM materials (24).

The surface finish of zirconia, achieved by mechanically polishing or glazing, is an important determinant of its and antagonists' wear properties (33). It has been stated that when the antagonist comes to contact with the restoration, the friction causes the 20 to 50 µm superficial glaze layer to wear revealing the underlying ceramic. If the underlying ceramic is not mechanically polished, its surface roughness is more likely to be higher which increases the wear on both the material and the antagonist (2,19,33,34). The present study showed no significant differences between the wear of glazed Zir and polished Zir. Many studies comparing the wear behavior of glazed and polished zirconia detected higher volume loss and wear depth on glazed specimens (2,19,33-36) however Çakmak et al (1) stated that glazing or polishing did not affect the wear resistance of the material or its antagonist. Similar to the present study, Çakmak et al (1) tested the materials for approximately 1 year in vitro. On the other hand, studies that found significant results tested their materials for longer periods of time up to 5 years in vitro (2,19,34). Determining which pretreatment yields the optimal results is difficult to say because different test parameters and periods of time, chewing simulators, and tested materials give different results.

Intraoral tribology has a complex mechanism that is challenging to mimic hence the in vitro methods for the evaluation of wear have greatly differed from one another. In vitro evaluation of wear is directly dependent on the testing conditions such as load, frequency, lubricant, antagonist, and time. It has been stated that cycle numbers under 5000 were insufficient to measure the wear of zirconia (37), therefore in the present study, the equivalent of 1 year of mastication which is 240 000 cycles were performed. The adjustment of the chewing simulator directly affects the observed wear rate. Heintze (38) stated that vertical biting force ranges between 20 to 120 N, and was affected by different factors such as the region of the mastication in the oral cavity, the hardness of the food, and the age of the patient. In order to match physiological parameters and achieve a clinically accepted intraoral simulation, the occlusal load was selected as 50 N applied with a frequency of 1.1 Hz with a lateral movement of 0.6 mm. During the chewing movement, the temperature fluctuates intraorally hence thermocycling with temperature differences between 5 and 55^{0}C was applied simultaneously by using distilled water as a lubricant (22). Distilled water also acted as an agent to remove debris, decreasing the friction in the medium (22).

There is no set method for the use of antagonist material in wear test mechanism protocols in the literature (24). Numerous research has imitated clinical conditions for the relationship between the natural tooth and its antagonist using steatite (10,25,39), aluminum oxide (22), stainless steel (2), zirconia (3,29,40), or human enamel (1,41,42). Due to variations in enamel thickness, mineralization, cusp anatomy, and morphology, human enamel is prone to inhomogeneities. Moreover, extensive preparation and alteration are required in order to standardize enamel, which further reduces the validity of the test results (43). Therefore, as proposed in the literature (38), monolithic zirconia cusps that were 3 mm in diameter (3) were used in the present study to accurately assess the wear of CAD/CAM restorative materials in standardized experimental conditions. Throughout the whole test period, they kept their shape, which minimized the impact of any changes to the antagonist surface on specimen wear (44), and no difference was found between the volume loss and wear depths of the antagonists (3,21,45) ($p>0.05$).

The present study evaluated the wear properties of novel strength-gradient monolithic zirconia and zirconia-reinforced lithium silicate in comparison to lithium disilicate. One of the limitations of this study is that the control group was identified as lithium disilicate as opposed to enamel. In addition, monolithic zirconia was used as an antagonist material in this study. In order to make a better deduction about the wear resistance and abrasiveness of these materials, enamel and other various restorative materials are needed in comparison to the materials and also as antagonists. Lastly, 240 000

masticatory cycles were performed which was equivalent to 1 year in vivo. Further research may be conducted investigating the effect of prolonged times of mastication to the wear resistance of these materials.

5. CONCLUSION

The current technique showed that when subjected to simulated chewing cycles, various materials exhibit statistically significant wear resistance characteristics.

Strength-gradient zirconia is a new material in the market. Further research that investigates the wear resistance and wear pattern of strength-gradient zirconia for extended time periods both in vitro and in vivo is needed.

Even though Celtra Duo can be mechanically polished and cemented right after milling, it is advised to be subjected to a glaze firing cycle to slightly increase its mechanical and esthetic properties, and wear resistance.

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Clinical and Experimental Health Sciences

The Effect of Theory-Based Care on Breastfeeding Self-Efficacy, Anxiety and Breast Milk Release

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ABSTRACT

Objective: The effect of nursing care provided according to Dennis' breastfeeding self-efficacy theory on breastfeeding self-efficacy, anxiety, and breast milk secretion was evaluated.

Methods: In this quasi-experimental study, 60 mothers in the first week postpartum were examined. The mothers and their supporters in the Dennis Theory-Based Nursing Care group were trained. Before the training, mothers were given the personal information form and the breastfeeding diary form to be filled out for 15 days. The perception of breastfeeding self-efficacy of mothers was evaluated using the "Postpartum Breastfeeding Self-Efficacy Scale". Their anxiety was determined using the "State Anxiety Scale", and breast milk release was assessed using the "Daily Form for Baby's Adequate Nutrition". The parameters were measured on the first day and 15 days after the training. Routine hospital standard nursing care was provided to the mothers in the control group.

Results: The number of formulas given by mothers in the Dennis Theory-Based Nursing Care group to their babies was significantly lower than the number of formulas given by the mothers in the control group ($Z=-0.90$, $p<.001$). While the post-evaluation breastfeeding self-efficacy scores of the mothers in the experimental group were significantly higher ($Z=-6.82$, $p<.001$), the post-evaluation anxiety scores were significantly lower than those of the mothers in the control group ($Z=-6.38$, $p<.001$).

Conclusion: We found that applying Dennis' Theory-Based Nursing Care increased the breastfeeding self-efficacy level of the mothers and decreased their level of anxiety and the number of formulas that the babies received.

Keywords: Dennis theory-based care; self-efficacy; breast milk release; anxiety

1. INTRODUCTION

In Türkiye, babies are traditionally breastfed; 71.3% of newborns are breastfed within the first hour after birth (1). However, reasons such as the hospitalization of the infant in the neonatal intensive care unit (NICU) greatly hinder breastfeeding (2). Hospitalization of babies in the NICU may cause intense stress in their families, especially in mothers, which in turn can decrease breastfeeding self-efficacy (BSE) and negatively affect milk production (3, 4). The secretion of human milk, which is important for babies hospitalized in the NICU, is suppressed or decreased (2). Additionally, increasing the quantity of milk secreted or restarting milk secretion is possible in mothers whose milk secretion is suppressed (5). Studies have shown that the factors that increase the secretion of human milk include supporting the mother (2), nipple warning (6), and providing theory-based education (7). Dennis' BSE theory contributes to understanding and strengthening mothers' BSE behaviors.

Following Bandura's definition of self-efficacy theory, Cindy-Lee Dennis created the "Breastfeeding Self-Efficacy Theory" in 1999 by determining the factors and sources that affect the perception of breastfeeding self-efficacy. Dennis stated that mothers are influenced by four sources of information while choosing, applying, and maintaining a behavior (8). Factors affecting mothers' perception of BSE include previous experiences, examples from others, environmental support, and psychological states (8–10). The positive and negative experiences of mothers with breastfeeding influence the effort and the outcome of the current effort to achieve breastfeeding success (8, 11). For the mother to achieve individual success, her self-efficacy must first be increased (12). Peer mothers with successful breastfeeding experiences should be used as positive role models to encourage breastfeeding behaviors among new mothers or mothers who have failed at breastfeeding. This can increase the impact of the modeled behavior (8). For example, a mother breastfeeding her baby for the first time will feel more

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comfortable when she sees others breastfeed their babies. This will ensure that the baby is satiated and breastfeeding is successful (13, 14). Some studies have stated that focusing attention on successful aspects of a breastfeeding act and praising the mother's current breastfeeding skills increases their self-efficacy (8). The support provided by a spouse to the mother taking care of the baby increases her perception of breastfeeding self-efficacy (12). The support provided to mothers by lactation consultants, health professionals, peers, family members, and friends is effective in increasing breastfeeding success (9, 14). Dennis emphasized that the success of breastfeeding depends on whether the mother is emotionally comfortable (8).

No study based on Dennis' BSE theory has been conducted with mothers whose babies were hospitalized in the NICU. Therefore, this study was conducted with mothers of babies admitted to the NICU, and the effects of nursing care provided to the mothers on their BSE, anxiety, and milk were evaluated according to Dennis's BSE theory.

Research Hypotheses

Nursing care was given according to Dennis' BSE theory.

H_{1a}: The number of formulas given by mothers in the Dennis Theory-Based Nursing Care group (Dennis TBNC group) to their babies and that given to the babies by mothers in the control group is different.

H_{1b}: The BSE perceptions of the mothers in the Dennis TBNC group and the control group are different.

H_{1c}: The anxiety levels of the mothers in the Dennis TBNC group and the control group are different.

2. METHODS

2.1. Research Type

This was a pretest-posttest quasi-experimental study.

2.2. Population and Sample

The study was conducted between 2018 and 2020. The participants included mothers of infants hospitalized with weight loss in the NICU of a state hospital in the Central Anatolia region in Türkiye.

Number of samples: The number of samples required was calculated based on the criteria of 80% power and 5% margin of error, according to the power analysis. In total, 60 participants, 30 each in the Dennis TBNC group and the control group, were included in the study along with their supporters (Figure 1). According to the power analysis conducted at the end of the research, the effect size was found to be .3679.

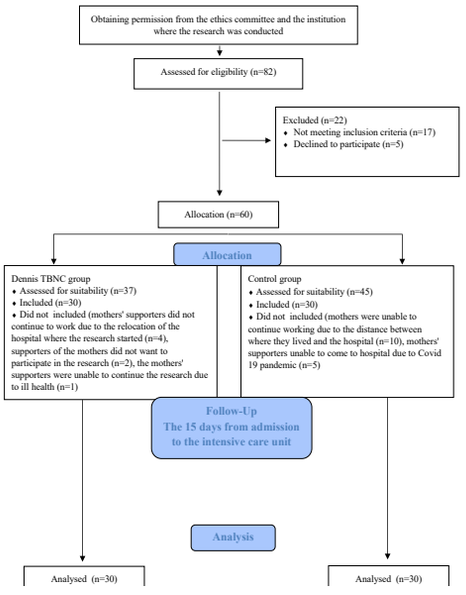

Figure 1. *Flow chart*

The inclusion criteria for the study were as follows: individuals were at least 18 years old, did not have any disease that might affect milk secretion and breastfeeding, had little or no human milk, were not on drugs that could prevent breastfeeding, had a relative who could support them (preferably their spouse), and whose supporter agreed to participate in the training program. The inclusion criteria for babies were as follows: they were less than seven days old, did not have any problem that might affect sucking, were born at a normal gestational week and weight, had a weight loss of at least 7% compared to their birth weight, and had dark urine output six times a day or less.

2.3. Data Collection Tools

The data were collected using a personal information form, breastfeeding diary form, postpartum BSE scale (BSES), and state anxiety scale.

Personal information form: The form was prepared based on a literature review performed by the researchers (9, 10, 15). The form consisted of 21 items on maternal sociodemographic, obstetric, and breastfeeding characteristics and infant gender, birth weight, birth week, weight during admission to the intensive care unit, diet, and urinary characteristics.

Breastfeeding diary form: The form was developed by the researcher based on previous studies (2, 3, 5, 6) and included questions about the amount of fluid intake of the mother the previous day, the amount of breast stimulation, the practices performed by the supporter to the mother, the evaluation of these practices, and the emotional state of the mother during the day.

Postpartum BSE scale (BSES): The BSES was used with the permission of the person who translated it into Turkish

(M. Aluş Tokat, personal communication, July 16, 2017). To evaluate the BSE levels of mothers, BSES was used by Dennis and Faux (1999) (16), whose initial version had 33 items; a shorter version with 14 items was developed in 2003. It is a five-point Likert-type scale (1="I am not sure at all" and 5="I am always sure"). As the total score on the scale increases, the self-efficacy of breastfeeding increases. Alpha coefficient reliability value of BSES is .78.

State Anxiety Scale (SAS): The SAS was translated into Turkish by Öner and Le Compte (1983). We used the Turkish version of the scale to evaluate the anxiety levels of mothers participating in the study. Emotions or behaviors expressed in the scale are answered by marking one of the options (1) none, (2) a little, (3) a lot, and (4) completely, according to their level of experience. A high total score obtained on the scale reflects a high level of anxiety (17). Alpha coefficient reliability value of SAS is .87.

2.4. Procedure

To prevent interaction between the mothers in the experimental and control groups, the study was first conducted with the mothers in the Dennis TBNC group. After the follow-up period of the mothers in the Dennis TBNC group was over, the study was performed with the mothers in the control group.

The amount of breast milk was evaluated according to the amount of formula the newborns received in addition to breastfeeding and their weight gain.

2.4.1. Dennis TBNC group

On the first day of admission to the NICU, a personal information form was filled out and pretests (BSE and SAS) were performed. Then, the mothers and their supporters received 1 h of training based on examples from previous studies and the opinions of five experts in the field. The training program included content prepared based on previous experiences, the psychological state and the support systems of the mother, and examples of other breastfeeding mothers. The training was provided to mothers after assessing their perception of breastfeeding self-efficacy. Additionally, the content of the training included discussion of breastfeeding experiences, fears, perceived positive and negative thoughts, such as the importance of breastfeeding, correction of misinformation and perception about breastfeeding, the way breast stimulation (massage, expressing milk, breastfeeding, etc.) is performed, formulating a breastfeeding and nutrition plan, and the instances where the supporter can help the mother (back massage, support for expressing milk, and comforting the mother). After the training, mothers were given a "breastfeeding diary form" to be filled out for 15 days. Mothers and their supporters were followed up for 15 days. During the follow-up period, the researcher sent a reminder to mothers to make nipple warnings (about expressing milk or giving a massage) via text message on their mobile phones, thrice a day. While their babies were in the NICU, the mothers were encouraged to communicate with and observe other mothers breastfeeding their babies. On the last day of the study, post-tests (BSE and SAS) were administered to the mothers, the baby's weight was measured, and the forms filled out by the mothers for 15 days were received.

2.4.2. Control group

On the first day of admission to the NICU, a personal information form was filled out and pretests were performed. The mothers were given a "breastfeeding diary form" to fill out for 15 days. Mothers and their supporters were followed up for 15 days. Routine hospital standard nursing care was provided to the participants in the control group. On the last day of the study, post-tests were administered to the mothers, the baby's weight was measured, and the forms filled out by the mothers for 15 days were received.

2.5. Data Analysis

Statistical tests were performed using SPSS (SPSS, 24.0). Frequency tables and descriptive statistics were used to interpret the results. Among parametric tests, the independent samples t-test (t-table value) was performed to determine the differences in the data between two independent groups, and the paired samples t-test (t-table value) was performed to determine the differences in the data between two dependent groups. Among non-parametric methods, the Mann-Whitney U test (Z-table value) was performed to determine the differences in the data between two independent groups, and the Wilcoxon test (Z-table value) was performed to determine the differences between two dependent groups. "Fisher-Exact", "continuity correction" and "Pearson-$\chi 2$" crosstabs were used to assess the relationships between two qualitative variables. Pearson correlation was used to analyze the relationship between two quantitative variables with a normal distribution; in cases where even one quantitative variable was not normally distributed, the Spearman correlation coefficient was used.

2.6. Ethical Considerations

The study was approved by the Ethics Committee of the Ankara Pediatrics Hematology Oncology Training and Research Hospital (19 March 2018; approval number 2018–033). Permission was obtained from the head of the NICU where the research was conducted. Written informed consent was obtained from the mothers and their supporters. The mothers and their supporters were informed that the information collected for the research would be kept confidential and only be used for scientific purposes. The study was conducted following the ethical principles outlined by the "World Medical Association's Declaration of Helsinki".

3. RESULTS

The sociodemographic and obstetrics characteristics of the women and infants in the study are presented in Table 1.

The age of the mother was significantly different between the groups (χ^2= 5.62; p=.01). We found that 76.7% of the mothers in the Dennis TBNC group were below 30 years old, and 56.7% of the mothers in the control group were 30 years old or older. The mean length of stay in the intensive care unit for the newborns in the Dennis TBNC group (5.66 ±0.14) was significantly lower than that in the control group (7.10±0.75) (Z=–5.36; p<.001). The education level of the mother, number of pregnancies, number of births, delivery method, breastfeeding experience, and supporters were not significantly different between the groups (p>.05) (Table 1).

Table 1. *Distribution of the findings related to some descriptive characteristics of mothers and infants*

Characteristics	Dennis TBNC group (n=30)		Control group (n=30)		Statistic
	n	%	n	%	
Age					χ^2=5.62
<30	23	76.7	13	43.3	p=.01
≥30	7	23.3	17	56.7	
Educational level					
Primary/ Secondary school	8	26.7	6	20.0	χ^2=0.41
High school	14	46.7	15	50.0	p=.93
Associate degree	3	10.0	3	10.0	
Undergraduate/ Postgraduate	5	16.6	6	20.0	
Number of pregnancies					χ^2=4.43
1	12	40.0	5	16.7	p=.10
2	9	30.0	10	33.3	
≥3	9	30.0	15	50.0	
Number of births					χ^2=2.03
1	13	43.3	8	26.7	p=.36
2	12	40.0	14	46.6	
≥3	5	16.7	8	26.7	
Delivery method					χ^2=0.29
Vaginal delivery	18	60.0	21	70.0	p=.58
Caesarean section	12	40.0	9	30.0	
Breastfeeding experience					χ^2=0.67
Yes	18	60.0	22	73.3	p=.41
No	12	40.0	8	26.7	
Who supported					
Spouse	15	50.0	16	53.3	χ^2=0.09
Mother	9	30.0	8	26.7	p=.99
Sister	1	3.3	1	3.3	
Mother-in-law	5	16.7	5	16.7	
Hospitalization in NICU	x̄ ±SD	Mdn [IQR]	x̄±SD	Mdn [IQR]	Statistical analysis *
The day number of postpartum	4.73 ±0.94	5.0 [1.3]	3.97 ±1.04	4.0 [2.0]	Z=-2.84 p=.01
Total length of stay in hospital/ day	5.66 ±0.14	5.50 [1.0]	7.10 ±0.75	7.0 [2.3]	Z=-5.36 p<.001

TBNC: Theory-Based Nursing Care

**Wilcoxon test, p< .05.*

The discharge weight and the control weight of the newborns in the Dennis TBNC group were significantly higher than those in the control group (p<.05) (Table 2).

Table 2. *Distribution of weight measurement values of newborns from birth to the control period*

Newborn weight	Dennis TBNC group (n=30)		Control group (n=30)		Statistic*
	x̄±SD	Mdn [IQR]	x̄±SD	Mdn [IQR]	
Birth weight/ gr	3279.33±280.40	3260.0 [427.5]	3131.33±232.33	3025.0 [395.0]	Z=-1.90 p=.05
Weight of hospitalization in NICU/gr	2993.83±238.63	3020.0 [336.3]	2866.83±225.20	2780.0 [338.8]	Z=-1.86 p=.06
Discharge weight/gr	3211.17±296.24	3180.0 [497.5]	3030.00±220.61	2942.5 [368.8]	Z=-2.38 p=.01
Control weight/gr **	3527.00±310.33	3492.5 [487.5]	3243.33±227.17	3155.0 [340.0]	t=4.04 p<.001

** "Independent Sample-t" test (t-table value) for comparison of measurement values of two independent groups in data with normal distribution; "Mann-Whitney U" test (Z-table value) statistics were used to compare the measurement values of two independent groups in the data not having normal distribution.*

*** Control weight is the weight measured on the day (15th day) of the baby at the end of the research period.*

Mdn [IQR] : Median [Interquartile Range]

NICU: Neonatal İntensive Care Unit

The mean of the total number of formulas (30.20±7.64) that the newborns in the Dennis TBNC group received from the moment they were admitted to the NICU (30.20±7.64) was significantly lower than that in the control group (53.63±16.29) (Z=–0.90; p<.001). The difference in the mean of days when the newborns were fully fed only human milk (6.00±1.08) between the Dennis TBNC group and the control group was significant (12.03±1.81) (Z=–6.69; p<.001) (Table 3).

Table 3. *Distribution of the mean number of formulas, excluding human milk, which the newborns received daily during the application process*

Number of formulas according to days	Dennis TBNC group (n=30)		Control group (n=30)		Statistical analysis
	x̄±SD	Mdn [IQR]	x̄±SD	Mdn [IQR]	
1st day 0	7.50±1.14	8.0 [0.0]	7.70±1.32	8.0 [0.0]	Z=-1.19 p=.23
Formulas taken outside of human milk for 15 days	30.20±7.64	29.0 [8.75]	53.63±16.29	50.00 [15.50]	Z=-0.90 p<.001
Day of transition to be fed just human milk	6.00±1.08	6.0 [1.0]	12.03±1.81	12.0 [2.3]	Z=-6.69 p<.001

Before the study, the anxiety levels of the mothers in the Dennis TBNC group were higher than the anxiety levels of the mothers in the control group. The effect size was medium-level (d:0.74). The NCI post-test scores of the mothers in the Dennis TBNC group were significantly lower and the effect size was higher compared to those of the mothers in the control group (d: –2.81). The pretest (BSES) scores of the mothers in the Dennis TBNC group were significantly higher than those of the mothers in the control group. The effect size was medium-level (d:.63). The post-test scores of the mothers in the Dennis TBNC group were significantly higher than those of the mothers in the control group. The effect size was high (d:3.65) (Table 4).

Table 4. *Distribution of the SAS and BSE Perception pre-test and post-test mean scores of the mothers*

Score average of the scales		Dennis TBNC group (n = 30)		Control group (n = 30)		Statistical analysis	Effect size (%95 CI*)
		x̄±SD	Mdn [IQR]	x̄±SD	Mdn [IQR]		
SAS	Pre – Test	71.97±4.92	72.0 [7.3]	67.90±5.94	67.0 [8.5]	t=2.88 p =.01	0.74 [0.20-1.28]
	Post-test	22.07±2.38	21.0 [3.0]	31.10±3.86	30.0 [5.3]	Z=-6.38 p<.001	-2.81 [-3.68-1.93]
BSE	Pre – Test	39.27±6.25	37.5 [9.3]	35.70±4.94	35.0 [8.0]	t=2.45 p=.01	0.63 [0.09-1.16]
	Post-test	69.27±1.64	70.0 [0.3]	58.20±3.95	59.0 [5.5]	Z=-6.82 p<.001	3.66 [2.58-4.72]

**CI: Confidence interval*
SAS: State Anxiety Scale
BSE: Breastfeeding Self-Efficacy

4. DISCUSSION

In this study, we investigated the effects of nursing care provided according to Dennis' BSE theory on mothers' BSE, anxiety, and breast milk secretion. In the nursing care provided with information sources based on Dennis's BSE theory, mothers receive not only information but also encouragement and care (9). This approach reduces anxiety in mothers, by focusing on previous breastfeeding situations and increasing support from the environment, which positively affects the psychology of the mother (8, 9). However, factors such as giving the baby food other than human milk, insufficient social support of the mother, anxiety level, and BSE negatively affect the release of human milk.

In our study, the amount and number of formula given to newborns in the Dennis TBNC group was less. In addition, the mean number of days that newborns were fed exclusively with breast milk was shorter than in the control group (Table 3). The milk secretion occurred sooner in the mothers in the Dennis TBNC group than in the mothers in the control group. Based on these results, the H_{1a} hypothesis was accepted in our study. In other studies, the investigators found that educating mothers and the participation of their spouses increased the rates of breastfeeding of infants (18–20). Although these studies were conducted using different methods, they supported our findings. These results showed that the support of the mother and the inclusion of the supporter were effective in increasing milk secretion.

The BSE levels and the anxiety levels of mothers are key factors affecting breastfeeding success and human milk secretion. In our study, the pre-test and post-test BSE scores of the mothers in the Dennis TBNC group were significantly higher than those of the mothers in the control group (Table 4). Based on these results, the H_{1b} hypothesis was accepted in our study. Some studies reported results similar to those of our study; however, in those studies, the level of BSE was examined without relying on Dennis's BSE theory. The investigators found that breastfeeding education given to mothers with the participation of their spouses increased the BSE levels of the mothers (9, 10, 20–24). A study found that the nursing care given to mothers with text messages and phone calls to motivate breastfeeding in the postpartum period positively affected the exclusive breastfeeding status of infants and the BSE levels of the mothers (15). In our study, the post-test SAS scores of the mothers in the Dennis TBNC group were significantly lower than those of the mothers in the control group (Z=6.38; p=.001) (Table 4). Based on these results, the H_{1c} hypothesis was accepted in our study. Similar to our findings, O'Biren et al. (25) showed that the supportive and family-centered care provided to the parents of babies hospitalized in the NICU reduced their anxiety levels. Another study showed that mothers with low anxiety in the postpartum period had higher BSE levels and a longer period of breastfeeding (26). Although these studies were conducted with different methods and were not based on Dennis' BSE theory, the techniques used, such as the education given to mothers, environmental support, and family-centered care, reduced the anxiety level of the mothers and increased their perception of self-efficacy, which were similar to our findings.

Social support based on strengthening BSE perceptions of mothers enhances their BSE. The positive support of spouses increases the BSE and breastfeeding success of women. NICU nurses should use a holistic approach while caring for the newborn and the mother. They need to consider the stress and anxiety of the mother. Breastfeeding education based on Dennis' BSE theory, which is given by nurses to mothers and their supporters in the postpartum period, greatly helps in managing the process, as it is a continuous and individualized form of care.

The number of formulas that the mothers in the Dennis TBNC group gave their babies other than human milk was significantly lower than that in the control group. The mean day of onset of milk secretion of the mothers in the Dennis TBNC group was earlier than that in the control group (Table 3). The BSE post-evaluation mean scores of the mothers in the Dennis TBNC group were significantly higher than those of the mothers in the control group. The post-evaluation anxiety mean scores of the mothers in the Dennis TBNC

group were significantly lower than those of the mothers in the control group (Table 4).

Limitations and Difficulties

This study had five major limitations. First, due to the insufficient sample size, the "Previous Experiences" step, which constitutes the conceptual framework of Dennis' theory, could not be met by including mothers without breastfeeding experience in the study. Second, before the training, the mean breastfeeding self-efficacy scores of the mothers in the Dennis TBNC group were higher than those of the mothers in the control group. Third, since no intervention was allowed to affect the milk release of the mothers in the control group, the amount of milk of the mothers in the Dennis TBNC group and control group could not be controlled by expressing milk. Fourth, the training provided to mothers and their supporters was conducted in a single session. Fifth, randomization was not performed in this study. Our study had two difficulties. First, the hospital where the study was conducted was moved to a newly constructed site during the study. Second, it was difficult to meet the sample size criterion due to the COVID-19 pandemic, which prolonged the application process.

5. CONCLUSIONS

Nursing care based on Dennis' TBNC decreased the number of formulas other than breast milk fed to babies and the anxiety of the mothers. It also helped increase the BSE levels of the mothers and earlier secretion of breast milk. Our findings showed that when nurses working in the NICU provide care to mothers based on Dennis' TBNC, they can administer systematic care with a holistic approach.

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Clinical and Experimental Health Sciences

The Effect of Music on Pregnancy Complaints with Sleep and Quality of Life in Risky Pregnant Women

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ABSTRACT

Objective: This study aimed to examine the effect of music therapy on pregnancy complaints and quality of sleep and life in risky pregnant women.

Methods: This is a prospective randomized controlled study. The sample of the study consisted of a total of 112 pregnant women who referred to a hospital in a city in Turkey for pregnancy follow-up (56 in the experimental group, 56 in the control group). Risky pregnant women in the experimental group were listened to music for four weeks before going to sleep, and those in the control group received no intervention. The data were collected between July and October 2022, using an introductory information form (IIF), a risk assessment form (RAF), the Assessment Scale for Pregnancy Complaints and Their Impact on Life Quality (ASPCILQ), and the Richard-Campbell Sleep Questionnaire (RCSQ).

Results: Risky pregnant women in the experimental group had higher ASPCILQ and RCSQ post-test mean scores than those in the control group, and the difference between them was statistically significant (p<.001).

Conclusions: A music therapy reduced pregnancy complaints in risky pregnant women and increased their sleep and life quality.

Keywords: Risky pregnant women, pregnancy complaints, quality of life, sleep quality

1. INTRODUCTION

Pregnancy is one of the most significant physiological event women have throughout their life. A pathological event threatening maternal and fetal health occurs in 5%-20% of pregnancies, which are called risky pregnancy (1). Although the rate of risky pregnancy has decreased over time in Turkey, two out of every three pregnancies are still considered risky pregnancy (2, 3).

During pregnancy, women have several physiological, psychological, and biochemical changes in their bodies to ensure fetal growth and development and prepare for birth. Pregnancy-related physiological changes bring along pregnancy complaints such as nausea, vomiting, edema, low back pain, fatigue, and frequent urination. Pregnancy complaints can negatively affect the quality of life and sleep in pregnant woman (4-7). Pregnancy complaints affects the quality of life even in normal pregnancy, and can have dramatic effects in risky pregnancy, causing severe stress, fear, frequent pregnancy follow-ups, doctor check-ups, and limiting the ability of pregnant women to do their daily work (8). Erbaş and Demirel conducted a study with a total of 392 pregnant women and reported that the quality of life was affected more negatively in risky pregnant women than healthy ones (9).

Pregnancy-related physical changes not only affect the quality of life, but also cause significant changes in sleep and sleep quality of pregnant women. Studies have reported that during pregnancy, sleep quality is affected by several symptoms such as nausea, back pain, hormonal changes, fetal growth, frequent urination, leg cramps, restless legs syndrome, and snoring (10,11). Especially in the third trimester of pregnancy, 91% of pregnant women reported sleep disturbance (12, 13). During pregnancy, sleep problems and poor sleep quality may lead to increased fear and anxiety as well as inadequate care in pregnant women, increasing the incidence of glucose intolerance and gestational diabetes and causing preterm birth, low birth weight, and fetal developmental issues (14, 16). Therefore, a good sleep is important for a healthy pregnancy, but it is even more important for risky ones (17).

Music therapy is an organized and managed treatment method to optimize the psychological and physical effects of musical sounds and melodies to treat various mental

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disorders (18). Music therapy can relieve physical ailments by lowering heart rate, body temperature, blood pressure and respiratory rate. Music therapy aims to improve one's mood, reducing stress, pain, and anxiety. Therefore, music therapy can improve the quality of life and help people express themselves more freely (19). Although there is a limited number of studies on the effect of music therapy on sleep quality, these studies have shown that music therapy has a palliative effect on insomnia. One study was conducted with a total of 121 Taiwanese pregnant women to determine the efficacy of music in improving sleep quality and reported that listening to music reduced stress and anxiety and increased sleep quality in pregnant women with sleep disorders (20).

There are studies in which music therapy is used for the psychological care of pregnant women (21, 22). However, there are limited studies on the effects of music therapy on pregnancy complaints, quality of life and sleep in high-risk pregnant women. This study aimed to determine the effect of music therapy on pregnancy complaints and quality of life and sleep in pregnant women with risky pregnancy.

Research hypotheses included:

H1. A music therapy reduces pregnancy complaints and increases the quality of life in risky pregnant women.

H2. A music therapy increases the quality of sleep in risky pregnant women.

2. METHODS

2.1. Study Design

This randomized controlled study was carried out at Turgut Ozal Medical Center pregnant training class, Türkiye.

2.2. Participants

Pregnant women attending the outpatient department of the Turgut Ozal Medical Center pregnant training class, Malatya, were randomly screened for eligibility to ensure that each pregnant women had an equal chance of being selected. The study inclusion criteria were: (1) being a pregnant women who had a risky pregnancy according to the risk assessment form, published by the Turkish Ministry of Health (this form consists of a total of 23 Yes/No questions about pregnant women's risks related to obstetric history, current pregnancy, general medical history, and medical diagnosis risk where any "yes" response suggests that the pregnant woman is at high risk and must be referred to a health institution with a gynecologist) (Ministry of Health, 2011); (2) Being at 20-36. weeks of pregnancy. Among the risky pregnant who participated in the study, those who did not use a smart phone, did not like listening to music and did not fully participate in the feedback received at the end of the study and the music application were excluded from the trial. Similarly, the study excluded pregnant women with mental illness couldn't speak, understand, and write in the national language and communication problems. All pregnant women were included in the study by simple random sampling method. The study sample consisted of pregnant women who referred to a hospital in eastern Turkey for prenatal follow-up. The sample was selected using the CONSORT criteria (Figure 1).

2.3. Sample Size

A web-based sample size calculation method was used to calculate the sample size for the study. The sample size was determined to include a total of 112 pregnant women (56 in experimental group, 56 in control group) with 5% error level, 95% confidence interval at bidirectional significance level and 80% representation power (23).

2.4. Randomization

Pregnant women were assigned randomly to the experimental and control groups, using the Random Integer Generator method, which is included in the Numbers sub-title at "random.org". The caregivers and researchers in the intervention group were not blinded.

2.5. Study Settings

This prospective randomized controlled study was conducted to examine the effect of music therapy on pregnancy complaints and quality of sleep and life in risky pregnant women.

2.6. Measures

The data were collected using an introductory information form (IIF), a risk assessment form (RAF), the Assessment Scale for Pregnancy Complaints and Their Impact on Life Quality (ASPCILQ), and the Richard-Campbell Sleep Questionnaire (RCSQ).

IIF: The form was prepared by the researchers in line with the literature. It consisted of questions about pregnant women's introductory (age, family type, marital status, educational level, etc.) and obstetric characteristics (week of gestation, parity, number of children, etc.).

ASPCILQ: The scale measures the effects of pregnancy complaints on quality of life. Its Turkish validity and reliability study was performed by Özorhan. The scale has 42 items and consists of two parts. The first part evaluates how often pregnant women have complaints in the last month of pregnancy, scoring "0=never", "1=rarely", "2=sometimes", and "3=often". If a score between 1-3 is received for each complaint in this part, the second part is applied. The second part measures how pregnancy complaints affect daily life activities of pregnant women, scoring "1=not limiting at all", "1= limiting little", "2=limiting a lot". The scale has no cut-off point. A higher total scale score indicates a lower quality of life. The Cronbach's alpha reliability coefficient of the scale

was 0.91 (24). In this study, the Cronbach's α value of the scale was found to be 0.90.

RCSQ: This scale, developed by Richards, is a 6-item scale to measure one's perception of their depth of night sleep, sleep onset latency (time to fall asleep), frequency of awakening, sleep onset latency after awakening, overall sleep quality, and level of noise in the environment. Each item is evaluated using a chart with numbers from 0 to 100. The 6th item, which evaluates the level of noise in the environment, is excluded from the total score evaluation, therefore the total score is evaluated over 5 items. A higher scale score indicates a higher sleep quality. The Turkish validity and reliability study of the scale was performed by Karaman Özlü and Özer where the Cronbach's alpha reliability coefficient of the scale was found as 0.91 (25). In this study, the Cronbach's α value of the scale was determined as 0.84.

2.7. Outcome Measures

The primary outcome introductory information form (IIF), a risk assessment form (RAF) was evaluated at the beginning the study by administering the NDI questionnaire to the participants and having them check the appropriate category. The secondary outcome was assessed at end visit by allowing the patient to mark an Assessment Scale for Pregnancy Complaints and Their Impact on Life Quality (ASPCILQ), and the Richard-Campbell Sleep Questionnaire (RCSQ).

2.8. Data Collection

The data were collected from July to October 2022. Pregnant women were informed about the study, and those with risky pregnancy (who obtained one (1) or higher according to the RAF) were invited to participate in the study. The introductory characteristics of pregnant women, such as age, educational level, employment status, income level, status of having pregnancy plan, and fetal gender were recorded in the IIF. IIF, ASPCILQ and RCSQ were applied to pregnant women before the intervention. Their pretest data were collected by the researchers using face-to-face interview method at the pregnant school in the hospital. Then, a 30-minute music of nature sounds (26) compiled by the researchers was sent to pregnant women in the experimental group via the WhatsApp program to the individual smart phones of the participants. Participants were asked to listen for at least 30 minutes a day before going to bed for four weeks. No intervention was applied to pregnant women in the control group. All participants were contacted by the researchers four week after the first interview, and ASPCILQ and RCSQ were administered as a posttest.

2.9. Intervention

Pregnant women in the experimental group were listened to music, consisting of 30 minutes of relaxing and peaceful nature sounds compiled by the researchers. The music was sent to their smartphones, and they were asked to listen to it for four weeks when appropriate before bed. No intervention was applied to pregnant women in the control group. A written consent was obtained from all pregnant women who agreed to participate in the study. They were informed about the study, explaining that their personal information would be protected. Pregnant women who participated in the study were informed about the purpose and duration of the study, how and where their data would be used. Necessary permissions for the study were taken from University Non-Interventional Clinical Research Ethical Board and the relevant units (Ethics committee no: 2022/3410). Besides, The Coordinator ship of Scientific Research Projects at Inonu University was applied for financial support for the design of this study (Project No: TSA-2022–3021).

2.10. Research Variables

Dependent variables: Pregnancy complaints quality of life and sleep qualty level

Independent variables: Music intervention applied to risky pregnant women

2.11. Statistical Methods

The data were evaluated using the SPSS 25.0 for Windows software (SPSS, Chicago, Il, USA). The chi-square test was used to compare the categorical independent variables. The Kolmogrow-Smirnov test was used to determine whether the data had normal distribution. As the data had normal distribution, the independent samples t-test was used for the comparisons of two groups, and the dependent sample t-test for the comparison of intragroup. A value of $p<.05$ was considered statistically significant.

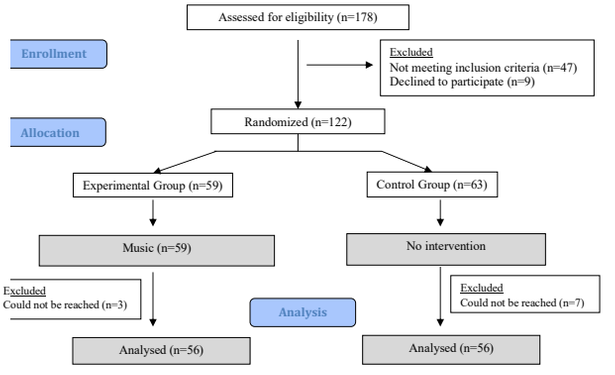

Figure 1. *Allocation of subjects according to the CONSORT 2010 flow diagram*

3. RESULTS

A total of 178 pregnant women were reached in this study. However, 47 pregnant women who did not meet the inclusion criteria were excluded from the study. Therefore, a total of 131 pregnant women were randomly assigned to the experimental and control groups. During the study, three

of those in the experimental group and seven of those in the control group were also excluded from the study as they could not be reached. Thus, the study was completed with a total of 122 pregnant women, 56 in the experimental group and 56 in the control group (Figure 1).

The characteristics of the participants (including, age, education status, employment status, social security, place of live, planned pregnancy, gender of fetus, number of pregnancy) in each of the groups were similar (p >.05) (Table 1).

Table 1. *Characteristics of the participants*

Variables	Experimental group (n=56)		Control group (n=56)		Test[a] and p value
	n	%	n	%	
Age (year)					
18-34	43	76.8	40	71.4	x^2=0.419
≥ 35	13	23.2	16	28.6	p=.518
Education status					
High school or below	37	66.1	41	73.2	x^2=0.676
University or above	19	33.9	15	26.8	p=.411
Employment status					
Yes	11	19.6	7	12.5	x^2=1.059
No	45	80.4	49	87.5	p=.303
Social security					
Yes	48	21.9	42	17.2	x^2=2.036
No	8	78.1	14	82.8	p=.154
Place of live					
Province	40	71.4	36	64.3	x^2=0.655
Villages/towns	16	28.6	20	35.7	p=.418
Planned pregnancy					
Yes	48	85.7	41	73.2	x^2=2.681
No	8	14.3	15	26.8	p=.102
Sex of fetus					
Girl	35	62.5	21	55.4	x^2=0.590
Boy	21	37.5	25	44.6	p=.442
Number of pregnancy					
1	16	28.6	12	21.4	x^2=2.971
2	21	37.5	16	28.6	p=.226
≥3	19	33.9	28	50.0	

[a]*Pearson's Chi-Squared Test.*

The comparison of the ASPCILQ and RCSQ pretest-posttest mean scores of the women in the experimental and control groups is given in Table 2. When the pretest mean scores of the pregnant women in the experimental and control groups were compared; It was determined that the difference between the groups was not statistically significant (p>.05). When the posttest ASPCILQ and RCSQ scores were compared after music therapy given to risky pregnant women, it was determined that music therapy reduced pregnancy complaints, increased the quality of life and sleep, and the difference between the groups was statistically significant in favor of the experimental group (p<.001).

Table 2. *Comparison of the ASPCILQ and RCSQ pretest–posttest mean scores of the women in the experimental and control groups (n=112)*

	Experimental group (n=56)	Control group (n=56)	Test[a] and p value
	Mean ± SD	Mean ± SD	
ASPCILQ			
Pretest	79.41±24.69	71.48±20.82	t=-1.837, p=.069
Posttest	65.64±19.26	73.80±19.49	t=-2.228, **p=.028**
Test[b] and p value	t= – 4.513, **p<.000**	t=-0.670, p=.505	
RCSQ			
Pretest	32.23±6.22	32.64±6.40	t=-0.344, p=.732
Posttest	35.07±4.18	31.14±4.30	t=4.897, **p<.001**
Test[b] and p value	t= – 2.809, **p=.007**	t=1.504, p=.138	

ASPCILQ: Assessment Scale for Pregnancy Complaints and Their Impact on Life Quality
RCSQ: Richard Campbell Sleep Questionnaire
[a]*Independent samples t-test*
[b]*Dependent samples t-test*

4. DISCUSSION

The number of studies on the effect of music therapy on psychological health in pregnant women is increasing day by day. However, there is no definite evidence in the literature about the effect of music therapy on pregnancy complaints and quality of life and sleep. This study revealed that music therapy had a significant effect on pregnancy complaints and quality of life and sleep in pregnant women with risky pregnancy. Accordingly, after music therapy was applied to risky pregnant women, their pregnancy complaints decreased, and their quality of life and sleep increased significantly (p<.001). Although there is no study which used music therapy to reduce pregnancy complaints and increase quality of life and sleep in risky pregnant women, there is several studies on the effect of music therapy on quality of life and sleep quality separately (10,11,27).

Literature has reported that music has a positive effect on relaxation, reducing stress (18, 20, 27). KS and Kisilevsky et al. have stated that a classical music played to expectant mothers makes them happy and directly affects their emotional state (27-29). This finding shows that music genres can have positive effects even if they are different.

One study was conducted to determine the effect of music preferences of university students on their quality of life and determined that music increased their quality of life. In addition, several studies on the benefits of music therapy support our results, suggesting that a music therapy increases comfort and has several positive effects on physical and psychological health, reducing nausea, vomiting and need for medication and relieving pain, anxiety and stress (30-32). Our study determined that music therapy reduced

pregnancy complaints such as nausea, low back pain, fatigue, heartburn and increased the quality of life.

The present study determined that pregnant women in the experimental group had higher sleep quality than those in the control group, and the difference between the groups was statistically significant (p<.001). Lafçı and Öztunç evaluated the effect of music therapy on sleep quality in breast cancer patients and found that music therapy improved sleep quality, whereby patients in the experimental group had higher subjective sleep quality than those in the control group (33). Another study was conducted with a total of 160 risky pregnant women to determine the effect of music therapy on anxiety and sleep quality in risky pregnant women during hospital bed rest and found that music therapy increased their sleep quality (34). A total of 121 Taiwanese pregnant women were listened to music for two weeks to determine the efficacy of listening to music at home in improving sleep quality. As a result, their anxiety levels decreased and their sleep quality increased (35).

Considering these results, which support the results of our study, a music therapy administered to women with risky pregnancy can reduce their pregnancy complaints and increase their quality of life and sleep.

5. CONCLUSION

This study revealed that music therapy reduced pregnancy complaints and increased quality of life and sleep in risky pregnant women. Therefore, pregnant women with risky pregnancy should be informed about and encouraged to receive a music therapy during their pregnancy by midwives and other health professionals, thus they can have a better quality of life and sleep. In the future, alternative methods should be introduced for risky pregnant women to have a better quality of life and be paid more attention in health institutions that provide preventive health services for risky pregnant women.

This study has some limitations. In this study, no evaluation was made according to the type and severity of risky pregnancy. It did not evaluate the long-term effect of music therapy (in postnatal period). Only risky pregnant women were included in the study, but those with healthy pregnancy were not included. As pregnant women in the experimental group did not listen to music under the supervision of the researchers, the time they listened to music could not be controlled. Another limitation of the study is that only natural sound type music is played and there is no different types of music.

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Clinical and Experimental Health Sciences

Assessment of Knowledge of Cancer Risk Factors and Awareness of Early Cancer Warning Signs among University Students

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ABSTRACT

Objective: To predict the level of knowledge about cancer risk factors and the level of awareness of the most common warning symptoms of cancer among university students in Kyrenia, Northern Cyprus.

Methods: A cross-sectional descriptive study was conducted in Kyrenia, Northern Cyprus among university students from different academic disciplines, including medical and non-medical disciplines, using a structured questionnaire.

Results: A total of 150 students participated in this study, half of them were non-medical students (51.3%). There was a low level of knowledge of cancer risk factors reported by most of the respondents of both groups. The difference between the responses to risk factors between the medical and non-medical students was found to be statistically significant regarding alcohol consumption (9.6% vs. 13%; p=0.0004), consumption of processed red meat (12.3% vs. 54.5%; p<0.0001), family history of cancer (4.1% vs. 6.5%; p<0.0001), respectively. Permanent unexplained pain was significantly recognized by the respondents of the medical group compared to the non-medical group (48% vs. 18.2%; p<0.001). The medical and non-medical participants reported a low mean knowledge (2.24±1.52 vs. 3.11±1.60); and mean awareness (1.70±0.91 vs. 1.00±0.81), respectively.

Conclusion: There is a gap and low knowledge about cancer prevention and awareness of cancer signs among medical and non-medical undergraduates. Efforts should be made to increase cancer knowledge and awareness through continuing education programs for all university students at various levels to detect cancer early.

Keywords: Awareness, Cancer, Risk factors, Cancer signs, University students

1. INTRODUCTION

With an estimated 10 million deaths, Cancer is a major public health problem with an enormous burden worldwide with an estimated 10 million deaths in 2020 [1]. Despite significant progress in reducing cancer-related morbidity and mortality, cancer prevention remains a major challenge. According to the American Cancer Society (ACS) clinical guidelines, the increased incidence of cancer can be attributed to a combination of genetic, behavioural, and environmental risk factors, including sedentary lifestyles, insufficient fruit and vegetable consumption, low physical activity, obesity or overweightness, tobacco use, alcohol consumption, pollution, and viral infections [2, 3]. However, cancer fatalism, especially the belief that cancer development and prognosis are beyond control, hinders cancer prevention. Nearly half of cancer diagnoses are due to modifiable factors, according to a recent cancer report from the National Cancer Institute. Therefore, the incidence of many types of cancer can be significantly reduced by avoiding modifiable risk factors, such as tobacco use, a lack of exercise, or an unhealthy diet. Additionally, raising awareness of the early signs of cancer may contribute to an early diagnosis. In this line, it is important to recognise these factors early in life to make lifestyle changes that can prevent cancer later in life [4, 5].

Previous literature has mainly focused on cancer perceptions, knowledge, and cancer risk behaviours among adults and older age groups [8, 21]. For Example, a cross-sectional study by Hatem et al. [8] found knowledge gaps among Lebanese adults' knowledge and beliefs of cancer risk factors and early cancer. However, a dearth of studies are conducted among university students to assess knowledge of risk factors and awareness about the warning symptoms of cancer. University students constitute a vulnerable population of young adults to be involved in early cancer awareness and education.

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This is crucial for university students because they are in the stages of development following puberty when they are establishing health behaviours that will have an impact on them to reduce the prevalence of harmful risk factors and delay long-term cancer incidence rates. In addition, raising the level of awareness of risk factors and warning signs of cancer among this group could disseminate knowledge to the population [12-14]. Meanwhile, university students may not perceive their behaviour as a cancer-related risk due to insufficient awareness of cancer and insufficient commitment to risky health behaviours. Earlier studies conducted on selected cancers, such as colorectal, cervical, and breast cancers, found significant differences between assessments of knowledge and awareness of cancer risk and the perceived cancer readiness and actual health outcomes among university students [9-11, 15, 16]. Therefore, this study specifically sought to predict the level of knowledge of cancer risk factors and awareness about the most common warning symptoms of cancer among undergraduate university-aged students in Northern Cyprus.

2. METHODS

2.1. Study Design and Participants

This cross-sectional descriptive study was conducted from January to April 2021 with a convenient sample of undergraduate university students in three provinces of Northern Cyprus, which are Famagusta, Nicosia, and Kyrenia. This study was approved by the Research Ethics Committee (2020-21/002) of the Girne American University, Kyrenia, Northern Cyprus. A total of 230 participants were approached for this study, but 150 participants responded to all items on the questionnaire, yielding a response rate of 65.2% using Cochran's sample size formula, ±5% accuracy, and a 95% confidence level for large populations whose degree of variability is unknown.

The inclusion criteria were undergraduate university-aged students from different academic disciplines. A student who agreed to participate in this study received written informed consent and verbal information about the purpose of the study. In addition, all participants were informed that participation was voluntary and that anonymity and confidentiality of responses were guaranteed. Those who declined to participate or gave incomplete responses to survey questions were excluded.

2.2. Questionnaire Design

The questionnaire was developed for the study after extensive literature research on well-known databases [3, 8, 20, 32, 33]. The structured items of the questionnaire were assessed for reconstruction and relevance by two academic experts in medicine and pharmacy faculties. The purpose of the survey was stated in the referral letter included with the questionnaire, which took approximately 10 minutes to complete. The final version of the questionnaire consisted of 26 questions divided into three parts. The first part consisted of eight items about the demographic characteristics of the participants (age, gender, nationality, family history of cancer, academic discipline, medical and non-medical discipline, and academic year). In the second part (11 items), data were collected to assess knowledge of cancer risk factors, and respondents were given the option to answer yes, no, or don't know. The third section included nine items assessing the respondent's knowledge of warning signs of cancer, with options to answer "yes," "no," or "don't know."

2.3. Statistical Analysis

The Statistical Program for Social Science Research, edition 23.0, and Microsoft Office Excel 2013 were used for analyzing the data. The descriptive data were presented as numbers, percentages, and means (standard deviations) to present comparisons of group proportions to items on the knowledge assessment questionnaire. A cut-off level of ≤50% was set for negative knowledge, awareness, and perceptions, and a cut-off level of ≥50% was set for positive knowledge, awareness, and perceptions. A score of 1 was given to positive knowledge and awareness, while a score of 0 was given to negative knowledge and awareness towards every statement. Knowledge and awareness scores for individual statements were summed up and calculated as means (standard deviations) to give the total knowledge, awareness, and perceptions score of a participant. Data were subjected to the Shapiro test to confirm their normality. Independent t-test was used to assess the differences in means between the two groups. The chi-square test was used to assess the association among groups. The p-value was considered significant at ≤0.05 and highly significant at ≤0.01.

3. RESULTS

The demographics of study participants are shown in Table 1. With a mean age of 21.1±2.6 years, nearly half of the participants (56%) were female. Most students are from Nigeria (30%), followed by Turkey (15.3%). 92.7% of participants reported no family history of cancer. In terms of academic fields, more than half of the participants were non-medical students (51.3%). Pharmacy students (39.7%) followed by medical students (23.3%) constituted the most common participants in the medical group. Students from the engineering faculties (42.9%), followed by students from the economics faculties (20.8%) constituted the most common participants among the non-medical group. Most of the participants were from the 4-5 grade year (66.7%).

Table 1. *Demographic characteristics of the study participants*

Variables	Number (n)	Percentage (%)
Gender		
Males	66	44
Females	84	56
Nationality		
Cameroon	11	7.3
Egypt	8	5.3
Ghana	8	5.3
Iran	11	7.3
Iraq	7	4.7
Nigeria	45	30
Sudan	21	14
Türkiye	23	15.3
Others	16	10.7
Family history of cancer		
Yes	139	7.3
No	11	92.7
Academic discipline		
Medical	73	48.7
Non-medical	77	51.3
Medical discipline (N=73)		
Medicine	17	23.3
Dentistry	9	12.3
Pharmacy	29	39.7
Nursing	18	24.7
Non-medical discipline (N=77)		
Art and design	4	5.2
Chemistry	11	14.3
Economics	16	20.8
Engineering	33	42.9
Information Technology	7	9.0
Law	3	3.9
Psychology	3	3.9
Academic year		
1-2 year	50	33.3
3-5 year	100	66.7

Although there were no significant findings, most of the medical and non-medical participants reported a low knowledge level of cancer risk factors regarding low consumption of fruits and vegetables (27.4% vs. 33.7%), being over 70 years old (2.7% vs. 3.9%), history of human papillomavirus infection (5.5% vs. 2.6%), obesity and overweight >25 kg/m^2 (12.3% vs. 22%), and physical inactivity less than 30 min. of 5 times per week (21.9% vs. 11.7% respectively. Nevertheless, the non-medical students reported a significant rate of poor knowledge level regarding family history of cancer than the medical students ($p<0.0001$). On the other hand, the medical students reported a significant rate of poor knowledge level regarding alcohol consumption ($p=0.0004$) and processed meat consumption ($p<0.0001$) than the non-medical students. Meanwhile, very few risk factors were known correctly by the participants, particularly smoking (65.8% vs. 57.1%), and second-hand smoke (75.3% vs. 68.8%), respectively, but were found to be statistically insignificant between the medical and non-medical students, as shown in Table 2.

Table 2. *Knowledge of cancer risk factors among the study participants*

Variable	Medical students N=73 n (%)	Non-medical students N=77 n (%)	P-value
Cigarettes smoking			
Yes	48 (65.8)	44 (57.1)	0.52
No	17 (23.3)	21 (27.3)	
Do not Know	8 (10.9)	12 (15.6)	
Second-hand smoking			
Yes	55 (75.3)	53 (68.8)	0.23
No	15 (20.5)	15 (19.5)	
Do not Know	3 (4.1)	9 (11.7)	
Alcohol consumption (more than 1 unit/day)			
Yes	7 (9.6)	10 (13)	**0.0004**
No	62 (84.9)	45 (58.4)	
Do not Know	4 (5.5)	22 (28.6)	
Fruit and vegetable consumption (1 unit of a day)			
Yes	20 (27.4)	26 (33.7)	0.58
No	45 (61.6)	41 (53.2)	
Do not Know	8 (11)	10 (13)	
Processed red meat consumption (more than once/day)			
Yes	9 (12.3)	42 (54.5)	**<0.0001**
No	61 (83.6)	31 (40.3)	
Do not Know	3 (4.1)	4 (5.2)	
Elder age (over 70 years old)			
Yes	2 (2.7)	3 (3.9)	0.90
No	64 (87.7)	66 (85.7)	
Do not Know	7 (9.6)	8 (10.4)	
Family history of cancer			
Yes	3 (4.1)	5 (6.5)	**<0.0001**
No	39 (53.4)	71 (92.2)	
Do not Know	31 (42.5)	1 (1.3)	
Getting sunburnt as a child (more than 1)			
Yes	14 (19.2)	14 (18.2)	0.24
No	44 (60.3)	38 (49.4)	
Do not Know	15 (20.5)	25 (32.4)	
Human papillomavirus infection			
Yes	4 (5.5)	2 (2.6)	0.18
No	9 (12.3)	4 (5.1)	
Do not Know	60 (82.2)	71 (92.2)	
Obesity and overweight (BMI greater than 25 Kg/M^2)			
Yes	9 (12.3)	17 (22)	0.25
No	62 (85)	57 (74)	
Do not Know	2 (2.7)	3 (4)	
Physical inactivity (less than 30 min. of 5 times/week)			
Yes	16 (21.9)	9 (11.7)	0.27
No	53 (72.6)	51 (66.2)	
Do not Know	4 (5.5)	7 (9.1)	

Table 3. *Awareness of warning cancer signs among the study participants*

Variable	Medical students N=73 n (%)	Non-medical students N=77 n (%)	P-value
Change in mole appearance			
Yes	2 (2.7)	0 (0)	0.20
No	16 (21.9)	23 (29.9)	
Do not Know	55 (75.3)	54 (70.1)	
Permanent change in bowel or bladder habits			
Yes	6 (8.2)	3 (3.9)	0.30
No	35 (48)	32 (41.6)	
Do not Know	32 (43.8)	42 (54.5)	
Permanent coughing or hoarseness			
Yes	11 (15.1)	9 (11.7)	0.71
No	42 (57.5)	43 (55.8)	
Do not Know	20 (27.4)	25 (32.5)	
Permanent swallowing difficulty			
Yes	4 (5.5)	3 (3.9)	0.44
No	45 (61.6)	41 (53.2)	
Do not Know	24 (31.1)	33 (42.9)	
Permanent unexplained pain			
Yes	35 (48)	14 (18.2)	**<0.001**
No	12 (16.4)	20 (26)	
Do not Know	26 (35.6)	43 (55.8)	
Unhealed sore			
Yes	8 (11)	6 (7.8)	0.79
No	19 (26)	20 (26)	
Do not Know	46 (63)	51 (66.2)	
Unexplained bleeding			
Yes	7 (9.6)	4 (5.2)	0.36
No	45 (61.6)	44 (57.1)	
Do not Know	21 (28.8)	29 (37.7)	
Unexplained losing weight			
Yes	8 (11)	5 (6.5)	0.36
No	25 (34.2)	34 (44.1)	
Do not Know	40 (54.8)	38 (49.4)	
Unexplained swelling or lump appearance			
Yes	41 (56.2)	31 (40.3)	0.14
No	10 (13.7)	13 (16.9)	
Do not Know	22 (30.1)	33 (42.8)	

Similarly, most of the medical and non-medical participants also reported a low level of awareness and unable to recognize the common warning signs of cancer, including permanent change in bowel or bladder habits (8.2% vs. 3.9%), permanent coughing (15.1% vs. 11.7%), permanent swallowing difficulty (5.5% vs. 3.9%), unhealed sore (11% vs. 7.8%), unexplained bleeding (9.6% vs. 5.2%), unexplained losing weight (11% vs. 6.5%). However, permanent unexplained pain was significantly recognized by the respondents of the medical group compared to the non-medical group (48% vs. 18.2%; p<0.001). Although there were no significant findings, respondents were also able to recognize unexplained lump appearance as a warning cancer symptom (56.2% vs. 40.3%), as shown in Table 3. In addition, although there were no significant findings, the medical and non-medical participants reported a low mean knowledge of cancer risk factors (2.24±1.52 vs. 3.11±1.60); and mean awareness of cancer warning signs (1.70±0.91 vs. 1.00±0.81), respectively, as shown in Table 4.

Table 4. *Comparison of mean knowledge and awareness among the study participants*

Variable	Medical students	Non-medical students	P-value
Knowledge of cancer risk factors	2.24±1.52	3.11±1.60	0.69
Awareness of warning cancer signs	1.70±0.91	1.00±0.81	0.56

4. DISCUSSION

Understanding cancer knowledge and awareness among university students can be viewed as a valuable tool for improving cancer prevention, early detection, and survival. In this context, knowledge of cancer risk factors and awareness of symptoms are not isolated events. Most of the students who participated in this study correctly identified certain cancer risk factors, such as smoking and second-hand smoking. These results are consistent with a study conducted by Merten et al. [12] to examine cancer risk factor knowledge among college students. The study found that smoking and second-hand smoke were the most prominent risk factors.

Although there were no significant findings, the medical and non-medical participants reported a low mean knowledge of cancer risk factors. Nevertheless, the non-medical students reported a significant rate of poor knowledge level regarding family history of cancer than the medical students. On the other hand, the medical students reported a significant rate of poor knowledge level regarding alcohol consumption and processed meat consumption than the non-medical students. A possible explanation for the responses displayed by this sample of medical participants regarding these two risk factors might be related to previous data reported that eating more than 90g of red or processed meat each day is considered carcinogenic or drinking two units of alcohol per day could increase the risk of cancer incidence [35, 36]. Although the literature on cancer risk factors is extensive [16, 18], these factors are not well recognised in the current study, and knowledge of cancer risk factors is low in many areas reported by most participants, including medical and non-medical students. Our results are consistent with a previous study conducted by Xu et al. [20] in the USA to examine college students' cancer-preventative knowledge and health behaviours. The study found that participants recognized an average of 6.69 out of 11 risk factors. Similarly, White et al. [21] in a study to assess the prevalence of several cancer risk

factors among young adults reported that obesity, physical inactivity, binge drinking, cigarette smoking, and frequent consumption of red meat were the most common cancer risk factors.

As expected, awareness of cancer signs was no better than knowledge of cancer risk factors, and participants generally had low or no awareness of the most common warning signs of cancer. This is also observed by a low mean awareness of cancer warning signs and symptoms. Recognition of cancer indications in the current study is believed to be low compared to previous studies conducted by Radi et al. [22], Al Qadire et al. [23], and Al-Azri et al. [24]. Generally, the results from these studies found that the majority of respondents were unable to identify the common signs and symptoms of cancer. Moreover, the results of the present study are also consistent with a previous study by Al-Zalabani et al. [25] to explore women's breast cancer knowledge, practices, and screening in primary health care. The findings of this study reveal a lack of knowledge about the warning signs of breast cancer. Another large study conducted by Ahmad MM [26] in Jordan examined the knowledge of cancer among the Jordanian population and found knowledge gaps and inappropriate practices.

Low levels of knowledge and awareness of cancer risk factors and symptoms can be explained by low levels of education. This is supported by the fact that lower educational attainment has been reported to be associated with lower cancer awareness among patients [27, 28]. A study conducted by Macleod et al. [27] found that there is strong evidence of an association between lower education level and delay in breast and colorectal cancers. Many previous studies have shown that the higher the level of education (school and college), the higher the knowledge and awareness [29-31]. However, risk factor knowledge and cancer symptom awareness are low in the current study sample. This is consistent with a previous study reported in Jordan by Mhaidat et al. [32] to assess undergraduate awareness of colon cancer (CRC) warning signs and risk factors. The study included undergraduates from various universities in Jordan, divided into medical and non-medical majors. The study found that CRC perceptions of both warning signs and risk factors were most strongly associated with the educational group of participants. Medical students were significantly more aware of both warning signs and risk factors than other students. In our study, permanent unexplained pain was significantly recognized by the respondents of the medical group compared to the non-medical group ($p<0.001$).

As cancer is a major problem worldwide, there is a need to raise public awareness about early detection and diagnosis of this disease. Therefore, more attention should be paid to health promotion programs. Future health education and health promotion programs should emphasize the links between risk factors and cancer and provide more evidence-based interventions to university students. In addition, more attention should be paid to undergraduate education by improving study programs and involving students in health promotion campaigns. This allows most medical students to disseminate knowledge to other students and includes awareness programs in their education to educate students.

To our knowledge, this study was the first attempt to assess knowledge of cancer risk factors and awareness of the cancer warning signs among university students in Northern Cyprus. However, some limitations should be pointed out. First, this study included some academic disciplines without taking into account other academic professions among universities in Northern Cyprus. Second, because the survey was self-reported, students' understanding of the questions may have been inconsistent. Given these limitations, more research is needed to assess knowledge and awareness of cancer risk factors and warning signs.

5. CONCLUSION

The results of this study revealed gaps in cancer risk factors and cancer warning signs among medical and non-medical students as the participants' knowledge level about the majority of cancer risk factors and warning signs was low. There were very few risk factors correctly known by the participants of both groups, particularly about smoking and second-hand smoking. There is a statistical difference between non-medical students and medical students in terms of knowing risk factors regarding alcohol consumption, consumption of processed red meat, and family history of cancer. Therefore, efforts to focus more attention on increasing cancer knowledge and awareness through continuing education programs involving all university students at various levels that encourage early detection of cancer are necessary.

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Design of the study: AA
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Clinical and Experimental Health Sciences

The Effects of Antenatal Education on Level of Exclusive Breastfeeding in the First Two Months

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ABSTRACT

Objective: Breastfeeding is a wonderful event that requires strength and dedication from mothers. Effective breastfeeding education provided to pregnant women in the prenatal period can increase the success and level of breastfeeding.
This study aimed to determine the effect of prenatal education intervention on the first two-month exclusive breastfeeding level.

Method: This experimental study was carried out at a primary family health center between July 2019 and February 2020. One hundred thirty-three pregnant women were included in the study's control and intervention groups. The Prenatal and postnatal information form, the Infant Feeding Attitude Scale (IIFAS) and the Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF) were used to collect the data.

Results: The first two-month exclusive breastfeeding level was 33.1% in the control group and 68.7% in the intervention group ($p < .05$). The exclusive breastfeeding status in the first two months was adversely affected 10.5 times by feeding food other than breast milk as the first food after birth, 4.3 times by using pacifier-bottles, and 2.8 times by not receiving breastfeeding education. The weekly progression of the gestational week had a positive effect by 1.6 times, and each unit increase in the number of daily breastfeeding had a positive effect of five times ($p<.05$)

Conclusion: Prenatal breast milk and breastfeeding education increased the first two-month exclusive breastfeeding level. The education also had a positive effect on daily breastfeeding frequency, pacifier-bottle use, night breastfeeding levels and water use.
Keywords: Pregnancy, prenatal breastfeeding education, effect on breastfeeding

1. INTRODUCTION

The health of individuals is directly related to their nutrition in early infancy. International organizations state that breastfeeding is the most appropriate nutritional choice for the newborns. All newborns should be breastfed immediately after birth and should be exclusively breastfed for the first six months. Afterwards, breastfeeding should be continued with complementary foods for up to two years (1-3).

Growth retardation, infectious diseases, sudden infant deaths, and allergic diseases are less common in breastfed infants (4,5). Breastfeeding protects against postpartum bleeding, ovarian and breast cancer, osteoporosis, and cardiovascular diseases. Breast milk provides support to the family and social economy as it protects against formula food costs and health problems caused by the use of formula (6-8).

The "Breast Milk Promotion and Baby-Friendly Hospitals Program" has been carried out in cooperation with UNICEF in Turkey since 1991. Moreover, breastfeeding and breast milk counseling is provided to all pregnant women under the "Prenatal Care Program" (9). In Turkey, 71.0% of mothers breastfeed for the first time within one hour after birth. Exclusive breastfeeding decreases from 59.0% in the two-month period to 41.0% in the first six months. The median breastfeeding alone duration is 1.8 months. The exclusive breastfeeding level in the first six months is 41.0% worldwide, and according to a previous study, it was 15.0% for Sanliurfa.

Bad habits such as giving water in the early period and using a pacifier-bottle are frequently seen in mothers (10,11). Despite the implemented programs and support, exclusive breastfeeding has not reached desired levels worldwide, as well as in Turkey and in Sanliurfa. Many mothers stop breastfeeding in the first two months after birth, which is caused by the mother not being ready to deal with postpartum difficulties and from being insecure. The main factor that helps mothers feel adequate during breastfeeding by preparing for the breastfeeding process from pregnancy is prenatal breastfeeding education (12,13).

This study aimed to determine the effect of prenatal education intervention and other factors on the level of exclusive breastfeeding in the first two months.

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2. METHODS

2.1. Type of the Study

This study followed an experimental research approach.

2.2. Ethics

Ethics approval was obtained from the University Faculty of Medicine Non-Interventional Research Ethics Committee (08.04.2019/04). Written permission was obtained from Provincial Health Directorate and verbal consent was obtained from all participants.

2.3. Population and Sample of the Study

This study was conducted in a family health center (FHC) located in a semi-urban area between July 2019 and February 2020. The research was conducted in a single health center. The population of the study consisted of women in the last trimester of their pregnancy (27-40 weeks) registered with the FHC. The inclusion criteria were that the participants spoke Turkish and agreed to participate in the research.

2.3.1. Sample Size

In our previous research in the city, we found the level of only breast milk use in the first 6 months of 52.0%. Since there is no other research conducted in the city on the use of only breast milk, 52.0% was taken as a reference in calculating the sample size (11). In the study, the exclusive breastfeeding level for the first two months was 52.0% with a confidence level of 95% and a power of 80%. At the end of the training, it was aimed to increase the nutritional status of only breast milk by 12% in the first two months (11,14). In the calculation, the necessary sample size formula was used to test a group ratio. The following values are used in the formula:

1.96: Statistical equivalent of 95% confidence interval,

0.52: exclusive breastfeeding reference level,

0.64: target level with 12% increase after training,

0.84: Statistical equivalent of 80% power (Research power is 80%). In light of this aim, the number of participants to be included in both the control and intervention groups was calculated as 133 (15).

2.3.2. Sample Selection-Grouping

In the study, no matching was made between the control and intervention groups in terms of the main variables affecting breast milk. By making a random selection (randomization), the groups will be similar and a sample will be created that will represent the population. The first 133 pregnant women who applied to the FHC and met the required criteria were included in the control group without skipping. Using the same method, the next 133 pregnant women were included in the intervention group without missing any of them. It took seven weeks to identify the participants for the control group and eight weeks to identify the participants for the intervention group.

2.4. Data Collection Tools

The prenatal and postnatal information form, the Infant Feeding Attitude Scale (IIFAS) and the Breastfeeding Self-efficacy Scale-Short Form (BSES-SF) were used to collect the data. The forms were completed using face-to-face interviews with the participants.

2.4.1. Prenatal-Postnatal Information Form

The prenatal information form consisted of 11 questions. In the form, the mother's age, education level, employment status, social security status were requested, along with the father's employment status, family income level, family type, planned pregnancy status, and mother's breastfeeding experience. There were 14 questions in the postnatal information form. In the form, the infant's birth style, birth weight, sex, place of birth were requested, along with the gestational week, the first food given after birth, the first breastfeeding time, the first person to help to breastfeed, pacifier-bottle use status, daily number of breastfeeding, night breastfeeding status and exclusive breastfeeding duration.

2.4.2. Infant Feeding Attitude Scale (IIFAS)

The IIFAS is used to predict breastfeeding time and which formula breastfeeding mothers prefer in infant nutrition. The scale is a five-point likert type, where 1 represents 'strongly disagree' and 5 represents 'strongly agree'. Nine items in the scale contained positive statements about breast milk and eight items were about formula nutrition. The items regarding formula nutrition were scored inversely (1=5, 2=4, 5=1). The participants with a total score of 70-85 were considered to be prone to breastfeeding, a total score of 49-69 represented participants who were undecided in nutritional preference, and a total score of 17-48 represented participants who were prone to formula feeding. Cronbach's alpha internal consistency coefficient was .71 for the scale adapted into Turkish (16). Cronbach's alpha value was found to be .69 in this study.

2.4.3. Breastfeeding Self Efficacy Scale-Short Form (BSES-SF)

This form was created by converting the items of the first form developed by Dennis and Faux (17) in 1999 into future expressions. There were 14 items in the short form. All items were represented by a five-point Likert type rating (1=I am not sure at all, 5=I am always sure). The lowest (14) and the highest (70) scores could be obtained from the scale. Cronbach's alpha value of the form adapted to Turkish was .87 (18). Cronbach's alpha value was found to be .89 in this study.

2.5. Procedure

All participants completed the postnatal information form at the end of the second month after birth. The entired control group was reached after birth. Two participants in the intervention group were excluded from the study due to the death of their infants in the first two months (Figure 1). Antenatal information form, IIFAS and BSES-SF were administered once during the prenatal interview to the groups in the 3rd trimester. The IIFAS and BSES-SF scales were not repeated after birth, as the increase in the level of exclusive breastfeeding in the first 2 months with breastfeeding education meant that the IIFAS and BSES-SF scales were positively affected by the education. It was accepted that both groups received standard breastfeeding counseling from FHC personnel within the scope of prenatal care. After completing the forms, no procedure was applied to the control group, while breastfeeding and breast milk training was provided individually to each participant in the intervention group. In the training, a 15-minute presentation and a video were used. The content included the benefits and content of breast milk, the correct positioning of the baby at the breast, proper breastfeeding and proper infant feeding. At the end of the training, each participant asked her questions in a five-minute question and answer session. A training booklet and brochure were then given to the participants. Educational materials were prepared using the publications of the Ministry of Health of the Republic of Turkey and of UNICEF (19,20). The training content included all the information that the ministry recommended to be provided in the prenatal period.

2.6. Statistical Analysis

A two-step approach was applied in the analyses. In the first stage, the effectiveness of the educational intervention was evaluated. In the second stage, the effect of the educational intervention was re-examined by the researchers together with the factors that were not taken under control. The Kolmogorov-Smirnov test was used to determine the suitability of the data for a normal distribution. Descriptive statistics (number, percentage, median, minimum and maximum), the Mann-Whitney U-test, and the chi-squared tests were used to compare the control-intervention groups and to determine the factors affecting the first two-month exclusive breastfeeding status. Logistic regression analysis was performed to evaluate the effect of educational intervention on the first two-month exclusive breastfeeding status together with other variables. The variables with significant effect in univariate analyses were as follows: breast milk and breastfeeding education status, mother's education status, type of birth, first food given after birth, breastfeeding status in the first half hour, pacifier-bottle use status, night breastfeeding status, gestational week, birth weight, daily breastfeeding number, BSES-SF score, and IIFAS. The Backward Stepwise (conditional) method was followed in the logistic regression analysis.

3. RESULTS

The control and intervention groups were similar in terms of major prenatal variables that may affect the breastfeeding status (p>.05) (Table 1).

Table 1. *Distribution of prenatal variables of mothers by control and intervention groups*

	Control Group		Intervention Group			
Characteristics	**N**	**%***	**N**	**%***	**χ^2**	**p**
Educational status						
Illiterate	38	28.6	27	20.6	4.09	.53
Literate (not finished elementary school)	14	10.5	17	13.0		
Elementary school	33	24.8	42	32.1		
Secondary school	25	18.8	21	16.0		
High school	10	7.5	8	6.1		
University and higher	13	9.8	16	12.2		
Employment status						
Working	16	12.0	22	16.8	0.86	.35
Not working	117	88.0	109	83.2		
Employment status of fathers						
Working	121	91.0	110	84.0	2.35	.12
Not working	12	9.0	21	16.0		
Income level						
Income less than expenses	95	71.4	102	77.9	1.12	.28
Income is equivalent to expenses and higher	38	28.6	29	22.1		
Social security status						
Yes	72	54.1	65	49.6	0.37	.54
No	61	45.9	66	50.4		
Family type						
Extended	45	33.8	40	30.5	0.19	.65
Nuclear	88	66.2	91	69.5		
Planned pregnancy						
Yes	92	69.2	90	68.7	0.00	1.00
No	41	30.8	41	31.3		
Breastfeeding experience						
Yes	104	78.2	94	71.8	1.13	.28
No	29	21.8	37	28.2		
	Median (Min. – Max.)		**Median (Min. – Max.)**		**MWU**	**p**
Age of mother	27(16-42)		27(16-41)		8085.0	.31
Number of children	2(0-9)		2(0-9)		8018.5	.25
BSES-SF score**	53(26-68)		52(32-70)		8632.0	.89
IIFAS* scale score**	58(39-83)		59(50-70)		7775.5	.13

**Column Percentage,*

***BSES-SF: Breastfeeding Self Efficacy Scale-Short Form*

****IIFAS: Infant Feeding Attitude Scale*

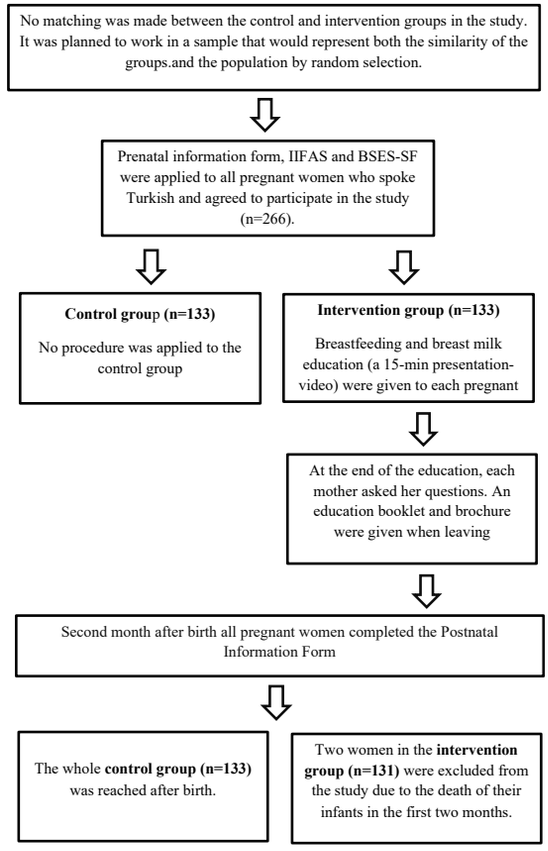

Figure 1. *CONSORT Flow diagram*

The median age of the participants in the control and intervention was 27, and the median number of children they had was two. The median self-efficacy score was 53 in the control group and 52 in the intervention group. The median IIFAS score in the control group was 58, 4.0% of the group were inclined to formula, 9.0% were inclined to breastfeed, and 88.0% were undecided about the way of feeding their baby. The median IIFAS score in the intervention group was 59. 2.3% of the group were inclined to breastfeed, and 97.7% were undecided on the choice of nutrition *(p*>.05) (Table 1).

Initiation of breastfeeding in the first half hour was 43.6% in the control group and 48.1% in the intervention group. Of the participants who started breastfeeding after the first half hour, 44.1% stated that their baby had a health problem, 24.5% stated that they did not have milk, 22.4% stated that their health problems and 9.1% did not want to breastfeed. There was no difference between the control and intervention groups in terms of the variables of first food given and breastfeeding status in the first half hour after birth (*p*>.05). Pacifier-bottle use was higher in the control group (73.7%) than in the intervention group (54.2%) (*p*<.05). The night-time breastfeeding levels of the participants in the intervention group was 96.9% better than the control group (88.7%) (*p*<.05) (Table 2). The median number of breast feedings per day was higher in the intervention group (10 times a day) than in the control group (eight times a day) (*p*<.05) (Table 2).

Table 2. *Distribution of breastfeeding characteristics by control and intervention groups*

Characteristics	Control Group N	Control Group %*	Intervention Group N	Intervention Group %*	χ^2	p
First food after birth						
Breast milk	79	59.4	90	68.7	2.092	.148
Other	54	40.6	41	31.3		
Breastfeeding within the first half hour after birth						
Yes	58	43.6	63	48.1	0.369	.544
No	75	56.4	68	51.9		
Pacifier-bottle use						
Yes	98	73.7	71	54.2	10.049	**.002**
No	35	26.3	60	45.8		
Night breastfeeding status						
Yes	118	88.7	127	96.9	5.510	**.019**
No	15	11.3	4	3.1		
Daily number of breastfeeding	**Median (Min. – Max.)**		**Median (Min. – Max.)**		**MWU**	**p**
	8(0-13)		10(0-13)		5444.5	**<.001**

**Column Percentage*

Table 3. *Distribution of the first two-month exclusive breastfeeding status by control and intervention groups*

Variable	Control Group N	Control Group %*	Intervention Group N	Intervention Group %*	χ^2	p	OR	95% Confidence interval
First two-month exclusive breastfeeding								
Yes	44	33.1	90	68.7	32.091	**<.001**	2.1	1.66-2.85
No	89	66.9	41	31.3	32.091			

**Column Percentage, OR: Odds Ratio*

The first two-month exclusive breastfeeding was 33.1% in the control group and 68.7% in the intervention group, which indicated that the breast milk and breastfeeding education increased the first two-month exclusive breastfeeding level 2.1 times (*p*<.05) (Table 3).

The participants in the control and intervention groups stated that the most common reason for not only feeding breast milk for the first two months was due to insufficient breast milk. This was followed by drinking water and health problems in the babies, respectively. From the distribution of reasons for not only feeding breast milk in the first two months, which is common for both groups, insufficient milk (32.7%) and drinking water (20.0%) were lower in the intervention group than in the control group (67.3% and 80.0%, respectively) (*p*<.05). Except for breast milk and breastfeeding education, the factors affecting exclusive breastfeeding in the first two months were examined. The level of exclusive breastfeeding in the first two months of illiterate women was lower (30.8%) (*p*<.05).

Table 4. *Logistic regression model of factors affecting the first two-month exclusive breastfeeding status (latest model, step 6)*

Variables	B	Standard deviation	p	OR	95% Confidence interval
Pregnancy week	-0.4	0.2	.044	0.6	0.40-0.98
Not taking breast milk as the first food after birth	2.3	0.7	.002	10.5	2.45-45.36
Not using pacifier-bottle	1.4	0.5	.004	4.3	1.61-11.94
Daily number of breastfeeding	-1.4	0.2	.000	0.2	0.14-0.37
Not receiving breast milk and breastfeeding education	1.0	0.4	.029	2.8	1.11-7.09

OR: Odds Ratio

Among the prenatal variables questioned, the mother's employment status, father's employment status, income level, social security status, family type, planned pregnancy status, and breastfeeding experience variables did not affect the first two-month exclusive breastfeeding status (p>.05). When the effect of the variables encountered during and after birth was examined, it was determined that the first two-month exclusive breastfeeding level was higher in the participants who had a normal birth (57.3%) than those who gave birth by c-section (42.1%); higher in those who received breastfeeding as the first food in the first half hour (66.3%) than in those who did not (39.2%); higher in those who did not use pacifier-bottles (83.2%) than those who did (32.5%); higher in those who breastfed at night (54.7%) than those who did not (0.0%); higher in those who received prenatal breastfeeding education (68.7%) than those who did not (33.1%) (p<.05).

The baby's gender, place of birth, and first breastfeeding assistant variables did not affect the first two-month exclusive breastfeeding level (p>.05). The first two-month exclusive breastfeeding infants were found to have a higher gestational week, birth weight, daily breastfeeding number of mothers, self-efficacy score, and IIFAS score than non-breastfeeding infants (p<.05). The maternal age and number of children variables did not affect the first two-month exclusive breastfeeding status (p>.05).

In the logistic regression model, the exclusive breastfeeding status in the first two months was adversely affected 10.5 times by feeding food other than breast milk as the first food after birth, 4.3 times by using pacifier-bottles, and 2.8 times by not receiving breastfeeding education. The weekly progression of the gestational week had a positive effect by 1.6 times, and each unit increase in the number of daily breastfeeding had a positive effect of five times (p<.05) (Table 4).

4. DISCUSSION

The study was conducted in a region with low-income families. Most of the participants had primary or lower educational levels, were unemployed, and had no social security. A large family structure is often seen in the region (Table 1). In this study, as a result of the educational intervention, the level of exclusive breastfeeding increased 2.1 times in the first two months (Table 3). In the study, an increase was achieved with breastfeeding education, well above the target of 12%. Some studies in the literature also support this result (21,22). In another study, the exclusive breastfeeding status of mothers who did not receive prenatal breastfeeding education was adversely affected 1.73 times in the 6th week and 1.92 times in the 3rd month (23). Mattar et al (24) increased the exclusive breastfeeding level by 29% in the first six weeks with prenatal breastfeeding education. Individual prenatal breastfeeding education applied by Chekol et al (25) to mothers increased breastfeeding rates in the second week after birth and positively affected the duration of breastfeeding. However, in a study conducted in Hong Kong, prenatal breastfeeding education could not increase the exclusive breastfeeding levels in the 6th postnatal week or in the 3rd postnatal month. Researchers argued that prenatal breastfeeding education alone was insufficient in societies with high breastfeeding levels and should be supported by postnatal education (26). Consistent with the results, in this study, conducted in the region where education and socioeconomic levels were low, it was determined that prenatal breastfeeding education achieved more success in exclusive breastfeeding and the education had much more positive effects (27).

The prenatal breastfeeding education applied in this study also had a positive effect on the frequency of pacifier-bottle use, night breastfeeding, and breastfeeding (Table 2). Nonetheless, the first food and first breastfeeding time after birth did not demonstrate any positive results after the education. It is understood that prenatal breastfeeding education alone is not sufficient in the onset and continuation of breastfeeding in the early period and the counseling and support provided by postnatal hospital health personnel in the are also vital (26).

In the study, the breastfeeding level was 98.5% in the control and intervention groups for a while. The continuation of breastfeeding for the desired period is a substantial problem. Breast milk and breastfeeding education provided a significant increase in the first two-month exclusive breastfeeding level. However, it should not be overlooked that other factors are also effective on the process. The use of pacifier-bottles decreased the first two-month exclusive breastfeeding by 4.4 times (Table 4). In many studies, it has been reported that the use of pacifier-bottles adversely affects breastfeeding and shortens the duration of exclusive breastfeeding. These apparatuses used to calm the infant cause nipple confusion in the infant. This confusion leads to less breastfeeding and reduced milk production, thus, early introduction of additional food for the baby (11,28,29). The negative effects on breastfeeding make it necessary to combat pacifier-bottle

use. This research has shown that the use of pacifier-bottles can be reduced from 73.0% to 54.0% with education.

In this study, the failure to start breastfeeding the newborn negatively affected the continuation of the first two-month exclusive breastfeeding by 10.3 times (Table 4). Across Turkey, food intake before breastfeeding is an essential problem with 24.0% (10). The first feeding of the newborn with breast milk after birth increases the likelihood of successful breastfeeding continuation (30).

Feeding the newborn with substances or liquids before breastfeeding is called prelacteal feeding (19,20). Prelacteal feeding, which is defined as not performing the first breastfeeding, leads to the failure of mother-infant contact. This results in the absence of milk and the continuation of nutrition with foods other than breast milk (31). Especially during c-section deliveries, problems are encountered in the first breastfeeding due to delays in milk production and surgical site pain. Mothers who give birth by c-section are at higher risk of performing the first feed with foods other than breast milk compared to mothers who give birth naturally (32,33). As a matter of fact, in this study, exclusive breastfeeding was found to be lower in the participants who gave birth by c-section (42.1%) than those who had a natural birth (57.3%). Hospitals also play a large role in starting the first postnatal nutrition with foods other than breast milk. In the first feed, the encouragement of health personnel in hospitals, especially regarding the use of formula, causes the first step to be taken incorrectly. Therefore, the behavior of the healthcare personnel in directing the mother is crucial for the continuation of exclusive breastfeeding (34). Early initiation of breastfeeding is a requirement of being a baby-friendly hospital. In this respect, the fact that all births took place in the hospital should be seen as an advantage in the study and it should be considered as an important opportunity to start breastfeeding (35).

In this study, the most common reason for mothers to start breastfeeding late is due to health problems in their infants. It is estimated that premature births contribute to health problems that occur in the first moments of life. Starting breastfeeding and continuing breastfeeding in premature babies is more difficult than in full-term babies. The need to stay in incubators and receive health care increases in premature births. It causes delays in mother-infant contact, thus, delays in the first breastfeeding. Preterm births also reduce exclusive breastfeeding levels (36).

As a matter of fact, in this study, the increase in gestational week positively affected the first two-month exclusive breastfeeding by 1.6 times. The increase in the number of daily breastfeeding in the study positively affected the first two-month exclusive breastfeeding by five times. (Table 4). One of the main criteria for adequately producing breast milk and continuing breastfeeding is the number of daily breastfeeding (11,37). Prenatal breastfeeding education provided a successful increase in breastfeeding frequency. The increase in the frequency of breastfeeding meets the need for water as well as adequate breastfeeding. In countries with hot climates, mothers worry that their babies are thirsty. Nevertheless, a baby who receives enough breast milk, the majority of which is water, can meet all their water needs. Water use was found to be the second most common cause of deterioration of the first two-month exclusive breastfeeding status in the study. The hot summer season in Sanlıurfa is the main reason for this perception (11). In a study conducted in Mauritius, the most common reason that negatively affected exclusive breastfeeding was giving water to babies. This reason was followed by starting work and the lack of milk (38).

In this study, the most common reason for an early transition to additional food was the lack of milk. Mothers are concerned that their milk will not be sufficient especially in the first days after birth due to reasons such as having a premature baby, c-section delivery, incorrect positioning and attachment, and incorrect breastfeeding (36). Many studies have demonstrated the concern that breast milk will not be sufficient as the main reason for the early transition to supplementary food (39,40). 60% of mothers, who start breastfeeding, stop breastfeeding earlier than the recommended period. Mothers most often have this feeling when their babies cry a lot and stop breastfeeding regardless of their baby's age and start formula food or additional food (41). In accordance with the literature, breast milk and breastfeeding education provided an improvement in both drinking water levels and in the perception of lack of milk in the intervention group (13).

Limitations of the Research

In the study, it was preferred to study the short-term results of the first two months due to the difficulties in follow-ups and the time constraints in the field in showing the effect of prenatal education on the status of exclusive breastfeeding.

5. CONCLUSION

Breast milk and breastfeeding education increased the first two-month exclusive breastfeeding level by 2.1 times. The educational intervention had a positive effect on daily breastfeeding frequency, night breastfeeding level, pacifier-bottle use habit, insufficient breast milk perception, and water use. Early onset and continuation of breastfeeding depend on qualified prenatal breastfeeding education and effective support mechanisms in the maternity hospital.

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Design of the study: SG, İK
Acquisition of data for the study: SG
Analysis of data for the study: SG, İK
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Clinical and Experimental Health Sciences

A Scale Development Study: The Vitamin D Health Belief Scale According to The Health Belief Model

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ABSTRACT

Objective: This study was conducted to develop Vitamin D Health Belief Scale based on the health belief model in adult women and determine its validity and reliability.

Methods: The sample of the study consisted of 404 women who were aged between 18 and 65, volunteered to participate in the study, and met study criteria. The theoretical framework of the scale was based on the health belief model. During the scale development stage, exploratory factor analysis and index values were evaluated by using confirmatory factor analysis, item-total correlation, and mean scores.

Results: The content validity index of the scale was found as 91.52%. As a result of the factor analysis, the variables were gathered under 6 factors with a total explained variance of 58.22%. Cronbach's alpha value of the scale was determined as.884.

Conclusion: As a result of all analyses, a 5-point Likert-type scale that consisted of 31 items was developed. Six factors were obtained from the scale: perceived sensitivity, caring, health motivation, perceived benefits, perceived barriers, and self-efficacy. The total score of the scale gives the Vitamin D Health Belief score. The lowest and highest scores on the scale which consists of 31items are 31 and 155 respectively. It is recommended to use this scale to determine vitamin D health beliefs in adult women.

Keywords: VitaminD, health belief scale, women, reliability, validity.

1. INTRODUCTION

Vitamin D, which is a fat-soluble vitamin, functions like a hormone in the body. It takes part in calcium absorption, bone development, and bone remodeling. (1) The Food and Drug Administration (FDA) has reported that vitamin D is an important factor in the control of serum calcium levels and bone homeostasis (Title 21: Food and Drugs Part 101 Food) (2). The functions of vitamin D include keeping serum calcium and phosphorus levels within a certain range, stimulating intestinal calcium absorption, and stimulating the activity of osteoclasts in the bone (3,4). It has been reported that one million people in the world suffer from vitamin D deficiency, and babies, girls, and women with pregnancy in almost all age groups are affected more than others (5,6). However, recent studies have shown that vitamin D deficiency may play a role in many chronic diseases, including cardiovascular diseases, diabetes, hypertension, depression, and autoimmune diseases, especially cancers(7-10). In fact, it has been reported that the coronavirus disease has been seen more frequently, it has progressed more severely, and mortality has increased significantly in individuals with vitamin D deficiency during the COVID-19 pandemic. It has been stated that the probability of catching the disease and the severity and mortality of the disease decrease in people with adequate vitamin D levels or who are given vitamin D (11). There is very little information about individuals' knowledge and beliefs about and attitudes towards vitamin D (10,12).

Some studies conducted on vitamin D knowledge and behavior have shown that women do not know how to benefit from vitamin D and cannot state vitamin D sources correctly (10,13). Also, 63.2% of the women in a study conducted in China and 53% of the women in a study conducted in Vietnam stated that they did not like to be exposed to sunlight (14,15). In another study conducted in Saudi Arabia, only 31% of the participants stated that vitamin D had an effect on bones and 77% had not heard anything about vitamin D (16). Similarly, in a study conducted with university students in China, 68% of the students stated that they did not have accurate knowledge about vitamin D and that vegetables and fruits were important sources of vitamin D (14). Many theories and conceptual models help nurses to prevent diseases and improve health (15,17). One of these models is the "Health Belief Model." It is the most commonly used model to explain health behaviors. The model explains determining factors related to the implementation of preventive health behaviors (18). When the health belief model is considered within the scope of health behaviors, it is the first model that has been adapted to reduce the probability of catching a disease and the severity of the disease and to prevent the disease as a result of health behaviors to be taken. This model guides us to learn about individuals' beliefs and perceptions about a disease (19).

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The Health Belief Model also motivates individuals to acquire positive health behaviors and avoid negative health behaviors. (18, 20). As a result, a vitamin D health belief scale is needed to find out women's level of attitudes, knowledge, and beliefs about vitamin D, which is an important problem, especially for them. No scale has been developed on this subject in Turkey. The aim of this study is to develop a Vitamin D Health Belief Scale, which is appropriate for Turkish society, for adult female individuals, and to determine its psychometric properties.

2. METHODS

2.1. Type of the Study

This study was conducted in a methodological descriptive research design to develop a vitamin D health belief scale for adult women and to determine its psychometric properties.

2.2. Study Setting

The study was conducted in a family health center in Istanbul province. The center provides primary health care, adult health screenings, and treatment services.

2.3. Population and Sample of the Study

The sample of the study consisted of female individuals who were literate, were aged between 18 and 65 presented to the family health center between June 2018 and September 2018, and agreed to participate in the study (Count of Items): (Count of observations/persons) ratio, which is a sample size calculation method suggested for scale development studies was used for calculating the study sample. According to this calculation method, a ratio of 5-30 observations per item is recommended. (21) The study was completed with 404 female individuals (n=404). In the literature, there are criteria regarding the determination of the sample group in relation to the number of items applied. However, it is stated in the literature that the sample size is very good with 500 people and excellent with 1000 people. From this point of view, the number of samples was kept high (22).

2.4. Data Collection

Data were collected based on self-reports under the guidance of the researcher. Before the draft form of the scale was applied to the study group, it was piloted to a small group (not included in the study, n=40) meeting the inclusion criteria of the study to test the intelligibility of the items. Afterward, the questionnaire was applied to 404 people. The purpose of the study and data collection methods were explained to the FHC administrators. After necessary permissions were obtained from the managers of the institution, the data collection tools were applied to the participants by the researcher. The data collection tools consisted of an information form, a demographic questionnaire with items about age, gender, educational status, and individual characteristics, and the final form of the scale. The scale development process took place in three stages.

Stage 1: Content Analysis and Item Production

Items should be defined in an observable and measurable way based on the theoretical definition of the feature to be measured. In the literature, it is stated that an item pool can be created by examining the scales developed related to the subject during the production of the items (23). However, no scale on health beliefs about vitamin D was found in the literature. During the production of the scale items, the following types of studies were utilized:(a) studies on vitamin D deficiency in women; (b) studies on the factors affecting women's knowledge, attitudes, and behaviors about vitamin D; (c) scale development studies in which health belief model was utilized as a framework. One of the most frequently used models in nursing in explaining individuals' health behaviors is the Health Belief Model (HBM). The model explains the determining factors for implementing preventive health behaviors. The theoretical framework of the scale developed in this study was created in line with the Health Belief Model (HBM). This allowed all levels of compliance to be measurable with a single measurement tool. An item pool that covered the six domains of HBM (perceived sensitivity, caring, health motivation, perceived benefits, perceived barriers, and self-efficacy) was created. The 39-item draft version of the scale was prepared by using the items selected from the item pool. The questions on the Osteoporosis Health Belief Scale developed by Kim Horan were used to create the item pool (24). Special care was taken to ensure that the items on the draft version were clear and intelligible. The evaluation style of the scale items was determined so that the items could be scored. It was decided to use a five-point Likert-type scale to evaluate each item that determined the feature to be measured. The options for scoring each item were as follows: "strongly disagree," 1 point; "disagree," 2 points; "undecided," 3 points; "agree," 4 points; "strongly agree," 5 points (25).

Stage 2: Content Validity Index

The draft scale was submitted to 10 academic nurses to determine its content validity. A space was left under each item to allow expert academicians to make explanations, and the experts were told that they could make corrections on the items if necessary. Experts were asked to evaluate each item on a four-point scale with the following options: very appropriate/very relevant (4 points); appropriate/relevant (3 points); somewhat appropriate/somewhat relevant (2 points); inappropriate/unrelated (1 point). Both item level (I-CVI) and scale level (S-CVI) content validity were calculated. (26). The I-CVI was obtained by dividing the count of experts who gave 3 or 4 points to an item by the total count of experts. The S-CVI was calculated by the ratio of the count of items that each expert gave 3 or 4 points to (28). After the forms were collected from the experts, all the evaluations were

combined into a single form. The item level CVI values varied between 80 and 100, with the mean value being 91.53. The scale level CVI values varied between 64.10 and 100, with the mean value being 91.52. The values obtained as a result of the content validity evaluation of the scale were higher than the recommended value of 90 (27), and it was decided that the scale had good content validity.

Phase 3: Pilot Study

The pilot study of the draft form of the scale was conducted on 40 female individuals to test the readability and intelligibility of the items. No changes were made to the scale items as a result of this study.

2.5. Statistical Analysis of Data

The data obtained in the study were analyzed on the SPSS (Statistical Package for Social Sciences) for Windows 22.0 and AMOS software packages. The kurtosis and skewness values of the normal distribution of the scale items were examined. In the relevant literature, it is accepted as a normal distribution that the results of the kurtosis skewness values of the variables are between +2.0 and – 2.0 The kurtosis and skewness values of the scale items were found between +2.0 and – 2.0. (27) Correlation coefficients were calculated to examine the distribution of each item. Construct validity of the scale was examined by using exploratory factor analysis. The varimax rotation method was used to maximize the variance explained in the exploratory factor analysis performed to examine the factor structure of the scale. Principal component analysis of exploratory factor analysis was used. The count of the factors of the scale was determined by evaluating the eigenvalue of each factor. The Barlett test was used to determine the factor loads of the Vitamin B Health Belief Scale, the regression coefficients of the items, and the relationship between the variables included in the factor analysis. Data collected from the field related to the scale were analyzed by using descriptive statistics, such as counts, percentages, means, and standard deviation values.

2.6. Ethical Aspects of the Study:

Before the research was initiated, the approval of the Ethics Committee of a university was obtained (date: June 4, 2018, protocol no: 150). During the data collection phase, participants were informed about the purpose of the study, and their verbal consent was obtained.

3.RESULTS

3.1. Characteristics of Participants

Of the participants, 32.2% were aged between 21 and 30, and 54% were single. It was determined that 59.2% of the participants were university graduates, 46.8% had been diagnosed with vitamin D deficiency before, and that 58.7% had received information about vitamin D before.

3.2. Content Validity

The CVR values of the scale items ranged from 0.8 to 1, and the CVI value was found as.915.

3.3. Exploratory Factor Analysis

Cronbach's alpha, which is the internal consistency coefficient, was calculated to determine the reliability of 31 items on the Vitamin D Health Belief Scale. The general reliability of the scale was found to be very high with an alpha value of 0.884. The explanatory factor analysis method was applied to reveal the construct validity of the scale. As a result of the Barlett test (p=.000<.05) it was determined that there was a relationship between the variables included in the factor analysis**.** As a result of the test (KMO=.896>.60), it was determined that the sample size was adequate for factor analysis. The correlation value of the scale's split-half method was found to be.899 The factor structure determined by using explanatory factor analysis was tested with confirmatory factor analysis in the factor analysis, the varimax method was chosen to ensure that the structure of the relationship between the factors remained the same. As a result of factor analysis, the variables were gathered under 6 factors with a total explained variance of 58.22%. The factor structure of the scale is shown below (Table 1)

3.4. Confirmatory Factor Analysis and Construct Validity

The criteria for the goodness of fit obtained as a result of confirmatory factor analysis are given below (Table 2). The findings obtained in the research were evaluated at.05 significance level.

The diagram of confirmatory factor analysis is given below. (Figure 1)

Figure 1. Diagram of the confirmatory factor analysis for the vitamin D health belief scale

Standardized factor loads, t values, and explanatory (R^2) values of the items are given below (Table:3).

The reliability analysis of the scale was conducted, and the alpha coefficient was found to be.884. The item analysis regarding the effect of items on internal consistency is given below (Table 4)

The difference of the scale scores between the Lower 27% group and the Upper 27% group is given below (Table 5)

***Table 1**. Factor structure of the vitamin D health belief scale*

Dimension	Factor load
Self-efficacy (Eigenvalue =8.887; Explained variance=12.405; Alpha=0.868)	
1. I can sunbathe correctly.	0.791
2. I can sunbathe at the appropriate time and duration (I sunbathe my face, arms, and legs for 10-15 minutes 2-3 times a week).	0.789
3. I can prevent fractures stemming from vitamin D deficiency.	0.767
4. I know the steps that I need to take to protect my bone health.	0.761
5. I believe that I can feed on foods that are rich in vitamin D (salmon, shrimp, mushrooms, liver, milk, yogurt, etc.).	0.707
Caring (Eigenvalue =3.167; Explained variance =11.770; Alpha=0.850)	
1. Suffering from vitamin D deficiency is a serious problem for me.	0.762
2. I am worried that vitamin D deficiency is a common problem in society.	0.740
3. I am worried about the damages that will occur due to vitamin D deficiency in the future.	0.666
4. Vitamin D deficiency can cause other diseases in women apart from fractures.	0.666
5. Vitamin D deficiency can lead to disorders, such as cardiovascular diseases, blood pressure, diabetes, and cancer.	0.613
6. If I do not eat enough calcium-containing foods, I'm more likely to have a vitamin D deficiency.	0.540
7. If I consume small amounts of calcium-containing foods, I will suffer from vitamin D deficiency.	0.535
Perceived sensitivity (Eigenvalue =2.055; Explained variance =9.767; Alpha=0.787)	
1. I think I will have vitamin D deficiency at some point in my life.	0.721
2. I think that I will suffer from vitamin D deficiency if I do not benefit from sunlight enough.	0.682
3. I think that vitamin D is necessary for my bone health.	0.680
4. As a woman, I am very likely to suffer from vitamin D deficiency.	0.625
5. My vitamin D absorption may slow down as I get older.	0.577
Perceived benefits (Eigenvalue =1.457; Explained variance =9.337; Alpha=0.815)	
1. If I do not suffer from vitamin D deficiency, I will not experience osteoporosis.	0.750
2. If I use milk and dairy products (yogurt, buttermilk, cheese, etc.) regularly, I will not suffer from vitamin D deficiency.	0.718
3. If I get enough vitamin D, my bones are less likely to break when I fall.	0.672
4. If I eat foods rich in vitamin D (salmon, shrimp, mushrooms, milk, yogurt, egg yolk, etc.), I will be less likely to suffer from vitamin D deficiency.	0.665
5. If I sunbathe my face, arms, and legs for 10-15 minutes 2-3 times a week, I will be less likely to suffer from vitamin D deficiency.	0.497
Perceived barriers (Eigenvalue =1.294; Explained variance =8.598; Alpha=0.755)	
1. I do not have the opportunity to sunbathe in my living environment.	0.807
2. It is not possible for me to sunbathe for 15-20 minutes a day.	0.740
3. I do not like sunbathing (in open areas, such as pools, seaside, balcony, park, etc.).	0.699
4. My dressing style prevents me from taking advantage of sunlight.	0.670
5. I sometimes overlook the importance of the sun for vitamin D synthesis.	0.588
Health motivation (Eigenvalue =1.188; Explained variance =6.343; Alpha=0.733)	
1. I would like my vitamin D deficiency to be determined early.	0.788
2. Maintaining my bone health is very important to me.	0.779
3. I take care to eat foods rich in vitamin D (salmon, fish, shrimp, mushrooms, yogurt, milk, etc.).	0.448
4. I seek new information to protect and improve my health.	0.419

Total variance =%58.22; General reliability (Alpha)=0.884ww

***Table 2.** The goodness of fit indices obtained as a result of confirmatory factor analysis for the vitamin d health belief scale*

Index	Normal value	Acceptable value	Vitamin D Health Belief Scale
χ2/sd	<2	<5	2.07
GFI	>0.95	>0.90	0.90
AGFI	>0.95	>0.90	0.90
CFI	>0.95	>0.90	0.91
RMSEA	<0.05	<0.08	0.05
RMR	<0.05	<0.08	0.07

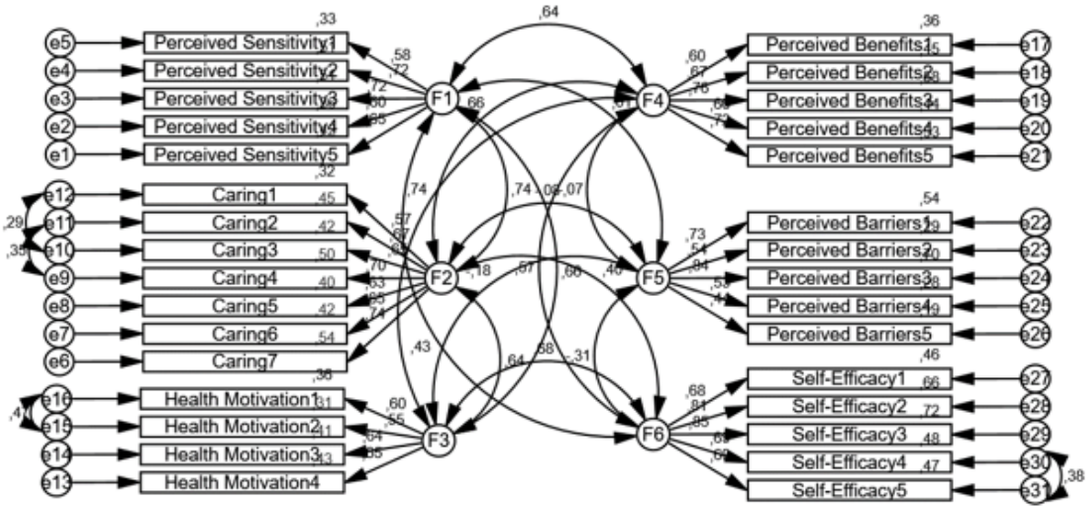

Figure 1. *Diagram of the confirmatory factor analysis for the vitamin d health belief scale*

Table 3. *Factor loads of the vitamin D health belief scale and regression coefficients for the items*

Items		Factor	β	Std. β	S. Error	t	P	R^2
Perceivedsensitivity5	<—-	F1	1,000	0,647				0,470
Perceivedsensitivity4	<—-	F1	1,021	0,603	0,101	10,106	p<,001	0,478
Perceivedsensitivity3	<—-	F1	1,069	0,717	0,092	11,565	p<,001	0,716
Perceivedsensitiviyt2	<—-	F1	1,213	0,717	0,105	11,567	p<,001	0,655
Perceivedsensitivity1	<—-	F1	1,000	0,579	0,102	9,770	p<,001	0,457
Caring7	<—-	F2	1,000	0,735				0,544
Caring6	<—-	F2	0,976	0,648	0,081	12,072	p<,001	0,463
Caring5	<—-	F2	0,876	0,632	0,074	11,774	p<,001	0,700
Caring4	<—-	F2	0,971	0,704	0,075	13,015	p<,001	0,523
Caring3	<—-	F2	0,978	0,649	0,081	12,062	p<,001	0,538
Caring2	<—-	F2	0,975	0,674	0,078	12,433	p<,001	0,525
Caring1	<—-	F2	0,849	0,565	0,081	10,472	p<,001	0,440
Healthmotivation4	<—-	F3	1,000	0,653				0,576
Healthmotivation3	<—-	F3	1,002	0,641	0,098	10,183	p<,001	0,452
Healthmotivation2	<—-	F3	0,639	0,553	0,071	9,007	p<,001	0,447
Healthmotivation1	<—-	F3	0,745	0,603	0,077	9,684	p<,001	0,463
Perceivedbenefits1	<—-	F4	1,000	0,604				0,439
Perceivedbenefits2	<—-	F4	1,097	0,672	0,104	10,569	p<,001	0,410
Perceivedbenefits3	<—-	F4	1,221	0,759	0,107	11,451	p<,001	0,426
Perceivedbenefits4	<—-	F4	1,118	0,663	0,107	10,470	p<,001	0,477
Perceivedbenefits5	<—-	F4	1,167	0,725	0,105	11,123	p<,001	0,454
Perceivedbarriers1	<—-	F5	1,000	0,734				0,422
Perceivedbarriers2	<—-	F5	0,803	0,538	0,083	9,661	p<,001	0,496
Perceivedbarriers3	<—-	F5	1,192	0,837	0,091	13,073	p<,001	0,469
Perceivedbarriers4	<—-	F5	0,791	0,534	0,083	9,583	p<,001	0,420
Perceivedbarriers5	<—-	F5	0,596	0,439	0,075	7,916	p<,001	0,541
Self-efficacy1	<—-	F6	1,000	0,676				0,436
Self-efficacy2	<—-	F6	1,273	0,810	0,091	13,939	p<,001	0,514
Self-efficacy3	<—-	F6	1,276	0,846	0,089	14,370	p<,001	0,514
Self-efficacy4	<—-	F6	1,050	0,691	0,086	12,191	p<,001	0,482
Self-efficacy5	<—-	F6	0,987	0,685	0,082	12,095	p<,001	0,419

Table 4. *Item analysis*

	Scale score when the item is removed	Variance when the item is removedz	Item-total correlation	Cronbach's alpha when the item is removed
Perceivedsensitivity1	109,3193	224,630	,490	,879
Perceivedsensitivity2	109,0297	222,873	,561	,877
Perceivedsensitivity3	108,7450	225,491	,547	,878
Perceivedsensitivity4	109,3094	226,244	,448	,880
Perceivedsensitiviyt5	109,1386	224,685	,554	,878
Caring1	109,4307	224,931	,469	,879
Caring2	109,3515	221,315	,609	,876
Caring3	109,4183	223,549	,511	,878
Caring4	109,3020	223,541	,565	,877
Caring5	109,5124	225,551	,492	,879
Caring6	109,3886	224,258	,488	,879
Caring7	109,1955	223,944	,559	,878
Health motivation1	108,7178	227,474	,517	,879
Health motivation2	108,6064	229,371	,475	,880
Health motivation3	109,1881	225,285	,464	,879
Health motivation4	109,1634	224,946	,487	,879
Perceived benefits1	109,3738	225,972	,460	,879
Perceived benefits2	109,1906	223,455	,553	,878
Perceived benefits3	109,1906	222,854	,583	,877
Perceived benefits4	109,5545	224,347	,504	,879
Perceived benefits5	109,2203	222,693	,588	,877
Perceived barriers1	110,3342	239,816	,005	,890
Perceived barriers2	110,1139	237,287	,060	,890
Perceived barriers3	110,2450	237,292	,067	,889
Perceived barriers4	110,4233	241,471	-,043	,892
Perceived barriers5	110,1807	233,508	,179	,886
Self-efficacy1	109,2772	226,275	,454	,880
Self-efficacy2	109,4282	225,913	,435	,880
Self-efficacy3	109,4629	226,428	,439	,880
Self-efficacy4	109,4678	224,915	,485	,879
Self-efficacy5	109,4282	226,201	,471	,879

Table 5. *Differentiation of Health Belief Scores Regarding Vitamin D According to the Lower 27%-Upper 27% Groups*

Gruplar	Lower%27 (n=110)		Upper %27 (n=110)		t	sd	p
	Ort	Ss	Ort	Ss			
Self – efficacy	2,960	0,788	4,200	0,725	-12,143	218	,000
Caring	2,887	0,614	4,373	0,437	-20,666	218	,000
Perceived sensitivity	3,231	0,789	4,551	0,415	-15,533	218	,000
Perceived benefits	2,967	0,680	4,366	0,530	-17,012	218	,000
Perceived barriers	2,744	0,901	3,158	0,938	-3,342	218	,001
Health motivation	3,530	0,856	4,643	0,370	-12,526	218	,000
General Health Belief Regarding Vitamin D	3,027	0,355	4,211	0,245	-28,826	218	,000

Independent Groups T-Test

Scale scores show significant differences between the Lower 27% group and the Upper 27% group (p<.05). This finding shows that the scale makes discriminative measurements.

4. DISCUSSION

One of the important health problems in women in adulthood is vitamin D deficiency and the emergence of related problems (28). For this reason, it is important for public health nurses to determine individuals' vitamin D health belief levels in society and to plan health-protective and improving programs for both the individual and society. There are many scales that measure the health beliefs of individuals in different periods in society (15,29,30). The fact that this scale is based on a model and that it addresses health beliefs about vitamin D is thought to be useful and practical, especially for public health nurses and other health workers. The health belief model explains the determining factors related to the implementation of preventive health behaviors (31,32). Six domains of HBM (perceived sensitivity, caring, health motivation, perceived benefits, perceived barriers, and self-efficacy) help determine the individual's vitamin D health beliefs (33)

The scale developed in this study was found to have a six-factor structure (Table 1). These factors are compatible with HBM. They can be used as a whole, or they can be considered separately. Perceived self-efficacy, which is the first factor, is the level of confidence that the individual perceives in fulfilling preventive health behaviors. This is important in terms of women's beliefs that they can benefit from vitamin D. Caring, which is the second factor, is the individual's perception of the consequences of vitamin D deficiency as a threat. This is the conclusion women draw based on the consequences of their vitamin D deficiency. This affects the perception of seriousness/caring. The third factor is perceived sensitivity. The individual's feeling that he/she can be sick means perceiving vitamin D deficiency as a threat. The fourth factor is perceived benefit. It is about believing in the recommended actions to reduce the risks associated with vitamin D deficiency. The fifth factor is perceived barriers. This dimension is related to the obstacles that the individual perceives at various levels, including both the individual and societal levels, in maintaining preventive health behaviors. The last factor is health motivation. It defines the compelling conditions created for the individual to start health behaviors. Participants' mean scores on self-efficacy, caring/seriousness, perceived sensitivity, and perceived benefits were found to be high. Results showed that participants in the study had good vitamin D health beliefs. Results regarding sub-dimensions showed that participants had some barriers in the level of taking/benefiting from vitamin D and that they had inadequate motivation to maintain positive health behaviors. This suggests that they had barriers to obtaining vitamin D and that they did not have enough motivation to maintain positive health behaviors.

This newly developed scale is expected to achieve two features, namely validity and reliability. The validity of a scale is a concept related to whether a test or scale actually measures the feature it intends to measure. When it is considered in this way, a scale is said to have validity if it measures the feature it intends to measure fully and accurately without confusion with other features. The psychometric properties of the scale showed that it was valid and reliable. Experts were consulted for content validity, factor analysis was performed for construct validity, and internal consistency measurements of the total scale and all sub-factors were found to be high (34-36).

The construct validity of the scale was analyzed by using exploratory factor analysis. However, before the analysis is carried out, it is necessary to test whether the sample is adequate. To do this, the varimax method was chosen to ensure that the relationship between the factors remained the same. As a result of the factor analysis, the variables were gathered under 6 factors with a total explained variance of 58.22%. The higher the total variance ratios of a scale are, the stronger the factor structure of the scale is. In the literature, it is recommended that the common factor variances of items should be greater than 0.66 and as much close to 1.00 as possible. However, since it is difficult to meet this condition in practice, a total explained variance by factor loads between 40 and 60 is considered adequate (25)

Confirmatory factor analysis is a type of structural equation model (SEM) that can measure the relationship between observed and latent variables (34). Confirmatory factor analysis is used to validate a scale whose factor structure has been established. The decision about validity is made according to the goodness of fit indices following the confirmatory factor analysis. In the study, the most frequently used goodness of fit indices in studies in the literature were used. In addition to the goodness of fit values, the correlation coefficient between the factors should be less than.85. The discriminant validity, which shows that factors diverge from each other, should be achieved. In addition, factor loadings should be high, error variances should be low, and the explanatory (R^2) values of the items on factors should be high (33-36).

The fit statistics calculated by using confirmatory factor analysis showed that the model was compatible with the real data collected from the participants at an acceptable level. This indicated that the scale fitted the explanatory factor structure determined before well. Content validity is the indicator of whether the items on the measurement tool adequately represent the behavior/feature to be measured in terms of quantity and quality (37). One of the rational ways to test content validity is to consult experts. For this purpose, the items of the scale were submitted to expert opinions for content validity. Scores obtained from experts were evaluated with the content validity index (CVI). According to a study in the literature, the CVI value should be at least 83%, and according to another, it should be between 90-100% (38). The CVI value in this study was found as 91.52%, which showed that the scale had very good content validity.

Reliability shows how accurately the scale measures the quality that is intended to be measured and the consistency between the answers given by the individuals to the scale items. Reliability is a measure of time-dependent invariance and is a factor affecting the validity of a test (21). Every valid

scale is reliable, but not every reliable scale is valid (15). One of the most commonly used methods to measure internal consistency for reliability is the calculation of Cronbach's alpha coefficient. The higher the alpha coefficient is, the higher the internal consistency of the scale is said to be (32). In the literature, it is stated that an alpha coefficient between 0.60-0.80 proves the reliability of the scale, and a value between 0.80-1.00 indicates that the scale has high reliability (22,32). Cronbach's Alpha value of the scale developed in this study was found as 0.884, which indicated that the internal consistency of the scale was adequate (38,39).

Reliability analysis was applied to determine the internal consistency of the scale. Reliability analysis shows whether the items on the scale are consistent with each other and with the overall scale. It also determines whether all subjects understand scale expressions in the same way. Reliability is the consistency between the answers given by the participants to the scale items (32). In the literature, the reliability (internal consistency) of the scale is commonly determined by using Cronbach's Alpha coefficient. This coefficient is interpreted as follows:.00 ≤ α <.40, the scale is not reliable;.40 ≤ α <.60, the scale has low-reliability;.60 ≤ α <.80, the scale is quite reliable;.80 ≤ α < 1.00, the scale is highly reliable (31,32).

Responses to items are expected to have a positive correlation with the items and the total scale. This shows that participants understand the propositions correctly and give objective answers. When an item on a scale has a correlation coefficient of ≥.3 with the total items, it indicates that it has a high discrimination power (40). Scale scores differ significantly between the Lower 27% group and the Upper 27% group (p<.05). This finding shows that the scale makes distinctive measurements (Table 5).

5.CONCLUSION

The findings of this study showed that the scale developed in the study was appropriate for determining the health beliefs of adult female individuals about vitamin D. It is thought that the scale will provide support for the evaluation of women's health beliefs about vitamin D and health education and counseling to be given to women. On the other hand, since there are no similar scales in the literature, it is thought that the scale developed in the present study will be a reference for studies to be carried out on the topic. The vitamin D health beliefs scale in women was determined to be a valid and reliable measure; however, it may still require a retest procedure. A retest evaluation can be done to strengthen the validity of the scale.

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Clinical and Experimental Health Sciences

A Follow-Up Study of Children Diagnosed with Delayed Speech and Language

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ABSTRACT

Objective: The aim of our study was to examine the current health status of children with normal peripheral hearing who were referred to the audiology clinic with complaints of speech and language delay in early childhood.

Methods: The data of a retrospective file review in which the information of 105 children with normal hearing ages 12-60 months referred to the Audiology Clinic with complaints of speech and language delay were used in the study. After the initial diagnosis of delayed speech and language (approximately two years), their medical condition was assessed through semi-structured telephone interviews. The obtained data are presented with descriptive statistics.

Results: Out of 105 children, 54 (51.4%) were diagnosed with other additional diagnoses including; autism spectrum disorder:21 (20%), general developmental delay: 13 (12.3%), attention deficit and hyperactivity disorder: 9 (8.5%), epilepsy: 4 (3.8%).7 (6.6%) of children followed from endocrine, neurology, genetics, cardiology, nephrology and ophthalmology departments. 51 children (48.57%) have achieved the average level of speech and language development with interventions such as speech and language therapy and/or social support in the following period, and they do not currently have any medical follow-up.

Conclusion: The results indicated that cases where children who apply with the complaint of speech and language delay may have additional diagnoses in the future, or they can achieve the average level of speech and language development with specialist interventions. Long-term follow-up of this delay is important in terms of providing effective communication skills and the probability of being a diagnostic marker.

Keywords: delayed speech; delayed language; diagnostic marker.

1. INTRODUCTION

Language is the conceptual processing of communication that includes receptive language (understanding) and expressive language (the ability to communicate information, feelings, thoughts, and ideas). A verbal production of language is speech (1). The fact that the child does not develop speech and language at the expected rate compared to typically developing peers is called speech and language delay (1). While atypical speech and language development can first appear as speech and language problems, it can also be a secondary feature of physical and developmental problems (2). Primary types of speech and language delay include developmental speech and language delay, expressive language disorder, and receptive language disorder. Secondary speech and language delays can be attributed to other conditions, such as intellectual disability, autism spectrum disorder, selective mutism, physical speech problems, or hearing loss (2).

Speech and language disorders in children are associated with increased difficulty in reading, writing, attention, and socialization (3). Studies evaluating these associations, evidence from both cross-sectional and prospective longitudinal studies of children with speech-language disorders indicate an increased risk of psychiatric disorders in children with speech and language disorders (4). Although the relationship between speech and language disorders and psychiatric problems cannot be clearly explained, it has been reported that more than 50 % of children referred to psychiatric counseling have disorders in speech and language development. This suggests that speech and language delay may be a diagnostic marker of some psychiatric disorders (5). Being a diagnostic marker essential for cases where early diagnosis and treatment may have better results (autism, general developmental delay, etc.), and medical follow-up should be done. Scientific reports indicate that untreated speech and language delay can persist in 40%–60% of children, and these children are at a higher risk of psychosocial, behavioral, and cognitive problems in adulthood (6).

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Parents of children with delayed speech should be informed about this diagnostic marker status and possible scenarios. Although the child and family are the main denominators in the solution of delayed speech and language problems, they should be told to the family that the situation should be managed by a large team such as pediatrics, child psychiatry, neurology, otolaryngology, audiology, speech and language specialists, according to the needs of the patient (7). Speech and language delay, which has different reasons and different outputs, should be followed up on how will take shape after the first detection. The status of the child population with speech and language delay at first application to the clinic and then detailed follow-up, recovery, or additional diagnosis is very important in terms of providing information about the approach to this population.

The study aimed to examine the current medical conditions of children with normal peripheral hearing who were referred to the Audiology Clinic with complaints of speech and language delay in early childhood. We also emphasize the probability of delayed speech being a diagnostic marker, the importance of the long-term follow-up and raise awareness by stating how the diagnosis of speech and language delay can lead to various consequences.

2. METHODS

This study was approved by the Ethics Committee of the Medical Faculty of Marmara University (Protocol no:09.2022.1542). Moreover, it has been carried out by the Declaration of Helsinki. Informed consent was obtained from all participants and their parents.

The study was based on parental reports of patients who were referred to the Audiology Clinic by the Department of Child Psychiatry between 2015 and 2019 with complaints of delayed speech and language. It is a cross-sectional follow-up study. Children who had delayed speech and language complaints and normal bilateral peripheral hearing were randomly selected from the medical record system. In the evaluation of peripheral hearing as within normal limits, it is necessary to have bilateral type A tympanograms and bilateral acoustic reflexes (0.5, 1,2,4 kHz), and to have passed bilateral transient evoked and distortion product otoacoustic emissions tests. In addition, conditional play/behavioral audiometry and/or clinical ABR were performed according to the child's age and cooperation status, and it was also required to include the statement that "peripheral hearing is within normal limits" in the medical record system. The study continued with the families of 105 children who gave consent to the research out of 138 phone calls. Taking into account the conditions such as a diagnosis by performing the necessary tests and initiation of treatment/therapy, their medical conditions after at least two years of initial diagnosis were questioned retrospectively.

A semi-structured telephone interview was conducted with the mother and/or father to investigate the aftermath. Information about the current communication and health status of the cases was obtained, and the educational support and treatments they received during the follow-up were questioned. Interviews were conducted in a semi-structured manner based on predetermined questions. Interviews lasted between 10 and 15 minutes, and all parents could cooperate with the interview, understood the questions asked, and gave appropriate answers. Telephone interviews which information was obtained, were made with mothers who are primarily responsible for the self-care of children. All interviews were conducted by the same person; thus, it was aimed to prevent differences between evaluations. The interview questions are shown in Table 1.

Table 1. *Interview questions*

Is her/his speech at the same level as her/his peers, is there any delay in speech and language?
Does he/she make sentences? /Does he/she follow verbal instructions?
Is his/her speech and language understandable by others?
Were there any medical problems pre – and post-natally?
Is there a consanguinity between his/her mother and father?
What is the educational status of the parents?
Is the child growing up in a bilingual or multilingual environment?
When was the delayed speech and language complaint noticed first?
Are there any other individuals in the family who have/had a speech and language delay/disorder?
Did Child Psychiatry make any other additional diagnosis? If yes; what is it? Is he/she taking any medication?
Is there any follow-up from any other medical departments? If yes; what is his/her medical diagnosis?
Does he/ she take speech and language therapy? If yes; when did speech and language therapy begin, how long did it last, is it ongoing?
Does he/she take special education? If yes; when did special education begin, how long did it last, is it ongoing?
Does he/she take physiotherapy? If yes; when did physiotherapy begin, how long did it last, is it ongoing?
Does he/she take ergotherapy? If yes; when did ergotherapy begin, how long did it last, is it ongoing?
Does he/she take any other training/therapy/rehabilitation? If yes; when did it begin, how long did it last, is it ongoing?

3. RESULTS

The ages of the cases, which consisted of 84 males and 21 females, were between a minimum of 12 months and a maximum of 60 months (Mean ± SD= 28 ± 2.7 months, SD: standard deviation).

According to the non-medical feedback based on parents' personal opinions; 52 (49.52 %) of children had speech and language delays compared to their peers. 74 (70.47 %) of children can form sentences with the number of words appropriate for their age (2 years-2 words, 3 years-3 words, etc.). Children who could not follow verbal instructions were 36 (34.28 %). The number of children whose speech is understandable by others was 65 (61.90 %). The number of children with consanguinity between their mother and father was 32 (30.47 %). The number of mothers and fathers

for educational status, respectively; primary school: 14, 9; secondary school: 23, 21; high school: 46, 48; undergraduate/ graduate degree: 22, 29. The number of children growing up in a bilingual or multilingual environment was 43 (40.95 %) (female:19; male:24). some medical risk factors affect speech and language development (8).

A total of 105 children included in our study, 99 children had some of these risk factors. These risk factors and our participant distribution are shown in Figure 1. The first suspicions of parents about speech and language delay are around 13±1.8 months.

According to the data of the medical diagnosis; 51 (49 %) of children had a diagnosis of only delayed speech and language. These children reached an average level of speech and language. They are not currently followed up by any medical department. 54 (51 %) of children had other diagnoses in addition to delayed speech and language. The follow-ups of the children after diagnosis of delayed speech and language are shown in Table 2.

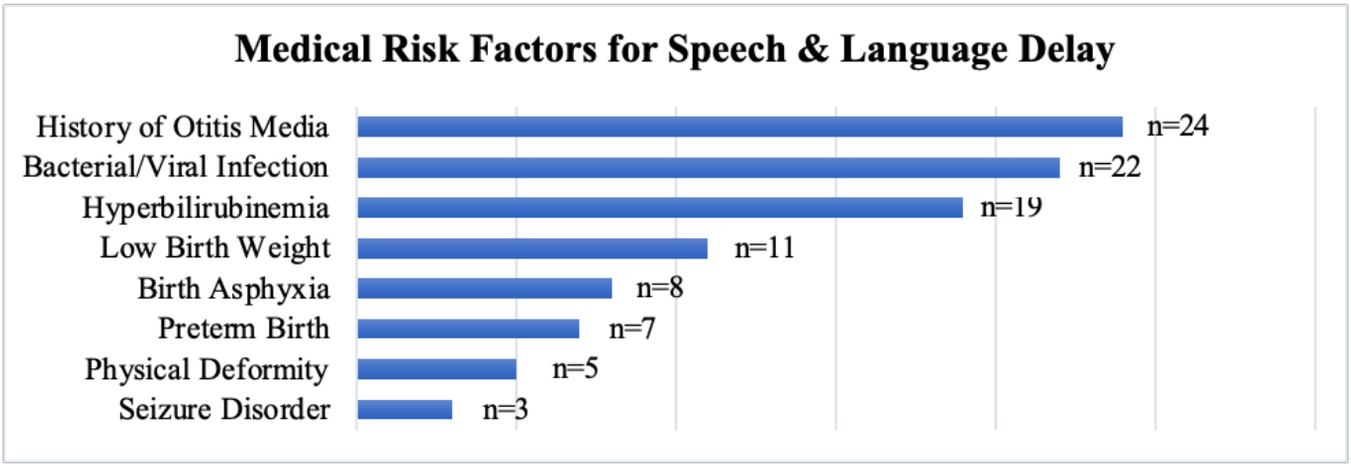

Figure 1. *The number of children with medical risk factors associated with speech and language delay*

Table 2. *Medical conditions in the middle childhood of children diagnosed with speech and language delay in early childhood*

Delayed speech and language + Other diagnoses	**(n=54) (%)**
Autism spectrum disorder	21 (20%)
General developmental delay	13 (12.3%)
Attention deficit and hyperactivity disorder	9 (8.5%)
Epilepsy	4 (3.8%)
Followed by other medical departments*	7 (6.6%)
Only delayed speech and language	**(n=51) (%)**
Recommendations and social environment support	22 (20.9%)
Recommendations, social environment support and Speech and language therapy	29 (27.6%)

**Departments such as metabolism, endocrine, neurology, genetics, cardiology, nephrology and ophthalmology.*

Moreover, there was a history of delayed speech and language in the family of 14 participants. 3 of them have autism spectrum disorder, 2 of them have attention deficit and hyperactivity disorder, 7 of them have achieved average speech and language levels, 2 of them with follow-up from other medical departments, and one has epilepsy.

The medical condition of the children at least two years after the delayed speech and language diagnosis and the types of therapy they received are shown in Table 3. In addition, children who received speech and language therapy and whose speech and language development have achieved average levels are only under follow-up for other medical diagnoses.

Table 3. *Types of therapy for children with delayed speech and language and other diagnoses*

Delayed speech and language + Other diagnoses (n=54)	SLT	SE+SLT	PT+SLT	SE+PT+SLT	Achieved average speech and language level
Autism spectrum disorder (n=21)	3	10	1	3	4 T.D: 12.1±2.3 months
General developmental delay (n=13)	3	4	3		3 T.D: 8.3±3.2 months
Attention deficit and hyperactivity disorder (n=9)	2	5			2 T.D: 9.2±2.1 months
Epilepsy (n=4)		1	1		2 T.D: 6.3±2.1 months
Followed by other departments (n=7)		1	1		5 T.D: 8.3±3.1 months
Only delayed speech and language diagnosis (n=51)					
Recommendations and social environment support (n=21)					Without speech and language therapy
Recommendations, environment support, and speech & language therapy (n=29)					29 T.D: 11.1±4.5 months

S.E.: special education, S.L.T.: speech and language therapy, PT: physiotherapy, T.D.: therapy duration: Mean ± standard deviation

4. DISCUSSION

Delayed speech and language complaints are a common problem among preschool children (9). It has been reported that 6-7% of children have delays in speech and language development when they reach the school starting age (10).

In a study in which children aged 1-12 years who applied to pediatric outpatient clinics were screened, the prevalence of speech and language delay was reported as 2.53% (11). Due to the lack of a gold standard definition of speech and language delay (12) and methodological differences between studies, different rates are reported in studies investigating the prevalence of speech delay. However, it was also emphasized that the information about the prognosis is not consistent, it is not easy to define the predictors of the prognosis, and there are conflicting results between studies (13). In addition, there are very few studies in the literature on how the process progresses after the initial diagnosis, recovery, or encountering other problems.

Such studies are important because they can contribute to both the management of the process and the understanding of the systems in which speech and language development are related. Our study results, which aimed to examine the situation after the diagnosis of speech and language delay, showed that more than half of 105 randomly selected children had speech and language delay as the possibility of being a diagnostic marker of other disorders/diseases.

Moreover, our study was designed for children with normal peripheral hearing to eliminate the direct effect of hearing loss on speech and language development and to prevent delayed speech from affecting the possibility of being a diagnostic marker. As a limitation of our study, we should state that conventionally evaluating only the peripheral system is not sufficient to evaluate the effect of the auditory system on speech and language development.

One of the most important factors for speech and language development is the processing of auditory stimuli (7). For this processing, the peripheral and central auditory systems must work in harmony, otherwise this will negatively affect speech and language development (8).

There were no medical records regarding the evaluation of the participants in terms of auditory processing disorder after delayed speech and language diagnosis. The hearing system should be examined in two main parts peripheral and central hearing system. The peripheral hearing system can be evaluated with many tests starting from the neonatal period. However, due to the complex nature of the central auditory system, sufficient information cannot be collected about it in the first years of life (14). For this reason, children with normal peripheral hearing may be overlooked despite the risk of auditory processing disorder. Although the peripheral auditory system is within normal limits, there can be a problem in the central auditory system, which may affect speech and language development (15). Hence, central auditory system involvement should be considered in the diagnosis of speech and language delay and follow-up if necessary. In addition to the peripheral hearing systems of children with speech and language delays, central hearing systems should also be evaluated (15).

Speech and language develop together with biological, neurological, psychosocial, psychosexual, and cognitive processes and closely affect each other (16). External factors are as important as the characteristics of the individual in speech and language development. Attention should also be paid to issues such as receiving adequate auditory stimulus, establishing effective communication, and supporting social development. When these factors are not taken into account, there may be delays in speech and language development. Counseling should be offered to families regarding the importance of these external factors (17).

In our random selection, 51 (49 %) of our participants were diagnosed with only speech and language delay. 22 of the children survived the process only with expert advice (preventing screen exposure, social media support, effective communication, etc.), and 29 with both advice and speech-language therapy support. At the end of a period of about 1 year with speech and language therapy, children have reached the average level of speech and language development. This shows that psychosocial problems can be prevented by early diagnosis and intervention of speech and language delay. Their parents also reported that their children were not followed up in any medical department and they did not receive any warning from their teachers about their communication two years after the diagnosis. These reports are important because they inform us about the communication of cases in a real-life environment. On the other hand, the most important limitation of our study is that the cases were not evaluated face to face, but data were collected through telephone interviews with families. Therefore, data from the study are based on reports from families, with the possibility of recall or response bias. In cases where speech and language delay were diagnostic markers, autism spectrum disorder, general developmental delay, and attention deficit and hyperactivity disorder (ADHD) were frequently encountered. Early diagnosis and intervention are critical in terms of the effectiveness of treatment and rehabilitation, which will be applied in the first years of life using high neuroplasticity in such disorders (18).

Complaints of speech and language delay should not be ignored in terms of the probability of being a diagnostic marker. More detailed studies are needed to establish a relationship between follow-ups from other medical departments and speech development. Although indirect, speech and language delay can be a diagnostic marker or outcome for pathologies that affect important anatomical and physiological structures in speech development. Therefore, speech and language skills should be closely monitored. In addition, it is important to record medical conditions that can be a risk in terms of speech and language delay in the first years of life and to monitor them in terms of speech and language development. Many medical risk factors can cause speech and language delays. Such as; hearing loss, persistent otitis media, seizure disorder, birth asphyxia, low birth weight, preterm birth, and physical (oro-pharyngeal) deformity (8). While some of them have known mechanisms of action, some have different theories about them. For example, it is clearly stated in the literature that speech delay is more common in children with otitis media in early childhood (19). In our study, the highest rate was in children with a history of otitis media. Although our data is presented with small and descriptive statistics, it is valuable in terms of providing knowledge. It is also clear that this type of knowledge should be recorded, data should be created and the groundwork should be prepared for comprehensive studies.

Future medical follow-up of children diagnosed with speech and language delay is important in terms of providing data on whether this delay will be a diagnostic marker. In the case of being a diagnostic marker, a detailed examination of its relationship with other disorders may also contribute to the understanding of delayed speech and language mechanisms. Although there are many studies on speech and language delay, it is thought that the few descriptive studies in the style of study we present will be useful in terms of drawing a general framework for speech-language development and the conditions in which it can be related. When taking the anamnesis of language-speech delay, it should be taken from a broad perspective, including the general health status of the patient. Timely diagnosis and early intervention should be made multidisciplinary manner with the necessary health professionals according to the patient's health needs (20). This can reduce the emotional, social, and cognitive deficits of speech and language delay and improve outcomes (20).

5. CONCLUSION

While speech and language delay diagnosed in early childhood can be a problem on its own, it can also be a symptom or result of other disorders in some cases. In our study, this rate was almost half. The reasons should be evaluated for the effective management of speech and language delay from multiple perspectives and the process management should be planned accordingly. It is also important to examine the medical conditions of children in middle and late childhood which are diagnosed in early childhood, in terms of providing information about possible scenarios and giving an idea about the approach to this population. Speech and language disorders will negatively affect the child's psychosocial, academic, and communication skills. Hence, the initial diagnosis and subsequent process should be followed closely, and early treatment/therapy interventions should be applied according to the needs of the child.

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Clinical and Experimental Health Sciences

Presumptive Molecular Interconnections Between COVID-19 And Huntington's Disease

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ABSTRACT

Objective: The healthcare system worldwide has faced unparalleled challenges as a result of the coronavirus disease of 2019 (COVID-19) pandemic. While respiratory tract disease is the most common symptom of COVID-19, there is increasing evidence of neurological damage caused by the virus. To guide the clinical management of the disease, it is essential to elucidate the mechanisms underlying the pathophysiology of COVID-19. Various research indicate that COVID-19 patients exhibit reduced levels of brain-derived neurotrophic factor (BDNF), which is also a hallmark of Huntington's disease, a neurodegenerative disorder. The objective of this study is to investigate the possible links between COVID-19 and Huntington's disease. This aim is motivated by the need to guide the clinical management of COVID-19, especially given the increasing evidence of neurological damage caused by the virus, including reduced levels of BDNF, a hallmark also observed in Huntington's disease.

Methods: The comprehensive literature review conducted for both COVID-19 and Huntington's disease, focusing on the genes associated with both conditions. These genes were then analyzed using the STRING database to determine protein-protein interactions, aiming to elucidate the mechanisms underlying the pathophysiology of COVID-19 and its potential connections to Huntington's disease.

Results: The outcomes of the study indicate that there could be molecular-level interactions between COVID-19 and Huntington's disease, based on the literature research and STRING database analysis. Although the primary mechanism behind these interactions is not yet fully understood, the hypothesis suggests that BDNF and its high-affinity receptor TrkB may play a crucial role. Additionally, the study highlights olfactory dysfunction as a common symptom of COVID-19, which is also linked with various neurodegenerative conditions, including Huntington's disease.

Conclusion: This work emphasizes the connection between COVID-19 and neurodegenerative diseases, particularly through the lens of olfactory dysfunction, a common symptom shared by COVID-19 and Huntington's disease. The potential molecular interactions observed suggest that COVID-19 could exacerbate neurodegenerative processes. This underscores the critical need for further research focused on olfactory dysfunction as a key symptom, to better understand and manage the implications of COVID-19 in patients with neurodegenerative conditions.

Keywords: Olfactory dysfunction, amyloid – β, α-synuclein, BDNF, ACE2, NTRK2

1. INTRODUCTION

The rapid transmission and high mortality rate associated with SARS-CoV-2, the virus responsible for COVID-19, has turned this outbreak into a global emergency. Respiratory droplets are the main mode of transmission for the virus, and it can be disseminated by individuals who are presymptomatic, asymptomatic, or symptomatic (1). The prevalent symptoms of the virus consist of dry cough, shortness of breath and fever. Additionally, there may be radiographic and laboratory anomalies, such as elevated lactate dehydrogenase and lymphopenia (2). Severe COVID-19 cases have been linked to unregulated inflammatory responses, where proinflammatory cytokines are released, leading to abnormalities in granulocytes, monocytes, and lymphocytes, as well as lymphocyte dysfunction and lymphopenia (3). Additionally, there is growing evidence of neurological damage caused by COVID-19, highlighting the need to better understand the disease's pathophysiology (4).

Newer research indicates that the angiotensin-converting enzyme 2 (ACE2) is the functional receptor for SARS-CoV-2 in human body. ACE2 is an enzyme that plays a role in normal brain function and the production of neurotrophic factors such as BDNF through the mediation of proteins like Mas which is a critical component of the renin-angiotensin system

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(RAS), specifically within the ACE2/Ang-(1-7)/Mas axis that is known to exert protective effects in the brain (5,6). BDNF is essential for neural development, neurogenesis, and the protection against neurodegeneration, and plays a role in mood regulation and cognitive performance. Decreased ACE2 activity or expression can result in disruptions to normal neurological and mental function, with long-term consequences (7).

SARS-CoV-2 enters cells by employing ACE2 as a coreceptor, and the viral coat expresses a protein called spike (S protein), which binds with high affinity to the extracellular domain of ACE2 (8). Previous studies have shown that ACE2 is linked to a decrease in BDNF levels(9)and it is thought that SARS-CoV-2 downregulates ACE2 in cells (10). This downregulation could result in decreased BDNF levels in the brain, leading to neurodegeneration and mental disorders such as anxiety, depression, and cognitive impairment(10). In 2020, a study revealed that individuals with moderate to severe COVID-19 had reduced levels of BDNF compared to those with mild symptoms, and as patients recovered, their BDNF levels returned to normal. (11).

Both BDNF and its high-affinity receptor (TrkB) are expressed not only in the central nervous system (CNS), but also in numerous peripheral organs (12). In experimental cases of and traumatic injury of the brain and spinal cord, the activation of TrkB by BDNF exhibits neuroprotective properties by promoting synaptic plasticity and cellular survival (13). On the other hand, mutations in TrkB have been linked to various neurological disorders (14,15).

Huntington's disease (HD) is a neurodegenerative disorder characterized by movement abnormalities, cognitive impairment, and psychiatric symptoms. The worldwide prevalence of HD is 2.7 per 100,000, with higher rates observed in Europe, North America, and Australia (5.7 per 100,000) compared to Asia (0.4 per 100,000) (16). HD is the result of a pathogenic expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeat in the huntingtin (HTT) gene on chromosome 4, with 36 repetitions being the threshold for developing the disease (16). Various mechanisms, including the direct effects of the exon 1 mHTT fragment, are responsible for neuronal dysfunction and death caused by mutant huntingtin (mHTT). mHTT's proclivity for forming aberrant aggregates, and its effects on cellular proteostasis, mitochondrial function, and synaptic function (17). HD patients often exhibit atrophy, or shrinkage, of the caudate nucleus and putamen in the dorsal striatum, which are brain regions involved in motor control and cognitive processing, leading to severe motor dysfunction, behavioral disorders, and cognitive impairment (18,19).

The significance of BDNF lies in its role in promoting neuron survival, and its relation to the pathogenesis of HD has been the subject of extensive research. Reduced levels of BDNF in the striatum have been hypothesized to explain neuronal loss in HD (20). In 2008, a study demonstrated a significant decrease in both BDNF mRNA and protein levels in the cortex of patients with HD. The study also found low TrkB related mRNA levels in caudate tissue (21). This suggests that imbalanced neurotrophic receptor signaling is present in HD. The loss of BDNF has been extensively studied and has been shown to play a key role in the degeneration of medium spiny neurons (MSNs) in HD (22).

NTRK2, also known as TRKB, is the primary receptor for BDNF. In HD-MSNs, there is a downregulation of NTRK2, suggesting that mHTT might cause a decrease in BDNF signaling at the receptor level (22). Studies on HD mouse models have shown a reduction in retrograde movement of TrkB vesicles into striatal dendrites, as well as reduced BDNF/TrkB-induced signaling via ERK phosphorylation and c-fos activation (22,23). This change in transport could exacerbate BDNF-TrkB survival signaling within the corticostriatal connection, which is particularly impaired in HD (23). HD patients exhibit reduced expression of NTRK2 encoding the TrkB receptor (24).

In summary, HD is caused by a genetic mutation in the HTT gene, leading to neuronal dysfunction and death through various mechanisms. BDNF has been extensively studied in relation to HD pathogenesis, with reduced levels of BDNF in the striatum hypothesized to explain neuronal loss. The downregulation of NTRK2 at the receptor level, the primary receptor for BDNF, in HD-MSNs implies that mHTT could cause a reduction in BDNF signaling. Reduced retrograde movement of TrkB vesicles into striatal dendrites exacerbates BDNF-TrkB survival signaling impairment within the corticostriatal connection in HD. HD patients exhibit reduced expression of NTRK2 encoding the TrkB receptor.

2. METHODS

A comprehensive review of the literature was carried out for both conditions by using the keywords; COVID-19, Huntington's disease, SARS-CoV-2, and Brain-Derived Neurotrophic Factor. The genes linked to the developmental stages of each disease were identified, extracted, and analyzed from the genes mentioned in the papers. The identified genes were thoroughly studied, including their roles, the molecular paths they are entitled with, and molecular backgrounds. Using this dataset, the genes linked with COVID-19 and HD were categorized and presented in a list. To determine the protein-protein interactions, these genes have been added to the STRING ver.12.0 database (25). By combining known and anticipated interactions from a range of sources, the database and online resource STRING generalizes access to protein interaction data. Based on comprehensive orthology classifications and a consistent body of fully sequenced genomes, the underlying infrastructure enables the transfer of interaction evidence between species. While the primary purpose of creating the resource was for protein interaction analysis, it has also demonstrated success in other fields, including comparative genomics, phylogenetics, and network studies. Access to the database backend through programming and the availability of compressed download files enable the aforementioned

applications. Predicted functional partners were displayed following the initial input. The selection of network settings involves representing various forms of evidence as network edges, with experiments, databases, text mining, co-expression, location, gene fusion, and co-occurrence being the active sources of interaction.

3. RESULTS

It is hypothesized that molecular interactions between COVID-19 and HD could occur, potentially involving BDNF and its receptor NTRK2. COVID-19 disrupts the BDNF pathway, leading to low BDNF levels which have been observed in COVID-19 patients. Low BDNF and NTRK2 levels are also indicative of HD. In addition, the presence of olfactory dysfunction as a symptom of COVID-19 could serve as a clinical indicator of underlying neurodegenerative disorders, including HD. While the precise mechanisms of these potential interactions remain unclear, understanding their possible links could aid in the development of effective therapies for both diseases (26).

3.1. Molecular Mechanisms and Physiology of the Related Genes

Initially, COVID-19 was believed to only affect the respiratory system, but it has since been discovered that it can impact other systems, including the nervous system. One common symptom is anosmia, or the loss of smell and taste, which can occur even without other severe symptoms. This indicates that SARS-CoV-2 interacts with olfactory cell populations in unique ways (27). The olfactory epithelium, a complex tissue consisting of multiple cell types, can be affected by conductive, sensorineural, or both processes leading to olfactory disorders (OD). Direct injury to sensory neuronal systems from viruses and head trauma is a typical cause of sensorineural disease (28). While many viruses can cause OD, the high prevalence and quick recovery time associated with SARS-CoV-2 infection suggest a different mechanism. Studies have shown that OD develops early and recovers quickly during COVID-19, revealing unique interactions between the virus and the OD (29,30). The understanding of COVID-19's effects on the nervous system is still evolving, but the growing evidence suggests it goes beyond respiratory symptoms.

SARS-CoV-2 enters host cells through the ACE2 receptor, which is primed by the serine protease TMPRSS2 (31). The expression of ACE2 is strongly associated with olfactory dysfunction (OD) during SARS-CoV-2 infection. The virus can reach the central nervous system (CNS) through transneuronal and hematogenous pathways. In 2020, a study identified SARS-CoV-2 specific antigens and RNA in the cerebrum of COVID-19 patients, indicating the virus's ability to enter the CNS (32). However, it remains unclear whether SARS-CoV-2-induced OD is caused by direct viral infection of olfactory neurons or not (33). While early studies suggested direct infection of olfactory neurons, recent evidence indicates that ACE2 is not expressed in the olfactory bulb's olfactory neurons (33). Brann et al. demonstrated high levels of ACE2 and TMPRSS2 expression in SUS cells, progenitor/stem cells, and Bowman's glands, suggesting that the virus may enter olfactory neurons indirectly through these cells (33).

CNS injury during COVID-19 infection can be caused by two main factors. The first factor is the ACE2 receptors, which are expressed in many neurons and non-neuron cells, including astrocytes, endothelial cells, olfactory-bulb vascular pericytes, and oligodendrocytes (32–35). Coronaviruses can directly attack these cells and destroy the blood-brain barrier, causing damage and releasing proinflammatory mediators. The damage of blood vessels around the olfactory bulb can lead to insufficient blood supply and damage to neurons, resulting in olfactory dysfunction (35,36). The second factor is associated with the immune system's dysfunction causing excessive synthesis of cytokines and the cytokine storm induced by SARS-CoV-2 and immune-mediated toxicity can compromise the blood-brain barrier, resulting in secondary harm. Elevated levels of IL-6 in acute COVID-19 disease have been linked to an augmented permeability of the blood-brain barrier (37,38).

New studies have revealed links between COVID-19 and neurodegenerative diseases. The spike protein receptor binding domain of SARS-CoV-2 binds to heparin and heparin binding proteins, leading to abnormal aggregation of potentially pathogenic proteins such as TDP-43, α-synuclein, amyloid-β, and tau (39,40). Mechanisms resembling this phenomenon have also been observed in HSV-1 and Alzheimer's disease. In the latter case, HSV-1 is known to accelerate the aggregation of amyloid-β (39). Viruses have been shown to interfere with mitochondrial and lysosomal functions and autophagy, all of which are implicated in neurodegenerative diseases (41). Recent studies have revealed a possible association between COVID-19 and neurodegenerative diseases (ODs) through altered autophagy, mitochondrial, and lysosomal activities in infected lung cells (42). The spike protein receptor binding domain of SARS-CoV-2 has been found to interact with proteins involved in neurodegeneration, potentially leading to abnormal protein aggregation and neurodegeneration (39,40). Rab7a and NUP62 are two of the most promising interaction candidates between COVID-19 and OD (43). A study conducted in 2020 identified the susceptibility of CNS structures to SARS-CoV-2 and its ability to cause neuronal death, changes in tau hyperphosphorylation, and distribution (44). Molecular-level investigations have identified protein interactions as a link between COVID-19 and olfactory dysfunction. This suggesting long-term inflammation and neuronal death as potential consequences (43).

ACE2 is a functional receptor for SARS-CoV-2 invasion, identified in both in vitro and in vivo experiments. ACE2 expression is linked to the level of virus infectivity, and upon infection, S glycoprotein binds to ACE2 with the aid of TMPRSS2, leading to ACE2 downregulation. ACE2 deficiency

is associated with a decrease in BDNF expression, which was found to be low in SARS-CoV-2 patients and restored during the recovery period. This suggests a higher risk of neurodegenerative diseases in COVID-19 patients due to ACE2 receptor downregulation during infection, which inhibits the BDNF-TrkB pathway (9,45).

Accumulating evidence indicate that BDNF plays a crucial role in the development and onset of HD by facilitating neurogenesis in the human body (46). BDNF is co-localized with huntingtin in 75% of striatal neurons and 99% of pyramidal motor cortical neuron, and it is required for the survival of striatal medium spiny neurons (MSNs) and healthy cortico-striatal synaptic activity (46). However, mHTT, the mutated huntingtin protein, is thought to prevent BDNF from reaching the striatum by interfering with its transport and activity-dependent release (46,47). Low levels of BDNF were observed in animal models of HD and post-mortem human HD brains, indicating its crucial role in MSN degeneration (21). A 2018 study revealed that the downregulation of BDNF signaling in HD-MSNs may be induced by mHTT at the receptor level, as levels of NTRK2 (TrkB), the main receptor for BDNF, were found to be down-regulated in the striatal neurons of HD-MSNs (21,22). Impairment of TrkB receptors was suggested to mediate postsynaptic dysfunction of MSNs in mouse models of HD, although changes in NTRK2 mRNA levels were not detected in HD mouse models (22). Furthermore, another study in 2018 indicated the protective potential of NTRK2 in HD and suggested that targeting BDNF receptors as a treatment method for HD may help preserve frontal gray matter (48).

3.2. Interconnection of COVID-19 and Huntington's Disease molecular mechanisms

ACE2 is known to serve as a functional receptor for coronaviruses, particularly the COVID-19 virus but it also plays an important role in regulating normal brain function and the release of neurotrophic factors such as BDNF through the mediation of the Mas protein (5,6). Studies have shown that decreased activity or reduced expression of ACE2 due to natural or acquired accidents can impair normal neurological and mental function, leading to long-term effects (49). BDNF is heavily associated with brain plasticity, which is crucial for learning and memory, and is widely distributed in neuronal cell bodies. The signaling pathway of BDNF is initiated by binding to its high-affinity receptor TrkB and can act through autocrine and paracrine mechanisms depending on the location of cell surface receptors (50). It is hypothesized that COVID-19 infection inhibits ACE2 and its downstream effects in the brain, resulting in a decrease in BDNF levels (10). Additionally, the mutant huntingtin protein is believed to be involved in the transport and activity-dependent release of BDNF, and its presence can prevent BDNF from reaching the striatum in HD (46,47). Research has shown low levels of BDNF in animal models of HD and post-mortem human HD brains, suggesting its crucial role in MSN degeneration (21). Therefore, regulation of BDNF and its receptors is essential for both COVID-19 and HD. Targeting the BDNF signaling pathway may represent a potential therapeutic approach for the treatment of both disorders.

Separate collections of genes related to the onset of SARS-CoV-2 infection and HD were compiled based on insights gleaned from the literature. After that we used STRING database to be able to comprehend their protein-protein interactions belonging to these genes. Protein–protein interactions were as we assumed and supporting our hypothesis. Fig 1 provides compelling evidence of protein-protein interactions between these two diseases through multiple genes. The genes depicted in Fig 1 served as inputs, and the predicted associations are displayed accordingly. In line with the results obtained from this figure, COVID-19 and HD related genes are associated directly with BDNF via interactions, co-expression, and text mining. Apart from the protein-protein interaction network, the co-expression of these genes was also examined using the STRING database. The results are shown in Fig 2. The heat map in the STRING database represents co-expression levels, with light pink indicating weak co-expression and dark pink indicating strong co-expression. The figure provides valuable information for future research and supports the study's hypothesis. On the left-hand side of the figure, there are light-pink boxes that denote poor co-expressions of specific genes in Homo sapiens. These genes include SNCA and MAPT, SNCA and NTRK2, as well as RAB7A and HTT. Meanwhile, a dark-pink box indicates strong co-expression between MAPT and NTRK2 in Homo sapiens. On the right side of the figure, co-expressions of the same genes among other organisms are also shown, with Mus musculus, Gallus gallus, and Xenopus tropicalis exhibiting co-expression between SNCA and NTRK2.

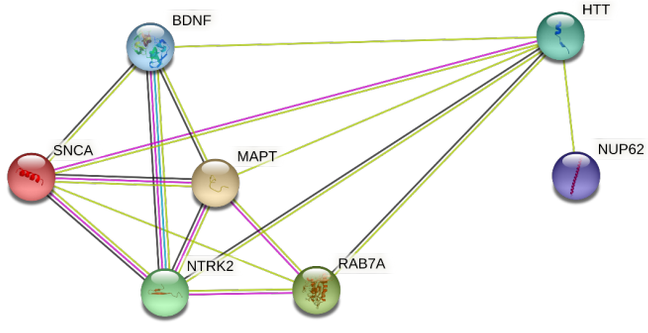

Figure 1. *The generated network of protein interactions by STRING database. This figure displays protein interactions sourced from the STRING database, showcasing the genes associated with both COVID-19 and Huntington's disease. The light-blue lines connecting the genes represent associations based on the curated databases, whereas the pink lines indicate experimentally determined interactions between the genes. Yellow lines demonstrate textmining co-occurrence and black lines point outs co-expression. As it is shown in the figure, the important connection between COVID-19 and Huntington's disease is between HTT, SNCA and BDNF, from curated database, interactions, text mining and co-expression.*

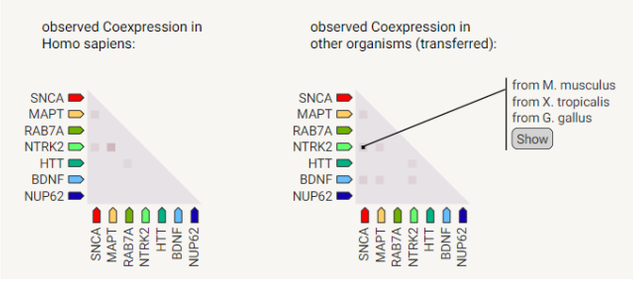

Figure 2. *Data from the STRING database was utilized to conduct gene co-expression analyses for both COVID-19 and Huntington's disease. This figure shows the STRING database results for the co-expression of genes associated with COVID-19 and Huntington's disease. Light-pink boxes on the left side of the figure denote poor co-expressions of the genes SNCA and MAPT, SNCA and NTRK2, RAB7A and HTT in Homo sapiens. Dark-pink box shows strong co-expression between the genes MAPT and NTRK2 in Homo sapiens. The co-expressions of the same genes among the other organisms are presented on the figure's right part. Mus musculus, Gallus gallus and Xenopus tropicalis have showed co-expression between SNCA and NTRK2 The heat map visualizes the co-expression scores obtained from the ProteomeHD database, which were constructed according to the RNA expression patterns and protein co-regulation. These scores were then visualized using the STRING database.*

4. DISCUSSION

COVID-19 was once considered to only influence the respiratory system; however, it now appears to affect a variety of other systems, including the nervous system. Since COVID-19 could be linked to several neurodegenerative conditions, we aimed to examine whether there is a molecular relationship between COVID-19 and HD. According with literature review, several genes linked to HD, including HTT, BDNF, NUP62, and SNCA, and some genes associated with SARS-CoV-2 infection, including BDNF, TrkB, RAB7A, and MAPT, have demonstrated some relationships among each other. Further examination of these relationships through STRING analyses to better understand their protein-protein interactions yielded promising results. As mentioned earlier, the literature research conducted on the genetic and molecular underpinnings of COVID-19 and HD suggests that both conditions could be connected pathophysiologically via the BDNF signaling pathway. After gathering sufficient evidence, the relationship between SARS-CoV-2 infection and another neurodegenerative disorders may be improved in the future aspects of this study.

5. CONCLUSION

In conclusion, this study provides illumination on the intricate correlation between COVID-19 and neurodegenerative disorders, specifically HD, surpassing the initial comprehension of COVID-19 as a respiratory affliction. Our examination, centering on genes associated with both HD and SARS-CoV-2 accentuates a potential pathophysiological connection through the BDNF signaling pathway. Importantly, the presence of olfactory dysfunction, a symptom shared by COVID-19 and diverse neurodegenerative ailments, underscores the significance of these discoveries. This symptom serves as a pivotal point of intersection, suggesting that COVID-19 might exacerbate neurodegenerative processes. Our discoveries emphasize the necessity for additional research into the molecular mechanisms in operation, particularly regarding olfactory dysfunction and its role in the advancement of neurodegenerative diseases within the framework of COVID-19. The comprehension of these associations is crucial for the formulation of targeted treatments and management strategies for patients with neurodegenerative conditions in the era of COVID-19, emphasizing the importance of an interdisciplinary approach in forthcoming investigations.

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Clinical and Experimental Health Sciences

The Effect of Spousal Support on Postpartum Depression and Quality of Life

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ABSTRACT

Objective: The study was conducted to determine the effect of spousal support on postpartum depression and quality of life.

Method: The descriptive and correlational study was conducted with 201 mothers between the 4th and 12th week postpartum in a Lokman Hekim Hospital of Ankara. The data were collected with the Personal Information Form, the Spouse Support Scale, the Edinburg Postpartum Depression Scale, and the World Health Organization Quality of Life Scale-Short Form. The data were evaluated using the SPSS 22.0 program, parametric methods, correlation and regression analyses and descriptive statistics.

Results: The mean scores of the participants were 66.23±18.19 on the Spouse Support Scale, 6.14±7.90 on the Edinburg Postpartum Depression Scale and 15.09±3.72 on the World Health Organization Quality of Life Scale. The postpartum depression rate was 25.4%. There was a negative and high correlation between the Spouse Support Scale and the Edinburgh Postpartum Depression Scale (r=-.84, p<.05), and a positive and high correlation between the Spouse Support Scale and the World Health Organization Quality of Life Scale (r=.82, p<.05).

Conclusion: The support women receive from their husbands reduces the risk of postpartum depression and enhances their quality of life in the postpartum period. It is recommended that fathers be included in training during pregnancy and birth to prevent postpartum depression.
Keywords: Postpartum, depression, spousal support, quality of life

1. INTRODUCTION

Pregnancy, also known as the antepartum period, lasts for around nine months and ten days and plays a significant role in a woman's life. The period following the birth event is called postpartum (1). The mother goes through several physiological, psychological, and social changes during the postpartum period (2). She is also going through a time of psychological distress as she attempts to adjust to her new tasks and obligations. Postpartum depression may develop at this time due to depression symptoms, including mood swings and a lack of enjoyment in life, which may progress to postpartum depression (3). A psychiatric condition called as postpartum depression often starts 2–6 weeks after delivery and can persist for up to a year (4). The prevalence of postpartum depression is reported to be 5-20%, but the baseline frequency is estimated to be 10% (5). Several factors can contribute to postpartum depression, such as underlying unhappiness and anxiety, difficulty caring for children, harsh living conditions, an unhappy marriage, an unplanned or unexpected pregnancy, socioeconomic status, and a lack of social support (6). The absence of social support is one of the most potent causes of the formation of negative psychotic states in the postpartum period (7). The most significant form of social support for a woman is marital support, which she receives from her spouse with whom she shares parental responsibilities. The husband is the one with whom the mother shares the same social environment, has the same issues, spends the most time in the same location, and shares parenthood duties. Accordingly, the mother's receiving both social, physical, and mental support from her partner, such as baby care, housework, and communication support, will enable her to carry out the postpartum period in a healthy way. When the literature is examined, it is reported that the support a woman receives from her husband during the postpartum period has a reducing effect on postpartum depression (8-10).

Another important issue in the postpartum period is quality of life. Quality of life is a broad concept that can be affected by many factors. The quality of life can be favorably or adversely influenced by a person's physical and mental health, emotional state, amount of independence, social connections, and environmental factors. By identifying uncomfortable circumstances and acting, people's quality of life can be

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enhanced, and their level of happiness raised (11). In addition to postpartum depression, the mother's quality of life may be significantly impacted, particularly during the postpartum period when women are emotionally sensitive. The maternal quality of life may be significantly influenced by insomnia, adjusting to new responsibilities, caring for the newborn, and hormonal, physical, emotional, and social changes encountered during the postpartum period (12). The spouse's support during these procedures may have a favorable effect on the maternal quality of life. This support can be given through participating in infant care, helping with housework, supporting the mother emotionally, and sharing, thus contributing positively to the improvement of the maternal quality of life (9,13-16).

According to the relevant literature, the postpartum period is a significant issue that affects the mother, the infant, the family, and even society as a whole. Spouse support is believed to have a significant role in this crucial process that affects postpartum depression and quality of life. Studies on the postpartum period are generally related to social support and adjustment to motherhood. Especially the spousal support provided in the postpartum period has not been covered much in the literature we examined. Field research findings highlight the significance of looking at these interactions (17,18). For this reason, this descriptive and correlational study in nature was conducted to determine the effect of spousal support on postpartum depression and quality of life.

1.2. Research Questions

1.Does the spousal support women receive affect the risk of postpartum depression?

2.Does the spousal support women receive affect their quality of life?

3.Is there a relationship between spousal support received by women and postpartum depression and quality of life?

2. METHODS

2.1. Design and Sample

This descriptive and correlational study was conducted in Lokman Hekim Hospital of Ankara between February and May 2022. The population of the study consisted of mothers who were admitted to this hospital between the 4th and 12th week after delivery. The sample size calculate formula for unknown population was used to calculate the sample size of the study ($n=t^2.[p*q]/d^2$). Using the sampling formula, the sample size for this non-homogeneous universe was calculated as $n = (1.96)^2(0.15)(0.85)/(0.05)^2 = 196$. Considering case losses, 201 women who met the inclusion criteria were recruited for the study.

Inclusion criteria of the study; were being at the age of 18-45 years of age, being between 4 and 12 weeks postpartum, having an alive and healthy fetus, having no communication problems, and not having any previously diagnosed psychological disorder in herself or her partner and volunteering to participate in the study. Foreign national women were excluded from the study. The women included in the sample were selected using the random sampling method.

2.2. Data Collection Process

The data were collected through face-to-face interviews between February 2022 and May 2022. The Personal Information Form, postpartum the Spouse Support Scale (SSS), the Edinburg Postpartum Depression Scale (EPSDS), and the World Health Organization Quality of Life Scale-Short Form (WHOQOL-SF) were used for data collection.

The Personal Information Form: Prepared by the researcher (in line with the literature), the form consists of 10 questions about personal characteristics, pregnancy, and the health status of the woman (6,8,10,13).

The Spouse Support Scale (SSS): The Spousal Support Scale was developed by Yıldırım (2004) to determine the level of perceived spousal support. It consists of 27 items and has a 3-point Likert type. The maximum score that can be obtained from this scale is 81, and a high score refers to high perceived spousal support. The SSS has 4 sub-dimensions: emotional support, instrumental and information support, appraisal support, and social support. Cronbach's alpha coefficient of the Spouse Support Scale was found to be.95 (19) in the original study and.98 in our study.

The Edinburg Postpartum Depression Scale (EPDS): It was developed by Cox and Holden in 1987 and adapted into Turkish by Engindeniz (1996). The 10-item scale is a 4-point Likert-type and is based on self-report. Responses with four options are scored between 0 and 3. The minimum and maximum scores to be obtained from the scale are 0 and 30. Cronbach's Alpha was found to be.79 in the validity and reliability study conducted by Engindeniz and.96 in our study. The cut-off point of the EPDS is 13, and those with a score of 13 or more were considered the risk group (20).

The World Health Organization Quality of Life Scale-Short Form (WHOQOL-SF): Turkish adaptation study of the scale was conducted by Eser et al. (1999), and there are 27 questions in total in the Turkish version of the scale. In the Turkish version, unlike the original 26-question short form, the 27th question is not included in the scoring and is evaluated separately. The WHOQOL-SF has 4 sub-dimensions: physical, mental, social, and environmental quality of life. The scale does not have a total score, and each domain is evaluated over 20 or 100 points. The Cronbach's alpha internal consistency coefficients of the scale were.76 for the physical quality of life,.67 for the mental quality of life,.56 for the social quality of life, and.74 for the environmental quality of life. In the study conducted by Eser et al., Cronbach's alpha internal consistency coefficient was found to be.86 (21). In our study, the reliability of the WHOQOL-SF was found to be Cronbach's Alpha=.98.

2.3. Data Assessment

Data evaluated with SPSS 22.0 statistical program. Frequency and percentage analyses were used to determine the descriptive characteristics of the women, and mean, and standard deviation statistics were used to analyze the scale. Kurtosis and Skewness values were analyzed to determine whether the research variables were normally distributed. In the relevant literature, results regarding kurtosis and skewness values of variables between +1.5 and – 1.5 (22), +2.0 and – 2.0 (23) are considered normal distribution. Parametric methods were used to analyze the data. The relationships between the dimensions that determine the scale levels of women were examined through correlation and regression analyses.

2.4. Ethical Approval

Ethical permission was obtained from the Health Sciences University Hamidiye Scientific Research Ethics Committee on 05.11.2021(number of approval:3/18). Institutional permission was obtained from Lokman Hekim Hospital of Ankara (date:23.02.2022; number:260). In addition, all the participants gave written and verbal informed consent to participate in the study. Necessary permissions were obtained for the use of the scales.

3. RESULTS

The mean age of the women was 26.13±4.26 years, 50.2% were university graduates, and 52.2% had income equal to their expenses. Most of the women (72.1%) spent most of their lives in metropolitan cities, 62.7% got along well with their husbands, 43.3% gave birth 4 weeks ago, 78.6% had planned pregnancies, 41.8% had two children, 62.7% had cesarean sections. 51 (25.4%) of the participants who scored 13 and above on the EPDS were considered at risk for postpartum depression (Table 1).

The analyses showed that the mean total score was 66.23±18.19 for the Spouse Support Scale, 22.04±5 for the emotional support, 16.92±4.95 for the instrumental and information support, 19.71±5.47 for the appraisal support, and 7.54±2.22 for the social support sub-dimensions. The mean score of the WHOQOL-SF was 15.09±3.72. The mean scores for the sub-dimensions were 15.25±3.78 for the physical quality of life, 15.13±3.75 for the mental quality of life, 14.62±4.61 for the social quality of life, and 15.38±3.33 for the environmental quality of life (Table 2).

As seen, a high level of negative correlation was found between the total score of the EPDS and the total and sub-dimensions of the SSS (p<.001). A positive and high correlation was found between the total score of the WHOQOL-SF and the total and sub-dimensions of the SSS (p<.001). Physical quality of life, mental quality of life, social quality of life and environmental quality of life scores, the sub-dimensions of WHOQOL-SF, were found to be positively and highly correlated with the total and sub-dimensions of the SSS (p<.001)(Table 3).

Table 1. *Descriptive, Obstetric Characteristics and Postpartum Depression Status of Women*

Characteristics	N=201	
	n	%
Age		
20-25 ages	41	20.4
26-30 ages	98	48.8
30 + ages	62	30.8
Education level		
High school and below	58	28.9
University	101	50.2
Postgraduate	42	20.9
Income level		
Income less than expenses	50	24.9
Income equal to expenses	105	52.2
Income more than expenses	46	22.9
Place of residence		
Metropol	145	72.1
City – Province	56	27.9
Relationships with spouse		
Good	126	62.7
Moderate	49	24.4
Bad	26	12.9
Time of the last birth		
4 weeks ago	87	43.3
5-8 weeks ago	55	27.4
9-12 weeks ago	59	29.3
Planning status of the last pregnancy		
Planned	158	78.6
Unplanned	43	21.4
Number of children		
1	71	35.3
2	84	41.8
3 and over	46	22.9
Mode of delivery		
Vaginal Birth	75	37.3
Cesarean Birth	126	62.7
Risk of postpartum depression		
In the risk group (13 and over)	51	25.4
Not in the risk group (under 13)	150	74.6

Table 2. *Total and Sub-dimension Scores of the Scales.*

Scales	N=201		
	Mean ±SD	Min.	Max.
Spouse Support Scale total	66.23±18.19	27.00	81.00
Emotional support subscale	22.04±5.91	9.00	27.00
Instrumental and information support subscale	16.92±4.95	7.00	21.00
Appraisal support subscale	19.71±5.47	8.00	24.00
Social support subscale	7.54±2.22	3.00	9.00
Postpartum Depression Scale total	6.14±7.90	0.00	29.00
Overall Quality of Life Scale total	15.09±3.72	6.06	19.83
Physical quality of – life subscale	15.25±3.78	4.00	20.00
Mental quality of life subscale	15.13±3.75	6.67	20.00
Social quality of life subscale	14.62±4.61	4.00	20.00
Environmental quality of life subscale	15.38±3.33	7.56	20.00

Mean: Average SD: Standard deviation, Min: Minimum, Max: Maximum, SD: Standard deviation

Table 3. *Correlation Between Spouse Support, Postpartum Depression, and Quality of Life*

		Spouse support	Emotional Support	Instrumental and Information Support	Appraisal Support	Social Support
Postpartum Depression	r	-.84*	-.81*	-.81*	-.83*	-.84*
Overall Quality of Life	r	.82*	.79*	.79*	.81*	.79*
Physical Quality of Life	r	.73*	.71*	.71*	.73*	.70*
Mental Quality of Life	r	.81*	.79*	.78*	.82*	.79*
Social Quality of Life	r	.81*	.79*	.80*	.80*	.79*
Environmental Quality of Life	r	.78*	.76*	.76*	.79*	.75*

**p<.001; Pearson correlation analysis was used*

Table 4. *The Effect of Spouse Support on Postpartum Depression and Quality of Life*

Dependent Variable	Independent Variable	ß	t	p	F	Model [p]	R^2
Postpartum Depression	**Constant**	**30.32**	**26.43**	**.000**	**477.56**	**.000**	**.70**
	Spouse Support Total	-0.36	-21.85	.000			
Overall Quality of Life	**Constant**	**3.96**	**6.94**	**.000**	**408.41**	**.000**	**.67**
	Spouse Support Total	0.16	20.20	.000			
The physical quality of life	**Constant**	**5.15**	**7.48**	**.000**	**230.87**	**.000**	**.53**
	Spouse Support Total	0.15	15.19	.000			
The mental quality of life	**Constant**	**3.96**	**6.83**	**.000**	**398.17**	**.000**	**.66**
	Spouse Support Total	0.16	19.95	.000			
The social quality of life	**Constant**	**0.91**	**1.27**	**.200**	**395.40**	**.000**	**.66**
	Spouse Support Total	0.20	19.88	.000			
The environmental quality of life	**Constant**	**5.82**	**10.60**	**000**	**325.19**	**.000**	**.61**
	Spouse Support Total	0.14	18.03	.000			

Linear Regression Analysis was used

ß: Coefficient of expansion, t, p, F: Test significance values, R^2: Explanation variance ratio

The linear regression analysis conducted to determine the cause-and-effect relationship between the SSS and the EPDS was found to be significant. The regression analysis between the SSS and the total and sub-dimensions of the WHOQOL-SF was found to be significant (p<.001). Spousal support explained 70% of the total change in the level of postpartum depression, and spousal support decreased the level of postpartum depression. 67% of the total change in the overall level of quality of life was explained by spousal support, and spousal support increased the level of quality of life Spousal support affected the physical quality of life by 53%, the mental quality of life by 66%, the social quality of life by 66%, and the environmental quality of life by 61%, and it was concluded that spousal support increased the level of physical, mental, social, and environmental quality of life of women (Table 4).

4. DISCUSSION

Postpartum depression is a problem that cannot be ignored in women, both in terms of its effects and frequency. Studies can offer us an indication, even if it is impossible to declare that the prevalence of postpartum depression reveals the precise rates owing to various factors. In a study conducted in Israel with 280 women in the postpartum period, the prevalence of PPD was reported as 22.6% (24). In a study conducted with 1584 women in Sweden, a scale to determine the prevalence of PPD was applied at the 8th and 12th weeks postpartum, and the rates were found to be 12.5% and 8.3% in these weeks, respectively (25). When the prevalence of PPD was examined in studies conducted in our country, it was found to be 33.3% in the study of Dağlar et al (2018) (26). The prevalence of PPD was determined to be 23.8% in a meta-analysis research that included 52 publications published between 1999 and 2015 to explore its prevalence and the variables influencing it in our country (27). In the current study, PPD was found to be 25.4%, close to the rates in our country (Table 1). These differences may be related to the structure of the society in which the study was conducted, the differences in diagnostic measurements, the time of application of the measurements, and the way the scales were applied.

Spousal support is an integral element of social support systems. The need for spousal support increases even more in the postpartum period. As seen in Table 2, the mean score of SSS was found to be 66.23±18.19. This value can be interpreted as the women participating in the study receiving moderate spousal support (19). In the literature, like the current study, Yüksekal et al (2021) found the mean total score of the SSS to be 68.99±10.8 (28). It was observed that the subscale scores of the relevant studies were similar to our study. There are a limited number of studies in the literature examining spousal support in the postpartum period. In addition, there are a few studies conducted with the "Spouse Support Scale" in the postpartum period. In the literature, it

is emphasized that women need spousal support in postnatal processes and that these critical processes become less stressful in this way and lack of spousal support at the time of need may cause irreparable problems (29).

Postpartum depression is a mood disorder that mothers may encounter after giving birth. In the present study, the mean score of EPDS was found to be 6.14±7.90 (Min=0; Max=29) (Table 2). This score can be interpreted as the average scale score of the women participating in the study being below average. In parallel with the current study, the mean score of EPDS was found to be 5.61±4.51 (Min=0; Max=24) by Özşahin et al. (2020), and 5.66±4.72 (Min=0; Max=29) by Sunay et al. (2021) (30,31). The current study is similar to the literature in this regard, but small differences are thought to be due to measurement time, personal and cultural factors.

The quality of life of women in the postpartum period can sometimes be ignored. The mean overall score of WHOQOL-SF scale, which we applied to measure the quality of life of women in the postpartum period who participated in our study, was found to be 15.09±3.72 (Min = 6.06; Max: 19.83). These values and subscale scores are listed in Table 2. This score can be interpreted as the general quality of life of the women participating in the study being at a medium level. When the literature was examined, other studies evaluating postpartum quality of life found studies in which the postpartum quality of life of mothers was at a moderate level, similar to our study (32,33). Some studies have also reported that postpartum quality of life is at good levels (34,35). These differences are thought to result from differences in time, group, culture and measurement tool.

Social support appears to have a direct impact on PPD risk (36). Here, we took the spouse as the primary source of support for the woman in the postpartum period, and the highly negatively correlated correlation between spousal support and PPD has demonstrated that as spousal support increased, PPD risk decreased (Table 3). This result can be interpreted as the incidence of postpartum depression decreases as spousal support (all support including emotional, instrumental and informational, assessment and social support) increases. In a study, it was reported that 14.7% of women who received support from their spouses were diagnosed with PPD, while 42.9% of women who did not receive support from their spouses were diagnosed with PPD (37). Similarly, there are other studies with similar findings stating that the risk of PPD is higher in women who cannot receive support from their husbands in the postpartum period (38,39). Although the results in the literature are similar to our results, it can be said that regardless of place, time and culture, it is important for women to receive support from their husbands, especially in the postpartum period. In our study, the relationship of spousal support with quality of life, as well as its relationship with PPD, was examined. A high positive correlation was determined between the total score of the WHOQOL-SF and the total and sub-dimensions of the SSS, namely ''emotional support'', ''instrumental and information support'', ''appraisal support'', and ''social support'' (Table 3). Consistent with our results, noted that spouse support has a major impact on quality of life, so it can be concluded that as spousal support grows, so does quality of life. In a similar study, a moderately strong and positive relationship was found between spousal support and all its sub-dimensions and general quality of life and its sub-dimensions (40). Similar to our study, it has been observed in the literature that spousal support increases the quality of life.

Current study results revealed that spousal support reduces the level of postpartum depression and increases the quality of life (Table 4). Although there are no studies in the literature that examine both the relationship between spousal support and postpartum depression and quality of life simultaneously, there are studies that examine this relationship separately. It has been observed that the results in the literature and our study results are generally similar (39-41). Regardless of the place, time, culture and measurement tool where the study was conducted, it is an expected result that spousal support reduces depression and increases the quality of life during this important and difficult period for women.

5. CONCLUSION

Postpartum depression poses a risk to one-fourth of women. Spousal support is a powerful tool in lowering the prevalence of postpartum depression, and women's perceptions of spousal support improve their quality of life. Considering these results, health professionals working in the relevant units of hospitals can be trained on the prevention, diagnosis, and treatment of postpartum depression and the importance of including the woman's partner in the whole process during pregnancy, birth, and the postpartum period. PPD screening might also be included in standard postpartum examinations.

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Clinical and Experimental Health Sciences

Is Cranial Imaging Necessary in Children with First-Time Focal Seizures?

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ABSTRACT

Objective: Seizures in children represent a common cause of admission to the emergency department. This study aimed to determine clinically significant intracranial abnormalities in children presenting to the pediatric emergency department with first-time focal seizures.

Methods: Patients aged 1 month-18 years, who presented to the pediatric emergency department with first-time focal seizures between 2009 and 2019, were retrospectively screened. Patients with a history of trauma, cases in which focal neurological signs could not be assessed, and patients with pre-existing structural brain or neurological abnormalities, and metabolic disorders were excluded from the study. Cranial computed tomography findings were re-evaluated by a pediatric radiologist. The fourth and fifth-level according to the classification of the International League Against Epilepsy were interpreted as urgent intracranial pathologies requiring medical or surgical intervention. The univariate analysis was performed using the chi-square test for categorical data and the Mann-Whitney U test for continuous data.

Results: The mean age of the 121 patients was 46.8±44.4 months, and 52.5% were male. Clinically significant emergency intracranial pathologies were detected in the neuroimaging of eight patients. Intracranial masses, bleeding, and hematomas were the most common pathologies. The presence of focal neurologic findings and an age below six months were clinically determined as predictors of an urgent intracranial pathology.

Conclusion: We found the rate of urgent cranial pathologies to be 6.6% in patients presenting to the emergency department following the first focal seizure. Children younger than six months with focal neurological signs should be evaluated for emergency neuroimaging.

Keywords: Children, computed tomography, emergency department, focal seizure

1. INTRODUCTION

Seizure is a very common condition among children, accounting for 4-10% of all pediatric neurological disorders (1). Approximately 10% of children have a seizure once in their lifetime (2). Most of these seizures are short-term, and more than 50% are focal seizures in children younger than two years (3,4). Most children with seizures present to emergency services, and the decision on whether neuroimaging is necessary in these patients varies according to the clinician. Studies have reported that the rate of large structural lesions in pediatric patients with new-onset seizures is between 0% and 21% (5-8). In the literature, the importance of neuroimaging for pediatric patients presenting with afebrile seizures remains a controversial issue (6). The American Academy of Neurology (AAN), the Child Neurological Society, and the American Epilepsy Society (AES) have also published guidelines on neuroimaging for the evaluation of a child with a non-febrile seizure. These guidelines indicate immediate neuroimaging for children with persistent postictal neurological deficits and those who do not return to their baseline neurological status within a few hours (9). Clinicians should decide whether to perform emergency neuroimaging in selected cases based on medical history and physical examination findings to identify urgent intracranial pathologies. However, during this process, unnecessary neuroimaging and radiation exposure, risks associated with sedation, and side effects of contrast media should also be considered (9,10).

This study aimed to investigate the frequency of abnormal neuroimaging and to identify clinical variables that could predict clinically significant intracranial abnormalities in children who were evaluated by computed tomography and presented to the pediatric emergency department for the first time with focal seizures.

2. METHODS

For data collection, approval was obtained from the Clinical Research Ethics Committee of Keçiören Training and Research Hospital (2012-KAEK-15/2070), and official permission was received from the Medical Specialization Education Board of Health Sciences University Dr Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital.

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2.1. Population

The study was conducted in a tertiary pediatric emergency department between January 2009 and December 2019. Patients aged 1 month-18 years, who presented to the pediatric emergency department following the first focal seizure, were retrospectively screened using the computer registry system of the hospital.

2.2. Data Collection

All children that had a seizure with focal symptoms for the first time and underwent neuroimaging (Cranial Computed Tomography) within 24 hours of the seizure at the emergency department were included in the study. Excluded from the study were patients with a history of trauma, cases in which focal neurological symptoms could not be evaluated (e.g., intubated patients and those with pre-existing hemiparesis), patients with pre-existing structural brain or neurological abnormalities (e.g., tumor, stroke, hydrocephaly, arterio-venous malformation, and presence of ventriculoperitoneal shunt), those aged <1 month or >18 years, and those with metabolic disorders (e.g., hypoglycemia and hyponatremia).

Focal manifestations were defined as any recorded transient impairment of motor function, such as eye deviation, head deviation, and isolated limb twitching. The presence of Todd's paralysis following a generalized seizure was accepted as a focal symptom. Age, gender, seizure characteristics, neurological examination findings, and radiological results were evaluated.

Table 1. *Classification of neuroimaging results (11)*

Abnormality	Definition	Examples
(1) Non-specific	Lesions not requiring immediate intervention that may be responsible for seizure	Periventricular leukomalacia, generalized cerebral atrophy
(2) Static-remote	Non-progressive lesions of the central nervous system that occurred remotely in time	Porencephaly, other malformations of cortical development
(3) Focal	Focal lesions responsible for the seizure but not requiring immediate intervention	Focal cortical dysplasia, mesial temporal sclerosis
(4) Sub-acute or chronic	Process responsible for the seizure that does not require immediate intervention but has important therapeutic or prognostic implications	Brain tumor or mass, adrenoleukodystrophy
(5) Emergent	Acute process requiring immediate, urgent intervention	Ischemic stroke, cerebral hemorrhage, hydrocephalus, encephalitis, meningitis, metabolic cytopathy, cerebral edema, acute cerebral herniation, skull fracture with bleed, new hypoxic injury

The cranial Computed Tomography (CT) findings were screened from the radiological reports over the computer system. The findings were re-evaluated by a single pediatric radiologist who was blinded to the patient's clinical history and results. Neuroimaging findings were evaluated according to the International League Against Epilepsy (ILAE) imaging guideline on new-onset epilepsies published in 2009 (11) (Table 1). According to this classification, the fourth and fifth-level seizures were interpreted as urgent intracranial pathologies requiring medical or surgical intervention.

2.3. Statistical Analysis

The Statistical Package for the Social Sciences for Windows version 23.0 software package was used for data analysis. The demographic and clinical data of the cases were expressed as mean and standard deviation using descriptive statistics, and frequency data were presented as numbers and percentages. The univariate analysis was performed using the chi-square test for the analysis of categorical data and the Mann-Whitney U test for continuous data. Statistical significance was calculated with a p-value of $< .05$. The radiological results were recorded as "normal brain CT" (normal and Class I – III findings) or "abnormal brain CT" (Class IV – V findings).

3. RESULTS

During the study period, cranial CT was performed in 121 patients who presented to the pediatric emergency department with febrile and afebrile focal seizures. The mean age of the patients was 46.8 ± 44.4 months, and 64 (52.5%) were male. Most patients (45.5%) were younger than 24 months. The patients' demographic characteristics are given in Table 2, and significant emergency neuroimaging findings are in Table 3. Clinically significant emergency intracranial pathologies were detected in the neuroimaging of eight patients. The characteristics of patients with and without clinically urgent intracranial pathologies are in Table 4. The risk of CT abnormalities was found to be significantly higher in patients with focal neurological findings ($p < .05$).

Table 2. *Demographic characteristics of the patients presenting with focal seizures*

Demographic data n (%)	
Age (mean ± SD), month	46.8 ± 44.4
1-12 months	39 (32.2)
13-60 months	42 (34.7)
61-132 months	32 (26.4)
133-215 months	8 (6.6)
Gender	
Female	57 (47.1)
Male	64 (52.9)
Febrile seizure	59 (48.8)
Afebrile seizure	62 (51.2)
Seizure duration	
<5 minutes	34 (28.1)
5-15 minutes	46 (38)
≥15 minutes	41 (33.9)
Seizure recurrence (two or more)	
Present	77 (63.6)
Absent	44 (36.4)
Neurological examination findings	
Normal	115 (95)
Focal signs	6 (5)
The prolonged state of impaired consciousness	
Absent	109 (90.1)
Present	12 (9.9)

Table 3. *Characteristics of the patients with abnormal brain CT findings*

	Age	Gender	Number of seizures	Fever >38°C	Seizure recurrence within 24 hours	Focal neurological sign	The prolonged state of impaired consciousness	CT finding
1	169 months	Female	<5 min	Absent	Absent	Present	Absent	Intracranial mass
2	9 months	Male	10 min	Absent	Present	Present	Present	Epidural hematoma
3	55 months	Male	5 min	Absent	Present	Absent	Absent	Intracranial mass
4	4 months	Female	10 min	Absent	Present	Absent	Absent	Subdural hemorrhage
5	2 months	Male	<5 min	Absent	Present	Present	Absent	Subdural hematoma
6	66 months	Male	10 min	Absent	Absent	Absent	Absent	Intracranial cystic mass
7	37 months	Female	>15 min	Present	Present	Absent	Absent	Cerebral edema (meningoencephalitis)
8	3 months	Male	<5 min	Present	Present	Absent	Absent	Subarachnoid hemorrhage

CT: Computed Tomography

Table 4. *Characteristics of the patients with and without clinically urgent intracranial pathologies*

	Clinically urgent intracranial pathology present (n = 8)	Clinically urgent intracranial pathology absent (n = 113)	p-value	OR
Age	43.13 ± 56.75	47.1 ± 43.71	.317	
<24months ≥24 months	4 4	51 62	1.000	1.216
Gender (F/M)	3/5	53/60	1.000	1.132
Fever (≥38°C) Present Absent	2 6	57 56	.274	.327
Seizure recurrence within 24 hours (two or more)	6	71	.709	.563
Seizure duration <15 min ≥15 min	7 1	73 40	.263	3.83
Focal neurological sign	3	3	**.004**	**22.00**
Todd's paralysis	0	3	1.000	1.073
Prolonged state of impaired consciousness	1	11	.578	.75

OR: Odds Ratio

4. DISCUSSION

In this study, the data of 121 patients younger than 18 years, who had focal seizures for the first time, were retrospectively analyzed, and their demographic, clinical, and neuroimaging results were evaluated.

Despite the availability of relevant guidelines, there are still differences of opinion among physicians concerning which patients should undergo emergency cranial CT in clinical practice. Studies have concluded that routine emergency cranial CT is unnecessary in patients presenting with new-onset afebrile seizures, and the decision should be made based on the clinical history and neurological examination findings of each case (4,7,10).

In studies evaluating the neuroimaging findings of patients with seizures, it has been reported that prolonged seizure, focal seizure, and the presence of abnormal brain fog are risk factors for CT abnormalities (6,12,13). In the study conducted by Sharma et al. (7), evaluating patients presenting to the emergency department following the first afebrile seizure, clinically significant findings were found in 8% of patients on cranial CT. The authors determined that the presence of focal seizures and age below 33 months were risk factors that indicated the necessity of cranial CT (7). In another study, the presence of multiple seizures and age lower than 24 months were reported to predict abnormal CT results (14).

There are only limited studies involving the evaluation of risk factors for CT abnormalities in pediatric patients presenting to the emergency department with focal seizures. In our study, clinically urgent intracranial pathologies were detected in eight (6.6%) patients on CT. In a previous study, Aprahamian et al. (15) detected the rate of urgent intracranial pathologies as 4.1% among patients presenting with focal seizures (infarction, bleeding, and thrombosis). The authors stated that the presence of focal seizures, Todd's paralysis, and age below 18 months predicted abnormal clinically urgent pathologies in neuroimaging, but the presence of multiple seizures was not one of the predictive factors (15).

Studies have reported that the younger age group is at a higher risk of having intracranial abnormalities in neuroimaging (7,12,16). In contrast, there are also researchers demonstrating that such abnormalities are not associated

with age (13,17). In our study evaluating focal seizures, when the results were compared between the children younger and older than 24 months old, no significant significance was found in terms of CT abnormalities (p = 1.000). However, emergency cranial CT was required in those younger than six months old [p = .032, odds ratio (OR): 6.93].

In studies conducted with patients with first-time afebrile seizures, the risk factors of intracranial abnormalities have been determined as long-term seizures, Todd's paralysis, and the presence of pathological neurological findings (11,18). In the current study, the risk of CT abnormalities was found to be significantly higher in the patients with focal neurological findings (p = .004; OR: 22.0). Todd's paralysis was not observed in any of the patients with CT abnormalities. The presence of multiple seizure was also not a predictive factor indicating the necessity of emergency cranial CT.

The American Academy of Neurology and the American Epilepsy Society recommend emergency neuroimaging in pediatric patients with first-time afebrile seizures in case of persistent postictal focal neurologic deficits or if the seizure does not return to baseline within a few hours (9). In our study, a nine-month-old male patient who presented to our emergency department following an afebrile focal seizure took a long time to return to the initial state after the seizure and had ongoing focal neurological findings. Among the remaining two patients with focal neurological findings, a subdural hematoma was present in a two-month-old male patient and an intracranial mass in a 169-month-old female patient.

In febrile seizures, children with focal and/or prolonged seizures have been reported to be more likely to have abnormal brain imaging findings. However, it has also been shown that most of these abnormalities do not affect the clinical management of patients (19). There are many studies demonstrating that complicated febrile seizures are less likely to have abnormal neuroimaging findings that require immediate medical or surgical intervention (20,21). Yücel et al. (22) evaluated the neuroimaging findings of children with complicated febrile seizures with postictal deficits and focal seizures and detected no emergency imaging findings in any of the patients. In another study conducted with children with complicated febrile seizures, emergency cranial CT findings were present in four cases with focal seizures or a prolonged state of impaired consciousness (23). In our study, CT findings requiring urgent treatment were detected in two patients with a fever, a three-month-old male patient with a subarachnoid hemorrhage and a 37-month-old female patient with cerebral edema due to meningoencephalitis and meningeal contrast enhancement.

Our study has important limitations. The first concerns the retrospective design and data being evaluated by screening patient files. Second, seizure characteristics may not have been adequately explained by parents, others witnessing the seizure and clinicians. Prospective multicenter studies with a large number of patients are needed to better define factors that may predict the need for emergency cranial CT in patients presenting to the pediatric emergency department with focal seizures.

5. CONCLUSION

In this study, in which we evaluated patients who presented to the pediatric emergency department with first-time focal seizures and underwent cranial CT, we determined the rate of urgent intracranial pathologies as 6.6%. Emergency physicians should primarily exclude life-threatening intracranial pathologies that require immediate medical and surgical intervention in pediatric patients presenting with focal seizures. In our study, three infants younger than six months were seen presenting with focal seizures. Based on our data, similar to the literature, we recommend that emergency neuroimaging should be performed in children younger than six months who present with focal seizures and have focal neurological findings. Considering the negative consequences of unnecessary neuroimaging, such as radiation exposure, sedation, and cost, it is important to determine which children require this procedure by evaluating their medical history and physical examination findings.

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Design of the study: AT, EA, ASE, CDK, NT
Acquisition of data for the study: AT, BÖ, İB, AAÇ, AG, CDK
Analysis of data for the study: AT, EA, ASE, CDK, NT
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Clinical and Experimental Health Sciences

The Impact of Body Fat Distribution on COVID-19 Vaccine Response: An MRI-Based Study

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ABSTRACT

Objective: Subcutaneous and visceral adipose tissue have distinct physiological roles. The correlation between the amount of visceral tissue and the immunity response following vaccination remains unclear, despite its known effects on immunity. The purpose of this study is to examine the relationship between SARS-CoV-2 IgG antibody levels after vaccination and body fat tissue values measured using a specialized software on specific magnetic resonance imaging sequences.

Methods: After ethics committee approval, prospectively 60 volunteers (27 males, 33 females; median age of 33 years) were vaccinated with inactivated SARS-CoV-2 vaccine and tested for IgG levels. Abdominal MRI was performed to measure subcutaneous and visceral fat tissue areas using a semiautomatic application.

Results: The median value of IgG antibody titers after vaccination was 1039 (113 – 6613). Median subcutaneous adipose tissue(cm^2), visceral adipose tissue (cm^2), SAT index (SATI) (cm^2/m^2), VAT index (VATI) (cm^2/m^2), total fat area (TFA) (cm^2), and SAT/VAT (cm^2) were 178.5 (38.1-552.5), 51.5 (7.1-273.2), 61.4 (14.3-213.1), 19.1 (2.7-90.6), 251.3 (45.3-683.2), and 3.3 (0.4-12.3) respectively. There was no significant correlation between the adipose tissue measurements and antibody titers (p>.05).

Conclusion: This study demonstrated that automated software can efficiently and accurately evaluate body fat distribution using MRI. However, the results showed no significant association between fat distribution and the immunization response to the SARS-CoV-2 vaccine.

Keywords: Covid-19, CoronaVac, SinoVac, body fat distribution, Magnetic Resonance Imaging

1. INTRODUCTION

Obesity is a significant risk factor for respiratory infection during the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). It has been proposed that adipose tissue-related systemic inflammatory response plays a role in the pathophysiology of this condition (1,2). Obesity-related inflammation and impaired pathogen response in obese individuals have been the subject of research for many years (3–5).

While studies have traditionally used body mass index (BMI) data as a measure of overall adipose tissue, it is now recognized that obesity is a heterogeneous disease group. It is known that visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) show significant differences in their characteristics. For this reason, body fat distribution is detailed by calculating VAT and SAT values (6). VAT has more inflammatory and immune cells than SAT, but has less preadipocyte differentiation capacity (6).

As of December 2022, the ongoing COVID-19 pandemic has affected 396 million people worldwide and caused the death of 6.6 million people (7). Efforts to develop vaccines to control the pandemic are ongoing, and there are many vaccines currently in clinical trials or in use. One of them, CoronaVac, is an inactivated SARS-CoV-2 vaccine produced by Sinovac Life Sciences (Beijing, China).

The vaccines are being applied to a broader population every day, and the rates and duration of immunity in vaccinated individuals are being studied. Age, gender, smoking, drinking, obesity, and immunity status are among the main factors that may affect immunization and its continuity. Studies have shown that obese patients have a poor response to vaccines and produce lower antibody titers to different vaccine types (8,9).

In this prospective study, obesity was quantified by calculating the body fat distribution based on VAT and SAT values. Antibody response to the CoronaVac vaccine was measured

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by spike glycoprotein antibody titers, and the relationship between obesity and antibody titers after vaccination was investigated.

2. METHODS

2.1. Study Design and Subjects

This study is a single-center, prospective observational study. Written informed consent was obtained from each participant before enrolment. The Ethics Committee (2021/90-1322) approved the clinical trial protocol and informed consent form.

This study was conducted among healthcare workers who received the CoronaVac vaccine. The study included sixty adult volunteers aged 18 or older, with a median age of 33 years (27 males and 33 females). All participants received two doses of the vaccine and were tested for SARS-CoV-2 IgG levels. In addition, they underwent abdominal magnetic resonance imaging (MRI) to measure fat tissue related parameters. Participants with immunosuppression, a history of taking immunomodulatory or immunosuppressive drugs, previous COVID-19 infection, or contraindications for MRI were excluded from the study.

2.2. CoronaVac vaccination and SARS-CoV-2 IgG detection

CoronaVac is an inactivated SARS-CoV-2 vaccine (Sinovac Life Sciences, Beijing, China). 0.5 ml CoronaVac vaccine containing 600 SU antigens, maintained at +20 to +80 degrees, was administered intramuscularly in 2 doses with 28-day intervals. The first dose was administered on January 16, 2021, and the second dose was administered on February 13, 2021. SARS-CoV-2 IgG (spike glycoprotein) levels were tested 14-21 days after administration of the second dose of the vaccine.

SARS-CoV-2 IgG II Quant (Abbott, Ireland Diagnostics Division, Finisklin Business Park, Sligo, Ireland) test is used clinically to diagnose SARS-CoV-2 and evaluate the immune status of individuals by measuring antibodies against the spike protein of SARS-CoV-2. This test kit uses the chemiluminescent microparticle immunoassay (CMIA) method to qualitatively and quantitatively determine the presence of IgG antibodies against SARS-CoV-2 in human serum and plasma. The test was performed on the Abbott ARCHITECT plus ci4100 device following the manufacturer's recommendations, with a cut-off value of ≥50 AU/ml.

2.3. Abdominal Magnetic Resonance Imaging

All MRI exams were performed at a single center with a 1,5T MR scanner (Magnetom Aera, Siemens Erlangen, Germany). A sixteen-element phased abdominal coil (16-channel coil) was used. Participants were imaged during a single breath-hold after expiration in the supine position, and GE T1 Dixon Fat Only sequences were obtained. (FOV 380 mm, matrix 240x380 mm, TR 6.64 ms, TE 2.39 ms, slice thickness 2.5 mm, gap 1.0 mm, NEX 1). It took averagely 15 seconds to obtain the sequence for each volunteer.

2.4. Fat Tissue Quantification

A single acquisition with the GE T1W Vibe Dixon sequence can generate four image series: in-phase, out-of-phase, water-only, and fat-only. The analysis was performed on the fat-only image series from a single slice at L3 vertebral level. The intensity inhomogeneities that can occur in MR imaging due to tissue differences, magnetic field variations, devices, and coil types make it difficult to determine a standard signal value in MR images. Therefore, while measurements can be made with standardized Hounsfield unit levels in CT imaging, it is not possible to determine a standard signal value in MR images (10). Many methods are described to reach quantifiable standard data by eliminating the problem of signal inhomogeneity in images (11–14). Classifying voxels has an important place among these methods, and the two most used classification methods are; k-means clustering and fuzzy c-means clustering methods.

The study was conducted with the ImageJ application, an image processing program produced by NIH, and FATCALC, which works as a macro plugin of this application (15,16). FATCALC software provides VAT and SAT tissue segmentation and quantification after processing images with multiple algorithms. The algorithm of statistical region merging (SRM) and the spatial fuzzy c-means clustering (SFCM) are used in this software. The technical details of the software are explained widely in the paper of Maddalo et al. (16).

In the fat-only Dixon MR images, the section corresponding to the L3 vertebra level was determined, and VAT and SAT tissue areas were calculated as cm^2 by using FATCALC software. The software allows manual editing after the automatic calculations are done, and the radiologist modifies the minor errors if necessary. Fig. 1 shows an example of axial fat-only Dixon MR image and VAT and SAT segmentation by FATCALC.

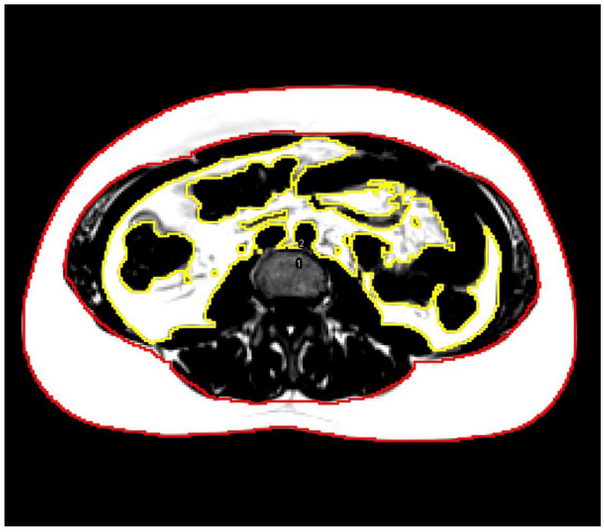

Figure 1. *Example of axial fat-only Dixon MR image and VAT and SAT segmentation by FATCALC. In the axial fat-only Dixon MRI image obtained from the level of the L3 vertebral body, subcutaneous and visceral fat tissues can be easily distinguished. FATCALC software automatically selected areas of adipose tissue (red contoured area, subcutaneous adipose tissue; yellow contoured areas visceral adipose tissue).*

2.5. Statistical Analysis:

Subcutaneous adipose tissue area (SAT, cross), Visceral adipose tissue area (VAT), subcutaneous adipose tissue index (cross-sectional areas (cm^2) of SAT, normalized by the square of one's height (m^2)), visceral adipose tissue index (cross-sectional areas (cm^2) of VAT, normalized by the square of one's height (m^2)), subcutaneous adipose tissue/visceral adipose tissue ratio (SAT/VAT), Total fat area (SAT+VAT) values were obtained for statistical analysis.

Mean, standard deviation, median, minimum, maximum value frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. Mann-Whitney U tests were used to compare quantitative data, and the Chi-Square test was used to compare the qualitative data. The significance level was set at 5% (P ≤.05). SPSS 27.0 was used for statistical analyses.

3. RESULTS

Sixty healthy healthcare worker volunteers were included in the study. The baseline characteristics of the volunteers are summarized in Table 1. Of note, the median age of volunteers was 33 years (23-58), the female-male distribution was 33-27 (55%-45%), the median BMI was 24.7kg/m^2 (16.9-35.9), and 32 (53.3%) had a BMI below 25kg/m^2, compared to 28 (46.7). %) was 25kg/m^2 or more. Median SAT (cm^2), VAT (cm^2), SATI (cm^2/m^2), VATI (cm^2/m^2), TFA (Total Fat Area, sum of SAT and VAT) (cm^2), and SAT/VAT (cm^2) were 178.5 (38.1-552.5), 51.5 (7.1-273.2), 61.4 (14.3-213.1), 19.1 (2.7-90.6), 251.3 (45.3-683.2), and 3.3 (0.4-12.3) respectively (Table 2).

Table 1. *Demographic characteristics of the volunteers*

Age (years)	
Median	33.0
Mean ± SD	35.2 ± 9.5
Range	23-58
Sex — no. (%)	
Male	27 (45.0)
Female	33 (55.0)
Smoking status — no. (%)	
Yes	13 (21.7)
No	47 (78.3)
Alcohol consumption — no. (%)	
Yes	39 (65.0)
No	21 (35.0)
Hypertension — no. (%)	
Yes	2 (3.3)
No	58 (96.7)
Diabetes Mellitus — no. (%)	
Yes	1 (1.7)
No	59 (98.3)
Cardiovascular disease — no. (%)	
Yes	2 (3.3)
No	58 (96.7)
SARS-CoV-2 spike antibody titers (AU/mL)	
Median	1039.0
Mean ± SD	1253.0 ± 1128.0
Range	113.0-6613.0
Height (m)	
Median	1.67
Mean ± SD	1.69 ± 0.09
Range	1.54-1.93
Weight (kg)	
Median	69.5
Mean ± SD	72.1 ± 15.8
Range	45.0-115.0
Body mass index (BMI) (kg/m^2)	24.7
Median	25.1 ± 4.1
Mean ± SD	16.9-35.9
Range	32 (53.3)
< 25 — no. (%)	28 (46.7)
≥ 25 — no. (%)	

Table 2 *Summary statistics of each body composition according to spike antibody titers.*

Variables	All	≤ 1000 (AU/mL)	> 1000 (AU/mL)	*P* value
Age Median Mean ± SD	33.0 35.2 ± 9.5	33.0 36.0 ± 9.9	33.0 34.5 ± 9.3	.589
Sex Male Female	27 (45.0%) 33 (55.0%)	15 (51.7%) 14 (48.3%)	12 (38.7%) 19 (61.3%)	.311
Height (m) Median Mean ± SD	1.67 1.69 ± 0.09	1.70 1.70 ± 0.09	1.65 1.68 ± 0.09	.260
Body mass index (BMI) (kg/m^2) Median Mean ± SD *< 25* *≥ 25*	24.7 25.1 ± 4.1 32 (53.3%) 28 (46.7%)	24.8 25.4 ± 4.2 15 (51.7%) 14 (48.3%)	24.5 24.7 ± 4.0 17 (54.8%) 14 (45.2%)	.690 .809
Subcutaneous adipose tissue area (SAT) (cm^2) Median Mean ± SD	178.5 180.8 ± 84.0	169.5 171.0 ± 93.4	186.3 189.9 ± 74.6	.171
Visceral adipose tissue area (VAT) (cm^2) Median Mean ± SD	51.5 84.0 ± 73.4	51.9 86.1 ± 71.8	51.2 82.0 ± 76.1	.853
Total fat area (TFA) (cm^2) Median Mean ± SD	251.3 264.8 ± 129.5	238.2 257.1 ± 134.6	251.7 271.9 ± 126.4	.501
Subcutaneous adipose tissue index (SATI) Median Mean ± SD	61.4 63.9 ± 31.0	59.0 59.4 ± 34.9	70.1 68.0 ± 26.9	.063
Visceral adipose tissue index (VATI) Median Mean ± SD	19.1 28.8 ± 24.3	19.4 29.4 ± 24.6	18.8 28.2 ± 24.5	.853

Adequate antibody titers (≥50 AU/ml) were obtained after vaccination in all subjects participating in the study. The median value of IgG antibody titers was 1039 AU/ml and ranged from 113 AU/ml to 6613 AU/ml. The mean value of the titer data was calculated as 1000 AU/ml. Thus, statistical comparison was made by dividing the subjects into two groups with a titer value of ≤1000 AU/ml and >1000 AU/ml.

There was no statistically significant relationship between antibody titers and subcutaneous adipose tissue areas, visceral adipose tissue areas, and index values (p>.05). Table 2 summarizes the statistical results.

4. DISCUSSION

To the best of our knowledge, no previous studies have examined the relationship between antibody levels following SARS-CoV-2 vaccination and body fat distribution. Central obesity was quantified by measuring abdominal circumference instead of BMI in a study examined the relationship between antibody titers and central obesity in individuals who received an mRNA vaccine, and antibody titers developed after the mRNA vaccine were found to be lower in central obesity patients (17). In their meta-analysis on obesity and vaccine immunization, Painter et al. stated that obese people tend to develop poor response to vaccination (18). It is generally accepted that TNF-alpha, IL-6, leptin, and resistin, produced by adipocytes and macrophages in fatty tissue, play a role in poor immunization values in obese individuals (19–21). Studies on obesity have shown that body fat tissue has different functions on different locations. It is stated that visceral adipose tissue is more cellular vascular and contains more inflammatory cells than subcutaneous adipose tissue. In addition, the adipocytes contained in the visceral adipose tissue are metabolically more active than those found in the subcutaneous adipose tissue, and they show more insulin resistance (6).

Given the known relationship between visceral adipose tissue and inflammation, we hypothesized that there might be a relationship between antibody titers and measures of subcutaneous and visceral adipose tissue. However, our results did not support this hypothesis. Although we did not observe a statistically significant relationship between antibody titers and measures of subcutaneous and visceral adipose tissue, our study demonstrated that MRI can be used to accurately measure subcutaneous and visceral adipose tissue.

After the widespread use of SARS-CoV-2 vaccines, people's response rates to vaccines are being investigated by the scientific world, which also causes public debate. Many factors can affect the antibody responses of vaccinated individuals. Among the factors, we investigated whether

obesity, which has effects on a large part of the population and immunization, affects the antibody response in vaccinated individuals.

CT images were started to use for evaluating body fat distribution since the obesity has been recognized as a heterogeneous disease. CT has a more widespread use than MRI, and provides much faster image acquisition. Adipose tissue related measurements can be made with standardized density values due to CT physics. These factors have made CT the first-choice method in this regard. However, the development of automated software and the availability of short acquisition times, standardized measurements of adipose tissue can now be obtained from MRI images as well. To our knowledge, there are very few publications on adipose tissue quantification over MR images with automated software. In a study in 2018, a review was done for the limited number of automated programs that perform fat and muscle tissue analysis from MR images, and the paper stated that many of these methods are not accessible to researchers (10). As stated in the same study, only FATCALC, AMRA® Researcher, and SliceOmatic software are accessible and usable for researchers (10,16,22–24). This study used the FATCALC algorithm, implemented in the NIH's ImageJ application, to quantify abdominal adipose tissue from Dixon MR images (15,16). Compared to manual techniques, the measurement of fat tissue on MR images with automated software has become more standardized, more comparable, and easier to obtain. With the advantages of better soft-tissue resolution provided by MRI and the absence of ionization radiation, furthermore, the opportunity of getting images as fast as CT screening as shown in this article, it can be predicted that the MRI sequences will be used more broadly for quantification of adipose tissue. Moreover, the broad usage of deep learning and artificial intelligence technologies is increasing the requirement for making these measurements by automated software.

This study has limitations. One limitation of this study is that it was conducted on a small sample of healthy healthcare workers with relatively narrow ranges of BMI and body fat distribution. Of the 60 people included in the study, 25 had a BMI of 25 and above, and only 7 had a BMI of 30 and above (obese according to the WHO classification). In addition, the number of volunteers remained low due to the general contraindications and claustrophobic nature of the MR device.

5. CONCLUSION

This study investigates the relationship between SARS-CoV-2 vaccine-induced antibody levels and measures of subcutaneous and visceral adipose tissue using a novel MRI-based method that involves the use of automated software to calculate body fat tissue distributions. This study found no statistically significant relationship between antibody levels and adipose tissue distribution. However, findings demonstrate the feasibility of using MRI and automation algorithms to obtain these measurements. Future research with larger, more diverse samples including individuals with a range of BMIs and body fat distributions could provide more comprehensive insights into this relationship. These insights may have important implications for the design of vaccination strategies that are tailored to specific populations.

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Acquisition of data for the study: UB, HKS
Analysis of data for the study: UB, ME
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Clinical and Experimental Health Sciences

Effect of the Practice of Guided Imagery on the Perceived Stress Level in High-Risk Pregnancies

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ABSTRACT

Objective: This research was conducted to identify the effect of the practice of Guided Imagery on the perceived stress level in high-risk pregnancies.

Methods: The study was designed as a prospective, randomized, and single-blind study. The research was performed with the participation of a total of 128 women (64 in the experimental group, 64 in the control group) who had high-risk pregnancies between February-May, 2021. The data were evaluated with the Perceived Stress Scale.

Results: The experimental group obtained a lower mean of post-test scores (26.36±5.96) from the Perceived Stress Scale than the control group (30.48±3.93), and this difference was statistically significant (p<.05). Also, the experimental group obtained lower mean scores from the Perceived Stress Scale in the post-test phase than the one in the pretest phase, and this difference was statistically significant (p<.05).

Conclusion: Nurses and midwives should include the practice of Guided Imagery in the care processes to reduce the stress levels of women with high-risk pregnancies.

Keywords: Guided imagery, perceived stress, high-risk pregnancies.

1. INTRODUCTION

Even if the pregnancy that is one of the most important events experienced by the women across the lifetime is a natural phenomenon, it is also a process when several physiological, psychological, and social changes take place (1).

The cases that threaten maternal or fetal health, increase morbidity and mortality, and also include physiological, social, and emotional dimensions are described as the 'high-risk pregnancy' (2). In the relevant literature, it is put forward that the prospective mothers had worry and fear about the survival and development of the fetus during the pregnancy, and the pregnant women who had worries about themselves and the fetus felt more intense stress (3). In high-risk pregnancies, uncertainties about having a healthy newborn or a healthy delivery frustrate the pregnant women, and this situation, in turn, can raise maternal anxiety and stress levels. While the increase in stress levels affects maternal and fetal health negatively and gives rise to problems such as the risk of preeclampsia, gestational diabetes mellitus, pre-term labor, and spontaneous abortion, it can also affect fetal development and lead to the delivery of babies with low birth weight (2).

The risky cases that affect maternal and fetal health negatively should be evaluated physiologically, socially, and emotionally as a whole (4). Nurses and midwives offering care to a woman with a high-risk pregnancy should be aware of the stressors in the high-risk pregnancy and ensure that proper stress coping techniques are used hence, the prospective mother and newborn have better health outcomes. One of the methods to be used by nurses and midwives in promoting maternal well-being is guided imagery (5,6).

Guided imagery is the mind-body practice in which the power to imagine physical, emotional, and spiritual dimensions is used. The objects that are seen and the emotions that are felt in daily life are recorded by us. The images stimulate our physical and emotional responses and help us understand and make sense of the events (7).

In general, guided imagery uses imaging techniques that will ensure that the pregnant woman will imagine herself in a

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place where she can feel relaxed, safe, happy, and peaceful. These techniques move the pregnant woman's mind away from her disturbing emotions and thoughts about daily life and positively affect her emotional well-being and quality of life by producing different mental images (8,9).

It is discerned that the guided imagery method is applied to different disease groups. For example, it was used as an analgesic in the postoperative period (10), in alleviating the negative effects of chemotherapy (11), in ensuring the functional remission of individuals with schizophrenia (12), in reducing individuals' stress levels (13), in lowering pregnant women's stress levels (5), and in controlling blood pressure in pregnant women with hypertension (6).

Knowing the risks associated with increasing levels of anxiety during high risk pregnancies, there is a need for health professionals to be prepared to intervene effectively, reducing the risk of their incidence and promoting recovery through non-pharmacological methods. There is limited evidence to inform practice about the use of guided imagery for high risk pregnancies. Since the nurses and midwifes are responsible for providing care to women in order to promote their health and their adaptation to parenting, it is essential that they are aware of the most effective methods in the prevention or treatment of anxiety. Nurses and midwives can contribute to reducing stress levels by including guided imagery in the care processes of high-risk pregnant women.

1.1. Objective

This study aimed to identify the effect of the practice of guided imagery on the perceived stress level in high-risk pregnancies.

The hypothesis was; The guided imagery has a positive effect on the reduction of perceived stress levels in women with high-risk pregnancies.

2. METHODS

2.1. Study Design and Participants

The study was designed as a prospective randomized single-blind trial. The research was conducted on women who had high-risk pregnancies and received inpatient treatment on 1 February – 1 May 2021 at the perinatology service of a maternity and children's hospital located in the Anatolian side of Istanbul province of Turkey.

The research population was comprised of all women who had high-risk pregnancies and received treatment at the perinatology service of the aforementioned hospital in the above period. To calculate the sample size, the G*Power for Windows (copyright 2010-2013 Heinrich-Heine-Üniversitat Düsseldorf) was utilized. As per the power analysis (α=0.05, 1-β=0.80), the sample size was identified as 128 participants. A total of 64 pregnant women were randomly assigned to each study group. To this end, "Simple Random Sampling", a probability sampling method, was used. A total of 150 participants on the randomization list were invited to the study.

2.2. Randomization

The participants used a computer-aided simple random sampling method and were assigned to the two study groups as per the table of random numbers. The two group lists were put into either of two envelopes; the researchers randomly selected one of the two envelopes as the intervention group and the other as the control group. Sample selection and assignment to groups were made by a researcher other than the principal researcher who did not practice guided imagery. There was no interaction between the participants since the experimental and control groups were included in the study on different days.

Ten participants were excluded from the study because of communication problems, and 4 because they refused to participate. Four participants from the experimental group and four participants from the control group left the study. The study was completed with 128 participants. Details are given in Figure 1.

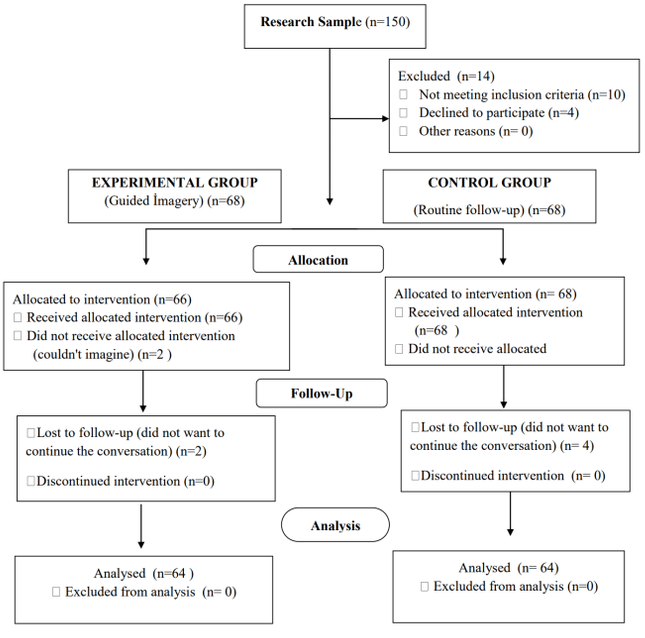

Figure 1. *Study design*

Criteria for being included in the research are having a high-risk pregnancy, being aged 18 years or above, agreeing to participate in the study and being literate in Turkish.

2.3. Criteria for being excluded from the research

The pregnant women who voluntarily wanted to leave the research at any stage after being included in the study, could not communicate verbally, had a visual or hearing disorder, and were previously diagnosed with a psychiatric disease were excluded from the research.

2.4. The experimental group (practicing guided imagery)

The women who were hospitalized at the perinatology service for having high-risk pregnancies and agreed to participate in the research were asked to consent in written format to take part in the study.

Upon receiving consent in written format from the pregnant women to take part in the study, the pregnant women's stress levels were evaluated by using the Perceived Stress Scale in a period when they felt comfortable.

The researcher invited the pregnant woman to imagine herself in a calm and peaceful place. After the pregnant woman said that she was ready, the researcher asked her to imagine herself at the edge of 20-step stairs and instructed her to step down the stairs and reach the place where she desired to be and felt happy, stressless, and carefree. Next, the pregnant woman was asked to imagine that, in each step, her entire body gradually had relaxation starting from her toes. The pregnant woman was given time (2-3 minutes) to imagine, in a stressless manner, experiencing a situation, which she liked or enjoyed, in a place or state that she dreamed about. When the pregnant woman stated that she had relaxation to the extent that she desired, she was once again told to come to the edge of the same stairs. This time, she was instructed to step up the stairs and imagine that her entire body, again starting from her toes, gradually gained strength in each step and she reached the 20th step by growing stronger with each step that she took (14).

The first practice of guided imagery was performed face-to-face with pregnant women. At the end of 20 minutes, the pregnant women's stress levels were reevaluated by using the Perceived Stress Scale.

Control group (routine follow-up): The guided imagery was applied also to the pregnant women in the control group due to ethical considerations after the collection of research data was finalized.

2.5. Measurements

The research data were collected with the Demographic Questionnaire and the Perceived Stress Scale.

Demographic questionnaire form is comprised of 11 questions that were prepared by the researchers in light of the relevant literature and addressed the participant pregnant women's descriptive characteristics such as age, gender, marital status, education level, and income level and the number of their previous pregnancies (6, 14-16).

Perceived Stress Scale was developed by Cohen, Kamarck, and Mermelstein (1983). Comprised of 14 items in total, the scale was designed to measure the extent to which circumstances in one's life are perceived as stressful. The respondents evaluate the items based on a five-point Likert scale that is scored from '0: Never' to '4: Very Often'. Seven positively-stated items are reverse scored. The minimum and maximum scores to be obtained from the scale are successively 0 and 56 points. A high score obtained from the scale indicates that the respondent has high-level stress perception. Eskin et al. (2013) performed the study to test the validity and reliability of the scale in Turkish and the Cronbach's Alpha coefficient was calculated as 0.87 for the scale in this respect (17). The Cronbach alpha coefficient value of the scale in this study was found to be 0.84.

2.6. Data collection

The data were collected during the time period from February 2021 to May 2021. The duration of each session of data collection was approximately 20-25 min per patient. The face-to-face interview technique, performed by the researcher, was used for data collection. The application was carried out between 15:00 and 17:00, which is the most suitable time for pregnant women (time interval other than visit, treatment and sleep hours). Only the pregnant was allowed to stay in the room during the interventions.

2.7. Data Analysis

The research data were analyzed via IBM SPSS 26.0. The frequencies (number, percentage) were used for the categorical variables in the research whilst the descriptive statistics (mean, standard deviation) were utilized for the numerical variables. The Kolmogorov-Smirnov test was employed to test whether the numerical variables were normally distributed, and it was ascertained that some variables were not normally distributed. Therefore, both parametric and non-parametric statistical methods were utilized in the study. The relationships between the two independent categorical variables were examined via the chi-square test. In cases where the assumption of expected frequencies did not hold under the chi-square test, the Fisher Exact Test was utilized. The independent samples t-test was used in the comparison of differences between the two groups of independent variables with normal distribution whilst the Mann-Whitney U Test was employed in the comparison of differences between the two groups of independent variables with non-normal distribution. The dependent samples t-test was utilized in the comparison of differences between the two groups of dependent variables with normal distribution. Statistical significance was determined as p-value of $p<.05$. As per the results of Post Hoc power analysis, it was found that the research had an effect size of.816 and power of 98.4%.

Table 1. *Demographic characteristics each study group*

Characteristics	Experimental group (n=64)		Control group (n=64)		Total (n=128)		Z	p
	Mean	SD	Mean	SD	Mean	SD		
The average age	31.97	5.90	29.91	5.82	30.94	5.93	-1.942	0.052
	n	%	n	%	n	%	Chi-Square	p
Education level								
Primary school	19	29.7	13	20.3	32	25.0	2.91	.23
High school	21	32.8	30	46.9	51	39.8		
Associate/Undergraduate program or higher	24	37.5	21	32.8	45	35.2		
Employment status								
Working	26	40.6	30	46.9	56	43.8	0.50	.47
Not working	38	59.4	34	53.1	72	56.3		
Duration of marriage								
Below 1 year	5	7.8	9	14.1	14	10.9	6.16	.10
1-5 years	28	43.8	37	57.8	65	50.8		
6-10 years	18	28.1	12	18.8	30	23.4		
11 years or above	13	20.3	6	9.4	19	14.8		
Gravidity								
First pregnancy	23	35.9	28	43.8	51	39.8	0.81	.36
Two pregnancies or above	41	64.1	36	56.3	77	60.2		
Month of Pregnancy								
1-3 months	2	3.1	5	7.8	7	5.5	5.22	.07
4-6 months	30	46.9	39	60.9	69	53.9		
7-9 months	32	50.0	20	31.3	52	40.6		
Diagnosis								
Risk of miscarriage	8	12.5	13	20.3	21	16.4	7.76	.10
Premature rupture of membrane/risk of premature birth	23	35.9	12	18.8	35	27.3		
Preeclampsia/eclampsia	13	20.3	22	34.4	35	27.3		
Hyperemesis gravidarum	1	1.6	2	3.1	3	2.3		
Gestational diabetes	19	29.7	15	23.4	34	26.6		
Income level								
Income below expenses	19	29.7	9	14.1	28	21.9	4.74	.09
Income equaling expenses	32	50.0	37	57.8	69	53.9		
Income above expenses	13	20.3	18	28.1	31	24.2		

Z: Mann-Whitney U Test

Table 2. *Inter-group and intra-group comparisons of the pretest and post-test Perceived Stress Scale scores*

	Experimental group (n=64)		Control group (n=64)		Inter-group comparisons	
	Mean	SD	Mean	SD	t^a	p
Pretest	31.53	4.40	30.50	3.92	1.40	.16
Post-test	26.36	5.96	30.48	3.93	-4.62	**.000***
Intra-group comparisons	t^b=9.548	p=**.000***	t^b=.08	p=.93		

*a: Independent samples t-test b: Dependent samples t-test *p<.05*

2.8. Ethical Considerations

The written permissions necessary for conducting the research and collecting data were obtained (decision dated: 23.12.2020 and numbered: 130/10) from the Scientific Research and Publications Ethics Committee of a university and the hospital where the research took place. After information about the research was presented to the pregnant women, they were asked to consent in written format and verbally to participate in the research before the study was launched. Social distancing and other protective measures related to the pandemic were taken during the data collection process.

3. RESULTS

To the results of this study, there was no statistically significant difference between the pregnant women in the experimental and control groups as per the variable of age ($p>.05$) (Table 1). According to the results of the chi-square test, there was no statistically significant difference between the participant women in the experimental and control groups as per the variables of education level, employment status, duration of the marriage, gravidity, month of pregnancy, diagnosis, income level, mental state ($p>.05$) (Table 1). In light of these results, it is discerned that the experimental and control groups were homogeneous in terms of the variables of age, education level, employment status, duration of the marriage, gravidity, month of pregnancy, diagnosis, income level ($p>.05$) (Table 1).

According to the results of the independent samples t-test, there was a statistically significant difference in the means of the post-test Perceived Stress Scale scores of the experimental and control groups ($p<.05$) and the experimental group obtained a lower mean of post-test Perceived Stress Scale scores than the control group (Table 2). As per the results of the dependent samples t-test, there was a statistically significant difference in the means of pretest and post-test Perceived Stress Scale scores of the experimental group ($p<.05$), and the experimental group obtained a lower mean of Perceived Stress Scale scores in the post-test phase than the one in the pretest phase (Table 2).

4. DISCUSSION

The effect of the practice of guided imagery on the perceived stress level in high-risk pregnancies was analyzed in this study.

In this research, it was found that the women who practiced guided imagery in high-risk pregnancies obtained a lower mean of perceived stress scores after the practice than the one obtained before the practice whereas there was no statistically significant difference in the means of perceived stress scores obtained in the pretest and post-test phases by the pregnant women who did not practice guided imagery (Table 2). The advent of a high-risk case in pregnancy raises the stress experienced by the woman during the pregnancy period and can exert additional emotional, mental, and physiological effects on the pregnant woman (2,3). Guided imagery is an evidence-based complementary practice that is effective in lowering stress levels, developing the positive emotional state further, and improving the negative emotional state (18,19). The results in the relevant literature are similar to the finding of this current study. Likewise, in the study performed by Jallo et al. (2014) on African American pregnant women, it was identified that the practice of guided imagery reduced maternal stress and was effective in lowering stress in pregnant women who received inpatient treatment for having high-risk pregnancies (16). In the study by Shakiba et al. (2019), it was ascertained that the practice of guided imagery was effective in lowering nausea and vomiting in pregnancy (20). In the study by Furtado et al. (2019), it was found that the practice of guided imagery reduced maternal anxiety and perceived discomfort during pregnancy (21). In the study conducted by Khojasteh et al. (2016) on the nulliparous pregnant women in Iran, it was discerned that the practice of guided imagery lowered anxiety in pregnant women (22). In the study conducted by Mokaberian et al. (2021) on primiparous women with unwanted pregnancies, it was ascertained that the practice of imagery-based progressive muscle relaxation was effective in enhancing attachment between the prospective mother and fetus and ensuring that the pregnant women felt mentally better (23). In the study performed by Azimian et al. (2017) to examine the effect of progressive relaxation and guided imagery on gestational hypertension, it was identified that both methods significantly reduced blood pressure values (24). In the study by Jupriyono et al. (2017), it was indicated that guided imagery was effective in lowering maternal anxiety and stress (15).

The strength of this study is; as a research method, it was carried out with a single-blind method and randomization in the experimental design. Its limitation is; data is limited by the accuracy of the answers given by the participants to the scale items. Another limitation was that the application was performed only once, and the result was measured immediately. Studies requiring longer follow-ups are needed for long-term results.

5. CONCLUSION

At the end of the research, it was identified that the practice of guided imagery reduced the perceived stress in women with high-risk pregnancies. In this respect, ensuring the use of guided imagery as a complementary method to make pregnant women relax and making the use of this practice more popular are recommended. It is recommended that nurses and midwives support women with high-risk pregnancies by helping them imagine through assuring narratives likely to make them relax (i.e. asking them to imagine pleasing scenes such as sea, lake, and forest).

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Author Contribution:

Research idea: NAD, KDB, AD
Design of the study: NAD, KDB, AD
Acquisition of data for the study: AD
Analysis of data for the study: NAD, KDB, AD
Interpretation of data for the study: NAD, KDB, AD
Drafting the manuscript: NAD, KDB
Revising it critically for important intellectual content: NAD, KDB
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Clinical and Experimental Health Sciences

Evaluation of the accessory canals of canalis sinuosus via Cone Beam CT

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ABSTRACT

Objective: Canalis sinuosus (CS) is a common anatomical variation in the anterior maxilla that originates from the infraorbital canal and carries the anterior superior alveolar nerve and vessels. This study aimed to examine the presence, frequency, and features of CS and its accessory canals (ACs) using cone beam computed tomography (CBCT) images.

Methods: A total of 495 CBCT images were retrospectively analyzed in axial, sagittal, and coronal sections. Patient age and sex, presence or absence of CS, location as right, left, or bilateral if CS was present, and number of ACs were recorded. In addition, the end regions of the ACs were recorded as central incisor, central-lateral incisor, lateral incisor, lateral incisor-canine, and canine regions. All recorded data were statistically analyzed.

Results: At least one CS was found in 54 (10.9%) of 495 CBCT images. CS(s) were bilateral in 26 (48.2%) cases and unilateral in 28 (51.8%; 25 on the left and 3 on the right side). The ACs of the CS predominantly terminated in the lateral incisor region (p =.025). The frequency of CS was not statistically different between males and females (p =.313).

Conclusion: Accessory canals in the anterior maxilla are mostly associated with branches of the CS. In the current study, the prevalence of CS was 10.9%, and most of the CSs were opening in the lateral incisor region. Detection of accessory canals in the anterior maxilla and examination of this region with CBCT will prevent misdiagnoses and postoperative complications arising from damage to these structures.

Keywords: Anatomical Variation, anterior maxilla, canalis sinuosus, cone-beam CT

1. INTRODUCTION

Dental procedures, such as dental implant placement, orthognathic surgery, extraction of supernumerary and/or impacted teeth, cyst and tumor surgery, and endodontic and periodontal surgery, are frequently performed on the anterior maxilla (1,2). Before performing these procedures, any variations in the anatomy of this region should be identified to avoid damage to neurovascular structures.

The maxillary nerve, one of the branches of the trigeminal nerve, divides into the posterior superior alveolar nerve, the nasopalatine nerve, the greater palatine nerve, and the infraorbital nerve. The infraorbital nerve passes through the infraorbital foramen, which divides into a lateral branch called the canalis sinuosus (CS), through which the anterior superior alveolar (ASA) nerve passes (3). The ASA nerve is a branch of the infraorbital nerve that passes through the CS after exiting the infraorbital foramen.

The CS reaches the anterior edge of the nasal cavity from the anterior end of the inferior nasal concha and opens at the side of the nasal septum in front of the incisive canal (4). Its opening is typically anterior to the incisive canal, although it shows anatomical variations in the anterior palatine called accessory canals (3-6). The ASA nerve innervates the incisors and canines (6,7). The CS contains the ASA nerve and its associated arteries and veins (4,8). Clinicians do not devote attention to this anatomical formation unless it causes complications, such as bleeding or paresthesia. Dentists sometimes misdiagnose CS as a periapical lesion, and it is difficult to identify on conventional radiographs (3).

Although two-dimensional imaging methods such as periapical and panoramic radiography are widely used in dentistry, they do not provide sufficient information for in-depth analysis of anatomical structures due to limitations such as distortion, superposition, and magnification. Three-dimensional imaging with cone beam

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computed tomography (CBCT), on the other hand, provides high-resolution cross-sectional images and detailed examination at low radiation doses compared with helical computed tomography (CT). CBCT also significantly reduces the overlap of images, permits linear and angular measurements, and allows for multiplanar reconstruction of images (9-12). A detailed three-dimensional evaluation using CBCT thus provides information regarding anatomical variations that can help clinicians avoid damaging anatomical and neurovascular structures.

The aim of this study was to confirm the presence and reveal the frequency and characteristics of CS accessory canals using CBCT examination.

2. METHODS

The study protocol, including all changes and revisions, was carried out according to the principles described in the Declaration of Helsinki. The local ethics committee of Bolu Abant İzzet Baysal University approved the study (Protocol No:173/2020).

Images of 495 patients between 16-81 years of age who underwent CBCT between 2015 and 2020 at the Department of Oral and Maxillofacial Radiology for reasons such as impacted teeth, cysts, and tumors, and implant evaluation were selected and retrospectively evaluated.

The CBCT images were acquired using an i-CAT imaging system (Imaging Sciences International, Hatfield, PA, USA) with the following parameters: 120 kVp and 15 mA, 0.3 mm voxel size, and 4.8 sec. exposure time. Images were analyzed using the i-CAT Vision Q imaging software (Imaging Sciences International, Hatfield, PA, USA). The maxillary sinuses, dental arches in the upper alveolar process from the lower edge of the orbit, and posterior region of the maxilla were included in the field of view (FOV) of all individuals' CBCT images. The FOV sizes of the images were 16x6 cm, 16x8 cm, and 16x10 cm.

Images were excluded if any artifact prevented the examination of the anterior maxilla. Patients with pathological disorders such as trauma, congenital malformations, implanted plates and screws, bone graft material, cysts, tumors, supernumerary and/or impacted teeth, foreign bodies, and fractures in the anterior maxilla were excluded from the study population.

Tomographic examinations were evaluated by an oral and maxillofacial radiologist with 3 years of experience. Multiplanar images with 0.3 mm slice thickness were examined in detail in the radiographs studied. The CS was first defined in the coronal section, and then the sections were continued to be scanned by scrolling. CS was recorded as present in the presence of corticated, partially corticated or uncorticated bone canal, any bone canal other than the NPC in the anterior maxilla, and any bone canal detected in all three (coronal sagittal, and axial) sections of the CBCT (Figure 1a, 1b, and Figure 2). The presence or absence of the CS, the location of the CS (right or left) if present, and the total number of accessory canals were noted for each patient. The location of the end of the CS trajectory was characterized as central incisor, central–lateral incisor, lateral incisor, lateral incisor–canine, and canine regions. Patient age and sex were recorded. In order to calculate the intra-observer reliability, the images of 55 patients were re-evaluated 1 month later by the same observer.

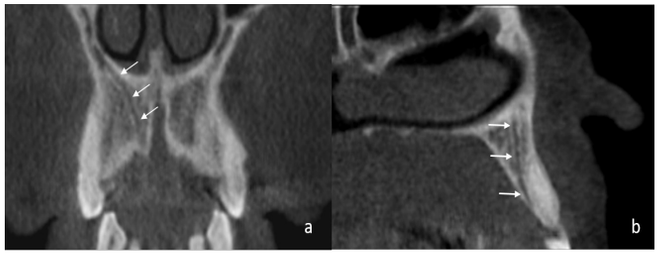

Figure 1. (a) *Right unilateral CS on coronal section (white arrows),* ***(b)*** *CS on sagittal section (white arrows).*

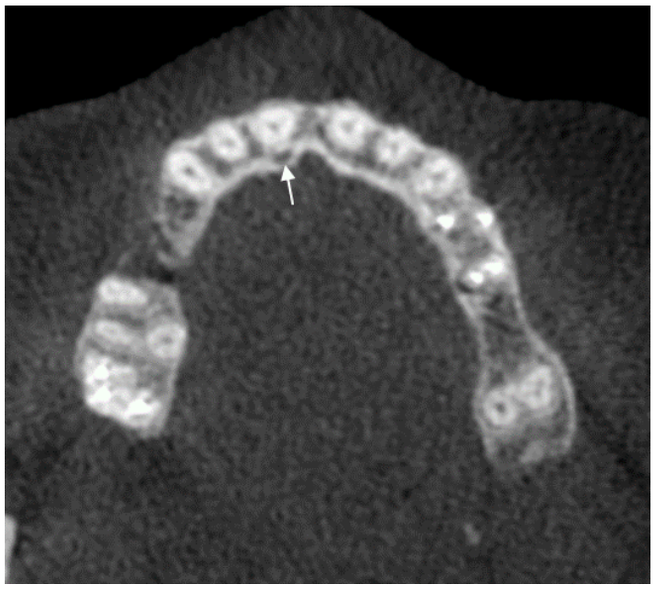

Figure 2. *Unilateral CS on axial section (white arrow)*

Statistical Analysis

Descriptive statistics were performed on the collected data and presented as numbers, percentages, means, and standard deviations. The Shapiro–Wilk test was used to test the assumption of normality. The relationship between categorical variables was examined using the chi-square test.

All analyses were performed using the Statistical Package for the Social Sciences software (SPSS version 24.0, Inc., Chicago, IL, USA). A level of $p < .05$ was accepted as the level of significance.

3. RESULTS

The intra-observer agreement was found to be high (Intra-observer correlation coefficient was 0.889). In this study, a total of 495 images of 246 males (mean age 45.89 ± 15.81 years) and 249 females (mean age 42.74 ± 14.77 years) were evaluated. The mean age of the patients was 44.30 ± 15.36 years.

Table 1 shows the distribution of CS and age according to sex. At least one CS accessory canal was found in 54 (10.9%) images. The incidence of accessory canals was higher in women than in men, although the difference was not statistically significant (p =.313).

Table 1. *Presence of the Canalis sinuosus according to gender*

	Female (n=249)	Male (n=246)	Total
CS absent (%)	218 (87.6)	223 (90.7)	441 (89.1)
CS present (%)	31 (12.4)	23 (9.3)	54 (10.9)
Total	249 (100)	246 (100)	495 (100)

n: number of cases

Table 2 presents the data on the presence of CS according to age. No difference was found between age groups in the presence of CS (p =.956). CS was bilateral in 26 (48.2%) and unilateral in 28 (25 on the left, 3 on the right) of the 54 patients. The prevalence of CS was significantly higher on the left than on the right (p =.014) (Table 3).

Table 2. *CS presence according to age groups Presence of the CS according to age groups*

Age Groups (Years)	Absent n (%)	Present n (%)	Total
16-19	26 (%89,7)	3 (%10,3)	29
20-29	69 (%87,3)	8 (%12,7)	77
30-39	72 (%90)	8 (%10)	80
40-49	94 (%90,4)	10 (%9,6)	104
50-59	97 (%87,4)	14(%12,6)	111
60-69	64 (%88,9)	8 (%11,1)	72
70-79	19 (%95)	1 (%5)	20
Total	441	54	495

n, number of cases; CS, Canalis sinuosus

Table 3. *CS presence according to sides*

CS	Right	Left	p value
Absent	466[a]	444[b]	*.014
Present	29[a]	51[b]	

CS, Canalis sinuosus

The CS accessory canals predominantly terminated in the lateral incisor region (p =.025) (Figure 3).

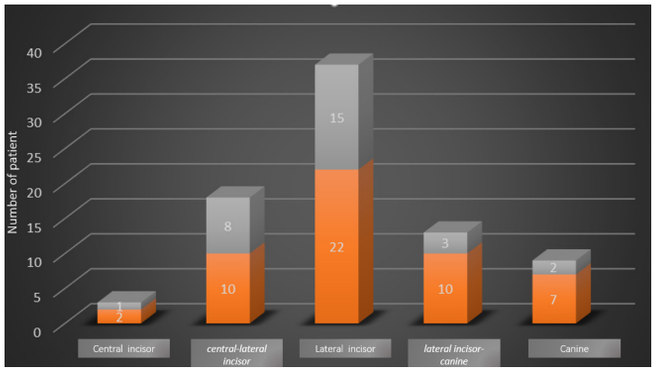

Figure 3. *The end of the CS trajectory. Orange bar shows left side and gray bar shows right side.*

4. DISCUSSION

Mandibular and maxillary nerve structures and their courses have been described in numerous articles and anatomy textbooks (13-15). Considering the previous data in the literature, it is clear that these nerve structures have several anatomical variations, some of which require careful clinical examination (16). The infraorbital canal gives a small branch, called the CS, near the midpoint of the lateral aspect of the face, through which the ASA nerve passes. The CS, a neurovascular canal containing the ASA nerve, artery, and vein, is an anatomical structure that is not sufficiently understood by clinicians (17). The ASA nerve reaches the anterior maxillary region and innervates the incisors, canines, and soft tissues in this region (6).

The integrity of the CS may be compromised in craniofacial trauma, after Le Fort 1 osteotomy, and during dental surgery. Sensory complications, such as localized hypoesthesia, paresthesia, and neuropathic pain, may occur due to damage to the ASA nerve.

If surgeons do not consider the presence of accessory canals, patients may be at increased risk of experiencing neurosensory changes, excessive bleeding, or other complications during surgical procedures (5). Due to the proximity of the CS accessory canals to the apex of the teeth, inappropriate treatment may be performed without proper knowledge of the patient's anatomy (8).

Except for a few case reports in which symptoms of pain and paresthesia have been reported (18-21), no evidence is available regarding the effects and clinical significance of surgical injury to the accessory canals of the canalis sinuosus or anterior maxilla. More clinical studies are needed to support the clinical significance of CS.

This study investigated the prevalence of CS and the termination of its trajectory on CBCT images. CS was found in the anterior maxilla in 10.9% of the 495 patients in the present study. The prevalence of CS was reported by Ghandourah et al. (22) as 67.6%, by Von Arx et al. (2) as 55.1%, by Aoki et al. (3) as 66.5%, by Machado et al. (1) as 51.7%, by de Oliveira Santos et al. (6) as 15.7%, by Anatoly et al. (23) as 67%, by Fernandes et al. (24) as 18%, and by Shan et al. (25) as 36.9%.

In the studies on Turkish population, the prevalence of CS was determined by Tomrukçu et al. (17) as 34.6%, by Orhan et al. (26) as 70.8%, while Beyzade et al. (27) and Gürler et al. (5) found the prevalence of CS as 100%. In our study, the prevalence of CS was found to be lower than in previous studies.

Significant difference between the prevalence may be derived from variety of reasons like methodological differences (voxel size, using of different CBCT scanners, different exposure parameters, inclusion/exclusion criterias etc), racial differences, study groups' distribution or may be just coincidental.

In another study on Turkish population, Sekerci et al. (28) analyzed the presence of the accessory foramina and canals having a diameter of at least 1 mm within the premaxilla in 368 pediatric patients using CBCT. Eighty-two patients had additional

canals; in 6 of them, the canals presented as a direct extension of the CS. There are not many studies on this subject in the pediatric group. In addition, since our study population did not include pediatric patients, a comparison could not be made.

Similar to the studies by Ghandourach et al. (22) and Manhaes Junior et al. (29), the frequency of CS in this study did not differ significantly between genders. While some previous studies found a higher prevalence of CS in males (1,3,24), Şekerci et al. (28) and Anatoly et al. (23) found more CS accessory canals in females. The results of the studies are variable regarding the difference in the frequency of CS between the genders. These discrepancies may be due to differences in the male-to-female ratio in the populations studied or racial differences.

In this study, we detected 48.2% bilateral and 51.8% unilateral accessory canals arising from the CS. In comparison, Aoki et al. (3) reported 54.14% bilateral and 45.86% unilateral CS, de Oliveira Santos et al. (6); 21.4% bilateral and 78.6% unilateral CS, Wanzeler et al. (16); 87% bilateral and 1% unilateral CS, Beyzade et al. (27); %94.5 bilateral and %5.5 unilateral CS, Anatoly et al. (23); %45.7 bilateral and %54.3 unilateral CS and Gürler et al. (5) and Ghandourach et al. (22) both reported 100% bilateral CS. The prevalence rates of CS in this study and previous studies differ according to the sides. Previous studies used different voxel size and slice thicknesses and considered a diameter of less than 1 mm to identify CS. The differences in the results may be due to these methodological inconsistencies.

In the present study, we did not observe a significant difference in the presence of CS between age groups. Similarly, previous studies have reported no association between the presence of CS and patient age (3,6,16,23). However, in the study by Von Arx et al. (2), no one under the age of 20 had an accessory canal, whereas more than one accessory canal was observed in older people. In the study of Gürler et al. (5), five out of six patients under 20 years of age had an accessory canal. In this study, the prevalence of CS in under the age of 20 was found to be similar to other age groups. The prevalence of CS differed between studies according to age groups. Differences in age distribution, observer subjectivity, and image-related dissimilarities in the studies may account for the differing results.

In our study, the endpoint of the CS occurred predominantly in the lateral incisor region by 46.25%. Similarly, Manhaes Junior et al. (29) evaluated 500 CBCT images and reported that the location of this anatomical variation was the palatine of the lateral incisor. Similarly, Neves et al. (4) and Gürler et al. (5) reported that the CS opened to the foramina on the palatal portion of the lateral incisor. Fernandes et al. (24), Anatoly et al. (23) (33.5%), and Beyzade et al. (27) (46.8%) reported that the CS was most frequently opened to the lateral incisor region. Ghandourach et al. (22) observed that the lateral canine region (27.8%) on the left side was the most common location, followed by the central incisor region (22.2%). Aoki et al. (3) showed that 44.39% of CSs terminated in the central incisor region, 21.95% terminated in the lateral incisor region, and 14.15% terminated in the canine region. Shan et al. (25) stated that CSs were most frequently opened to the central and lateral incisor regions (61.9%). In several additional previous studies, (1,2,6) the most common termination location was the central incisor region. When the bucco-palatal localization of the ACs is evaluated, Machado et al. (1) reported that only 5.1% of ACs had a terminal ending at the buccal cortical plate, and Tomrukçu et al. (17) reported that 3 out of 214 ACs had a terminal ending at the buccal cortical plate. Beyzade et al. (27) showed that the terminal ends of all ACs are located in the palatal cortical plate. Similar to Beyzade et al. (27), in our study, in all cases ACs had a terminal ending at the palatal cortical plate.

Most of the studies in the literature were performed with CBCT, but the lack of standardization in the methodology of the studies led to different results. In addition, it is not clearly stated that the structure evaluated in the studies is the main CS canal or an accessory branch. In this study, the CS terminate in the alveolar process of the anterior maxilla was evaluated. Therefore, no comment on its origin has been made.

The main limitation of the present study is that the voxel size of the images is 0.3 mm. Smaller accessory canals can be seen, and more accurate results can be obtained in images with higher resolution obtained with a smaller voxel. The other limitation of the present study is that only one observer's results are included in the study.

5. CONCLUSION

The prevalence of CS in this study was 10.9%, and the most common endpoint of the CS was the lateral incisor region at 46.25%. There was no difference in the prevalence of CS between genders or age groups. Identification of the CS by CBCT is crucial to preventing complications and optimizing patient prognosis.

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Clinical and Experimental Health Sciences

The Relationship Between Intensive Care Experience and State Anxiety in Patients Treated in Coronary Intensive Care Units

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ABSTRACT

Objective: This study aimed to determine the correlation between the intensive care experience and the state anxiety of patients hospitalized in the coronary intensive care unit.

Methods: This descriptive cross-sectional study included 192 patients from the coronary intensive care unit of a university hospital. Data were collected using a Patient Information Form, the Intensive Care Experience Scale (ICE), and the Spielberger State Anxiety Inventory (STAI-I). The analysis was conducted using SPSS software version 25.0. Descriptive statistics were reported as counts, percentages, means, and standard deviations. A p-value of less than 0.05 was considered to indicate statistical significance.

Results: Among the participants, 38% were aged 65 and older, 76.6% were male, 93.2% were married, 63% were admitted to the intensive care unit from the emergency room, and 88.5% had prior experience in an intensive care unit. The total and sub-dimension scores of the ICE and STAI-I were moderate. We found a weak positive correlation between the STAI-I total score and the ICE total score (r= 0.320). There was a very strong positive correlation between pessimistic experiences in the intensive care unit and the STAI-I total score (r=0.907). Additionally, there was a moderate negative correlation between satisfaction with care received in the intensive care unit and the sub-dimensions of memory of experiences (Awareness of Surroundings, Satisfaction with the Care, Recollection of Experiences) (r=0.252, r=-0.489, r=-0.496).

Conclusion: The study found that pessimistic experiences in the intensive care unit can significantly impact patients' state anxiety.

Keywords: intensive care, anxiety, nursing

1. INTRODUCTION

Coronary intensive care units specialize in the interventional-medical treatment and care of patients with severe cardiovascular conditions (1). Intensive care units have many technical equipment in the relevant field, unlike general clinics, due to their nature. In these units, complex technological devices aimed at better patient care are used, more interventional applications are made, and patients are followed up more closely (2,3).

Intensive care units, designed for intensive treatment, can be a source of stress for patients (1, 2,3). Patients may experience anxiety about the severity of their condition, unfamiliar surroundings, insufficient natural light, disrupted sleep patterns, inability to keep track of time, and separation from their loved ones, which can have a negative psychological impact on them (2,3). Studies have found that being in an unfamiliar environment is one of the most significant factors contributing to the stressful ICU experience (2,4).

Stressful situations can trigger an inflammatory response in the brain and other systems, which can lead to the release of inflammatory mediators and result in different symptoms depending on the intensity and quality of the stressor (5). While the primary objective of the ICU process is to improve the patient's physical condition, it is equally important to prioritize their mental and social well-being. Therefore, a holistic approach should be taken to provide care to patients in the ICU, which includes interventions to improve the patient's physical health and provide psychological and social support to them and their families.

It is possible for patients to have a positive experience during the ICU process, despite their serious health problems and the many stressors they have to face, by providing care that is individualized, systematic, and holistic, as well as by improving the environmental conditions (5). Patients who are critically ill or require close monitoring and treatment after an invasive procedure may experience more physical, psychological, and social anxiety (6).

Staying in coronary intensive care units can be very stressful for patients, and it is believed that this stress can have a significant impact on their well-being (2,6). Research has

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shown that patients with coronary artery disease who experience depression and anxiety may be at higher risk of mortality and morbidity (6,7).

Unfortunately, there are very few descriptive studies that have focused on the experiences of patients in coronary intensive care units (8). This is largely due to the poor health of these patients (8,9). However, understanding and improving the experiences of patients in these units is essential to standardize care and improve its quality (8). Additionally, evaluating patients' experiences in the coronary intensive care unit can help guide nursing practices and improve the physical environment.

This study aims to ascertain the correlation between intensive care experiences and the state anxiety levels of patients in coronary intensive care units.

2. METHODS

2.1. Type of Research

This descriptive and cross-sectional study was planned to determine the relationship between intensive care experience and state anxiety of patients hospitalized in the coronary intensive care unit at a university hospital in Ankara.

2.2. Population and Sample of the Research

The research was carried out in the coronary intensive care unit of a university hospital in Ankara between 16.03.2022 and 20.06.2022. In this time period, 227 patients were admitted to the clinic. A total of 192 coronary artery disease patients who were hospitalized in the coronary intensive care unit at the time of the study and met the inclusion criteria were included in the study. Thirty-three people who did not meet the research criteria and 1 person who did not agree to participate in the study were not included. The rate of participation in the research is 84.5%. Inclusion criteria for the study were hospitalization in the coronary intensive care unit for at least 24 hours, being diagnosed with coronary artery disease, being older than 18 years of age, not having auditory, visual and verbal disabilities, and being literate.

2.3. Data Collection Tools

The research data were collected face-to-face using a data collection form consisting of a Patient Information Form, created by the researchers based on the literature, the Intensive Care Experience Scale, and the Spielberger State Anxiety Inventory (STAI-I).

Patient Information Form

In the first part of the form, there are short questions to record patient descriptive data. Personal characteristics such as age, gender, marital status, education level, place of residence, the type of admission to intensive care, the number of previous intensive care hospitalizations, experiencing a physical limitation, witnessing a death in the intensive care unit, history of needing mechanic ventilation, and the status of receiving visitors were questioned.

Intensive Care Experience Scale (ICE)

The ICE was developed by Rattray et al. in 2004 to evaluate the experiences of patients in intensive care (10). Turkish validity and reliability study was made by Demir et al. in 2009 (14). The scale consists of a total of 19 5-point Likert-type items. The scale has 4 sub-dimensions: Awareness of Surroundings, Frightening Experiences in the intensive care unit, Recalling of Experiences in the intensive care unit, and Satisfaction with the Care received in the intensive care unit. The minimum score to be taken from the scale is 19 and the maximum score is 95. As the total score obtained from the scale increases, the patient's experience is considered positive (11). The Cronbach's alpha coefficient of the original scale was 0.79. The Cronbach alpha coefficient of this study was 0.70.

Spielberger State Anxiety Inventory (STAI-I)

The scale was developed by C.D. Spielberger, R.L. Gorsuch and R. Lushene in 1970 to determine the state anxiety level (12). The Turkish adaptation, reliability and validity studies of the scale were carried out by Necla Öner and Ayhan Le Compte between 1974 and 1977 (13). This self-report scale has twenty 4-point Likert-type items. The total score in the scale varies between 20 and 80. High scores indicates high anxiety. The state anxiety scale indicates the level of anxiety in a particular situation. The Cronbach alpha coefficient of the original scale was 0.86 (16). The Cronbach alpha coefficient of this study was 0.73.

2.4. Ethical Considerations

Ethics committee approval (Decision No. 2022/42 No: 2022033) was obtained from the non-interventional ethics committee. Institutional permission was also obtained from the chief physician of the hospital where the study was conducted. After informing the patients about the study, their verbal and written consents were obtained. The study adhered to the principles declared in the Declaration of Helsinki.

2.5. Data Analysis

Research data were evaluated with the SPSS 25.0 program. In the research, descriptive statistics are presented as number, percentage, arithmetic mean, and standard deviation. Kurtosis and Skewness values were examined to determine whether the research variables showed a normal distribution. In the relevant literature, it is accepted as a normal distribution that the results of the kurtosis skewness values of the variables are between +1.5 and – 1.5 (14). Considering the homogeneity of the data in the comparison of

sociodemographic characteristics and scale scores, Student's t test was used to compare two groups in homogeneous groups and One Way ANOVA test was used to compare three or more groups. In case of non-homogeneous distribution, the Mann Whitney U test was used to compare two groups and the Kruskal Wallis test was used to compare three or more groups. When there was a significant difference between three or more groups, the Tukey and Bonferroni corrected Mann Whitney U test were used to determine the group that revealed the difference. Pearson correlation analysis was used to determine the relationship between scale scores. A p values less than 0.05 was considered significant.

3. RESULTS

It was determined that 38% of the patients were 65 years old or older, 76.6% were male, and 93.2% were married. Of the patients, 47.9% were bachelor's degree and 94.3% lived in the city. Sixty three percent of the patients were transferred to the intensive care unit from the emergency room, 11.5% had no previous history of intensive care unit, 29.7% were hospitalized in an intensive care unit once, 37.5% were hospitalized twice, and 21.4% were hospitalized three times or more. It was determined that 30.7% of the patients witnessed the death of a patient during their stay in the intensive care unit. Twelve percent of the patients were previously connected to a mechanical ventilator and physical restraint was applied to 3.1%. It was determined that 44.8% of the patients had visitors in the intensive care unit (Table 1). The mean ICE score of the patients differed according to age ($p< .001$), and the reason for this difference was that the scores of the patients under the age of 45 were significantly lower than the scores of the other patients ($p< .05$). There was no significant difference between the mean ICE scores according to gender and education level ($p> .05$). The mean ICE score of the married patients was significantly higher than that of single patients ($p< .01$). It was determined that the mean ICE score of the patients living in the city was significantly higher than the scores of the patients living in districts ($p< .001$) (Table 1).

The mean ICE score of the patients differed according to the way they were admitted to the intensive care unit ($p< .001$), and this difference was due to the significantly lower scores of the patients coming from the inpatient service than the other patients ($p< .05$). The mean ICE score of the patients previously hospitalized in the intensive care unit was higher than the scores of the other patients ($p< .01$) (Table 1).

The mean ICE score of the patients differed according to the number of hospitalizations in the intensive care unit ($p< .001$). The reason for this difference was that the scores of the patients who were not admitted to the intensive care unit before were lower than those of the other patients ($p< .05$) and that the scores of the patients who were hospitalized twice in the intensive care unit were higher than the scores of the other patients ($p<.05$). The mean ICE score of the patients who received visitors in the intensive care unit was significantly higher than the other patients ($p< .001$) (Table 1).

The mean ICE score of the patients who were previously connected to mechanical ventilation during their stay in the intensive care unit was significantly higher than the scores of the other patients ($p< .05$). There was no significant difference between the mean ICE scores according to the physical restraint history ($p>.05$). The ICE score of the patients who witnessed the death of a patient during their stay in the intensive care unit was higher than the scores of the other patients ($p< .001$) (Table 1).

The STAI-I scores of the patients participating in the study differed according to age ($p< .01$), and this difference was due to the higher scores of the patients under the age of 45 ($p< .05$). The STAI-I scores of the male patients were significantly higher than the scores of the female patients ($p< .001$). STAI-I scores of the married patients were significantly higher than those of the single patients ($p< .001$). The STAI-I scores of the patients differed according to their education level ($p< .01$), and this difference was due to the lower scores of the patients who graduated from high school ($p< .05$). The STAI-I scores of the patients did not differ according to the place of residence ($p> .05$) (Table 1).

There was a significant difference ($p< .001$) between the STAI-I scores according to the way of admission to the intensive care unit, and this difference was due to the higher scores of the patients admitted to the emergency department than those of the other patients ($p< .05$). There was no significant difference between the mean scores of STAI-I according to the history of intensive care unit stay, being connected to a mechanical ventilator, receiving physical restraint, and witnessing the death of a patient during their stay in the intensive care unit ($p> .05$). It was determined that there was a significant difference ($p< .001$) between the number of hospitalizations in the intensive care unit and the STAI-I score, and this difference was due to the fact that the state anxiety scores of the patients who were hospitalized once in the intensive care unit were lower than those of the other patients ($p< .05$). The STAI-I scores of the patients who were visited during their stay in the intensive care unit were significantly higher than those of the other patients ($p< .001$) (Table 1).

The mean total score of the patients on ICE was 59.30±4.31. The mean score of the sub-dimension of awareness of the environment was 16.50±2.74; pessimistic experiences in intensive care sub-dimension mean score was 17.61±2.33; the mean score of satisfaction with the care received in the intensive care unit was 10.51±0.76; remembering experiences in intensive care sub-dimension mean score was 14.66±2.12. The mean STAI-I score of the patients was 50.32±8.65.

A weak positive correlation was found between the STAI-I score and the ICE total score and the sub-dimension of awareness of the environment, and a strong positive correlation was found with the pessimistic experiences in the intensive care unit score ($p< .001$). There was a moderate negative correlation between the scores of the satisfaction with the care received in the intensive care unit and the sub-dimension of remembering the experiences in the intensive care unit of the STAI-I score ($p< .001$) (Table 2).

Table 1. *Comparison of the descriptive characteristics of the patients with their ICE and STAI-I scores*

Descriptive Characteristics (N=192)	n	%	ICE	STAI-I
Age			**Mean±SS**	**Mean±SS**
45 years and under	38	19.8	57.13±4.97	45.57±6.72
46-64	81	42.2	59.97±4.16	50.83±8.98
65 years and older	73	38.0	59.68±3.78	52.21±8.36
Test and p value			**X=22.351 p=0.0001**	**X=7.719 p=0.005**
Gender				
Male	147	76.6	59.29±4.43	51.64±8.31
Woman	45	23.4	59.31±3.97	46±8.42
Test and p value			t=-0.016 p=0.987	**t=3.974 p=0.0001**
Marital status				
Single	13	6.8	56.76±6.13	41.07±1.18
Married	179	93.2	59.48±4.11	50.99±8.58
Test and p value			**U=634.000 p=0.003**	**U=448.500 p=0.0001**
Education				
Primary and Secondary School	58	30.2	59.58±2.67	50.32±8.41
High school	42	21.9	59.28±3.55	45.88±7.68
Bachelor's degree	92	47.9	59.13±5.37	52.34±8.54
Test and p value			X=7.169 p=0.058	**X=14.543 p=0.001**
Place to live				
County	11	5.7	53.81±3.65	49.18±2.08
Province	181	94.3	59.63 ±4.13	50.39±8.89
Test and p value			**t=-4.558 p=0.0001**	U=935.000 p=0.720
How admitted to intensive care				
Polyclinic	45	23.4	59.04 ±4.12	47.00±8.57
Emergency room	121	63.0	60.22±2.99	52.84±8.08
Inpatient service	26	13.5	55.46±7.05	44.34±6.46
Test and p value			**X=23.807 p=0.0001**	**X=24.374 p=0.0001**
Intensive care experience				
Yes	170	88.5	60.07±3.28	50.23±8.89
No	22	11.5	53.31±6.33	51.00±6.64
Test and p value			**U=1094.500 p=0,001**	U=1687.000 p=0,429
Number of intensive care unit admissions				
Never	22	11.5	53.31±6.33	51.00±6.64
1 time	57	29.7	59.78±3.39	45.57±8.11
2 times	72	37.5	61.23±1.56	53.87±8.33
3 times and above	41	21.3	58.43±4.46	50.31±8.00
Test and p value			**X=31.560 p=0.0001**	**F=11.389 p=0.0001**
Witnessing death in intensive care				
Yes	59	30.7	61.01±1.63	51.94±8.93
No	133	69.3	58.54±4.88	49.60±8.46
Test and p value			**Z=-3.706 p=0.0001**	t=1.743 p=0.083
Connecting to a mechanical ventilator				
Yes	23	12.0	60.95±1.79	52.13±8.79
No	169	88.0	59.07±4.51	50.07±8.63
Test and p value			**U=1481.500 p=0.046**	t=1.068 p=0.287
Physical restraint				
Yes	6	3.1	61.66 ±0.81	56.00±7.34
No	186	96.9	59.22±4.36	50.13±8.65
Test and p value			t=1.366 p=0.174	U=341.500 p=0.086
Being visited in intensive care				
Yes	82	44.8	61.95±0.31	58.54±2.87
No	110	55.2	57.32±4.83	44.19±6.02
Test and p value			**Z=-11.864 p=0.0001**	**Z=-11.443 p=0.0001**

F: One-way ANOVA; t=Student-t Test; U, Z=Mann Whitney U Test; X= Kruskal-wallis test

Table 2: *Relationship between intensive care experience scale and state anxiety scale scores*

		STAI-I score
Intensive care subject scale total score	**N**	192
	r	0.320
	p	**0.0001**
Awareness of Surroundings	**N**	192
	r	0.252
	p	**0.0001**
Frightening Experiences	**N**	192
	r	0.907
	p	**0.0001**
Satisfaction With the Care	**N**	192
	r	-0.489
	p	**0.0001**
Recalling of Experiences	**N**	192
	r	-0.496
	p	**0.0001**

r= Correlation coefficient

4. DISCUSSION

Intensive care units are specifically for the treatment and care of patients with serious life-threatening illnesses (15,16). In these units, factors such as the patient's health status, physical conditions, continuous monitoring of vital signs, placement of tubes and cables, experiencing pain and other physical limitations, and restriction of communication with their relatives may cause limitations in patients (6,7).

Considering this situation, the importance of a positive intensive care experience in improving health parameters of patients hospitalized in the coronary intensive care unit becomes evident once again. The nurse has an important role in reducing the negative impact of staying in the intensive care unit on the patient and providing a positive intensive care experience (6). In the literature, there are findings supporting the idea that providing adequate patient information increases the treatment compliance of the patients and reduces the level of anxiety (6,17-19).

Therefore, in this study, the effect of intensive care experience on state anxiety of patients treated in coronary intensive care unit was evaluated.

The total mean ICE score of the patients included in the study was 59.30±4.31, which showed that the awareness levels of the patients were above the average and their experiences in the intensive care unit were positive. It can be said that this situation is due to the positive nature of the nursing care applied in the intensive care unit. In another study, it was determined that 190 patients who were discharged from the intensive care unit evaluated their intensive care experience and received a high mean ICE score (62.1±5.2) (20). In this study, it was determined that the average score in the following sub-dimensions of the intensive care experience scale was moderate: the sub-dimension of awareness of the environment; pessimistic experiences in intensive care sub-dimension score; satisfaction with the care received in the intensive care sub-dimension score; and recall of experiences in intensive care sub-dimension score. Our research is compatible with the literature in this respect (1,2,6).

The sociodemographic characteristics of the patients, age, marital status, and place of residence had an effect on the ICE scores, but gender and educational status did not have an effect on the ICE scores. Our research is compatible with the literature in this respect (20,21), but in the study conducted by Dinlegör & Ünsar (22), it was determined that male intensive care patients had a positive intensive care experience compared to female intensive care patients.

In the study, the mean ICE score of the patients differed according to the way of admission to the intensive care unit, previous intensive care experience, and the status of receiving visitors. It is thought that this result is due to the lack of companions of the patients in the intensive care unit. In other studies, it has been reported that there is no statistically significant difference between the characteristics of the patients hospitalized in the intensive care unit (type of hospitalization, type of room, hospitalization experience, number of hospitalizations) and the scores they received from the sub-dimensions of the scale (22,23). In some sources in the literature, it has been reported that the increase in the length of stay in the intensive care unit negatively affects the intensive care experience of the patients (24). It was found that there is a statistically significant difference between the ICE scores of patients who were connected to mechanical ventilation during their stay in the intensive care unit or who witnessed the death of a patient during the intensive care unit stay. In other study, similar to our study, no statistically significant difference was found between the ICE scores of patients who were previously connected to a mechanical ventilator or who witnessed the death of a patient during the intensive care unit stay (25).

The mean STAI-I score of the patients participating in the study was 50.32±8.65. This outcome is due to the severity of the disease, the fact that they stay in the intensive care unit, and the fact that they are exposed to many invasive interventions. Similar to the present findings, in a study conducted in emergency and intensive care units, the STAI-I scores of the patients were found to be 43.6±10.5 (21).

It was determined that there was a statistically significant difference between the sociodemographic characteristics of the patients (age, gender, marital status and educational status) and STAI-I scores. In a study, statistically significant difference was found between age and anxiety. However, no relationship was found between gender and anxiety in the same study (11). Another study, unlike our study, women's state anxiety was found to be higher than men's (26). In our study, it was found that the state anxiety of married patients was higher than that of single patients. In other study, similar to our study, a statistically significant difference was found between the mean scores of anxiety and depression and the marital status of the patients (23). In a study similar to

our study, it was determined that the educational status of the patients and the place they lived had effects on their state anxiety (23,26). Among the patients in our study, the anxiety score of the group living in the city was found to be high. In the study conducted by Türker & Bedük (26), it was determined that the anxiety scores of patients living in villages were higher. According to the way of admission to the intensive care unit, it was determined that the STAI-I scores of the patients transferred from the emergency department were higher than the other patients. This outcome is probably due to the sudden and unplanned development of patients' admission to the emergency department compared to their admission the outpatient clinic or inpatient service. Sarıgül & Kavurmacı (23) it was determined that this factor did not have an effect on the state anxiety of the patient. In our study, it was determined that patients with previous intensive care experience had lower STAI-I scores than the other patients. In other study, it has been concluded that this factor did not have an effect on the state anxiety score (23). It was determined that the STAI-I scores of the patients who were visited during their stay in the intensive care unit were significantly higher than those of the other patients. It can be thought that this situation is probably due to the fact that patients who are conscious and in communication feel lonely after the visit. In a study evaluating the intensive care experience of patients and their relatives, it was found that patients thought that there was uncertainty at every stage of treatment, and as a result of this situation, the anxiety of both groups increased (24,25).

In our study, there was a weak positive correlation between STAI-I score and ICE total score and environmental awareness sub-dimension score; positive and strong correlation with pessimistic experiences in intensive care sub-dimension score; and, a moderate negative correlation with the satisfaction with the care received in the intensive care sub-dimension and the sub-dimension of remembering the experiences in the intensive care unit. Other studies have also found a relationship between anxiety scores and ICE scores (10,15,19).

5. CONCLUSION

According to the results, the increase in the pessimistic experience of intensive care in patients hospitalized in the coronary intensive care unit increased the patient's anxiety level, and the increase in the patient's satisfaction with the care provided in the intensive care unit decreased their anxiety level. The increase in the number of intensive care unit admissions increased the patient's anxiety and the anxiety level of the patients transferred from the emergency to the intensive care unit was higher.

Patients are admitted to the intensive care unit when their medical needs increase and the need for close and intensive follow-up arises. In this case, it is expected that patients will primarily worry about critical health problems. However, in addition to health problems, negative intensive care experiences can increase patients' anxiety level. During the patient's stay in the intensive care unit, the role of the whole healthcare team, primarily nurses, is important in reducing anxiety and ensuring acceptance of care. It is necessary for the nurse to evaluate the patient in a holistic and systematic way during their stay in the intensive care unit and to prioritize the social and spiritual needs of the patient as well as their physical needs.

In the literature, it is recommended that attempts should be made to improve the intensive care experience of patients by increasing the number of multicenter studies addressing the intensive care experiences and concerns of intensive care patients. It is recommended to raise awareness in the healthcare team about the problems that patients face due to negative intensive care experiences. It is recommended that healthcare professionals working in the coronary intensive care unit receive training to improve their communication skills.

Limitations of the Research

The findings of this study can only be generalized to the population under study.

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Clinical and Experimental Health Sciences

Effect of Simulated Gastric Juice on Color Stability of Different Artificial Teeth

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ABSTRACT

Objective: The current study aimed to evaluate the gastric juice effect on the artificial teeth discoloration in patients with gastroesophageal reflux disease (GERD) under in vitro conditions.

Methods: Three different artificial teeth (Ivostar, Vivodent PE, Phonares II) were used in the study (n=12). A spectrophotometer (VITA Easyshade Compact; VITA Zahnfabrik, Bad Säckingen, Germany) was used for initial color measurements after keeping the specimens in distilled water for 24 h. Then, they were immersed in 5% hydrochloric acid (HCl) at 37°C (pH=2) for 91 h and the color measurements were repeated. The CIEDE2000 formulation was used to calculate the color changes. The statistical analysis was performed with one-way ANOVA and Tukey HSD tests.

Results: Although the color differences of Vivodent PE and Phonares II materials did not exhibit a statistically significant difference (p=0.95; p > .05), there was a significant difference between Ivostar and other materials (p=0.02, p=0.01). The 50:50% detection threshold (PT) was exceeded with Vivodent PE and Phonares II materials, while the 50:50% acceptability threshold (AT) was exceeded with Ivostar material.

Conclusion: After exposure to gastric acid, all groups exhibited perceptible color differences. In the group of acrylic resin artificial teeth, the color difference was above acceptability threshold and would be better to improve. While the acrylic resin artificial teeth exhibited the highest discoloration, artificial teeth containing nanohybrid composite resin showed the least discoloration. These should be considered in the selection of artificial teeth in patients with GERD.

Keywords: artificial teeth, color stability, discoloration, gastric acid, gastroesophageal reflux disease

1. INTRODUCTION

Artificial teeth are important in the functional, phonetic, and esthetic success of removable dentures by replacing missing natural teeth (1,2). There are different kinds of artificial teeth such as composite resin, acrylic resin, highly cross-linked acrylic resin, and porcelain (3). The esthetic properties of all artificial teeth should be maintained for a long time without any color change. The discoloration is usually observed due to coloring agents and the acidity of consumed food and beverages (4-6).

Another important condition that creates an acidic environment in the mouth is gastroesophageal reflux disease (GERD), which is an important health problem due to its complications and negative impact on quality of life. It is usually caused by improper relaxation of the lower esophageal sphincter and backflow of stomach contents into the esophagus (7). The proteolytic pepsin in the gastric juice returning to the oral environment removes the protective dental membrane on the tooth surface and has an abrasive effect on the teeth (8,9). It is indicated that reflux affects not only natural teeth, but also the surfaces of restorative materials (10-13). Myklebost et al (14) investigated the gastric juice effect on the surface roughness of various filling materials and reported that the surface roughness of these materials increased. Another study indicated that acidic beverages changed the color stability and surface roughness of artificial teeth (4).

Spectrophotometers have been used for the measurement of these color changes (6) with CIELAB or CIEDE2000 formulas (15). Two main thresholds are used for these formulas, namely the acceptability threshold (AT) and the perceptibility threshold (PT). They offer quality control to evaluate dental materials' clinical performance and facilitate their selection, as well as interpret various findings in clinical dentistry and dental research (16). The 50:50% PT means that half of the observers notice a color difference between two items, while the others observe no difference. In the 50:50% AT, half of the

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observers consider that the color difference is acceptable, while the others consider it unacceptable (15,17).

In the literature, there have been studies on the effect of gastric acid juice on different restorative materials (11,12,18-21), but there has been no study on artificial teeth. Therefore, the aim of the current study was to evaluate the gastric juice effect on the discoloration of artificial teeth in patients with GERD under in vitro conditions. The null hypothesis was that simulated gastric juice would not affect the discoloration of artificial teeth.

2. METHODS

The tested artificial teeth and their chemical compositions are shown in Table 1. Since the sample size was determined as 11 in each group according to the power analysis (95% confidence interval and 5% margin of error), a total of 36 artificial teeth (A2 color, n=12) were used. A spectrophotometer (VITA Easyshade Compact; VITA Zahnfabrik, Bad Säckingen, Germany) was used for initial color measurements after keeping the specimens in distilled water for 24 h. Following the initial measurements, the specimens were immersed in 5% hydrochloric acid (HCl) at 37°C (pH=2) for 91 hours, which is equivalent to 1 year of HCl exposure in a patient with GERD (13). The samples were washed with distilled water, and dried, and the color measurements were repeated. Color changes (ΔE_{00}) were calculated with the CIEDE2000 formulation.

$$\Delta E_{00} = \sqrt{\left(\frac{\Delta L'}{k_L S_L}\right)^2 + \left(\frac{\Delta C'}{k_C S_C}\right)^2 + \left(\frac{\Delta H'}{k_H S_H}\right)^2 + R_T\left(\frac{\Delta C'}{k_C S_C}\right)\left(\frac{\Delta H'}{k_H S_H}\right)}$$

The ΔL', ΔC', and ΔH' in the formulation describe the variation in hue, chroma, and lightness between two different measurements. RT is the rotation factor and S is the weighting function. KH, KC, and KL, representing parametric factors, were standardized to 1. The 50:50% AT was accepted as ΔE_{00}:1.8 and the 50:50% PT as ΔE_{00}:0.8 (16).

Statistical analysis was performed with IBM SPPS V23 software (IBM Corp., NY, USA). One-way analysis of variance (One-way ANOVA) and Tukey HSD tests were used to compare ΔE_{00} values. The significance level was set at $p < .05$.

Table 1. *The artificial teeth with their chemical composition.*

Artificial tooth	Manufacturer	Composition
Ivostar	Ivoclar Vivadent	conventional polymethylmethacrylate acrylic resin
Vivodent PE	Ivoclar Vivadent	highly cross-linked DCL acrylic
Phonares II	Ivoclar Vivadent	nano-hybrid composite

DCL: Double cross-linked.

3. RESULTS

Table 2 demonstrated the results of the color change of each material. The One-way ANOVA test indicated a statistically significant difference in color stability of the tested materials exposed to the acidic solution ($p=0.007$; $p < .05$). Although the color differences of Vivodent PE and Phonares II materials did not exhibit a statistically significant difference ($p=0.95$; $p > .05$), there was a significant difference between Ivostar and other materials ($p=0.02$, $p=0.01$) according to Tukey HSD test.

The highest color difference was observed in the Ivostar material (ΔE_{00}=2.14±0.40), while the lowest was observed in the Phonares II material (ΔE_{00}=1.72±0.23). Color differences in Vivodent PE and Phonares II materials exceeded the 50:50% PT (ΔE_{00}=0.8) and Ivostar material exceeded the 50:50% AT (ΔE_{00}=1.8).

Table 2. *The color change results of the materials.*

Material	n	Mean ± SD	F	p
Ivostar	12	2.14 ± 0.40[a]	5.879	0.007
Vivodent PE	12	1.77 ± 0.31[b]		
Phonares II	12	1.72 ± 0.23[b]		
Total	36	1.88 ± 0.36		

**Different letters indicate a statistical significant difference; SD:Standard deviation.*

4. DISCUSSION

The null hypothesis that simulated gastric juice would not affect the discoloration of artificial teeth was rejected. Because, the simulated gastric juice affected the color stability of all tested artificial teeth and the color differences of all groups exceeded the 50:50% PT value.

Color stability is an important feature for all dentures, as discoloration may indicate damage or aging of the material (6). Therefore, artificial teeth should be resistant to staining and remain for a long time without discoloration, as well as have an esthetic appearance (22). It has been reported in the literature that commonly consumed acidic and colored beverages caused color changes in both the denture and acrylic resin teeth (4,6,22,23). Because, these beverages can disrupt artificial teeth, induce abrasion, irregularities, and discoloration, and eventually reducing the lifespan of the denture (6).

The CIELAB (ΔE^*_{ab}) and CIEDE2000 (ΔE_{00}) formulations are used to calculate color differences. The CIEDE2000 formula is more useful in the measurement of color differences in a clinical context, because it reflects the human perception of color differences better than the other formula (15). Tieh et al (14) also recommended using the ΔE_{00} formula instead of the traditional ΔE*ab for a more reliable interpretation of changes in clinical instrumental color analysis. The acceptability threshold (AT) and the perceptibility threshold (PT) are used in this formula (16). PT defines the lowest perceptible color difference that can be detected by an

observer, AT defines the acceptable color differences (15,17). Although, a comprehensive review stated that different AT and PT values exist in the literature (17), a study on tooth-colored restorative material was selected as a reference for the present study (16). The color differences in the Vivodent PE and Phonares II groups were above 50:50% PT, meaning they were just noticeable changes and still below acceptable color differences. Therefore, these color differences were not required to correct. On the other hand, the color difference in the Ivostar group was above 50:50% AT and would be better to improve.

GERD is a gastrointestinal system disease that is seen in many individuals in society, but its serious damage cannot be noticed. Studies indicated a correlation between GERD and dental erosion (9,25). It has been reported that the average rate of dental erosion in patients with GERD is 24%, and the rate of GERD in patients with dental erosion is 32.5% (26). In these patients, the low pH gastric fluid entering the oral environment affects not only natural teeth but also restorative materials (10,11,18,20,21). Cengiz et al (11) investigated the effects of gastric juice on indirect laboratory composite materials and concluded that gastric acid affected these materials causing clinically unacceptable discoloration. In another study, resin composite CAD/CAM (computer-aided design/computer-aided manufacturing) materials (Paradigm MZ100, Lava Ultimate) exhibited surface modifications after exposure to acid (20). Gastric acid exposure had varying degrees of influence on different properties of some CAD/CAM ceramic materials (19,21) and caused some surface changes even in zirconia (12).

In the present study, a significant difference was observed between the color stability of tested artificial teeth after gastric acid exposure. The differences in content of these materials may cause this result. The highest color change was observed in the Ivostar group (ΔE_{00}=2.14), which may be related to the conventional polymethylmethacrylate (PMMA) acrylic resin content. Because, PMMA-containing teeth have a significant conversion rate and low levels of dibenzoyl peroxide remaining after the conversion reaction, which can induce color instability (22). The material also has no cross-linked chains and is less resistant to plasticizer loss (3). Therefore, gastric acid may induce the PMMA plasticization period, which increases the discoloration effect. The Vivodent PE material contains highly cross-linked DCL (Double Cross-Linked) acrylic according to the manufacturer. This material is a modified version of PMMA, and both its matrix and polymer are cross-linked (27). Its statistically significant lower color change (ΔE_{00}=1.77) compared to the Ivostar group may be associated with this structural difference, as its highly cross-linked structure can be more resistant to acidic environments. The Phonares II group (ΔE_{00}=1.72) demonstrated the lowest color change. The material contains nano-hybrid composite and PMMA. It also includes a urethane dimethacrylate (UDMA) matrix and many different fillers (3). In a study of Yuzugullu et al (3), it was indicated that different cleansing solutions did not significantly affect the surface roughness or microhardness of the material, which proves the structural stability of the material.

The absence of clinical conditions such as saliva, dietary habits and cleansing procedures, and the use of a single brand material for each type of artificial teeth are some of the limitations of the present study. Further studies are necessary to compare more artificial tooth brands and analyze the other features such as surface gloss, roughness and microhardness.

5. CONCLUSION

Within the limitations of the current study;

1. After exposure to gastric acid, all groups exhibited perceptible color differences.
2. In the group of acrylic resin artificial teeth, the color difference was above acceptability threshold and would be better to improve.
3. While the acrylic resin artificial teeth exhibited the highest discoloration, artificial teeth containing nanohybrid composite resin showed the least discoloration.

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Clinical and Experimental Health Sciences

Localization of Mandibular Canal in Dentulous and Edentulous Regions

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ABSTRACT

Objective: Retrospective determination of the changes in the mandibular canal (MC) course in male and female in the second premolar, first molar and second molar regions of the dentulous and edentulous mandible.

Method: In CBCT images of 274 patients aged 18-88 years who were systemically healthy, the distances of the outer cortex of the MC to the mandible superior, lingual, inferior and buccal cortical bone border were measured in the right and left mandible 2nd premolar, 1st molar and 2nd molar regions. In these regions, the differences in MC course between left and right hemimandible, dentulous and edentulous, and males and females were examined by independent t-test and paired t-test ($p<.05$).

Results: As a result of the statistical analysis, statistical significance was observed in the linear measurements of the MC to the superior cortical bone border in dentulous and edentulous patients in the relevant regions. In female and male patients, the distance of the MC to the inferior cortical edge of the mandible in the dentulous and edentulous dentition was statistically lower in females. The superior distance of the mandible was found to be lower in the edentulous regions than in the dentulous regions.

Conclusion: The course of the MC in the posterior mandible is generally close to the inferior and lingual wall, but it changes direction towards the superior and buccal regions as it approaches the mental foramen. Furthermore, in women, the MC is located closer to the inferior border of the mandible compared to male.

Keywords: Cone-beam computed tomography; edentulous; mandibular canal; mandible

1. INTRODUCTION

The mandibular canal (MC) contains the inferior alveolar nerve, artery and vein vessel-nerve package. The MC starts from the lingual region of the ramus in the mandible and proceeds towards the mental foramen (MF) and performs the vital functions of the mandible. Complications may occur as a result of damage to the vessel and nerve package in the MC. Various complications may occur as a result of interventions performed in the posterior region of the mandible. MC surgery complications may occur at a rate of over 60% in dental implants and orthognathic surgeries (1). For this reason, it is of great importance to be able to accurately determine the course of MC.

Studies in the literature show that the course of MC in the bone changes in dentulous, edentulous, and partially dentate patients, different locations of the bone and osteotomies and the course of MC is affected by age and gender(1-3). Yet studies in the literature were conducted has lower number of subjets. It is important to learn how MC is affected by dentition and gender with a high number of subjects with higher accuracy, in order to prevent complications that may occur in surgical procedures.

Although computed tomography (CT) is the best technique for bone evaluation, the use of high-dose radiation and expensiveness makes this imaging method difficult to use in dental use. However, the use of cone beam computed tomography (CBCT), which is one of the advanced imaging techniques of the maxillofacial region, provides advantages due to its superior features such as the lack of magnification and superpositions compared to the panoramic imaging method, the use of low-dose radiation, and the lower price compared to CT and also it is sufficient for the necessary evaluation of the MC (3-5).

This study aimed to assess the changes in the trajectory of the MC by utilizing CBCT scans to measure the distance between the MC and the mandibular bone edges. The measurements were conducted in both dentulous and edentulous regions, specifically the 2nd premolar, 1st molar, 2nd molar regions, for both female and male. The null hypothesis tested is that the dentition and gender will not affect the trajectory of the MC.

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2. METHODS

This study was conducted retrospectively in full accordance with the applicable ethical principles, including the World Medical Association Declaration of Helsinki of 1964 and a later version. The Research Ethics Committee of the Recep Tayyip Erdogan University, Faculty of Medicine (date/number17/08/2021-2021/135) approved this study.

This study consisted of 548 hemimandible of 274 patients aged 18–88 years who had mandibular CBCT scans recorded in the archive of the Recep Tayyip Erdogan University, Dentomaxillofacial Radiology Department between 2017 and 2021. All CBCT images were acquired using a Planmeca ProMax 3D Classic (Planmeca Promax 3D; Planmeca Oy; Helsinki, Finland) with the following parameters: 90 kV, 4–10 mA, 200 µm voxel size. The acquisition process was performed according to the manufacturer's recommended protocol. The measurements were done with Planmeca Romexis 4.6.2.R software (PLANMECA Romexis, Helsinki, Finland). Each-intraexaminary patient gave informed consent to the use of examination in scientific research. The systemic anamnesis taken from the patients who applied to clinic before the x-ray is obtained during the examination is processed into the faculty system information. In this way, when retrospective scanning is required, the patient's information can be easily re-evaluated through the hospital system.

Patients under the age of 18, skeletal position anomalies and position disorders detected in the mandibular and maxilla, the presence of anatomical variations such as MC and accessory canal of the MF, any bone or soft tissue pathologies (cyst, tumour, etc.), periodontitis symptoms, previous osteotomies, fractures, unmeasurable image distortions or artefacts were excluded from the study. The third molar region was excluded from the study because it is the region that is not used for implant surgery (6). In addition, since the MF region is the region with the least change in the course of MC, the 1st premolar region was not included in the study and the cases where MF was seen in the 2nd premolar region were also not measured in the study(7).

Before the measurement, the three planes were oriented. Right and left mandible inferior margins are positioned parallel to each other and the occlusal plane. On the cross-sectional sections obtained, measurements were made in a total of 6 regions, from the regions of the 2nd premolar, 1st molar and 2nd molar teeth in each hemimandible.

For each region, the distance of the MC from the superior cortical border to the top of the crest (MC-SD), the distance of the MC from the inferior cortical border to the lower edge of the mandibular bone (MC-ID), the distance of the MC from the buccal cortical border to the buccal outer edge of the mandibular bone (MC-BD) and the distance of the MC from the lingual cortical border to the lingual outer edge of the mandibular bone (MC-LD), a total of 4 distance measurements were made. (Figure 1) Measurements were made by a dentomaxillofacial radiologist with more than ten years of experience. One month after the first measurements, the same measurements were repeated for the second time and the intraexeminary agreement coefficient (ICC) was calculated.

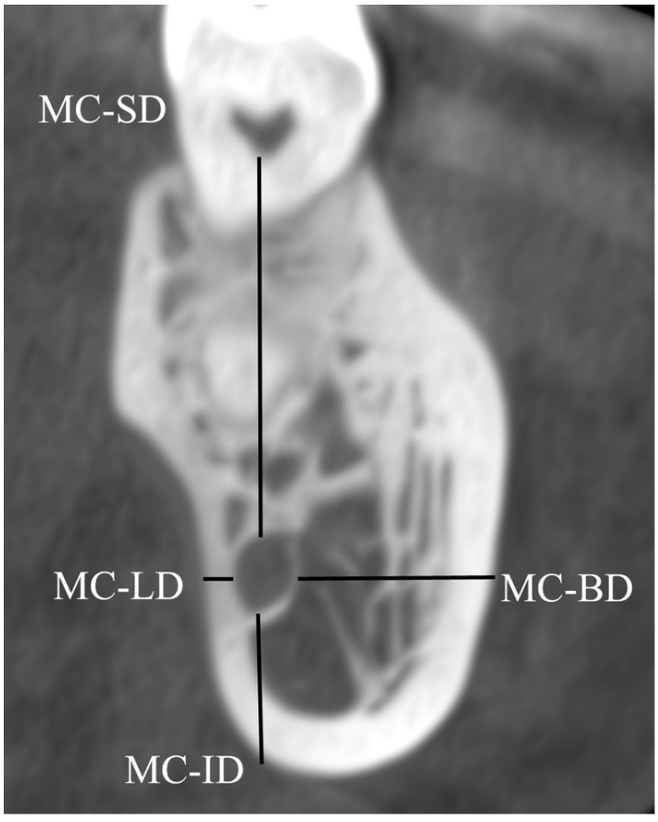

Figure 1. *Linear measurements of the Mandibular Canal to the superior (MC-SD), lingual (MC-LD), inferior (MC-ID), and buccal (MC-BD) cortical edges of the mandible on CBCT cross-section images (0.2 mm slice thickness)*

If there is no tooth in the relevant regions and adjacent regions, the tooth location that should be in occlusion concerning the opposing tooth in the upper jaw was determined and the measurement was made in that region. If there is no tooth in the opposing jaw, the region is determined according to the distance of the missing tooth from the adjacent tooth according to the average tooth crown diameter and measurements are carried out in the relevant region. Thus, the 2nd premolars mean value of the mesiodistal crown width was 7.1 mm, the 1st molars were 11.4 mm, and the 2nd molars were 10.8 mm. Additionally, we considered the mean widths of the identical mesiodistal crowns, which were 7.35 mm for the second premolar, 12.5 for the first molar, and 11.3 mm for the second molar(6).

Obtained measurements, descriptive analyses, paired t-tests and independent t-tests ($p<0.05$) were analysed using IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA). The power of the sample size was calculated using the G-Power 3.1 software (Heinrich-Heine University of Dusseldorf, Germany).

To establish the minimal sample size necessary to test the study hypothesis, a power analysis was carried out using

G Power version 3.1. For independent and paired t-tests, a significance level of .05 and a sample size of 80% moderate effect were calculated (8). The resulting sample size of N = 274 is sufficient to test the study's main claim.

3. RESULTS

ICC values lower than 0.5 are low reliability, values between 0.5 and 0.75 are moderate reliability, values between 0.75 and 0.9 are good reliability and values higher than 0.9 are excellent reliability. Our ICC has been calculated as 0.91, which is excellent reliability(9).

A total of 274 patients were analysed and of the patients, 140 (51.1%) were female and 134 (48.9%) were male. The mean age of females was 46.94±13.52, and the mean age of males was 48.32±14.89.

The relationship between MC-SD, MC-LD, MC-BD and MC-ID according to dentition and gender is calculated by independent t-test and given in table 1. When the results were examined, it was determined that MC-ID was significantly lower in females than males in all dentulous and edentulous regions.

The relationship between MC-SD, MC-LD, MC-BD and MC-ID according to dentition is calculated by independent t-test and given in table 2. The only value that showed a significant difference in each region was found as MC-SD. In the left mandible 2nd premolar, 1st molar and 2nd molar regions, MC-SD dentulous and edentulous region significance levels were found as $p < .01$, In the right mandible 2nd premolar, 1st molar and 2nd molar regions, MC-SD dentulous and edentulous region significance levels were found as $p < .001$.

The measurement results of the 2nd premolar, 1st molar and 2nd molar regions are given in Tables 3 and 4 in dentulous and edentulous patients, regardless of gender. According to the results obtained, it was determined that the mean values of MC-LD and MC-ID measurements increased from the 2nd molar region to the 2nd premolar region, from the posterior to the anterior, while the average of MC-BD values decreased.

Table 1. *Significance levels of the linear measurements of the mandibular canal to the mandible superior, lingual, inferior, and buccal cortical borders in the mandible 2nd premolar, 1st molar and 2nd molar regions, according to gender by independent t-test*

Tooth	Dentition	Gender	n	MC-SD		MC-LD		MC-ID		MC-BD	
				Mean/SD	p	Mean/SD	p	Mean/SD	p	Mean/SD	p
Mandibular Left 2nd premolar	Dentulous	Female	57	16.00/2.55	p=.03*	7.46/1.59	p=.46	3.59/1.08	p=.00*	3.24/1.35	p=.42
		Male	67	16.97/2.44		8.55/1.64		3.41/1.69		3.05/1.13	
	Edentulous	Female	29	11.56/3.92	p=.13	7.55/1.55	p=.43	3.60/1.16	p=.00*	2.96/0.94	p=.91
		Male	24	11.56/3.92		9.10/1.34		3.88/1.36		2.93/1.11	
Mandibular Right 2nd premolar	Dentulous	Female	59	16.13/2.41	p=.45	7.46/1.64	p=.14	3.63/1.23	p=.03*	3.33/1.19	p=.18
		Male	60	16.48/2.68		8.46/1.95		3.23/1.61		2.77/1.07	
	Edentulous	Female	35	11.05/4.33	p=.21	7.53/1.43	p=.98	3.42\1.21	p=.00*	2.76/1.09	p=.49
		Male	28	13.71/4.55		9.06/1.18		3.42/0.96		2.95/1.05	
Mandibular Left 1st Molar	Dentulous	Female	34	16.47/2.25	p=.08	5.84/1.35	p=.78	2.33\0.98	p=.00*	4.33/1.38	p=.56
		Male	43	17.44/2.47		7.94/1.78		2.39/1.07		4.16/1.26	
	Edentulous	Female	106	12.43/3.66	p=.01*	7.06/1.56	p=.91	2.80\1.11	0.00*	3.91/1.06	p=.21
		Male	91	13.63/3.25		7.99/1.73		2.78/1.18		4.13/1.40	
Mandibular Right 1st Molar	Dentulous	Female	32	16.56/1.91	p=.03*	6.23/1.49	p=.94	2.59/1.07	p=.00*	3.98/1.24	p=.71
		Male	41	17.61/2.19		8.22/1.78		2.57/1.50		4.10/1.39	
	Edentulous	Female	107	12.23/3.99	p=.00*	6.80/1.43	0.36	2.64/1.03	p=.00*	4.06/1.12	p=.87
		Male	89	13.85/3.56		7.82/1.57		2.50/1.12		4.03/1.27	
Mandibular Left 2nd Molar	Dentulous	Female	53	14.70/2.28	p=.02*	6.45/1.60	p=.03*	2.21/1.00	p=.03*	5.00/1.52	p=.23
		Male	68	15.74/2.57		7.09/1.68		1.82/0.97		5.32/1.52	
	Edentulous	Female	87	11.15/3.78	p=.06	6.43/1.48	p=.38	2.41\0.93	p=.00*	4.93/1.26	p=.74
		Male	66	12.29/3.72		7.42/1.90		2.27/1.04		5.00/1.37	
Mandibular Right 2nd Molar	Dentulous	Female	60	14.62/2.71	p=.00*	6.41/1.39	p=.03	2.04/0.87	p=.05*	5.29/1.18	p=.51
		Male	71	16.21/2.90		6.99/1.99		1.72/0.82		5.43/1.23	
	Edentulous	Female	79	10.46/3.88	p=.04*	6.52/1.40	p=.00*	2.45/0.98	p=.00*	5.03/0.89	p=.71
		Male	59	11.88/4.23		7.53/1.45		1.99/0.92		4.96/1.14	

** Significant results according to independent t-test (p<.05).SD: Standard Deviation, MC-SD: The distance of the Mandibular Canal (MC) from the superior cortical border to the top of the crest, MC-ID: The distance of the MC from the inferior cortical border to the lower edge of the mandibular bone, MC-BD: The distance of the MC from the buccal cortical border to the buccal outer edge of the mandibular bone, MC-LD: The distance of the MC from the lingual cortical border to the lingual outer edge of the mandibular bone.*

Table 2. *Significance levels of linear measurements of the mandibular canal to the mandible superior, lingual, inferior, and buccal cortical borders in the mandible 2nd premolar, 1st molar and 2nd molar regions, according to the dentition status by independent t-test*

Tooth	Dentition	n	MC-SD		MC-LD		MC-ID		MC-BD	
			Mean/SD	p	Mean/SD	p	Mean/SD	p	Mean/SD	p
Mandibular Left 2nd premolar	Dentulous	124	16.52/2.52	p=.00*	3.49/1.44	p=.30	8.05/1.70	p=.46	3.14/1.24	p=.33
	Edentulous	53	12.29/3.92		3.73/1.25		8.25/1.64		2.95/1.01	
Mandibular Right 2nd premolar	Dentulous	119	16.30/4.59	p=.00*	3.43/1.44	p=.96	7.97/1.88	p=.38	3.06/1.16	p=.22
	Edentulous	63	12.23/4.59		3.42/1.09		8.21/1.52		2.84/1.06	
Mandibular Left 1st Molar	Dentulous	77	17.01/2.41	p=.00*	2.36/1.03	p=.00*	7.01/1.91	p=.04*	4.23/1.31	p=.18
	Edentulous	197	12.99/3.52		2.79/1.14		7.49/1.70		4.01/1.31	
Mandibular Right 1st Molar	Dentulous	79	17.15/2.12	p=.00*	2.58/1.32	p=.99	7.35/192	p=.71	4.05/1.32	p=.98
	Edentulous	196	12.97/3.88		2.58/1.07		7.26/1.58		4.05/1.19	
Mandibular Left 2nd Molar	Dentulous	121	15.28/2.50	p=.00*	1.99/1.00	p=.00*	6.81/1.67	p=.81	5.18/1.43	p=.19
	Edentulous	153	11.64/3.78		2.35/0.98		6.86/1.74		4.96/1.31	
Mandibular Right 2nd Molar	Dentulous	131	15.48/2.92	p=.00*	1.87/0.85	p=.00*	6.73/1.76	p=.26	5.36/1.21	p=.00*
	Edentulous	138	11.07/4.08		2.25/0.98		6.95/1.50		5.00/1.00	

**Significant results according to independent t-test (p<.05)SD: Standard Deviation, MC-SD: The distance of the Mandibular Canal (MC) from the superior cortical border to the top of the crest, MC-ID: The distance of the MC from the inferior cortical border to the lower edge of the mandibular bone, MC-BD: The distance of the MC from the buccal cortical border to the buccal outer edge of the mandibular bone, MC-LD: The distance of the MC from the lingual cortical border to the lingual outer edge of the mandibular bone.*

Table 3. *Right and left hemimandible significance levels of linear measurements of the mandibular canal to the superior, lingual, inferior, and buccal cortical borders of the mandible in the mandible 2nd premolar, 1st molar and 2nd molar regions in dentulous patients by paired t-test*

Tooth	n	MC-SD		MC-LD		MC-ID		MC-BD	
		Mean/SD	p	Mean/SD	p	Mean/SD	p	Mean/SD	p
Mandibular Left 2nd premolar	37	16.71/2.15	p=.50	3.57/1.77	p=.78	7.99/1.50	p=.37**	2.90/1.10	p=.05*
Mandibular Right 2nd premolar	37	16.47/2.46		3.66/1.77		8.23/2.09		2.47/0.78	
Mandibular Left 1st Molar	45	16.97/2.37	p=.40	2.25/1.01	p=.04**	6.92/2.03	p=.01**	4.19/1.27	p=.12
Mandibular Right 1st Molar	45	17.21/1.95		2.48/1.43		7.26/2.06		3.92/1.28	
Mandibular Left 2nd Molar	45	15.79/2.26	p=.33	1.68/0.73	p=.61	6.44/1.91	p=.70	5.56/1.54	p=.64
Mandibular Right 2nd Molar	45	16.06/2.76		1.72/0.66		6.36/2.09		5.46/1.19	

** Significant results according to paired t-test (p<.05).SD: Standard Deviation, MC-SD: The distance of the Mandibular Canal (MC) from the superior cortical border to the top of the crest, MC-ID: The distance of the MC from the inferior cortical border to the lower edge of the mandibular bone, MC-BD: The distance of the MC from the buccal cortical border to the buccal outer edge of the mandibular bone, MC-LD: The distance of the MC from the lingual cortical border to the lingual outer edge of the mandibular bone.*

Table 4. *Right and left meaning levels of linear measurements of the mandibular canal to the superior, lingual, inferior, and buccal cortical borders of the mandible in the mandible 2nd premolar, 1st molar and 2nd molar regions in edentulous patients by paired t-test*

Tooth	n	MC-SD		MC-LD		MC-ID		MC-BD	
		Mean/SD	p	Mean/SD	p	Mean/SD	p	Mean/SD	p
Mandibular Left 2nd premolar	30	11.71/4.11	p=.16	3.26/1.15	p=.45	7.78/1.57	p=.39	2.87/1.17	p=.01*
Mandibular Right 2nd premolar	30	11.06/4.32		3.38/1.17		8.00/1.79		2.47/1.07	
Mandibular Left 1st Molar	64	10.96/3.71	p=.01**	2.91/1.24	p=.00**	7.22/1.94	p=.48	3.77/1.33	p=.49
Mandibular Right 1st Molar	64	10.23/4.09		2.57/0.94		7.10/1.43		3.88/1.10	
Mandibular Left 2nd Molar	64	10.21/3.77	p=.06	2.41/1.01	p=.12	6.76/1.59	p=.90	4.56/1.17	p=.04**
Mandibular Right 2nd Molar	64	9.60/4.07		2.18/0.94		6.79/1.44		4.86/0.95	

** Significant results according to paired t-test (p<.05).SD: Standard Deviation, MC-SD: The distance of the Mandibular Canal (MC) from the superior cortical border to the top of the crest, MC-ID: The distance of the MC from the inferior cortical border to the lower edge of the mandibular bone, MC-BD: The distance of the MC from the buccal cortical border to the buccal outer edge of the mandibular bone, MC-LD: The distance of the MC from the lingual cortical border to the lingual outer edge of the mandibular bone.*

The difference between the right and left hemimandible was examined with the paired t-test. A statistically significant difference was found in the MC-LD in the 1st molar region, MC-ID in the 2nd premolar region, MC-ID in the 1st molar region, and MC-BD in the 2nd premolar region between the right and left hemimandible in dentulous patients. ($p<.05$, $p> .05$, $p< .05$, $p\leq .05$, respectively). In edentulous patients, a statistically significant difference was found in MC-SD and MC-LD in the 1st molar region and MC-BD in the 2nd premolar and 2nd molar regions. ($p< .05$) (Tables 3 and 4)

4. DISCUSSION

In this study, the distances between the MC and the mandibular cortical bone borders were measured in four directions: right and left premolar, molar, and edentulous regions. The findings revealed a significant decrease in the superior bone distance, particularly in edentulous regions compared to dentulous regions. Moreover, MC-ID was found to be lower in female than in male within the relevant regions. These findings suggest that both dentition and gender significantly influence the trajectory of the MC, leading to the rejection of the study's null hypothesis.

Due to magnification and distortions, accurate MC detection cannot be achieved using 2D techniques. CBCT is the most commonly used advanced imaging method in dentistry, providing sufficient information for MC detection (1, 10). Therefore, CBCT is considered an appropriate imaging modality for the detection of MC.

In contrast to study of Kalabalık and Aytugar (11), which included only dentulous patients and found no difference between measurements taken in the right and left jaws, this study revealed a statistically significant difference between the right and left hemimandibles in specific regions and measurements. In dentulous regions, significant differences were observed in the MC-LD measurement of the 1st molar region, MC-ID measurement of the 2nd premolar and 1st molar regions, and MC-BD measurement of the 2nd premolar region. In edentulous regions, significant differences were found in the MC-SD and MC-BD measurements of the 1st molar region, as well as the MC-BD measurements of the 2nd premolar and 2nd molar regions. These differences may be attributed to variations in the duration of edentulousness between the right and left sides of the same regions. This discrepancy in measurements between the right and left hemimandibles, which was observed in our study, can be considered as one of the limitations. The differing durations of edentulousness in the corresponding regions of the right and left sides may have contributed to the significant differences observed in certain measurements.

In the literature, it is commonly described that the MC is situated on the lingual and inferior sides in the posterior region of the mandible. However, as it approaches the MF, the course of the MC tends to shift towards the buccal cortical border and superior border of the mandible (1-3, 5, 10). Contrary to these findings, Kalabalık and Aytugar (11) observed that the course of the MC in the MF region was closer to the inferior and lingual borders. Nimigean et al. (6) reported a decrease in MC-BD from the second molar region to the second premolar region, while the MC-LD decreased from the second premolar region to the second molar region. Sekerci and Sahman (5) determined that the MC-BD was highest in the second molar region. In our study, we found that the MC-BD and MC-SD distances in the second premolar, first molar, and second molar regions decreased from the second molar region to the second premolar region, while the MC-LD and MC-ID increased in both the dentulous and edentulous regions (Tables 3 and 4).

In a study conducted by Kim et al. (12), they classified the course of the MC based on its localization within the mandibular bone. According to their classification, they identified three types: type 1 MC (70%) had a course close to the lingual side, type 2 MC (15%) followed a path in the middle of the bone, specifically in the ramus and distomolar region, and approached the lingual side in the first and second molar regions, and type 3 MC (15%) had a course in the middle or close to 1/3 part of the lingual cortex. Our study corroborated these findings as we also observed that the MC tended to have a close course to the lingual cortex, aligning with the previous study.

In this study, it was observed that the MC-ID measurement in the molar region is lower than in the premolar region, both in dentulous and edentulous regions. As the MC moves towards the MF, it changes its course towards the buccal and superior aspects before exiting the MF. Additionally, as the MC progresses towards the MF, it reaches its most inferior point within the bone. This particular region corresponds to the area with the highest thickness of the mandibular corpus (3, 13). Subsequently, the MC extends from the molar region to the premolar region while shifting superiorly.

According to the findings of Ylikontiola et al. (14), their study demonstrated that if the buccal bone thickness of the MC is less than 2 mm, therfore is a significant increase in the risk of damage to the inferior alveolar vascular-nerve bundle. Consequently, based on the results of this study, the second premolar tooth region, which has the lowest MC-BD, exhibits the lowest buccal bone thickness and poses the highest surgical risk within the region.

In similar studies in the literature, it has been concluded that the height of the superior alveolar bone significantly decreases in edentulous patients (15, 16). Consistent with these findings, our study also observed a reduction in the amount of superior bone in edentulous patients. This decrease in superior bone height is attributed to the atrophy of the edentulous jaws**.** It is crucial to consider this factor, particularly in surgical procedures especially implant surgeries involving edentulous areas.

Nimigean et al. (6) reported that there was no significant atrophy in the horizontal length measurements of the MC in edentulous mandibles compared to dentulous mandibles. Similarly, Asari and Lagravere (4) concluded that the

differences in horizontal measurements (buccal and lingual bone changes) between dentulous and edentulous patients were less pronounced compared to vertical measurements. They suggested that vertical distance measurements were more affected by atrophy than horizontal measurements. Also, in the classification by Cawood and Howell (17), it was emphasized that vertical resorption is more severe in the mandibular posterior region with edentulism.

According to the statistical findings of this study, a significant and consistent difference in the course of the MC was observed only in the MC-SD measurements, both in dentulous and edentulous regions, when considering both horizontal and vertical directions. This result can be attributed to the high resorption pattern that occurs in the edentulous ridge, leading to changes in the superior-inferior dimension of the MC.

According to the findings of Kilic et al. (16) in their cadaver studies, the course of the MC varied depending on the dentition status and the region of the mandible. In the distal region of the mandibular 2nd molar, the MC was close to the lingual bone cortex in dentulous, edentulous, and partially dentulous groups. In the 1st molar region, edentulous patients showed a middle position of the MC in the horizontal direction within the bone, while dentulous and partially dentulous patients had the MC close to the lingual bone border. In the MF region, the MC was close to the buccal bone border in edentulous patients, while it was close to the lingual cortical border in dentulous and partially dentulous patients. Moreover, edentulous patients exhibited a superior extension of the MC in the posterior region compared to dentulous and partially dentulous patients. However, in the present study, the MC was found to be close to the lingual cortex in the second molar region in both dentulous and edentulous groups. In the first molar region and the second premolar region, the MC extended towards the MF with a course close to the buccal cortex in all groups, which contradicted the previous study. The differences in the duration of edentulism and the sample sizes may explain these discrepancies.

The literature presents varying results regarding the relationship between gender and the course of the MC. Some studies suggest that there is a difference between males and females in terms of bone measurements around the MC, with higher values found in males (1, 5). However, other studies indicate no significant gender-related differences in the course of the MC (10, 11, 15, 16). For example, Khorshidi et al. (1) found that the horizontal and vertical bone measurements around the MC were lower in women compared to men. Sekerci and Sahman (5) reported that except for the third molar region, there were no gender-based differences in the vertical bone measurements around the MC in the superior and inferior directions. Bhardwaj et al. (18) also noted that the distance between the MC and the inferior cortex was greater in males. Similarly, in our study, only MC-ID showed a statistically significant difference, with higher values observed in males in all regions. It is worth mentioning that differences between genders in the dimensions of the mandible have been identified in previous studies, with male generally exhibiting larger bone measurements than female (19, 20). In our study, significant differences between males and females were observed in MC-SD measurements in several regions, including the left dentulous 2nd premolar, edentulous left 1st molar, dentulous and edentulous right 1st molar, dentulous left 2nd molar, and right dentulous and edentulous 2nd molar regions. In MC-LD, significant differences were found between males and females in the dentulous left 2nd molar and dentulous and edentulous right 2nd molar regions.

The limitation of this study is the unknown duration of edentulism in edentulous areas. For this reason, the change in the course of MC and the difference between the genders and sides of this change could not be evaluated.

5. CONCLUSIONS

In dentulous and edentulous patients' posterior of the mandible, the MC course is close to the lingual and the inferior cortex, while it approaches the buccal cortex towards the MF and displaces superiorly. Alveolar crest resorption occurring in edentulous areas is greater in the superior direction. Also, MC being closer to the base of the mandible in female is a difference that should be considered in preoperative surgical evaluations.

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Design of the study: MEN, TEK, DNG, ZY
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Clinical and Experimental Health Sciences

Evaluation of Stress Distributions in All Ceramic Conometric Single Crown Restorations: 3-Dimensional Finite Element Analysis

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ABSTRACT

Objective: The aim of the study is to compare the effect of monolithic translucent zirconia ceramic (TZI) and monolithic lithium disilicate glass ceramic (LDS) restorative materials on stress distributions in implant components and surrounding bone tissues in implant-supported conometric single crown restorations with a conical connection system by using 3D finite element analysis.

Methods: Restorations produced with two different all-ceramic materials using a conometric abutment and a conometric cap on the implant with a conical connection system were placed in the maxillary right second premolar region. 3D finite element analysis was used to examine the amount and distribution of stresses in implant components, in cortical and cancellous bone tissues surrounding the implant and in crowns under vertical and oblique loading. For the statistical analysis one-way ANOVA and independent samples t-test were used ($p<.05$).

Results: In oblique 100N simulation, maximum stress distribution in implant and its components occurred at the implant abutment contact as 475.63 MPa for the LDS. The screw's peak stress values were determined to be 239.09 MPa in the transition zone and 280.061 MPa in the thread. On the bone surface, maximum and minimum cortical principal stress values were 61.25 MPa and – 62.028 MPa. During oblique loading, LDS exhibited the greatest surface stress on the cap as 441.33 MPa. Generally, tapping phase showed the lowest stress ($p<.05$). There was no significant difference regarding the materials ($p> .05$).

Conclusion: von Misess and principal stresses are not very high in any location therefore conical connections are more promising in terms of future success.

Keywords: Conometric abutment, finite element analysis, stress, conical connection

1. INTRODUCTION

One of the most essential laws in dentistry is preserving the structural integrity of the tooth and restoring function without harming the surrounding tissues. Implant-retained fixed prostheses, conventional fixed prostheses and adhesive bridges are among the prosthodontic treatment options for missing single tooth (1,2). Due to the good survival rates, in cases when systemic and surgical implant applications are not contraindicated, the implant option has become a standard treatment for complete and partial edentulism. The success of implant therapies is dependent not only on osseointegration but also on the use of prosthetic superstructures (3). In implant therapies, complications can be classified as surgical complications and prosthetic issues. Implant treatments have a 90% brand-independent surgical survival rate, but mechanical and biological difficulties originating from prosthetic applications account for the bulk of failures. These problems include screw loosening, abutment fracture, screw fracture and cement-induced periimplantitis (4). Success in the prosthetic phase is dependent on the selected form of connection and retention, the emergence profile of the restoration and the subgingival and supragingival restoration materials (5). The connection between the implant and abutment is one of the key variables influencing the implant's biomechanical success over the long term. The implant-abutment interface is one of the biomechanical components that affect the strength, stability and lateral/rotational load resistance of the connection (6).

The connection at the implant-abutment fixture can be broadly categorized as either external or internal. Future bone resorption is more likely to occur as a result of microleakage and bacterial colonization due to micro gaps detected in Branemark's original external connection (7). The abutment is attached to the inner surface of the implant in the internal

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connection and is developed to eliminate the disadvantages of the external connection. With this sort of connection, the goal is to minimize the formation of micro-gaps, lower the stresses communicated to the implant and surrounding tissues after lateral loading and shield the abutment screw from excessive occlusal loads. The frictional force at the interface between the abutment wall and implant plays a role in the conical connection, which is a specific sort of internal connection (8). Due to this adaptation at the implant-abutment interface, occlusal loads and stresses can be adjusted and transmitted to the implant and surrounding tissues, resulting in a stronger connection between the two components (9).

When cement fixation is preferred for retention in implant-fixed prosthetic rehabilitation, the likelihood of uncontrolled cement escape to peri-implant tissues and subsequent peri-implantitis is relatively significant if the abutment margin/ margins are prepared subgingivally. Also, the screw hole causes aesthetic issues in screw-retained restorations (10). Conometric abutments are a sort of cone-in-cone connection brought to the market in order to remove the problems of screw and cement retention. In this kind of retention, the restoration is cemented to the conometric cap that will be put on the crown outside the mouth and it is frictionally connected to the abutment by applying a slight push (11).

Another important issue in the success of implant treatments is the forces acting on the restoration surface and the material preferred in the prosthetic supra-structure. In the present study, the second premolar tooth area was preferred due to the greater effectiveness of chewing forces. Monolitic lithium disilicate glass ceramic (LDS, IPS emax CAD, Ivoclar Vivadent, Liechtenstein) and monolithic translucent zirconia ceramic (TZI, InCoris TZI, Dentsply Sirona, USA) materials were preferred due to their superior mechanical and aesthetic properties and widespread use in the studies. Unlike the recent similar study (20), it aims to affect the effect of the gingival level height of the abutment used on stress distribution.

The purpose of this study, which is unique as a retention type that does not involve cement or screws, was to compare the effect of monolithic TZI and LDS materials on stress distributions in the implant components and surrounding bone tissues in implant-retained conometric single crown restorations with a tapered connection system under functional loads using three-dimensional finite element analysis.

The first hypothesis of the present study is that there will be no difference in the stresses caused by the functional loads on the implant, abutment, abutment screw and the cortical and cancellous bone around the implant. The second hypothesis of the study is that the stresses induced by different restorative materials on the surface of the conometric cap will not differ.

2. METHODS

In the present study, bone level implant (AstraTech, OsseoSpeed EV, Dentsply Implants Manufacturing GmbH, Sweden) with 4.2 diameter 11mm length and 3mm gingival height was positioned on the right maxillary second premolar (15), along with a 5 mm diameter conometric abutment (Conometric Abutment EV, Dentsply Implants Manufacturing GmbH, Sweden) and conometric cap (Conometeric Final Cap, Dentsply Implants Manufacturing GmbH, Sweden).

For the modeling and analysis of the structures, a computer with an Intel i7-6850K 3.60 GHz processor, 2.5 Tb Harddisk, 64 Gb RAM, the Windows 10 Pro operating system, the three-dimensional modeling software MeshLab (Visual Computing Lab, Pisa, Italy) and the analysis software ANSYS 19 R2 (Southpointe 2600 Ansys Drive, Canonsburg, USA) were used.

2.1. Geometrical and Mathematical Modelling

Class III crest morphology and type3a bone density were employed to model the bone structure using geometric modelling (12,13).

A Nikon XT H 225 (Nikon Industrial Metrology, Japan) three-dimensional tomographic scanner was used to produce 3D images of the implant and its components. The dental anatomy book (14) was consulted for the images of the related teeth to be used in the study, and the crown model was kept constant for all situations. Using tetrahedral elements with 10 nodes, the mathematical models were constructed.

2.2. Boundary Conditions

The produced models were immobilized in the upper cross-sectional region of the bone. It was considered that the connection between the implant and bone was 100 percent osseointegrated.

2.3. Material Properties

It was determined that the cement thickness between the abutment and the cap was 30μm (15).

In the table below, Young's modulus and Poisson's ratios of the virtually visible structures are displayed (Table 1) (15,16,17).

Table 1. *Young's Modulus and Poisson's Ratios of the materials used in the study.*

Material	Young's Modulus (GPa)	Poisson Rate
Cortical Bone	13,7	0,30
Cancellous Bone	1,37	0,30
Titanyum Implant and Conometric Cap (Grade 4 Titanyum)	104,5	0,37
Conometric Abutment ve Abutment Screw (Grade 5 Titanyum)	114	0,33
Translusent monolitic zirkonya	210	0,26
Monolitic lithium disilicate glass ceramic	95	0,2
Resin cement	18,6	0,28

2.4. Loading Conditions

In the present investigation, a three-stage analysis of the conometric concept was conducted, which included preload, tapping, vertical (200 N) and oblique (100 N) masticatory force. The preload force, which is employed to hold the implant and its components together, was calculated using the formula of Bulaqi et al (18,19). For the computation of the tapping force, the silicone replica method was utilized to compute the amount of movement on the cap surface during the tapping action and the "Remote Displacement" function of the Ansys program was used to define a movement of 0.25 mm (20).

2.5. Assessment of Stresses

The interface surface of the abutment in contact with the implant, the screw transition zone, the screw groove zone, the surface of the implant in contact with the cortical bone, the surface of the implant in contact with the spongious bone and the surface of the cortical and cancellous bone in contact with the implant were identified as the critical areas for stress evaluation on the created virtual model (Figure 1).

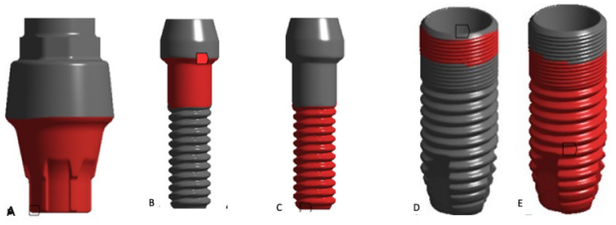

Figure 1. *Critical locations for stress assessment A: The interface of the abutment in contact with the implant B: the screw passage area C: the screw thread area D: the surface of the implant in contact with the cortical bone E: the surface of the implant in contact with the cancellous bone*

In the stress evaluation phase, von mises stress values for resorbable structures like titanium and maximum main stress values for brittle structures (crown, cortical and spongious bone) were evaluated (16). The mean and maximum stresses at critical areas were compared. LDS and TZI were statistically compared using the independent sample t-test and the stages were compared using the one-way ANOVA test (preload, tapping, vertical and oblique). The alpha value of statistical testing was .05. The stress levels in the implant, implant components and bone surface were interpreted based on their yield strengths, whereas the stress levels in the crown material were interpreted based on their biaxial bending strengths.

3. RESULTS

von Mises stress values in critical areas were shown in Table 2. Critical areas where the highest values are observed were the interface of the abutment in contact with the implant, the screw thread area and the surface of the implant in contact with the cancellous bone (Figures 2A-2C).

In the LDS material, the oblique 100N force stage frequently exhibited the greatest stress values at all critical surfaces identified by the present stress study. To study the stress distributions in the screw region, it was separated into two sections: the screw passage and the screw thread. The thread region of the screw had the highest stress in the LDS material, as preload: 286.31 MPa, tapping: 285.22 MPa vertical: 275,38 and obligue: 280,61 (Figure 2B).

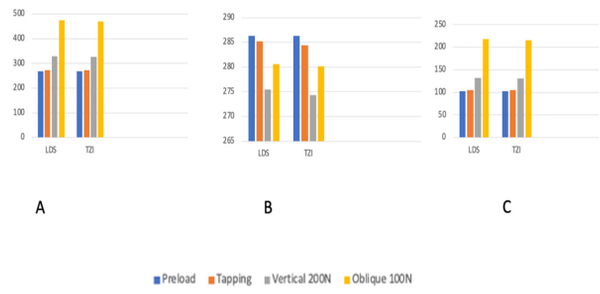

Figure 2. *Critical locations with the highest Von mises stresses A: The surface of the abutment in contact with the implant, B: the screw thread area C: the surface of the implant in contact with the cancellous bone*

Table 2. *von Mises stress values at critical areas.*

Location	Preload	LDS			TZI		
		Tapping	Vertical 200N	Oblique 100N	Tapping	Vertical 200N	Oblique 100N
Interface of the abutment in contact with the implant	267,29	273,38	328,78	475,63	272,09	327,07	470,27
Screw passage area	220,75	219,77	210,94	239,09	219,15	210,11	238,08
Screw thread area	286,31	285,21	275,38	280,61	284,39	274,28	280,13
Surface of the implant in contact with the cortical bone	73,574	74-523	83,906	199,12	74,221	83,482	195,82
Surface of the implant in contact with the cancellous bone	102,69	105,62	132,08	218,85	105,08	131,34	215,91

In the simulations of vertical 200N and oblique 100N chewing forces, the maximum stress distribution at the interface of the abutment in contact with the implant occurred at the oblique 100N stage with 475,63 MPa (Figure 2A). The highest stress value of the surface of the implant in contact with the cancellous bone was 218, 85 MPa in the LDS material oblique simulation. In the chewing force simulation, the LDS material induced more stress concentration, similar to the preload and tapping stages. The stresses at the implant abutment interface and the implant surfaces in contact with the cancellous bone increased as simulations progressed from preload to masticatory forces, whereas stresses in the screw groove area decreased (Figures 2A-2C).

When the principal stresses on the bone surface were examined (Figure 3), higher stress distribution occurred in the cortical bone. Under an oblique force of 100N, the cortical bone surface experienced a maximum principal stress of 61.65 MPa and a minimum stress of – 61,02 MPa. Stress values of 61,65 MPa and minimum stress principal: – 61,02 MPa were observed in LDS material (Figure 3).

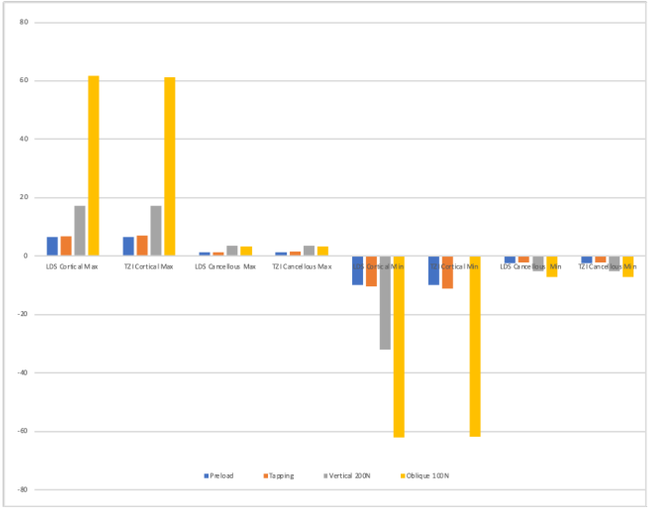

Figure 3. *Maximum and minimum principal stress values on cortical and cancellous bone surface*

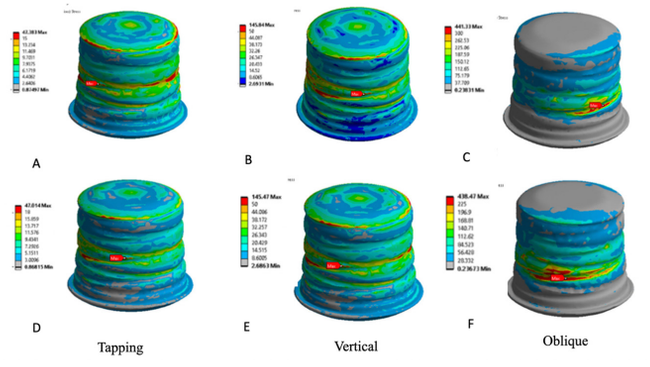

Figure 4. *Von Mises stress values on the cap surface A, B, C: Tapping, vertical, oblique force steps for the LDS crown. D, E, F: Tapping, vertical, oblique force steps order for the TZI crown.*

During oblique loading of the conometric cap surface, the LDS material was stressed by 441.33 MPa (Figure 4). There is no statistically significant difference between the average Von Mises stress values on the cap surface in terms of material ($p > .05$).

Tapping simulation stage presented the lowest stress value at critical areas while vertical loading stage presented the lowest stress value at conometric cap surface ($p < .05$).

4. DISCUSSION

Implant treatments are dependent on the stress delivered to the bone tissue surrounding the implant. The distribution of stress depends on the diameter of the implant, the type of connection and retention used and the bone quality. Finite element analysis enable to analyze stress values. To evaluate the stress values, the design of mathematical models should be performed with care and should reflect reality, necessities such as boundary conditions, material properties and loading conditions should be defined (22). Although cortical and cancellous bone has an anisotropic, viscoelastic, and inhomogeneous structure, finite element analysis studies record it as homogeneous and isotropic (23,24). Contrary to reality, cortical and cancellous bone was represented as homogenous, linear elastic and isotropic in the present study, similar to the other studies (15,20). Although 100% osseointegration at the bone implant interface is not observed clinically, finite element stress analysis accepts that the bone implant contact is 100% osseointegrated. Similar to the literature (24,25), 100% osseointegration was assumed and analyzed at the bone implant interface in the present investigation.

A large number of elements and nodes should be employed to improve the accuracy and reliability of the finite element approach (23,26,27). In a study conducted by Kaleli et al., 52451 nodes and 207931 elements were utilized, while in a study conducted by Kitagawa et al., 255106 nodes and 161485 elements were utilized. For the analysis of the present study, there are 721234 elements and 1077879 nodes, since it contains more elements and nodes than many previous studies (28,25,29,15,30). Thereby, higher quality mesh structure has been developed in an effort to improve the precision of the results.

Linkevicius et al., reported that the choice of cement retention resulted in cement-related problems in the peri – implant tissues (31). Wittneben et al., stated that the screw hole in screw-retained prostheses creates aesthetic and occlusion problems (42). The absence of cement and screw connection in the conometric retention type emphasizes the clinical importance of the retention type (32).

Numerous studies have been conducted on the determination of preload force. In a number of experiments, Kaleli et al., (15) ignored the preload value, while Jörn et al., (43) reported that the preload force should be 65-75% of the screw yield strength, and Bulaqi et al., (18) used a special formula to calculate the preload value. In the present study, the preload

was computed to be 473. 94 N using a formula (18). This preload value was applied to the screw of abutment using the '' Bolt Pretension'' function of the Ansys program (35) and the stress values for all components were collected at this point.

As prosthetic possibilities for conometric restorations, monolithic zirconia, monolithic lithium disilicate and fluorapatite-containing lithium disilicate have been described in the literature (32, 36, 37). While Degidi et al., (11) reported that no complications were observed in the 2-year follow-up of conometric restorations produced with LDS material, another study stated that no problems were encountered on the restoration and cap surface in the 5-year follow-up of conometric restorations produced with monolithic zirconia (32). Similar to previous researches (11,32,36), the present study employed monolithic TZI and LDS materials for the implant supported conometric restoration. On the conometric cap, conometric abutment, abutment screw and implant surface, greater von Mises stress concentrations were seen in the simulation with LDS, even though there was no statistically significant difference between the materials.

In the present investigation, stress analysis was performed at critical locations (Figure 2) using Grade 4 titanium implants and Grade 5 titanium abutments and abutment screws. Grade 5 titanium has an 835 MPa yield strength, while Grade 4 titanium has a 485 MPa yield strength (21). The maximum von-Mises stresses during the tapping, vertical and oblique force phases for two distinct crown materials did not surpass the yield value at any crucial surface. Maximum and average von-Mises stress values at selected important points and the cap surface were higher at the oblique 100N stage, refusing the first hypothesis.

Stresses in fragile structures such as bone should be evaluated according to the maximum and minimum principal stress values (15). In the present study, both the maximum (61.65 MPa) and minimum (-62.028 MPa) primary stress values in cancellous and cortical bone were less than the yield strength of bone (114 MPa) (21). Similar to the literature, the cortical bone exhibited the highest primary stress values (29, 38, 39, 40).

Frictional adhesion exists between the Grade 4 titanium conometric cap and the conometric abutment (20). The surface strains of the conometric cap reached 441 MPa at LDS. The values on the cap surface approach the yield strength of Grade 4 titanium, indicating that deformation may occur on the cap surface. Although there is no significant difference between two materials, TZI material resulted in reduced surface stresses. Consequently, second hypothesis was likewise invalidated.

Various applications exist for assessing the loading conditions in many researches (33, 34, 22). Lemos et al., in a recent study where they evaluated the effect of implant abutment connection, retention and restorative material type on stress distribution, applied a vertical force of 200 N and an oblique force of 100 N. More stress distributions were observed during the oblique loading phase like the present study. Cement retention caused more screw stress than screw retention. Lemos et al., reported that the Morse taper implant type may be a biomechanically better alternative in terms of the stresses arising from bone and screw changes (41).

The number of finite element analysis studies in which the conometric retention type is preferred is quite limited. Tezulas examined the stress distributions induced by two distinct restorative materials placed on Ti-base and conometric abutments in single crowns on implants (20). Crown material and oblique loading conditions were similar to the present study. In contrast to present study, a conometric abutment with a gingival height of 1 mm was utilized and the vertical loading condition was applied as 100 N from each tubercle, for a total of 200N. Although the critical areas such as bone and conometric cap surface stress values of the recent study, were higher than present study. Tezulas reported that the material difference did not have a significant effect on the stress distribution in the implant components, conometric abutment, conometric cap and surrounding bone tissue, like in the present study (20).

The method of finite element analysis is a hypothetical simulation of reality. The limitation of the present study is that the value of the tapping force is not known exactly. Therefore, more investigations are needed to determine the numerical value and effects of the tapping force and also enable the conometric retention type to be used in bridge restorations.

5. CONCLUSION:

The results of stress distributions in the implant components and surrounding bone tissues and conometric cap are between the reference yield and fracture strength values. While the simulation with the TZI material revealed the lowest stresses, there was no statistically significant difference between the stress values for any material. The use of LDS material in the conometric concept carries the risk of deformation on the cap surface over time, as it causes more stress on the cap surface under oblique force. However, further in vitro studies are needed to increase the usability of the conometric concept and to determine the effect and numerical value of the tapping force.

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Clinical and Experimental Health Sciences

The Relationship of Mental Health and Cognitive-Emotional States with Family Planning Attitudes in Young Women with Chronic Diseases

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ABSTRACT

Objective: The aim of this study was to determine the relationship of mental health and cognitive emotional states with family planning attitudes in young women with chronic diseases.

Method: This cross-sectional and descriptive study was conducted between 12 January 2022 and 01 April 2022. The study included a total of 410 young women with chronic diseases who were hospitalized in the internal medicine clinics of a university hospital or presented to the internal medicine clinics for examination. Data were collected using a Personal Information Form, the Mental Health Continuum–Short Form (MHC–SF), the Cognitive Emotion Regulation Questionnaire (CERQ), and the Family Planning Attitude Scale (FPAS).

Results: It was found that 20.2% (n=83) of the young women with chronic diseases had scores below the FPAS (135.5±22.1) cut-off point (<119). Women with a poor mental health, those using maladaptive cognitive coping strategies (self-blame, rumination, catastrophizing, other-blame), and those using compatible cognitive coping strategies less (acceptance, refocusing on planning, positive refocusing, positive reappraisal, and putting into perspective) had a negative family planning attitude (p<.05). In addition, the followings were found to be important associated risk factors for family planning attitude: poor mental health, self-blame (CERQ sub-dimension), use of maladaptive cognitive coping strategy, and decreased use of adaptive positive refocusing (CERQ sub-dimension) (p< 0.5).

Conclusion: It was determined that young women with chronic illness with a poor mental health, who use adaptive cognitive coping strategies less, and who use maladaptive cognitive coping strategies more have negative family planning attitudes.
Keywords: Young women, chronic disease, mental health, cognitive psychology, family planning

1. INTRODUCTION

Chronic diseases, including physical and mental illnesses, are a significant burden for both patients and the health system (1). Chronic diseases constitute an important part of the deaths in the 20-64 age group, covering the reproductive period and beyond, and the number of deaths due to chronic diseases is globally increasing. Due to the increase in the incidence of chronic diseases at early ages, the reproductive health of women of reproductive age may be adversely affected (2-4). One in 10 reproductive age women between the ages of 18 and 44 has a chronic illness, including hypertension, diabetes, high cholesterol, arthritis, asthma, or other respiratory diseases. Five of the top 10 diseases that are among the causes of death of women in Türkiye are chronic diseases (hypertension, diabetes, cardiovascular diseases, etc.) (5). In addition, one in 10 women experiences major depression or anxiety disorder in a year.

Every pregnancy and birth carries a health risk for women, and pre-existing chronic medical conditions can further increase this risk in women (3,4,6). In addition, reproductive health problems in the pre-pregnancy period and physical changes caused by pregnancy can significantly affect chronic diseases. This situation increases hospitalization during pregnancy and the postpartum period and leads to restrictions in daily activities (3,6). The risk of experiencing complications such as pre-eclampsia, congestive heart failure, arrhythmia, preterm birth, intrauterine growth retardation, growth retardation, preterm birth, and miscarriage varies between 40% and 70% in women with chronic diseases (4,7,8). Despite all these risks, the desire for pregnancy is not affected by chronic diseases (9). However, women with chronic diseases are more likely to have an unwanted pregnancy than women without chronic diseases (7,10). While common chronic diseases and mental health problems are recognized as leading causes of morbidity and mortality, less attention has been paid to their impact on women's reproductive health and family planning (FP). Studies have reported that chronic diseases, depression, anxiety, and stress are associated with decreased fertility,

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increased perinatal and infant morbidity, "risky" sexual and contraceptive behaviors, and increased rates of unwanted pregnancy and sexually transmitted infections (11). Women older than 20 years with chronic diseases are less likely to want to conceive and use postpartum contraception than women with no chronic disease (12).

Mental health is recognized as an integral part of general health. Mental health is the state of "being at peace with oneself, with other people, and with the society, and being able to maintain the required effort to maintain a constant balance, order, and harmony" (13). Mental health is an important component of women's health but is often overlooked. One in ten women (11%) is diagnosed with psychology disorders (14). People with mental health problems usually show varying degrees of inconsistency, inappropriateness, and inadequacy in their emotions, thoughts, and behaviors (13). There are many factors that affect women's mental health. Women are exposed to more risk factors than men throughout their life, starting from intrauterine life and during childhood, adolescence, adulthood, and old age. Women are more exposed to stress due to negative experiences such as violence, poverty, excessive workload, learned helplessness, powerlessness, and being obedient, altruistic, and passive; thus, they experience psychological problems more (14). These risks that women are exposed to during their lifetime may affect the mental health of women with chronic diseases more negatively. Women with depression and stress use contraceptives less (15). Young women with depression and stress symptoms experience more unwanted pregnancies, and increased stress is associated with an increase in conception (16).

Cognitive emotion regulation means that when we acquire information that affects us emotionally, we cope with this information cognitively (17). With the use of cognitive processes, negative emotions caused by distressing life events can be controlled. Emotion regulation processes involves both internal and external processes. Emotion regulation includes cognitive, behavioral, and physiological processes that people use to regulate their negative and positive emotions, which are revealed as a result of life experiences (18). There exists no study in the literature on cognitive-emotional sensations of women with chronic diseases. We think that the cognitive-emotional states of women with chronic diseases, depending on their chronic illness, and their living conditions may affect their family planning attitude. Therefore, this study aimed to examine the relationship between the mental health and cognitive emotional states of women with chronic diseases and their family planning attitude.

Research questions;

1. Is there a relationship between the mental health status of young women with chronic illness and their family planning attitude?

2. Is there a relationship between the cognitive emotional states of young women with chronic diseases and their family planning attitude?

2. METHODS

2.1. Study Design

This is a descriptive cross-sectional study.

2.2. Study Setting

The study was carried out between 12 January 2022 and 01 April 2022 in the internal medicine in-patient units and out-patient clinics of a Faculty of Medicine Hospital in Konya in the Central Anatolian Region of Turkey. This hospital was chosen because it has the largest capacity (approximately 2000-3000 patients per month) in the province.

2.3. Study Participants

Sample Size

The sample of the study was based on the FPAS mean score (Mean: 131.4 ± 14.3), as reported by Erenoglu and Sekerci (2020). It was calculated using the G*Power-3.1.9.2 program that 410 women should be included in the sampling to achieve a 2-point deviation, 5% margin of error, and 80% power (19). At the beginning of the study, 490 women were reached. However, the data of women who did not want to participate in the study (60) and who filled out the forms incompletely (10) were excluded from the study. Data were collected from women who met the inclusion criteria using a means of convenience sampling method.

Inclusion and exclusion criteria of the participants

Young women with chronic diseases who were hospitalized in the internal clinics of the hospital or applied to the internal polyclinics for examination were included in the study. Young women who were of reproductive age (18-45 years old), married/living with a partner, sexually active, with chronic diseases (hypertension, diabetes, heart, thyroid diseases, etc.), can communicate in Turkish, and volunteered to participate in the research were included in the study. Young women who were under the age of 18 or over the age of 45, menopausal women, those who had alcohol/substance abuse, and those who did not have a partner were not included in the study.

2.4. Data Collection

Data were collected using a Personal Information Form, the Mental Health Continuum–Short Form (MHC–SF), the Cognitive Emotion Regulation Questionnaire (CERQ), and the Family Planning Attitude Scale (FPAS).

Socio-Demographic Form: A 29-item structured questionnaire prepared by the researchers in line with the relevant literature was used (5,20) to question age, education, work, spouse's/partner's age, income perception, family type, marriage year, marriage decision, BMI (Body mass index), chronic illness, duration of the chronic illness, age at first pregnancy, number of births, number of living children, miscarriage and abortion

status, knowing and using family planning (FP) methods, receiving FP counseling, source of FP counseling, if sexual life was adversely affected in chronic illness, considering having a child in the future, the state of wanting to get pregnant after the diagnosis of the illness, and the state of experiencing baby loss due to the chronic disease.

The Mental Health Continuum–Short Form (MHC–SF): The Mental Health Continuum–Short Form was developed by Keyes et al. and its Cronbach's alpha internal consistency reliability coefficient was found to be 0.74 (21). Its Turkish validity and reliability were established (22) with internal consistency reliability coefficients of 0.84, 0.78, and 0.85 for the three sub-dimensions, and 0.90 for the scale. It has 14 items and 3 subscales. Items 1, 2, and 3 are in the sub-dimension of emotional well-being; items 4, 5, 6, 7, and 8 are in the sub-dimension of social well-being; and items 9, 10, 11, 12, 13, and 14 are in the sub-dimension of psychological well-being. The scale starts with this question: "how often have you felt the following emotions during the last month?". The MHC-SF is a 6-point Likert scale (0-Never/5-Everyday) with a score range of 0-70. There is no reversely scored item. The total score is obtained by summing the 14 items. In addition, emotional, social, and psychological well-being subscales can be scored. High scores obtained from each sub-dimension of the scale indicate better well-being in that area. "Flourishing" is defined as those who marked the expressions "almost every day" or "every day" in one of the three statements in the emotional well-being dimension of the scale, and those who marked the statements "almost every day" or "every day" in six of the eleven statements in the psychological and social well-being dimensions. "Languishing", being not well, is defined as those who marked "never" or "once or twice" in one of the three statements in the emotional well-being dimension of the scale, and those who marked the expressions "never" or "once or twice" in six of the eleven statements in the psychological and social well-being dimension. Others are considered to be in normal mental health. In this study, the internal consistency reliability coefficient was 0.95 for the entire scale.

Cognitive Emotion Regulation Questionnaire (CERQ): The scale was developed by Garnefski, Kraaij, and Spinhoven based on a 36-item form evaluating the cognitive aspects of emotion regulation (23), and then this short 18-item form was created by Garnefski and Kraaij (24). Its Turkish validity and reliability were established (25). This 18-item scale is a five-point Likert type scored between 1 and 5. It has 9 sub-dimensions that include adaptive and maladaptive cognitive coping strategies, namely, adaptive coping strategies – acceptance, refocusing on planning, positive refocusing, positive reconsideration, putting into perspective; and, maladaptive coping strategies – self-blame, rumination, catastrophizing, and other-blame. The score of each sub-dimension ranges from 2 to 10. A high score from a sub-dimension indicates that the strategy determined by that sub-dimension is used more. Cronbach's alpha reliability coefficients obtained from the scale ranged from 0.63 to 0.74. In this study, the Cronbach's alpha internal consistency coefficient for the nine sub-dimensions of the scale ranged between 0.94 and 0.70. Cronbach's alpha internal consistency coefficient for the whole scale is 0.78.

Family Planning Attitude Scale (FPAS): The FPAS was developed by Örsal and Kubilay in 2007 to measure people's attitudes towards FP (26). This 34-item scale is a 5-point Likert type (strongly agree=1-totally disagree=5). The scale has three sub-dimensions, namely, "Attitude of the Society towards Family Planning", "Attitude towards Family Planning Methods", and "Attitude towards Pregnancy". The score range is 34-170. A higher score indicates a positive FP attitude. The cut-off point of the scale is 119. Örsal and Kubilay reported the Cronbach Alpha of the scale as 0.90, and in this study, the Cronbach Alpha internal consistency coefficient was found to be 0.92.

2.5. Data Collection Procedure

Data were collected from women who met the inclusion criteria using a means of convenience sampling method. Interviews with the women were conducted by the researchers in a private room in inpatient or outpatient clinics and data were collected in these rooms via face-to-face interviews. Before data collection, each woman participating in the study was informed about the purpose and method of the study. They were told that the data obtained would only be used within the scope of the study, that their names would not be included in the questionnaire, and that it was their decision whether or not to participate in the study. Women were not paid any incentive for participating in the study. It took approximately 15-20 minutes to fill out each form.

2.6. Ethical Dimension of Research

Approval of the Selcuk University Faculty of Health Sciences Ethics Committee (29.12.2021/ 1915) was obtained for the study. Institutional permission was obtained from Necmettin Erbakan University Rectorate, Meram Medical Faculty Hospital Chief Physician (12.01.2022/E-14567952.900.141130). An informed consent form was obtained from the women participating in the study before the interview after explaining the research. To ensure privacy, each participant was interviewed in a separate room in this hospital. In addition, the participants were informed that they could withdraw from the study at any time without giving any reason, their participation was completely voluntary, and their identities would be kept confidential. Permissions to use all scales used in the study were obtained from the relevant authors.

2.7. Data Analysis

Data analysis was performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA). In the normality analysis, since the Skewness and Kurtosis values of all scales were between – 1.50 and +1.50, parametric tests were performed (27). Number, percentage, arithmetic mean, and Standard Deviation (SD) were used for descriptive statistics. The independent-sample t-test was used in the evaluation of the relationship between FPAS cut-off scores (1< 119, 0 ≥ 119) and scale scores. Bivariate (Binary) logistic regression analysis was

performed with the Enter method to evaluate the effects of other categorical and continuous variables on the FPAS. All significant variables were included in the regression analysis. A p-value of <.05 was considered statistically significant.

3. RESULTS

Participants' mean age was 35.1±7.3 years and they had an average of 12.8 ± 8.3 years of marriage. They were all married and had chronic diseases for 7.3 years. Their first gestational age was 22.9 years and they had an average of 2.1 births. On average, the women had 0.2 miscarriages and 0.1 abortions, and 75.6% of the participants used modern FP methods. The women had a mean FPAS score of 135.5 According to the FPAS, 20.2% (n=83) scored below the cut-off point (FPAS < 119) (Table 1).

Table 1. *Socio-demographic, obstetric, and some family planning characteristics of young women with chronic diseases (n = 410)*

Characteristic features	n	(%)
Education		
Primary School	130	31.7
High School	127	31
University and higher	153	37.3
Employment status		
Full-time housewife	240	58.5
Employed	170	41.5
Perceived Income Level		
Good	106	25.9
Moderate	283	69
Poor	21	5.1
BMI		
Poor	28	6.8
Normal weight	253	61.7
Over-weight	129	31.5
Current chronic diseases		
Endocrine system	136	33.2
Cardiovascular system	109	26.6
Respiratory system	70	17.1
Hematological system	47	11.5
Nervous system	48	11.7
Status of knowing FP methods		
Yes	355	86.6
No	55	13.4
Status of current use of FP method		
IUD	78	19
Pills	50	12.2
Condoms	168	41
Injections	14	3.4
Coitus interruptus	64	15.6
How to decide on this method		
I decided myself	49	12
My partner/spouse decided	47	11.5
We decided together	314	76.6
Status of receiving education about the FP method		
Yes	283	69
No	127	31
The state of the chronic disease negatively affecting sexual life		
Yes	96	23.4
No	314	76.6
The effect on the idea of having children in the future		
Yes	138	33.7
No	272	66.3
Pregnancy status after diagnosis of chronic disease		
Yes	203	49.5
No	207	50.5
Wanted pregnancy (n=203)		
Yes	86	42.4
No	117	57.6
Pregnancy loss after diagnosis of chronic disease		
Yes	33	8
No	377	92

It was determined that women with negative FPAS have weaker mental health than women with positive FPAS. In addition, women with negative FPAS use maladaptive cognitive coping strategies more and adaptive cognitive coping strategies less than women with positive FPAS (p < .05) (Table 2).

Table 2. *Comparison of mental health and cognitive emotion regulation characteristics and sub-dimensions with FPAS in young women with chronic diseases*

Variables that may be associated with FPA	Negative FPA (FPAS < 119) *n* = 83 Mean±SD	Positive FPA (FPAS ≥ 119) *n* = 327 Mean±SD	t	p
MHC–SF	27.6 ± 14.7	41.7 ± 13.2	7.154	**< .001**
CERQ sub-dimension				
Self-blame	7.6 ± 2.8	4.3 ± 1.5	-9.829	**< .001**
Rumination	7.3 ± 2.6	6.4 ± 2	-2.868	**.005**
Catastrophizing	6.8 ± 2.9	4.9 ± 1.9	-5.718	**< .001**
Other-blame	6.7 ± 3	4.1 ± 1.9	-7.382	**< .001**
Acceptance	4.8 ± 2.9	6.3 ± 1.9	4.350	**< .001**
Refocus on planning	4.7 ± 2	6.7 ± 1.9	7.892	**< .001**
Positive refocusing	4.1 ± 2.2	6.5 ± 1.9	8.621	**< .001**
Positive reappraisal	4.2 ± 1.8	5.8 ± 2	6.905	**< .001**
Putting into perspective	5.3 ± 1.9	6.3 ± 1.9	4.377	**< .001**

Independent sample t-test was used.
SD=Standard Deviation, MHC-SF: Mental Health Continuum–Short Form, CERQ: Cognitive Emotion Regulation Questionnaire, FPA: Family Planning Attitude

Variables that were statistically significant according to the AP cut-off score were included in the logistic regression analysis. The regression model was significant for risk factors that may affect FPAS ($\chi 2$ = 207.582, p < .001) and explained 62% of the variance. Based on the findings in our regression analysis, the following factors were important associated risk factors for FPAS: poor mental health (OR=0.959, 95% [CI]= 0.931-0.988); using self-blame maladaptive cognitive coping strategy (CERQ sub-dimension) (OR=1.751, 95% [CI]= 1.456–2.104), and less use of adaptive positive refocusing cognitive coping strategy (p< .05) (Table 3).

Table 3. *Logistic regression analysis according to factors affecting FPAS*

Variables that may affect FPA	FPA (FPAS < 119)					
	B	S.D.	*Odds Ratio (OR)*	*P*	% 95 Confidence Interval (CI)	
					Low Value	High Value
MHC–SF	-0.42	0.015	0.959	**.006**	0.931	0.988
CERQ sub-dimension						
Self-blame	0.560	0.094	1.751	**< .001**	1.456	2.104
Rumination	0.188	0.108	1.207	.080	0.977	1.491
Catastrophizing	1.141	0.094	1.151	.133	0.958	1.383
Other-blame	0.102	0.086	1.108	.237	0.935	1.312
Acceptance	-0.124	0.088	0.883	.158	0.744	1.049
Refocus on planning	-0.141	0.119	0.868	.234	0.688	1.096
Positive refocusing	-0.395	0.103	0.673	**< .001**	0.550	0.824
Positive reappraisal	-0.175	0.104	0.840	.093	0.685	1.029
Putting into perspective	0.152	0.125	1.164	.224	0.911	1.488

Binary Logistic Regression Analysis with Enter Method was used;
Cox & Snell R Square = .397; Nagelkerke R Square = .626
FPA: Family Planning Attitude, MHC-SF: Mental Health Continuum–Short Form, CERQ: Cognitive Emotion Regulation Questionnaire,

4. DISCUSSION

This study revealed that poor mental health, less use of adaptive cognitive coping strategies, and more use of maladaptive cognitive coping strategies negatively affect FPAS in young women with chronic diseases. The mean FPAS score of the women with chronic diseases who participated in our study was found to be 135.5 ± 22.1. Since the FPAS cut-off score is <119, we can say that women's FPAS are positive. In studies conducted with women without previous chronic diseases, FPAS scores ranged from 109.1±18.7 to 134.20±27.34 (28,29). In a study, the FPAS scores of women with chronic diseases were at an appropriate level, nearly half of them used an effective contraceptive method; and, the characteristics of education level, number of pregnancies, desire to have a child in the future, knowing birth control methods, and using any contraceptive method affected their attitudes towards FP (30). The mean FPAS scores of women in these studies were similar to those of previous studies. On the other hand, in a study conducted in Eastern Turkey, the mean FPAS score was found to be lower (31). It is thought that this difference was caused by the differences in the region, clinic, place, and socio-demographic, obstetric, and cultural characteristics of the women.

According to our regression analysis, mental health was found to be a related factor that negatively affects women's FPAs (Table 3). In addition, 49.5% of the women became pregnant after the diagnosis of chronic disease and 57.6% (n=203) did not want pregnancy. A negative relationship was shown between unintended pregnancies and women's psychological health (32). Women with depression and stress use contraceptives less (15). It was stated in a cohort study that unplanned pregnancies were associated with psychiatric illness or psychological distress in women (33). Women who do not plan to become pregnant are more likely to have miscarriages during pregnancy and moderate-to-high levels of stress and depression symptoms are observed in these women (34). There is evidence of an association between adverse pregnancy outcomes in women who experienced stress or stressful life events during pregnancy (35,36). It was noted that women with symptoms of stress and depression experience risky pregnancy more than two-fold compared to those without symptoms, and these increased stress and depression symptoms in women increase further in case of conception (16).

According to the results of the regression analysis, it was determined that the FPAS of women who used self-blaming maladaptive coping strategies and who did not use positive refocusing cognitive coping strategies were negatively affected (Table 3). The literature on the cognitive emotion regulation skills of women with chronic disease and their FPAS is quite limited. However, women with mental disorders such as depression and anxiety use more maladaptive cognitive coping strategies. Women can manage the stressful process they are in through coping (24). Coping is the cognitive and behavioral efforts presented when faced with certain demands that are considered to be difficult or exceed one's resources (37). Stable or 'usual' coping style is one's dispositional coping style (38). Women who cannot cope with stress and use maladaptive coping strategies have a high rate of unwanted pregnancies, and the majority of these pregnancies result in premature birth (34). Women's maladaptive cognitive coping skills may impair their psychosocial adjustment and negatively affect their mental health, which may lead to negative FPAS. Studies indicate that cognitive-behavioral therapy can be used as a treatment option to reduce anxiety, stress, and depression in women (39).

Since the participants were from only one hospital, the results cannot be generalized to the country. However, our results can be generalized province-wide since the hospital is one of the largest hospitals in the province, and many patients visit the internal medicine clinics from surrounding provinces and

districts. It is an important study investigating both mental health and cognitive emotion regulation of young women with chronic diseases, so we think that it will make important contributions to the literature.

5. CONCLUSIONS

One in every five young women with chronic diseases (20.2%) has negative FPAS. It was found that women with poor mental health, who used maladaptive cognitive coping strategies, and who used adaptive cognitive coping strategies less had negative FPAS. In addition, poor mental health, use of "self-blame (adaptive cognitive coping strategy)", and less use of "positive refocus (adaptive cognitive coping strategy)" were found to affect FPAS negatively. In line with the results of the research, health professionals should encourage women to participate in motivational interviewing or intervention programs based on social-cognitive factors for problem resolution by evaluating the mental health and adaptive cognitive coping characteristics of young women with chronic diseases for positive FPAS.

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Clinical and Experimental Health Sciences

The Validity and Reliability of the Postpartum Symptom Inventory in Turkish Women

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ABSTRACT

Objective: Postpartum period is a significant period that covers approximately 6 weeks after childbirth, progresses with various symptoms, and affects the life of the woman. The study was conducted in order to test the validity and reliability of the Postpartum Symptom Inventory (PSI-20).

Methods: The study was conducted on 310 participants with a descriptive, cross-sectional, and methodological design. The study data were collected through Identifying Information Form, Postpartum Symptom Inventory, and Edinburgh Postnatal Depression Scale as a parallel form. In the analysis of the data, factor analysis, Cronbach's alpha coefficient, and item-total score correlations were used.

Results: The scale consisted of 20 items under 6 subscales with a variance of 71%. The Cronbach's alpha coefficient of the Turkish version of the scale was 0.86. According to split-half test reliability, Cronbach's alpha coefficients of the first and second halves were found to be 0.71 and 0.73, respectively, Guttman split-half coefficient was 0.94, and the correlation coefficient between the halves was determined as 0.88. According to confirmatory factor analysis, Root Mean Square Error of Approximation Index (RMSEA) 0.072, Goodness of Fit index (GFI) value was 0.89, Comparative Fit Index (CFI) value was 0.94, Relative Fit Index (RFI) was 0.89, Incremental Fit Index (IFI) was 0.94, and Tucker-Lewis index (TLI) value was found as 0.93.

Conclusion: As a result of the study, it was determined that the Turkish version of the Postpartum Symptom Inventory (PSI-20) was a valid and reliable tool in order to measure postpartum symptoms in Turkish women.

Keywords: Postpartum care, symptom, inventory, validity, reliability.

1. INTRODUCTION

Postpartum period covers a process in which the physiological changes that occur in the woman's body throughout pregnancy return to pre-pregnancy conditions. This process is of vital importance for the maintenance of the well-being of the mother and the neonate in the long term (1). In this period, many physical, social, and psychological symptoms that could affect women's health and quality of life may develop (1,2). It is necessary to provide a comprehensive and quality care in order to recognize these symptoms well and for the mother and the neonate to adapt to the new period in a healthy way (3). Sleep problems, fatigue, sexual concerns, breast problems-breastfeeding difficulties, and pain and psychological changes that the mother could experience can negatively affect their adaptation to this period (1,2). As these physical and psychological symptoms experienced by the mother will not only affect maternal health but it will also lead to a decrease in their performance in maternal roles, they can also affect neonatal health (4–6). In studies conducted, a relationship was shown between physical symptoms that develop in the early postpartum period (0-3 months) and depressive symptoms observed in the postpartum 6th and 12th months (7–9). Depressive and physical symptoms can negatively affect both maternal and neonatal health and quality of life (10). By evaluating these symptoms in early period well and taking necessary precautions, it will be possible to reach the goal set by the World Health Organization (WHO) which aims at improving maternal health and decreasing postpartum illness and mortality rates (4). Postpartum counselling should include planning educational programmes for the problems identified for the mother to spend the postpartum period well and providing counselling on the needs of the mother. In this context, midwives, family physicians and public health nurses can recognize and diagnose physical symptoms while

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planning such care, and intervene early in this important stage of life for women. Currently, there is an 18-item single-subdimensional scale developed in 2009 to determine the frequency and persistence of postnatal physical symptoms (11). Edinburgh Postpartum Depression Scale and Patient Health Questionnaire (PHQ-9) are used to measure mental problems (12–15). It is thought that the Postpartum Symptom Inventory will contribute to the literature in terms of consisting of 6 sub-dimensions and providing researchers with the opportunity to evaluate on a system basis if necessary (2).

The aim of the study is to test the validity and reliability of the "Postpartum Symptom Inventory" developed by Schaffir et al. in Turkish women.

2. METHODS

2.1. Study Design and Participants

The study was conducted with a descriptive, cross-sectional, and methodological design. The study was conducted with the participation of the puerperia who presented to two state hospitals in the northwest of Turkey between December 2019–March 2020. Postpartum women who a) gave birth in 37-42 gestational week (term), b) had a healthy baby, c) were in postpartum day 5-42, and d) volunteered to participate in the study and gave written consent were included in the study. Postpartum women who a) were not mentally able to answer the study questions, b) had health problems and complications during pregnancy and childbirth, c) had their babies in intensive care or lost their babies were excluded from the study. In studies of measurement tool development and adaptation, a sample size of 1,000 or more is recommended as excellent, 500-1,000 as very good, and 200-500 as good (16), and accordingly the study was conducted with 310 postpartum women who met the inclusion criteria and gave verbal and written consent. In addition, the research used the population sampling formula with a known population to calculate the sample. The total number of women giving birth in two hospitals in one year is approximately 7000. The number of women to be interviewed with a 90% confidence level and 5% margin of error was 261, and the study was completed with 310 participants, allowing for possible data loss. A total of 57 mothers who did not speak or understand Turkish and whose babies were in intensive care were excluded from the study.

2.2. Ethics Committee Approval

Prior to the study, permission was taken from the author who developed the scale through e-mail (2). In addition, ethical approval for the study was obtained from non-interventional research ethics committee (GOKAEK-2019/334), and official written permission was taken from the institutions where the study was conducted.

2.3. Data Collection Tools

The study data were collected through Identifying Information Form, Postpartum Symptom Inventory, and Edinburg Postnatal Depression Scale as the parallel form.

Identifying Information Form: The form developed by the researchers in line with the literature (2,17–19) consists of 22 questions inquiring about the participants' sociodemographic and obstetric characteristics.

Postpartum Symptom Inventory: The scale developed by Schaffir et al. in 2018 investigates 20 parameters. The 5-point Likert type inventory is responded according to the symptom status experienced in the last 7 days (Never=0, Always=4). The lowest score to be obtained from the scale is 0, and the highest score is 80 (2). Permission for the validity and reliability study of the scale was taken from the author of the inventory.

Edinburg Postnatal Depression Scale: The scale was developed by Cox et al. in order to screen and determine depression risk in women in postpartum period. It is a self-evaluation scale which consists of 10 items that assess the psychological status of the individual in the last 7 days. Each item is scored on a 4-point Likert type scale from 0 to 3 ("Yes, always", "Yes, most of the time, "No, not frequently", and "No, never"). The total score to be obtained from the scale ranges between 0-30. The cutoff point is 12.5, and a high score indicates the severity of depression (15). The Turkish validity and reliability study of the scale was conducted by Aydin et al., and permission was taken from the authors (12).

2.4. Linguistic Validity

In ensuring psycholinguistic properties and linguistic validity of the scale, ISPOR (The Professional Society for Health Economics and Outcomes Research) Cultural Adaptation Guideline was followed (20,21). Firstly, the scale was translated to Turkish by two independent language experts who had mastery of health terminology and English language, the researchers reviewed it, and an agreement was reached. Then, the draft Turkish version of the scale was translated back to English by two independent translators who had mastery of health terminology and English language, and it was reviewed by the researchers and prepared for expert opinion (Figure 1).

2.4.1. Expert Opinion

Content validity shows the relevance of the items of a measurement tool with the quality that needs to be measured and its scope. It has been recommended to benefit from at least three expert opinions in order to determine content validity of scales (22,23). In determining the construct and content validity of the scale, expert opinions were taken from 10 experts who were competent in childbirth and midwifery. The experts were asked to evaluate the original scale and the Turkish version on a scale from 1 (the item is not suitable) to 4 (the item is suitable), and then item content validity index

(I-CVI) and scale content validity index (S-CVI) were calculated (22,24), and in order to analyze expert consistency, CVI (content validity index) was used. CVI for the general scale was >0.90 according to the 4-point scale, and it was found adequate in terms of item content validity(22,24).

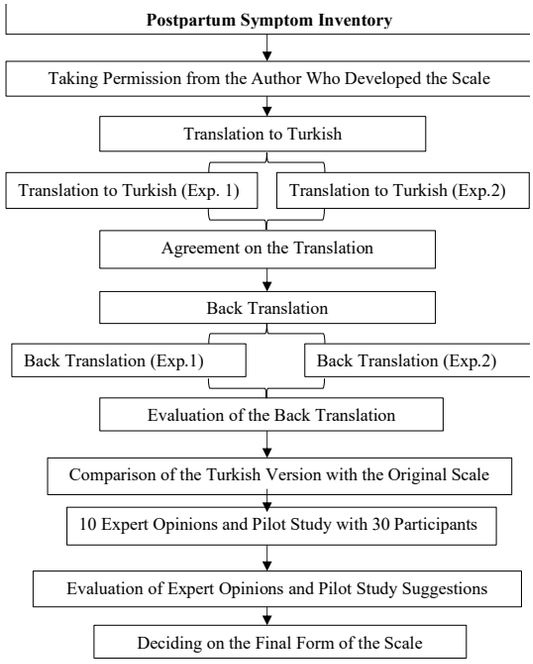

Figure 1. *ISPOR Sample Linguistic Validity Guidelines*

2.4.2. Pretest

Following the expert opinions, the measurement tool was applied to 30 mothers in postpartum period with similar traits. In the literature, the minimum sample size for a pilot study has been recommended as 30 (25). Comprehensibility of the measurement tool was found to be adequate in the pilot study, and then, it was applied to the whole sample. Pilot study data were not included in the study data.

2.5. Data Collection Process

Firstly, the participants were informed about the study by the researchers, and their consent to participate in the study was taken. Later, they were administered the scales used in the study. It took approximately 15-20 minutes for each mother to fill in the forms, and the forms were found comprehensible by the mothers.

2.6. Statistical Analysis

The study data were analyzed by using SPSS statistics software (v.22.0; SPSS, Chicago, Illinois, USA) and AMOS software package. Descriptive statistics regarding sociodemographic characteristics were presented as frequency, percentage, and mean value.

In ensuring the validity of the Turkish form of the scale, content validity and construct validity were tested, and in the evaluation of inter-expert consistency, Content Validity Index (CVI) was used (22,24).

For the validity of the Turkish version of the Postpartum Symptom Inventory, Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) were performed. In order to identify the relationship between item and factor, EFA was employed. Before performing EFA, in order to evaluate the suitability of the data for factor analysis, Kaiser-Meyer-Olkin (KMO) test and Bartlett's sphericity test were used (26,27).

CFA was used in order to determine the degree of items and subscales to explain the scale structure. Model confirmation of Comparative Fit Index (CFI) was performed on the basis of Chi-square test, degree of freedom, the Root Mean Square Error of Approximation (RMSEA), Goodness of Fit (GIF), and Normed Fit Index (NFI) (25).

For reliability analysis, item-total score analysis, Cronbach's alpha coefficient, parallel scale analysis, and Guttman split-half values were used. For item-total score analysis, Pearson correlation analysis was performed, and significance level was accepted as $p<.05$

3. RESULTS

Sociodemographic and obstetric characteristics of the participating mothers are presented in Table 1.

Table 1. *Sociodemographic and obstetric characteristics of the participants (n=310)*

Characteristics	Mean ± SD	Min – Max.
Age	28.3 ± 6.65	19 – 47
Number of pregnancies	2.60 ± 1.41	1 – 6
Number of births	2.26 ± 1.24	1 – 6
	n	**%**
Educational status		
Primary school	68	21.9
Secondary-High school	192	61.9
University	50	16.1
Employment status		
Employed	25	8.1
Unemployed	285	91.9
Income status		
Good	10	3.2
Moderate	285	91.9
Poor	15	4.8
Planned pregnancy		
Yes	232	74.8
No	78	25.2

3.1. Validity Analysis

In the study, in order to ensure the validity of the Turkish version of the measurement tool, content validity and construct validity were employed.

3.1.1. Content Validity

10 expert opinions were taken for the Turkish version of the measurement tool, and the opinions of 10 experts were evaluated through Content Validity Index according to Polit and Beck. Item Content Validity Index (CVI) for each item on the scale varied between 0.80-1.00, and Item Content Validity index for the total scale was found as 0.98.

3.1.2. Construct Validity

For the construct validity of the Turkish version of the Postpartum Symptom Inventory, EFA and CFA analyses were used. The scale's compliance with factor analysis was evaluated with KMO and Bartlett's sphericity tests. In the factor analysis, p<.05 Bartlett Chi-square test score is required, and a KMO value approximating 1 is accepted as excellent, while <.50 is accepted as suitable. The scale's KMO value was found to be 0.81, and the sample was determined to be adequate for factor analysis. In addition, according to Bartlett's test result, it was seen that the scale was significant for factor analysis, so factor analysis could be performed (x^2=4283,62; p<.000).

In the original scale, factor structure was formed under one subscale, but in the exploratory factor analysis performed, 6 subscales were determined. The total variance of the subscales is 71.39%. Besides, the factor load of the scale ranges between 0.61 and 0.97. Item-total score correlations vary between 0.30-0.60 (Table 2).

Table 2. *Factor loads for Postpartum Symptom Inventory and item-total score correlations (n=310)*

Items	Factor 1	Factor2	Factor3	Factor 4	Factor 5	Factor 6	Corrected Item-Total Correlation
Item17. Painful veins (varicose veins)	0.916						0.522
Item20. Hot flashes	0.770						0.414
Item 4. Nausea	0.676						0.584
Item 18. Abnormal and continuous vaginal bleeding	0.646						0.478
Item 16. Pain during sexual intercourse		0.972					0.362
Item15. Change in sexual desire		0.863					0.362
Item19. Vaginal leak		0.856					0.378
Item12. Abdominal/pelvic pain			0.840				0.497
Item 11. Backpain/hip pain			0.826				0.508
Item 13. Breast pain			0.765				0.435
Item 14. Vaginal pain			0.742				0.492
Item 6. Urinary incontinence				0.813			0.361
Item 7. Increased urination frequency				0.801			0.356
Item 8. Fecal incontinence				0.614			0.374
Item 1. Fatigue or exhaustion					-0.935		0.586
Item 2. Insomnia					-0.893		0.583
Item 3. Headache					-0.777		0.598
Item 10. Hemorrhoids						0.935	0.413
Item 9. Constipation						0.934	0.440
Item 5. Heartburn /indigestion						0.801	0.559
Variance Explained (%)	29.2	12.6	9.5	7.7	7.1	5.0	
Total Variance Explained (%)	71.396						
Eigenvalue	6.13	2.72	2.19	1.86	1.65	1.33	

F1:Circulatory System Symptoms, F2: Sexual Dysfunction Symptoms, F3: Pelvic Arch Symptoms, F4: Urinary/Fecal Incontinence Symptoms, F5: Neurological Symptoms, F6: Gastrointestinal Symptoms. Extraction Method: Principal Axis Factoring, Oblique rotation (Direct oblimin) method was used. Only values higher than 0.32 are presented.

3.2. Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA)

As a result of CFA applied to the scale, factor loads were found to vary between 0.61 and 0.98. Regarding factor loads of the subscales, the factor load for the subscale of F1 (Circulatory System Symptoms) was found to vary between 0.61 and 0.88, for F2 (Sexual Dysfunction Symptoms) between 0.86 and 0.98, for F3 (Pelvic Arch Symptoms) between 0.68 and 0.90, F4 (Urinary/Fecal Incontinence Symptoms) between 0.69 and 0.79, for F5 (Neurological Symptoms) between 0.83 and 0.92, and for F6 (Gastrointestinal Symptoms) between 0.87 and 0.94 (Figure 2). In terms of model fit index, Chi-square (χ2) was found as 395.78 (df: 153) and mean square root approximation error (RMSEA) was found to be 0.072. Chi-square/degree of freedom was <5 (χ2/df = 2,587). Other values were found as GFI:0.89, NFU:0.91, RFI:0.89, IFI:0.94, TLI (NNFI):0.93, and CFI:0.94 (Table 3).

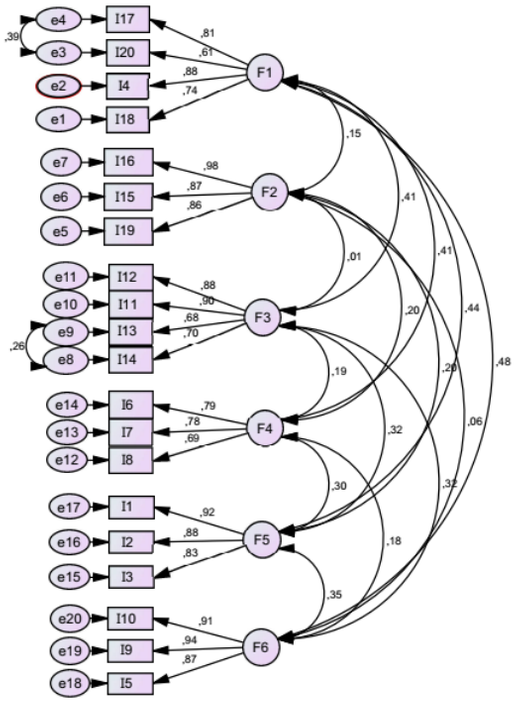

Figure 2. *CFA results of the Turkish version of the Postpartum Symptom Inventory. F1: Circulatory System Symptoms, F2: Sexual Dysfunction Symptoms, F3: Pelvic Arch Symptoms, F4: Urinary/Fecal Incontinence Symptoms, F5: Neurological Symptoms, F6: Gastrointestinal Symptoms.*

Table 3. *Model Fit Indices (n=310)*

Six-Factor Model	X^2	X^2/SD	RMSEA	GFI	NFI	RFI	IFI	TLI	CFI
	395.78	2.58	0.072	0.89	0.91	0.89	0.94	0.93	0.94

RMSEA: Root Mean Square Error of Approximation Index; GFI: Goodness of Fit index; CFI: Comparative Fit Index; RFI: Relative Fit Index; IFI: Incremental Fit Index; TLI: Tucker-Lewis index.w

Table 4. *Reliability Analysis Results for Subscales (n=310)*

Sub-Dimensions	Cronbach α	First half Cronbach α	Second half Cronbach α	Guttman split-half	Two halves between correlation	Hotelling T^2	p
Factor 1	0.84	0.71	0.73	0.94	0.88	856.91	<.001
Factor 2	0.92						
Factor 3	0.88						
Factor 4	0.77						
Factor 5	0.91						
Factor 6	0.93						

3.3. Criterion-Related Validity

3.3.1. Simultaneity Validity

In determining criterion-related validity of the Postpartum Symptom Inventory (PSI), whose validity and reliability analyses were performed, the Edinburg Postnatal Depression Scale (EPDS), which is frequently used as a parallel form, was employed. The correlation coefficient was found to be r=0.83 (p<.001). Hence, it can be stated that there is adequate correlation that allows similar measurements, and that the scale is valid in this regard.

3.4. Reliability Analysis

The Cronbach's alpha coefficient of the Turkish version of the scale was found as 0.86, and according to split-half test reliability analysis, the Cronbach's alpha coefficients of the first and second halves were 0.71 and 0.73, respectively, while Guttman split-half coefficient was found to be 0.94 and the correlation coefficient between the halves was 0.88. The scale had 6 factors, which were Factor 1 (Circulatory System Symptoms) with Cronbach's alpha coefficient of 0.84, Factor 2 (Sexual Dysfunction Symptoms) with Cronbach's alpha coefficient of 0.92, Factor 3 (Pelvic Arch Symptoms) with Cronbach's alpha coefficient of 0.88, Factor 4 (Urinary/Fecal Incontinence Symptoms) with Cronbach's alpha coefficient of 0.77, Factor 5 (Neurological Symptoms) with Cronbach's alpha coefficient of 0.91, and Factor 6 (Gastrointestinal Symptoms) with Cronbach's alpha coefficient of 0.93. In the floor and ceiling effect analysis of the scale items, there was no significant accumulation. Besides, in order to determine whether the participants' responses to the scale items were equal or not, Hotelling T^2 test was performed. As result of this test, Hotelling value of the scale was found as T^2=856.915, p<.000. No response bias was determined on the scale (Table 4).

4. DISCUSSION

Postpartum symptoms can negatively affect the woman's physical and emotional health and cause her to face a series of diseases, while affecting neonatal care adversely (17–19). Therefore, it is highly important that health professionals should recognize the physical symptoms in the postpartum process and intervene in cases when necessary. PSI developed by Schaffir et al. can help health professionals in this regard (2). With this study, validity and reliability of PSI was analyzed in the context of Turkey.

In studies on scales, content validity index value is desired to be 0.80 (22,24,28). According to the scale content validity (S-CVI) and item content validity (I-CVI) analyses, it was seen that there was a high level of consistency between experts, and that the scale items adequately represented the targeted measurement. In the study, KMO and Bartlett X^2 tests were used in order to determine the suitability of the sample for factor analysis. The most important parameters that show a scale to be suitable for factor analysis are KMO value being above 0.60 and Bartlett's test being significant (29). Especially in measurement tools with 2 and more subscales, more than 40% of the variances are expected to be explained, which shows the power of the measurement tool. The results obtained in the validity and reliability analysis of the scale showed that the scale was suitable for measuring postpartum symptoms of Turkish women (25).

As no factor analysis was performed on the original scale and it was evaluated over one dimension, within the framework of the data obtained in the study, the presence of the subscales of the scale was evaluated through Principal Axis Factoring method. It is recommended in the literature to analyze the presence of subscales of measurement tools by using Principal Axis Factoring method (30,31). The analysis of the factor loads of the items of the scale in the study was performed by taking the values higher than 0.32. It has been particularly emphasized in the literature that the factor loads being over 0.30 ensures the desired measurement by the scale (32).

In the intercultural adaptation studies of measurement tools, it is recommended to do first the exploratory factor analysis and then confirmatory factor analysis together (33). As a result of the confirmatory factor analysis performed, it was seen that Chi-square/degree of freedom was <5, RMSEA value was 0.072, small fit indexes of GFI and RFI values were at the limit of 0.89, while others were higher than 0.90, and the factor loads of all items were higher than 0.30.

Cronbach's alpha coefficient evaluates internal consistency of scale items; in other words, it assesses the changing degree of the item set and total score together. An alpha coefficient of 0.70 is generally accepted as an acceptable threshold for reliability; however, for the psychometric quality of scales, values between 0.80 and 0.95 are preferred more (16,25). Cronbach's alpha coefficient of the scale was found as 0.86, which shows that the scale has high reliability. In addition, split-half test reliability analysis is an important factor in scale studies, and Cronbach's alpha coefficients of both halves were found to be over 0.70, Guttman split-half coefficient was 0.94, and the correlation coefficient between the two halves was 0.88. These values show that the scale has high reliability (34). Ceiling and floor effect in scales is an indicator of homogeneity of the scale, and the highest score indicates ceiling effect, while the lowest score shows floor effect. What is desired in scale items is that there is no significant accumulation in ceiling and floor effect analysis (35), and the scale met this criterion. In studies conducted on measurement tools, whether participants respond to the items on a scale according to their own opinions or in line with the expectations of the society or the researchers is called response bias, and it is evaluated through Hotelling T^2 test. In order to avoid response bias, the statistical result obtained from the test must be significant (36). In the study, no response bias was determined.

The relationship between total scale score and scores obtained from scale items is tested through item-total score analysis, and the lowest score is desired to be 0.30

in some sources (25,37) and 0.33 in other sources (32,38). Item-total score correlations were found to range between 0.30 and 0.60 in the study. This information shows that the scale measured the targeted feature, and that the scale had high reliability. It was shown as a result of the study that the "Postpartum Symptom Inventory" (PSI) can be used as a measurement tool in order to determine the symptoms experienced by women in the postpartum period. Healthcare providers can plan care aimed at the symptoms experienced by women in the postpartum period by using this scale, and they can increase their chances of early intervention in risky situations. It is recommended to conduct various descriptive studies in which the correlation of the scale with other measurement tools such as postpartum depression scale or sadness scale used in the postpartum period is examined and to conduct longitudinal and experimental studies in which long-term effects are investigated. The Postpartum Symptom Inventory (PSI) can be used at postpartum clinics and family health and public health centers where postpartum women are followed up in order to determine postpartum symptoms.

4.1. Limitations

The study has certain limitations. The study data were collected from the puerperae who presented to two district family health centers and two state hospitals, and therefore, there is a risk of bias. Hence, the results' degree of representing the universe is reduced, and generalizability is limited. Besides, the original scale is in English, and its exploratory and confirmatory analyses have not been performed. Therefore, intercultural comparisons could not be made.

5. CONCLUSION

As a result of the analyses, it was determined that the Turkish version of the Postpartum Symptom Inventory (PSI) has 6 subscales, that its Cronbach's alpha coefficient is high, and that it ensures cultural equivalence. In conclusion, it has been found that the Turkish version of the Postpartum Symptom Inventory (PSI) is a valid and reliable measurement instrument that can be used in measuring symptoms in women in the postpartum period. This measurement tool can be used by midwives, women's health and public health nurses, obstetricians, family physicians and researchers specialised in the subject. It is also recommended to conduct research on its relationship with other measurement tools used in the postpartum period and its use.

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Author Contributions:
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Design of the study: SDA, ND, ASK
Acquisition of data for the study: BK
Analysis of data for the study: SDA
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Clinical and Experimental Health Sciences

Determination of Early Diagnostic Biomarkers of Renal Dysfunction After Cardiopulmonary Bypass: miR-21 and miR-10a Mediated Postoperative Inflammation

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ABSTRACT

Objective: Acute renal failure (ARF) prevalence is high among patients who undergo cardiopulmonary bypass (CPB), and this condition can only be diagnosed via serum creatinine level (sCr) conventionally within 48 hours. Therefore, we need early novel diagnosis biomarkers to start preventive treatment of ARF. For that reason, we aimed to analyze if plasma miR-21 derived from heart, correlates with kidney-enriched miR-10a during inflammatory IL-6, IL-1β, and TNF-α response in terms of acute renal failure 30 minutes after CPB.

Methods: Patients (n=46, Female:8 and Male:38), aged 61.08±9.41, who underwent CPB surgery were included. Blood samples were collected during the pre – and post-CPB (30 minutes after CPB). Demographic data of all cases were collected. Quantification of expression levels of miR-21 and miR-10a was done via quantitative PCR (qPCR). Determination of plasma concentration of relevant cytokines, IL-6, IL-1β, and TNF-α was done via ELISA.

Results: The circulating level of miR-21 during post-CPB period (-11.78±6.98) was significantly higher ($p \leq 0.05$) than pre-CPB period (-6.55±7.11), but there was no significant change ($p > 0.05$) in the circulating level of miR-10a between pre – (-12.22±3.55) and post-CPB (-11.60±3.36) periods. When we compared the mean ΔΔCt values of miR-21 and miR-10a, downregulation was observed in the expression level of miR-10a (0.62±3.77) whilst the expression level of miR-21 (-5.22±7.25) was upregulated ($p \leq 0.05$). The levels of plasma concentration of IL-6 (2.74±2.50 ng/l) and TNF-α (83.63±9.33 ng/l) were increased during post-CPB period (both were ***$p < 0.0001$). Whilst, IL-1β concentration level during pre-CPB period (3.95±0.47 ng/l) was found to be decreased (0.38±2.04 ng/l and *$p < 0.05$) according to post-CPB.

Conclusion: Prospectively, these data suggests that high miR-21 levels is a promising indicator and can be a candidate as an early novel biomarker for diagnosis of acute renal failure 30 minutes after CPB.

Keywords: MiR-21, miR-10a, biomarker, cardiopulmonary bypass, cytokines, inflammation, renal dysfunction

1. INTRODUCTION

Acute renal failure (ARF) is manifested by acute tubular necrosis of the renal tissue in 45% of hospitalized patients after operations done with CPB (1). If individuals with pre-existing renal failure are exposed to CPB, these patients need dialysis as a result of chronic renal failure (2). Renal failure is a complex syndrome and can be diagnosed via conventionally used method which is the increase in serum creatinine level (3). Acute renal failure that may develop after CPB, can be diagnosed 48 hours after the onset of damage (4). Therefore, serum creatinine level is not sufficient as a clinical early diagnosis biomarker (5). On the other hand, it has been suggested that acute inflammation is one of the triggering factors of damage that causes acute renal failure (6). During CPB, inflammation is triggered due to the reactions that occur as a result of the contact of blood with unknown surfaces (7). In these reactions, inflammatory mediators like cytokines are involved and the promotion of IL-6, IL-1β, and TNF-α (8). How inflammation after CPB links to organ failure remains unknown.

Under normal conditions, during the controlled up-regulation of miR-21 in cardiac tissue, it acts as a protective factor. Excessive up-regulation of miR-21 leads to tissue damage. These two opposing effects of miR-21 lead to its definition as a “double-edged sword” in the literature. It has been shown that cardiac MiR-21 is up-regulated through IL-6 release

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depending on the severity of inflammation and exacerbates tissue fibrosis, leading to chronic renal damage (9, 10).

MiR-10a is down-regulated due to inflammation. Thus, it has been known as a negative regulator of proinflammatory cytokines. Moreover, the downregulation of miR-10a is mediated via IL-1β, and TNF-α cytokines. MiR-10a-mediated activation of NF-kB stimulates the production of many cytokines (11, 12).

To the best of our knowledge there has been no association shown between several cytokines, miR-21 and miR-10a renal failure shortly after CPB. Possible inflammatory pathway regulated by IL-6, IL-1β, and TNF-α may cause renal failure after CPB is shown in Figure 1.

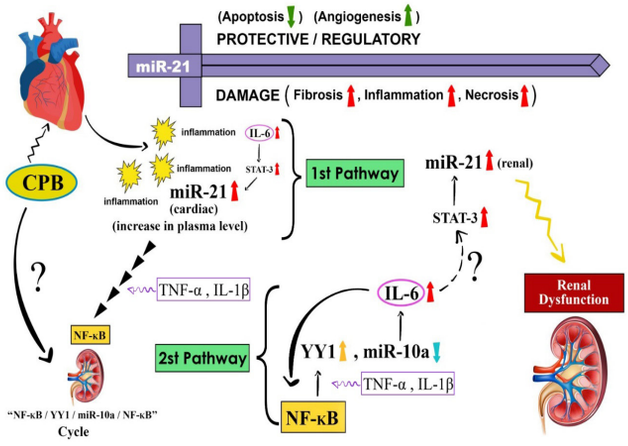

Figure 1. *Possible renal dysfunction biomarkers in patients after CPB; possible biochemical mechanism of miR-21 and miR-10a mediated postoperative inflammation. This figure is drawn by Çağıl F.Z.*

We illustrated that in the heart tissue during post-CPB period, miR-21 is excessively upregulated and released into the blood circulation and reaches kidneys where blood is being filtered. And it initiates the miR-10a / NF-kB cycle and cytokine release in renal tissue. We hypothesized that the trigger/initiator of this damaging mechanism could be miR-21 (1st pathway in Figure 1). In addition, the downregulation of miR-10a in renal tubules is mediated via IL-1β and TNF-α and induces IL-6 release. The increase in the level of IL-6 may also increase the level of renal miR-21. Together with the cardiac miR-21, this cycle becomes a continuous damaging mechanism (2nd pathway in Figure 1). For that reason, we studied plasma miR-21, miR-10a, IL-6, IL-1β, and TNF-α expressions for acute renal failure 30 minutes post CPB.

2. METHODS

2.1. Study Population and Design

Research Ethics Committee Approval is obtained from Marmara University (Protocol Number: 09.2019.859). All participants have been informed consents. All patients (n=46, Female:8 and Male:38), aged between 52 and 70 61.08±9.41, who underwent elective CPB surgery at Marmara University, Pendik Research and Training Hospital, School of Medicine, Cardiovascular Surgery Department between the dates 08/16/2021 and 11/15/2021 were included in the study. Patients who had abnormal pre-operative serum cardiac troponin (cTnI) values, patients applied heparin pre-operatively, and cases with combined heart surgery were not included in the research.

2.2. Collection of Blood Samples for Cytokine Analysis

To determine concentration levels of cytokines; 5 mL of blood samples were collected into vacuum tubes containing 3.2 % sodium citrate (BD Vacutainer) during pre – and post-CPB period. The blood samples taken were centrifuged at 2500 *rpm* for 20 minutes at 4 °C. Plasma samples were put in tubes as 500 µL aliquots. Then, aliquots were stored at – 80 °C for further use of downstream reactions.

2.3. Determination of Cytokine Level via ELISA

IL-6, IL-1β, TNF-α levels were measured via commercially available sandwich ELISA Kits (Catalog numbers are EK710267, EK710260, EK710127, respectively) (AFG Scientific, Northbrook, IL). Each sample was run in duplicate. Wash buffer was prepared. Wash buffer was warmed to get rid of crystals in the concentrate. Standard solution was diluted. Citrate treated plasma was thawed. 50 µL of standard was put in each well. Then, sample diluent was added in each well. After that 10 µL of sample was pipetted in wells in duplicates. All wells are covered and incubated for 30 min at 37°C. All wells are washed with wash buffer 5 times. Then, HRP-Conjugate reagent added in each well, except blank well. All wells are covered and incubated for 30 min at 37°C. All wells are washed with wash buffer 5 times. Color reaction was done with 50 µL of Chromogen Solution A and 50 µL of Chromogen Solution B to each well. At this step wells are avoided light and kept for 15 min at 37°C. Stop reaction was done via 50 µL of stop solution. Color change was obtained from blue to yellow. Plasma concentration of cytokines was measured at a wavelength of 450 nm absorbance via ELISA Reader, (Rayto Rt-2100c).

2.4. Collection of Blood Samples for Quantification of miR-21 and miR-10a

5 mL of blood samples were collected into vacuum tubes containing K2 EDTA 7.2 mg (BD Vacutainer). The blood samples were centrifuged at 2500 *rpm* for 20 minutes at 4 °C. Plasma samples were put in aliquots as 500 µL. Then, stored at – 80 °C for further use of downstream reactions.

2.5. Quantification of miR-21 and miR-10a via qRT-PCR

2.5.1. RNA Isolation

Total RNA was extracted from 500 µl EDTA treated plasma samples using 1000 µL Trizol-TRI Reagent according to the manufacturer's instructions (Merck/Sigma Aldrich). The RNA

was stored at – 80 °C for later analysis. The purity of RNA was assessed according to 260/280 ratio of absorbance value using the NanoDrop 2000 Spectrophotometer. The RNA concentration was calculated by multiplying the absorbance value and multiplying the RNA coefficient and the dilution coefficient:

RNA concentration (µg/mL) = OD at 260 nm x CC x 40 µg/mL

where: OD = optical density, nm = nanometer, CC = coefficiency coefficient, and an absorbance of 1 Unit at 260 nm corresponds to 40 µg of RNA per mL (A260 = 1 = 40 µg/mL).

2.5.2. Reverse transcription and quantification of miR-21 and miR-10a via qRT-PCR

Complementary DNA (cDNA) synthesis from total RNA was performed using the miRNA All-In-One cDNA Synthesis Kit (AbmGood, Catalog No: G898) according to the manufacturer's protocol. Sequences of primers are listed in Table 1. Expression of miR-21 and miR-10a were obtained as cycle threshold (Ct) values. All samples were run in duplicates. Mean values of Ct values were used for the calculation. The expression difference between pre-operative and post-operative mean ΔΔCT values was calculated as Mean of [ΔΔCT=ΔCT (a miRNA of post-CPB (30 minutes after CPB))-ΔCT (miRNA of pre-CPB as a normalizer accounting for sample to sample variation)]. To analyze the relative expression of miR-21 and miR-10a the fold change (relative quantification) was calculated via the $2^{-\Delta\Delta CT}$ formula (13).

Table 1. *Primer sequences designed specifically for miR-21 and miR-10a*

Primer	5'-3' primer sequence
hsa-miR-21-5p (Forward)	*GCAACCGGTAGCTTATCAGACTGATGT*
hsa-miR-10a-5p (Forward)	*GCAACCACTTACCCTGTAGATCCGAAT*
Universal Revers primer	*CAGTGCAGGGTCCGAGGTCAGAGCCACCT*

2.6. Statistical Analysis

The GraphPad Prism 5.0 software (GraphPad, San Diego, CA) was used for statistical analysis. The student's t-test was used to compare the mean values of groups. Non-parametric comparisons were done using the Mann-Whitney u test. Descriptive results of continuous variables are expressed as mean ±SE. Pearson correlation analysis was used to analyze the relation of miR-21 and miR-10a expression levels with IL-6, TNF-α, and IL-1β. Statistical differences between the pre-operative period and the postoperative period were analyzed. p ≤0.05 level was considered as statistically significant.

3. RESULTS

Clinical and demographic parameters are given in Table 2. The number of male cases (n=38) was higher than females (n=8). There was no significant difference between the ages of males and females (p>0.05). The mean body mass index was slightly higher in females when compared to males (p>0.05). No significant differences were found in serum creatinine level, e-GFR, CPB period, period of hospitalization, and period of ICU between the pre-op and post-op (p>0.05).

Table 2. *Clinical and demographic parameters of the study population.*

	Total Patient	Female	Male	p value
Sex (Female/ Male)	n:46	n:8	n:38	
Age (Years)	61.08±9.41	66.25±13.55	60.0±7.86	p>0.05
BMI (kg/m^2)	27.55±1.50	28.22±1.01	27.40±0.05	p>0.05
Pre-op e-GFR (ml/min)	111.82±21.52	123.5±11.52	109.36±22.32	p>0.05
Post-op e-GFR (ml/min)	107.91±23.09	119.75±13.89	105.42±23.85	p>0.05
Serum Creatinine (mg/dL)	1.07±0.43	1.03±0.31	1.08±0.44	p>0.05
CPB Duration (min)	167.65±19.61	165.0±25.98	168.21±17.94	p>0.05
Duration of Hospitalization (Days)	3.78±0.65	4.0±0.70	3.73±0.63	p>0.05
Duration of ICU (Days)	1.56±0.64	1.25±0.43	1.63±0.66	p>0.05

The values are expressed as mean ± SE. Parametric comparisons were done using the student's t-test and non-parametric comparisons were done using the Mann-Whitney u test. BMI: Body mass index, e-GFR: Estimated glomerular filtration rate, CPB: Cardiopulmonary bypass, ICU: Intensive care unit.

In the comparisons between the pre-op and post-op 30 minute after CPB we evaluated the post-op level of IL-6 (7.15±2.08 ng/L) was found to be significantly higher than the pre-op (2.74±2.50 ng/L) (***p<0.0001) (Figure 2).

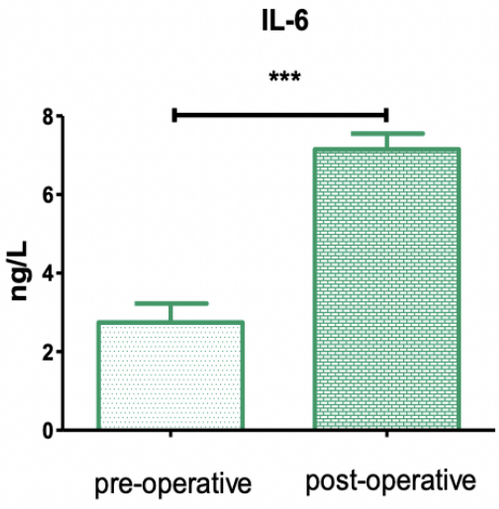

Figure 2. *The levels of plasma concentration of IL-6 during the pre-operative and the post-operative CPB (***p<0.0001).*

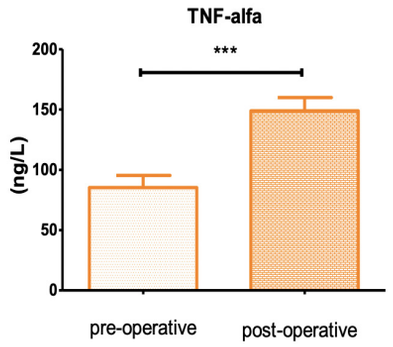

Figure 3. *The levels of plasma concentration of TNF-α during the pre-operative and the post-operative CPB (***p<0.0001).*

Likewise, TNF-α during the post-op (150.67±14.57 ng/L) was found to be significantly higher than the pre-op (83.63±9.33 ng/L) (***p<0.0001) (Figure 3). On the other hand, pre-op level of IL-1β (3.95±0.47 ng/L) significantly decreased during the post-op (0.38±2.04 ng/L and *p<0.05) (Figure 4).

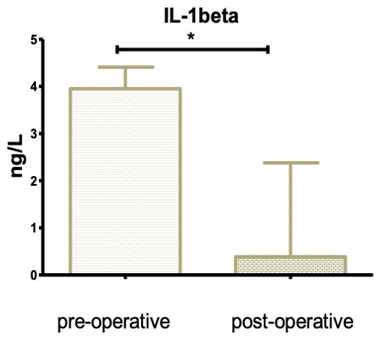

Figure 4. *The levels of plasma concentration of IL-1ß during the pre-operative and the post-operative CPB (*p<0.05).*

The mean ΔCt values of miR-21 expression levels in the pre-op (-6.55±7.11) and post-op (-11.78±6.98) periods of 46 patients who underwent Cardiopulmonary Bypass were compared, it was found that miR-21 expression significantly increased in the post-op (-11.78±6.98) (*p≤0.05) (Figure 5a).

When the mean ΔCt values of miR-10a expression levels in the pre-op (-12.22±3.55) and post-op (-11.60±3.36) periods were compared. This value was not found to be statistically significant (p>0.05) (Figure 5b).

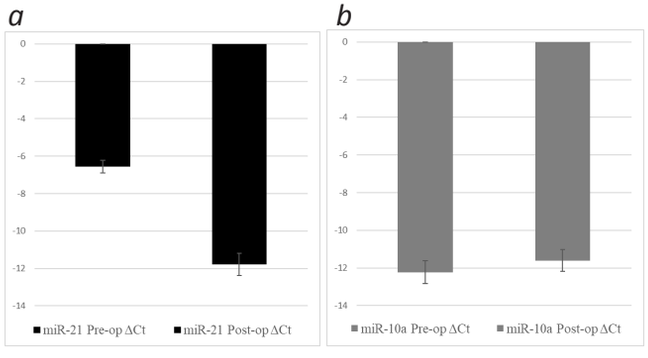

Figure 5.Expression *levels of pre-operative and post-operative total miR-21 mean ΔCt values (a) and expression levels of pre-operative and post-operative total miR-10a mean ΔCt values (b).*

When we compared the mean ΔΔCt values of miR-21 and miR-10a, downregulation was observed in the expression level of miR-10a (0.62±3.77) whilst the expression level of miR-21 was up-regulated (-5.22±7.25) (*p≤0.05) (Figure 6).

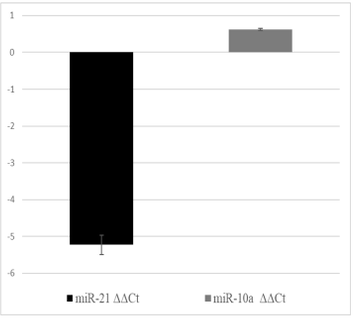

Figure 6. *Difference in expression levels of total miR-21 and miR-10a mean ΔΔCt (PostΔCt-PreΔCt) values.*

After the comparison of the mean pre-op and post-op ΔC_T values of miR-21 and miR-10a, we calculated the fold change or relative quantification as $2^{-\Delta\Delta CT}$. No significant downregulation was observed in the expression level of miR-10a (4.11±6.81) whilst the expression level of miR-21 was excessively up-regulated (27981.70±101673.90) (*p≤0.05) (Figure 7).

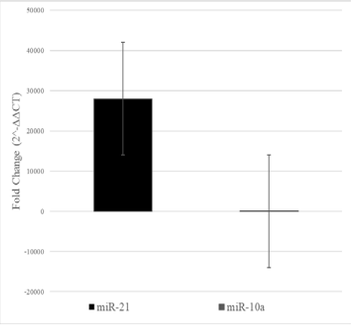

Figure 7. *The fold change and relative quantification (2 – ΔΔCT) of total miR-21 and miR-10a between pre-operative and post-operative (30 minutes after CPB) periods.*

After the full analysis of correlations between all the cytokines and miRNAs, those showing a significant (p<0.05) positive or negative correlation is given in Table 3. Pre-op IL-6 showed a high positive correlation with both post-op IL-6 and post-op IL-1β whereas it moderately correlated with pre-op miR-10a and showed low negative correlation with pre-op miR-21. None of the variables showed high correlation with eachother during the post-op period. Yet, post-op IL-6 showed low negative correlation with post-op miR-10a, low positive correlation with post-op miR-21, and moderate positive correlation with IL-1β. Also, post-op miR-21 showed moderate negative correlation with post-op miR-10a. Also, pre-op TNF-α exhibited a high positive correlation only with post-op TNF-α. Post-op TNF-α showed low negative correlation with post-op miR-21. Pre-op IL-1β was found to be negatively correlated with post-op TNF-α. Pre-op miR-21 showed a high positive correlation with post-op miR-21 and high negative correlation with pre-op miR-10a whereas it showed negative correlation with post-op miR-10a.

Table 3. *Pearson correlation between pre-operative and post-operative plasma concentrations of IL-6, TNF-α, IL-1β, and expression levels miR-21 and miR-10a. In each row, r represents correlation coefficient and p represents p value. Significant correlations are shown in bold.*

		IL-6 Pre-op	IL-6 Post-op	TNF-α Pre-op	TNF-α Post-op	IL-1β Pre-op	IL-1β Post-op	miR-21 Pre-op	miR-21 Post-op	miR-10a Pre-op	miR-10a Post-op
IL-6 Pre-op	r		0,742	0,126	-0,043	0,205	0,587	-0,202	-0,078	0,416	0,115
	p	1	**0,0001**	0,5957	0,8546	0,3844	**0,0065**	0,392	0,7423	0,0678	0,6281
IL-6 Post-op	r	0,742		-0,068	-0,093	0,293	0,407	-0,240	0,103	0,291	-0,113
	p	**0,0001**	1	0,7744	0,6951	0,2095	0,0747	0,3074	0,6648	0,2131	0,6337
TNF-α Pre-op	r	0,126	-0,068		0,705	-0,223	0,009	-0,147	-0,325	0,234	0,106
	p	0,5957	0,7744	1	**0,0005**	0,3444	0,9680	0,5340	0,1616	0,3201	0,6538
TNF-α Post-op	r	-0,043	-0,093	0,705		-0,447	-0,090	-0,233	-0,212	0,038	0,221
	p	0,8546	0,6951	**0,0005**	1	**0,0478**	0,7051	0,3213	0,3687	0,8713	0,3477
IL-1β Pre-op	r	0,205	0,293	-0,223	-0,447		0,387	0,052	0,085	0,030	0,218
	p	0,3844	0,2095	0,3444	**0,0478**	1	0,0909	0,8269	0,7192	0,8980	0,3555
IL-1β Post-op	r	0,587	0,407	0,009	-0,090	0,387		-0,043	0,037	0,077	0,214
	p	**0,0065**	0,0747	0,9680	0,7051	0,0909	1	0,8551	0,8761	0,7457	0,3634
miR-21 Pre-op	r	-0,202	-0,240	-0,147	-0,233	0,052	-0,043		0,523	-0,648	-0,451
	p	0,3929	0,3074	0,5340	0,3213	0,8269	0,8551	1	**0,0179**	**0,0019**	**0,0457**
miR-21 Post-op	r	-0,078	0,103	-0,325	-0,212	0,085	0,037	0,523		-0,186	-0,311
	p	0,7423	0,6648	0,1616	0,3687	0,7192	0,8761	**0,0179**	1	0,4308	0,1813
miR-10a Pre-op	r	0,416	0,291	0,234	0,038	0,030	0,077	-0,648	-0,186		0,163
	p	0,0678	0,2131	0,3201	0,8713	0,8980	0,7457	**0,0019**	0,4308	1	0,4899
miR-10a Post-op	r	0,115	-0,113	0,106	0,221	0,218	0,214	-0,451	-0,311	0,163	
	p	0,6281	0,6337	0,6538	0,3477	0,3555	0,3634	**0,0457**	0,1813	0,4899	1

4. DISCUSSION

Acute renal failure (ARF) prevalence is high among patients who undergo CPB (13). This condition can only be diagnosed via serum creatinine level (sCr) conventionally within 48 hours (14). Therefore, we need early novel diagnosis biomarkers to start preventive treatment of ARF before 48 hours (15). Inflammation mediated post-op consequences like ARF are caused by the contact of the blood with unknown surfaces (16). Recent studies point out a promising role for circulatory miRNAs in inflammation related unfavorable outcomes (17). Present study focused on inflammation induced cardio-renal biochemical pathway to quantify expression patterns of miR-21 and miR-10a during inflammatory response by IL-6, TNF-α, and IL-1β 30 minutes after CPB. Where the roles of miR-21 and miR-10a together or separately link to ARF in inflammatory pathway needs to be clarified. In our data, inflammatory IL-6 and TNF-α were found to be increased (***p<0.0001) shortly after CPB. Also, the ΔΔCT values (*p≤0.05) and fold change (*p≤0.05) manifested that post-op expression level of miR-21 was highly up-regulated. It has been reported that expression of miR-21 is excessively up-regulated and positively correlated with renal failure due to the increase of inflammatory IL-6 (18). Also, miR-21 expression was up-regulated in human renal epithelial cells when treated with different concentrations of TNF-α both in vitro and in vivo (19). Previous study done by X. Xu and A. J. Kriegel et. al. on the increase of IL-6 promoting excessive up-regulation of miR-21 demonstrated miR-21 as a damaging agent on renal tissue (9). IL-6, TNF-α are the most abundant inflammatory mediators in inflamed tissue (20). Thus, according to our data we demonstrated increased plasma levels of IL-6, TNF-α are primarily involved in inflammatory response 30 minutes after CPB. As we hypothesized, we have shown CPB-related inflammatory cytokines IL-6 and TNF-α excessively increase up-regulation of miR-21 shortly after CPB in vivo.

On the other hand, the post-op IL-1β was decreased (*p≤0.05). CPB is a complex operative application in which many cardio-renal biochemical pathways cross (21). The effect mechanism of cytokines is intracellular (22). Literature manifests that normally myostatin, also a cytokine, is over-expressed into the circulation by pathological heart tissue, it positively correlates with IL-1β increase. Previous study has shown that treatment of heart tissue cells with miR-21 mimic, prevented myostatin-induced increase of IL-1β (23). Our study supported the literature that there is a negative correlation between miR-21 and IL-1β concentration shortly after CPB. Thus, we propose the excessive up-regulation of miR-21 may have decreased the concentration level of IL-1β via over-expression of myostatin after CPB. Post-op miR-10a didn't change significantly and the fold change of miR-10a seems invisible compared to miR-21. However, the ΔΔCT values showed that miR-10a was down regulated (0.62±3.77) shortly after CPB. MiR-10a is mediated in renal tubules as the negative key regulator of cytokines (24). The intensity of down-regulation is mediated by TNF-α and IL-1β together (11). We think that the decrease in post-op IL-1β may cause low intensity of miR-10a down-regulation shortly after CPB. We hypothesized that after CPB, inflammation-related excessive release of miR-21 into circulation triggers down-regulation of miR-10a in renal tissue. Our data showed

that intensity of down-regulation of miR-10a has been suppressed due to the decrease of post-op IL-1β via CPB induced excessive expression of miR-21.

Additionally, despite not significant, miR-10a showed high positive correlation with IL-6 during pre-op period and low negative correlation during post-op period. The rate of IL-6 release depends on the down-regulation level of miR-10a (25). MiR-10a has been extensively reported on various tumor types (26). While miR-10a is positively correlated with advanced tumor, it negatively correlated with distant metastasis. It has been discussed that the heterogeneity of tumor cells may be the cause of different roles of miR-10a in tumor progression (27). We suggest that different correlation patterns of miR-10a and IL-6 in disease progression should be considered for future studies.

In addition, the release of IL-6, TNF-α, and IL-1β release during extracorporeal circulation like CPB is conflicting (28). There are many responsible possible reasons for such conflicting data (29). First is the mean period of CPB. In our study, the mean period of CPB was as twice longer than the previous study (30). Therefore, the longer contact of the blood with extracorporeal surfaces, the higher levels of primary cytokines shortly after CPB. Second, hypothermic CPB has been discussed to decrease some cytokines to a greater extent (31). Third, hemofiltration is being used to reduce the effects of inflammatory response during CPB (32). These factors may cause different levels of cytokine patterns after CPB. Hence, the contradictory release of IL-1β and TNF-α in the biochemical pathways after CPB needs clarification via further studies.

According to *Pearson* correlation coefficient analysis, no significant correlation has been found between cytokines and miRNAs after CPB. We quantified miR-21 and miR-10a based on total RNA. At this point we suggest that exosomal miR-21 and miR-10a may contribute a considerable amount of miRNA in the results (33). We believe that a significant correlation could be possible via expanding the data with exosomal miRNA isolation in the future studies. Previous findings on IL-6-induced excessive expression of miR-21 has been demonstrated as a damaging mechanism in renal tissue (34). Therefore, post-op miR-21 may be a reliable target in inflammation related renal tissue failure. Some studies manifested the protective role of miR-21 (35), whilst miR-21 is a comprehensively studied microRNA on renal disease progression (36). In one study done with nephropathy patients demonstrated glomerular filtration rate negatively correlated with urinary levels of miR-21. Up-regulation of urinary exosomal miR-21 has been showed to be a potential non-invasive biomarker for chronic kidney disease (37). Even though, back in 2008 Ronco et. al. addressed that heart and kidney dysfunction coexist as a result of systemic inflammatory pathway (38), Huang et. al. also recently discussed cardio-renal syndromes in relation with miR-21 (39). In the light of previous studies it has been demonstrated that miR-21 may cause renal failure. Underlying biochemical pathway needs to be clarified. Report by Glowacki et al. demonstrates that miR-21 has a central role and may represent a novel and predictive blood marker of kidney fibrosis (40). In that study, up-regulation of miR-21 was observed at day 4 with the disease progression. Also, their sample collection was based on renal tissue samples and serum. In our study, we quantified circulating high levels of miR-21 in plasma 30 minutes after CPB and shown that IL-6 and TNF-α trigger excessive up-regulation of miR-21. At the same time, we suggest that miR-21 induced post-op suppression of miR-10a pathway is also regulated via IL-1β. Hence, we suggest miR-21 and miR-10a to be non-invasive early diagnosis biomarker to detect acute renal failure 30 minutes after CPB. Our study includes supporting data for future studies.

There are some limitations to our study as the sample size was small. Therefore, larger cohort studies are needed. Moreover, due to Covid-19 restrictions we could not follow up the patients if they developed ARF after hospitalization. Findings of the present study is preliminary to illuminate the biochemical pathway between inflammatory cytokines, miR-21, and miR-10a on the way to ARF. We suggest this data to be considered for future studies. As we hypothesized, our study prospectively demonstrates for the first time that how post-CPB inflammation through IL-6 and TNF-α triggers excessive up-regulation of miR-21 and how suppression of miR-10a in this biochemical pathway being operated via miR-21 induced decrease of post-op IL-1β in vivo.

5. CONCLUSION

Prospectively, these data suggests that high miR-21 levels is a promising indicator and can be a candidate as an early novel biomarker for diagnosis of acute renal failure 30 minutes after CPB.

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Design of the study: FZÇ, ŞT
Acquisition of data for the study: FZÇ, GÖ, KA, AS
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Clinical and Experimental Health Sciences

Possible Anti-Obesity Role of Flavonoids Through Brown Adipose Tissue

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ABSTRACT

Worldwide, the incidence of overweight and obesity is increasing day by day, and this makes the control of body weight and complications a primary health problem. Weight loss diet therapy has long been a primary role in the prevention and management of obesity. Evidence supporting the specific anti-obesity effects of certain nutrient components, in particular, polyphenolic compounds, are increasing, as well as a strategy to limit energy intake to achieve control of body weight. Active brown adipose tissue in adult individuals is gaining interest as a new and feasible target for controlling body weight by triggering and increasing energy expenditure. Flavonoids are one of the polyphenolic compounds that draw attention by regulating non-shivering thermogenesis. Although each flavonoid has its health benefits; many phytochemical compounds classified as flavonoids have an anti-obesity effect by regulating oxidation, synthesis, uptake, and transport of fatty acids. In this study, current studies on the therapeutic effect of flavonoids on obesity by regulating energy expenditure through various mechanisms of action in brown adipose tissue are reviewed.

Keywords: Flavonoids; brown adipose tissue; obesity; thermogenesis.

1. INTRODUCTION

Obesity is defined as abnormal or excessive fat accumulation that presents a health risk, and a body mass index (BMI) above 30 kg/m^2 is classified as to have obesity. According to this criterion, the World Health Organization (WHO) states that 13% of the adult population in theworld has obesity and that obesity and its complications are one of the most difficult public health problems (1). Although energy restriction is the best-known dietary intervention to reduce the prevalence of obesity, potential anti-obesity effects of bioactive or functional food components such as polyphenols are also discussed (2-4).

Flavonoids are plant pigments groups that are responsible for the colors in many fruits and flowers. Flavonoids, estimated to be over 4000, are abundant in tea, apples, onions, legumes, tomatoes and red wine. In various studies, it is stated that besides the antioxidant properties offlavonoids, they have anti-obesity, anti-inflammatory, antiviral, anti-allergic, antithrombotic and other functions (5-8).

The discovery of the presence of brown adipose tissue (BAT) in neonates and adult individuals has led to an increase in research into the development of a new therapeutic approach to fighting obesity (9). Increasing energy expenditure with BAT activation is thought to be promising for the control of obesity (10). BAT's capacity to influence energy expenditure is based on the ability to dissipate energy as heat and depends on the expression of the uncoupling protein-1 (UCP-1) in brown adipocytes. UCP-1 separates the electron transport system (ETS) from ATP synthesis, thus dissipating energy (11). The presence of BAT in human tissue correlates negatively with BMI, body fat mass percentage, and plasma glucose (12-14).

This review presents a critical review of the literature describing the possible role of flavonoids in therapeutic strategies against obesity through BAT activation and browning.

In this review, studies included in the databases Pubmed, Science Direct, Web of Science, and Google Scholar were

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evaluated, which were performed until December 2021 with no time limitation. In vivo and in vitro studies written in English, and review articles about flavonoids and obesity are included in the study. A comprehensive study was carried out by two researchers. For flavonoids the keywords 'flavonoids', 'flavones', 'flavonols', 'flavanones', 'flavanols', 'anthocyanins', 'isoflavones', and for anti-obesity role the keywords 'brown adipose tissue', 'brown adipose tissue mechanism of action', 'browning', 'obesity', 'thermogenesis', 'non-shivering thermogenesis', and 'uncoupling protein-1' were scanned by using the conjunctions 'AND' and 'OR'. Titles of the articles were reviewed, and the first elimination was performed during the article evaluation process according to our specific subject. After that, abstracts were reviewed, and the articles eliminated were either included in the study over full text or excluded.

1.1. Properties of Adipose Tissue

Adipose tissue has an important role in regulating biological functions and especially energy metabolism with the enzyme, cytokine, growth factor and hormones it secretes. Adipocytes are made by lipoblasts differentiating from mesenchymal cells. Lipoblasts are transformed into two different adipose tissues, namely white adipose tissue (WAT) and BAT, with different functions and morphology in mammals (15, 16). Respectively, storing energy and preventing hypothermia are the main tasks of these tissues (17). In addition to WAT and BAT, the third type of adipose tissue called 'beige' has recently been identified. Adipocytes in the stores of beige adipose tissue (BeAT) are similar to white adipocytes but have the classic features of brown adipocytes (18, 19). The transformation of WAT into BAT, that is, the formation of BeAT, occurs as a result of increased expression of the UCP-1 pump in WAT cells via the irisin hormone stimulated by exercise and cold. WAT cells with increased UCP-1 pump in their mitochondria are referred to as BeAT. These cells work like BAT cells. Increased UCP-1 expression inhibits ATP synthesis, and heat production, which causes energy consumption in the cell, to increase, providing thermogenesis and glucose homeostasis (20-22). The characteristics of WAT, BAT, and BeAT are summarized in Table 1 (23, 24).

Table 1. *General characteristics of white, brown and beige adipose tissue*

	White Adipose Tissue (WAT*)	Brown Adipose Tissue (BAT*)	Beige Adipose Tissue (BeAT*)
Location	**Visceral WAT:** Around the organs (mesenteric, omental, perigonadal and retroperitoneal) **Subcutaneous WAT:** Inguinal, intramuscular	Interscapular, perirenal	Neck and supraclavicular region
Morphology	Unilocular/Large lipid droplets	Multilocular/Small lipid droplets	Unilocular, large/multiple small lipid droplets
Lipid content	Single large droplet covering 90% of cell volume	Multiple small lipid droplets	Uncertain
Function	Energy storage Endocrine organ	Heat production	Adaptive thermogenesis
Mitochondria number	+	+++	++
UCP-1	-	+++	++
Vascularization	Few	Abundant	Uncertain
Obesity	Positive	Negative	Negative
Insulin resistance	Positive	Negative	Negative
Activators	High-fat diet	Cold, thyroid hormone, thiazolidinediones, FGF21*, BMP7*, BMP8b*, natriuretic peptide	Cold, thiazolidinediones, a natriuretic peptide, FGF21*, irisin, catecholamines, β-adrenergic receptor agonists

** BAT; brown adipose tissue, BeAT; beige adipose tissue, BMP7; bone morphogenetic protein 7, BMP8b; bone morphogenetic protein 8b, FGF21; fibroblast growth factor 21, UCP-1; uncoupling protein-1, WAT; white adipose tissue.*

1.2. Effect Mechanism of Brown Adipose Tissue

Brown adipose tissue has a negative correlation with BMI, fat mass percentage and plasma glucose. It contributes to energy expenditure by using energy as heat energy. This effect is due to UCP-1 expression in BAT. UCP-1, which is capable of separating ATP production from mitochondrial respiration, dissipates large amounts of stored energy as heat by allowing protons to re-enter the matrix (25).

Norepinephrine is released near the postganglionic nerve endings in BAT to increase activation of the sympathetic nervous system and situations requiring increased body temperature (26). Norepinephrine binds to the b3-adrenergic receptor (b3AR) on the surface of brown adipocytes.

Binding to b3AR provides cyclic AMP (cAMP) to be produced by adenylate cyclase. Increasedintracellular cAMP concentrations activate hormone-sensitive lipase (HSL) and protein kinase A (PKA) which phosphorylated perilipin to promote triglyceride hydrolysis. Then the releasedfree fatty acids (FFAs) are opened to the mitochondria via carnitine palmitoyltransferase-1 (CPT-1). In mitochondria, FFAs activate UCP-1 and fatty acid oxidation produce cofactors forETS. UCP-1 uses the proton gradient generated by ETS to produce heat and thus dissipates energy (27, 28).

In parallel with the direct activation of thermogenesis, norepinephrine stimulation leads to transcriptional regulation of genes important for thermogenesis, that is, the induction of the "thermogenic program". The activated PKA also activates cAMP response element-binding protein (CREB) and p38 mitogen-activated protein kinase by phosphorylating the transcription factor. Respectively, the p38 mitogen-activated protein kinase phosphorylates transcription factors such as activating transcription factor 2 or transcriptional coactivator PPAR-g coactivator 1a (PGC-1a) to induce UCP-1 expression. Phosphorylated CREB enhances transcription of type 2 iodothyronine deiodinase, which converts inactive tetraiodothyronine to triiodothyronine (T3), which promotes binding of T3 receptor. When the receptor is not bound to T3, it acts as a UCP-1 transcriptional suppressor. Therefore, T3 indirectly increases UCP-1 expression (Figure 1) (27, 29, 30).

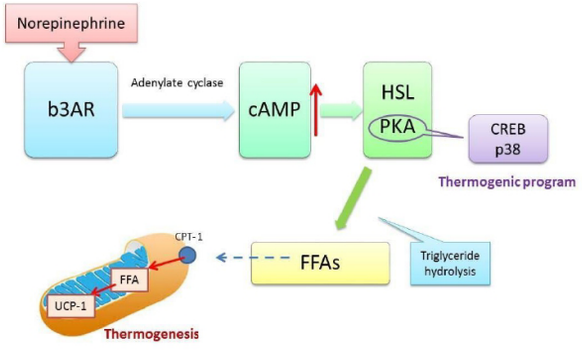

Figure. 1. *Brown adipose tissue's effect mechanism. b3AR; b3-adrenergic receptor, cAMP; cyclic AMP, HSL; hormone-sensitive lipase, PKA; protein kinase A, CREB; cAMP response element-binding protein, p38; p38 mitogen – activated protein kinase, FFAs; free fatty acids, CPT – 1; carnitine palmitoyltransferase-1, UCP-1; uncoupling protein-1.*

White adipocytes are highly sensitive to norepinephrine. It stimulates lipolysis through norepinephrine-like intracellular signaling events, thereby promoting the release of FFA, which is used as energetic substrates in BAT to maintain thermogenesis (27). In particular, it causes UCP-1 activation called "beige" or "brite" in subcutaneous and retroperitoneal stores in WAT(31). Beige adipocyte loss has been shown to cause obesity, but increasing the amount of beigeadipocyte in WAT may compensate for the thermogenic activity of descending BAT (24, 32). However, the increase in the amount of UCP-1 and adipocytes in human WAT is still highly debated and conflicting results have been reported (33, 34).

1.3. Flavonoids

Flavonoids are a group of plant pigments that are responsible for the colors in many fruits and flowers. They took 'flavonoid' name because they are yellow derived from 'flavus' which means yellow in Latin. They have 2-phenyl benzopyrone (diphenyl propane) structure of 15 carbon atoms (C6-C3-C6). Various flavonoids are formed by binding – OH groups to different carbons in the phenyl benzopyrone structure (35). Flavonoids, estimated to be over 4000, are abundant in tea, apples, onions, legumes, tomatoes and red wine. Flavonoids are composed of six subgroups; Flavones, Flavonols, Flavanones, Flavanols, Anthocyanins, and Isoflavones (35, 36).

The family of flavonoids has been shown to indicate some pharmacological activities that exhibit antioxidant, anti-inflammatory, anti-obesity, anti-carcinogenic, anti-diabetic, anti – allergic, anti-tumor properties (6, 8). While these properties may explain the success of some herbal medicines in the treatment of inflammatory and infectious diseases, their mechanism of action is often not fully understood (35, 37). The structural similarity between flavonoids, steroids and other cholesterol derivatives suggests that flavonoids may exert some of their effects through the nuclear receptor family. The random nature of the nuclear receptor ligand – binding domain is thought to facilitate direct transcriptional regulation of cells through the dietary intake of flavonoids (36).

1.4. Flavonoids and BAT Activation

The most studied species related to BAT activation from flavonoids are oligomers such as procyanidins (flavanol), catechins, epigallocatechin gallate (EGCG), theaflavins, quercetin. Activation of these flavonoid species on BAT is provided by biological pathways such as BAT thermogenesis, WAT browning, activation of the AMPK / SIRT1 / PGC-1α pathway, mitochondrial biogenesis, etc. (25).

Many mechanisms underlying the effects of flavonoids from dietary polyphenols on thermogenesis, lipid metabolism, and mitochondrial biogenesis. Selective activation of β3-AR leads to stimulation of lipolysis and thermogenesis; it provides the development of white-brown adipocyte phenotype in WAT. PKA then leads to increased lipolysis through HSL stimulation, a carrier enzyme for lipolysis. In conclusion, stimulation of PKA and HSL-mediated lipolysis causes increased mitochondrial respiration, in

fatty acids, proton's UCP-1-dependent mitochondrial entry and separation from ATP production. The stimulating effect of β3-AR on AMPK leads to activation of β-oxidation and provides to reduce lipid deposition. Provide full activation of PPAR ligands, including PPARα and PPARγ, is required (38-40). In particular, PPARα acts directly as the transcriptional master regulator of PGC1α gene transcription and plays a role in WAT browning, brown adipocyte determination, and function (41, 42). Induction of PPARγ ligand is a prerequisite for stimulated activation by stimulating the β-adrenergic receptor of brown adipocytes and also stimulates the formation of beige adipocytes in WAT. The coordination of all these processes results in increased thermogenic capacity and mitochondrial biogenesis, and it causes to browning of 3T3-L1 adipocytes. Furthermore, the B3-AR / PKA signaling pathway has been reported to stimulate the activation of p38 MAPK and the browning of white adipocytes, a target for PGC1α (Figure 2) (38, 43).

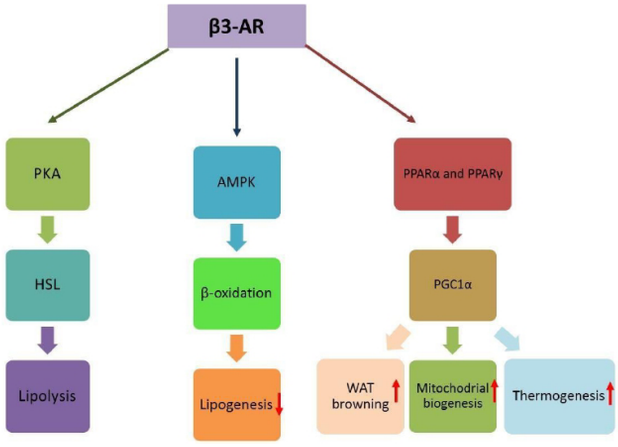

Figure. 2. *Flavonoids in BAT activation. ß3-AR; ß3-adrenergic receptor, PKA; protein kinase A, HSL; hormone-sensitive lipase, AMPK; AMP-activated protein kinase, PPARα; peroxisome proliferator-activated receptor – alpha, PPARγ; peroxisome proliferator – activated receptor gamma, PGC1α; peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, WAT; white adipose tissue.*

Besides, the efficacy of dietary flavonoids (e.g. flavan-3-ol, green tea catechins, quercetin, etc.) influences weight management by increasing BAT thermogenesis and provides white adipocyte browning. The different signaling pathways of BAT activation are effectively provided by forming different combinations of polyphenol subtypes in the diet. Mechanisms can act as a therapeutic task for stimulation of BAT thermogenesis, body weight loss and improved metabolic status. Therefore, diet modulation of brown and beige fat tissue development and metabolism is considered a promising target for the prevention and treatment of obesity (44).

1.4.1. Flavones

Flavone and flavone glycosides are light yellow compounds found in almost every plant formed by the coupling of the hydroxyl group to C3 atom. Flavones are much less common than other subclasses of flavonoids (45). Flavones are divided into various subgroups based on side chains attached to backbone molecules such as hydroxylation, methoxylation, isoprenylation and glycosylation (46). The major dietary sources of flavones are olives, extra virgin olive oil, essential oils derived from rosemary, parsley, celery, and citrus fruits. The main flavones are apigenin, luteolin, chrysin and tangeretin (47). Flavones are effective on BAT activation by increasing SIRT1, PGC1α, UCP-1, PRDM16 activation in white and beige adipose tissue (22, 48-51). In vitro studies in adipose cells, it has been reported that different flavon species (sudachitin; chrysin; luteolin) applied in various amounts (30 nM; 1-50 µM; 100 nM) increased UCP-1 secretion in adipose tissue, induced browning of white adipocytes through AMPK / SIRT1 / PGC-1α pathway activation (22, 48, 49). In studies in which animals are given high – fat diet and different flavon types, flavone groups' body weight, and fat percentage are reduced, WAT browning and, as a result, O2 consumption was found to increase (22, 48, 50). In Table 2, in vitro and in vivo studies related to the activity of flavones on BAT activation are summarized.

Table 2. *In vitro and in vivo studies on the effects of flavones on non-shivering thermogenesis*

Authors	Flavone Type	Study Group	Treatment	Result
Tsutsumi et al. 2014 (48)	Sudachitin	Primary myoblasts	30 nM	SIRT1*, PGC1α*, UCP-1* increase
Choi and Yun 2016 (49)	Chrysin	3T3-L1	1-50 µM	UCP-1, PGC1α, PRDM16*, FGF21* increase AMPK phosphorylation increase
Zhang et al. 2016 (22)	Luteolin	Primary adipocytes from BAT* and sWAT*	100 nM	UCP-1, PGC1αand SIRT1 increase AMPK* phosphorylation increase
Shen et al. 2014 (50)	Olive leaf extract (luteolin and apigenin)	C57BL/6N male mice	HFD* with 0.15% olive leaf extract 8 weeks	Body weight, fat percentage decrease Browning and mitochondrial biogenesis increase
Tsutsumi et al. 2014 (48)	Sudachitin	C57BL/6 and db/db mice	HFD with 5 mg/kg sudachitin 12 weeks	Body weight, fat percentage O2 consumption, and energy expenditure decrease UCP-1 in WAT* increase
Thaiss et al. 2016 (51)	Apigenin and naringenin	C57BL/6 male mice	80 mg/kg 2 weeks	UCP-1 in BAT increase
Zhang et al. 2016 (22)	Luteolin	C57BL/6 male mice	HFD with 0.01 % luteolin 12 weeks	O2 consumption and CO2 production increase BAT activation increase WAT browning increase AMPK / PGC1α signalization increase

**AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, FGF21; fibroblast growth factor 21, HFD; high-fat diet, PGC1α ; peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, PRDM16; positive regulatory domain containing 16, sWAT; subcutaneous white adipose tissue, SIRT1; silent mating type information regulation 2 homolog 1, UCP-1; uncoupling protein-1, WAT; white adipose tissue.*

1.4.2. Flavonols

Flavonol group compounds which are in the structure of 3-hydroxy flavone are commonly found in glycoside form in foods. Major flavonol species include quercetin, myricetin, kaempferol, and routine. Flavonols are mostly found in cabbage, onion, apple, tea, buckwheat and broccoli (52, 53). Studies have shown that flavonols increased non-shivering thermogenesis by increasing UCP-1, Cpt1α, Tbx1, PGC1α activation in general (54-60). In vitro studies have shown that flavonol species act through mechanisms that trigger BAT activation (54-57). In studies performed in experimental animals, increase in AMPK phosphorylation, SIRT1 and UCP-1 expression, BAT browning, O2 consumption, and body temperature were found, resulting in a decrease in body weight and white adipose tissue mass in flavonol-treated groups compared to HFD-fed groups (54-60). In vitro and in vivo studies associated with the efficacy of flavonols on BAT activation are summarized in Table 3.

1.4.3. Flavanones

Flavanones are flavonoids found in nature as aglycones and glycosides having an unsaturated carbon-carbon bond in the C ring (53). Naturally existing flavanones are naringenin, hesperidin, eriodicthiol, narirutin and erythocytin (61). As the main source, citrus fruits such as satsuma mandarin and valentine orange are examples of foods that contain narirutin and hesperidin (62). Hesperidin is insoluble in water and does not dissolve well in the intestine, however, G – hesperidin is water-soluble and absorbs faster than hesperidin. It has been shown in experimental studies that flavanone species, like other flavonoids, have potential effects on increasing energy expenditure and increase in body temperature as a result of increased BAT sympathetic nerve activity through BAT activation (63-65). Table 4 summarizes in vitro and in vivo studies about the efficacy of flavanones on BAT activation.

1.4.4. Flavanols

Flavanols, which is most common in foods, are flavonoid subclass called flavan-3-ol since they contain a group of – OH in the C3 atom (66). A study using data obtained from NHANES 1999 – 2002 showed that the average daily intake of flavan-3-ol was the highest among other flavonoids and accounted for 82% of average flavonoids intake (67). Flavanols are commonly found in tea, wine, apple and chocolate (68, 69). Flavanol monomers are classified as catechin, epicatechin, epigallocatechin (EGC), epicatechin gallate (EG) and EGCG (70). Flavanols have been shown to increase UCP-1 activation and BAT activation and thus be effective in energy expenditure (71-80). Experimental animal studies in which different types of flavanol are given have reported reducing body weight by triggering signaling pathways that increase the energy expenditure of flavanols (72, 80). While there are many in vitro and in vivo studies on the efficacy of flavonoids on energy expenditure, human studies are more limited. In a study examining EGCG activity in healthy young men, a gel capsule of green tea extract containing 1600 mg EGCG and 600 mg caffeine was given after 3 hours of cold exposure. It was observed that energy expenditure was increased in the group that received green tea extract and lipids had more contribution to total energy expenditure than placebo (74). In another study, it was found that BAT concentration increased in healthy young female subjects receiving catechin – enriched beverage (540 mg/day catechin) (78). In vivo studies regarding the effectiveness on BAT activation of flavanols are summarized in Table 5.

1.4.5. Anthocyanins

As a flavonoid species, anthocyanins are water-soluble pigments that provide blue, purple and red colors in fruits such as blackberries, raspberries, pomegranates, black and red currants and in vegetables such as eggplant and red cabbage (81). Major anthocyanins are peonidine, pelargonidine, malvidine, cyanidine, petunidine and delphinidine (82). It has been reported they have many positive effects on health such as antioxidant, anti-inflammatory, antidiabetic and anti-carcinogenic properties (81). Anthocyanins have been shown to increase UCP-1, PGC1α, Cpt1α, PRDM16 expression in white and brown adipocytes, and increase energy expenditure by increasing body temperature (83-86). Cell studies have reported increased AMPK phosphorylation and mitochondrial biogenesis in studies of different doses of cyanidin (83, 84). In experimental animal studies where diverse anthocyanin varieties were applied in different amounts and time, it was observed that energy expenditure increased as a result of increased AMPK activity (85, 86).

1.4.6. Isoflavones

Isoflavones, known as phytoestrogens, are found in a variety of legumes, mainly soy and soybeans. Among the isoflavones, daidzein, genistein, glisitin, and formononetin are prominent (87). It increases O2 consumption and CO2 production by increasing UCP-1 function and affects BAT activation by increasing browning (88-92). In animal studies in which isoflavone subtypes were given, it was found that BAT browning and energy expenditure increased as a result of increased UCP-1 secretion (89-92). Table 6 summarizes in vitro and in vivo studies of the efficacy of anthocyanins and isoflavones on BAT activation.

Obesity is a disease in which adipocytes grow by accumulating excessive amounts of lipids and is characterized at the cellular level by an increase in the number and size of differentiated adipocytes in adipose tissues (2, 4, 16). As treating obesity with medications is often associated with negative side effects and little long-term efficacy, some study results suggest that the use of natural plant extracts may be an interesting alternative for long-term weight management, and flavonoids can be suggested as one possible source (69, 93). In vitro and in vivo studies examined in this review have shown that some of the dietary flavonoids are effective at clinical levels. However, the majority of data show the effects of flavonoids on BAT and browning WAT at pre-clinical levels using mammalian cells and animals (48-51). Some types of flavonoids are metabolized by intestinal bacteria in the large intestine and then absorbed into the body. This suggests that the effects of flavonoids on non-shivering thermogenesis may be regulated by indirect signaling cascades such as the microbiome (94). In addition, the efficacy of dietary flavonoids is controversial because the number of flavonoids taken with diet is not known clearly like supplements. Because it is difficult to measure the BAT activity of dietary flavonoids in humans, more clinical studies should be conducted to confirm the effect of flavonoids on non-shivering thermogenesis before flavonoids can be recommended for improving metabolic diseases (5, 69, 95).

Table 3. *In vitro and in vivo studies on the effects of flavonols on non-shivering thermogenesis*

Authors	Flavonol Type	Study Group	Treatment	Result
Moon et al. 2013 (54)	Quercetin (onionpeel)	3T3-L1	25-100 µg/mL	CPT1α* increase
Lee, Parks, and Kang 2017 (55)	Quercetin	3T3-L1	25-100 µM	UCP-1*, CPT1α, TBX1*, PGC1α*, PPARγ*, PRDM16 * increase
Yuan et al.	Rutin	C H T cells 3 10 1/2	0.1-100 µM	UCP-1, PRDM16, PGC1α increase
2017 (56)				Deacetylation of PGC1α by stabilizing SIRT1* increase
Hu et al. 2018 (57)	Myricetin	C H T cells 3 10 1/2	0.001-10 µM	UCP-1, PGC1α, SIRT1 increase Adiponectin increase
Varshney et al. 2019 (58)	Quercetin Rutin Myricetin Kaempferol	3T3-L1 and L6 cells	1,10,50 µM	PPARγ and Fabp4* decrease Lipid and triglyceride decrease AMPK* phosphorylation increase
Moon et al. 2013 (54)	Quercetin (onionpeel)	Sprague Dawley male mice	HFD* with 0.36% and 0.72% OPE* 8 weeks	Body weight and fat content decrease UCP-1 and CPT1α (epididymal WAT*) increase
Dong et al.	Quercetin	C57BL/6 male	HFD with	Body weight, epididymal WAT decrease
2014 (59)		mice	0.1%	AMPK* phosphorylation, SIRT1 expression
			Quercetin 12	and UCP-1 increase
			weeks	
Lee, Parks, and Kang 2017 (55)	Quercetin (onion peel)	C57BL/6 male mice	HFD with 0.5% OPE 8 weeks	Adipocyte browning increase
Yuan et al.	Rutin	C57BL/6 male	HFD with 1	Mitochondrial biogenesis and energy
2017 (56)		mice	mg/kg rutin	expenditure increase
		And db/db mice	10 weeks	BAT* and browning increase
Hu et al. 2017 (60)	Rutin	Female rats with PCOS	100 mg/kg rutin 3 weeks	UCP-1, PPARα*, PGC1α, and CPT1α increase Body temperature increase
Hu et al. 2018 (57)	Myricetin	db/db male mice	HFD with 400 mg/kg myricetin 14 weeks	Body weight, fat mass, blood glucose decrease d Body temperature, O_2 consumption, BAT activity increase Browning, mitochondrial biogenesis increase
Varshney et al. 2019 (58)	Quercetin Rutin Myricetin Kaempferol	C57BL/6 male mice	HFD with 25 mg/kg (each flavonols) 7 weeks	Body weight decrease Serum triglyceride, cholesterol, LDL Blood glucose level decrease Glucose tolerance, insulin sensitivity increase

**AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, Cpt1α; carnitine palmitoyltransferase 1 alpha, Fabp4; Fatty Acid-Binding Protein 4, HFD; high fat diet, OPE; onion peel extract, PGC1α ; peroxisome proliferator-activated receptor-gammacoactivator 1 alpha, PPARα; peroxisome proliferator-activated receptor – alpha, PPARγ; peroxisome proliferator – activated receptor gamma, PRDM16; positive regulatory domain containing 16, SIRT1; silent mating type information regulation 2 homolog 1, TBX1; T-box transcription factor, UCP-1; uncoupling protein-1, WAT; whiteadipose tissue.*

Table 4. *In vitro and in vivo studies on the effects of flavanones on non-shivering thermogenesis*

Authors	Flavanone Type	Study Group	Treatment	Result
Choi et al. 2016 (63)	Hesperidin	3T3-L1	12.5 and 50 µg/mL	UCP-1* and PRDM16* increase
Shen et al. 2009 (64)	G-hesperidin	Male Wistar rats	60 mg of oral G – hesperidin	BAT* sympathetic nerve activity increase Body temperature decrease Cutaneous sympathetic nerve activity decrease
Choi et al. 2017 (65)	Hesperidin	ICR male rats	HFD* with 50 and 200 mg/kg/day 7 weeks	Body weight, fat mass, insulin, TG* decrease AMPK* phosphorylation, and BAT activity increase

AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, HFD; high fat diet, PRDM16; positive regulatory domain containing 16, TG; triglyceride, UCP-1; uncoupling protein-1.

Table 5. *In vivo studies on the effects of flavanols on non-shivering thermogenesis*

Authors	Flavanol Type	Study Group	Treatment	Result
Dulloo et al. 2000 (71)	Green tea extract (catechin and EGCG*)	Male SD rats	0-200 µM	BAT* activation and O_2 uptake rate increase
Choo 2003 (72)	Green tea (EGCG)	Male SD rats	HFD* with 20 g/kg green tea extract	Body weight decrease Energy expenditure, BAT intensity increase
Nomura et al. 2008 (73)	Tea catechins (TC*)	Male SD rats	LFD* and HFD with 0.5% TC 5 weeks	UCP-1* (LFD with TC group) increase No difference in the HFD group (-)
Gosselin and Haman 2012 (74)	EGCG	Healthy young men	3 hours cold exposure 1600 mg EGCG and 600 mg caffeine	Energy expenditure increase Shivering thermogenesis decrease
Yan, Zhao, and Zhao 2013 (75)	Green tea catechins	Male SD rats	LFD and HFD with 100 mg/kg 5 weeks	PPARδ*, UCP-1, CPT1α* increase
Matsumura et al. 2014 (76)	Cocoa flavanols	Male ICR mice	10 mg/kg cocoa flavonoid	BAT activity, AMPK* phosphorylation increase Plasma catecholamine level increase
Yamashita et al. 2014 (77)	Oolong, black tea	Male ICR mice	Tea boiled with 2 g tea leaves in 100 mL 7 days	Weight of WAT* decrease AMPK phosphorylation and UCP-1 increase
Nirengi et al. 2016 (78)	Catechin	Healthy young women	540 mg/day catechin 12 weeks	BAT density increase
Rabadan – Chávez et al. 2016 (79)	Cocoa flavanols	Male Wistar rats	HFD with 1 g/kg cocoa powder, 100 mg/kg cocoa extract and 10 mg/kg epicatechin (EC*) 8 weeks	UCP-1, PPARγ*, PPARα*, SIRT1*, PGC1α* increase AMPK phosphorylation increase Plasma catecholamine level increase
Gutiérrez – Salmeán et al. 2014 (80)	Epicatechin	Male Wistar rats	HFD for 5 weeks with – EC (1 mg/kg) for an extra 2 weeks	Browning increase Body weight decrease

AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, CPT1α; carnitine palmitoyl transferase 1 alpha, EC; epicatechin*, EGCG;* Epigallocatechin gallate*, HFD; high fat diet, LFD; low fat diet, PGC1α ; peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, PPARα; peroxisome proliferator – activated receptor-alpha, PPARγ; peroxisome proliferator-activated receptor gamma, PPARδ; peroxisome proliferator-activated receptor sigma, SIRT1; silent mating type information regulation 2 homolog 1, TC; tea catechins, UCP-1; uncoupling protein-1.*

Table 6. *In vitro and in vivo studies on the effects of anthocyanins and isoflavones on non – shivering thermogenesis*

Authors	Type	Study Group	Treatment	Result
Anthocyanin				
You et al. 2015 (83)	Cyanidin	C_3 H_{10} $T_{1/2}$ cells	10 µg/mL mulberry extract, mulberry wine extract	Increase; UCP-1*, PGC1α*, Cpt1α*, PRDM16*p38 phosphorylation Cellular O_2 respiration
Matsukawa etal. 2017 (84)	Cyanidin	3T3-L1	50 or 100 µM	Increase; Cellular cAMP* concentration AMPK* phosphorylation UCP-1, PGC1α Mitochondrial biogenesis
Takikawa et al. 2010 (85)	Bilberry extract	Male KK-Ay mice	27 g/kg diet 5 weeks	AMPK in sWAT* and skeletal muscle increase
You et al. 2017 (86) t	Cyanidin	Male db/db mice	1 mg/mL 16 weeks	Energy expenditure, O_2 consumption increase BAT* activation, body temperature, mitochondrial biogenesis increase Browning increase Body weight gain, the weight of WAT* decrease

Table 6. *(Continued)*

Isoflavone				
Aziz et al. 2017 (88)	Genistein	3T3-L1	100 µM	UCP-1*, PGC1α*, SIRT1* increase O_2 consumption increase
Gautam et al. 2017 (89)	Formononetin	3T3-L1	10 nM	AMPK* phosphorylation and β – catenin expression increase
Lephart et al. 2004 (90)	Isoflavone mixture	Long-Evans male and female rats	600 µg/g phytoestrogens	Body temperature during the light cycle, UCP-1 increase
Crespillo et al. 2011 (91)	Daidzein	Male Wistar rats	LFD* and HFD* with 50 mg/kg 2 weeks	UCP-1 (in HFD) increase
Kamiya et al. 2012 (92)	Puerariae flower extract (PFE*) and PFE isoflavone – rich fraction (ISOF*)	C57BL/6J male mice	HFD with 5% PFE and HFD with ISOF 6 weeks	Energy expenditure, O_2 consumption increase UCP-1 increase
Gautam et al. 2017 (89)	Formononetin	C57BL/6J male mice	HFD with 0.1, 1 and 10 mg formononetin	Browning increase

AMPK; AMP-activated protein kinase, BAT; brown adipose tissue, cAMP; cyclic AMP, CPT1α; carnitine palmitoyltransferase 1 alpha, HFD; high-fat diet, ISOF; isoflavone-rich fraction, LFD; low-fat diet, PFE; Puerariae flower extract, PGC1α; peroxisome proliferator-activated receptor-gamma coactivator 1 alpha, PRDM16; positive regulatory domain containing 16, SIRT1; silent mating type information regulation 2 homolog 1, sWAT; subcutaneous white adipose tissue, UCP-1; uncoupling protein-1, WAT; white adipose tissue.

2. CONCLUSION

Increasing BAT activation and non-shivering thermogenesis is a potential approach to ameliorating metabolic diseases. While dietary energy restriction is the best-known intervention to reduce obesity, several studies have shown potential anti-obesity effects of bioactive or functional nutrient components such as flavonoids. Many flavonoid species are effective in activating some transcription factors in WAT browning, increasing BAT activation and thereby increasing energy expenditure. However, although flavonoids have a positive effect on energy metabolism by regulating non-shivering thermogenesis, low bioavailability of flavonoids and structure modification via the digestive system when taken into the body by diet should also beconsidered. More studies are needed to better understand the effects of flavonoids on anti – obesity in humans.

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Clinical and Experimental Health Sciences

The Roles of the Golgi in Various Diseases

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ABSTRACT

The primary function of the Golgi is to perform post-translational modifications on proteins, allow them to be transported within the cell. The Golgi has more functions in the cell, according to research into its unknown structure and functions. It has been discovered that, in addition to substance process and transport, it plays a role in autophagy, lipid formation, calcium homeostasis, and apoptosis regulation. The fact that the Golgi has so many tasks has caused question marks about what kind of illnesses or diseases it can cause in case of a problem with Golgi. A mutation at Golgi can disrupt its function by cause of the Golgi fragmentation. It can be seized by living organisms or molecules, called infectious agents, outside the mutation. Disintegration and disorders in the Golgi structure and function are examples of neurodegenerative diseases and cancer. In addition, studies prove that the SARS-CoV-2 virus, which causes pandemic in the world, is also linked to the Golgi. The diseases that can be caused by the Golgi are highlighted in this review, as are treatment studies. Treatment strategies for the Golgi that causes many diseases are still developing and studies are ongoing.

Keywords: Golgi, cancer, neurodegenerative diseases, SARS-CoV-2, treatment

1. INTRODUCTION

The Golgi is a central organelle of the secretory pathway, located at the junction of the exocytic and endocytic intracellular substance transport pathways. The Golgi has an important role in carrying the post-translational modification of proteins, classification of lipids, and proteins to their final targets. In addition to these duties, it also has an important effect on cellular responses such as apoptosis and stress (1). The Golgi was one of the first organelles to be discovered and studied in depth due to its enormous size. It was discovered in 1897 as part of Camillo Golgi's study of the nervous system and was defined as "apparato reticolare interno," "a thin and elegant network in the cell body completely within the nerve cells" (2). The Golgi in the cytoplasm is located near the endoplasmic reticulum (ER) and somewhere near the cell nucleus. While animal cells have one or more Golgi, there may be hundreds of the Golgi in plant cells. Its main function has been preserved throughout evolution and its structural organization varies among species. The Golgi is surrounded by a single-layer membrane and is found in eukaryotic cells. Immature mammalian red blood cells and sperms do not contain the Golgi. The Golgi is in charge of cell organization and defense, including cell division and apoptosis. The Golgi can give reactions that affect the future of the cell under the stress conditions seen in cells. Mutations in the relevant genes can cause the Golgi to become dysfunctional or seized by infectious agents, and it can be misregulated in multifactorial diseases like neurodegeneration and cancer, as well as COVID-19.

2. THE GOLGI' FUNCTIONS

The Golgi is a central node in intracellular membrane traffic at the intersection of exocytic and endocytic pathways, and thus plays an important role in separate to the newly synthesized and recovered proteins and lipids from the ER and transport them to their final destinations (3). The Golgi performs post-translational modification of proteins and also produces enzymes of the lysosome, an important organelle. Enzymes in cisterna perform glycolysis and phosphorylation processes of proteins as post-translational modification. Proteins are processed along with the Trans-Golgi network (2).

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In addition to protein modification and transport, the Golgi actively regulates mitotic entry, cytoskeletal organization, and apoptosis. The Golgi serves as a signaling platform for several cellular functions, including signaling initiated by receptors in this plasma membrane (1). It also mediates autophagy and protects the ER and axonal homeostasis (4). The Golgi promotes axon development and is thought to play a role in dendrite development (6).

3. STRUCTURE OF GOLGI

The Golgi consists of cisterna stacks arranged in a polarized manner, connected by membrane tubules to form the Golgi ribbon located near the centrosome. The cisterna cluster is functionally divided into three regions: cis Golgi network, medial Golgi network and trans Golgi network (TGN) (1). Each section contains different enzymes that selectively modify proteins based on their location. Cisterns also carry the structural proteins needed for their repair.

Several glycosidases and glycosyltransferases are found in the lower portions of the Golgi and are in charge of produce glycoproteins and glycolipids. During proteolysis, lumenal proteinases cleave many secretory proteins in TGN. Microtubule organization and Golgi matrix proteins are required for the development of the Golgi ribbon. The centrosome-derived microtubules are moved along by cytosolic dynein to the (-) end of the microtubules. The Golgi stacks are then held nearby by Golgi-oriented microtubules, which facilitate tubular connections between them (5).

The centrosome dissolves and becomes dispersible during neuronal differentiation, allowthem for the formation of microtubules and the formation of appropriate axonal and neuronal morphology. The formation of microtubules involves folding, dimerization, and polymerization of alpha and beta-tubulins. Tubulin-binding cofactors are supplemented with five tubule-specific chaperones known as TBCA-TBCE in the final stages of this complex process (6).

COP I coated vesicles bud in the ER-Golgi interstices or Golgi. COP II coated vesicles are vesicles budding from the ER and responsible for carry towards the Golgi.

4. PROTEINS OF GOLGI

The Golgi proteins can be divided into various protein classes such as structural proteins, cytoskeletal proteins, and molecular motor proteins. Golgi structural proteins are helical-coil proteins that have been expanded to form a proteinaceous matrix around the Golgi. Their dismantlement causes a structural change in the Golgi. Golgi Reassembly Stacking Proteins (GRASPs), golgins, kinases, phosphatases, ubiquitin E3 ligases, and deubiquitinases have all been identified as proteins with different functions in preserve the Golgi structure and regulate the Golgi function (5). Golgins are proteins found in the Golgi that form a matrix that aids in the maintenance of the organelle's structure. Golgins are also involved in vesicle transport regulation.

4.1. Structural Proteins of the Golgi

Golgi Reassembly Stacking Proteins (GRASP65 and GARSP55) have been shown to form tubular connections between Golgi stacks and contribute to trafficking order (6). GRASP65 belongs to the cis-Golgi region, whereas GRASP55 belongs to the medial / trans-Golgi (TGN) region. These two proteins form homodimers in their areas. Dimers act as an adhesive between cisterns, oligomerized, allowing them to stay together (5).

4.2. Metabolic Proteins of the Golgi

One of the Brain Imaging and Cognitive Disorders (BICD) genes, BICD2 gene, encodes the Bicaudal D2 protein, which is classified as a golgin due to its interaction with the Golgi small GTPase RAB6A. BICD2 activates the protein by binding to the dynein complex and ensures that it binds to the substances to be transported.

Sterol regulatory element-binding proteins (SREBPs) are lipid biosynthesis regulators. SREBPs are an example of a protein whose function is dependent on ER-regulated transport but does not directly affect ER or Golgi function. When cholesterol levels are low, COPII vesicles transport SREBP from the ER to the Golgi. SREBP can then be cleaved by Golgi-specific proteases. As a result, an N-terminal portion is released, which enters the nucleus and activates transcription of genes involved in cholesterol uptake and synthesis. Therefore, the Golgi is critical for the SREBP pathway (7).

4.3. Trafficking Proteins of the Golgi

Sacsin Molecular Chaperone (SAC), SAC1 is also in charge of ER and the Golgi trafficking. SAC1, unlike SREBPs, has a significant impact on the regulation of ER-Golgi localization and Golgi trafficking. Phosphatidylinositol-4-phosphate (PtdIns / 4 P) is essential for trafficking between the Golgi and the plasma membrane. On the cytosolic surface of the trans-Golgi, PtdIns / 4 P is excessive. The PtdIns / 4P binding protein functions in non-vesicular lipid transport (7). Therefore, SAC1 phosphorylates PtdIns / 4P to produce phosphatidylinositol. In cells without growth factors, SAC1 oligomerizes and provides trafficking from ER to the Golgi through the PtdIns / 4P. It activates the p38 / MAPK pathway in the presence of growth factors, allow the separation of SAC1 oligomers and SAC1 to transport the substance to the ER via COPI. This increases PtdIns / 4 P in the Golgi, causes substances to be transported from the Golgi to the plasma membrane (7).

Golgi Phosphoprotein 3 (GOLPH3L), which is found only in vertebrate salivary glands, small intestines, and skin tissues, is a phosphoprotein with multiple alternative phosphorylation sites. GOLPH3 is a peripheral membrane protein that regulates vesicle budding and membrane traffic from the TGN to the plasma. GOLPH3 binds to phosphatidylinositol 4-phosphate (PI4P), which causes it to be localized to the TGN. GOLPH3 dissociates from TGN when PI4P is depleted. GOLPH3 also binds to Myosin XVIIIA (MYO18A), an actin-based motor

protein, to connect the Golgi membranes to the actin cytoskeleton. This bridging effect generates the necessary tension for vesicle budding, trafficking, and the Golgi ribbon maintenance. Tensile force is lost when GOLPH3 or MYO18A levels are low, that leads to the Golgi strip to shrink and the number of vesicles formed in the TGN to decrease. The GOLPH3 complex is thought to be a hub for the regulation of the Golgi. It is known that GOLPH3 and MYO18A can cause cancer which is involved in the transport of substances between the Golgi and the plasma membrane. GOLPH3 degradation results in impaired phosphorylation of Protein kinase B (AKT). Similarly, over-expression of GOLPH3 stimulates enhanced protein phosphorylation. In breast cancer, overexpression of AKT and GOLPH3 decreases transcriptional activity and boosts cell proliferation through increase phosphorylation of AKT's substrate Forkhead box O (FOXO1) (7). The GOLPH3 complex is crucial for cellular responsiveness.

5. THE GOLGI AND STRESS

The Golgi is a crucial organelle for cellular homeostasis. Unstable membrane flow, altered microtubule dynamics, and incorrect modifications of proteins, which are the mechanisms that cause the Golgi fragmentation and dysfunction, can also cause stress in the Golgi (8). The Golgi stress response is an autoregulation system. The Golgi has been associated with numerous signaling molecules. Because of this, it has been proposed that the Golgi can recognize and send stress signals, act as a hub in the cellular signaling network (9). When the synthesis of the secretory and membrane proteins is more than the Golgi capacity, it cannot be modified or transported due to the insufficiency of the Golgi function (10). This situation causes stress in the Golgi. To cope with this stress, cells also activate some homeostatic mechanisms to increase the capacity of the Golgi in response to cellular needs (11). The most common response of the Golgi to stress is the Golgi fragmentation. The Golgi fragmentation occurs by various mechanisms.

One of the response mechanisms that cause stress breakdown is apoptosis. The morphology changes seen in the Golgi in cells exposed to stress may be the result of ongoing apoptosis or cause apoptosis. Examples are death receptor endocytosis and the Golgi disruption in the organellar response to apoptotic initiation. Some Golgi proteins have also been shown to regulate apoptosis (12).

5.1. Stress Responses of the Golgi

The Golgi stress response's mechanism is still being fully described. However, the Golgi responds to the stress that occurs in the cell through some mechanisms. These include apoptosis and overexpression or underproduction of certain proteins. Some studies have shown that some Golgi proteins have a role as stress agents.

When the GOLPH3 protein is phosphorylated, it is localized to TGN. Through its interactions with the retromer complex and activation of the mTOR inhibitor rapamycin, which boosts cell proliferation and size, GOLPH3 has been demonstrated to regulate cell proliferation. This DNA damage can abnormally increase the tensile strength for the Golgi fragmentation (12). It is well known that many cancers have excessive GOLPH3 expression. Cancer cells become more susceptible to substances that cause DNA damage when GOLPH3 levels are reduced, indicates that the Golgi fragmentation caused by GOLPH3 phosphorylation may act as a protective mechanism (13). In reaction to the stress brought on by oxygen-glucose deprivation, GOLPH3 encourages cell autophagy (14).

Stress responses caused by oxidative or intracellular damage can cause the Golgi fragmentation. Golgin-160 is the substrate for Caspase 2 found in Golgi membranes. Under stress conditions, Golgin-160 is impaired and may contribute to the stress response pathway by inducing gene expression (15).

In one study, the finding of decreased cell adhesion and migration with GRASP depletion from the Golgi adhesion proteins reinforces the essential role of the Golgi agglomeration in protein traffic, modification, and signaling. Under stress conditions, GRASP proteins also function as membrane bonds outside of the Golgi. GRASP proteins increase during substance exchange and under autophagy stress conditions. It suggests that GRASP55 may function as a stress sensor and an effector in the stress response due to its emerging roles as an energy sensor in the Golgi and a membrane thread in autophagy (16).

During apoptosis, caspase-3 and caspase-8 break the p115 protein. When p115 develops caspase resistance, it slows down the process of the Golgi fragmentation, which results from apoptosis, especially in cancer cells (12).

The Sun et al. study claims that, Soluble NSF Attachment Protein Receptor (SNARE) GS28, one of the other proteins of the Golgi causes apoptosis induced by cisplatin depending on p53 (17) According to this mechanism, overexpression of GS28 causes pro-apoptotic phosphorylation of p53. The cell stimulated by phosphorylation also becomes sensitive to cisplatin, which is an apoptosis inducer. Thus, GS28 controls apoptosis by regulate to the pro-apoptotic phosphorylation of p53.

It has been suggested that the ubiquitin-proteasome system also contributes to the Golgi autoregulation in addition to proteins. According to the study, Eisenberg-Lerner A and co-workers showed that the proteasome-mediated the Golgi cleavage is actively regulated and this degradation can be reversed. They showed that the Golgi can provide a signal to initiate apoptosis through C/EBP-homologous protein (CHOP) activation as an alternative response to stress (18).

When we consider the signal pathways mentioned earlier, some mechanisms attract attention. When we look at the molecular process, to identify the stress factor that happens in the Golgi, a sensor molecule, a transcription factor, and target genes produce Golgi-related proteins such as glycosylation enzymes are required (11). When the sensors are activated, down-regulation transcription factors cause transcriptional induction of the Golgi-related genes. This situation causes transcription factors such as Transcription

factor E3 (TFE3), cAMP response element-binding protein (CREB), and the genes related to Heat shock protein 47 (HSP47), and the Golgi that they affect to be directed towards the Golgi expansion and eventually apoptosis (19). Signal pathways and their responses are shown in Figure 1.

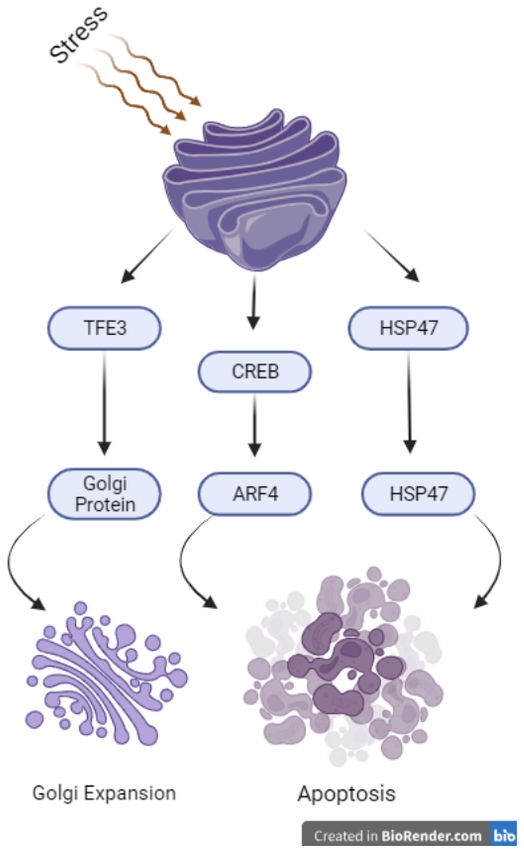

Figure 1. *Golgi-related signal pathways and their stres response. Transcription factor E3 (TFE3), cAMP response element – binding protein (CREB), Heat shock protein 47 (HSP47), ADP-ribosylation factor 4 (ARF4).*

There are studies examine TFE3, proteoglycan, CREB3, and HSP47 signaling pathways in terms of shadow.

5.1.1. TFE3 Signal Pathway

The TFE3 pathway improves the overall function of the Golgi. The TFE3 pathway has the Golgi structural proteins as target genes. TFE3 is phosphorylated at Ser108 and captured in the cytoplasm in properly expanding cells. TFE3 is dephosphorylated at Ser108 in response to the Golgi stress, which displaces the nucleus and stimulates transcription from Golgi stress response element (GASE) (11). TFE3 expression increases in the Golgi stress. Subsequently, in its promoters, the Golgi activates GASE expression, one of the stress response elements (20). According to one study, the Golgi expansion was noted along with the TFE3 pathway's impact on teh Golgi proteins as a second stress response after receive the signal (19).

5.1.2. CREB3 Signal Pathway

In a study examining Brefeldin A (BFA) and Granacalsin (GCA), which cause the Golgi to become stressed and lose its function, CREB was determined as another signal pathway (21). BFA causes the Golgi stress-induced apoptosis. BFA is used to enable the CREB3 path. BFA has been referred to as an anti-virus agent that prevents tiny G proteins like ADP-ribosylation factors **(**ARFs) from functioning (19). They identified these proteins in a study they conducted using Chronic Myeloid Leukemia Cells. They discovered that ARF4 is the gene impacted by Brefeldin A (BFA) on the CREB pathway (22). It has been noted that the Golgi-induced apoptosis is also decreased when ARF4 expression is inhibited by RNA interference. Death receptor 4 (DR4) and Trafficking Protein Particle Complex Subunit 13 (TRAPPC13) are two of the CREB3 pathway's target genes. While TRAPPC13 is a part of a TRAPP III complex that regulates autophagy flux under specific stress conditions, DR4 encodes a death receptor that governs cell death brought on by the Golgi stress (21).

5.1.3. HSP47 Signal Pathway

The target gene for the HSP47 pathway is HSP47, which is responsible for collagen folding in the ER. According to studies, collagen dynamics contribute to the Golgi stress-induced cell death. Treatment with BG (BenzylGalNAc), a glycosylation inhibitor, activates the HSP47 pathway (23). This pathway regulates the Golgi-induced apoptosis. In a study with BG in 2013, HSP47 was inhibited by RNA interference. As a result, the Golgi was fragmented and this caused apoptosis activation (23). In a study conducted on this study in 2017, they reported that BG-induced apoptosis decreased when the HSP47 pathway was overexpressed (19). Despite studies, the sensors, transcription factors, and enhancers that regulate the HSP47 pathways have not been clarified.

5.1.4. Proteoglycan Signal Pathway

Glycoproteins called proteoglycans are present in a variety of tissues, including cartilage (21). Glycosyltransferases are among the proteoglycan pathway's target genes, and they are all necessary for proteoglycan-type glycosylation. Syndecan 2 (SDC2) is the core protein of a proteoglycan. Overexpression of this protein can induce a deficiency in glycosylation enzymes that cause the Golgi stress due to proteoglycans (11).

Despite all of these research findings, the basic processes controll the Golgi morphology in stress response remain unknown. More research is required, particularly on signaling pathways. Even though the Golgi structure is changeable, it is carefully regulated. Mammalian cells rapidly deconstruct the Golgi's composition and function during the cell cycle and recombined (12) and may be impaired under stress conditions and pathological conditions such as DNA damage, energy/nutrient deprivation, and pro-apoptotic conditions.

6. DISEASES CAUSE BY THE GOLGI

The unbalanced membrane flow observed in the Golgi, altered microtubule dynamics, the modification of the Golgi structural proteins, and the proteolytic cleavage are the fragmentation mechanisms of the Golgi. Dysfunctions resulting from the breakdown of the Golgi structure have been observed in neurodegenerative diseases, some pathogen-borne diseases, and cancer. The fragmentation of the Golgi was first described in Amyotrofik lateral skleroz **(**ALS) patients' motor neurons (4). The loss of the Golgi organization is a common feature of many neurodegenerative diseases. Mutations in the appropriate code genes may cause the Golgi to become dysfunctional (1).

Unlike Somatic Golgi, the Golgi in Neurons creates "Golgi exit points" that allow local trafficking in neurites localized in axons and dendrites. Axonal transport is a type of neuronal transport that allows a substance to be transported between cellular proteins and vesicles in the axon, either towards or away from the cell (4).

There are also studies on the Golgi' effects on SARS-CoV-2 virus infection and COVID-19 disease.

6.1. Cancer

The Golgi, mitochondria, lysosomes, and ER organelles have many roles in cancer onset or progression. The Golgi is associated with protein/lipid synthesis and transfer. Additionally, it is crucial for tumor development, medication resistance, cancer metastasis, and immune evasion (25). Irregularities in the Golgi such as abnormal glycosylation, irregularity of kinases, and hyperactivation of myosin motor proteins may be related to cancer metastasis. Overactivation of the Rabs, work with golgins in protein transport and the Golgi building care, has been observed in a variety of cancer. Tumor cells were discovered to have elevated levels of kinases connected with the Golgi disorganization (5).

In some cancer genome studies, the GOLPH3, MYO18A and phosphatidylinositol transfer protein cytoplasmic 1 **(**PITPNC1) genes found in the Golgi have been commonly described as cancer-leading factors. GOLPH3, which is in charge of vesicle transport, creates a pull force for trafficking in cells (26). Any situation that affects the GOLPH3 function may cause disruption or even cessation of trafficking. This situation may cause even cancer formation.

High levels of GOLPH3, the first of the genes, are linked to a poor prognosis in numerous malignancies. GOLPH3 causes oncogenic transformation as a result of an increased expression, according to research on genes that frequently reproduce in cancer. GOLPH3 degradation affects transformation in the reverse direction, according to cell culture studies. The number of replicas of the GOLPH3 gene was found to be increased in 56% of lung carcinomas, 37% of prostate carcinomas, 32% of breast carcinomas, 33% of pancreatic carcinomas, 24% of colon carcinomas, and 37% of ovarian carcinomas (26). Another gene related to the Golgi MYO18A was shown to be one of the cancer-cause genes in a research of somatic copy alterations and gene expressions in the exploration of the causes of breast cancer. 11% of metastatic breast tumors and 21% of prostate cancers were discovered to have highly expressed MYO18A genes. The high expression of the PITPNC1 gene in breast cancer causes cancer cell migration and metastasis (26). It was observed that tumor formation increased as a result of PTEN destruction, which is responsible for the trafficking. PTEN-regulated alternative splicing (AS) irregularity is thought to be linked to cancer (27).

In another study, over-expression of GOLPH3, which is involved in the trafficking, leads to increased phosphorylation of AKT. GOLPH3 often replicates in various types of solid tumors such as melanoma, lung cancer, breast cancer, glioma, and colorectal cancer. GOLPH3 overexpression is linked to prognosis in a variety of tumor types, including 52% of breast tumors and 53% of glioblastomas (28). GOLPH3 roles in tumor formation may correlate with a variety of cellular activities including:

Contributing to malignant secretory phenotypes by regulating the Golgi-plasma membrane traffic.

Increasing glycosylation of cancer-related glycoproteins or controlling the recycling of key signal molecules.

It affects the genomic stability and responsiveness to DNA damage.

It demonstrates that GOLPH3 overexpression in these cancer types can be used as a positive biomarker for tumor progression and poor survival (25).

The Golgi fragmentation is thought to promote cell proliferation in breast cancer by decreasing transcription activity (6).

One of the most significant causes of cancer cell formation and spread is DNA damage. Excess GOLPH3 expression increases cancer cell survival in the presence of DNA damage (26).

6.2. Alzheimer's Disease (AD)

Alzheimer's Disease is a central nervous system disease, characterized by progressive memory loss. Structural changes, such as fragmentation of the Golgi, represent an early preclinical feature of various neurodegenerative diseases, including Amyotrophic Lateral Sclerosis, Alzheimer's and Creutzfeld-Jacob diseases, spinocerebellar ataxia type 2. Since the earliest stages of the development of the disease, fragmentation, and distribution of the Golgi have been observed in the neurons of those with Alzheimer's disease. Phosphorylation of GRASP65, one of the Golgi proteins, is known to cause Alzheimer's (2).

One of the effect hypotheses of the Golgi cleavage on AD is the accumulation of neurofibrillary tangles (NFT) in the neuron cells when the corrective protein Tau is phosphorylated. A small proportion of early Alzheimer's cases bind to mutations of Amyloid Precursor Protein (APP) or Presenilin proteins. Besides, more than 20 genes involved in lipid metabolism, inflammatory response, and endocytosis are risk factors for late AD (1).

Although there are still uncertainties about Alzheimer's causes, there are some hypotheses when looking at the causes at the cell level. One of them is the accumulation of neurofibrillary tangle (NFT) in the cell as a result of hyperphosphorylation of Tau, which is involved in the regulation of microtubules.

In many pathological studies, it is argued that the biggest reason for Alzheimer's is the accumulation of Ab peptides. The amyloid cascade hypothesis has also been studied in recent years for its effect on Alzheimer's disease. This theory is characterized by the accumulation of extracellular b – amyloid peptides (Ab) outside the cell caused by abnormal APP folding. Various studies based on this hypothesis prove its accuracy. The type I membrane protein APP, which is synthesized in the ER, is cleaved to produce the Ab peptide. This formed peptide is localized with in trans-Golgi network (TGN) after passing via the exocytic and endocytic processes. It has been demonstrated that peptide increased production is directly involved in a neurodegenerative cascade that results in synaptic dysfunction and neuronal death.

Ab can induce activation of the cyclin-dependent kinase 5 (CDK5), a serine/threonine kinase that is vital for neuronal function and causes the Golgi degradation as a result of its excess phosphorylation. In this case, it causes many neurodegenerative diseases, especially Alzheimer's (1). Ab effects are shown in Figure 2.

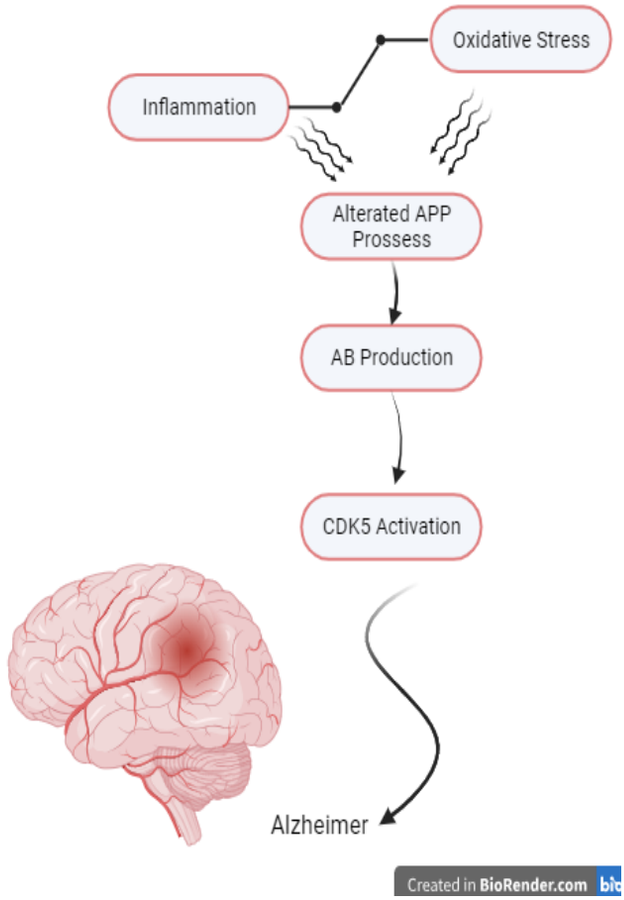

Figure 2. *Ab effects in Alzheimer's. Amyloid Precursor Protein (APP), b-amyloid peptides (Ab), cyclin-dependent kinase 5 (CDK5).*

6.3. Amyotrophic Lateral Sclerosis (ALS)

Motor neurons in the spinal cord, brainstem, and cerebral cortex gradually degenerate in Amyotrophic Lateral Sclerosis (ALS), a fatal neurological condition. Degradation of motor axons and loss of neuromuscular synapses leads to progressive muscle weakness and denervation of skeletal muscle fibers that cause paralysis and usually become fatal when reaching critical muscle groups 2-5 years after disease onset. Although the cause of ALS is uncertain, the disintegration of the Golgi has been detected in ALS patients' motor neurons and cellular disease models. More than 20 gene mutations, including superoxide dismutase (SOD1), and chromosome 9 open reading frame 72 (C9ORF72), may be related to ALS (6). The Golgi fragmentation and SOD1 or optineurin mutations have been defined in ALS patients (4). Mutations in the SOD1 gene form part of ALS forms. These forms are among the most frequently used ALS animal and disease models. As a result of the SOD1 mutation, unstable microtubules are observed (6).

Another known mutation is at the tubulin gene Tubulin Alpha 4a (TUBA4A), which encodes the adult spinal cord and the major alpha-tubulin isoform of the brain in rare forms of ALS. In vitro overexpression of various ALS-induced TUBA4A mutations causes serious changes in the somatic microtubule network. Varioustypes of human ALS and SMA result from mutations in a protein called Dynein, its regulator BICD2 or Optineurin, and mediate vesicle transport in the secretion pathway (6).

6.4. Spinal Muscle Atrophy (SMA)

SMA is a disease characterized by muscle weakness and degeneration of spinal motor neurons. This autosomal recessively inherited disease is caused by a mutation caused by the deletion of the Survival Motor Neuron (SMN) gene. It was observed that BICD2 mutation was inherited as an autosomal dominant form. The BICD2 gene synthesizes the Bicadual D2 protein found in the Golgi. 70% of the factors that cause autosomal dominant SMA are still unknown (2).

The typical SMA caused by the loss of the SMN (Survival Motor Neuron) gene may potentially be caused by a disruption of the communication between microtubules and COP I vesicles. Elevated Stathmin-1 levels are linked to microtubule degradation, axon degradation, and loss of neuromuscular connections In SMA cellular models. Besides, SMN has been shown to connect the COP I subunit to the a-COP and cooperate with the second trafficking on the motor axons. Interruption of SMN / a-COP interaction causes SMN to accumulate in the Golgi and decreased neurite enlargement. Therefore, the Golgi is assumed to be cleaved in SMA mice and patients with SMA / COPI / microtubule dysfunction (6).

6.5. COVID-19

The SARS-CoV-2 virus shows the single-stranded, positive-sense RNA genome; with four structural protein-coding

genes at the 3' end: spike (S), membrane (M), envelope (E), and nucleocapsid (N). Unlike S, the E protein of SARS-CoV-2 has not yet been extensively studied (29). Envelope (E) protein of SARS-CoV-2 is the least-studied protein type. The E protein is a key factor in ER-Golgi localization by affecting the intracellular activities of the host via the C-terminal end area, which is predicted to have a b-coil-b structure leading to its localization in the endoplasmic reticulum, the Golgi, and ER-Golgi space. has been proven. The outcome of a research, a significant difference was observed in the amino acid sequence at the C-terminal end of the E protein. The study's findings revealed that mutations in the region where the Golgi originated and played a crucial function during infection at the C-terminal end of the E protein. These results require more studies on the protein (30). One of the most prominent changes in cells infected with SARS-CoV-2 was the proliferation of the Golgi and related vesicles, as well as the expansion of Golgi sacs. In the study, they observed that particles filled with virions derived from the Golgi in virus-infected cells budded in the cytoplasm (31). It was shown that the majority of genes taken from the SARS-CoV-infected 2B4 cell line caused hyperactivation of the immune system, stimulation of signaling pathways, and subsequently cytokine storm. Phosphatase and tensin homolog (PTEN), which also strongly affects the Golgi, essential function in the activation of dendritic cells, B and T cells that cooperate with genes in cytokine storm in COVID-19 patients, and in the secretion of pro-inflammatory cytokines (32). Considering the studies carried out, we can think that SARS-CoV-2 affects the Golgi in the host cells they infect, it may also cause a change in morphology, and the organelle may undergo stress and cause different cellular responses. More recently, organelle-oriented treatments suggest that detailed studies will apply to COVID-19 disease.

7. TREATMENT APPROACHES IN THE GOLGI FRAGMENTATION

The Golgi, which plays an important role in the formation and maintenance of cellular integrity, is also crucial in disease treatment. As a treatment method, it is an important strategy to target the fragmentation of the Golgi in damaged cells. Small molecules act as inhibitors are known to target the components of the Golgi with different mechanisms of action. Some of these molecules affect the main regulators of the Golgi (such as GTPase, ARF, and PI4KIIIb); others inhibit the Golgi enzymes related to glycosylation or lipid transfer proteins (3). Brefeldin A (BFA), an inhibitor of ARF activation, is a fungal toxin that disrupts the structure of the Golgi. Glycosylation is the most common posttranslational modification. It is thought that inhibition of O-glycan synthesis, which provides the addition of oligosaccharides, may be useful for cancer treatment (3).

The first glycosyltransferase that changes ceramide into the universal precursor of all glycolipid species is glucosyl ceramide (GlcCer) synthase, which is in charge of create glycolipids. Clinically, GlcCer synthase inhibitors are used for substrate reduction therapy (SRT) in the treatment of hepatosplenomegaly, anemia, and thrombocytopenia brought on by the buildup of GlcCer. Currently, substrate reduction therapy (SRT) and enzyme replacement therapy (ERT) are being employed as treatments. In conjunction with ERT, the enzyme is ingested by macrophages and aids in the disintegration of accumulated GlcCer. SRT decreases the quantity of GlcCer by preventing GlcCer Synthase from synthesize it (3).

Inhibitory treatments planned to be used in Alzheimer's disease are still under investigation. GRASP65 is a caspase-3 substrate, which plays a role in the formation of Golgide protein cisterna stacks and the bonding of these stacks invertebrate organisms, and damage to this protein causes the Golgi fragmentation. Concerning this, it is thought that the Golgi integrity can be achieved with GRASP65 in model cell lines and that the modulation of GRASP65 will be therapeutically useful in prevent the expression of non-phosphorylated mutants (33).

Depletion of the Golgi structural proteins GRASP65 and GRASP55 reduces the level of a5b1 integrin. As a result of decreasing this integrin level, adhesion, migration, and invasion of HeLa cells and breast cancer decrease (34). According to this information, molecular treatment methods that can provide the formation or destruction of GRASP65 and GRASP55 proteins in cancer cells should be considered.

Many studies have shown that specific degradation of GOLPH3 returns cancer phenotypes and overexpression of GOLPH3 leads cancer to metastasis in cell culture. It is advised to consider the possibilities of GOLPH3 complex inhibition as a cancer treatment strategy. PITPNC1 is localized in the Golgi and its collapse results in the Golgi's compression, which disrupts the function of the GOLPH3 complex. Besides, knockout of PITPNC1 has previously led to impaired migration, invasion, and metastasis of aggressive breast and colorectal cancer cell lines. The Golgi PtdIns (4) Drugs target the P / GOLPH3 complex will represent a new therapeutic approach based on all available treatment approaches for cancer (26).

The tumor suppressor PTEN acts as a lipid and protein phosphatase. For the treatment of malignancies caused by PTEN loss, it is believed that the Golgi secretion inhibitors, either alone or in conjunction with PI3K/Akt kinase inhibitors, may be therapeutically beneficial (27).

In a study for the treatment of stomach cancer, M-COPA (2-methylcopropilinamide), which causes the Golgi breakdown in cancer cells, was used. M-COPA downregulates cell surface expression, inhibiting the development of gastric tumors that overexpress RTKs such the MET receptor for hepatocyte growth factor (35).

The majority of cancer-related deaths occur from lung cancer, and the five-year survival rate is also relatively low. Non-small cell lung cancer (NSCLC) develops resistance to platinum-based conventional chemotherapy, which is among the causes of this poor prognosis. In one of the studies,

Epidermal growth factor receptor (EGFR) – tyrosine kinase inhibitors (EGFR-TKI) were used to increase survival. These inhibitors have been shown to improve survival in people with non-small cell lung cancer (NSCLC) who have EGFR activate mutations. On the other side, it has been discovered that the disease gives resistance to chemotherapy. As an advanced study, M-COPA, previously used in the treatment of stomach cancer, was used in this study for this resistance. The M-COPA EGFR targeting the Golgi prevented the transport of the protein to the cell surface and proved to show an antitumor effect in resistant cells (35). This study also provides pre-clinical evidence for the treatment of resistant cells.

Because of the adhering studies, we can say that many treatment methods can be done by affecting the Golgi. For the treatment of a variety of diseases, medications that target the Golgi resident proteins are now in the clinical trial phase. Studies targeting the Golgi have been reported to continue the development of novel methods for delivering drugs, such as cell-penetrating peptides or nanoparticles, by minimizing side effects.

8. CONCLUSION

This article discusses the significance of the Golgi in the cell, its function, its responses to stress, and the diseases it causes are examined. Consequently, the Golgi is a central organelle and a key point in cell organization for the modification of proteins. The Golgi reacts to stress, which can cause fragmentation and even cell apoptosis or rescue the cell. Due to mutations that occur in the Golgi, they can also cause cancer, especially neurodegenerative diseases. Since the mutations that occur in the Golgi fragmentation, there are treatment studies on this subject. However, some difficulties observed in the treatment development are increasing the target's specificity and overcoming the cell membrane barrier.

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Acquisition of data for the study: HS.
Analysis of data for the study: HS.
Interpretation of data for the study: HS.
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Clinical and Experimental Health Sciences

The Relationship Between Capsaicin in Chili Pepper and Cancer: A Comprehensive Insight

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ABSTRACT

Capsicum plant consists of savage and tame types, and there is a substance named the capsaicin that causes burning sensation of the bitter peppers. Capsaicin has many effects in the body. In addition to its antioxidant and anti-inflammatory properties, it has benefits such as cancer prevention, reducing blood pressure, having analgesic effects in the body. There are different capsaicinoids such as dihydrocapsaicin, nordroydrocapsaicin, homocapsaicin in nature. These capsaicinoids provide anti-cancer activities by interacting with key signal molecules. Capsaicin can suppress the growth of cancer cells by changing the expression of the relevant genes of cancer cells. In summary, the capsaicin ensures anticancer activity by suppressing the proliferation, growth in cancer cells and to induce apoptosis which inhibit the metastasis. This situation can provide promising new treatment approaches in common and fatal cancer species today. This article revises the relationship between capsaicin and different types of cancer, anti cancer effect of capsaicin. Therewithal, studies examining the treatment of different cancer cells with various doses of capsaicin are included. Capsaicin can suppress the growth of cancer cells by changing the expression of the relevant genes of cancer cells.

Keywords: Capsaicin, cancer, TRPV1, anti-cancer, chili pepper.

1. INTRODUCTION

Red and hot peppers contain a bioactive phytochemical called capsaicin (CAP). It (8-methyl-*N*-vanillyl-6-nonenamide) is the basic content of the bitter peppers in the *Capsicum* plant genus, and it is mainly in membrane and essence of red peppers with red chilli. The domesticated species of the genus *Capsicum*, of which there are about 25 wild species, are *C. pubescens, C. chinense, C. annuum, C. frutescens and C. baccatum. C. Chinense* is the acridest type among the species (1,2). In addition to capsaicin, there are different capsaicinoids in nature, including dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin, which can cause a burning sensation when consumed (3,4). Dihydrocapsaicin and capsaicin are present in mature *Capsicum* at 1:1 and 2:1 (1,5).

Pepper has rich antioxidant features; it contains provitamin A, vitamins C and E, and carotenoids. It has been described that capsaicin has antioxidant and anti-inflammatory qualities, which have a role in lowering blood pressure, supporting weight loss, relieving pain, and preventing cancer (6). In fact, the most widely used therapeutic property of capsicum is its analgesic activity. For this reason, capsaicin is used topically as an analgesic in treating inflammation and pain in various diseases (7). It is known that transient receptor potential vanilloid type-1 (TRPV1) channels are associated with the sense of pain and are important in stimulating sensory neurons responsible for transmitting and determining pain. The active components of chili pepper stimulate TRPV1 receptors, and excessive exposure to these components causes channel desensitisation (8). TRPV1 is from the transient receptor family of cation channel receptors and mediates the analgesic effect. As a result, desensitization of sensory neurons that might cause analgesic effects and depletion of substance P are triggered by the binding of TRPV1 to capsaicin. This has also facilitated the synthesis and isolation of capsaicin-like compounds (TRPV1 agonists) with stronger analgesic effects than capsaicin (9). It has been attempted to show anti-cancer activity within human cancer, mouse models and cell culture. Synthetic and natural TRPV1 agonists could show growth inhibitory effects similar to capsaicin, and it is stated that capsaicin and its analogs show exactly independent anti-cancer activity from the TRPV1 receptor. Synthetic capsaicin mimics and natural capsaicinoids are TRPV1 ligands, but their anti-cancer activities do not include the TRPV1 receptor (6). It is shown that cancer-related pain was less experienced in TRPV1 gene suppressed rats than in the control group, which indicates that TRPV1 channels are associated with pain (10).

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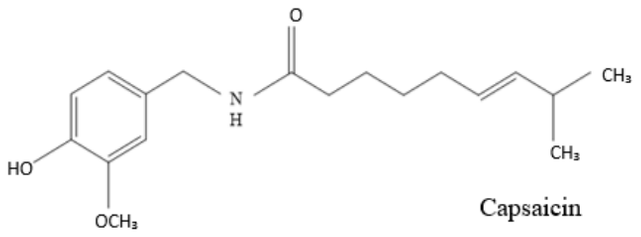

Figure 1. *The structure of capsaicin, whose anti-cancer activity was investigated in cell and animal models.*

It is estimated that 19.3 million cancer cases worldwide in 2020 will reach 28.4 million, with an increase of 47% in 2040 (11,12). The realization of anti-cancer activity is interceded by the interactivity of capsaicinoids with the key signaling molecules of the metabolic, mitochondrial and cytoplasmic survival pathways (1,7,9,13). Although capsaicin and its cellular pathways relating the anti-cancer mechanism are not clearly understood, increased intracellular calcium, suppression of mitochondrial respiration, induction of calpain activity, formation of reactive oxygen species (ROS), inhibition of coenzyme Q, multiple mechanisms included inhibition of transcription factors such as nuclear factor-kB, STAT 3 (signal transducer and transcription activator) and p53 (tumor protein 53) are included in the relevant processes (9,13-15). While the growth of human cancer cells is suppressed by capsaicin, the apoptic activity of cancer chemotherapy agents is supported by multiple mechanisms (9,13,16,17). The p-glycoprotein efflux transporters are inhibited by capsaicin in KB-C2 human endocervical adenocarcinoma cells, and the sensitization of cells to apoptosis and an increase in vinblastine concentration in the cellular microenvironment occurs as a result of treatment of KB-C2 cells with an antimicrotubule drug in the presence of capsaicin (18).

The improving of capsaicin, which is thought to be clinically beneficial for cancer treatment or pain relief, can be prevented by its side effects (9,19). Naturally, such information leads to the pursuit for capsaicin-like compounds that exhibit more anti-cancer activity than capsaicin, which has a fewer side-effect profile. Obtaining compounds with enhanced biological half-life, pharmacological activity, bioavailability, specific therapeutic index relative to capsaicin constitutes another method for the notion of capsaicin-based drug candidates (9).

Related literature review was carried out from March 2020-June 2021 through the selected websites, including World Health Organization (WHO), PubMed, Cochrane Central, Science Direct, Google Scholar, The MEDLINE, Web of Science, Embase, and www.ClinicalTrials.gov. The articles were searched using the keywords such as “capsaicin, capsaicin and its analogs, capsaicin health benefits/effects, apoptotic mechanisms in cancer cells, cancer and capsaicin, capsaicin-cancer chemoprevention mechanisms, cancer – TRPV1 – active ingredient, cancer types and apoptosis capsaicin, cancer therapies and capsaicin, proliferation in cancer”. Studies on cancer and capsaicin have investigated animal, clinical human, *in vivo* and *in vitro* studies.

2. ACTIVE COMPONENTS, MECHANISMS AND ANTI-CANCER EFFECT OF RED PEPPER

Capsaicin, the active ingredient of peppers, is said to have significant antimutagenic and anticarcinogenic activities, and capsaicin has an inhibitive effect on tumor growth in many malignant cell lines. Indeed, it can repress the growth of various cancer cells by stimulating apoptosis in many malign cell lines (20).

When the nutrient content of 100 g of edible red pepper is evaluated, and it is observed that it contains 8.81 g carbohydrates; 1.87 g of protein; 88 g of water; 1.5 g of pulp; 534 µg of beta carotene; 1.24 mg of niacin; 144 mg of ascorbic acid; 43 mg phosphorus (21). Capsaicin, a bioactive phytochemical ample in red and hot peppers, has been observed to change the expression of some genes related to cancer cell survival, metastasis, angiogenesis and growth arrest (13). Furthermore, it has been noted that capsaicin has anti-cancer properties in various cancer models (22).

Inhibition of the activity of TRPV1 channel, which is widely scattered in several non-neuronal tissues and the brain, is associated with the mechanism of action of capsaicin, becomes an anti-cancer agent in many different cancer types (7). Tumor progression is inhibited by capsaicin via suppressing angiogenesis. Capsaicin disrupts the biology of cancer stem cells, alerts non-apoptotic cell death pathways in cancer cells, kills cancer cells resistant to pro-apoptotic stimuli and is bioselective (23). Intraperitoneal implementation of capsaicin has been detected to reduce lipid peroxidation and contribute to the antitumor effect against capsaicin BP-induced lung tumorigenesis in the lungs of Swiss albino mice (15,24). It has been proclaimed that pretreatment of myoblasts with capsaicin significantly inhibits NF-jB and can alleviate LPS-induced inflammation. In contrast, small concentration of capsaicin treatment relieves systematic inflammatory cytokines during different stages of sepsis in rats (25,26). Capsaicin inhibits the proliferation of *Helicobacter pylori (H. pylori)* stimulated human gastric cancer (AGS) cells, which is manifested by decreased TNF-alpha expression and reduced infiltration of mononuclear cells into the gastric corpus and antrum (27).

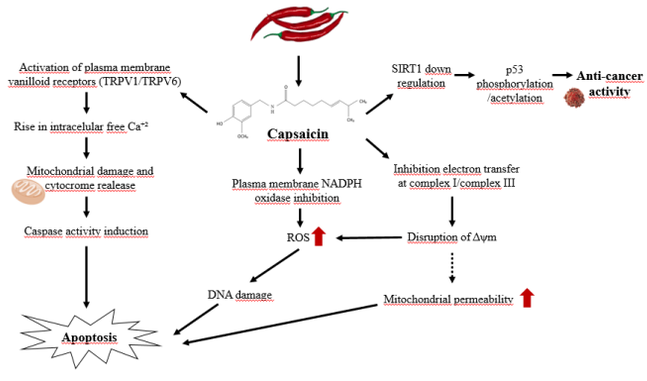

Figure 2. *Apoptosis mechanism and anticancer activity of capsaicin (28, 34)*

Arguably, identifying molecular targets involved in tumor development steps will ensure a promising strategy to fight cancer (13). Apoptosis is when cells generally destroy themselves, regulated by genes, programmed, requiring RNA, protein synthesis and energy, and maintaining homeostasis in the organism (30). Capsaicin, an alkaloid derived from peppers, has conflicting effects in both experimental and human carcinogenesis. Proposed anti-cancer mechanisms of capsaicin stimulate an increase in cell cycle arrest and apoptosis, howbeit the precise cellular mechanisms are still poorly understood (31). Nevertheless, capsaicin has been shown to target a few proteins involved in the mitochondrial death pathway in order to promote apoptosis in various cancer cell lines (13). CAP, a member of the vanilloid family, is the main component of peppers. It has been widely studied for its various pharmacological effects and impact on cell physiology, such as apoptosis and axonal growth of tumor cells is vital. It plays an important role in determining the proliferation of stem cells, in particular by modulating various signaling pathways such as CAP, C/EBPα, PPARγ and Notch signaling (32). Capsaicin shows antioxidant and antiproliferative activities. It can stimulate DNA fragmentation by apoptosis in human esophageal adenocarcinoma (OE19) and human colon adenocarcinoma (Caco-2) cell lines. Addedly, the evaluation of the selectivity index of capsaicin, defined by testing the antiproliferative activity of capsaicin in human fibroblasts, confirms the higher cytotoxicity of this spicy molecule against cancer cells within humans compared to the other cells. To examine the differences in the mechanism of action of capsaicin between cancer cells and other cells in humans, the emphasis must be placed on evaluating the different expression levels of TRPV (transient receptor potential vanilloid) receptors. These receptors play a vital role in apoptic death, determining the increase in intracellular Ca^{+2} (33). Among the proposed capsaicin anti-cancer mechanisms are cell cycle arrest and increased apoptosis (13, 34). Capsaicin can act as a carcinogen or co-carcinogen (35). It has been pinpointed that capsaicin has chemosensitizing effect and anti-cancer activity in many different human cancer types. It has been found that capsaicin compresses progression and tumorigenesis by specifically linking to the transient receptor potential TRPV1 to encourage a transient Ca2+ influx and boost Ca2+ concentration in cancer cells, suppressing proliferation and elevation of apoptosis. Some arguments support that capsazepine as a TRPV1 antagonist cannot entirely inverse the inhibitive effects of capsaicin in cancer cells. This may point to powerful mechanisms other than the TRPV1 signaling pathway that need further investigation (36). It was determined in a study that capsaicin and tNOX (tumor associated NADH oxidase) interacted to trigger the proteasomal degradation of tNOX and inhibition of NAD^{+} dependent SIRT1 (sirtuin 1) acetylase by capsaicin. As a result, acetylation levels of p53 and c-Myc, which increased cell cycle arrest and suppressed the activation of g-cyclin/cyclin-dependent kinase complexes in cancer cells, induced (37). In a study by Sarpras et al. *C. chinense* given at low doses can show cancer chemopreventive effects, induction of apoptosis and upregulation of proapoptotic genes in both cancer cell lines and mouse bone marrow cells, higher *C. chinense* dose can be used for targeted cancer therapy (38). A tumor associated NADH oxidase (ENOX2, tNOX) is inhibited by capsaicin. Thus, stimulating apoptosis reduces cancer cell growth, and capsaicin-mediated inhibition of tNOX prolongs the cell cycle. These molecular events have not been clarified (37). Another study declared that overexpression of the tribbles-related protein 3 (TRIB3) increases capsaicin-induced apoptosis. Apoptotic cell death in cancer cells occurs by regulating TRIB3 expression by capsaicin. Along with these, protein stability and gene expression improvements have also been confirmed to have a key role in capsaicin-induced regulation of TRIB3 (39). More than half of the gradual dissipation of the mitochondrial transmembrane potential and fragmentation of the mitochondria, and subsequent defective superoxide production in mitochondrial electron transport appeared to be associated with apoptosis (1). Cyclin-dependent kinases (CDKs), CDK inhibitors and cyclins form the basis of the cell cycle. When activated, CDKs allow cells to transition from one phase to another (40). It is reported that capsaicin prevents the proliferation of 5637 bladder carcinoma cells through cycle arrest by inhibition of CDK2, CDK4 and CDK6 (1).

Capsazepine is a synthetic analogue of capsaicin (29). It has been enunciated that the TRPV1 antagonist capsazepine exhibits potent anti-tumor activity in osteosarcoma cells and human prostate cancer and shows significant anti-proliferative effects against multiple tumor types *in vitro* (29, 41). In a study, it was indicated that xenograft models in athymic mice and growth of human oral squamous cell carcinoma in cell culture were suppressed by capsazepine. It has also been propounded that the apoptotic activity of capsaicin is independent of TRPV1 (41). Endoplasmic reticulum stress, increased ROS, and subsequently increased intracellular calcium in a phospholipase C-independent pathway by inducing the apoptotic activity of capsazepine. Also, an inhibitor of JAK/STAT3 signaling in prostate cancer cells is capsazepine (42). Nonetheless, capsazepine A549 sensitizes lung cancer cells to radiation therapy (41). Capsazepine can exhibit various pharmacological effects by suppressing the Ca^{2+} flow and blocking the TRPV1 channel (43). Thereupon, although its clinical use has been hindered due to its weak pharmacokinetic properties, it can be used effectively in the prevention and treatment of inflammatory conditions and various cancers (29).

3. TYPES OF CANCER AND CAPSAICIN

Recently, capsaicin has been documented to show anti-cancer activity in a fair number of human cancer types by arresting the cell cycle, suppressing proliferation, alerting apoptosis, and preventing metastasis (1,13,36). In this context, the activity of prostate cancer stem cells via Wnt/beta-Catenin was suppressed by capsaicin. Production of ROS in colon cancer cells disrupted the mitochondrial transmembrane potential and induced apoptosis (36,44,45). Capsaicin is inclined to show preventive

activity against various cancers, including the epithelial, breast, gastric, pancreatic and colon cancers (46). These activities are thought to result from capsaicin-induced activation of ASK-1 and p53 or from NADH oxidase, EGFR-HER2 signaling, MAPKs signaling and Wnt signalling (47,48). It is also agreed that capsaicin remarkably alerted apoptosis of breast cancer *in vivo* and *in vitro* and suppresses the proliferation (36). In addition, primary effusion lymphoma (PEL) is an aggressive lymphoma often resistant to conventional chemotherapies. It is divulged that capsaicin significantly inhibits the growth of Kaposi's sarcoma-associated herpesvirus (KSHV) latent infected PEL cells by inhibiting ERK, p38 MAPK and expression HIL-6, which are known to contribute to PEL survival and growth (48).

4. GASTROINTESTINAL SYSTEM CANCERS

4.1. Esophageal Cancer

In a study using the human ESCC (esophageal squamous cell carcinoma) Eca109 cell line, it was pronounced that capsaicin used at different doses prevented the proliferation of Eca109 cells. Compared to the control groups, the protein expression of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) was significantly decreased by capsaicin, and capsaicin increased the protein expression of SIRT1 in Eca109 cells, AMPK/NF-κB p65 signaling pathway. It has been ascertained that ESCC cells can inhibit the invasion and migration of ESCC cells (49). In another study, capsaicin-induced inhibition of tumor glycolysis occurred in ESCC cells. A decrease in the expression of hexokinase-2 (HK-2) involved in tumor glycolysis was observed as a result of capsaicin treatment (50).

4.2. Gastric Cancer

Gastric cancer has risk factors such as smoking, low vegetable and high salt diet, chronic gastritis with intestinal metaplasia, EBV (Epstein-Barr virus) and *H. pylori* infection (51,52). Some cancers are associated with *H. pylori* infection, whilst others are associated with different causes viz. excessive body weight, damage to gastroesophageal reflux disease (12,53). *H. pylori* infection is accepted as the main cause of non-cardiac gastric cancer (12,54). A study determined that capsaicin is a more potent pro-apoptic agent than eugenol in the presence of p53 (55). In another study, different doses of capsaicin were treated for 48 hours in colon cancer SW-480, gastric mucosal GES-1 and gastric cancer MGC-803 cells. Cytotoxicity due to capsaicin amount was defined in all three cell lines, 16 µg/mL capsaicin eliminated 80% of all living cells, capsaicin-induced cytotoxicity was not solely witnessed in cancer cells; it inhibited proliferation in cancer cells and suppressed cell growth by shifting histone acetylation in gastric cancer cell lines (52).

4.3. Liver Cancer

Aflatoxin, chronic infection with hepatitis B and C virus, excessive alcohol intake, type 2 DM and smoking constitute the main risk factors for hepatocellular carcinoma (HSC) (12,56). In a study, one HSC cell line (PLC/PRF/5, HepG2, HuH7), normal human liver cell line (HL-7702), capsaicin and kinase inhibitor drug were used at different doses. Concomitant use of capsaicin and kinase inhibitor drug significantly induced HSC cell apoptosis and enhanced the suppression of cell proliferation. Additionally, capsaicin dose-dependently boosted the phosphorylated ERK levels in PLC/PRF/5 cells, increased kinase inhibitor sensitivity, and a synergistic suppression occurred in tumor cells (57). In another study, male Wistar rats were fed a diet containing 0.01% and 0.02% capsaicin for 3 weeks. At the end of the third week, 0.02% capsaicin taken with diet increased the antioxidant glutathione system while reducing liver CD68-positive macrophages, lipid peroxidation, serum alanine aminotransferase levels and decreased hepatocyte necrosis and hepatocarcinogen diethylnitrosamine (DEN)-induced oxidative damage. In conclusion, it has been mentioned that capsaicin may be a promising chemopreventive agent when used in the early stages of hepatocarcinogenesis (58).

4.4. Pancreatic Cancer

The incidence of pancreatic cancer is higher in men than in women, and dietary factors, i.e., smoking, diabetes, increased body fat, red and processed meat consumption, and excessive alcohol intake are known to be associated with the disease (59,60). In a study, adding a combination of capsaicin and resveratrol to radiotherapy caused ROS. Capsaicin and resveratrol were found to inhibit radiotherapy-induced DNA damage molecule answer by strongly limiting the first steps of DNA double-strand break repair, keeping cells in the cell cycle and stimulating exacerbated apoptosis (61). In pancreatic cancer cells, capsaicin was found to reduce complex-I and complex-III activity in AsPC-1 and BxPC-3 cells, causing ROS formation. It is articulated that antioxidant levels in tumor cells in capsaicin-treated mice are lower than in control, mitochondrial damage and resulting in ROS accumulation. Thusly, it was determined that capsaicin treatment decreased antioxidant levels in pancreatic cancer cells by producing ROS through mitochondria and caused mitochondrial damage and apoptosis (59,61).

4.5. Colorectal Cancer

In an *in vivo* study, oral gavage administration of 20 mg/kg body weight capsaicin for four weeks reduced intestinal polyp count and the tumor burden of APCmin/+ mice. In the subsequent *in vitro* study, it was determined that capsaicin induced the phosphorylation of cyclin D1 in threonine 286 and decreased the expression of cyclin D1 in a dose – and time-dependent manner. Henceforth, it has been annunciated that capsaicin may be a potential anti-cancer agent targeting cyclin D1 degradation and proteasome activity in colon cancer (62). In another study, the Caco-2 colon cancer cell line was used, and different doses of capsaicin were applied. It illustrated that increased capsaicin dose treatment reduced the mean AgNOR

number and TAA/NA ratio (63). After colon carcinogenesis was onset in male Wistar rats, the animals were given 5 or 50 mg/kg of capsaicin three times a week by gavage for 24 weeks. High-dose capsaicin has been recorded to reduce cell proliferation and the total number of preneoplastic abnormal crypt foci (ACF) in adjacent normal-appearing colonic crypts. It was verified that capsaicin had no effect on total tumor incidence, diversity, cell proliferation, volume and apoptosis in both dose interventions (31).

5. UROGENITAL SYSTEM CANCERS

5.1. Bladder Cancer

All mammalian cells are surrounded by a multifunctional glycan layer, the glycocalyx (64,65). Between the cells and the extracellular space is the outer glycan layer, and controls processes such as endocytosis, cell adhesion and intracellular signalling (65). The glycocalyx of cancer cells depart from the healthy cells concerning the changes in the profile of proteoglycans and glycoproteins (65-69). The ability of the glycocalyx to bind cytokines and growth factors is associated with its tumor-promoting effect (65,68-70). In a study, urothelial UROtsa, human bladder cancer cell line T24, metastatic melanoma cell lines, MV3 and BLM cells were used and Ki-NCs have loaded with model lipophilic cytotoxic drug capsaicin. High-dose capsaicin ingestion has been noted to be lethal for T24 and UROtsa cells (65). In another study, the T24 bladder cancer cell line was used. The effect on the 24-hour cell migration rate was investigated using different doses of capseisin (control, 10, 100 and 200 µM). The usage of 100 and 200 µM capseicin was effective in cell migration in T24 cells, and SIRT1 expression was found to be decreased in T24 bladder cancer cells (71).

5.2. Prostate Cancer

It has been communicated that capsaicin has anti-tumor properties against prostate cancer, inhibits the development of prostate cancer cells, and reduces prostate enlargement in animal models (72,73). At the same time, capsaicin can initiate apoptosis in human prostate carcinoma cells by causing cell cycle arrest (73). It was observed that capsaicin alerted prostate cell death with time and dose difference and rised the amount of cargo protein with LC3-II, which is an autophagy marker. Capsaicin treatment increases lysosomes localized with LC3 positive vesicles and inhibits autophagolysosome degradation. In conclusion, ROS-mediated capsaicin-induced autophagy obstruction promotes antiproliferation in prostate cancer cells (73). In another study, prostate cancer PC3 and LNCaP cell lines were used to treat capsaicin with chemotherapy. It has been uttered that there is a significant decrease in the growth of cells in the combined use of capsaicin and chemotherapy drug (74). Another study stated that the viability of human prostate cancer DU145 and PC-3 cells was decreased by capsaicin, and the Wnt/β-catenin pathway, which is the leading pathway in regulating the activity of cancer stem cells, was inactivated by capsaicin (45).

6. OTHER CANCERS

6.3. Breast Cancer

It is recommended to define and improve other efficient therapeutic agents to reduce side effects and develop the treatment efficacy of chemotherapy in breast cancer (36). In this study, capsaicin induced apoptosis while inhibiting proliferation in breast cancer cells. At the same time, capsaicin inhibits proliferation and promotes apoptosis, which is closely related to FBI-1 (for factor that binds to the inducer of short transcripts). The primary mechanism may be relatived to FBI-1-mediated down-regulation of the NF-κB pathway, and linking capsaicin and FBI-1 may provide an encouraging treatment for breast cancer patients (36).

6.4. Lung Cancer

Small cell lung cancer (SCLC) corresponds to 15-20% of lung cancer cases. It is the most aggressive type of lung cancer (75-77). In a study investigating the anti-cancer activity of the drug and capsaicin combination, it was determined that low-dose capsaicin synergized with the drug and induced apoptosis at the high levels in human SCLC cells. It was reported that human SCLC cells were sensitized to the apoptotic activity of the drug by capsaicin (77). The combined treatment of capsaicin with 5-FU in NSCLC (non-small cell lung cancer) cells and its cytotoxicity were investigated. To determine the relationship between TS expression and capsaicin, H1703 and H520 cells were given 100 µM or different doses of capsaicin for 4-24 hours. It has been reported that while capsaicin decreases protein expression and TS mRNA in a time and dose-dependent manner, it also decreases phospho-p38 MAPK expression through capsaicin (78).

6.5. Bone Cancer

The incidence varies depending on many factors such as age, gender, race (79,80). In a study, the human osteosarcoma cell line MG-63 was used. Using different doses of capsaicin and cisplatin, capsaicin and cisplatin significantly inhibited the growth of MG-63 cells in a dose-dependent manner. Capsaicin is defined as an anti-cancer agent that can induce immunological cell death in human osteosarcoma cells *in vitro* (81). In another study, OS cell lines HOS, 143B and MG63 were used, and when capsaicin was used at different doses, it caused a dose-dependent to reduce in cell viability in all 3 OS cell lines. High concentrations of capsaicin can activate caspase-dependent apoptotic signaling pathways in OS cells. Capsaicin also reduced colony formation ability in 3 OS cell lines from 100-µM dose (82). The studies evaluating the anti-cancer activity of capsaicin and capsazepine in different cancer types are shown in Table 1.

Table 1. *Studies evaluating the anti-cancer activity of capsaicin and capsazepine in different cancer types*

Cancer Types	Study Design	Intervention	Effects
Breast Cancer (83)	*In vitro* study MDA-MB-231 breast cancer cell Control group MCF10A healthy breast cells Induction with capsaicin at doses of 10, 50, 100, and 200 µM	MTT, cell scratch analysis, cell cycle analysis, cell transfection, reverse transcription-quantitative PCR, and western blotting	Viability and migration of MDA-MB-231 breast cancer cells were inhibited by capsaicin Capsaicin induced G2/m cell cycle arrest in MDA-MB-231 cells
Breast Cancer (84)	Polyethylene glycol-conjugated CAP[a] (PEG-Fmoc-CAP_2) polymeric prodrug micelle carrier designed and physically encapsulated with PTX[b] (PTX:paclitaxel)	Synergistic anti-cancer therapy with PTX and CAP	70.5% reduction in tumor growth in mice treated with PTX/CAP-loaded micelles Compared to other treatments, PTX/CAP-loaded micelle shows high *in vivo* antitumor activity in inhibiting tumor growth.
Lung Cancer (77)	Small cell lung cancer cells	Capsaicin and camptothecin at doses of 0, 0.01, 0.1, 1.0, 10.0, 100.0 µM Concomitant use of camptothecin and capsaicin	Human small cell lung cancer cells are sensitized to the apoptotic activity of camptothecin by capsaicin.
Lung Cancer (78)	Non-small cell lung cancer cells H520 and H1703 cells	Concomitant use of capsaicin and 5-FU[c] at different concentrations	Concomitant use of 5-FU and capsaicin has a synergistic cytotoxiceffect on H520 and H1703 cells.
Lung Cancer (85)	Human lung cancer cell line-H1299	Capsaicin at 100 and 200 µM doses	Capsaicin reduces mutant p53 levels and helps cancer cell destruction Reactivates wild-type p53 protein and promotes reactivated p53 cell death
Gastric Cancer (52)	SW-480, gastric cancer MGC-803 and gastric mucosa GES-1 cells	Capsaicin at doses of 0, 2, 4, 8, 16 µg/mL	Inhibited proliferation in cancer cells Suppresses cell growth by altering histone acetylation
Gastric Cancer (55)	The human stomach cell line AGS	Capsaicin in different doses (50, 100, 150, 200, 250, 300, 350 µM) Eugenol in different doses (0.1, 0.4, 0.7, 1.0, 1.4, 1.7 mM)	Capsaicin is a more potent pro-apoptic agent than eugenol.
Prostate Cancer (73)	Human prostate epithelial PC-3 and LNCaP cells	Capsaicin at 20 and 80 µM doses	Increased amount of cargo protein with autophagy marker LC3-II Capsaicin has an anti-proliferative effect on LNCaP and PC-3 prostate cells.
Prostate Cancer (74)	PC3 and LNCaP human prostate cancer cell lines	Concomitant use of Capsaicin and Docetaxel	Capsaicin and docetaxel inhibited the growth of prostate cancer cells with a synergistic effect.
Prostate Cancer (45)	Human prostate cancer PC-3 and DU145 cells	Capsaicin at doses of 1, 5, 10 µM	Dose-dependent capsaicin significantly reduced the viability of PC-3 tumors PC-3 and DU145 down-regulated the protein and mRNA expression of CD133, CD44, ALDH1A1, OCT-4, Nanog and Sox2 in cancer stem cells Capsaicin inactivated the Wnt/β-catenin pathway
Colon Cancer (62)	*In vivo* $APC^{min/+}$ mice *In vitro* Human colon cancer cells (SW480, HCT116, LoVo and Caco-2)	*In vivo* Oral gavage administration of capsaicin at a dose of 20 mg/kg body weight for 4 weeks *In vitro* Capsaicin in different doses (0, 12.5, 25, 50 µM)	*In vivo* A tendency to reduce polyp count and tumor burden in the gut of $APC^{min/+}$ mice was observed. *In vitro* Capsaicin induces phosphorylation of cyclin D1 at T286 and decreases cyclin D1 expression in a dose – and time-dependent manner.
Colon Cancer (63)	Human colon cancer Caco-2 cells	Capsaicin in different doses (25uµ, 50uµ and 75uµ)	Mean AgNOR number and TAA/NA ratio decrease with increasing capsaicin dose therapy.
Colon Cancer (31)	Male Wistar rats	Capsaicin 5 or 50 mg/kg 3 times a week by gavage for 24 weeks	High-dose capsaicin induced cell proliferation in adjacent normal-appearing colonic crypts and reduced total number of preneoplastic ACFs.

Bladder Cancer (86)	Human bladder cancer T24 cell line Second degree carcinoma, cat 5637 cells Male NOD/SCID mice	Capsaicin was given at doses of 0, 50, 100, 150, 200 and 300 µm.	Capsaicin inhibited cell proliferation and migration in bladder cancer cells Capsaicin injection suppressed tumor growth *in vivo* Induces ROS production in bladder cancer cells via the FOXO3a-mediated pathway. Triggered cell cycle arrest in G0/G1 phase
Bone Cancer (81)	Human osteosarcoma cell line MG-63	0.50, 100, 150 µg/ml doses of cisplatin and 0, 100, 200, 300, 400 and 500 µM doses of capsaicin were given.	Capsaicin and cisplatin significantly inhibited the growth of MG-63 cells in a dose-dependent manner. Capsaicin induces immunological cell death in OS[d] cells
Bone Cancer (82)	OS cell lines MG63, 143B and HOS	Capsaicin was given in doses of 50-100-150-200-250-300 µM	Decreased cell viability Inhibitory effect on cell proliferation Activation in caspase-dependent apoptotic signaling pathways
Bone Cancer (87)	Human osteosarcoma cell line MG-63	5, 10, 20, 40 µM capsaicin was given	Capsaicin induces loss of cell viability and apoptosis Capsaicin activates AMPK[e], p53 and JNK[f]. Capsaicin causes cell death by activation of TRPV1[g]-dependent and independent pathways in MG-63 cells.
Liver Cancer (57)	PLC/PRF/5, HuH7, HepG2 hepatocellular carcinoma cell lines and human liver HL-7702 cell line	Capsaicin (0.50,100,150,200,250 µM), sorafenib (0-0.3-1-3-10-30 µmol/L) were given	Suppression of cell proliferation significantly increased Suppression of tumor growth
Liver Cancer (58)	Male Wistar rats	Diet containing 0.01% and 0.02% capsaicin was given for 3 weeks	Decreased serum alanine aminotransferase levels, lipid peroxidation, liver CD68-positive macrophages Decreased oxidative damage and hepatocyte necrosis caused by hepatocarcinogen diethylnitrosamine
Liver Cancer (88)	Human hepatocellular carcinoma HepG2 cell line and human hepatoma cell line Huh-7	Capsaicin was given in doses of 10, 20, 40, 75 µM, sorafenib was given in doses of 0.2, 0.4, 1.5, 2 µM	The combination of capsaicin and sorafenib strongly inhibited growth in HepG2 and Huh-7 cells An increase in apoptosis has been observed Capsaicin alone and in combination with sorafenib induced AMPK activation and acetyl CoA carboxylase phosphorylation in HCC[h] cells.
Pancreatic cancer (61)	8 to 12 week old Swiss male mice and pancreatic cancer cell lines	When tumors reached approximately 100mm^3, mice were given resveratrol and capsaicin in combination with gavage.	Addition of resveratrol and capsaicin combination to radiotherapy increased ROS production Significantly reduced tumor volume in mice
Esophageal Cancer (49)	Human ESCC Eca109 cell line	Capsaicin was given in different doses (0, 25, 50 and 100 µM)	Inhibited proliferation in Eca109 cells Decreased expression of MMP-9 and MMP-2
Esophageal Cancer (50)	Esophageal squamous cell carcinoma (ESCC) cells	Capsaicin was treated at doses of 0, 30, 60, 120 µM.	Decreased HK-2 expression Inhibition on tumor glycolysis in ESCC[i] cells

CAP[a] = capsaicin, PTX[b] = paclitaxel, 5-FU[c] = fluorouracil, OS[d] = osteosarcoma, AMPK[e] = 5' adenosine monophosphate-activated protein kinase, JNK[f] = c-Jun N-terminal kinase, TRPV1[g] = transient receptor potential vanilloid member 1, HCC[h] = hepatocellular carcinoma, ESCC[i] = Esophageal squamous cell carcinoma, STAT3[j] = signal transducer and activator of transcription 3, OSCC[k] = oral squamous cell carcinoma

7. CONCLUSIONS

Capsaicin is a bioactive compound that has recently attracted scholarly attention with its applications in pharmacobiology against cancer. Even though different Capsicum species include high levels of capsaicin, not all of these species can be used as capsaicin sources. More studies on anti-cancer targets of capsaicin, the potential of new treatments in the future, and the possible efficacy in cancer treatment and prevention seem to be required. That said, although clinical studies are not sufficient, it is argued that data on capsaicin concentrations, ways of administration and long-term side effects should be well understood prior to use.

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Clinical and Experimental Health Sciences

Ketogenic Diet Interventions in Inborn Errors of Metabolism: A Review Article

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ABSTRACT

Objective: The ketogenic diet, which has been used in the treatment of epilepsy since the 1920s, is a diet containing high fat, sufficient protein, and low carbohydrate. The ketogenic diet mimics the metabolic effects of fasting by shifting metabolism towards fat utilization. The ketogenic diet, which has different variants, such as the classical ketogenic diet, modified Atkins diet, and medium-chain triglyceride diet, is used in inborn errors of metabolism to target the underlying metabolic state by bypassing the damaged metabolic pathway or to treat the clinical symptoms of inborn errors of metabolism, such as epileptic seizures. In this review, we assessed the evidence for ketogenic diet interventions in the treatment of inborn errors of metabolism.

Methods: The Google Scholar search engine, PubMed, Scopus, and Science Direct databases were used to find studies on the use of ketogenic diet interventions in the treatment of inborn errors of metabolism.

Results: The beneficial effects of different variants of the ketogenic diet on glucose transport type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency have long been recognized. There are also favorable data on its use in myopathic glycogen storage diseases, mitochondrial diseases, and nonketotic hyperglycinemia accompanied by epilepsy.

Conclusion: The evidence is mostly based on individual case reports, case series, and clinical trials with small sample sizes and is insufficient to make recommendations.

Keywords: Ketogenic diet, modified Atkins diet, glycogen storage disease, mitochondrial disease, GLUT1 deficiency.

1. INTRODUCTION

The ketogenic diet (KD), which has been used in the treatment of epilepsy since 1921, is a diet containing high fat, adequate protein, and low carbohydrate. KDs increase ketone (β-hydroxybutyrate, acetoacetate, and acetone) production in the liver by shifting metabolism towards the use of fats as the primary energy source, mimicking the metabolic effects of fasting (1). There are different types of KDs such as the classical ketogenic diet (CKD), modified Atkins diet (MAD), and medium-chain triglyceride (MCT) diet (2). In CKD, the fat-to-protein and carbohydrate ratio is 4-3:1 (4-3 g fat per 1 g protein + carbohydrate), thus reducing carbohydrate intake (3). Due to the restrictive properties of CKD, new variants have emerged, such as MAD with high-fat content, which allows higher protein intake and does not restrict calories and fluid (4). The MAD was first used in 2006 by Kossoff et al (5) in the treatment of intractable epilepsy. The fat/protein + carbohydrate ratio in MAD is 1:1, which offers a more palatable alternative. The MCT diet, is an alternative diet first developed by Huttenlocher et al (6) in 1971 to provide higher carbohydrate intake. The ketogenicity ratio is approximately 1.2:1, which is more palatable than that of CKD. However, it is less commonly used in clinical practice due to its potential gastrointestinal side effects (7).

KDs are used in inborn errors of metabolism (IEMs) to target the underlying metabolic state by circumventing the damaged metabolic pathway or to treat the clinical manifestations of IEMs, such as epileptic seizures (Figure 1). Ketosis must be attained and maintained without catabolism as symptoms may worsen (8). This review aims to examine the efficacy of KDs in the treatment of IEMs and to make recommendations based on current evidence.

2. GLYCOGEN STORAGE DISEASE TYPE III

Glycogen storage disease type III (GSD III, OMIM #232400), also known as Cori disease, is an autosomal recessive IEM

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caused by mutations in the ADL gene, resulting in a deficiency of glycogen debranching enzyme (amylo α-1,6-glucosidase) (9). The debranching enzyme is necessary for comprehensive glycogen breakdown. In GSD III, glycogenolysis and free glucose formation are limited, resulting in limit dextrin accumulation in the liver, muscle, and heart tissues, and hypoglycemia (10). In GSD III patients, glycogenolysis is impaired, whereas glycolysis and gluconeogenesis are preserved. Traditionally, nutritional therapy consists of adequate carbohydrate intake supplemented with raw cornstarch to maintain normoglycemia and adequate protein intake to provide gluconeogenic amino acids, which are substrates for gluconeogenesis (11). The GSD III consensus guideline published by the American College of Medical Genetics and Genomics recommends high protein (25% of total energy) and low complex carbohydrate (<50% of total calories) intake, as well as avoidance of simple sugars (10). Although these measures are effective in achieving metabolic control, they are ineffective in preventing long-term complications. There is no consensus on the optimal nutritional therapy to prevent long-term liver, cardiac, and muscle complications, even in well-metabolically controlled patients. However, eucaloric KD improves energy balance by increasing the blood levels of ketone bodies, which are alternative substrates for energy production in the brain, heart, and skeletal muscles (10). In addition to conventional treatment, novel nutritional therapies, including CKD, MAD, high-fat diet, and synthetic ketone bodies, applied to maintain normoglycemia and improve long-term complications such as cardiomyopathy (CMP) have been reported in recent studies (12-15).

The MAD was reported to lower creatine kinase (CK) levels and improve CMP in 8 pediatric GSD III patients (Olgac et al (12) (n=6), Mayorandan et al (13) (n=2)). Similar results were found in case reports evaluating the efficacy of MAD in three adult patients who reported improved heart and liver functions (Fischer et al (14) (n=2), Francini-Pesenti et al (15) (n=1)). In the evaluation of these 11 patients, asymptomatic hypoglycemia, increased low-density lipoprotein (LDL) cholesterol levels, and weight loss were reported as side effects of MAD. Case reports suggest that carbohydrate-restricted, high-fat, and high-protein diets may be effective in improving CMP in pediatric patients with GSD III (16, 17). A high-protein diet may reduce the accumulation of limit dextrin in myocardial cells and increase protein utilization through gluconeogenesis. A high protein intake can also increase the synthesis of muscle proteins. However, high-fat diets not only increase the activity of gluconeogenesis but also facilitate adenosine triphosphate (ATP) production from fatty acid oxidation and ketolysis as an alternative energy source (10). In a case report with the highest follow-up period, in which a 2:5:1 ratio of CKD was applied for 4 years, CMP and hepatopathy improved, but blood lipid levels were mildly to moderately elevated (n=1) (18). In a different case report, the combined use of a high protein 2:1 CKD and synthetic ketone bodies (3-hydroxybutyrate) for 24 months in a 2-month-old infant improved CMP and no side effects were observed (19). All case studies are reported in Table 1. In a recent systematic review by Rossi et al (20), a significant decline in CK concentration and cardiac hypertrophy was observed in 28 pediatric GSD III patients with cardiomyopathy/myopathy who were given a high-fat diet. Evidence supports the efficacy of a high-fat diet in pediatric GSD IIIa patients with cardiac hypertrophy; however, long-term monitoring is required to avoid potential complications (20). According to these findings, the necessity of raw corn starch in GSD III patients, in whom high protein and high fat diets are sufficient to maintain normoglycemia, is controversial because it causes hyperinsulinemia.

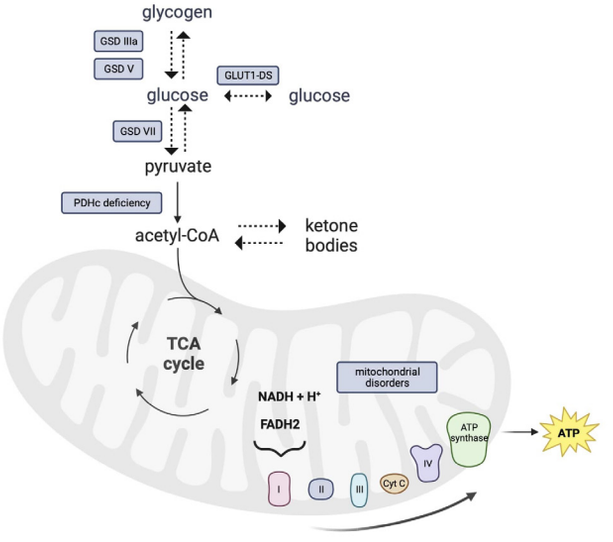

Figure 1. *Inborn errors of metabolism treated on a ketogenic diet (8) Abbreviations: ATP: Adenosine Triphosphate; Cyt C: Cytochrome C; GLUT1-DS: Glucose Transporter Type 1 Deficiency Syndrome; GSD: Glycogen Storage Disease; PDHc: Pyruvate Dehydrogenase Complex; TCA: Tricarboxylic Acid.*

3. GLYCOGEN STORAGE DISEASE TYPE V

Glycogen storage disease type V (GSD V, OMIM #232600), also known as McArdle disease, is an autosomal recessive IEM caused by myophosphorylase enzyme deficiency in the skeletal muscle due to mutations in the PYGM gene, which encodes the muscle isoform of the glycogen phosphorylase enzyme (21). Myophosphorylase, which catalyzes the first step in glycogenolysis by converting intracellular glycogen to glucose-1-phosphate, is responsible for energy production during anaerobic and high-intensity exercise. The absence of myophosphorylase activity in GSD V patients blocks glycogenolysis in the skeletal muscle, leading to exercise intolerance. All activities that require energy expenditure can result in muscle contracture, rhabdomyolysis, and renal failure in extreme cases (21, 22). To date, there is no effective and satisfactory treatment to improve exercise intolerance in patients with GSD V. Strategies to increase the utilization of alternative energy sources in the muscles during exercise are reasonable. Oral sucrose intake before exercise may alleviate muscle symptoms, but excessive consumption may lead to weight gain (23, 24). Interventions to increase fat oxidation are among other reasonable methods.

Table 1. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with glycogen storage disease*

Author, year	Type of GSD	Number of patients	Age at KD start	Duration on KD	Type of KD	Outcomes	Side effects
Olgac et al (12)	GSD III	6	6y (Range: 3y-31y)	6m (Range: 3m-7m)	MAD	• Transaminase levels dropped. CK levels dropped in 5 out of 6 patients.	Hypoglycemia was evident in 2 patients but was resolved by adding uncooked cornstarch to diet.
Mayorandan et al (13)	GSD III	2	9y-11y	Range: 32m-26m	MAD	• CK levels dropped. CMP improved.	Transient asymptomatic hypoglycemia.
Fischer et al (14)	GSD III	2	Unknown	Unknown	MAD	• Reduction of CK, stabilization of blood glucose.	Muscle weakness, tachycardia, stress dyspnea, tremor and a vertigo at the initiation in 1 patient. Weight loss in both.
Francini-Pesenti et al (15)	GSD III	1	34y	12m	MAD	• Heart and liver functions improved.	Increase of uric acid plasma level and C-LDL.
Marusic et al (18)	GSD III	1	11y	4y	2:5:1 CKD	• Improvement of CMP and hepatopathy.	Mildly-to-moderately elevated lipid levels.
Valayannopoulos et al (19)	GSD III	1	2m	24m	Combined use of ketone bodies (3-OH butyrate) and 2:1 KD and high protein diet	• Improvement of CMP.	None.
Løkken et al (29)	GSD V	8	Range: 18y-64y	3w	fat/pro/CHO; Diet 1: 65%/15%/20% Diet 2: 75%/15%/10% Diet 3: 80%/15%/5%	• Improvement of fatty acid oxidation rates and exercise capacity in all diet regimes. • Diet 2 had the highest acceptability score.	3 reported mild fatigue and headaches. 2 reported mild nausea in the beginning of the first week.
Løkken et al (30)	GSD V	8 patients, 4 healthy controls	42y (Range: 25y-70y	-	Administration of a drink containing 395 mgKE/kg D-β-hydroxybutyrate esters or placebo 25 min before a submaximal cycle exercise test.	• No improvement in exercise capacity.	None.
Busch et al (26)	GSD V	1	55y	1y	CKD (80% fat, 14% protein)	• Improvement of exercise tolerance. • Improvement of maximum strength and activity duration. • Reduction of CK. • No improvement in ^{31}P – MRS data during rest, work, and recovery.	Unknown.
Reason et al (28)	GSD V	3	Range: 12y-54y	Unknown	LCKD	• Improvement of activity and exercise tolerance. • Reduction of CK. • Improvement of quality of life.	Unknown.
Vorgerd and Zange (27)	GSD V	1	55y	1y	CKD + creatinine supplementation	• Reduction of CK. • Improvement of exercise tolerance. • No improvement in muscle energy metabolism.	Unknown.
Similä et al (33)	GSD VII	1	59y	5y	MAD	• Alleviation of muscle symptoms. • Improvement of exercise performance, and oxygen uptake.	Increase of cholesterol values.
Swoboda et al (32)	GSD VII	1	4m	1y8m	3:1 CKD	• Alleviation of clinical symptoms. • Improvement of motor skill development. • Improvement of muscle strength.	Unknown.

Abbreviations: CHO: Carbohydrate; CK: Creatine Kinase; CKD: Classical Ketogenic Diet; CMP: Cardiomyopathy; C-LDL: Low Density Lipoprotein Cholesterol; GSD: Glycogen Storage Disease; KD: Ketogenic Diet; LCKD: Low Carbohydrate Ketogenic Diet; MAD: Modified Atkins Diet; P-MRS: Phosphorous Magnetic Resonance Spectroscopy; m: months; y: years.

KD induces the production of ketone bodies by mimicking the metabolic effects of fasting. Ketone bodies are converted to acetyl-CoA, participate in the citric acid cycle (TCA cycle) and are thus used as an alternative energy source for muscle glycogenolysis during exercise (25). Busch et al (26) and Vorgerd and Zange (27) evaluated the effects of the KD in a 55-year-old male patient with GSD V. Administration of a KD containing 80% fat and 14% protein for 1-year increased exercise tolerance by 3-10 fold. Activity duration and maximal strength increased, whereas CK levels decreased. However, 31-phosphorus magnetic resonance spectroscopy data did not improve during rest, work, or recovery. In three adult GSD V patients, a low-carbohydrate KD was similarly reported to improve activity and exercise tolerance, lower CK levels, and improve quality of life (28). No side effects of KD were reported in these case reports. In a randomized pilot study of eight adult patients with GSD V, participants were assigned to one of three ketogenic dietary patterns (#1: 65%/15%/20%; #2: 75%/15%/10%; #3: 80%/15%/ 5%; fat, protein, and carbohydrate) for 3 weeks. Fatty acid oxidation rate and exercise capacity increased in all participants. The second dietary pattern containing 75% fat was found to have the highest acceptability score (29). In a randomized placebo-controlled, crossover study involving the same eight GSD V patients and four healthy controls, 395 mgKE/kg D-β-hydroxybutyrate-containing beverage consumption 25 minutes prior to a submaximal exercise test failed to enhance exercise capacity in both groups (30). Oral ketone ester supplementation probably leads to reduced availability of free fatty acids and glucose in the muscles. On the basis of the current investigation, oral ketone ester supplementation alone is not recommended for patients with GSD V.

4. GLYCOGEN STORAGE DISEASE TYPE VII

Glycogen storage disease type VII (GSD VII, OMIM #232800), also known as Tarui disease or muscle phosphofructokinase deficiency, is an autosomal recessive IEM characterized by muscle cramps, exercise intolerance, and mild myopathy caused by mutations in the PFKM gene. Phosphofructokinase enzyme deficiency in muscle tissue blocks the formation of pyruvate from glucose via glycolysis, preventing glucose from being used in energy metabolism in muscles. Therefore, energy sources other than glucose must be used in the muscle tissue in GSD VII (31).

To date, only two case reports have evaluated the effectiveness of KD in patients with GSD VII. In a child with phosphofructokinase deficiency who presented with severe myopathy, initiation of 3:1 CKD at 4 months of age relieved clinical symptoms, enhanced motor skills, and muscle strength (32). MAD administered to a 59-year-old patient with GSD VII for 5 years alleviated muscle symptoms, increased exercise performance and oxygen consumption. However, high total and LDL cholesterol levels have been reported as side effects of MAD (33).

5. NONKETOTIC HYPERGLYCINEMIA

Nonketotic hyperglycinemia (NKH, OMIM #605899) is an autosomal recessive neurometabolic disorder resulting from mutations in the GLDC or AMT genes that reduce the activity of the glycine-cleavage enzyme complex. Glycine accumulates in body fluids and tissues, including the brain, because of insufficient activity of the glycine-cleaving enzyme complex (34). Currently, there are no effective treatments for severe NKH. Although there are some clinical reports on the use of drugs that lower glycine levels, such as high-dose sodium benzoate, or drugs that reduce the stimulatory effects of the N-methyl-D-aspartate receptors, such as ketamine and dextromethorphan, there has been no significant improvement in the relief of symptoms, such as epileptic seizures (35). It has been reported that combining low-dose sodium benzoate with 3:1 CKD lowers plasma glycine concentrations and offers more stable low glycine concentrations than high-dose benzoate therapy alone (36). Decreases in glycine levels in cerebrospinal fluid (CSF) have also been reported in other studies (37). The underlying mechanism involves a reduction in the glycine pool due to the utilization of glycine for gluconeogenesis. Therefore, ketosis is not the goal of KD in NKH but to support this mechanism with glucose restriction. However, ketosis may have additional benefits. Endogenous utilization of glycine by gluconeogenesis results in a significantly decreased glycine index and concomitant reduction in the required benzoate dose (36).

KD has been proven effective in treating refractory seizures in pediatric patients with different epileptic syndromes. KD mimics the biochemical response to fasting, meeting the brain's energy demand from ketone bodies instead of glucose (38). In recent years, the use of CKD in combination with pharmacological treatment in small groups of NKH patients has shown a reduction in the frequency and severity of seizures and an enhancement in quality of life (36, 37, 39, 40). Table 2 summarizes the study findings. The mechanism of action of KD in the treatment of epilepsy is not fully understood. The neuroprotective properties of KD are explained by increased energy production in the brain through upregulation of genes involved in energy metabolism, mitochondrial biogenesis, and increased energy reserves. KD-induced energy production modifies amino acid metabolism and stabilizes membrane potential in neurons, raising the seizure threshold and exerting anti-convulsant effects (41).

Table 2. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with nonketotic hyperglycinemia*

Author, year	Number of patients	Age at KD start	Duration on KD	Type of KD	Outcomes	Side effects
Kava et al (39)	1	7m	35m	3.5:1 CKD	Reduction in seizure severity and frequency. Normalisation of plasma glycine levels. Reduction in spasticity and hospital admissions. Improvement in quality of life.	Unknown.
Shelkowitz et al (36)	6	Range: 1m-26m	5/6 (Range: 6m->2yr) 1/6 discontinued after 1w.	3:1 CKD	Reduction in plasma glycine levels on average 28%. Reduction but not normalization in brain glycine levels. Reduction in seizure frequency in half of the patients.	Electrolyte perturbations, feeding intolerance.
Shbarou et al (40)	2	Range: 3d-1m	Range: 10m-2.5yr	4:1 CKD	Reduction in plasma glycine levels. Improvement of tonic spasms and tonic-clonic seizure control. Resolution of tonic-clonic seizures.	None.
Daida et al (37)	1	15m	9m	3:1 CKD	Reduction in CSF glycine levels. Reduction of focal seizures. Improvement in quality of life.	None.

Abbreviations: CKD: Classical Ketogenic Diet; CSF: Cerebrospinal Fluid; KD: Ketogenic Diet; d: days; m: months; y: years.

6. MITOCHONDRIAL DISEASES

Mitochondrial diseases are a diverse group of IEMs caused by mutations in genes encoding mitochondrial proteins required for substrate oxidation via the TCA cycle and oxidative phosphorylation (OXPHOS) for ATP production (42). Mitochondrial diseases, which are characterized by abnormal metabolic pathways, cause decreased ATP production and a range of clinical symptoms. Heterogeneous symptoms can occur at any age, particularly in tissues with high energy demands, such as the brain, skeletal, and cardiac muscles (43). The fact that no effective curative treatment has yet been developed makes supportive care for symptom relief a priority. KD stimulates mitochondrial biogenesis, enhances mitochondrial function, and decreases oxidative stress and glycolytic rate. Consequently, it has been suggested as a potential treatment option for mitochondrial diseases accompanied by epilepsy (44).

Current guidelines on the KD report a better response to the KD in respiratory chain complex I deficiency compared to epilepsy (45). Fatty acid beta-oxidation leads to a partial bypass of complex I by producing 5.7 times more $FADH_2$ that can enter complex II compared to carbohydrate oxidation. But since NADH is supplied from all substrates, complex I cannot be bypassed completely (46). Lee et al (47) evaluated the efficacy of 4:1 CKD in 24 patients with mitochondrial respiratory chain enzyme deficiency accompanied by epilepsy. It was reported that seizure frequency decreased by more than 50% in 75% of the patients and no seizures occurred in 50%. In a retrospective review of 20 patients with Lennox-Gastaut syndrome with mitochondrial dysfunction in whom MAD or 4:1/3:1 CKD was administered, it was found that seizure frequency decreased by 75% in 2 patients, 50% in 3 patients, 25% in 1 patient, and no seizures occurred in 2 patients (48). In a retrospective review of 14 patients with complex I, II, and IV defects, it was reported that seizure frequency decreased by more than 90% in one patient, 50-90% in two patients, and no seizure occurred in seven patients during 4:1 CKD intervention. However, four patients did not respond, and the intervention was discontinued due to complications (49). There is only one prospective controlled trial evaluating the effectiveness of KD in the treatment of mitochondrial diseases. In this study evaluating the 12-week intervention of 2:1 CKD, a total of 33 patients were randomized into intervention (n=22) and control (n=11) groups. The control group received a typical diet for one month, followed by three months of KD intervention. After 3 months of intervention, seizure frequency decreased by more than 50% in 40.9% (9/22) of the patients in the intervention group and 72.7% (8/11) of the patients in the control group. KD has been reported to be particularly effective and safe in mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS) syndrome, and pathologic variants of mitochondrial DNA (50). In a recent systematic review study, it was reported that seizure control was achieved in 7/8 patients with mitochondrial disease (no seizure in 5 patients, reduced seizure frequency in 1 patient, and stabilization in 1 patient) (51). There are also case reports regarding the effect of KD in mitochondrial diseases. Satisfactory therapeutic effects of KD have been observed in mitochondrial diseases such as mitochondrial respiratory chain complex I deficiency due to Landau-Kleffner and Ohtahara syndromes, MELAS syndrome, Alpers-Huttenlocher syndrome, POLG disease, MTO1 deficiency, AGC1 deficiency (52-55). The findings of these studies are presented in Table 3.

Table 3. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with mitochondrial diseases*

Author, year	Number of patients	Type of MD	Age at KD start	Duration on KD	Type of KD	Supplements	Outcomes	Side effects
Kang et al (49)	14	9 had Complex I defects 1 had a Complex II defect 3 had Complex IV defects 1 had combined Complex I and IV defects	45m	18m	4:1 CKD	CoQ, B2, L-carnitine	• 7 patients became seizure-free. • Reduction of seizure greater than 90% in 1 patient. • Reduction of seizure between 50% and 90% in 2 patients. • No improvement in 4 patients.	Symptomatic persistent hypoglycemia and persistent metabolic acidosis.
Lee et al (47)	24	Mitochondrial respiratory chain defects	Unknown	Unknown	4:1 CKD	CoQ, L-carnitine, B complex, C, E	• Decrease in seizure frequency over 50% in 18 patients (75%). • 12 (50%) patients became seizure-free.	Dehydration, gastrointestinal discomfort, infection, hyperlipidemia, hypo – glycemia, metabolic acidosis.
Na et al (48)	20	Lennox-Gastaut syndrome	4.6y	13.5m	MAD or 4:1/3:1 CKD	Mitochondrial cocktail treatment	Improvement of seizures and cognitive function.	Vomiting, diarrhea, metabolic acidosis.
Huang et al (50)	KD group: 22 Control group: 11	MELAS, suspected MELAS, MERRF, PDHD, Leigh, COQ10D7 with epilepsy, uncategorized	KD group: 79m Control group: 76m	12w	2:1 CKD	Unknown	• Reduction of seizures.	Vomiting, cold, bloating, gastrointestinal disturbance, hyperlipidemia.
Köse et al (52)	1	Mitochondrial DNA depletion syndrome 13	9m	5d	KD	B1, B2, B7, CoQ	• Non reported.	Metabolic acidosis, hyperlactatemia.
Pfeiffer et al (53)	1	Cerebral aspartate-glutamate carrier isoform 1 (AGC1) deficiency	21m	>4m	4:1 CKD	Unknown	• Reduction in seizures. • Improvement of head and neck control.	Unknown.
Koessler et al (54)	1	POLG disease	16y	3m	4:1 CKD	B1, B2, CoQ	• Improvement of seizures only short-term.	Unknown.
O'Byrne et al (55)	1	MTO1 deficiency	7y	10y	4.75:1/2:1 CKD	B1, B2, CoQ, E, D, L-carnitine	• Temporary seizure reduction.	Reduction in bilateral visual acuity, ptosis and generalized weakness.

Abbreviations: B1: Thiamine; B2: Rivoflavin; B7: Biotin; C: Vitamin C; CKD: Classical Ketogenic Diet; CoQ: Coenzyme Q10; D: Vitamin D; E: Vitamin E; KD: Ketogenic Diet; MAD: Modified Atkins Diet; MD: Mitochondrial Disease; MELAS: Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes; d: days; m: months; y: years.

Considering the high rates of side effects, the KD should be considered as an individual treatment option in this patient group and requires an experienced team (56). Although studies have demonstrated the effectiveness and safety of KD in the treatment of mitochondrial diseases, most of these are case reports and case studies with small sample sizes. To fully comprehend the pathophysiology of mitochondrial diseases and to determine which individuals may benefit from therapeutic effects, further prospective clinical trials are required.

7. PYRUVATE DEHYDROGENASE COMPLEX DEFICIENCY

The pyruvate dehydrogenase complex (PDHc), which links glycolysis to the Krebs cycle, is central to energy metabolism. In PDHc deficiency, the glycolytic end product, pyruvate, cannot be metabolized by the TCA cycle, leading to increased lactate synthesis and impaired ATP synthesis through the mitochondrial respiratory chain. During a carbohydrate-restricted diet, cellular energy is derived from the breakdown of fatty acids instead of glycolysis. The brain uses ketone bodies generated via fatty acid oxidation as an alternative energy substrate to glucose (8).

Nutritional therapy is the CKD, which lowers intracellular pyruvate and lactate levels by providing energy from fat. However, even early initiation of KD is not sufficient to prevent neurologic and metabolic complications (57). Low long-term dietary adherence reduces the beneficial effects. A less restrictive, 10% carbohydrate KD provided clinical stability and improved compliance in neonatal-onset patients with low compliance to standard KD (58). A study evaluating CKD and MAD's long-term efficacy in 19 patients with PDHc deficiency reported that treatment mainly improved epilepsy, sleep disturbance, ataxia, speech and language development, and hospitalization frequency (59). Following the diagnosis of PDHc deficiency, it is recommended to start KD as soon as possible to prevent brain damage (59). The long-term efficacy of KD depends on regular monitoring of plasma ketone levels and adjustment of diet composition to maintain ketosis. In a case report in which intravenous KD was administered within the first 24 hours postpartum, lactic acidosis resolved immediately with no apparent adverse effects, developmental outcomes improved, and the cases did not show epilepsy (60). However, KD may cause some side effects, particularly energy and nutrient deficiencies, which can result in weight loss and growth retardation, and temporary elevation of plasma lipid levels (61). Therefore, triglyceride and cholesterol levels should be monitored periodically in patients with PDHc deficiency on KD, especially during acute illness, and adequate energy intake should be assessed to prevent growth retardation and the risk of energy deficiency (62). Data evaluating the efficacy of KD in PDHc deficiency are based on a few case reports (Table 4). Therefore, clinical studies evaluating adherence to KD variants and the long-term effects of less restrictive ketogenic dietary practices are needed.

Table 4. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with pyruvate dehydrogenase complex deficiency*

Author, year	Number of patients	Age at KD start	Duration on KD	Type of KD	Outcomes	Side effects
Inui et al (60)	2	1d	Range: 1y-2y	Intravenous KD	• Improvement of lactic acidosis. • Better developmental outcomes. • Epilepsy did not exhibit.	None.
El-Gharbawy et al (58)	1	15m	1y	#1 4:1 CKD and 3:1 CKD with MCT oil. #2 A less restrictive KD including ketocal formula, allowing 10% of CHO.	• Improvement of compliance. • Remaining clinically stable. • Showing developmental progress.	None.
Sofou et al (59)	19	2.5y (Range: 1w-15y3m)	2.9y (Range: 6m-6y11m)	7/19 received CKD 12/19 received MAD	• Improvement in epilepsy, ataxia, sleep disturbance, speech/language development, social functioning, and frequency of hospitalizations.	Acute pancreatitis in 1/19.
Pisa et al (62)	1	2.5y	6m	3:1 CKD	• Reduction of seizure frequency. • Improvement of psychomotor development.	Increase in cholesterol and TG.

Abbreviations: CHO: Carbohydrate; CKD: Classical Ketogenic Diet; KD: Ketogenic Diet; MAD: Modified Atkins Diet; MCT: Medium Chain Triglyceride; TG: Triglycerides; d: days; m: months; y: years.

Table 5. *Case reports, case series and clinical studies referring to the effect of the ketogenic diet in the management of patients with glucose transporter type 1 deficiency syndrome*

Author, year	Number of patients	Age at KD start	Duration on KD	Type of KD	Outcomes	Side effects
Ito et al (75)	6	Range: 7y-16y	Range: 1m-42m	MAD	• Reduction of epileptic seizures and other paroxysmal events. • Improvement in the background activity and disappearance of epileptic discharges. • Improvement of motivation and cognitive function. • Improvement of non-paroxysmal permanent ataxia, spasticity, dysarthria, and dystonia.	No serious side effects Nausea, vomiting, fatigue, headache, constipation, opsoclonus, hyperlipidemia, and hyperuricemia at the beginning.
Pong et al (72)	64	4y	>5y	4:1 CKD	• 67% (41/61) were seizure-free and 68% of seizure-free patients (28/41) resolved in <1 week and 76% (31/41) in <1 month.	None.
Bekker et al (79)	7	8y (Range: 4y-11y10m)	Range: 1w-3y8m	CKD, MAD, or MCT-KD	• Failure to reduce seizure frequency.	Nausea, belching, abdominal pain, diarrhea, constipation, vomiting.
Ramm-Pettersen et al (74)	10	15 y (Range: 3m-49y)	Unknown	2.5-4:1 CKD or MAD	• Disappearance of epileptic seizures. • Improvement of paroxysmal exercise-induced dyskinesias except 2 of the patients treated with MAD.	Hypoglycemia.
Sandu et al (73)	4	Range:7y-13y	Range: 6m-2y	MAD	• Improvement of movement disorder. • Improvement of seizures control.	Abdominal pain.
Fujii et al (76)	31	12y (Range: 3y–35y)	44m (Range: 1m–96m)	17/31: MAD 11/31: CKD 3/31: MCT-KD	• Improvement on seizures, transient aggravation after fasting and ataxia. • No improvement in intellectual development.	None.
Gumus et al (70)	6	2.5y-13y	Range: 6m-24m	4:1 CKD	• Disappearance of epileptic seizures in 5/6. • Less improvement in ataxia, spasticity, and dystonia. • No improvement in the intelligence quotient level or microcephaly. • Moderate improvement of alertness, concentration, motivation, and activity.	5 reported nausea, vomiting, constipation, and fatigue.
Amalou et al (77)	10	Range: 4m-16y	2.5y (Range: 6m-6y)	MAD	Improvement in epileptic seizures. Control of movement symptoms. Improvement in physical abilities and growth parameters.	Constipation, compliance.
Ruiz Herrero et al (78)	18	5y2m (Range: 3.5m-17y4m)	463d (Range: 170–1863d)	6/18 had 3:1 CKD 12/18 had MAD	Improvement in movement disorder. Reduction in seizures.	Constipation, hypercalciuria, hyperlipidemia.

Abbreviations: CKD: Classical Ketogenic Diet; KD: Ketogenic Diet; MAD: Modified Atkins Diet; MCT-KD: Medium Chain Triglyceride-Ketogenic Diet; d: days; m: months; y: years.

8. GLUCOSE TRANSPORT TYPE 1 DEFICIENCY SYNDROME

Glucose transport type 1 deficiency syndrome (GLUT1-DS, OMIM #606777) is caused by mutations in the SLC2A1 gene, which encodes the GLUT1 protein involved in transporting glucose across the blood-brain barrier (63). Mutations in this gene block the transport of glucose into brain cells and cause low levels of glucose in the CSF, hypoglycorrhagia. GLUT1-DS is typically characterized by early onset epilepsy, growth retardation, complex movement disorders, and microcephaly (64). Since the identification of the disease in 1991, KD has been administered to an increasing number of GLUT1-DS patients (65). KD is considered the gold standard in the treatment of GLUT1-DS. In the brain, glycogen stores are quickly depleted during starvation. Since amino acids and lipids cannot be used for the generation of energy, ketones are used to maintain normal brain function. Ketones are produced by fatty acid oxidation in the liver and taken up into brain cells by facilitated diffusion regulated by the monocarboxylate transporter 1 (MCT1) transporter. When administered early, KD attenuates GLUT1-DS related

seizures. However, its effect on other symptoms is variable and moderate (66).

Treatment of GLUT1-DS with KD is not different from treatment of intractable epilepsy. Dietary carbohydrates should be restricted, individually calculated, and supplemented with multivitamins and minerals (67). A recent systematic review of 270 GLUT1-DS patients with a median follow-up of 53 months reported that epilepsy improved in 83% of 230 patients, movement disorders in 82% of 127 patients and cognitive function in 59% of 58 patients, and that the beneficial effects were more pronounced in patients who started treatment early (68). Epileptic seizure frequency was reported to be reduced by more than 50% in 95% of GLUT1-DS patients treated with KD and by more than 90% in 80% (69). The majority of GLUT1-DS patients have thus far been treated with 3:1/4:1 CKD (70). It has been reported that seizures did not occur in 60% of patients and movement disorders improved in 80% after CKD intervention (71). As a result of the intervention of 4:1 CKD for more than 5 years in 64 patients, 67% (41/61) were seizure-free and 76% (31/41) resolved in less than 1 month (72). In infants under 2 years of age, 4:1 CKD may be more effective in inducing ketosis, but it may cause growth retardation as it does not provide sufficient protein. Therefore, it has been suggested that 4:1 CKD may be effective in infants with severe phenotypes, whereas 3:1 CKD is recommended for infants with mild phenotypes and older patients (65).

Considering the long-term side effects of CKD, such as growth retardation and dyslipidemia due to high fat content, and the lack of compliance of patients with the diet, more palatable and easier-to-administer KD alternatives, such as MAD, have been tried, especially in school-age children and adolescents. For this reason, MAD has been used in GLUT1-DS patients in the last 10 years and its beneficial effects have been demonstrated (73, 74). Ito et al (75) reported the benefits of MAD used for 1-42 months in six patients aged 7-16 years. MAD resulted in a reduction of epileptic seizures and other paroxysmal events. Improvements in cognitive function, ataxia, spasticity, dysarthria, and dystonia have been reported with no serious adverse effects. In similar studies reported in the following years, it was reported that the frequency of epileptic seizures decreased, and movement disorders improved with MAD intervention (Fujii et al (76) (n=17), Amalou et al (77) (n=10), Ruiz Herrero et al (78) (n=12)). To date, the efficacy of the MCT diet has been evaluated in four patients. Fujii et al (76) (n=3) reported improvement in seizure frequency and ataxia, while Bekker et al (79) (n=1) reported no reduction in seizure frequency. All data from literature are reported in Table 5. Findings regarding the effects of KD on cognitive functions are contradictory. Some studies (80-83) reported improvement in cognitive function, while others (70,76,84) show no benefit of KD. Since the developing brain requires more energy in the first years of life, starting KD treatment as early as possible in the presence of suspected GLUT1-DS is essential for better cognitive outcomes (85).

The side effects of KD in GLUT1-DS patients are similar to those in children treated for refractory epilepsy. Growth retardation and dyslipidemia are among the long-term adverse effects and remain a cause for concern. Nonetheless, it should be continued until adolescence to satisfy the growing energy needs of the developing brain. The ketogenicity of MAD is similar to CKD and there are data reporting similar beneficial effects. Considering that MAD may be as effective as CKD in patients with GLUT1-DS, is less restrictive and has fewer side effects, it is recommended that the type of CKD to be applied should be decided individually.

9. CONCLUSION

Overall, KD has shown promising results in treating a range of IEMs and is becoming a more widely accepted treatment option. Numerous studies have demonstrated the efficacy of KD in treating GLUT1-DS and PDHc deficiency, and its positive effects are increasingly being reported for other IEMs. KD is used in IEMs to bypass the damaged metabolic pathway or to treat clinical symptoms such as epileptic seizures. The data regarding the improvement of the clinical outcome in GSDs with myopathy, NKH and mitochondrial diseases accompanied by epileptic seizures are promising, but the evidence is based on a few case reports and case series and is insufficient to make recommendations. Therefore, further research and clinical trials are needed to establish the efficacy and safety of these treatments in larger populations. It is important for healthcare professionals to continue monitoring and assessing the potential benefits and risks of these treatments for patients with these conditions.

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