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The Relationship Between the Social Support Perceived by the Mothers and Their Motherhood Experience

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ABSTRACT

Objective: Becoming a mother, is one of the most important developmental events in a woman's life. This study, by making Turkish validity and reliability study of Being a Mother scale which was developed by Matthey, was conducted methodologically and analytically in order to determine social support which mothers perceived and motherhood experiences.

Methods: The study universe consists of 588 volunteer mothers, who have a child between 0-3 year range, that holds the criteria for the study and applied September 2015-March 1016 University Training and Research Hospital. Data was gathered with question form, which was prepared by researchers, Being a Mother Scale (BaM 13) and Multi-dimensional Perceived Social Support Scale (MDPSSS). Data were evaluated with the help of IBM SPSS Statistics 23 and IBM SPSS AMOS 23 statistics programs.

Results: It was determined that 45.7% of mothers remain in the 28-34 year range and 47.1% were primary school graduates. It was seen that the Being a Mother Scale has good psychometric characteristics. It was determined that the model, which consists of 25 statements with 6 factors integrated structure of Being a Mother Scale and Multidimensional Perceived Social Support, generally fits for the research purposes.

Conclusions: As a result of the validity and reliability study of the Being a Mother scale, it was seen that it is applicable for Turkish society. A decrease of satisfaction from motherhood was determined accordingly decreasing social support.

Keywords: Motherhood, social support, motherhood experience, reliability, validity scale

1. INTRODUCTION

Being a mother is among the most crucial developmental phases of a woman (1). The bond between the mother and her child starts during maternity and increases gradually over time (2). The intimacy between the mother and the baby during the early postpartum period facilitates the adaptation to the role of being a mother (3). According to Mathey perceived social support is a significant factor in the increase of motherhood satisfaction (4).

Motherhood is a flexible concept affected by several factors including the social, cultural, political, and ethical ones. It is fictionalized culturally, and women are thought to be a mother in the socialization process. The motherhood experience has similar universal characteristics and is affected by the culture (5).

Being a mother is seen as a duty to be conducted in Turkey just as in other cultures and mothers culturally prepare themselves to fulfill this duty. Motherhood is a dynamic process with different excitements assigning extra responsibilities to the other members of the family as well (6,7). The age, education, social status, work status, socioeconomic condition, personality characteristics of the mother as well as problems during the pregnancy can be listed as some of the factors affecting the adaptation to motherhood (8).

Social support can be defined as the relationship among the people required for psychosocial, economical, and cognitive support and it has a crucial role in maintaining and sustaining the state of health (9). For the last 25 years, social support has been in the center of interest for coping strategies and as a preventive health care method (10). The social support system is a powerful source in terms of the solutions to psychosocial problems, prevention of these problems, and also coping with tough conditions. There are various studies in the literature on the positive relationship of social support on psychological and physical health (11-13). Since the motherhood period refers to the lives of two people – the mother and the baby –, it can be considered as one of the most important intervals whenever social support is vital.

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According to Mathey (2011) perceived social support is significant for the increase in the satisfaction of maternity. Social support is also an indicator for the mothers' own consideration in regard to the feeling of adequacy as a parent, positive marital relationship, antenatal mental well-being, and satisfaction towards maternal role and baby-care (4,14,15).

The adaptation of the mother to her new role is significant in terms of having adequate knowledge and skill to fulfill the care requirements. The consultancy has given by the healthcare professionals starting with the prenatal stage functions as social support in gaining the feeling of adequacy and minimizing the anxiety level (14,16,17).

This study was conducted on the basis of the assumption that establishing the support requirements for mothers will guide the healthcare professionals in their consultancy and training processes.

2. METHODS

2.1. Aim and Type of the Study

This study was conducted methodologically and analytically in order to determine the relationship between the perceived social support and the maternal experience after the Turkish validity and reliability assessment of Being a Mother Scale-BaM 13.

2.2. Research Consent

For the application of Being a Mother Scale-BaM 13 written permission was taken from Stapphen Matthey who developed the scale. Besides, necessary permissions were taken from Sakarya University Training and Research Hospital and Sakarya University Faculty of Medicine Clinical Research Ethics Committee (2015/71522473/050.01.04/99) in order to conduct the research which was conducted on a volunteer basis.

2.3. Validity and Reliability Study of the Scale

2.3.1. Universe and Sample

The universe of this study contains the mothers of the children between the age range of 0 and 3 who were staying in the clinics of Sakarya University Training and Research Hospital and who applied to the hospital between September 2015 and March 2016. Besides, 588 (five hundred and eighty-eight) volunteer mothers who applied to the above-mentioned clinics and who are matching the criteria generated the sample. And the test-retest method was conducted with the participation of 30 mothers.

2.3.2. The Tools Used for Data Collection

Questionnaire Form: This form includes 28 questions on personal characteristics and on general medical condition all of which was prepared by the researcher in accordance with the literature review (4,11,13,14)

Being a Mother Scale (BaM-13): Being a Mother Scale (BaM 13) was developed by Matthey in 2011 to determine the maternity experience of the mothers of a child between the age range of 0 and 3. The scale consists of 13 questions. The Cronbach'sAlphavaluewasfoundas0.798inMatthey'sstudy(4).

Scoring: The scale consists of 13 items each of which are scored between 0 and 3 and in which the higher scores indicate a lower satisfaction for the maternal experience. To facilitate the scoring each item was scored in the same manner: 0, 1, 2, 3. The total score varies between 0 and 39. The data with a score of 9 and above indicate a significant level of maternal dissatisfaction. The 13th, 9th, 12th, 3rd, 10^{th,} and 11th questions evaluate the sub-dimension of child experience, the 5th, 6th, 7th, 11th, 2^{nd,} and 8th questions evaluate the sub-dimension of adult experience, and the 1st and the 4th questions evaluate the sub-dimension of emotional intimacy (4).

Multi-Dimensional Perceived Social Support Scale (MDPSSS): Multi-Dimensional Perceived Social Support Scale was developed by Zimet et all in 1988 (41,18) and it was adapted to Turkish adaptation by Eker, Arkan and Yaldız. In the factorial structure, validity, and reliability study of the revised version of the MDPSSS by Eker, Arkan & Yaldız (2001) the Cronbach's Alpha reliability coefficient was found as 0.80-0.95 (10). The scale consists of 12 questions all of which can easily be understood by anyone regardless of the education level. In this study, the Cronbach's Alpha reliability coefficient was found as .921.

2.3.3. The Validity Study of the Scale

Content Validity: The directives and the questions of the scale which were translated into Turkish were sent to various faculty members of the High School of Nursing and Medical Schools in Turkey and to the experts in order to evaluate the accuracy in terms of language and expression and the comprehensiveness in terms of the topic. 12 expert opinions were regarded, and the items were corrected in terms of language and expression. The interscore concordance of these 12 experts for the content validity of the 13 items in the scale was examined with Kendall Coefficient of Concordance Correlation Test. To evaluate the concordance of the scores of the experts Kendall's coefficient of concordance (W) was calculated. It was concluded that the experts reached an agreement on the content of the items and that all the expressions are in accordance with Turkish culture and represent the targeted scope (p=0.115).

Construct Validity-Exploratory Factor Analysis (Being a Mother Scale – BaM – 13): In this study which was conducted with 588 participants to determine the relevance of Being a Mother Scale (BaM-13) to Turkish society, the data were transferred to IBM SPSS Statistic 23 program. First, exploratory factor analysis was performed with 147 randomly chosen participants in the data set, and "Principal Components Analysis" was preferred as the factor exploratory method.

Factor number related to any scanting was not made. For factor load, statements above 0.500 were preferred (Table 1).

Table 1. *Results of KMO and Bartlett*

Kaiser-Meyer-Olkin (KMO)		0.768
Bartlett Sphericity Test	X^2	480.031
	Sd	78
	P	**<0.001***

** Statistical significance*

According to this table, Kaiser-Meyer-Olkin (KMO) value was found as 0,768. Therefore, it is likely that the factor analysis results to be performed with the data will be useful and applicable. With the results of Bartlett Sphericity test, it was inferred that there is a significantly high correlation among the variables and that the data are suitable for the performance of factor analysis (X^2: 480.031, SD: .78, p<0.001).

After the factor analysis the numbers of the items – which was 13 – were unchanged. According to the results of the content validity of these 13 items, three factors were found out and all the factor loads were over 0.500.

The sub-dimension of the adult experience expresses 21.526% of the total variance; the sub-dimension of the child experience expresses 17.838% of the total variance and the sub-dimension of emotional intimacy expresses 13.294% of the total variance. Thus, all these three factors express 52.658% of the total variance.

Confirmatory Factor Analysis (Being a Mother Scale – BaM): Confirmatory factor analysis was applied via IBM SPSS AMOS 23 program with 294 randomly chosen participants from the data set of 588 participants.

In the first phase, a first-order CFA model where the three-factor-dimension (F1: Adult Experience, F2: Child Experience, F3: Emotional Intimacy) were the latent variable and the expressions generating these factors where the indicator variables were created in Figure 1. As the latent variable wasn't metrical, a value of 1 should be assigned to one of the lines drawn from the latent variable to the indicator variable (the factor load should be equated to 1) or any value (mostly 1) should be assigned to the variant of the latent variable to estimate the parameter values (19,20).

In the second phase, the maximum likelihood method which is generally used for structural equation modeling and which gives reliable results even when the data weren't distributed normally was used for estimation of the model and estimation of the errors of the observed variables, the variances of the latent variables and the parameters including the regression coefficients regarding the lines drawn from the latent variables to the observed variables were targeted. For the betterment of the fit indices, a two-way relationship was established between the error terms in the questions of "I had difficulties in coping with the situation when my baby cried." and "I felt guilty." both of which have the highest modification indices values in Being a Mother Scale. Besides, a relational set-up among the dimensions was assembled to establish the expected covariance among the dimensions and these relationships among the dimensions are illustrated in Figure1. Finally, in the last phase, the fit indices constructed for the three-dimensional first-order CFA Model were examined. It was observed that the three-factor-structure of Being a Mother Scale consisting of 13 items generally correlates well.

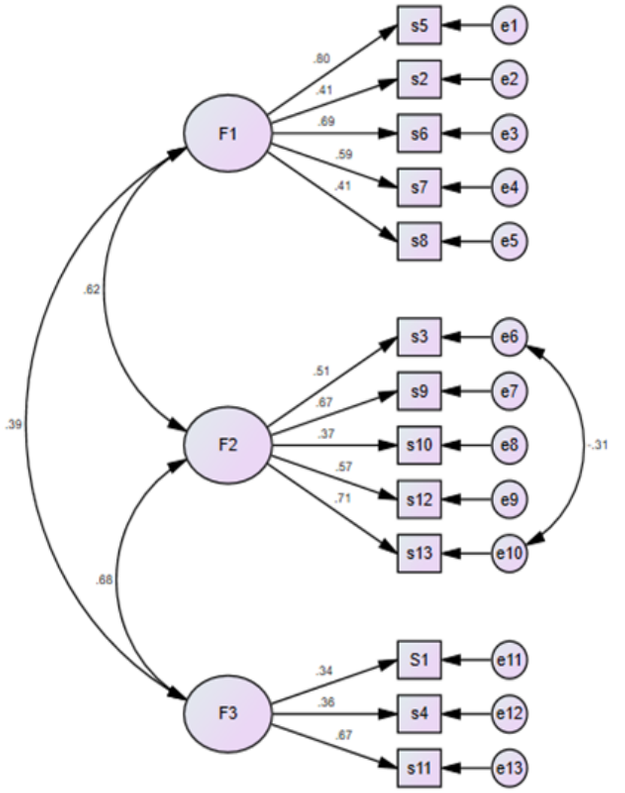

Figure 1. *A first order CFA Model with three different sub-dimensions*

On looking at the obtained adaptive value it can be stated that while χ2/df, GFI, RMSEA, and SRMR values are good, IFI, TLI, and CFI values are unacceptable (3,19,20,21). According to the fit indices it can be declared that Being a Mother Scale is acceptable.

Second-Order Confirmatory Factor Analysis (Being a Mother Scale – BaM-13) and Multi-Dimensional Perceived Social Support Scale (MDPSSS): Confirmatory factor analysis was applied via IBM SPSS AMOS 23 program with 294 randomly chosen participants from the data set of 588 participants. In the first phase, a second-order CFA model where two scales and the six-factor-dimension (F1: Adult Experience, F2: Child Experience, F3: Emotional Intimacy, F4: Family, F5: Friend, F6: A Special Person, F7: Multi-Dimensional Perceived Social Support Scale, F8: Being a Mother Scale) were the latent variables and the expressions generating these factors where the indicator variables were created in Figure 2. As the latent variable wasn't metrical, a value of 1 should be assigned to one of the lines drawn from the latent variable to the indicator variable (the factor load should be equated to

1) or any value (mostly 1) should be assigned to the variant of the latent variable to estimate the parameter values (4,10). In the second phase, the maximum likelihood method which is generally used for structural equation modeling and which gives reliable results even when the data weren't distributed normally was used for estimation of the model and estimation of the errors of the observed variables, the variances of the latent variables and the parameters including the regression coefficients regarding the lines drawn from the latent variables to the observed variables were targeted. For the betterment of the fit indices a two-way relationship was established between the error terms in the questions of "I felt lonely and isolated" and "I felt like I wasn't supported", the questions of "I had difficulties in coping with the situation when my baby cried." and "I felt guilty, the questions of "I was worried about something bad might happen to my baby" and "I was worried because I thought I am not as good as the other mothers", the questions of "I was sure that I can take care of my baby when he/she was born" and "I felt close to my baby" in Being a Mother Scale as well as the questions of "In can get the necessary emotional help and support from my family" and "I can talk to my family about my problems", the questions of "I can count on my friends when things do not go well" and "I have friends with whom I can share my happiness and sorrow", the questions of "There is a person other than my family and friends with me whenever I need" and "There is a person other than my family and friends with whom I can share my happiness and sorrow" in the multi-dimensional perceived social support scale, all of which have the highest modification indices values. Besides, establish the expected covariance among the dimensions, and these relationships among the dimensions are illustrated in Figure1. Besides, a relational set-up among the dimensions was assembled to establish the expected covariance among the dimensions and these relationships among the dimensions are illustrated in Figure 2.

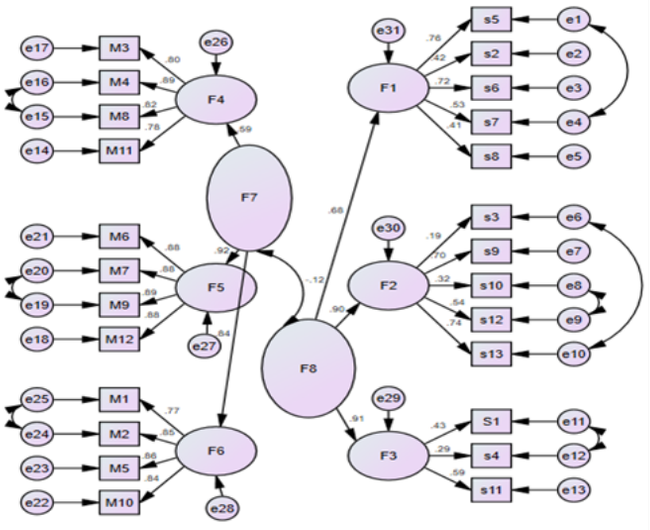

Figure 2. *Two scales and second order CFA model with the six-factor*

In the last phase, the fit indices for the two scales and the second-order CFA model with six-factor dimensions were analyzed. On examining the obtained findings, it can be concluded that the model generally correlates well respecting the usability of the 25 expressions and the six-dimensional structure of both Being a Mother and Multi-Dimensional Perceived Social Support Scale together.

On looking at the obtained adaptive value it can be stated that while χ2/df, GFI, IFI, TLI, CFI, RMSEA, and SRMR values are good, the GFI value is unacceptable (2023).

Reliability of the Scale and the Dub-Dimensions: A calculation was made for each scale and sub-dimension and Cronbach's Alpha value was calculated (Table 3)

Table 2. *Scale factors*

	Factor Loads	Percentage of Variance	Eigenvalue
Adult Experience		**21.526**	**2.798**
I have felt lonely or isolated.	0.805		
I have felt unsupported .	0.771		
I have felt bored .	0.724		
I have felt alright about asking people for help or advice when I needed to .	0.669		
I have felt confident about looking after my baby/toddler.	0.520		
Child Experience		**17.838**	**2.319**
I have been worried that something would happen to my baby/toddler.	0.715		
I worry I am not as good as other mothers .	0.669		
I have felt guilty.	0.630		
I have felt nervous or uneasy around my baby/toddler.	0.519		
I have found it hard to cope when my baby/toddler cries.	0.503		
Emotional Intimacy		**13.294**	**1.728**
I have felt close to my baby/ toddler.	0.786		
I have felt confident about looking after my baby/toddler	0.661		
I have been annoyed or irritated with my baby/toddler.	0.521		
Total		**52.658**	**6.846**

Table 3. *Reliability of the Scale and the Sub-Dimensions*

		Questions	Item-Total correlation	Cronbach's Alpha When item deleted	Cronbach's Alpha	
Being a Mother Scale (BaM-13)	Adult Experience	s5	0,521	0,739	0,757	0,769
		s2	0,444	0,749		
		s6	0,541	0,738		
		s7	0,513	0,740		
		S8	0,260	0,768		
	Child Experience	s3	0,452	0,748	0,676	
		s9	0,557	0,742		
		s10	0,264	0,774		
		s12	0,422	0,751		
		s13	0,458	0,749		
	Emotional Intimacy	S1	0,273	0,765	0,509	
		S4	0,118	0,773		
		s11	0,357	0,762		
(MDPSSS)	Family	m11	0,600	0,917	0,867	0,921
		m8	0,620	0,917		
		m4	0,592	0,918		
		m3	0,623	0,917		
	Friend	m12	0,729	0,912	0,904	
		m9	0,751	0,912		
		m7	0,653	0,916		
		m6	0,795	0,909		
	Special Person	m10	0,686	0,914	0,882	
		m5	0,704	0,913		
		m2	0,718	0,913		
		m1	0,616	0,917		

Reliability of the Scale and the Sub-Dimensions: If the item-total score correlation coefficient is below 0.30 (if the sample is 400 or more, 0.20 is also accepted), it is considered that there is a serious problem with these items and these items can be removed from the scale. An item-total score correlation coefficient of 0.30 and above is interpreted as good for reliability. However, it is not used alone to eliminate items below this value, and the decision is made by evaluating the effect of the item on the Cronbach alpha coefficient (22,23). In this study, there were items below 0.30, but it was decided not to remove any item from the scale since it did not significantly change the Cronbach's alpha value when any item was deleted in the item analysis.

Being a Mother Scale (BaM-13) Test-Retest Reliability: Being a Mother Scale was reapplied to the 30 participants in two weeks. In Being a Mother Scale a very high relation of 94.2% was found. In the study conducted for internal consistency, the Cronbach's Alpha values were found respectively as 0.94 and 0.98 for the first and the second application scale with the same participant group (n=30).

Analyses of the Data: The obtained data of the study were computerized and evaluated with IBM SPSS Statistics 23 and IBM SPSS AMOS 23 statistical programs. For the reliability and validity of the scale, exploratory factor analysis was implemented on 147 participants and for the factor extraction method "Principal Components Factor Analysis" method was preferred. Factor number related to any scanting was not made. For factor load, statements above 0.500 were preferred.

Scale reliability was conducted with test-repeat-test reliability, total item score correlation, and internal consistency reliability analysis. In the determination of other data, percentage, average, independent sample t-test and ANOVA was used. $p<0.05$ were statistically accepted as significant. After analysis, firstly, for variance homogeneity, Levene Test was used, in order to determine where the difference comes from any group or groups, the "multiple comparison test" (Tukey or Tamhane's T2) was used. In addition, in furtherance of scales and sub-dimensions, Pearson Correlation Analysis has benefited.

3. RESULTS

It was determined that 45,7% of mothers remain in the 28-34 year range and 47,1% were primary school graduates. While 10.2% of the participants became mothers at the age of 18 and under, 27.4% were aged 19-22, 31.8% were aged 23-26 and 30.6% were aged 27 and over. The introductory characteristics of the mothers who participated in the study are presented in Table 4.

Table 4. *Distribution of the introductory characteristics of the mother*

		Number	%
Age	27 years and below	191	32.5
	28-34 years	269	45.7
	35 years and over	128	21.8
Age of the Spouse	30 years and below	182	31.0
	31-35 years	209	35.6
	36 years and over	196	33.4
Age of Marriage	18 years and below	111	18.9
	19-24 years	310	52.7
	25 years and over	167	28.4
Age of Being a Mother	18 years and below	60	10.2
	19-22 years	161	27.4
	23-26 years	187	31.8
	27 years and over	180	30.6
Educational Status	Secondary School	277	47.1
	High School	177	30.1
	Undergraduate	118	20.1
	Master's-PhD	16	2.7
Educational Status of the Spouse	Secondary School	217	37.0
	High School	219	37.3
	Undergraduate	117	19.9
	Master's-PhD	34	5.8
Work Status	Working	194	33.0
	Housewife	394	67.0
Economic Status	Income is more than Expense (Good)	121	20.6
	Income is less than Expense (Bad)	59	10.0
	Income and Expense are Equal (Moderate)	408	69.4
Type of the Family	Elementary Family	468	79.6
	Extended Family	113	19.2
	Broken Family	7	1.2
Number of Pregnancy	1	163	27.7
	2	196	33.3
	3 or more	229	38.9
Number of the alive child(ren)	No Children/1 Alive Child	207	35.2
	2 Children	229	38.9
	3 or more Children	152	25.9
Number of the miscarriage(s)	No Miscarriages	457	77.7
	Miscarriage(s)	131	22.3
Abortion	No Abortion	531	90.3
	Abortion(s)	57	9.7
Stillbirth	No Stillbirth	555	94.4
	Stillbirth(s)	33	5.6
Delivery Method	NSD (Normal Spontaneous Delivery)	166	28.2
	C/S (C-section)	422	71.8

A positive and moderately significant correlation between the sub-dimension of adult experience and sub-dimension of child experience and emotional intimacy was found (p<0.05). Besides, a positive and highly significant correlation between the sub-dimension of adult experience and Being a Mother Scale (BaM-13) was seen (p<0.05) (Table 5).

Table 5. *Examining the Correlation between Being a Mother Scale (BaM-13) and the Sub-Dimensions*

		Adult Experience	Child Experience	Emotional Intimacy	Being a Mother (BAM-13)
Adult Experience	r	1.000	0.480	0.351	0.857
	p		**<0.001***	**<0.001***	**<0.001***
	N		588	588	588
Child Experience	r		1.000	0.378	0.839
	p			**<0.001***	**<0.001***
	N			588	588
Emotional Intimacy	r			1.000	0.568
	p				**<0.001***
	N				588

** Statistical significance*

A positive and moderately significant correlation between the sub-dimension of child experience and the sub-dimension of emotional intimacy was identified (p<0.05). Besides, a positive and highly significant correlation between the sub-dimension of child experience and the Being a Mother Scale (BaM-13) was detected (p<0.05). A positive and moderately significant correlation between the sub-dimension of emotional intimacy and the Being a Mother Scale (BaM-13) was identified (p<0.05).

There was a positive and moderately significant correlation between the sub-dimension of family and the sub-dimension friend and special person (p<0.05). In addition, a positive and highly significant correlation between the sub-dimension of adult experience and the MDPSSS Scale was noticed (p<0.05) (Table 5).

A positive and moderately significant correlation between the sub-dimension of a friend and the sub-dimension of a special person (p<0.05). Likewise, there was a positive and highly significant correlation between the sub-dimension of child experience and the MDPSSS Scale (p<0.05). Similarly, a positive and highly significant correlation between the sub-dimension of a special person and the MDPSSS Scale was seen (p<0.05). It was also determined that there was a negative and lowly significant correlation between BaM Scale and MDPSSS Scale (Table 7).

Table 6. *Examining the Correlation between MDPSSS and the Sub-Dimensions*

		Family	Friend	Special Person	MDPSSS
Family	R	1.000	0.370	0.488	0.708
	P		**<0.001***	**<0.001***	**<0.001***
	N		588	588	588
Friend	R		1.000	0.606	0.846
	P			**<0.001***	**<0.001***
	N			588	588
Special Person	R			1.000	0.873
	P				**<0.001***
	N				588
MDPSSS	R				1.000
	P				
	N				

** Statistical significance*

Table 7. *Examining the Correlation between BaM Scale and MDPSSS*

		ÇBASDÖ (MDPSSS)
BaM	R	-0.190
	P	**<0.001***
	N	588

** Statistical significance*

4. DISCUSSION

This study was conducted to determine the relationship between the social support perceived by the mothers and their maternal experience by carrying out the Turkish validity and reliability study of Being a Mother Scale-13 (BaM – 13).

The sample size should be big enough to ensure correlation reliability to carry out the factor analysis. Kaiser-Meyer-Olkin (KMO) test was conducted to confirm the sufficiency of the data obtained from the sample. It is underlined that when the value of Kaiser is closer to 1, it is perfect; however, when the value is under 0.50, it is unacceptable. Besides, the Bartlett Sphericity test should be significant as well (26). Since the Kaiser-Meyer-Olkin (KMO) value was found as 0,768 in this study, the factor analysis results are thought to be useful and applicable. The results of the Bartlett Sphericity test revealed that there is a highly significant correlation among the variables and that the data are suitable for the application of factor analysis (X^2: 480,031, SD: 78, p<0,001).

Exploratory factor analysis was utilized in this study and the "Principal Components Method" was used as the factor extracting method. There wasn't any scaling on the number of the factors. Factor loads above 0,500 weren't included. After the factor analysis, the item number remained unchanged. Three factors occurred after the content validity of these 13 items and all the factors loads were above 0,500. The factor analysis of Being a Mother Scale (BaM-13) the total variance of the three sub-dimensions (factors) explains 17,83% of the Adult Experience Sub-Dimension, 17,838 % of the Child Experience Sub-Dimension and 13,294% of the Emotional Intimacy Sub-Dimension. All these 3 factors explain 52,658% of the total variance. The results of the factor analysis presented that the higher the variance percentage, the stronger the factor structure of the scale.

The eigenvalues are the sum of the squares of the factor loads. Since the sums of these factors are above 1 for each sub-dimension, all the questions under these sub-dimensions are adequate to explain the very sub-dimension. The total Cronbach Alpha coefficient for Being a Mother Scale (BaM-13) is .76.9. Considering that the predicted reliability levels for the measuring tools are between .70-.80, it can be inferred that the reliability level of the whole scale is adequate (27).

Confirmatory factor analysis of the study was applied via IBM SPSS AMOS 23 program. In the first phase, a first-order CFA model where the three-factor-dimension (F1: Adult Experience, F2: Child Experience, F3: Emotional Intimacy) was the latent variable and the expressions generating these factors were the indicator variables were created in Figure 1. As the latent variable wasn't metrical, a value of 1 should be assigned to one of the lines drawn from the latent variable to the indicator variable (the factor load should be equated to 1) or any value (mostly 1) should be assigned to the variant of the latent variable to estimate the parameter values (20). In the last phase, the fit indices for the two scales and the second-order CFA model with six-factor dimensions were analyzed. When the obtained findings are examined, it can be seen that the model generally correlates well respecting the usability of the 25 expressions and the six-dimensional structure of both Being a Mother and Multi-Dimensional Perceived Social Support Scale together.

On looking at the obtained adaptive value it can be stated that while $\chi 2/df$, GFI, IFI, TLI, CFI, RMSEA, and SRMR values are good, GFI value is unacceptable (21,22,25,26). Reliability is a definition indicating the consistency of the measurement tool. If the repeating measurements have the same result as the measurement tool, the scale is regarded as reliable. In terms of the study, reliability is the expression of the repeatability of the measurement results. It can be stated that if the validity of the measurement tool is confirmed, its reliability is confirmed as well (27).

In the repetition of the scale method, the measurement tool is reapplied to the same subject group under the same circumstances and during the time periods which are long enough to avoid the significant remembrances but short enough to avoid significant changes to be measured (28). In this study Being a Mother Scale (BaM-13) was reapplied to the 30 mothers and Pearson Correlation Technique was utilized for the analysis. The repetitive measurements of the Being a Mother Scale (BaM-13) did not present any change against the time.

There is a hypothesis that the measurement tool has experimentally independent sections with common and equal significances for fulfilling the desired target of the scale (29). Item statistics is one of the methods for evaluating internal consistency. In this method which is also known as

item reliability or item statistics variance of each item in the test is compared to the variance of the total test score and the correlation between them is evaluated. If the item loads in the scale are uniformly significant and independent, a high correlation coefficient between each item and total values is expected. If there is an item with a lower correlation compared to the total score, it can be inferred that that item measures a different qualification of the test (30).

The results of the study on determining the validity and reliability of the Being a Mother Scale (BaM-13) presented that the scale is a valid and reliable measuring tool that can be applied to Turkish mothers. It was also established that the model was generally in accordance in terms of the structure of the Being a Mother Scale (BaM-13) and Multi-Dimensional Perceived Social Support Scale both of which had 25 expressions and 6 factors that can be used together. 36.4% of the mothers who participated in the study mentioned that they received support for baby care, while 45.3% of them were supported by their mothers, 10.3% of them were supported by their husbands. In the study of Çalışır (2003) 92.3% of the mothers stated that their husbands help them with baby care. Moreover, the study of Ertürk (2007) reported that 68,2% of the mothers took support for baby care and 41,2% of them took this support from their own mothers and 7,6% of them were supported by their husbands. Adaptation to motherhood is related to spouse support along with many factors. The mothers who were supported by their spouses during the pregnancy and labor period are seen to have a relatively easier and more comfortable pregnancy, labor, and postpartum period. A positive correlation between the spouse support during prenatal, labor, and postnatal period and the social support perceived by the mother was found out (31).

In their study, Ege Timur Zincir & Reeder (2008) mentioned that 68% of the mothers got support and 44% of them got this support from the family of their husbands and 9.3% were supported by their husbands. According to the study of Akın, Ege, Koçoğlu, Demirören & Yılmaz (2009), 61,5% of a group of mothers who were examined in terms of the social support during the postpartum period were supported by their families. Kavlak (2004) reported that 65.5% of the mothers received some support on baby care and while 55.5% of these mothers were supported by either their mothers or by their in-laws, 32.5% of them we supported by their husbands.

Support taken from the environment, particularly from the family, is one of the crucial factors affecting the bond between the mother and the baby positively (32). The study of Evcili, Abak Tali & Yurtsal (2014) reported that most of the mothers stating a good relationship with their husbands express their feelings on their children as “I feel very happy”, however, the mothers expressing a relatively good relationship with their husbands express their feelings on their children as “I feel insufficient”. Social support given by the family, spouse, and healthcare staff is an essential element for the satisfaction of the mother.

While a positive and moderately significant correlation between the sub-dimension of “Adult Experience” and sub-dimensions of “Child Experience” and “Emotional Intimacy” was found ($p<0.05$), a positive and highly significant correlation between the sub-dimension of “Adult Experience” and Being a Mother Scale (BaM-13) was also seen ($p<0.05$). Similarly, apart from the positive and moderately significant correlation between the sub-dimension of “Child Experience” and sub-dimension of “Emotional Intimacy” ($p<0.05$), a positive and highly significant correlation between the sub-dimension of “Child Experience” and Being a Mother Scale (BaM-13) were revealed ($p<0.05$). Finally, a positive and moderately significant correlation between the sub-dimension of “Emotional Intimacy” and Being a Mother Scale (BaM-13) was found out ($p<0.05$). If the adult experiences of the mothers are positive, their childhood experiences and emotional intimacy rates increase which positively affect the satisfaction of the mothers. In one study it was stated that women expressed the beginning of their maternal experience as “a horrible shock”. Sore and irritated nipples due to breastfeeding, long and sleepless nights, constantly crying and hard-to-soothe babies are some of the tough and stressful experiences for new mothers. Due to the postnatal experiences the number of mothers who wanted a large family decreased and thus they wanted to have fewer children (33). In the present study a positive and highly significant correlation between the sub-dimension of Adult Experience and MDPSSS Scale, a positive and highly significant correlation between the sub-dimension of Child Experience and MDPSSS Scale ($p<0.05$), and a positive and highly significant correlation between the sub-dimension of Special Person and MDPSSS Scale ($p<0.05$) were seen.

The positive and high correlation between all the sub-dimensions of Being a Mother Scale (BaM-13) and total scale score and MDPSSS Scale indicates that satisfaction of the mother is closely related to the perceived social support by the mother. The spouse and the family of the mother play a crucial role in solving the problems by supporting the mother. It has been accepted that the supportive relationship has a key factor in resisting the stress of life and strengthening the coping strategies. The most significant supporters of the mothers are close family members and particularly their spouses. Women whose maternal role was accepted by their husbands and who can share their problems with them had less trouble.

There is a negative and low significant correlation between the Being a Mother Scale (BaM-13) and MDPSSS Scale. Less social support decreases maternal satisfaction as well. Social support mechanisms are the most outstanding helpers for coping with the difficulties of life. It was notified that baby care help provided by the close relatives or environment would help reduce the stress and increase the perception of competence on baby care (34).

5. CONCLUSION

Being a Mother Scale treatment and (BaM-13) can be used for analyzing the new mothers in the postpartum period (three years after the birth) by the doctors, nurses, and the midwives in terms of planning the treatment and care and assessing the results. The scale can either be used alone for the studies on the subject or be used with other appropriate scales such as MDPSSS Scale.

This is a practical scale in terms of the services and programs which target increasing the pleasure from the maternal experience or increasing self-confidence of the mothers. It can help the clinician on exploring some of the difficulties that can be experienced by the women in the clinical environment. Applicability of the scale to a wide range of mothers (from birth to preschool time) – i.e. not including only the early babyhood period – proves its practicality.

While scanning is convenient for the women with cutoff scores are 9 and above which indicates concurrent and possibly serious problems, for clinical evaluation consideration of each item in the scale might be more convenient compared to the consideration of the total score of the scale.

The exclusion of nutrition and sleep both of which are among the essential requirement of life from Being a Mother Scale (BaM-13) is the limitation of the scale.

How might this information affect nursing practice? The application of this scale in the clinics might be useful for warning the clinicians on the problematic topics. As the developer of the scale, Matthey (2011) suggested the second item in the scale is not applicable for the mothers who adopted their children. The change in the expression of “before having this baby” with “before having an infant who started to walk” is a proposal for the clinicians and researchers who will use the Turkish form of the scale.

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Clinical and Experimental Health Sciences

The Effect of Bilirubin on Laboratory Investigations on Serum Creatinine: A Comparison Study Between Jaffe Reaction and Creatinase Enzymatic Method With Creatinine in Phosphate Buffered Saline Solution and Serum

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ABSTRACT

Objective: To determine the creatinine concentration in phosphate buffered saline solution and serum with different bilirubin concentrations using Jaffe reaction and Creatinase method.

Methods: In Phase 1, creatinine and bilirubin concentrations in the dilution series were 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 mg/dL and 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30 mg/dL, respectively. Each creatinine concentration was spiked with eleven bilirubin concentrations used in Phase 1. In Phase 2, serum with creatinine values 0.51, 2.41 and 7.33 mg/dL were spiked with 11 bilirubin concentrations. The total bilirubin, creatinine by Jaffe reaction and Creatinase method were measured.

Results: In Phase 1, Jaffe reaction showed a significant underestimation up to creatinine concentration of 2 mg/dL at all bilirubin concentrations. From 3 mg/dL onwards, a significant overestimation was observed with high bilirubin concentrations. In Phase 2, Creatinase method gave no significant underestimation in serum with 0.51 mg/dL of creatinine. But Jaffe reaction showed a significant underestimation from bilirubin concentration of 7.18 mg/dL. In serum with 2.41 mg/dL creatinine, Creatinase and Jaffe methods gave significant underestimations from bilirubin concentrations of 9.05 and 5.64 mg/dL, respectively. In serum of 7.33 mg/dL creatinine, significant underestimations were given from bilirubin levels of 3.6 and 8.18 mg/dL by Creatinase and Jaffe methods, respectively.

Conclusion: In normal to moderately high bilirubin concentrations the Creatinase method is more accurate than the Jaffe method in all creatinine concentrations used. At high creatinine concentrations Creatinase method gave significant underestimations which increased with bilirubin concentration.

Keywords: Bilirubin, Creatinine, Jaffe reaction, Creatinase method

1. INTRODUCTION

Creatinine is a metabolic waste product of creatine phosphate which is a high energy molecule used in the muscle to provide energy (1). Serum creatinine measurement is used as a marker of renal function and in calculating the glomerular filtration rate (GFR) because creatinine is excreted solely through the kidneys. It is of utmost importance to assess the renal function accurately for the proper management of renal failure and it is used in grading of different stages of chronic kidney disease (CKD). Therefore, the accurate measurement of serum creatinine levels is of great importance.

Jaffe reaction is the most commonly used test method for serum creatinine estimation in the medical laboratories world-wide as it is both simple and cost effective. However, this method has several major drawbacks due to interferences from endogenous substances such as bilirubin, ketone bodies, proteins, glucose and exogenous substances including drugs (2). Out of these interferences the present study was designed to study the bilirubin interference since it is more frequently encountered in the clinical environment. In hyperbilirubinemic patients the Jaffe reaction has shown to give a significant underestimation of the serum creatinine value (3). As a result, accurate renal assessment has become impossible in patients with hepatorenal failure, multi-organ failure and neonatal jaundice with impaired renal activity (4).

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This problem can be overcome by using the Creatinase enzymatic test method. This is more specific since it uses enzymes to carry out specific reactions (5). However, this cannot be widely used due to its relatively high cost.

Therefore, the objective of this study was to compare these two test methods and obtain a better understanding in the error caused in the Jaffe reaction and to identify the minimum bilirubin concentration that gives interference to the serum creatinine measurement.

2. METHODS

This is an analytical cross-sectional study with laboratory investigations. The study was carried out under 2 distinct phases.

2.1. Phase 1

Phase 1 of this study was carried out to determine the effect of bilirubin on creatinine in phosphate buffered saline solution.

2.2. Reagent preparation

The creatinine dilution series was prepared with 20 mg/dL of creatinine standard solution. The final creatinine concentrations in phosphate buffered saline were; 0, 2, 4, 6, 8 10, 12,14,16,18 mg/dL. By using bilirubin standard solution of 60 mg/dL following bilirubin concentration gradient was prepared; 0, 6, 12, 18, 24, 36, 42, 48, 54 and 60 mg/dL.

2.3. Preparation of final matrix with creatinine and bilirubin

The first creatinine dilution of 0 mg/dL was taken and 0.5 mL from this concentration was pipetted into 11 labeled khan tubes which were covered with aluminum foil. Then, 0.5 mL from each bilirubin solution prepared in the dilution series was added to the above khan tubes and mixed well. This procedure was repeated with all the creatinine dilutions to give 110 khan tubes. Table 1 indicates the creatinine and bilirubin concentration of each tube.

2.4. Phase 2

Phase 2 of this study was carried out to determine the bilirubin interference in serum creatinine. Prior to start the study ethical approval was obtained from the Ethical Review Committee, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka.

2.5. Preparation of serum pools

The serum specimens were collected in three groups depending on the serum creatinine values as (i) below 0.8 mg/dL, (ii) between 2 – 4 mg/dL (iii) above 6 mg/dL. Serum creatinine by Creatinase method and total bilirubin concentration of each pool was measured separately. Total bilirubin levels of serum pool 1, 2 and 3 were 0.45, 0.45 and 0.99 mg/dL, respectively.

The serum from each pool was placed on ice-packs within an insulating rigid foam box. The box was placed in an infant phototherapy incubator without a temperature regulator for 18 hours in order to photolyse the serum bilirubin. Ice packs were changed at every 6 hours to maintain serum pools at low temperature. The serum creatinine and total bilirubin values were then re-measured for all three pools to ensure that the serum creatinine values were unchanged and the total bilirubin concentrations were below 1.46 mg/dL (25 µmol/L). The serum pool 1, 2 and 3 gave serum creatinine values of 0.51, 2.41 and 7.33 mg/dL, respectively. The bilirubin concentrations of serum pool 1, 2 and 3 after phototherapy treatment were 0.05, 0.12 and 0.21 mg/dL, respectively which were well under the recommended maximum concentration (6).

2.6. Preparation of bilirubin dilution series

A series of bilirubin concentrations was prepared by mixing calculated volumes from bilirubin stock solution and 100 mM NaOH solution to get the bilirubin concentrations twenty-one times higher than what was required when mixed with the serum sample (7). This was done to minimize the dilution of the serum to a value below 5%.

The bilirubin stock solution was prepared with the concentration of 630 mg/dL as this concentration was required in order get the final dilution of the serum bilirubin to be no more than 5% (6). A series of bilirubin concentrations was prepared by using bilirubin stock solution with the concentrations of 0, 63, 126, 189, 252, 315, 378, 441, 504, 567 and 630 mg/dL.

2.7. Spiking of serum pools with bilirubin dilution series

All tubes used for mixing the solution were covered with aluminum foil to prevent exposure to sun-light. One milliliter from creatinine concentration of 0.51 mg/dL was pipetted into 11 khan tubes. Fifty microliters from each of the 11-bilirubin concentrations were added separately into each tube and mixed well. This was repeated for serum pools containing creatinine concentrations of 2.41 and 7.33 mg/dL.

2.8. Analysis of creatinine and bilirubin concentrations

Three reagent kits were used for the (i) creatinine enzymatic (ii) creatinine Jaffe reaction and (iii) total bilirubin assays and determination methods are as follows.

Creatinine enzymatic method: Creatinine is converted to sarcosine with the presence of creatininase and creatinase. Sarcosine is then converted to glycine, formaldehyde and hydrogen peroxide by sarcosine oxidase in the presence of oxygen. The hydrogen peroxide then reacts with 4-aminophenazone and 2,4,6-triiodo-3-hydroxybenzoic acid and form a quinone imine chromogen and this reaction

is catalyzed by peroxidase. The color intensity is directly proportional to the creatinine concentration and it can be measured by photometrically at 540 nm.

Creatinine Jaffe reaction: The reaction is based on the Jaffe method where creatinine forms a red color complex with an alkaline picrate solution. The intensity of the complex is measured at 510 nm.

Total bilirubin assay: The total bilirubin is coupled with p-nitrobenzenediazonium salt to form azobilirubin and the colour intensity is proportional to the concentration of total bilirubin.

An IndikoTM Clinical and specialty Chemistry System was used to analyze the samples. This is a fully automated, sample oriented and random-access analyzer. Prior to specimen analysis the analyzer was calibrated for all three test methods. All three test methods were calibrated using the same calibration fluid as specified by the manufacturers. Following the calibration of the analyzer, quality control samples were analyzed. The quality control samples were of two levels, normal and abnormal. Once the quality control results came out normal the specimens were analyzed. Once the analysis was completed the results were printed out.

2.9. Statistical analysis

The statistical software used was Minitab (Version 17.0) and the statistical method was Regression Analysis.

3. RESULTS

3.1. Phase 1

Creatinine concentrations of the final matrix prepared in Phase 1 was ranged from 0 to 9 mg/dL (see Table 1).

3.2. The effect of bilirubin on creatinine in phosphate buffered saline solutions: According to the Jaffe reaction

It could be observed that there was an underestimation of creatinine with increasing bilirubin concentrations up to the creatinine concentration of 2 mg/dL. After this point onwards an overestimation of creatinine concentration could be observed. To consider the underestimation as a significant value, the percentage of the difference between the creatinine measurement at 0 mg/dL and the given creatinine measurement should be more than 10% (8). The percentage of the difference was calculated by;

$$\frac{([\text{Creatinine}] \text{ at 0 mg/dL bilirubin} - [\text{Creatinine}] \text{ at X bilirubin concentration})}{[\text{Creatinine}] \text{ at 0 mg/dL bilirubin}} \times 100\%$$

X – Bilirubin concentration at which the interference is being analyzed.

The minimum bilirubin concentration which gives a significant underestimation for each of the creatinine standard solution is given in Table 2.

Table 1. *Preparation of final matrix with creatinine phosphate in buffered saline and bilirubin*

[Creatinine] (mg/dL) / [Bilirubin] (mg/dL)	0	2	4	6	8	10	12	14	16	18
0	0 / 0	1 / 0	2 / 0	3 / 0	4 / 0	5 / 0	6 / 0	7 / 0	8 / 0	9 / 0
6	0 / 3	1 / 3	2 / 3	3 / 3	4 / 3	5 / 3	6 / 3	7 / 3	8 / 3	9 / 3
12	0 / 6	1 / 6	2 / 6	3 / 6	4 / 6	5 / 6	6 / 6	7 / 6	8 / 6	9 / 6
18	0 / 9	1 / 9	2 / 9	3 / 9	4 / 9	5 / 9	6 / 9	7 / 9	8 / 9	9 / 9
24	0 / 12	1 / 12	2 / 12	3 / 12	4 / 12	5 / 12	6 / 12	7 / 12	8 / 12	9 / 12
30	0 / 15	1 / 15	2 / 15	3 / 15	4 / 15	5 / 15	6 / 15	7 / 15	8 / 15	9 / 15
36	0 / 18	1 / 18	2 / 18	3 / 18	4 / 18	5 / 18	6 / 18	7 / 18	8 / 18	9 / 18
42	0 / 21	1 / 21	2 / 21	3 / 21	4 / 21	5 / 21	6 / 21	7 / 21	8 / 21	9 / 21
48	0 / 24	1 / 24	2 / 24	3 / 24	4 / 24	5 / 24	6 / 24	7 / 24	8 / 24	9 / 24
54	0 / 27	1 / 27	2 / 27	3 / 27	4 / 27	5 / 27	6 / 27	7 / 27	8 / 27	9 / 27
60	0 / 30	1 / 30	2 / 30	3 / 30	4 / 30	5 / 30	6 / 30	7 / 30	8 / 30	9 / 30

Note: The final concentration of each analyte in the final tube is half the concentration of the initial solutions as they are diluted by 50% when mixing equal volumes of the two solutions. Each square in the above table gives the bilirubin and creatinine concentration in each individual tube.

Table 2. *The minimum bilirubin concentration causing significant underestimation in each creatinine concentration as determined by Jaffe reaction*

Creatinine concentration (mg/dL)	Minimum bilirubin concentrations which give significant underestimation in creatinine (mg/dL)
0	17.63
1	96.61
2	31.62
3	29.55
4	17.12
5	222.71
6	7.9
7	15.83
8	6.51
9	4.3

Excluding the bilirubin cut off points at creatinine concentrations of 5 and 6 mg/dL all other cut off points decreased with increasing creatinine concentration indicating that the error increases with the creatinine concentration.

3.3. The effect of bilirubin on creatinine in phosphate buffered saline solutions: According to the Creatinase enzymatic method

In the concentration series with no creatinine the enzymatic assay showed a reading of zero even with increasing bilirubin concentration. After this point the results indicated that, as the bilirubin concentration increases there is a slight underestimation in creatinine level. The underestimation increased with increasing bilirubin concentration. However, the rate at which the underestimation occurred, increased with the creatinine concentration itself. The minimum bilirubin concentration which gave a significant underestimation for each of the creatinine standard solution is given in Table 3. A specific pattern could not be observed in this sequence.

Table 3. *The minimum bilirubin concentration causing significant underestimation in each creatinine concentration as determined by Creatinase enzymatic method*

Creatinine concentration (mg/dL)	Minimum bilirubin concentrations which give significant underestimation in creatinine (mg/dL)
0	410.84
1	29.68
2	13.12
3	8.41
4	11.78
5	4.69
6	6.68
7	4.62
8	5.13
9	5.57

3.4. Comparison of Jaffe reaction and Creatinase enzymatic method in determination of creatinine concentration in phosphate buffered saline solutions

When comparing the two methods, Jaffe reaction showed underestimations relative to the enzymatic method at the initial creatinine concentrations. Jaffe reaction showed a significant underestimation in creatinine concentrations of 0, 1 and 2 mg/dL with all the bilirubin concentrations. From 3 mg/dL onwards, Jaffe reaction showed an overestimation with high bilirubin concentrations. The minimum bilirubin concentration required for overestimation varied with the creatinine concentration. According to the Creatinase method, as the bilirubin concentration increases, a significant underestimation was given by creatinine concentrations of above 2 mg/dL. The lowest bilirubin concentration needed for creatinine underestimation varied with the creatinine concentration. The underestimation observed with increasing bilirubin concentration increased when creatinine concentration of the standard solution increases. Comparison of these two methods can be done more accurately by plotting bias graphs. The creatinine values obtained by the Jaffe and enzymatic methods were used to calculate the bias and it was calculated according to the following equation.

Bias = [creatinine concentration by Jaffe reaction]–[creatinine concentration by Creatinase method]

The bias was then plotted against the bilirubin concentrations (see Figure 1). In these graphs the solution with 0 mg/dL creatinine (Figure 1 A) is the only concentration where the bias increases negatively. In the 1 mg/dl creatinine solution (Figure 1 B) the values indicated an initial negative bias but the negativity of the bias decreases as the bilirubin concentration increases. Even as the negativity of the bias reduces the bias still remains negative throughout the increasing bilirubin concentrations. However, after 1 mg/dL (Figure 1 C, D, E, F, G, H, I, J) the bias started giving positive values at high bilirubin concentrations. The bilirubin concentrations at which the bias becomes zero (i.e. the point at which the negative bias turns into a positive bias) in 2, 3, 4, 5, 6, 7, 8, and 9 mg/dL creatinine solutions are 20.79, 12.95, 10.47, 8.98, 8.808, 7.567, 8.55, 7.009, respectively. It can be seen that this value decreases with increasing creatinine concentration.

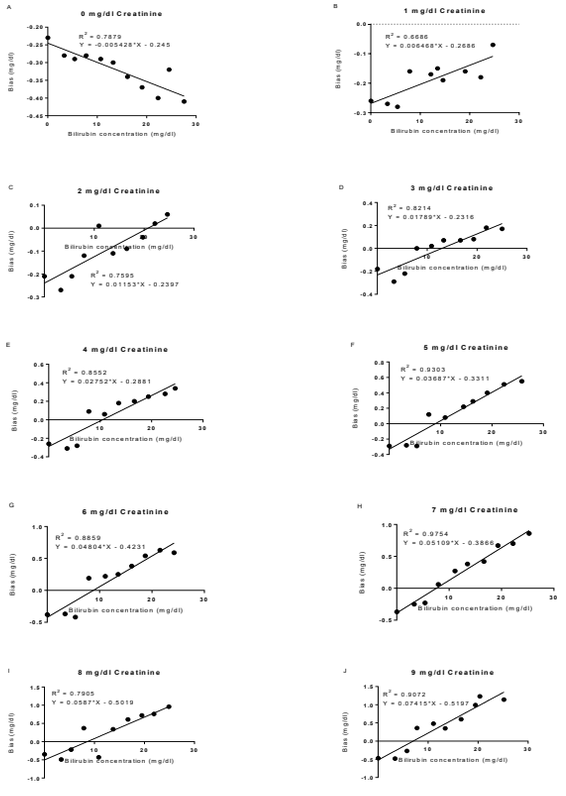

Figure 1. *Bias plot of creatinine. Bias plots compare Jaffe reaction and Creatinase enzymatic methods. Bilirubin concentrations used were 0, 3, 6, 9, 12, 15, 18, 21, 24, 27 and 30 mg/dL. Creatinine concentration of the stock solutions ranged from 0 to 9 mg/dL*

3.5. Phase 2

3.5.1. The effect of bilirubin on serum creatinine concentrations

Three serum pools had creatinine concentrations of 0.51, 2.41 and 7.33 mg/dL as determined by Creatinase method and negligible bilirubin concentrations of 0.05, 0.12 and 0.21 mg/dL, respectively after phototherapy treatment. These bilirubin values were less than the recommended maximum concentration of 1.46 mg/dL prior to spiking the serum with bilirubin (6).

3.5.2. The effect of bilirubin on 0.51 mg/dL serum creatinine concentration

Creatinase enzymatic assay showed no significant underestimation with bilirubin concentrations used in the present study. However, underestimation became significant at the bilirubin concentration of 41.17 mg/dL. The Jaffe method on the other hand showed a significant underestimation of creatinine at bilirubin concentrations of 7.18 mg/dL.

3.5.3. The effect of bilirubin on 2.41 mg/dL serum creatinine concentration

At 2.41 mg/dL serum creatinine, the Creatinase enzymatic method showed a significant underestimation of creatinine at the bilirubin concentration of 9.05 mg/dL. The serum creatinine values given by the Jaffe method also have significant underestimations which increased with the increasing bilirubin concentration. According to the Jaffe reaction the significant underestimation started with the bilirubin concentration of 5.64 mg/dL.

3.5.4. The effect of bilirubin on 7.33mg/dL serum creatinine concentration

At 7.33 mg/dL creatinine level, according to the Creatinase method a significant underestimation of creatinine was observed from the bilirubin concentration of 3.6 mg/dL whereas in the Jaffe reaction a significant underestimation was observed at the bilirubin concentration of 8.18 mg/dL.

3.5.5. Comparison of Jaffe reaction and Creatinase enzymatic method in determination of serum creatinine concentrations of 0.51, 2.41 and 7.33 mg/dL

The bilirubin concentration where the underestimation is significant becomes lower with increasing creatinine concentration. However, in all three serum pools the Jaffe reaction gave a negative reading at all bilirubin concentrations with respect to the Creatinase enzymatic method. The bias between the enzymatic and Jaffe method was calculated for each bilirubin concentration in all three serum pools according to the following equation.

Bias = [Serum creatinine of Jaffe reaction] – [Serum creatinine of Creatinase method]

All three pools showed an increasing negative bias up to a given concentration of bilirubin (See Figure 2). After this point the bias decreases for serum pool 2 (2.41 mg/dL creatinine) and 3 (7.33 mg/dL creatinine). The data available is not enough to predict what happens in pool 1 (0.51 mg/dL creatinine) after the downward trend. The bilirubin concentration at which the trend in the bias changes (i.e. the bilirubin concentration at the maximum bias) is different for three pools. With increasing creatinine concentration, the bilirubin concentration at which the highest bias occurs reduces.

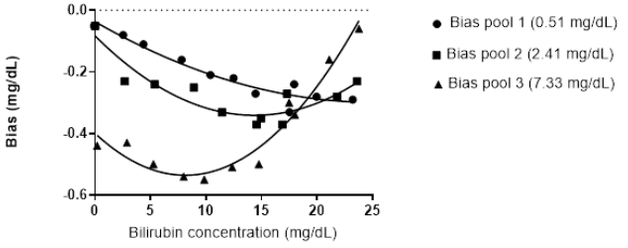

Figure 2. *Bias plot for creatinine with the bilirubin concentration*

3.5.6. Determination of the correction factor

Using the data collected in Phase 2 we were able to get equations for the bias of the Jaffe reaction relative to the enzymatic reaction. The bias can be added to the Jaffe reaction and thereby correction can be done. However, the data also showed that the bias varies with not only the bilirubin concentration but with the creatinine concentration itself as well. Hence, we got three separate equations for the three serum pools we used as follow.

Pool 1 Bias = (-0.034) + [-0.021x (bilirubin concentration)] + 0.000415 (bilirubin concentration)^2

Pool 2 Bias = (-0.078) + [-0.036x (bilirubin concentration)] + 0.001(bilirubin concentration)^2

Pool 3 Bias = (-0.399) + [-0.033x (bilirubin concentration)] + 0.002 (bilirubin concentration)^2

As a result, we could not calculate a single correction factor that could be applied for all creatinine concentrations.

4. DISCUSSION

Phase 1 was designed to give a broad view on all possible creatinine and bilirubin combinations. For a comprehensive study we required serum samples with different bilirubin and creatinine concentrations. This includes samples with high creatinine and bilirubin, high creatinine and low bilirubin, low creatinine and high bilirubin and low creatinine and low bilirubin. Due to the practical difficulty in obtaining such a large range of specimens covering the whole spectrum

we resorted to use an artificial matrix. Natural conditions in serum samples were stimulated as much as possible by adding Bovine serum albumin (BSA) and by maintaining the pH at 7.4. The creatinine and bilirubin concentrations used for Phase 1 were selected so as to cover all clinically significant values (9). Creatinine concentrations used ranged from 0 – 9 mg/dL.

Bilirubin can cause two kinds of interferences. A negative interference can be caused due to the conversion of bilirubin into biliverdin. A positive spectrophotometric interference can be caused as the absorbance of bilirubin, and the coloured complex produced by the Jaffe reaction have a similar wavelength (10,11).

In creatinine solutions of 0, 1 and 2 mg/dL the Jaffe reaction shows a significant underestimation with increasing bilirubin concentrations. This can be attributed to the negative interference being greater than the positive interference. At creatinine concentrations of 3, 4, 5, 6, 7, 8 and 9 mg/dL the Jaffe reaction shows a significant overestimation with increasing bilirubin concentrations. This can be due to the spectrophotometric interference caused by high bilirubin concentrations being greater than the negative interference. However, this does not explain why the spectrometric interference becomes greater than the chemical interference with increasing creatinine concentrations. Such an interaction in Jaffe reaction due to creatinine concentration itself has not been documented. Since the only changing factor between these solutions is creatinine concentration, we can assume that this trend is due a reaction involving creatinine molecules.

The enzymatic method has a non-significant underestimation at very low creatinine concentrations which slowly increases with increasing creatinine concentration. This tallies with a previous study (12). Our findings show that the underestimation increases with increasing creatinine concentration. In the enzymatic reaction the concentration is measured spectrophotometrically by measuring H_2O_2 produced in the reaction. The H_2O_2 can also oxidize bilirubin into biliverdin (5). However, it is mentioned that this error has been reduced by using efficient H_2O_2 acceptors (triiodo-hydroxy-benzoic acid), including potassium ferrocyanide and detergents (13). Our results indicate that these corrective measures are insufficient at very high bilirubin concentrations.

Both Jaffe and Creatinase enzymatic reaction show varying deviations with increasing creatinine concentrations. While no clear-cut answer can be given as to why this occurs, it can be assumed that it has to do with a chemical reaction involving creatinine molecules. Creatinine molecules may dimerize at high concentration which may have previously unidentified reaction with picric acid in the Jaffe reaction or with bilirubin itself. It may cause spectrophotometric variances as well. High creatinine concentrations may also have an allosteric effect on Creatinase causing an alteration in the reaction.

Although a wide concentration range was covered through Phase 1, for an experiment to be clinically applicable it should be done in a serum matrix. Hence, for Phase 2 we did a similar study using pooled serum of three creatinine concentrations. The three creatinine concentrations were 0.51, 2.41 and 7.33 mg/dL. These concentrations were chosen so as to have low, moderately high and very high creatinine concentrations. Bilirubin concentrations used to spike the serum pools were similar to that of Phase 1 (0 – 30 mg/dL). Prior to spiking the serum pools with bilirubin, any bilirubin already in the sera had to be removed. The guidelines suggested that the concentration of bilirubin before spiking should be less than 1.46 mg/dL in order to be considered negligible (6). Bilirubin breaks down under light of wavelength 420 – 510 nm (14). We used incubators used for neonatal phototherapy as they are specially designed to breakdown bilirubin. These incubators have light bulbs with similar wavelengths to that at which bilirubin break down takes place (14). The creatinine concentrations were also measured before and after incubation to ensure that the creatinine molecules did not undergo any breakdown.

According to the guidelines given by the Clinical Laboratory Standard Institute (CLSI) for interference testing, the serum matrix cannot be diluted more than 5% its initial concentration (6). Hence, we had to prepare a highly concentrated bilirubin stock solution of 630 mg/dL. The serum aliquots were then spiked at a ratio of 20:1 in order to fulfill the above criteria.

When analyzing the results of the Jaffe reaction it is obvious that it gives underestimations with increasing bilirubin concentrations at all creatinine levels as supported by most of the previous studies (15,16,12,17). This can be attributed to the negative interference caused by the conversion of bilirubin into biliverdin by NaOH (11).

However, when comparing this trend in the three serum pools, no significant pattern could be observed with the increasing creatinine concentration. These findings are somewhat contradictory to those of Phase 1 where high creatinine concentrations similar to the third serum pool (7.33 mg/dL) gave overestimations at high bilirubin concentrations. The only plausible reason for this change can be attributed to the difference in the serum matrix. This confirms that the Jaffe reaction is more prone to interferences caused by the matrix. The enzymatic reaction shows a minor underestimation in the first serum pool with low creatinine which can be considered as non-significant. The second and third serum pools also showed an underestimation with increasing bilirubin concentrations. This is compatible with the findings of Phase 1. This indicates that unlike the Jaffe reaction the enzymatic reaction is not prone to interferences from the matrix. When comparing the values, we can see that underestimation increases with increasing creatinine concentrations. This is similar to the findings of Phase 1. As mentioned above it can be suggested that this is due to a reaction involving creatinine molecules.

In all three serum pools at all bilirubin concentrations used the Jaffe reaction still gave an underestimation relative

to the enzymatic reaction. The Jaffe reaction gives an underestimation relative to the enzymatic reaction even at 0 mg/dL bilirubin concentrations. This is again validated in Phase 1. However, the difference between the values of Jaffe and enzymatic method at 0 mg/dL bilirubin remained constant in Phase 1 (0.2 ± 0.05). This difference seems to increase in Phase 2 (0.07, 0.19, and 0.58 for creatinine of 0.51, 2.41 and 7.33 mg/dL, respectively). A straight forward answer for this cannot be given. Since the only varying property between the three serum pools is the creatinine concentration it can be assumed that this is due to the creatinine concentration.

5. CONCLUSION

In a phosphate buffered saline (PBS) medium, at creatinine concentrations of ≤ 2 mg/dL the Jaffe reaction gives a significant underestimation relative to the enzymatic method. Hence, at these concentrations the Creatinase method is more accurate than the Jaffe method. At creatinine concentrations ≥3 mg/dL the Jaffe reaction gives a significant overestimation at high bilirubin concentrations. The exact bilirubin concentrations causing the interference depend on the creatinine concentration itself. In serum, Jaffe reaction gave a significant underestimation relative to Creatinase method at all creatinine concentrations. In both PBS and serum, Creatinase enzymatic method showed significant underestimations at high creatinine concentrations.

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Clinical and Experimental Health Sciences

Breastfeeding Experience of Mothers with Multiple Babies: A Phenomenological Study

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ABSTRACT

Objective: To determine the needs and underline the experiences of mothers by focusing on the experiences of mothers with multiple babies during their breastfeeding period.

Methods: This is a phenomenological, qualitative study. A total of 13 mothers with three – to 13-month-old babies were interviewed in-depth and individually. The data were collected by a single observer with a personal information form containing individual characteristics of the participants and an interview form with semi-structured, open-ended questions.

Results: The three main themes formed based on the interviews with mothers were the meaning of being a mother with multiple babies and breastfeeding them, challenging life experiences during breastfeeding, and the factors that affect motivation. The majority of the mothers expressed feelings including concern, fear, guilt, and frustration. All mothers stated that, after delivery, they needed a knowledgeable and dependable helper preferably not from the family and that they experienced conflicts in their relationships.

Conclusion: It is important to maintain social, emotional, and physical support for mothers with multiple babies. Similarly, avoiding judgmental, questioning, and accusing expressions is essential to circumvent conflicts in relationships. It is recommended for mothers' concerns to be addressed according to the source of the concern and for breastfeeding education content to be prepared accordingly. Each mother should be evaluated individually, and care plans and consultations should be prepared accordingly.

Keywords: Multiple Babies; Twins; Breastfeeding; Challenging Life Experiences

1. INTRODUCTION

Breastfeeding is the most cost-effective, health-promoting, and disease-preventing diet for the mother and the baby. The breastfeeding rates in multiple infants are not on a desirable level. The breastfeeding rates in multiple pregnancies were reported to be between 24% and 79% in different cultures and at a different time (e.g., at 2 months and at discharge) intervals (1-4). However, the rates of exclusive breastfeeding were reported as 3.3% in the 5th month and 4.1% in the 6th month (4,5).

Associated with the increased use of reproductive techniques, the incidence of multiple births in developed countries has risen since the 1970s. In the United States, rates increased from 19.3 to 30.7 per 1000 live births between 1980 and 1999, while in England and Wales the rate was increased from 10 per 1000 in 1980, to 16 per 1000 in 2011 (4). Since multiple babies are usually born preterm and with low birth weight, it is more important to be fed with breast milk (2).

The use of breast milk is associated with a decreased incidence of complications however, many babies from multiple births cannot obtain the amount of milk they need due to the inexperience of mothers in breastfeeding, inadequate knowledge, and the belief that mothers have insufficient breast milk for two babies. The mothers of twins have sufficient potential to breastfeed their babies, but they need support from their families and health professionals (5).

It was reported in the literature that some twins' mothers considered breastfeeding as a time-saving, more practical feeding method, while others found breastfeeding troublesome, stressful, and time-consuming (2,6).

Generally, in all mothers, anxiety regarding the insufficiency of the maternal milk, early and unexpected birth, breast and nipple problems, the requirement of returning to work, mother's reluctance to breastfeed, and misconceptions about breastfeeding are among the factors that affect the

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late start of breastfeeding and the low rates (2,7-10). A successful breastfeeding process helps both the mother's self-confidence and her embracement of the role of motherhood. Breastfeeding training provided by midwives and nurses, support and motivation are important factors in initiating and maintaining breastfeeding.

The low rate of breastfeeding in mothers of twin infants and the limited number of studies conducted with mothers of twin infants; suggests that more studies are needed on how to support mothers. The aim of this study was to determine the needs and difficulties of mothers with multiple babies based on their breastfeeding experiences. Furthermore, there are limited numbers of studies in the literature that reflect the emotions of mothers with multiple offspring. Therefore, it is anticipated that this study will contribute to the literature.

2. METHODS

2.1. Design and phenomenology

The research was planned according to the qualitative research paradigm based on the 32 item checklist (COREQ), which is a guideline for qualitative studies (11). The research was conducted with the qualitative data analysis method and the interpretive phenomenology approach (IPA). Phenomenology, as explained by Husserl, is a research design developed by Heidegger, Sartre, and Merleau Ponty (12-14). Phenomenology describes the common meaning of a few people's experiences related to a phenomenon or concept (12-14). In this study, the concepts of "mother with multiple babies" and "breastfeeding experience" were considered as the phenomena.

Phenomenology is based on philosophy without preconceptions. Interpreter and experimental are applied in two ways. Interpretive phenomenology emphasizes that researchers are mediators between two meanings (12-14). The aim of this study is to explain the relationship between "mothers with multiple babies" and "breastfeeding experience".

2.2. Participants and setting

The study was planned in Istanbul/Turkey. The data were collected between 04.12.2017 and 29-01.2018. The sample of the study was composed of mothers determined by the chain referral sampling method as a purposive sampling technique. Mothers with multiple babies were reached via social media (twin mothers club and happy mothers of twins, triplets, quadruplets club – Facebook social media platform), and those who agreed to participate in the study were included. The inclusion criteria: Mothers who had twin babies, whose babies are at the age of 3-24 months and whose babies did not need more than 1 week of hospitalization in postpartum Neonatal Intensive Care.

Using the theoretical sampling method, when the concepts and expressions that could be the answer to the research question started to repeat (when the saturation point was achieved), the data collection phase was terminated. A total of 15 in-depth interviews were conducted with the mothers that agreed to participate in the study. Two mothers whose babies were 17 and 23 months old were excluded from the sample so that the age range of the mothers was not too high. Themes and sub-themes were created in line with the statements of 13 mothers (baby age:3-13 months).

2.3. Data collection

Since the participants had at least 2 babies, the mothers decided the place and time of the interview. Mothers were asked to determine an environment and time (home, living room, café, etc.) where they could express themselves comfortably, and the interviews were planned accordingly.

Semi-structured interview questions were prepared by the researchers. In the interview questions; attention was paid to the principles of being easy to understand, not being multidimensional, not misleading, and not directing. Also, in terms of the understandability of the questions, the opinions of experts were received. Semi-structured questions were asked to the mothers one by one by the researcher and supported with explanatory questions when necessary. The questions administered to the participants were as follows:

a) What are your experiences during breastfeeding?

b) How did the social support in the breastfeeding period affect you?

c) What are the factors that affect your motivation for breastfeeding?

The data were collected by means of individual forms including a "personal information questionnaire" and the "interview form" consisting of semi-structured, open-ended questions.

The personal information form included questions on the mothers' age, education, type of delivery, working status, number of parities, and breastfeeding time (Table1).

A voice recorder was used to record the statements. The researcher also recorded and observed the reactions and facial expressions of the mother. A single researcher (first author) conducted and recorded the interviews (mean 25-60 min). At the end of the interviews, about 50 pages of written documents were obtained. Before starting the interview, written and verbal consent was obtained from each participant.

Table 1. *Characteristics of the sample*

Participant Code	Age of Mother	Education	Working	Parity	Age of Baby (month)	Breastfeeding Time
M1	27	University degree	Not working	1	4	Breastfed first 2 months
M2	27	University degree	Not working	1	13	Breastfeeding continues with complementary feeding
M3	33	Primary school	Not working	1	3	Breastfeeding continues with the formula.
M4	34	University degree	Not working	2	11	Breastfeeding was performed for 9 months.
M5	32	High school	Not working	2	13	Breastfeeding continues with complementary feeding
M6	33	University degree	Not working	2	7	Breastfeeding continues with the formula.
M7	34	University degree	Not working	2	13	Breastfeeding continues with complementary feeding.
M8	32	High school	Not working	1	4	Breastfeeding continues with the formula.
M9	34	University degree	Not working	3	6	Breastfeeding continues with the formula.
M10	31	Primary school	Not working	1	3	Breastfeeding continues with the formula.
M11	28	University degree	Not working	1	12	Breastfeeding was 6 months
M12	29	Masters degree	Not working	1	6	Breastfeeding continues with the formula.
M13	30	University degree	Working	1	6	Breastfeeding continues with the formula.

2.4. Role and preparation of the researcher in qualitative research

The interviewer was a member of the research team, and this researcher who conducted the interviews received "qualitative research methods" training and certification before starting the research. There was no connection with the participants before the study. Moreover, the sound recordings were transcribed into the word format by a third person independent of the research process (in addition to the two researchers). In this context, there was no risk of bias in the interviews.

2.5. Data Analysis

In the analysis of the data, inductive qualitative content analysis was used to create themes and categories within the scope of the research (12). All recorded interviews were converted to a text file using the Microsoft Word program. The transcribed interviews were read three times by the researcher, advisor, and an independent psychiatry nurse (S.K.). During the readings, the researcher, advisor, and nurse independently denoted the important and remarkable statements. Then, a common code list that constituted a coherent totality was formed from these expressions. The themes of the study were formed by combining the codes that were common between the researchers.

In general, three methods have been proposed to confirm the validity and reliability of the results in qualitative research. These were stated as credibility, participant confirmation, and expert examination. The expert examination method was used in the study. Experts who have a general knowledge of the topic of research and who specialize in qualitative research methods were asked to assess various dimensions of the present research.

2.6. Ethics

Approval was obtained from the Ethics Committee of Marmara University Health Sciences Institute (06.11.2017-199). Written consent was obtained by signing of a Voluntary Approval Form by the mothers who agreed to participate in the study. Participants were informed about the purpose of the study, research procedures, expected benefits, their right to withdraw from the study at any time, and safeguards to protect confidentiality. Before starting the interview, written and verbal consent was obtained from each participant.

3. RESULTS

The mean age of the mothers who participated in the study was 31.7±2.6, and 69.2% of them possessed an undergraduate degree. The mean age of the newborns was 6.0±4.2 months. 53% of mothers stated that they breastfeed their babies within the first 24 hours after delivery and provided the first skin contact.

The three main themes formed based on the interviews with the mothers were (a) the meaning of being a mother of multiple babies and breastfeeding them, (b) challenging life experiences during breastfeeding, and (c) the factors that affect motivation. Sub-themes were determined under the three main themes (Table 2). Some of the verbal statements of the mothers are provided as examples.

Table 2. *Themes and sub-themes identified in interviews*

Theme and sub-themes
1. The Meaning of Being a Mother of Multiple Babies and Breastfeeding Them
1.1. Positive meaning
Attachment/Bonding
Spending Quality Time
Miracle
Being Privileged
1.2. Negative meaning
Restrictive
Responsibility /obligation
2. Challenging Life Experiences During the Breastfeeding
2.1.Physical Difficulties
Fatigue/sleeplessness
Pain
Breast/Nipple Problems
2.2.Emotional Difficulties
Anxiety/fear
Guilt
Depressive emotions
Disappointment/anger
Trying to be strong
2.3.Relational Difficulties
The need for help
Relational Conflicts
3. The Factors Affecting the Breastfeeding Motivation
3.1.Pozitive motivation
Social Support
Awareness
Physiological Changes
Perseverance
3.2.Negative motivation
Social Orientation
Preconception
Presence of Health Problems

3.1. Meaning of Being a Mother with Multiple Babies and Breastfeeding Them

3.1.1. Positive meaning

Attachment/bonding*:* The vast majority of mothers expressed that breastfeeding provided a connection between them and their babies and that they felt more like mothers.

"… I think breastfeeding provides such a bond. Breastfeeding reinforces bonding…" (M2). *"… Raising a child, breastfeeding him/her, talking to him/her, bonding with him… in short, you better feel that you are a mother, a woman …"* (M10).

Spending quality time: The mothers who expressed that they could not devote enough attention to babies due to house chores said the following regarding the breastfeeding process:

"… Since I am a mother of multiple babies, I constantly get behind in household chores. I can rest only when I am breastfeeding the babies. Then, I spend a very high-quality time with my babies…" (M5)

Miracle*:* The breastfeeding period was described as sacred or a miracle despite all difficulties (three mothers). *"… I believe that breastfeeding is a sacred thing. It is something really miraculous. As soon as the baby is born, s/he is looking for it, s/he finds it and sucks it…"* (M2)

Privileged: The mothers who believed that they were privileged because it is not a common situation to have twins and breastfeed them expressed the following statements: *"…I think being a mother of twins is really a great privilege. It is also very difficult! This means we are very strong… what a blessing!"* (M1)

3.1.2. Negative meaning

Restrictive**:** Although the majority of the mothers had positive expressions about breastfeeding, 8 mothers stated that this process was restrictive and limiting. *"…Breastfeeding is very restrictive for me. The problem with the entire pregnancy was breastfeeding for me. ...because I always have to be at home, I could never leave the babies. I feel like I am locked up in a cage…" (M9)*

"…I was going out and sometimes and I had to breastfeed. I was trying to look for an appropriate place every time I was breastfeeding. Because of this burden, I didn't want to go out at all. So, I had a lot of trouble…" (M4)

Responsibility/obligation**:** Two mothers said breastfeeding was a nuisance, and breastfeeding was a religious responsibility. *"…It's my duty, I think… My duty to my children… So, the responsibility is a sacred debt. Maybe, even a worship. I will pay my debt for two years…" (M7)*

3.2. Challenging Life Experiences During Breastfeeding

This main theme was examined under three sub-themes as physical difficulties, emotional difficulties, and relational difficulties.

3.2.1. Physical difficulties

Fatigue/sleeplessness*:* All of the mothers expressed that they were very tired during this period. Even though they had social support, they stated that giving care to two babies and showing interest was frustrating. *"…once I was so tired that I tried to rest for a minute while heating the formula at 5:30 am. I lied down for a second. ...but at 7:30, my father woke me up. We were in smoke. If we'd been a little late, maybe we'd be burned. So, there is a desperate need for rest…" (M13)*

"… If I had a chance to get a good sleep and should there be others taking care of the babies, there would have been more milk. It would have been better for me. I could keep breastfeeding…" (M1)

Pain**:** The expressions of the mothers who indicated that pain affected their breastfeeding decision were as follows: *"…They brought the babies to me to breastfeed initially, but*

I refused due to the severe pain. I said, not right now, I'm in a very difficult situation…" (M8)

Breast – nipple problems**:** A mother indicating that a crack at the nipples had a negative effect on breastfeeding; *"… My nipple was wounded…, I was crying from the pain while breastfeeding… at that time I repeatedly said 'I'm not breastfeeding' …" (M13)*

3.2.2. Emotional difficulties

Anxiety/fear**:** Concerns about lack of breast milk, sense of inadequacy for babies and other family members, reduced breastfeeding, unfairness, sense of inability to provide proper care, and presence of judgments from the surroundings were expressed. *"... The notion that I couldn't handle both of them… I could have, but there is a psychological state urging otherwise..." (M2)*

"…I was very worried that they would be weaned, my milk would be insufficient or something. …and thus, sometimes I could not breastfeed due to these concerns…" (M6)

"…I was scared, I was afraid that something would happen, I was not sleeping at all… I was scared that something would happen, I would hurt them or something. That's why I was breastfeeding them one by one…" (M3)

Guilt: The mothers stated that they felt guilty about what they thought was incomplete or neglected while dealing with multiple babies.

"… I breastfeed one, another one cry, I breastfeed... I blame myself...I can't sufficiency,. .. something very different. I can't take both of them in my arms at the same time, I can't look at them, I can't baby care (M8)

Depressive emotions**:** Some mothers stated that their postpartum psychology was impaired, and their breastfeeding process was adversely affected. *"…There was a lot going on, and I was very upset during my postpartum period. I was crying a lot, crying for no reason…" (M4)*

Disappointment/anger**:** In the study, some mothers stated that the role of motherhood was more difficult than they expected, so they were disappointed, and fatigue sometimes caused anger. *"…initially I planned to spend time with my baby, I want to talk with my baby a lot. …but it's a little difficult with the twin babies. I couldn't even change the diapers enthusiastically. You know, it becomes a duty after a while…"* and *"…because I was running out of patience, sometimes I would raise my voice even for tiny problems..." (M8)*

Trying to be strong**:** Some of the mothers stated that they had to be strong despite all difficulties.*"…After the cases where I broke in tears, I got up immediately and told myself that I have to be strong, I have to do it, I have to accomplish it. In the end, they're my children…" (M5)*

3.2.3. Relational difficulties

Need for help**:** All mothers stated that they needed at least one helper during breastfeeding. The majority of the mothers stated that they wanted this support to be able to spend more time with their babies.*"…If I slept well, which means if there were other people who take care of babies other than me. (laughing). Maybe, I would have had more breast milk. Then, I could have breastfed the babies..."* (M1)

"…I think it is a requisite to have a helper with multiple babies. To help cleaning, laundry, cooking… I always think I should have all time devoted to the babies…" (M6)

Relational conflicts**:** Some mothers stated that they had conflicts with their families, some indicated incompatibility with their new motherhood role, and others with other mothers in the society. Many mothers stated that they had conflicts, especially with their own parents(grandmother), and stated that they did not want to get help from them. Therefore, they stated that they preferred help coming from a person other than a family member.

"… It would be better if the helper were closer to my mind set. I got angry because my mother-in-law was very involved... I asked her to stay out of it. …because I want to make my own decisions…" (M3). *"...helper person should not be a family member this period. I would prefer a nurse's support in that process ..."* (M10). *"... Mother, father, sister.. I don't want anybody... I want someone conscious, let me explain the process to him..."* (M4).

3.3. The Factors Effecting Breastfeeding Motivation

3.3.1. Positive factors

Presence of social support**:** Most mothers stated that having social support increased their motivation for breastfeeding. *"…My husband was very helpful. He was motivating me. He provided opportunities for me to rest. These were effecting me very positively…"* (M1)

Awareness**:** The mothers stated that knowing the benefits of breastfeeding motivated them more. *"…I knew that the babies should take breast milk, and this is a miraculous fluid. The first milk is like the first vaccine. I read all of these…"* (M2)

"…They always say the first six months of breastfeeding is crucial for the health of the child. 'I must breastfeed in the first six months, I must breastfeed.' this resonates in the head of the human being." (M6)

Physiological changes**:** A number of mothers stated that they were able to witness the growth of their babies and that these physiological changes motivated them. *"…Babies… Only that. You see that they are growing. I've been looking back and can see how far we have come. For example, their babbling started, and that is motivating me now." (M1)*

"…Losing weight… I was constantly drinking water when I was breastfeeding. …and I was losing a lot of weight." (M9)

Perseverance**:** Some mothers stated that some negative experiences increased their perseverance for breastfeeding, and this positively affected their breastfeeding experience. *"…I have always had a lot of ambition because of the common expression such as "breast milk will not be enough", "Oh those kids" that I have heard since I am a mother of twin babies. I said, 'I'm going to be sufficient. …seems it is possible. People can break taboos. There is that power inside of us. I usually say that Allah, who gave these twin children, will also adjust the breast milk accordingly…"* (M5)

3.3.2. Negative factors

Social orientations**:** Some mothers stated that they used a formula to feed their babies under the guidance of health workers, and others pointed to closer friends. They also remarked that the comments and interventions from these sources negatively affected their motivation for breastfeeding.*"…The nurses in the intensive care stated that they don't know the amount of breast milk the babies receive, so, they urged me to give the babies 30 cc of the formula anyway. They also speculated that the babies will never be replete. They've got these into my head. …but if they had not done that or if they had said 'feed them with the breastmilk as much as you can, do not feed them with the formula', I would have tried hard. I guess milk cessation would not happen…"* (M1)

"…The doctor urged me to feed the formula after two hours saying that the babies were hungry, and I did. I did whatever the doctors instructed me..." (M3)

"…I was thinking that I will only breastfeed my children. I didn't want to feed them with the formula. …but then, of course, my mother came, "you're constantly breastfeeding, and that means they are not satisfied" she said. Since then, I have started to supplement with the formula…" (M6)

Preconception: A few mothers thought that their own milk was not enough for twin babies, and therefore, the formula should be supplemented. *"…breastfeeding a single baby is not the same as breastfeeding twins. …because there is not enough time for the breast to refill the milk. An hour has to pass every time…"* (M11)

Presence of health problems: Some of the mothers stated that their psychology was affected due to their health problems. *"…When I was having very sad times, my milk was running out. My family had some health problems. My spouse also had health problems…"* (M7)

4. DISCUSSION

In this study, when the results on the meaning of being a mother of multiple babies and breastfeeding them were examined, a number of positive expressions such as bonding, spending quality time, miracle, and being privileged were deduced**.** Breastfeeding is very common in Turkish culture, and approximately 96% of babies are breastfed for some time (15). Culture is a factor affecting breastfeeding. In Turkish culture, breastfeeding is considered an act that glorifies motherhood (16). Similar to the study, the increasing effect of breastfeeding on the bonding between the mother and the baby was widely reported (17-19).

Two of the mothers stated that the best time spent with the babies was the duration of breastfeeding. Caring for twins is very tiring and time-consuming (e.g. diapering or baby bath requires effort). Breastfeeding is a more passive action, so, mothers can feel rested and relaxed while breastfeeding. Breastfeeding also provides physical (touch) and visual (eye-to-eye) contact. Oxytocin release increases with touch, temperature, smell, and positive emotional stimuli, and oxytocin is considered a factor of stress reduction (20, 21). Due to the increased oxytocin release during breastfeeding, feelings of relaxation and rest may develop in mothers. Positive emotional state perceptions (spending quality time, miracle, attachment, etc.) during breastfeeding may be explained in this context. Furthermore, experiencing all emotions in twin babies at the same time twice may explain feeling privileged.

The negative perceptions about the meaning of breastfeeding in the study were expressed as restriction and responsibility/obligation. Similarly, in Çınar's study (2), it was stated that breastfeeding is difficult, stressful, problematic, and time-consuming for twins' mothers. Being a mother and breastfeeding is a condition that may greatly affect everyday life. In addition to physiological and emotional changes, the social life and relationships of the family are also altered. In addition to differentiation in daily routines before babies, challenges caused by twin babies may affect mothers' perceptions of breastfeeding.

Fatigue, sleeplessness, pain, and breast and nipple problems were expressed as the physical difficulties in the study. Problems encountered in breastfeeding in similar studies were reported as pain, fatigue, nipple problems, insufficient milk amount, and difficulties in holding the breast. These problems may be experienced in twin babies more than singleton babies (2,8,19,22).

Emotional difficulties were expressed in the study as anxiety/fear, guilt, trying to be strong, depressed feelings, and frustration/anger. It was stated in a study examining the exclusive breastfeeding process that half of the mothers initially aimed to breastfeed, but only a few were able to achieve this goal. The expressions of guilt and shame were observed among the mothers who failed to reach their breastfeeding goals (23). In this study, it was observed that the mothers of multiple babies also felt guilty and were worried about being unfair.

In a different study, women experiencing problems in breastfeeding were reported as being blamed and criticized in their social circles or by healthcare personnel. In this context, it was emphasized that mothers' sense of failure may cause insufficiency and social isolation (7). In this study, we observed that the mothers who experienced similar situations wanted to isolate themselves from society.

It was reported in the study by Fathi et al. (24) that self-care, social life, and social activities were adversely affected in mothers with postpartum depression risk. In this study, we observed that the depressed mothers experienced more difficulties in their relationships and exhibited aggressive attitudes. Watkins et al. (25) suggested that depressive symptoms were more likely to occur in the second postpartum month among mothers who had a negative breastfeeding experience. Therefore, women with difficulty in breastfeeding should be followed for depressive symptoms.

In this study, the mothers with relational problems stated that these problems were caused by judgmental and advisory attitudes. Verbal communication models involving accusatory, judgmental, and advisory styles are factors that negatively affect communication (26). In this respect, using positive verbal communication methods may be more effective in motivating mothers during breastfeeding.

The participants of the study emphasized the importance of social support, adequate resting, and stress mitigation in increasing the motivation for breastfeeding in twins' mothers. Providing family support and breastfeeding counseling in twin babies were reported to increase breastfeeding success by 74% (27). It is known that the rate and duration of breastfeeding of multiple infants are lower than singletons and below the desired level. Additionally, stress and emotional surge from being a new mother may prevent the effective continuation of breastfeeding. Therefore, maternal motivation is an effective factor in breastfeeding success. Factors that negatively affect breastfeeding may be different in each mother. Individual identification of mothers' problems, taking precautions, and providing breastfeeding counseling have been reported as factors that may increase breastfeeding rates and durations (22,28,29).

In the study, the majority of the mothers expressed that they did not want to receive support, especially from grandmothers (theme – relational difficulties). They reported that they prefer people they trust and can communicate well with. Similar to the results of the study; advisory behaviors of people such as grandmothers and other mothers regarding breastfeeding were explained as a negative motivation factor. It was emphasized that mothers needed positive motivation sources during this period (5,8,16).

Cisko (29) reported that breastfeeding counseling affected breastfeeding decisions, and social support affected the duration of breastfeeding. In this context, husbands and grandmothers were described as the most prominent social support providers (29). In a systematic review, Negin et al. (30) emphasized that grandmothers are an important factor that can affect exclusive breastfeeding. However, they emphasized that there is no evidence-based conclusion regarding the most effective way, the most appropriate time or the most effective person for breastfeeding education and support for the mother in twins, and thus, there is a need for more comprehensive studies on the topic (4,31). It is important that Turkish mothers do not prefer grandmothers by reason of relational conflicts. A family-centered care/ philosophy may be used to prevent these conflicts.

In the study, especially the negative orientation of healthcare professionals about breastfeeding affected the motivation of the mothers. All studies reported that proper breastfeeding counseling and encouraging mothers have affected breastfeeding success and duration (32-34). In this context, it is important for healthcare professionals to be careful in their recommendations regarding breastfeeding and formula use even in social conversations.

Limitations

Since the number of twin mothers in the society is low, it took more time to reach the sample and interview them compared to singleton babies' mothers.

5. CONCLUSION

Twins' mothers are a risky group in terms of physical, emotional, and social/relational problems that may occur during breastfeeding. It is important to maintain and increase physical and social support for these mothers. In order to avoid relational conflicts, it is advisable to avoid judgmentally, accusing, or interrogative communication statements. Planning breastfeeding education in a way to address the concerns of the mothers with twin babies is crucial. Additionally, each mother should be evaluated individually to provide the most appropriate care plan and consultancy.

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Clinical and Experimental Health Sciences

Evaluation of Mother-Infant Bonding Status of High-Risk Pregnant Women and Related Factors

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ABSTRACT

Objective: This descriptive study was conducted to determine the prenatal mother-infant bonding levels of high-risk pregnant women and related factors.

Method: A questionnaire was applied to 351 risky pregnant women in a public hospital between 1st August-1st October 2015. Socio-demographic features and Prenatal Bonding Inventory (PBI) scale were included in this form. Data were analyzed with SPSS 16.0 statistical program.

Results: There was no significant relationship between the number of pregnancies and PBI scores. It was found that PBI scores of women who willingly got pregnant and became happy when they learned that they were pregnant were statistically significantly high. It was ascertained that mean PBI scores of pregnant women having a planned pregnancy, not intending to terminate, feeling baby movements, and having the desire to see a doctor except for routine controls were significantly high.

Conclusion: The number of pregnancies, the willingness of pregnancy, planned pregnancy, thought of termination of pregnancy, the feeling of baby movements, and desire to see a doctor except for routine controls affected the mother-baby bonding.

Keywords: Prenatal Bonding, pregnancy, relevant factors

1. INTRODUCTION

Although pregnancy is a physiological process, it is a process that requires bio-psychosocial adaptation for the pregnant woman and her family due to the deterioration of physiological and psychosocial balance, changing roles in family and work life, and trying to adapt to the parental role (1,2). The prenatal period involves the period from the onset of pregnancy to the moment of delivery. Pregnancy, considered a developmental crisis or a critical period, has a very important place in women's life (3). It is known that especially high-risk pregnancy is a factor that increases the stress level. Pregnancy period time for women at risk due to increased emotional distress and difficulties in interpersonal relationships. The risk population of pregnant women would report more difficulty bonding with the fetus than would a population is drawn from the community at large (4). A high-risk pregnancy is defined as a physiological and psychosocial condition that endangers the life and health of the mother, fetus, or newborn, and increases the risk of disease and death. Pregnancies with systemic diseases before pregnancy and pregnancies with complications such as placental anomalies developing during pregnancy, Rh incompatibility, premature rupture of membranes, preeclampsia, intrauterine growth retardation, and cervical insufficiency are included in the high-risk pregnancy group (1,5). In high-risk pregnancies, stress due to problems related to the mother or the baby is higher than in normal pregnancies (2). Studies suggest that experienced stress may have a negative effect on the maternal-infant bonding process (6,7).

Bonding is a concept that has an important role in the development process of humans. This process, which develops between mother and baby with birth, affects her development, relationships with other people, and psychological adjustment. The baby is dependent on the person who cares for him/her depending on the fact that his/her skills have not been sufficiently developed yet (8). Bonding theory is based on the fact that the baby sends a signal for its needs and that a safe baby-parent bonding occurs as a result of the appropriate response of the

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caregiver (3). Bowlby (1983), who suggested the bonding theory, defined the word 'bonding' as a strong bond between the two people. The bonding theory focuses on the bonding of the baby to the mother in the early period as a result of the baby's need for biological trust, whether the mother can be reached on condition that the baby needs her and how reactions and behaviors of the mother are interpreted by the baby. The theory alleges that bonding behavior established during infancy has an important function in forming and sustaining the individual's life in the future and argues that it affects close relationships with others (9,10).

Prenatal bonding is an emotional bond that expresses the unique relationship established between parents and their unborn child. Mother-infant bonding begins when the mother positively reacts to the pregnancy. A pregnant woman who develops strong bonds with her baby knows that her unborn baby contacts with her, that it is a separate individual, and that it is dependent on her to develop (9,11). Thinking about what her baby will look like, how it will act, what developments it will show throughout its life, and having such feelings about bonding help the pregnant woman be sensitive to the development and protection needs of her baby (7,10,12).

Maternal-fetal bonding involving at-risk groups is a small number of research. A few comparative studies that high and low-risk groups of pregnant women have shown conflicting results. The aim of the study is to determine prenatal mother-infant bonding levels of high-risk pregnant women and related factors.

2. METHODS

This descriptive study was conducted to determine the prenatal mother-infant bonding levels of high-risk pregnant women and related factors. The study was conducted on pregnant women in a public hospital gynecology and high-risk pregnancy service between 1st August-1st October 2015. The universe of the study was comprised of 3864 pregnant women hospitalized at a public hospital in Ankara. The sample size of the study was calculated with the formula used in cases where the frequency of the universe was unknown and it was determined as 351. 351 pregnant women in the high-risk pregnancy service and meeting the study criteria were included in the study. This risk of pregnancy situation is placental anomalies, Rh incompatibility, premature rupture of membranes, preeclampsia, intrauterine growth retardation, and cervical insufficiency. The women who were literate, with pregnancies of 20 weeks and over, and agreed to participate in the study were included in the study. Data were collected with a "questionnaire form" and "Prenatal Bonding Inventory (PBI)".

Questionnaire Form (Pregnant Diagnosis Form): A questionnaire form prepared by receiving an expert opinion and consisting of a total of 23 questions with open-ended and multiple-choice questions was used.

Prenatal Bonding Inventory (PBI); Prenatal Bonding Inventory is used for measuring the bonding level of pregnant women to their baby in the womb. There are a total of 21 items in the PBIaimed at measuring emotional bonding to the fetus. Each item is a four-point Likert type and the total scale score is between 21 and 84. The participants are asked to respond to the statement in each item choosing options such as "Almost never (1 point)", "Sometimes (2 points)", "Mostly (3 points)" and "Almost always (4 points)''. None of the statements in the inventory are scored reversely. High scores received from the inventory mean that the prenatal bonding is high, low scores mean that the prenatal bonding level is low. The validity and reliability of the scale were performed by Duyan et al. (2013). The Cronbach Alpha test value of the Prenatal Attachment Inventory was reported to be 0.789 (12). In our study, this value was found to be 0.791.

2.1. Collection of Data

The necessary ethics committee (Decree no: 2014/08-13). Approval and permission from the institution were obtained to conduct the study. Written and verbal consent was obtained from pregnant women who agreed to participate in the study. The data were collected by face-to-face interview technique. Each interview took approximately 10 minutes.

2.2. Data Evaluation

SPSS 16.0 program was used in statistical evaluation. The suitability of numerical variables to normal distribution was examined with the Shapiro-Wilk test. In descriptive statistics, numerical data were expressed as mean ± standard deviation and minimum-maximum values, categorical data as numbers and percentages. Mann-Whitney U test was used in the comparison of the two groups since parametric test assumptions were provided in terms of numerical variables and Kruskal-Wallis analysis of variance was performed in comparison of the three groups. The mean score of the scale was analyzed using t test and ANOVA test in independent groups according to sociodemographic characteristics. The results were evaluated within the 95% confidence interval and $p < 0.05$ was considered to be significant.

2.3. Ethic

Ethics committee approval was obtained from Zonguldak Bülent Ecevit Unıversıty Human Studıes Ethics Committee to conduct the research (Decree no: 2014/08-13).

3. RESULTS

The mean age of the pregnant women was 28.6±6.4 (min.: 17, max.: 49) years, 33% were high school graduates and 80.6% were housewives. It was determined that 68.4% of them lived in a nuclear family and the income of 57.5% was equal to their expenses. In addition, they were married for an average of 7.4±5.83 (min.: 1, max.: 32) years (Table 1). It was found that

25.1% of pregnant women had a chronic disease and used medication continuously, 81.8% got pregnant willingly, 27.1% had a planned pregnancy, 5.4% thought to terminate. 98% of pregnant women stated that they felt the movements of the baby, 29.3% felt the need to call their doctor in examinations other than routine examinations, and 50.1% wanted to see a doctor before the control date (Table 2).

Table 1. *Socio-demographic features of the study group (n=351)*

Socio-demographic Features	Number	%
Marital Status		
Single	1	0.3
Married	348	99.1
Other	2	0.6
Family Structure		
Nuclear Family	240	68.4
Large Family	111	31.6
Educational Background		
Illiterate	6	1.7
Primary School	82	23.4
Secondary School	98	27.9
High School	116	33.0
University	49	14.0
Employment Status		
Employed	68	19.4
Unemployed (Housewife)	283	80.6
Economic Situation		
My income is lower than my expenses.	115	32.8
My income is equal to my expenses.	202	57.5
My income is higher than my expenses.	34	9.7
Total	351	100.0

It was found that there was no statistically significant relationship between the mean PBI score of the pregnant women and their ages (p>0.05). It was determined that there was no significant difference in the mean PBI score according to the pregnant women's type of family, educational background, employment status, and levels of income (p>0.05) (Table 3).

The mean number of pregnancies of the participant was 2.4±1.45 (min.: 1, max.: 8) and it was determined that there was no significant relationship between the number of pregnancies and PBI score (p>0.05). It was detected that the mean PBI scores of women who became happy when they learned that they were pregnant and those who willingly got pregnant were statistically significantly higher (p=0.001). It was determined that the mean PBI scores of the pregnant women who had a planned pregnancy and those who did not intend to terminate their pregnancy were significantly higher (p=0.002). The mean PBI scores of women feeling the baby's movements (p=0.005) and those having the desire to see a doctor except for their routine controls (p=0.002) were found to be statistically significantly higher (Table 4).

Table 2. *Distribution of health and pregnancy features of women (n=351)*

Health and Pregnancy Features	Number	%
Chronic Disease		
No	263	74.9
Yes	88	25.1
Constant Drug Use		
No	263	74.9
Yes	88	25.1
Desire to Get Pregnant		
No	64	18.2
Yes	287	81.8
Termination of Pregnancy		
No	332	94.6
Yes	19	5.4
Planned Pregnancy		
No	256	72.9
Yes	95	27.1
Feeling Baby's Movements		
No	7	2.0
Yes	344	98.0
Desire to Have Testsexcept for Routine Tests		
No	306	87.2
Yes	45	12.8
Need to call the doctor		
No	248	70.7
Yes	103	29.3
Desire to see a doctor more often than once a month	175	49.9
No	176	50.1
Yes		
Total	351	100.0

Table 3. *Comparison of prenatal mother-infant bonding status according to the socio-demographic features of pregnant women*

Socio-demographic Features	Prenatal Bonding Scale ($\bar{x}$ ±SD)	Test Values; p
Age	28.6±6.4 (min17, max 49)	0.978[a]; 0.501
Family Structure		
Nuclear Family	63.1042±10.5 (33-84)	1.391[b]; 0.164
Large Family	64.9369±10.0 (21-84)	
Educational Background		
Literate	58.5000±17.0 (36-78)	1.159[c]; 0.329
Primary School	62.3537±10.7 (34-84)	
Secondary School	64.1633±10.2 (33-84)	
High School	63.6897±10.8 (21-84)	
University	65.5714±7.9 (40-78)	
Employment Status		
Employed	63.5588±10.2 (33-82)	0.123[b]; 0.902
Unemployed	63.7138±10.4 (21-84)	
Economic Situation		
My income is lower than my expenses.	63.4087±11.5 (33-84)	0.033[d]; 0.983
My income is equal to my expenses.	63.8564±9.7 (36-84)	
My income is higher than my expenses.	63.5882±11.0 (21-84)	

[a] Pearson Korelasyon, [b] Man Whitney U Testi, [c]Anova Testi , [d] Kruskall Whallis Testi

Table 4. *Comparison of prenatal mother-infant bonding status according to pregnancy features of women*

Pregnancy Features	Prenatal Bonding Scale ($\bar{x}$ ±SD)	Test Values; p
Number of Pregnancy	2.4±1.45 (min.: 1, max.: 8)	**2.602[a]; 0.13**
The number of Child Alive		
Pregnancy Continues	65.2761±8.8 (33-84)	**7.772[c]; 0.0001**
No Child Alive	64.4105±10.2 (39-84)	
1	61.7083±11.2 (33-84)	
2	54.8095±10.4 (21-76)	
Feelings When They Learnt That They were Pregnant		
Worried	51.9615±13.8 (21-70)	**11.219[c]; 0.0001**
Afraid	63.3750±10.3 (40-78)	
Surprised	61.9778±9.2 (42-81)	
Excited	63.6750±10.8 (42-84)	
Happy	65.4107±9.2 (38-84)	
Desire to Get Pregnant		
No	57.0625±12.6 (21-84)	**-4.975[b]; 0.0001**
Yes	65.1603±9.2 (40-84)	
Thought of Termination of Pregnancy		
No	64.0241±10.1 (33-84)	**-2.070[b]; 0.003**
Yes	57.7368±13.7 (21-80)	
Loss of Pregnancy		
No loss of Pregnancy	63.5622±10.7(33-84)	0.336[c]; 0.800
1	64.6438±9.7 (21-82)	
2	62.6400±10.2(39-84)	
3 and over	62.9000±10.1 (36-81)	
Current Week of Pregnancy	32.3±4.45 (min 20, max 40)	0.869[a]; 0.627
Is the current pregnancy a planned one?		
Yes	60.4211±12.4 (21-84)	**-3.108[b]; 0.002**
No	64.8945±9.3 (40-84)	
Feeling the Baby's Movements		
No	58.1429±19.6 (21-77)	**-1.422[d]; 0.005**
Yes	63.7965±10.1(33-84)	
Desire to Have Tests		
No	63.5654±10.5 (21-84)	-0.554[d]; 0.801
Yes	64.4889±9.8 (40-84)	
Desire to See a Doctor Frequently		
No	62.0971±10.8 (21-84)	**3.079[b]; 0.002**
Yes	65.2614±9.7 (33-84)	

[a] *Pearson Correlation,* [b] *Man Whitney U test,* [c]*Anova Test, d t-test*

4. DISCUSSION

In our study, the mean age of pregnant women was 28.6±6.4. A similar mean age was found in studies related to pregnant women in our country. Pisoni et al. (2016) stated that the mean age of the high-risk pregnant women was 32.5, Kartal and Taraman (2018) stated that the mean age of the majority of the pregnant women was 26.2, and Havutçu (2019) to be above the age of 25 (13,14,15). In our study, no statistically significant relationship was found between the ages of pregnant women and the mean PBI scores. Similarly, Akarsu and Oskay (2017), Lingesvaran and Bindu (2012) also stated that age did not affect the prenatal bonding status (16,17). Barone et al. (2014) reported that prenatal bonding increased with increasing age; however, Massey et al. (2015) stated that prenatal bonding decreased with increasing age (18,19). The reason for this difference may be due to the fact that the studies were conducted in different regions and cultures.

The majority of the pregnant women (33%) were high school graduates in the study. According to data from Turkey Demographic and Health Survey, 26% of women in our country have an education of high school or higher (20). It was determined that the education level of pregnant women participating in the study was higher. This may be due to the fact that the study was conducted in Ankara city center. In our study, there was no statistically significant difference between the educational background and the mean PBI score of pregnant women. Similar results were found in some studies conducted (17,21). However, when other studies in the literature were examined, it was stated that prenatal bonding increased the level of education increased (16,22,23,24). These differences may be due to the fact that the studies were conducted in different places, age groups, and different cultures. These differences were thought to be due to the fact that the studies were conducted in different places, age groups, and different cultures, as well as previous pregnancies, number of pregnancies and complications due to pregnancy, and chronic diseases present in the pregnant woman.

The majority of pregnant women participating in the study (57.5%) earned as much as their expenses and there was no statistical difference between PBI scores according to economic groups. Similarly, in Akarsu and Oskay's (2017) study, it was found that the economic situation did not affect the prenatal bonding level (16).

It was determined that more than half (80.6%) of the pregnant women who participated in the study were unemployed and there was no statistical difference in PBI scores in terms of employment status. However, in some studies, it was found that prenatal bonding was high in employed pregnant women (14,16,24,25). No statistical difference was found between the type of family and prenatal bonding level in this study. However, Alan stated that mothers with large families had higher maternal bonding scores than those with nuclear families, while Kartal and Taraman stated that pregnant women with nuclear families had higher prenatal bonding levels (14,26). These differences between employment status and the family type and prenatal bonding can be explained by the fact that individuals have different environmental and social support systems.

In our study, it was found that 72.9% of the pregnant women had an unplanned pregnancy, and the mean PBI score was significantly higher in those who had planned pregnancies. Similarly, in most studies, it was found that women with planned pregnancies had higher bonding levels (14,22,27,28,29). However, in some studies, it was found

that there was no relationship between prenatal bonding and the fact that whether the pregnancy was planned or not (23,24,25). Prenatal bonding in planned pregnancies is an expected result as the pregnancy is desired and the readiness of the mother exists.

A statistically significant difference was found between the PBI scores of the women included in the study when they learned that they were pregnant and the PBI scores and the idea of terminating their pregnancy and the PBI scores. It was determined that the PBI values of pregnant women who felt sad when they found out that they were pregnant and who thought to terminate their pregnancy were lower than the others. Therefore, it is thought that pregnancies of pregnant women who are sad and who are planning to terminate their pregnancy are not planned. When the literature is examined in this context; it was indicated that an unplanned pregnancy or an unwanted baby negatively affected mother-to-infant bonding (32,33). In the study performed by Top et al. in 2005 about the attitudes of pregnant women regarding their changing body image, they found that voluntariness for pregnancy had an effect on the adaptation to motherhood (33). The results of our study are in accordance with the other studies in the literature in this aspect. According to Brockington (2006), there was a strong correlation between bonding disorder and unwanted pregnancies and a lack of establishing a connection with the fetus during pregnancy (34). It can be thought that upset or unwanted pregnancies when they learn about their pregnancy negatively affect the mother-infant bonding and may pose a risk of attachment.

The majority of the pregnant women (81.8%) had a desire to become pregnant and it was determined that the mean PBI score was statistically very high. The studies conducted also supported our findings (26,35,36). There was a statistically significant difference between the states of maternal bonding and the desire to get pregnant (26,35,36). However, Dağlı did not find any difference in prenatal bonding despite the fact that more than half of the women desired the pregnancy (24). In families where pregnancy is desired, the arrival of the baby is met with love and attention. Therefore, prenatal bonding is expected to increase with the development of positive health behaviors.

In our study, the meanPBI score was higher and more significant in women who were primiparous and had no child alive. In similar studies, it was stated that prenatal bonding was higher in primiparous women and women who had never given birth (16,22,23,24,37). In addition, it was found that mothers giving birth more than three times had low bonding levels (22,27). These findings are in line with our research findings.

98% of the pregnant women felt the movements of the baby after the 20th week of pregnancy and the mean PBI score was found to be statistically significant. In addition, the means of bonding of mothers expressing their happiness for their current pregnancy were found to be very significant. In national and international studies, it was stated that as the gestation week increased, the bonding increased, too (38,39). These findings are in line with the literature. It can be thought that since the movements of the baby are felt more clearly with the progress of pregnancy, the feeling of the movements of the baby increases bonding in the prenatal period.

Limitations

The limitations of the study are that the study was conducted in a single center and that women with a pregnancy of 20 weeks or more were included in the study.

5. CONCLUSION

Prenatal bonding is the most unique sample of the communication between mother and baby in the prenatal period. There are a lot of factors affecting prenatal bonding (age, family structure, education, employment status, economic status, the health status of the person, features of marriage, number of children alive, gender of the baby to be born, planning of pregnancy, the status of desiring pregnancy, culture, attitude, and behaviors, etc.). Pre-identification and analysis of these factors are important to improve the nasty results of prenatal health. Especially in pregnant women with a weak bonding risk, appropriate interventions can be provided and prenatal bonding can be increased with training and consultancy. In this context, proper and on-time nursing care is required to ensure/increase prenatal bonding.

It was found that the mean PBI score of women willing to get pregnant and become happy when they learned that they were pregnant was statistically significantly higher. It was determined that the mean PBI score of the pregnant women having a planned pregnancy, not intending to terminate their pregnancy, feeling baby movements, and having a desire to see the doctor except for their routine controls was found to be significantly higher.

Longitudinal and experimental studies are required for the evaluation of bonding levels of pregnant women by midwives and nurses attentively during pregnancy and the postpartum period, the determination of the factors affecting bonding, and determination of the effects of bonding disorders on mother and baby.

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Clinical and Experimental Health Sciences

Evaluation of Sexual Functions in Women Using Hormonal or Non-Hormonal Contraceptives

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ABSTRACT

Objective: Female sexual dysfunction is a common condition that negatively impacts the psychological health and quality of life of the affected individuals. Therefore, this study aims to assess sexual function changes in women using hormonal and non-hormonal contraceptives.

Methods: We assessed 380 women who visited three Family Health Centers in Manisa, Turkey. Female Sexual Function Index (FSFI) and Beck Depression Inventory (BDI) questionnaires were used to get data. Regression and correlation analyses were applied to determine the relationship and level of sexual function of participants.

Results: According to FSFI cut-off score ≤26.55, the prevalence of female sexual dysfunction (FSD) was determined in 35.4% and 48.0% of sexual function changes and FSFI score was found 26.5±4.3 and 27.1±4.1 in women using non-hormonal and hormonal contraceptives. In regression analysis, women having higher education, satisfied with their sexual life, and women stating that their husband satisfied with non-hormonal contraceptive usage had high score in FSFI. Of those women, 6.6% scored ≥17 on the BDI.

Conclusion: The use of hormonal and non-hormonal contraceptives is important for the improvement sexual quality of women planning appropriate initiatives. Therefore, healthcare practitioners and providers should assess women's risk factors for FSD, arrange for extra follow-up and assist with early diagnosis and treatment to improve women's sexual life.

Keywords: Women, Sexual dysfunction, Hormonal, Contraception.

1. INTRODUCTION

Female sexual function is a complex and sensitive topic affected by many factors including neurologic, endocrine, vascular, physical, psychological, social, and cultural variables (1-6). Female sexual dysfunction (FSD) may occur at any stage of a woman's life and affect 27% to 73% of women in the world and 37% to 68% of women in Turkey (2,3,5,7-9). It was linked to a variety of socio-demographic variables such as age, educational level, marriage duration, presence of children, and socioeconomic position (4-6,8,9). Physiological (obesity, chronic diseases, low testosterone level, lack of lubrication), psychological (anxiety, depression), medical (medications), affective (love or arrange marriage), and interpersonal (marital adjustment) factors were found important factors for the etiology of FSD (1,2,5,6,9-15). It was also pointed that the effects of contraceptives on sexual function were another factor influencing couples' sexual lives (10,12,16-19).

When a couple's sexual life suffers as a result of their contraceptive methods, many of them modify or cease using it (7,13,20-23). Because of the negative effects, the dropout rate of oral contraceptive, which was one of the most prevalent hormonal methods in Turkey was so high (29.8 percent) (24). Unprotected sexual intercourse was widespread in Canada and United States, according to a survey of 5600 people, due to a loss of desire (20). The most prevalent adverse effects of IUDs in terms of sexuality were feeling of intrauterine devices (IUDs) strings by the women's partner (13,22) and abnormal bleedings (13,21).

Especially, female hormonal contraceptive usage has been associated with a variety of physical and psychological side effects. Earlier researchers found that combining oral contraceptive with high dosage ethinyl estradiol reduced free testosterone levels, which positively linked with sexual desire, arousal, and vaginal lubrication (14-16), genital vascular (18), and hormone concentrations (2-10).

It is difficult to determine if it is depression that impacts sexuality or whether marital stress produced by a lack of sexual satisfaction and sexual desire contributes to depressed thoughts (14,25) due to mood changes and depressive symptoms that effect of hormonal contraception. Furthermore, just a few published research compared

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FSD with contraceptive techniques (hormonal and non-hormonal) (25-28). The current study aimed to determine sexual functioning in women who used either hormonal or non-hormonal contraception. We planned this study due to that there was a limited number of studies published on this issue. In this context, the two research questions are listed as below:

Research question 1: Does the use of contraceptives methods impact women sexual function?

Research question 2: Does the use of hormonal or non-hormonal contraceptives impact women sexual function?

2. MATERIALS AND METHODS

2.1. Design and Data Collection

This research was a descriptive and cross-sectional study. The data were collected by home visit taking prior consent from the women from October, 2015 and September, 2016. Their address information was obtained from family health centres. The husband's data was based on their wife's expressions.

2.2. Research Sample

The data were randomly collected from women in family health centres in Manisa, Turkey. Family health centres classified in three groups according to the location (rural, urban and semi-urban) based on Manisa Population and Health Research. Then three family health centres were selected randomly among 11 family health centres (29). The study population consisted of 16.211 women, whose ages were between 15 and 49 years, according to data from Manisa Provincial Health Directorate in 2015. The minimum sample size was calculated as 375 in Epi Info 2000 program with 5% error share and 95% confidence interval (based on the unknown prevalence of 50%). We included 380 women out of 16.211 women between the ages of 18–49 years who expressed the desire to participate the research. Participants had sexual life and had used any contraceptive methods at least three months. Women who were pregnant, lactating, or in the climacteric phase, as well as those with depression, cancer, hysterectomy, pelvic relaxing (cystocele or rectocele), and chronic illness were not participated in this research. Participants were categorized into two groups: those who used hormonal methods (combined oral contraceptive pill (COCP), once-a-month combined injectable (mesigyna) and depot medroxyprogesterone acetate-(DMPA), and those who used non-hormonal methods (male condoms, IUDs, withdrawal, tubal ligation).

2.3. Measurement Instruments (Questionnaires)

Socio-demographic and reproductive characteristics forms that were prepared by the researcher and Female Sexual Function Index (FSFI) and Beck Depression Inventory (BDI) used for data collection. BDI was developed by Beck et al. (1961) (30), and adapted to Turkish by Hisli (1988)(31). It has 21 items and, women with a BDI score of 17 or higher were evaluated as having the possibility of experiencing depression. Its Cronbach alpha reliability coefficient was found as 0.87 in this study. FSFI was developed by Rosen et al. (2000) (32) and adapted to Turkish by Oksuz and Malhan (2005) (33). It has 19 questions and six dimensions: desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI total score ranges from 2 to 36, with higher levels indicating improved sexual function. A total FSFI score ≤26.55 is thought to indicate a high risk of sexual dysfunction (10,14). The Cronbach alpha reliability coefficient was found as 0.88 in this study.

2.4. Ethics approval and consent to participate

The study was authorized by the University of Manisa Celal Bayar's Ethics Committee (date: 27.05.2015/ number: 20478486) and the Manisa Health Director. The purpose of the study was described to all of the participants, and signed informed permission was obtained from all of the women.

2.5. Statistical analysis

Qualitative variables were represented as frequencies, and quantitative variables as mean ± standard deviation. The quantitative variables were analysed with the Kolmogorov–Smirnov normality test. Chi-Square test was used to evaluate the association between qualitative variables to compare a quantitative variable among groups, and independent-sample T test was used to determine the significance of associations between characteristics of women and FSFI total and sub-score. After confirming the data had normality, linearity and homoscedasticity we applied to multiple regression analysis to check the relationship the between independent, presented at Figure 1, and dependent variable (FSFI total and sub-scores). Pearson's correlation was used to examine the correlation between FSFI and BDI scores. The analyses were performed using the SPSS software version 15.0 and $p < 0.05$ was considered significant.

3. RESULTS

3.1. Descriptive characteristics of the participants

Descriptive characteristics of the participants are presented in Table 1. The groups were homogeneously aged, with a mean age of 33.5±6.5 years and of 51.1% with the range of 31 to 40. Overall, 37.4% of the women were primary school degree, 28.2% were employee and 48.7% had a normal body mass index. Most of the participants (59.5%) had loved marriages. In this study, 46.9% (30.3% COCP, 16.1% mesigyna, 0.5% DMPA) and 53.1% (14.2% male condom, 13.7% IUD, 13.2% withdrawal, 12% tubal ligation) of women using hormonal and non-hormonal methods. Women's satisfaction of their sexual life and contraceptive methods are presented in Table 2.

Table 1. *Descriptive characteristics of the women and husband (n=380)*

Characteristic of women	n	%	Characteristics of women	n	%
Age groups of women			**Age groups of husbands**		
18-30 age	128	33.6	18-30 age	74	19.5
31-40 age	194	51.1	31-40 age	192	50.5
≥41 age	58	15.3	≥41 age	114	30.0
Education of women			**Education of husbands**		
Illiterate / literate	35	9.2	Illiterate / literate	11	2.8
Primary school	142	37.4	Primary school	116	30.5
Secondary school	50	13.2	Secondary school	69	18.2
High school	105	27.6	High school	99	26.1
University	48	12.6	University	85	22.4
Employment status of women			**Employment status of husbands**		
Unemployed	273	71.8	Employed	368	96.8
Employed	107	28.2	Unemployed	12	3.2
Body mass index of women					
Underweight (≤19,7 kg/m^2)	28	7.3	**Income status of family**	91	23.9
Normal (19,8-26 kg/m^2)	185	48.7	Low	270	71.1
Overweight (26,1-29 kg/m^2)	87	22.9	Medium	19	5.0
Obese (≥29,1 kg/m^2)	80	21.1	High		
Number of pregnancy					
No pregnancy	4	1.0	**Marital adjustment**		
1 pregnancy	70	18.4	Very compatible	76	20.0
2 pregnancies	142	37.4	Compatible	190	50.0
3 pregnancies	84	22.1	Moderate compatible	101	26.6
≥4 pregnancy	80	21.1	Incompatible	13	3.4
Miscarriage			**Type of marriage**		
Yes	94	24.7	Arranged	154	40.5
No	286	75.3	Loved	226	59.5
Stillbirth			**Hormonal contraceptive method use**		
Yes	5	1.3	**(n=178)**	115	64.6
No	375	98.7	Combined oral contraceptive pill	61	34.3
Induced abortion			Mesigyna	2	1.1
Yes	78	20.5	DMPA	178	100.0
No	302	79.5	Total		
Health insurance			**Non-hormonal contraceptive method use (n=202)**		
Yes	368	96.8			
No	12	3.2	Male condom	54	26.7
Residence of place			Intrauterine device	52	25.7
Rural	96	25.3	Withdrawal	50	24.8
Semi urban	205	53.9	Tubal ligation	46	22.8
Urban	79	20.8	Total	202	100.0

3.2. The relationship between sexual dysfunction and the usage of contraception.

In this study rate of FSD was found as 42.1% among the women. As seen in Table 3, the risk of FSD in non-hormonal contraceptive users (48.0%) was considerably greater than in hormonal methods (35.4%) ($p<0.05$) Although the mean FSFI scores in the non-hormonal contraceptive users group (26.5±4.3) were lower than in the hormonal contraceptive users group, there was no statistically significant difference between the groups (27.1±4.1) ($p>0.05$).

3.3. The relationship between women characteristics, FSFI and sub-score

Figure 1 depicts the important factors found in univariate analysis between women's characteristics and FSFI and sub-score. The results of multiple regression analysis showed

that women's characteristics were revealed to be statistically significant with FSFI total and sub-score. According to the results of the regression analysis in Table 4, the most of the FSFI dimensions (desire, arousal, lubrication, satisfaction orgasm, and total score) were significantly lower in women who were dissatisfied with their sexual life ($p<0.05$). The desire and orgasm score was found higher in women of advanced age. Women with higher levels of education had higher levels of arousal and total FSFI. Also, women who had a compatible marriage with their husband scored higher on desire and contentment. Women who had a working husband had a greater level of contentment, women who had sexual intercourse three or more times per week had a higher desire score and women who indicated that their sexual desire increased after menstrual cycle had better arousal score. The sexual desire score was found to be lower among women who had four or more pregnancies. When compared to other participants, women who underwent tubal ligation showed a lower level of satisfaction. Women who were pleased with the use of COCP worked had higher orgasm scores. Participants who were unsatisfied with the usage of mesigyna scored lower on lubrication. It is found that women who stated that their husband was satisfied with non-hormonal contraceptive had better total FSFI score.

3.4. The correlation between dimensions of FSFI and BDI score

Pearson's correlation between dimensions of FSFI and BDI score was performed (see Table 5). Table 5 showed that the highest correlation was found between total FSFI score and arousal sub-score ($r=0.787$; $p< 0.0001$). While a statistically significant correlation was found between the total FSFI score and the averages of desire, lubrication, orgasm, and satisfaction scores ($p<0.0001$), a significant negative correlation was found between FSFI and BDI ($r=-0.230$, $p<0.0001$).

Table 2. *Women's satisfaction of their sexual life and hormonal or non-hormonal methods*

Characteristics	n	%	Characteristics	n	%
Frequency of sexual intercourse			**Change of sexual desire after menstruation**		
Once a week	96	25.3			
Twice a week	115	30.3	Increases	103	27.1
Three times a week	110	28.9	Decreased	38	10.0
Four times and more a week	59	15.5	Unchanged	239	62.9
Satisfaction of sexual life of women			**Satisfaction of sexual life of husband**		
Very satisfied	26	6.8	Very satisfied	43	11.3
Satisfied	262	68.9	Satisfied	283	74.5
Moderately satisfied	73	19.3	Moderately satisfied	31	8.2
Unsatisfied/ very unsatisfied	19	5.0	Unsatisfied/ very unsatisfied	23	6.0
Women's satisfaction of hormonal methods (n=178)			**Husband's satisfaction of hormonal methods (n=178)**		
Satisfied	143	80.3	Satisfied	170	95.5
Moderately satisfied	22	12.4	Moderately satisfied	3	1.7
Unsatisfied	13	7.3	Unsatisfied	5	2.8
Women's satisfaction of non-hormonal methods (n=202)			**Husband's satisfaction of non-hormonal methods (n=202)**		
Satisfied	171	84.6	Satisfied	162	80.2
Moderately satisfied	21	10.4	Moderately satisfied	21	10.4
Unsatisfied	10	5.0	Unsatisfied	19	9.4

Table 3. *Relationship between sexual dysfunction and contraception use*

	Sexual dysfunction				Test
Contraceptive methods ***	**With** FSFI score≤26.55		**No with** FSFI score>26.55		
	n	**%**	**n**	**%**	x^2**=6,188** **p=0.017***
Hormonal contraceptive	63	35.4	115	64.6	
Non-hormonal contraceptive	97	48.0	105	52.0	
Total	160	42.1	220	57.9	
	Total FSFI scores				
	Mean±SD		**Min/Max**		**Test**
Hormonal contraceptive	27.1±4.1		12.4/33.4		t=1.556 p=0.121**
Non-hormonal contraceptive	26.5±4.3		14.2/34.8		

Pearson Chi-square test, ** Independent-sample t test, * The percentage was calculated according to rows*

Table 4. *Relationship between characteristic of women and FSFI score according to regression analysis*

		Unstandardized Coefficients		Standardized Coefficients	t	p
		B	Std. Error	Beta		
Desire	(constant)	1.669	1.097		1.521	0.133
	Age of women	0.042	0.018	0.279	2.310	**0.024**
	*Marital adjustment	-0.294	0.123	-0.241	-2.385	**0.020**
	Number of pregnancy	-0.229	0.090	-0.273	-2.548	**0.013**
	*Women's satisfaction with their sexual life	-0.566	0.148	-0.412	-3.827	**0.000**
	Frequency of sexual intercourse	0.225	0.071	0.309	3.146	**0.002**
Arousal	(constant)	3.736	0.693		5.395	**0.000**
	Education of women	0.204	0.049	0.235	4.126	**0.000**
	*Women's satisfaction with their sexual life	-0.645	0.083	-0.386	-7.795	**0.000**
	*Change of sexual desire after menstruation	-0.119	0.054	-0.098	-2.197	**0.029**
Lubrication	(constant)	23.320	4.379		5.326	**0.000**
	* Health insurance	-4.464	1.918	-0.257	-2.327	**0.024**
	* Satisfaction of mesigyna	2.725	0.743	0.418	3.668	**0.001**
	*Women's satisfaction with their sexual life	-2.301	0.823	-0.370	-2.979	**0.007**
Orgasm	(constant)	15.246	2.232		6.831	**0.000**
	Age of women	0.082	0.038	0.192	2.162	**0.033**
	* Satisfaction of combined oral contraceptive	-0.936	0.454	-0.179	-2.062	**0.042**
	*Women's satisfaction with their sexual life	-2.362	0.483	-0.451	-4.891	**0.000**
Satisfaction	(constant)	5.780	0.582		9.929	**0.000**
	* Marital adjustment	-0.263	0.055	-0.222	-4.808	**0.000**
	*Employment status of husband	-0.532	0.226	-0.103	-2.356	**0.019**
	*Use tubal ligation	0.254	0.124	0.091	2.041	**0.042**
	*Women's satisfaction with their sexual life	-0.521	0.067	-0.368	-7.745	**0.000**
Pain	(constant)	4.567	0.578		7.909	**0.000**
	Body mass index of women	0.039	0.016	0.169	2.388	**0.018**
	*Husband's satisfaction of non-hormonal methods	-0.273	0.127	-0.149	-2.141	**0.034**
Total FSFI score	(constant)	27.457	3.674		7.474	**0.000**
	Education of women	0.734	0.272	0.225	2.699	**0.008**
	*Husband's satisfaction of non-hormonal methods	-1.104	0.426	-0.163	-2.589	**0.010**
	*Women's satisfaction with their sexual life	-2.541	0.418	-0.401	-6.085	**0.000**

**Reverse code*

Table 5. *Pearson's correlation between subscales of FSFI and BDI score*

		BDI	Desire	Arousal	Lubrication	Orgasm	Satisfaction	Pain
BDI	r							
	p							
	n							
Desire	r	-0.149(**)						
	p	**.004**						
	n	380						
Arousal	r	-0.153(**)	0.613(**)					
	p	**.003**	**.000**					
	n	380	380					
Lubrication	r	-0.098	0.186(**)	0.185(**)				
	p	.055	**.000**	**.000**				
	n	380	380	380				
Orgasm	r	-0.184(**)	0.502(**)	0.648(**)	0.178(**)			
	p	**.000**	**.000**	**.000**	**.000**			
	n	380	380	380	380			
Satisfaction	r	-0.266(**)	0.473(**)	0.604(**)	0.256(**)	0.623(**)		
	p	**.000**	**.000**	**.000**	**.000**	**.000**		
	n	380	380	380	380	380		
Pain	r	-0.086	0.186(**)	0.134(**)	0.234(**)	0.145(**)	0.109(*)	
	p	.094	**.000**	**.009**	**.000**	**.005**	**.034**	
	n	380	380	380	380	380	380	
FSFI	r	-0.230(**)	0.717(**)	0.787(**)	0.507(**)	0.778(**)	0.744(**)	0.481(**)
	p	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	n	380	380	380	380	380	380	380

** p<0.05, ** p<0.01*

4. DISCUSSION

In the current study, we evaluated relationship between sexual functions and usage of hormonal or non-hormonal contraceptives. The study is significant since it was the first to investigate the effects of hormonal or non-hormonal contraceptives on women's sexual functions in Manisa, Turkey. In the study, 42.1% of women had FSD. In the literature, there are several studies that support our research findings. According to a meta-analysis of 95 studies, the rate of FSD was found 40.9% all of the population 40.2% in Africa, 39.1% in Europe and 32.1% in non-European West (34). The prevalence of FSD in different countries ranged from 27% in US (35) and Iran (36), 38.7% in Pakistan (28), 60.2% in China (37) to 73% in India (2). In Turkey, the FSD rate has been found to range between 37.7% and 68.8% (3,5,9). Sexual dysfunction was a widespread concern and problem in women, as evidenced by the findings of these studies.

Age, educational level, health insurance, number of pregnancy, marital adjustment, satisfaction of contraceptive methods, frequency of sexual intercourse was found as risk factors for FSD in this research. Many other studies support these findings (2-10,15,26,35,38-44). Another finding of the study was that women who had tubal ligation were less satisfied with their contraceptive than women who used alternative contraceptive methods. Similarly, several Iranian studies resulted that satisfaction (45), sexual desire/arousal scores (19), and all FSFI sub-scale scores (46) were remarkably low in women who had tubal ligation.

In literature, there were different studies examined the effect of contraceptives on sexuality. FSD was lower in women who used hormonal methods in our study, which was consistent with previous research (25,37), but contradictory to those of other research (3,12,28, 47, 48). In women who used hormonal methods, studies found that desire (14), arousal (12,14,18), orgasm (12), and total FSFI scores (14,47) were low, but vaginal dryness (12) and pain (18) were high According to these studies, contraceptive has a negative impact on sexuality by decreasing circulating testosterone levels as well as serum levels of estradiol and progesterone. In contrast, several researchers have found that hormonal methods have a positive effect on sexuality. Women who used hormonal contraception, for example, had a lower risk of dyspareunia (16), as well as higher sexual activity, higher desire, and orgasm and FSFI scores (25). Non-contraceptive effects of hormonal methods are relief of gynaecologic pain, decrease of anxiety and discomfort, eliminate the fear of pregnancy, more stable levels of hormones throughout the cycle and less bleeding with the consequent lower risk of anaemia. All of these effects of hormonal contraception contribute to women's well-being and, as a result, to a probable enhancement in women's sexual function. Furthermore, many studies found no changes in sexual function as a result of contraceptive methods (16). The various findings on the

effects of hormonal contraception on women sexual function might be attributed to the fact that it is complicated and multidimensional. In addition, cultural differences between nations, perceptions of sexuality, and research methods all contributed to differences in results.

In this study women who used hormonal methods had a decreased FSD rate, and this finding is crucial for counselling women who plan to use hormonal methods. Because, in some countries, women had a negative perception of hormonal methods for a variety of reasons, including cancer, missed menstruation, sterility, nausea, back pain, headaches, dizziness, fatal abnormalities, infertility, hair loss, weight gain, and libido loss (13).

A negative correlation found between BDI and FSFI total and desire, arousal, orgasm and satisfaction sub-scores in this study. Subsequently, it confirming the suggestion that depression is a risk factor for FSD, as reported consistently in previous studies (2,9,13). On the other hand, depression may be associated with sexual problems. Further longitudinal studies are necessary to find the relationship between them.

5. CONCLUSION

This study assessed sexual function changes in women using hormonal and non-hormonal contraceptives. The main finding of this study is 40% of women had FSD and women using hormonal method had higher score of FSFI. Furthermore, women with a higher level of education, who were satisfied with their sexual lives, and whose husbands were satisfied with non-hormonal methods had a higher FSFI score. Healthcare practitioners and providers may assess women's risk factors for FSD, arrange for extra follow-up, give preventative care, and, if required, assist with early diagnosis and treatment to improve women's health. Potential sexual adverse effects of hormonal and non-hormonal methods should be thoroughly described, and a patient-centered decision should always be supported.

Study limitations

There are some limitations of this study. Firstly, the study was conducted as a cross-sectional study in Manisa, a city in the west of Turkey. Therefore, the findings may not be generalised in whole Turkey. Secondly, women's sexual functions before contraceptive use were not evaluated. Thirdly, husband's opinions of sexual life were evaluated according to women's expressions. Morever, another study limitation includes a small sample size. Future research and studies with a larger sample are needed to confirm the findings of this study.

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Clinical and Experimental Health Sciences

Evaluation of Readability of Turkish Websites on Obesity and Bariatric Surgery

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ABSTRACT

Objective: This study aimed to investigate the readability levels and contents of Turkish websites on obesity and bariatric surgery.

Methods: A search was performed in June 2019 with the words "obesity" and "bariatric surgery" in Google's search engine. We evaluated the websites on the first ten pages of Google's search engine results. Commercial websites, advertisement websites, chat websites, forum websites, magazine websites, websites containing only images or videos, and websites with less than ten sentences were excluded. Ateşman and Bezirci-Yılmaz's readability formulas were used to analyze the readability level. Websites were evaluated in terms of content (definition, risk factors, complications, and treatment of obesity) and were divided into three groups (Group 1: hospitals and specialist physicians, Group 2: national news websites, and Group 3: other websites).

Results: A total of 79 websites were evaluated. There were 43 (54.4%) websites in Group 1, 25 (31.6%) websites in Group 2, and 11 (13.9%) websites in Group 3. The readability level of all sites was 'difficult,' according to the Atesman readability formula, and at 'undergraduate level,' according to the Bezirci-Yılmaz readability formula. When the contents of these websites were examined, 51.9% contained a definition of obesity, 7.6% contained information on waist circumference, 12.7% contained obesity risk factors, and 43.0% contained obesity-related diseases.

Conclusion: This study revealed that the readability level of Turkish websites on obesity and bariatric surgery was above the average literacy level of the Turkish people. Furthermore, it determined that these websites did not provide adequate information about bariatric surgery risks, adverse effects, and contraindications.

Keywords: Obesity, bariatric surgery, readability, internet

1. INTRODUCTION

Obesity is one of the most critical health problems in all societies. With the rapid change of lifestyle in Turkey, obesity has become an increasing and health-threatening problem (1). The Turkish Diabetes Epidemiology Study-I (TURDEP-I) conducted among 24,788 adult Turkish people in 540 centers found that the prevalence of obesity was 22% (30% for females and 13% for males) (2). The Turkish Diabetes Epidemiology Study-II (TURDEP-II) involving 26,499 adult Turkish people also found that the prevalence of obesity was 31.2% (44% for females and 27% for males) (3). The results of TURDEP-I and TURDEP-II have demonstrated that the prevalence of obesity in Turkey has increased by 41% in the past 12 years (46% for females and 107% for males). Obesity has become a big problem not only for adults but also for children in our country. According to Turkey Nutrition and Health Survey data, the prevalence of obesity in children and adolescents was 8.5% (4).

Diet, exercise, cognitive behavioral therapy and pharmacotherapy are methods used in obesity treatment. In cases where these treatment methods fail, bariatric surgery is a treatment option required to reduce obesity-related morbidity and mortality and to improve organ function (5). A body mass index (BMI) greater than 40 kg/m² or a BMI greater than 35 kg/m² plus the presence of at least one obesity-related comorbidity (such as hypertension, diabetes mellitus, dyslipidemia, sleep apnea syndrome, nonalcoholic steatohepatitis, asthma) is an indication for bariatric surgery (6). The use of bariatric surgery has increased, especially in parallel with the increased rate of morbid obesity (7). It has

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increased by 85.1% from 1998 to 2013 worldwide. As a result, the number of physicians and medical centers interested in bariatric surgery is increasing in our country (8). This is related to the fact that non-surgical treatment methods used in obesity are insufficient to improve mortality and morbidity rates and show that bariatric surgery's incidence is gradually increasing.

As in the whole world, internet usage is growing, especially with the growth in smartphone usage in our country. According to the data released by the Turkey Statistical Institute in 2019, the internet usage rate was 18.7% in illiterates, 87.3% in primary school graduates, 94.5% in high school graduates and 98% in university graduates and over. The same data also showed that the number of people using the internet to search for health-related information was 69.3% (9).

Although internet usage seems to be a practical, easy and inexpensive method for obtaining information on diseases, medicines, and surgical methods, there are marked difficulties in understanding the obtained health information. One of the most important reasons for this is the readability level of health-related websites. Readability is defined as that texts are easy or difficult to understand by the reader and is an objectively measurable concept (10). Average word length, word frequency, number of words with more than one syllable, average sentence length, and number of words with more than one meaning affect the readability level (11). Even though many formulas are used to determine the readability level of texts, many have been developed for English texts. Studies show that the formulas developed for determining the readability level of English texts are insufficient in determining the readability level of Turkish texts (10,12). Atesman (13) and Bezirci-Yılmaz's (14) readability formulas are often used to measure the readability level of Turkish texts.

This study aimed to examine the readability levels of Turkish websites on obesity and bariatric surgery according to Atesman and Bezirci-Yılmaz readability formulas and evaluate the contents of these websites.

2. METHODS

The Hamidiye Scientific Research Ethics Committee approved this descriptive study of the University of Health Sciences (Decision Date: 13/06/2019 and Decision No: 48929119/774).

A search was performed in June 2019 by typing the words "obesity" and "bariatric surgery" in Google's search engine (https://www.google.com). We evaluated the websites on the first ten pages of Google's search engine results. Commercial websites, advertisement websites, chat websites, forum websites, magazine websites, websites containing only images or videos, and websites with less than ten sentences were excluded from the study. Informational texts on the websites were transferred to the "Microsoft Word" program. Training titles, author information, URLs, addresses, and links were deleted not adversely to affect readability results. Atesman and Bezirci-Yılmaz's readability formulas were used to calculate the readability level of Turkish websites on obesity and bariatric surgery. According to the institutions and organizations that prepared them, these websites were divided into three groups (Group 1: hospitals and specialist physicians, Group 2: national news websites, and Group 3: other websites).

2. 1. Bezirci-Yilmaz Readability Formula

This formula was developed in 2010 based on the features of various readability formulas developed until that day and the statistical properties of the Turkish population (13)**.** Two features are especially emphasized in the use of this new formula. They are the average sentence length and the average number of syllables. A large or small number of words in sentences affects the readability of texts. On the other hand, increased length of sentences in texts and increased number of syllables in words reduce the readability of texts.

This formula is as follows:

NRV:

$$\text{NRV:}\sqrt{ANW \times ((H3 \times 0.84) + (H4 \times 1.5) + (H5 \times 3.5) + (H6 \times 26.25))}$$

NRV: New readability value

ANW: Average number of words

H3: Average number of 3-syllable words

H4: Average number of 4-syllable words

H5: Average number of 5-syllable words

H6: Average number of words with 6 or more syllables

This formula explains readability levels of texts by corresponding to a certain grade level according to the education system in our country: 1-8: primary school; 9-12: secondary school (high school); 12-16: undergraduate, and ≥16: higher education (13).

2. 2. Atesman Readability Formula

It was adapted into Turkish from Flesch's Reading Ease Formula by Atesman (1997) and is a formula based on word and sentence length (14). This formula gives a score on a scale ranging from 0–100; 90-100: very easy, 70-89: easy, 50-69: moderate, 30-49: difficult, and 1-29: very difficult.

Readability Score= 198,825 – 40,175 x (total number of syllables/total number of words) – 2,610 x (total number of words/total number of sentences)

2. 3. Content Evaluation of Texts

The texts were evaluated regarding whether they contained information about the definition of obesity, waist circumference, body mass index, obesity risk factors,

obesity-related diseases when to treat obesity, obesity treatment options, medical nutrition, physical activity, cognitive behavioral therapy, and pharmacological treatment. In addition, they were evaluated in terms of whether they contained information about contraindications for surgical treatment, surgical treatment methods, complications of surgical treatment, and postoperative nutrition.

2. 4. Statistical Analysis

While categorical data were expressed as frequency and percentage, numerical data were expressed as mean ± standard deviation (SD). The Shapiro-Wilk test was used to assess whether the data were normally distributed. While the Kruskal-Wallis test was used to compare numerical data between independent groups, the Chi-square test was used to compare categorical data between independent groups. All statistical analyzes were performed bi-directionally at the 5% significance level and the 95% confidence interval. The SPSS® 21 (IBM Inc, USA) software was used to analyze the data.

3. RESULTS

A total of 79 websites from 325 websites were determined to meet the inclusion criteria. There were 43 (54.4%) websites in Group 1, 25 (31.6%) websites in Group 2, and 11 (13.9%) websites in Group 3. The mean±SD number of sentences was 70.04±7.43 (min: 15, max: 430). The mean±SD number of words was 977.78±99.502 (min: 228, max: 5193). The mean±SD number of letters was 6182.89±588.47 (min: 1466, max: 34162). The mean±SD number of syllables in each word was 2.86±0.3 (min: 1, max: 3.17). The mean±SD number of words in each sentence was 13.89±0.32 (min: 5.86, max: 24.04). The mean±SD number of words with 4 or more syllables in each sentence was 4.48±0.13 (min: 1.43, max: 8.80). The mean±SD Atesman and Bezirci-Yilmaz readability values were 45.95±1.12 (min: 15.96, max: 76.54) and 14.34±0.36 (min: 5.57, max: 26.04), respectively. Therefore, the readability level of the websites was “difficult,” according to the Atesman readability formula.

There were no statistically significant differences in the mean Atesman and Bezirci-Yilmaz readability values (p=0.169 and p=0.273, respectively), the average number of words with 4 or more syllables in each sentence (p=0.327) and the average number of syllables in each word (p=0.395) between the three groups (Table 1).

When the readability levels of the websites were examined according to the Atesman readability formula, 5 (6.3%) were ‘very difficult,’, 47 (59.5%) were ‘difficult,’, 26 (32.9%) were ‘moderate,’ and 1 (1.3%) was ‘easy.’ There was no statistically significant difference in the readability levels of the websites according to the Atesman readability formula between the three groups (p=0.211) (Table 2).

The contents of the website were analyzed, and we found the definition of obesity, information on waist circumference, body mass index, obesity risk factors and obesity-related diseases as 41 (51.9%), 6 (7.6%), 45 (57.0%), 10 (12.7%), and 34 (43.0%), respectively. In addition, 50 (63.3%) contained when to treat obesity, 78 (98.7%) contained obesity treatment options, 26 (32.9%) contained medical nutrition, 25 (31.6%) contained physical activity, 8 (10.1%) contained cognitive behavioral therapy, and 16 (20.3%) contained pharmacological treatment. While all websites gave information about bariatric surgery, only 6 (7.6%) contained contraindications for surgical treatment, 60 (75.9%) contained surgical treatment methods, 22 (27.8%) contained complications of surgical treatment and 23 (29.1%) contained postoperative nutrition.

Table 1. *Comparison of readability values of groups*

	Group 1 n=43 Mean ± SD	Group 2 n=25 Mean ± SD	Group 3 n=11 Mean ± SD	p
Atesman readability value	44.03±1.37	48.98±2.29	46.55±2.74	0.169
Bezirci-Yilmaz readability value	14.86±0.45	13.66±0.76	13.87±0.87	0.273
Average number of words with 4 or more syllables in each sentence	4.64±0.15	4.22±0.28	4.47±0.34	0.327
Average number of syllables in each word	2.90±0.01	2.86±0.01	2.69±0.24	0.395

SD: standard deviation, n: number; Kruskal-Wallis test

Table 2. *Evaluation of readability intervals of groups according to the Atesman readability formula*

Readability intervals according to the Atesman readability formula	Group 1 n=43 n (%)	Group 2 n=25 n (%)	Group 3 n=11 n (%)	p
Very difficult + difficult	32(74.4)	14(56.0)	6(54.5)	0.211
Moderate + easy	11(25.6)	11(44.0)	5(45.5)	

n: number; Chi-square test

4. DISCUSSION

Obesity is a significant health problem because it increases the frequency of cardiovascular diseases, dyslipidemia, type 2 diabetes mellitus, stroke, gallbladder diseases, osteoarthritis, sleep apnea syndrome, and cancer types. Obesity and its related diseases have not only biological effects but also psychosocial and economic effects on human life. It has been determined that obese people consult a doctor more often, have a more extended hospital stay, and take more drugs than ordinary people (5). In order to effectively combat obesity, the frequency of which is increasing in our country, it is necessary to ensure that individuals gain healthy habits such as balanced nutrition, regular exercise, or increased physical activity. Therefore, online informational patient educational texts may play a significant role in reducing the

frequency of obesity and bariatric surgical procedures in obesity treatment in our country.

In the digital age, patients often search for information using the internet before meeting physicians. Thus, Turkish texts must contain correct information and be easily read. To our knowledge, there are no studies in the literature evaluating the readability level of Turkish websites on obesity and bariatric surgery. Our study is the first study on this subject.

A study conducted in the USA found that the readability of texts below the 6th-grade level was easy, the readability of texts between the 6th-9th grade levels was moderate, and the readability of texts above the 9th-grade level was difficult (15). Kozanhan et al. examined patient information texts of anesthesia on Turkish websites and evaluated their readability. They revealed that undergraduate education was required to understand these texts (16). Our results were similar to the results of this study. The readability of internet-based patient education materials related to breast cancer and mammography used in breast cancer screening was evaluated in two different studies. Aksoy et al. examining the readability of internet informational texts on breast cancer showed that the readability level of these texts was 'moderate' according to the Atesman readability formula and at 'high school level' according to the Bezirci-Yılmaz readability formula (17). AlKhalili et al. demonstrated that the texts on mammography were 'difficult' according to the Atesman readability formula (18).

Cheng et al. investigating the readability of Australian online health information, reported that the readability of Australian health websites was above the average Australian levels of reading (5). Mathew et al. examining the readability of Consumer Medical Information Leaflets (CMILs) on obesity and lipid-lowering drugs in India, indicated that university graduates could understand these leaflets, but not by high school graduates (19). Similar results were found in other studies examining the readability of medical sites prepared in Turkish (9,20-22).

Meleo-Erwin et al. searching the words "weight loss surgery" on English websites, reported that 93% of websites received an unacceptable readability score (23). Our study found that the readability level of Turkish websites on obesity and bariatric surgery was 'difficult' according to the Atesman readability formula and at 'undergraduate level' according to the Bezirci-Yılmaz readability formula. The 2011 Human Development Report indicated that Turkish adults' average length of education was 6.5 years (24). Accordingly, it can be said that the readability levels of online Turkish informational texts on obesity and bariatric surgery are much higher than the education level of Turkish people.

The average sentence length in Turkish is 9-10 words according to the Atesman readability formula and 10-11 words according to the Bezirci-Yılmaz readability formula. The average word length in Turkish is 2.6 syllables, according to both formulas (13,14). Our study showed that the average number of words in each sentence was 13.89, and the average number of syllables in each word was 2.86. The fact that both the sentence and syllable lengths of texts included in our study were above the specified values suggests a low readability level. Health literacy is defined as how individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (25). Accordingly, the texts containing information about obesity should have a high readability level and high information content (such as importance, frequency, and prevention methods of obesity, obesity treatment methods, bariatric surgery indications, and surgical methods complications). Some studies have reported incorrect and unprofessional information on websites containing information about obesity and bariatric surgery (26,27). Our study showed that the texts on websites examined for obesity gave enough information about only obesity treatment. More than half of the texts on bariatric surgery included information about surgical treatment methods. Very few texts contained information about complications of surgical treatment and contraindications for surgical treatment. Hence this suggests that it is aimed at encouraging patients to bariatric surgery. For patients and their relatives to understand what they read on internet texts, a simple language should be chosen in which the number of syllables in words is small, sentences with a small number of words are used, and medical terms are preferred as little as possible.

5. CONCLUSIONS

This study demonstrated that the readability level of Turkish websites on obesity and bariatric surgery was very low. Furthermore, it was determined that these websites did not provide adequate information about the risks, adverse effects and contraindications related to bariatric surgery. Therefore, online informational texts on obesity and bariatric surgery should be prepared according to the readability criteria at a level that the general population can easily understand.

Limitations of the Study

The limitations of this study are that there are few sites included in the study and that these sites do not have the necessary medical certification.

Conflicts of Interest

There is no conflict of interest regarding the publication of this article.

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Clinical and Experimental Health Sciences

Are Nomophobia and Alexithymia Related? The Case of Health Students

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ABSTRACT

Objective: This paper aims to determine whether there is a relationship between nomophobia and alexithymia in nursing and midwifery students studying at the undergraduate level and the factors affecting nomophobia and alexithymia.

Method: This cross-sectional study was conducted with undergraduate nursing and midwifery students in a public university. No sampling was used. The response rate was 71.42%. Data were collected by a Personal Information Form, Nomophobia Scale, and Toronto Alexithymia Scale. The data were analyzed with the SPSS-22 program. Type 1 error level was considered as $p<0.05$.

Results: The nomophobia scores of female students, third-year students, and those who spent most of their lives in urban areas were higher and statistically significant. The Toronto Alexithymia Scale-20 scores of nursing students ($p=0.022$) and students with chronic diseases ($p=0.011$) were higher and statistically significant. There is a very weak positive correlation between the duration of daily telephone usage and nomophobia ($p<0.01$). In addition, a weak level positive correlation was found between nomophobia and alexithymia scores ($p<0.01$).

Conclusion: The participants' nomophobia scores were at a moderate level. The mean of the scores obtained by the participants from the alexithymia scale was close to half of the mean score to be taken from the scale. No significant difference was found between many socio-demographic characteristics and nomophobia groupings (low, moderate, severe).

Keywords: Nomophobia, Alexithymia, Nurse, Midwife

1. INTRODUCTION

While the number of smartphones used by a multitude of people was 1.57 billion in 2016, it increased to 2.53 billion in 2018 (1). According to a report published by the Turkish Statistical Institute (TSI), the rate of smartphone availability in Turkey rose from 53.7% in 2004 to 98.7% in 2018 (2).

Smartphones offer a wide range of applications, such as voice-text communication, connecting to the Internet, taking photos, listening to radio and music, finding addresses, shopping, banking, and playing games (3). With ever-increasing features, smartphones have positive effects on people's daily life, professional life, and learning processes. However, excessive and uncontrolled use of smartphones also brings along many problems. One of these problems is nomophobia (4).

Nomophobia, i.e., the fear of being deprived of mobile phones (a term coined with some letters from the words "No Mobile Phobia") is actually a digital and psychiatric disease that many smartphone users catch without even realizing it. The term was first coined in 2008. Clinical psychology has defined nomophobia as "the unreasonable and unintentional fear experienced when the individual cannot access or communicate on the mobile device." These people feel better when they access their phones, so they become more and more addicted to their devices over time (5-7).

The use of smartphones causes distraction among health professionals, which, in turn, leads them to be unable to remember important information. This disease also both threatens patient safety, privacy protection, and the security of personal data and disrupts communication between patients and staff (8). 78.1% of nurses working in hospitals use their mobile phones or other communication tools at work mostly to make calls, check/send e-mails, and text to their family members or friends (9). On the other hand, 23.4% of nursing students, who are prospective health professionals, always use smartphones in clinical applications and do not think that this creates a distraction (8).

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Alexithymia is a Greek word meaning difficulty in recognizing and verbally expressing one's emotions. Alexithymia, which was initially preferred to describe symptoms in psychosomatic patients (10,11), was later accepted as a personal disposition. It has even sometimes been recognized as a condition, disease, psychosomatic symptom, cognitive impairment, lack of skills, and neurological failure caused by a lack of social support (12). Failure to experience and voice emotions sufficiently when emotionally distressed can lead to the development of somatic symptoms (13-16). Alexithymic people usually tend to be addicted to something (17). Alexithymic people, who behave like a robot lacking creativity and have little empathy, have an external locus of control and prefer loneliness. They seem to adapt to social situations, but they are aware that they cannot be like others and prefer to conceal it (17,18).

Alexithymic individuals have poor social skills and often feel uncomfortable in face-to-face communication. communication through technology is therefore a less stressful way of social interaction for them (19). Social interaction problems experienced by alexithymic individuals can trigger the overuse of mobile phones and nomophobia. The fact that students who will work in the field of health, where communication skills and attention are very important, become almost dependent on mobile phones will negatively affect both the individuals they serve and their professional lives.

This paper aims to determine whether there is a relationship between nomophobia and alexithymia in nursing and midwifery students studying at the undergraduate level and the factors affecting nomophobia and alexithymia.

2. METHOD

2.1. Population and Sample

The population of this descriptive cross-sectional study comprises the students studying in the nursing and midwifery departments of a public university in the 2018-2019 academic year (742 students). No sampling was used. Using the data collection tools described below, the data were collected from the students who volunteered to participate in the study (530 students with a response rate of 71.42%) between 8 April and 12 May 2019.

Inclusion criteria

- being a midwife department or nursing student department
- volunteering to participate in the study
- have enough Turkish to answer questions

Exclusion criteria

- not being diagnosed with addiction / being treated for addiction (family/individual)
- not being diagnosed with a mental or social illness

2.1.1. Personal Information Form

The form consists of questions to reveal the participants' socio-demographic characteristics (age, gender, department, student classes, family type, place of residence, income level, employment status smoking/alcohol habit, chronic disease status) and mobile phone usage status **(**daily mobile phone usage time, the purpose of using the phone) (3,4,7).

2.1.2. Nomophobia Scale (NS)

The scale developed by Yildirim and Correira (6) to measure the nomophobia scores of individuals was adapted to Turkish by Yildirim et al. (20). This 7-point Likert type scale (1=strongly disagree, 7=strongly agree) consists of 20 items. The scale consists of four subscales: not being able to access information, losing connectedness, not being able to communicate, and giving up convenience. The scores range from 20 to 140. The average score of 20 points and below is considered as the absence of nomophobia, the average score of 20-60 is considered as low-level nomophobia, the average score of 60-100 is considered as moderate nomophobia, and the average score of 100 points or more is considered as severe nomophobia. The reliability coefficient of the Turkish version of the scale was calculated as .92 for the whole scale, and .94, .74, .and .91 for the subscales, respectively.

2.1.3. Toronto Alexithymia Scale-20 (TAS-20)

First developed by Bagby et al. in 1992, the scale was later revised and finalized as a 20-item scale. The validity and reliability analyses of the Turkish version of TAS-20 were performed by Kose et al. (21). In this 5-point Likert type scale ("Never," "Rarely," "Sometimes," "Often," and "Always"), respondents are asked to select the most appropriate option for themselves. The three subscales of the scale are as follows: difficulty in identifying feelings (TAS-1; 7 items); difficulty in expressing feelings (TAS-2; 5 items); expressive thinking (TAS-3; 8 items). Cronbach's alpha values of the subscales are 0.82, 0.75, and 0.72, respectively. In this study, they were calculated as 0.82, 0.68, and 0.70. The maximum score is 100 while the minimum is 20. High scores indicate a high alexithymia level.

2.2. Ethical Consideration:

Written permission was obtained from the Giresun University Clinical Research Ethics Committee (KAEK:2019-26) and the Dean's Office. As required by the Helsinki Declaration, the students were informed about the research with a document attached to the scales. The data were collected by the researchers in the first 20 minutes of the lessons by the face-to-face interview method.

2.3. Statistical Analysis

The data were analyzed with the SPSS-22 package program and error checks, tables, and statistical analyses were performed. The dependent variables of the study were Nomophobia, TAS-20, TAS-1, TAS-2, and TAS-3 scores. The independent variables were socio-demographic characteristics and smartphone usage. For descriptive statistics, percentages, medians, and min-max values were calculated. The chi-square test was used for categorical data, and the Kolmogorov Smirnov test was used to test the suitability of the data for normal distribution. Based on the normality analysis, Student's T-test/Mann Whitney-U or One-Way ANOVA/Bonferroni correction Kruskal-Wallis tests were performed. Means were expressed with standard deviation (mean ± SD), and statistical significance was set at $p < 0.05$.

3. RESULTS

The mean age of the students was 20.63 ± 1.87 (17-38), and 13.8% of them were male. 62.4% were nursing students (the ratio is similar to the school average). 2.7% had divorced parents. 11.7% spent most of their lives in rural areas. 4.8% stated that they were currently employed (Table 1).

Table 1. *Socio-demographic characteristics of students (N = 530)*

Variable	Characteristics	Number (n)	Percent (%)
Gender	Male	73	13.8
	Female	457	86.2
Department	Nursing	331	82.1
	Midwifery	199	15.2
Students classes	1.class	150	28.3
	2.class	144	27.2
	3.class	119	22.5
	4.class	117	22.1
Family type	Nuclear	437	82.5
	Extended	79	14.9
	Fragmented	14	2.6
Place of residence	Village	62	11.7
	Town	190	35.8
	Province	278	52.5
Employment status	Employed	25	4.7
	Not employed	505	95.3
Income level perception (n=519)	Low	73	14.1
	Moderate	434	83.6
	High	12	2.3
Smoking habit	Yes	60	11.3
	No	470	88.7
Alcohol habit	Yes	15	2.8
	No	515	97.2

In the study, the participants' perceptions of themselves were also evaluated. As a result of this evaluation where they answered multiple questions, it was found that 96.3% found themselves fair, 92.8% responsible, 93.8% open to new ideas, 88.6% confident, 81.9% determined, 79.9% inquisitive, 86.2% questioning, 70.6% creative, and 69.5% willing to take risks.

Participants reported that they use their mobile phones for an average of 5.46 ± 3.14 hours a day. Of the participants, 62.1% stated that they use their mobile phones to connect to social networks, 5.9% to listen to music, 43.3% to make a phone call, 72.9% to text on WhatsApp, 35% to watch movies, 34.7% to text messages, 39.1% to connect to the Internet, and 22.7% to play games.

As can be seen in Table 2, The TAS-20 score average of the participants in this study was 52.64±10.49 (min-max:25.00-83.00). For nomophobia, the average score is 76.83+25.00 (20.00-140.00). The reliability values of the scales used in this study are high, except for the externally oriented thinking sub-dimension of TAS-20 (Table 2).

Table 2. *Mean, standard deviation, and reliability values of nomophobia and its subscales and TAS-20 and its subscales*

Scales	Mean±SD	Min-Max	Cronbach alpha
Nomophobia	76.83±25.00	20-140	0.92
Not being able to access information	16.74±5.90	4-28	0.80
Losing connectedness	19.10±7.96	5-35	0.82
Not being able to communicate	26.30±9.47	6-42	0.91
Giving up convenience	15.07±3.30	5-25	0.90
Toronto alexithymia scale-20	52.94±10.49	25-83	0.78
Difficulty in identifying feelings	17.72±5.87	7-35	0.82
Difficulty in expressing emotions	13.97±3.74	5-25	0.63
Expressive thinking	23.05±4.24	11-25	0.31

As can be seen in Table 3, the nomophobia scores of female students, third-year students, and those who spent most of their lives in urban areas are higher and statistically significant ($p<0.05$). Also, the TAS-20 scores of nursing students and students with chronic diseases are higher ($p<0.05$). It was found that smoking, alcohol use, membership in any association or club, or participation in social activities did not make a significant difference in terms of both nomophobia and TAS-20 scores.

In addition, it was investigated whether some socio-demographic characteristics led to any differences in terms of NS grouping (no nomophobia, low-moderate-severe level of nomophobia). It was found that none of the variables (sex, department, year at university, marital status, family type, whether they lived in urban or rural areas, employment status, smoking status, alcohol use, having any chronic disease, being a member of an association or club, participating in social activities) led to a difference ($p>0.05$).

As can be seen in Table 4, there is a very weak positive correlation between the duration of daily telephone usage and nomophobia ($r=0.148$, $p<0.01$). In addition, a weak level positive correlation was found between nomophobia and alexithymia scores ($r=0.321$, $p<0.01$).

Table 3. *Distribution of the participants' mean scores of nomophobia and TAS-20 according to socio-demographic characteristics (N = 530).*

Socio-demographic characteristics		Nomophobia		TAS-20	
		Mean±SD Mean Rank	Test/p Value	Mean±SD Mean Rank	Test/p Value
Gender	Male	226.62	U=13842.50	284.75	U=15275.00
	Female	271.71	p=0.019	262.42	p=0.247
Department	Nursing	268.50	U=31942.00	277.27	U=29040.00
	Midwifery	260.51	p=0.561	245.93	p=0.022
Students classes	1.class	261.42	KW=11.77 p=0.008	261.63	KW=1.804 p=0.614
	2.class	232.97[a,b]		257.71	
	3.class	284.87[a]		281.61	
	4.class	291.07[b]		263.65	
Familiy type	Nuclear	76.44±25.43	F=0.380 p=0.684	52.57±10.11	F=0.485 p=0.616
	Extended	79.10±22.19		53.43±11.53	
	Fragmented	76.35±27.26		50.64±15.74	
Place of residence	Village	71.53±27.34	F=2.426 p=0.089	50.66±10.27	F=1.917 p=0.148
	Town	75.73±25.18		52.24±10.55	
	Province	78.77±24.19		53.37±10.49	
Employment status	Employed	74.28±28.19	U=0.572 p=0.601	53.92±8.84	U=1.881 p=0.536
	Not employed	76.96±24.85		52.58±10.57	
Income level perception (n=519)	Low	71.10±24.51	F=2.370 p=0.095	53.43±11.12	F=0.328 p=0.720
	Moderate	77.78±24.90		52.47±10.40	
	High	73.33±24.60		51.50±12.24	
Chronic diseases	Yes	77.92±27.82	t=0.337 p=0.736	56.07±10.78	t=2.543 p=0.011
	No	76.71±24.69		52.26±10.40	

**Groups with difference caused according to the Independent-Samples T test/ Mann Whitney U Test-One-Way ANOVA/Kruskall Wallis test. [a,b,c,d,e] Tukey HSD*

Table 4. *The relationship between the participants' age and daily telephone usage time and nomophobia and TAS-20 scores* (N=530)*

		Age	TimeDaily telephone usage	Nomophobia	TAS-20	TAS-1[a]	TAS-2[b]	TAS-3[c]
Age	r	1	-0.046	-0.065	-0.049	-0.060	-0.047	0.009
	p	-	0.299	0.137	0.255	0.165	0.277	0.828
Daily telephone usage	r	-0.046	1	0.148**	0.058	0.075	0.017	0.042
	p	0.299	-	**0.001**	0.188	0.087	0.695	0.345
Nomophobia	r	-0.065	0.148**	1	0.321**	0.334**	0.256**	0.174**
	p	0.137	**0.001**	-	**0.001**	**0.001**	**0.001**	**0.001**

**Pearson correlation analysis, [a]: Difficulty in Identifying Feelings, [b]: Difficulty in Expressing Feelings, [c]: Expressive Thinking*

4. DISCUSSION

The number of studies on nomophobia has increased particularly recently. There is also a plethora of studies on alexithymia. Most of these studies have focused on individuals with a health problem whereas some have focused on individuals with no health problems. However, to the best of our knowledge, no study has been conducted to explore the relationship between nomophobia and alexithymia in health professionals or prospective health professionals. But it should be noted that addiction to smartphones might cause emotional blunting in health professionals or students to become health professionals, which can lead to irreparable delays or disruptions in the patient care they provide. This study, which aimed to determine whether there was a relationship between nomophobia and alexithymia in nursing and midwifery students and the effect of socio-demographic characteristics on the two, was conducted with 530 volunteer participants.

It was found that the nomophobia scores of the participants were at a moderate level, that they spent approximately 5.5 hours a day with their smartphones, and that they mostly used their mobile phones to connect to social networks. Hosgor et al. found that students of vocational schools of health services spent 1-4 hours with their smartphones and that students felt the need to check their phones as soon as they woke up (22). In another study conducted with university students, it was found that 55% of the students were nomophobic, spent an average of 6.43 hours a day with their smartphones, and their nomophobia levels negatively affected their academic achievements (23). Individuals overusing technological devices face the danger of becoming

addicted to them and even develop a phobia when they are deprived of them. They also waste an important part of the day, which is a fact supported by various studies. Bilgic et al. found that nursing students felt the need to carry their smartphones with them constantly, that they felt bad when they did not have their phones with them, that they saw their phones as an object reflecting their identity, that they learned from their phones much easier, that they believed that their phones were important for them to socialize and have fun and that they admitted that they were addicted to their phones (24). Besides, Kalaskar found that those who spent 5-6 hours a day on their smartphones were more prone to anxiety, sleep disorders, stress, and apathy (25). In this study, which aimed to determine whether socio-demographic characteristics led to any difference in terms of nomophobia, it was found that the nomophobia scores of female students, third-year students, and those who spent most of their lives in urban areas were higher. On the other hand, considering the sex variable, some studies reported that men are more nomophobic (26,27) while some other studies reported that women are more nomophobic (28,29). Some studies reported that sex is not significant in terms of being nomophobic (30-32). Although the present study found no difference in terms of nomophobia between midwifery or nursing students, Hosgor et al. found a difference between nomophobia and students' departments (22). Considering other socio-demographic variables, Yorulmaz et al. found that year at university did not create a difference in terms of nomophobia, which is not consistent with this study, while they found that living in urban areas created a difference in terms of nomophobia, which is consistent with this study (30). Another study conducted with university students reported that none of the variables of age, sex, and education level made a difference in terms of smartphone addiction (33).

In terms of alexithymia, which is the other dependent variable of the present study, it was found that the mean of the participants' scores from TAS-20 was close to half of the total score from the scale. It was also determined that the mean alexithymia scores of nursing students and those having a chronic disease were higher. However, none of the variables of sex, year at university, family type, whether they lived in urban or rural areas, employment status, and perceived income level were found to lead to any difference in terms of alexithymia. In their study that examined the alexithymia levels of nursing students in terms of various variables, Aksoy and Coban found that the alexithymia scores of the participants were at a moderate level, which is consistent with this study, and that sex and perceived income level did not lead to any differences, which is also consistent with this study, but year at university and participation in social activities led to differences, which is inconsistent with this study (34). In the study, a positive correlation was found between nomophobia and smartphone usage duration. In the literature, some studies found a similar correlation (35,36) while some did not (22,37).

The findings of this study showed that the levels of nomophobia and alexithymia of nursing and midwifery students were related. Our research contributes to the literature as it is the first research that "examines the relationship between nomophobia and alexithymia in students nursing and midwifery", and we suggest that the results of this study will guide other researchers for further studies. In the literature, the positive relationship between nomophobia and alexithymia was mentioned in the study conducted by Yavuz et al. with 1817 adolescents (38). Ozen and Topçu, who conducted research on medical students, also reported a positive relationship between nomophobia and alexithymia (39). In this context, we suggest that the research be conducted in order to show whether there is a similar relationship with other students receiving health education. In the same way, it is considered important to conduct similar studies on healthcare workers. Because Bragazzi et al. describe nomophobia as a condition that should be included in the DSM-V criteria and psychotherapy – pharmacotherapy should be applied (40). The relationship between nomophobia and alexithymia is seen as important in the context of behavioral addictions. Based on the results, it is considered that both situations will cause negative effects both in personal life and in the professional process, and it is thought that early detection will be again on an individual and social basis.

5. CONCLUSION

Nomophobia scores of the participants were found to be at a moderate level. The mean of the scores obtained by the participants from the alexithymia scale was close to half of the mean score to be taken from the scale. No significant difference was found between many socio-demographic characteristics and nomophobia groupings (low, moderate, severe). It was determined that being a female student, is a third-year student, and having spent most of the life in urban areas created a significant difference in terms of nomophobia mean scores while being a nursing student and having a chronic disease created a significant difference in terms of alexithymia mean scores. The study concludes that there is a positive correlation between nomophobia and alexithymia scores. It is aimed that nurses/midwifery who have effective and important functions in service have sensory integrity and reflect this to care. On the other hand, the fact that the nursing and midwifery students are free from the negative effects of the mobile devices will help the patient to trust the health personnel and increase the patient nurse interaction. In this context, it is indispensable to ensure that nurses move away from mobile devices in order to increase their interactions with the patient, to establish programs to increase their sensory integrity and to ensure attendance by making them continuous and well-being for both patient and health personnel.

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Clinical and Experimental Health Sciences

In vitro Biological Activities of Different Extracts from *Alcea dissecta*

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ABSTRACT

Objective: *Alcea* genus belongs to Malvaceae family and this genus is represented by 85 taxa in the world and 21 taxa in the Flora of Turkey. The flowers of *Alcea* genus contain plenty of mucilage and are used for the treatment of respiratory diseases such as asthma and cough. *Alcea dissecta* is known as 'Govik, Hiro, Hero' in Turkey, and the flowers and leaves of this species have been used in the treatment of asthma, injury, colds, and gastrointestinal diseases in Turkey. To the best of our knowledge, there is no report on the effect of extraction methods on the biological activity of this plant. In addition, although this species is being used as a medical plant, there is no study of the antioxidant, anti-urease, esterase, and anticholinesterase activity of the plant. Therefore, the aim of this study was to evaluate *in vitro* antioxidant, anti-urease, esterase, anticholinesterase activities of *Alcea dissecta* using a variety of extracts.

Methods: The antioxidant activities of different extracts were examined by DPPH, ABTS, FRAP, and CUPRAC methods. The total phenolic compounds contained in the extracts were determined using the Folin-Ciocalteu reagent (FCR) method. Anti-urease and anticholinesterase activities of different extracts were evaluated by indophenol and Ellman methods respectively. In addition, esterase activities of plant extracts were determined.

Results: In the present study, ethanol:water (1:1, v/v) and chloroform extracts obtained maceration method showed stronger DPPH and ABTS radical scavenging activity than other extracts. The chloroform extract obtained Soxhlet method was found to have higher FRAP and CUPRAC values than other extracts. It was also found that the ethanol extract obtained maceration method showed the most potent anti-urease and anticholinesterase activity. According to the results, the strongest inhibitory effect on both hCA I and II isoenzymes was shown by the petroleum ether extract obtained Soxhlet method.

Conclusion: As a result, it was determined that different plant extracts have antioxidant, anti-urease, esterase, anticholinesterase activities. In addition, the data obtained from this study will shed light on future research on the biological activities of this species.

Keywords: *Alcea dissecta*, biological activity, medicinal plant

1. INTRODUCTION

Medical plants have gained considerable importance in the food and pharmaceutical industries due to their therapeutic properties (1). Phenolic and flavonoid compounds found in medicinal plants are known to be effective in the treatment of diseases caused by oxidative stress. Therefore, a great number of scientific studies on medicinal plants and extracts/compounds from these plants have increased during recent years (2). It is now known that gastric and duodenal ulcers are commonly caused by *Helicobacter pylori*. This organism releases urease that converts urea into ammonia. This enzyme produces an alkaline environment that makes it suitable for bacterial growth and the manifestation of the disease (3). For the past 20 years, the recommended first-line therapy for *H. pylori* eradication consisted of a combination of a proton pump cell inhibitor, omeprazole, and antibiotics including amoxicillin and clarithromycin. However, the increased *H. pylori* resistance of these antibiotics (especially clarithromycin) has made this treatment an unattractive option (4). In recent years, numerous studies have been carried out on the anti-urease activity of plant extracts, partially purified fractions, and natural compounds (5).

Alzheimer's disease is a chronic neurodegenerative disease that prevents memory, speech, problem-solving, and daily activities. One way to treat Alzheimer's disease is to inhibit

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the acetylcholinesterase (AChE) enzyme, which is responsible for ACh hydrolysis. In addition to Alzheimer's disease, AChE inhibition is considered promising for dementia, myasthenia gravis, glaucoma, and Parkinson's disease. The number of studies on the use of medicinal plants as an inhibitor of acetylcholinesterase, which is important in Alzheimer's disease, has increased in recent years (6, 7).

Carbonic anhydrases (CAs, EC 4.2.1.1) as ubiquitous widespread metalloenzymes catalyze the crucial reaction for all living organisms: the hydration process of CO_2 to HCO_3^- and H^+ (8, 9). Fifteen isoenzymes of CA encoded from the α-CA gene family have been identified and characterized for human beings as cytosolic forms (hCA I, II, III, VII, and XIII), membrane-bound forms (hCA IV, IX, XII, and XIV), mitochondrial forms (hCA VA and VB). hCA VI isoform was found in saliva. The three other ones (CA VIII, X, and XI) are determined as noncatalytic ones (10). Activation and inhibition investigations about CA catalytic activity are vital for treating many diseases and defects (11). The inhibitors of CA isoforms are carried out to discover and design drugs for some diseases such as glaucoma and epilepsy. Therefore, there is a great requirement in the pharmaceutical disciplines to develop new therapeutic agents (12, 13).

The selection and extraction method of solvent for the extraction of plant material to determine the potential activity of the extract is one of the most important factors since the solvent polarity and extraction method determines which compounds will be extracted and which will not. Thus, in many newly studied plants, various extracts are prepared using different extraction methods and solvents (2, 14).

Alcea genus belongs to Malvaceae family, and this genus is represented by 85 taxa in the world and 21 taxa in the Flora of Turkey (15, 16). *Alcea dissecta* is a perennial plant and mainly grows in calcareous fields and roadside areas in the eastern parts of Anatolia, North West Iraq, and Palestine (17). The Malvaceae family contains high amounts of polyphenol compounds, known as chemotaxonomic markers. Also, cyclopropane acids not found in other families are found in this family. The flowers of *Alcea* genus contain plenty of mucilage and are used to treat respiratory diseases such as asthma and cough (18). *Alcea dissecta* is known as 'Govik, Hiro, and Hero' in Turkey. The flowers and leaves of this species are used in the treatment of asthma, injury, cold and gastrointestinal diseases in Turkey (19-21).

To the best of our knowledge, there is no report on the effect of extraction methods on the biological activity of this plant. In addition, although this species has been used as a medical plant, there is no study of the antioxidant, anti-urease, esterase, and anticholinesterase activity of the plant. Therefore, the aim of this study was to evaluate in vitro antioxidant, anti-urease, esterase, anticholinesterase activities of *Alcea dissecta* using a variety of extracts.

2. METHODS

2.1. Identification of plant material

Alcea dissecta was collected from Tunceli province of Turkey and taxonomically identified by Dr. Ahmet DOĞAN. The voucher specimens, representative samples of the plant material, were archived in the herbarium of the Faculty of Pharmacy, Marmara University, and documented with the herbarium number of MARE:19141.

2.2. Preparation of Alcea dissecta extracts

Aerial parts of *Alcea dissecta* were dried at 25°C in the shade. Dried parts of the plant were treated with a mechanical grinder (Renas, RBT1250) for fine powder and proper weight. The two extraction methods were performed to gain crude extracts from the aerial parts of the plant. (i) Maceration: Plant powder (20 g) was extracted for 72 h with the use of petroleum ether (MP) (200 mL), chloroform (MC) (300 mL), ethanol (ME) (400 mL) and ethanol-water (1:1, *v/v*) (MEW) (400 mL). (ii) soxhlet extraction: 20 gram of plant powder was extracted in Soxhlet apparatus (300 mL) with petroleum ether (SP), chloroform (SC), ethanol (SE) and ethanol-water (1:1, *v/v*) (SEW). Eight different extracts from the plant were concentrated by rotary vacuum evaporator and lyophilized device. All obtained extracts were stored at 4°C for future analysis.

2.3. Quantification of total phenolic contents

Each extracts were prepared at 5 mg/mL concentrations. 5 µL sample from the extracts was taken in a tube and 225 µL distilled water was added on it. After this process, 5 µL Folin-Ciocalteu reagent was diluted with distilled water (1:3, *v/v*), and 15 µL of 2% sodium carbonate solution was added to the prepared mixture. Then the mixture was placed in a shaking water bath at room temperatures for 2 h, and the absorbance was determined against the reference molecule at 760 nm. 25 mg gallic acid was dissolved with water in a 25 mL flask, and a stock solution of 1 mg/mL was prepared. Then the working solutions at different concentrations (0.05-0.40 mg/mL) were prepared by diluting this stock solution with water. Gallic acid solutions prepared with 0.05-0.40 mg/mL concentrations were evaluated with Folin-Ciocalteu reagent to determine phenolic content. For the further procedures: (i) concentrations against the absorbance were plotted, (ii) a calibration curve was prepared, and (iii) the correct equation was obtained. The calibration equation for gallic acid is $A = 35.06x + 0.1214$ ($R^2 = 0.9966$). The total phenolic contents of the extracts were stated as mg gallic acid equivalents/g extract (22).

2.4. In vitro bioactivity assays

2.4.1. 2,2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging assay

240 µL 0.1 mM DPPH solution (9.9 mg radical was dissolved in methanol in 250 mL flask) was added to 10 µL sample of the extracts at 5 mg/mL, 4 mg/mL, 3 mg/mL, 2 mg/mL, 1 mg/mL and 0.5 mg/mL concentrations. The prepared mixture was stirred for 1 minute and placed at 25°C for 30 min. The mixture absorbance was determined against the reference at 517 nm. The control sample was carried out under the same conditions using 10 µL of methanol instead of experimental and standard materials and the control sample was measured daily. The % DPPH radical scavenging activity was calculated by the formula:

$$\% \text{ DPPH radical inhibition} = [(A_0 - A_1)/A_0] \times 100]$$

A_0: The absorbance of the control solution

A_1: Absorbance of plant extracts and standard solutions.

IC_{50} is the extract/standard concentration that causes a fifty percent reduction in the DPPH radical concentration. The IC_{50} value was calculated using the correct equation obtained by placing the % radical scavenging activity against the concentrations studied. The data gained from the investigation was given as IC_{50}=mg/mL. The investigation was performed three times, and the averages of the data and standard deviation were calculated (23).

2.4.2. 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonate) radical cation ($ABTS^{\cdot+}$) scavenging assay

The 7 mM ABTS ammonium salt (0.38 g of ammonium salt was dissolved in a 100 mL flask with water) and reacted with 2.45 mM potassium peroxidisulfate (0.066 g potassium peroxidisulfate was dissolved in a 100 mL flask with water) for 12 hours at room conditions for preparing $ABTS^{\cdot+}$ stock solution. Then the $ABTS^{\cdot+}$ stock solution was diluted with water at 734 nm to prepare 0.70 (±0.02) absorbance working solution. 50 µL of extracts were prepared at 5 mg/mL concentrations, then 50 µL of $ABTS^{\cdot+}$ working solution and 150 µL distilled water were added to the prepared extracts. The mixture absorbance was determined against the reference at 734 nm for 6 min. The control sample was prepared under the same conditions with the use of 50 µL distilled water instead of experimental and standard materials. 10 mM stock trolox solution was prepared to obtain trolox standard curve equation. Then, working solutions with 1 mM, 0.8 mM, 0.6 mM, 0.5 mM, 0.4 mM and 0.2 mM were prepared by diluting the stock solution with 75 mM phosphate buffer (pH 7.4). The control sample was measured daily. ABTS radical scavenging determination was applied to trolox solutions prepared at different concentrations (0.2-1 mM). The calibration equation for trolox is A = 37.22x + 1.66 (R^2 = 0.9899). The results from this study were given as mM trolox/g extract (24).

2.4.3. Ferric reducing/antioxidant power (FRAP) assay

The method of Benzie and Strain (1996) was applied to the extracts in order to estimate the ferric reducing ability. The FRAP reagent [25 mL 300 mM acetate buffer (pH 3.6), 2.5 mL of TPTZ solution and 2.5 mL 20 mM $FeCl_3 \cdot 6H_2O$] was kept at 37°C for 30 min. 190 µL FRAP reagent was mixed with 10 µL extract, and the mixture absorbance was determined at 593 nm after 4 min. 1 mM stock $FeSO_4$. $7H_2O$ solution was prepared to obtain the $FeSO_4$ standard curve equation. Subsequently, working solutions of 0.4 mM, 0.2 mM, 0.1 mM, and 0.05 mM were prepared by diluting the stock solution with water. $FeSO_4$. $7H_2O$ solutions prepared with different concentrations were evaluated with FRAP method. For the further procedures: (i) concentrations against the absorbance were plotted, (ii) a calibration curve was prepared, and (iii) the correct equation was obtained. The calibration equation for Fe^{2+} is A = 12.86x – 0.006610 (R^2 = 0.9986). FRAP values of the extracts were given as mM Fe^{2+}/mg extract (25).

2.4.4. Cupric ion reducing/antioxidant power (CUPRAC) assay

60 µL Cu(II)x$2H_2O$, 60 µL neocuproine, and 60 µL NH4Ac (1 M) were mixed. Then 60 µL of the extract and 10 µL of ethanol were added to the mixture. After the duration time of 60 min, the mixture absorbance was spectrophotometrically measured at 450 nm. 1 mM stock trolox solution was prepared to obtain trolox standard curve equation. Then, working solutions with 1 mM, 0.8 mM, 0.6 mM, 0.4 mM, 0.2 mM and 0.1 mM were prepared by diluting the stock solution with ethanol. Trolox solutions prepared with different concentrations were evaluated with the CUPRAC method. For the further procedures: (i) concentrations against the absorbance were plotted, (ii) a calibration curve was prepared and (iii) the correct equation was obtained. The calibration equation for trolox is A = 3.055x + 0.2344 (R^2 = 0.9933). CUPRAC values of the extracts were given as mM trolox/mg extract (26).

2.4.5. Anti-urease activity assay

Stock solutions (5 mg/mL) were prepared from different extracts obtained from the plant and these solutions were diluted to prepare working solutions at concentrations of 2 mg/mL. Working solution (100 µL) was taken and then urease (500 µL) was added on it. The mixture was incubated at 37°C for 30 min. Then, 1100 µL of urea was added on this mixture and kept in the incubator at 37°C for 30 min. R1 (1% phenol, 0.005% sodium nitroprusside) and R2 (0.5% NaOH, 0.1% sodium hypochlorite) reagents were added to the mixture, respectively. After the incubation period at 37°C for 2 h, the absorbance of samples was measured at 635 nm (27).

The % inhibition of urease was calculated by the formula:

$$\% \text{ enzyme inhibition} = [(A_0 - A_1)/A_0] \times 100]$$

A_0: The absorbance of the control solution

A_1: Absorbance of plant extracts and standard solutions.

2.4.6. Anticholinesterase activity assay

Inhibition activities of acetylcholinesterase (AchE) were measured using a microplate reader (AMR-100 Allsheng). Acetylcholinesterase derived from electric fish and acetylthiokolin iodide was used as enzyme and substrate, respectively. Yellow-colored 5,5-dithiobis – (2-nitrobenzoic acid) (DTNB) was used for the measurement of the activity. As a control, ethanol and galantamine, the alkaloid type drug isolated from the galanthus plant, were used as controls.

AChE % Inhibition Test: AChE (20 µL) and different concentrations of extracts (20 µL) were added to phosphate buffer solution (pH 8, 0.1 M, 40 µL). This mixture was incubated at 25°C for 10 min. After incubation, DTNB (100 µL) and AcI (20 µL) as substrate were added to the mixture. The same procedure was applied to the galantamine used as standard. 5-thio-2-nitrobenzoic acid was spectrophotometrically measured at 412 nm. Anticholinesterase activity of the extracts was calculated using the following equation as percentage inhibition relative to control (28).

% inhibition = (Acontrol – Asample/Acontrol)x100

2.4.7. Esterase activity assay

The method was carried out to assay the esterase activity of hCA I and II (29). Changes of absorbance in 4-nitrophenyl acetate (NPA) to 4-nitrophenylate ion were spectrophotometrically recorded at 348 nm at 25°C for 3 min (30). Before kinetic studies, the reference measurement without enzyme was carried out, and then bioactivities of the extracts were investigated. Each concentration of the extracts was examined three times. % Activity (%) – [Inhibitor] graphs were determined for the extracts (31).

2.5. Statistical analysis

The antioxidant, anticholinesterase and anti-urease experiments were done in triplicates, and all data were shown as mean ± SD. The data were analyzed by Graphpad Prism 5 program. Statistical differences between the experimental groups were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's Multiple Comparison test. Mean values were considered statistically significant when $p<0.05$.

3. RESULTS

3.1. In vitro evaluation of biological activities

3.1.1. Total phenolic contents

The total phenolic contents of different extracts were analyzed and presented in Table 1. The ethanol:water (1:1, *v/v*) and chloroform extracts prepared using the Soxhlet method were determined to contain higher phenolic contents than other extracts. In addition, chloroform and ethanol extracts obtained from the maceration method exhibited higher total phenolic contents than other extracts. When we compare extraction techniques and extracts, it was found that the maceration chloroform and ethanol extracts had the highest amount of phenolic content and maceration was the best method for total phenolic contents.

Table 1. *Total phenolic contents of different extracts from Alcea dissecta.*

Samples	Phenolics (mg GAE/g extract)	
	Soxhlet	Maceration
Petroleum ether	4.5±0.2	4.4±0.11
Chloroform	4.9±0.01	12.8±0.12
Ethanol	3.3±0.42	9.8±0.2
Ethanol:water (1:1, *v/v*)	5.8±0.7	4.7±0.3

Values are mean of triplicate determination (n = 3) ± standard deviation; GAE–Gallic acid equivalents.

3.1.2. In vitro antioxidant activity

The antioxidant activities of different extracts of the plant were shown in Table 2. The maceration ethanol:water (1:1, *v/v*) (IC_{50}: 0.09 mg/mL) and Soxhlet (IC_{50}: 0.13 mg/mL) extracts showed the strongest DPPH free radical scavenging activity. The petroleum ether extracts obtained from two extraction methods showed the lowest DPPH free radical scavenging activity. As shown in Table 2, the radical scavenging DPPH activities of all extracts showed lower than that of ascorbic acid (IC_{50}: 0.004 mg/mL) and butylated hydroxyanisole (BHA) (IC_{50}: 0.006 mg/mL).

The chloroform, ethanol, and ethanol:water extracts obtained from the Soxhlet method were found to have very close ABTS radical cation scavenging activity each other. When the results of all extracts were compared, it found that maceration chloroform extract (23.4 mM trolox/g extract) exhibited the highest ABTS radical cation scavenging activity. The petroleum ether extracts prepared using two extraction methods did not show ABTS radical cation scavenging activity in this study.

In the Soxhlet method, chloroform extract (0.47 mM Fe^{2+}/mg extract) showed stronger ferric reducing activity than other extracts. In maceration method, ethanol:water (1:1, *v/v*) extract (0.42 mM Fe^{2+}/mg extract) showed the highest ferric reducing activity. The petroleum ether extracts obtained from two extraction methods had the lowest ferric reducing activity. When the results of all extracts were compared, it was found that all extracts prepared by Soxhlet and maceration method exhibited close ferric reducing activity.

In Soxhlet method, chloroform (0.092 mM trolox/mg extract) and ethanol:water (1:1, *v/v*) (0.084 mM trolox/mg extract) extracts showed stronger cupric reducing antioxidant activity than other extracts. In maceration method, ethanol:water (0.075 mM trolox/mg extract) and chloroform (0.057 mM trolox/mg extract) extracts

exhibited the highest cupric reducing antioxidant activity. The petroleum ether extracts obtained from two extraction methods had the lowest cupric reducing antioxidant activity. When the results of the CUPRAC assay were examined, the all extracts showed lower cupric reducing antioxidant activity than BHA compounds.

The results obtained from this study showed that maceration and Soxhlet extraction techniques are the most suitable method to get the most powerful DPPH/ABTS and FRAP/CUPRAC activities. It was also found that chloroform was the most suitable solvent for obtaining high ABTS, FRAP, and CUPRAC values.

Table 2. *Effects of extracting solvents/methods on the antioxidant activity of Alcea dissecta extracts.*

Samples	DPPH (IC_{50}: mg/mL)		ABTS (mM trolox/g extract)		FRAP assay (mM Fe^{2+}/mg extract)		CUPRAC assay (mM trolox/mg extract)	
	Soxhlet	Maceration	Soxhlet	Maceration	Soxhlet	Maceration	Soxhlet	Maceration
Petroleum ether	0.61±0.02*	0.65±0.05*	NA	NA	0.09±0.01	0.08±0.03*	0.025±0.05*	0.020±0.02*
Chloroform	0.24±0.01*	0.41±0.09*	2.6±0.1*	23.4±0.6*	0.47±0.02*	0.26±0.02*	0.092±0.03*	0.057±0.07*
Ethanol	0.19±0.03*	0.47±0.01*	2.7±0.2*	1.3±0.3*	0.22±0.03*	0.15±0.04*	0.038±0.02*	0.033±0.05*
Ethanol:water (1:1, *v/v*)	0.13±0.01*	0.09±0.03*	2.8±0.3*	2.6±0.5*	0.32±0.04*	0.42±0.01*	0.084±0.07*	0.075±0.01*
Ascorbic acid	0.004±0.9	0.004±0.9	13±0.1*	13±0.1*				
BHT					1.1±0.12	1.1±0.12		
BHA	0.006±0.062	0.006±0.062					1.62±0.12	1.62±0.12

*BHA: butylated hydroxyanisole; DPPH: 2,2-diphenyl-1-picrylhydrazyl; CUPRAC: cupric ion reducing/antioxidant power; FRAP: ferric reducing antioxidant power; ABTS: 2,2-azinobis-(3-ethylbenzothiazoline-6-sulphonic acid); BHT: butylated hydroxytoluene; NA: not activity; Values are mean of triplicate determination (n = 3) ± standard deviation; * P < 0.05 compared with the positive control*

3.1.3. Anti-urease activity

The percentage of inhibition of urease enzyme at 12.5 µg/mL concentration of different extracts was determined by using the indophenol method, and the results were shown in Table 3. In Soxhlet method, ethanol:water (1:1, *v/v*) (21.66%) and ethanol (7.91%) extracts showed stronger anti-urease activity than other extracts. In maceration method, ethanol (38.59%) and ethanol:water (1:1, *v/v*) (19.87%) extracts exhibited the highest anti-urease activity. The petroleum ether and chloroform extracts obtained from Soxhlet and maceration methods did not show anti-urease activity in this study. Comparing the activity results of all the extracts, it was found that maceration ethanol extract had the strongest anti-urease activity, and all extracts showed lower activity than thiourea compounds (76.05%). In the present study, the maceration ethanol method/solvent was the most suitable solvent and method to get the strongest anti-urease activity.

Table 3. *Urease inhibitory activity of different extracts from Alcea dissecta.*

Samples	Urease inhibition (%) (12.5 µg/mL)	
	Soxhlet	Maceration
Petroleum ether	NA	NA
Chloroform	NA	NA
Ethanol	7.91±2.04*	38.59±0.7*
Ethanol:water (1:1, *v/v*)	21.66±0.5*	19.87±0.34*
Thiourea	76.05±0.60	76.05±0.60

*Values are mean of triplicate determination (n = 3) ± standard deviation; * P < 0.05 compared with the positive control; NA: not activity*

3.1.4. Anti-cholinesterase activity

The percentage of cholinesterase enzyme inhibition at 500 µg/mL concentration of different extracts was determined by using the Ellman method, and the results are shown in Table 4. In the Soxhlet method, ethanol:water (1:1, *v/v*) (80.89%) and ethanol (73.81%) extracts exhibited a higher percentage of inhibition of cholinesterase enzyme than other extracts. In maceration method, ethanol (94.66%) and ethanol:water (1:1, *v/v*) (69.51%) extracts showed the strongest anticholinesterase activity. The Soxhlet petroleum ether and maceration petroleum ether and chloroform extracts did not show cholinesterase inhibitory activity. When the results were compared, it was determined that the maceration ethanol and Soxhlet ethanol:water (1:1, *v/v*) extracts had anticholinesterase activity very close to the galantamine compound (85.10%, 200 µg/mL). In the present study, maceration ethanol methods/solvents were the most suitable solvent and method to get the strongest anticholinesterase activity.

Table 4. *Anticholinesterase activity of different extracts from Alcea dissecta.*

Samples	Enzyme inhibition (%) (500 µg/mL)	
	Soxhlet	Maceration
Petroleum ether	NA	NA
Chloroform	33.78±2.08*	NA
Ethanol	73.81±0.77*	94.66±0.59*
Ethanol:water (1:1, *v/v*)	80.89±2.36*	69.51±0.92*
Galanthamine (200 µg/mL)	85.10±0.14	85.10±0.14

*Values are mean of triplicate determination (n = 3) ± standard deviation; * P < 0.05 compared with the positive control; NA: not activity*

3.1.5. Esterase Activity

It has been reported that carbonic anhydrase inhibitors have potential usages in eye disorders treatment, osteoporosis, diuretic, anti-obesity, and anticancer agents. It was reported that CA activity in rat erythrocytes was significantly decreased exposed to naringenin, a natural flavone. In addition, it is known that the extracts containing polyphenols and flavones obtained from various plants and fungal species inhibit the activities of CA I and II (9). Inhibitory effects of the different extracts from *Alcea dissecta* on hCA I and II were determined for the first time in this study. Bioactivities of the extracts against hCA I and II were performed using the esterase activity method. In the maceration method, petroleum ether extract showed a strong inhibitory effect on both hCA I (IC_{50}: 0.008 mg/mL) and II (IC_{50}: 0.025 mg/mL) isoenzymes. The chloroform extract did not show an inhibitory effect on hCA II, but this extract showed a strong inhibitory effect on hCA I (IC_{50}: 0.01 mg/mL) enzyme. In addition, ethanol and ethanol:water (1:1, *v/v*) extracts did not show an inhibitory effect on both hCA I and II isoenzymes. In Soxhlet methods, petroleum ether extract showed a strong inhibitory effect on both hCA I (IC_{50}: 0.003 mg/mL) and II (IC_{50}: 0.015 mg/mL) isoenzymes. The chloroform extract did not show an inhibitory effect on hCA II, but this extract showed a strong inhibitory effect on hCA I (IC_{50}: 0.028 mg/mL) enzyme. The ethanol:water (1:1, *v/v*) extract exhibited moderate inhibitory effect on both hCA I (IC_{50}: 0.105 mg/mL) and II (IC_{50}: 0.512 mg/mL) isoenzymes. In addition, ethanol extract did not show an inhibitory effect on both hCA I and II isoenzymes. According to the results, the strongest inhibitory effect on both hCA I and II isoenzymes was shown by Soxhlet petroleum ether extract. The effects of different extracts on the hCA isoenzymes are summarized in Table 5.

Table 5. *Esterase activity of different extracts from Alcea dissecta on hCA I and II*

Samples	IC_{50} (mg/mL)	
	hCA I	hCA II
Maceration petroleum ether	0.008	0.025
Maceration chloroform	0.01	NA
Maceration ethanol	NA	NA
Maceration ethanol:water (1:1, *v/v*)	NA	NA
Soxhlet petroleum ether	0.003	0.015
Soxhlet chloroform	0.028	NA
Soxhlet ethanol	NA	NA
Soxhlet ethanol:water (1:1, *v/v*)	0.105	0.512

Values are mean of triplicate determination (n = 3) ± standard deviation; NA: not activity

4. DISCUSSION

Some reports on the biological activities of some *Alcea* species have been previously presented. Antioxidant and antimicrobial activities of dichloromethane, methanol, and water extracts from aerial parts (leaves, flowers, stems, roots) of *Alcea setosa* were investigated. According to the results, it was found that methanol extract from the leaves of the plant had higher DPPH radical scavenging (1 mg/mL, 72%) activity than other extracts. It was also found that these extracts did not show antimicrobial activity against *Pseudomonas aeruginosa* CMUL 241, *Escherichia coli* CMUL 577, *Staphylococcus aureus* CMUL 491, *Candida albicans* ATCC 10231 strains (32). In another study, it was found that methanol extract from *Alcea rosea* aerial parts showed strong and selective cytotoxic activity on HeLA (IC_{50}: 14.48 µg/mL) cells and C6 cell lines (37.63 µg/mL) (33). As a result of the *in vivo* experiment of water extract from flowers of *Alcea aucheri*, this extract has been disclosed to have strong anxiolytic and sedative properties (34). The antioxidant activities of flower, seed, and leaves methanol extracts from *Alcea hyrcana* were investigated by DPPH, nitric oxide, hydrogen peroxide, ferrous chelating, reducing power, and hemoglobin induced linoleic acid methods. In this study, leaves extract showed strong ferrous chelating (IC_{50}: 0.11 mg/mL) and nitric oxide (IC_{50}: 0.45 mg/mL) radical activity as well as seed extracts were found to have strong DPPH (IC_{50}: 421 µg/mL) and hydrogen peroxide (IC_{50}: 160.6 µg/mL) activity including, total phenolic contents (68.9 mg gallic acid/g extract) (35).

Total phenolic content and antioxidant activity of methanol extract from flowers of *Alcea pallida* were investigated, and the amount of phenolic content of the flower extract was determined as 2.82 mg GAE/g extract. In addition, this extract showed strong ABTS (83.68 µmol trolox/g extract) radical cation scavenging activity (36).

Unlike the above studies, to date, there have been no reports in the literature on the antioxidant, esterase, anti-urease, and anticholinesterase activity of *Alcea dissecta*. Therefore, the purpose of this study was to evaluate for the first time *in vitro* biological activity of this species' extracts obtained using different extraction methods. When the biological activities of *Alcea dissecta* plant were compared with other *Alcea* species, as in other species, it was found that polar (especially the ethanol: water and ethanol) solvent has been found to exhibit strong biological activity and total phenolic contents.

5. CONCLUSION

It is important to select an appropriate extraction technique to standardize plant products and phytochemical analysis. When different extraction methods and different solvents are used, different compounds are obtained, and in this case, the biological activity of the plants changes. In this study, *in vitro* antioxidant, esterase, anti-urease and anticholinesterase activities of different extracts from *A. dissecta* aerial parts were first time investigated. According to the results of this study, maceration ethanol:water (1:1, *v /v*) and chloroform extracts showed stronger DPPH and ABTS radical scavenging activity than other extracts. The soxhlet chloroform extract was found to have higher FRAP and CUPRAC values than other extracts. It was also found that the maceration ethanol extract showed the most potent anti-urease and

anticholinesterase activity. According to the results, the strongest inhibitory effect on both hCA I and II isoenzymes was shown by Soxhlet petroleum ether extract. Therefore, different extracts from this species may be a natural resource candidate for the pharmaceutical and food industry due to their antioxidant, anticholinesterase, anti-urease, esterase activities.

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Clinical and Experimental Health Sciences

Evaluation of a Psychoeducation Program Given to International Nursing Students for Healthy Lifestyle and Life Satisfaction

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ABSTRACT

Objective: This research was conducted to evaluate the effectiveness of a psychoeducation program given to international nursing students receiving education in the nursing department of a public university to improve their healthy lifestyle behaviors and life satisfaction.

Methods: The research was designed based on the single-group pretest-posttest model. The research sample consisted of 68 international students enrolled in the university's nursing department in the 2016-2017 academic year. Data were collected using the introduction form, Healthy Lifestyle Behaviors Scale, and Life Satisfaction Scale. Pre-education and post-education scores were compared using the dependent t-test.

Results: The total Healthy Lifestyle Behaviors Scale score and subscale scores significantly increased after the program ($p \leq 0.001$). The score obtained from the Life Satisfaction Scale was 20.1±4.6 before the program and 25.9±3.9 after the program, and this increase was statistically significant ($p \leq 0.001$).

Conclusion: The psychoeducation program given to international students effectively ensures that students gain healthy lifestyle behaviors, positively affecting life satisfaction.

Keywords: International student, psychoeducation, healthy lifestyle, life satisfaction, nursing

1. INTRODUCTION

Migration from abroad to Turkey for educational purposes has increased with the Examination for International Students (1). In Turkey, international students have been taken as a political sphere since the early 1990s. According to international students, studying in higher education in Turkey provides them gain prestige and finding a job easily in their own country. Students come to Turkey's universities from Azerbaijan, Cyprus, Turkmenistan, Bulgaria, etc., depending on the intensity of the geographical and cultural relations (2). An increasing number of students come to Turkey every year and make efforts to remain in the higher education system and be successful (3). During this process, students enjoy the idea of getting into university but encounter many problems in the social, cultural, and economic areas (1,4). In addition to the regular problems of university students, nursing students also encounter some problems arising from nursing education and the hospital environment. The mental health of nursing students is affected negatively due to the intense theoretical content of nursing education and communication with patients who suffer (4). With the problems faced in the social, cultural, and economic areas, it becomes even more difficult for international students to adapt to society. Studies show that international students experience loneliness, inadaptability, shyness, cultural shock, and psychological problems (1,5,6). Moreover, they may face risky health behaviors such as inability to make changes in their lifestyle, lack of good stress management (future concerns, limit-pushing behaviors, violence), inability to take responsibility for their health (smoking, alcohol and drug use, unprotected intercourse) or malnutrition (fast-food, poor nutrition) (1,7).

Health promotion involves using the capacity and energy effectively, living a satisfactory life, being productive, and using all the health-related skills (8). Primarily, it is necessary to determine the lifestyle behaviors of international students and organize training programs for their needs to ensure the acquirement of healthy lifestyle behaviors (9). Psychoeducation, one of the educational programs, provides group environments where individuals have the opportunity to share their problems and mutually help and support each other by sharing their problem-coping methods. When individuals in the group see that they have similar problems, a strong bond develops between them; they receive acceptance, understanding, and support from each other and can easily realize the events in their lives with

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the feedback they receive from the group members (10). Therefore, including international students in such a group environment can transform their healthy lifestyle behaviors into a lifestyle and improve their health status.

A psychoeducation program carried out in the group structure provides benefits such as interaction, social learning, and social support (11,12,13). This is considered important in ensuring international nursing students gain necessary healthy life behaviors and life satisfaction. The fact that there is no study for foreign students in the literature is essential in terms of the originality of our study.

Aim of the Study: This study was carried out to evaluate the effectiveness of a psychoeducation program given to international nursing students receiving education in the nursing department of a public university to improve their healthy lifestyle behaviors and life satisfaction.

Research Hypotheses

H1: The psychoeducation program given to international students during ensures gain healthy lifestyle behaviors.

H2: The psychoeducation program is given to international students during increases life satisfaction levels.

2. METHODS

2.1. Research Type

The quasi-experimental study was conducted in the 2016-2017 academic year based on the single-group pretest-posttest model.

2.2. Sample

The research population consisted of 70 international students who were receiving education in the nursing department of a public university health school in the 2016-2017 academic year. The sample size was calculated a priori using G*Power. Considering the pretest-posttest means and standard deviations in the article taken as the reference for the sample size (14), it was determined that 66 students were required in the sample for Type I Error (Alpha) of 0.01 and power of 99%. The sample of the study consisted of 68 international students. Students over 18 who could easily read and understand our language and who were willing to participate in the study were included in the sample. During the study, there were no students who withdrew from the study or took a break from education.

Procedure and Application

The student participating in the study filled the personal data form and scales in a quiet classroom environment around a round table. A single-group, 8-session psychoeducation program was carried out based on the pre-test and post-test model. Each focus group session was planned to be 60 minutes. Each student was given a number. The scope of the 8-session psychoeducation program includes meeting and determination of group rules, taking responsibility for health, nutrition, and exercise, using interpersonal communication and support, self-realization, stress management, and life satisfaction. The psychoeducation program was held in 8 sessions, 60 minutes each once a week. Each session was carried out on the days and hours determined previously with international students, according to the session's topic and in line with the specified objectives. In the sessions, the previous session was summarized in the first 10 minutes, the plan was applied in line with the session topic for 40 minutes, the session was evaluated, and the session was ended after summarizing the next session in the last 10 minutes. The content of the psychoeducation program was based on the sub-dimensions of the Healthy Lifestyle Scale and the Life Satisfaction Scale used in the study (15).

Sessions:

1. Meeting with the group members, introducing the group process, explaining the session topics,
2. Taking Responsibility for Health,
3. Gaining Positive Health Behaviors: Nutrition and Exercise,
4. Gaining Positive Health Behaviors: Using Interpersonal Communication and Support,
5. Gaining Positive Health Behaviors: Self-realization,
6. Gaining Positive Health Behaviors: Stress Management,
7. Life Satisfaction,
8. Evaluation of Psychoeducation Given to Improve Healthy Lifestyle and Life Satisfaction/Termination of the Group Session.

Sessions 4, 6, 7 lasted 90 minutes due to the long topic contents and time-consuming activities.

2.3. Instruments

In this study, a questionnaire consisting of 19 questions describing international students, the Healthy Life Style Behaviors Scale (HLBS), and the Life Satisfaction Scale (LSS).

Healthy Lifestyle Behaviors Scale (HLBS)

The scale was developed by Walker, Sechrist, and Pender in 1987 to measure one's health-promoting behaviors regarding a healthy lifestyle. It was adapted to Turkish by Esin, its validity and reliability study was performed, and the Cronbach's alpha internal consistency coefficient was found as 0.91. The scale is a four-point Likert-type scale consisting of 48 items and six subscales. The score of each subscale can be used alone, or the total score of all subscales can be used and gives a healthy lifestyle behaviors score. The highest score for the total scale is 192, and the lowest score is 48. A high scale score indicates better healthy lifestyle behaviors. All items of the scale have a positive expression, and no items are scored reversely. The subscales of the scale are as

follows. Self-realization: The subscale consists of 13 items, including questions 3, 8, 11, 12, 16, 17, 21, 23, 29, 34, 37, 44 and 48. It determines one's life goals, self-development ability, how well they know and can satisfy themself. Health responsibility: The subscale consists of 10 items (items 2, 7, 15, 20, 28, 32, 33, 42, 43 and 46). It determines one's level of responsibility for their health and how much they participate in their health. Exercise: The subscale shows one's level of exercise, a constant element of a healthy life, and consists of 5 items (4, 13, 22, 30, and 38). Nutrition: The subscale consists of 6 items, including questions 1, 5, 14, 19, 26, and 35. It determines one's values in choosing and organizing meals and food selection. Interpersonal support: The subscale determines one's communication with their close environment and level of continuity and consists of 7 items (10, 18, 24, 25, 31, 39, and 47). Stress management: The subscale consists of 7 items (6, 9, 27, 36, 40, 41, and 45) that determine one's level of stress source recognition and stress control mechanisms (15).

Satisfaction with Life Scale (SWLS):

University students' general life satisfaction was measured using the scale developed by Diener, Emmons, Larsen, and Griffin (1985) and adapted into Turkish by Köker (1991). The scale, which reflects how the individual evaluates his own life, measures the perceived general life satisfaction. The items of the scale, which has five positive items, are in seven-point Likert type. The increase in the scores obtained from the scale shows that the perceived general life satisfaction also increases (16).

2.4. Data Evaluation

Descriptive data were given with mean ± standard deviation, number, and perceentage (%). The distribution of the data was tested using the Shapiro-Wilk test. The dependent sample t-test was used to compare the pre-program and post-program scores. In all analyses, the statistical significance was accepted as p≤0.05.

2.5. Ethical Aspect of the Research

Ethics committee approval (Number: 2016/2, Date: October 26, 2016) was received from the ethics committee of Kastamonu University. Students were informed about the study, and their verbal and written consent was received.

3. RESULTS

Of the students, 55.9% were in the 18-20 age interval, 67.6% were first-grade students, and 67.6% were female. 95.6% had no metabolic disease, 51.5% had social security, 14.7% were smokers, 10.3% were alcohol users, and 58.8% had sufficient income (Table 1).

Table 1. *Distribution of socio-demographic characteristics of student*

SOCIO-DEMOGRAPHIC CHARACTERISTICS			
		n	**%**
Age	18-20 years old	38	55.9
	21 years old and older	30	44.1
		68	100
Class	1st	46	67.6
	2nd	16	23.5
	3rd	4	5.9
	4th	2	2.9
		68	100
Gender	Female	46	67.6
	Male	22	32.4
		68	100
Presence of metabolic disease	Yes	3	4.4
	No	65	95.6
		68	100
Social assurance	There is	35	51.5
	no	33	48.5
		68	100
Smoking status	Yes	10	14.7
	No	58	85.3
		68	100
Alcohol Use	Yes	7	10.3
	No	61	89.7
		68	100
Income status	Sufficient	40	58.8
	insufficient	28	41.2
		68	100

Of the students, 70.6% were living in Turkey for 1 to 5 years, 54.4% had family or relatives in Turkey, 42.6% were staying at home, most of them defined their Turkish speaking (85.3%) and writing (86.8%) skills as sufficient (Table 2).

As seen in Table 3, the *Healthy Lifestyle Behaviors Scale* and *Life Satisfaction Scale* scores displayed normal distribution; therefore, parametr ic techniques were used in all statistical procedures (Table 3).

When the pre-program and post-program total score and subscale scores of the students from the Healthy Lifestyle Behaviors Scale were compared, total and all subscale scores were found to increase after the program compared to the pre-program scores, and this increase was statistically significant (p≤0.001) (Table 4).

The mean scores of the students from the Life Satisfaction Scale before and after the program are presented in Table 5. The score was 20.1±4.6 before the program and 25.9±3.9 after the program, and the difference was statistically significant (p≤0.001) (Table 5).

Table 2. *Distribution of descriptive characteristics of students*

DESCRIPTIVE CHARACTERISTICS OF STUDENTS			
		n	%
How long has he/she been in	1-5 year	48	70.6
the country	6-10 year	11	16.2
	11-15 year	9	13.2
		68	100
***Do you have family and relatives in the country**	Yes	37	54.4
	No	28	41.2
		65	100
Where does he/she stay during his/her education?	Government dorm	27	39.7
	Private dormitory	7	10.3
	Home	29	42.6
	With family	5	7.4
		68	100
The competence of speaking the language of the country	Sufficient	58	85.3
	insufficient	10	14.7
		68	100
The competence of writing the language of the country	Sufficient	59	86.8
	insufficient	9	13.2
		68	100
Health perception	Excellent	10	14.7
	Very good	45	66.2
	Middle	12	17.6
	Bad	1	1.5
		68	100

**3 students did not answer.*

Table 3. *Healthy lifestyle behaviors scale and life satisfaction scale normality test results*

Variable	Shapiro-Wilk	
	Value	P
Healthy Lifestyle Behaviors Scale – pre-program scores	.978	.274
Healthy Lifestyle Behaviors Scale – post-program scores	.975	.200
Life Satisfaction Scale_ pre-program scores	.988	.778
Life Satisfaction Scale_ post – program scores	.970	.097

Table 4. *Comparison of the pre-and post-program scores of the total and sub-dimensions of the healthy lifestyle behaviors scale*

Healthy Lifestyle Behaviors Scale	Pre-Program Scores	Post-Program Scores	t*
	X±SS	X±SS	p
Total Score	110.5±11.6	143.7±15.3	21.446 **<0.001**
Self-Realization	32.5±4.2	41.4±4.2	16.731 **<0.001**
Health Responsibility	21.1±3.5	27.6±4.4	14.340 **0.000**
Exercise	9.7±2.5	13.6±2.9	11.631 **<0.001**
Nutrition	13.7±2.3	17.7±2.9	13.005 **<0.001**
Interpersonal Support	17.1±2.6	21.9±3.1	14.366 **<0.001**
Stress Management	16.2±2.2	21.2±2.8	15.501 **<0.001**

**Paired Samples T-Test*

Table 5. *Comparison of life satisfaction scale before and after program scores.*

Life Satisfaction Scale	Pre-Program Scores	Post-Program Scores	t*
	X±SS	X±SS	p
Total Scores	20.1±4.6	25.9±3.9	12.429 **<0.001**

**Paired Samples T-Test*

4. DISCUSSION

One of the biggest challenges of the 21st century is the fight against the continuous growth in the global burden of non-communicable diseases. One of the main objectives of the World Health Organisation's (WHO) Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013-2020 is to ensure individuals and the population make healthier choices and adopt a health-promoting lifestyle since health and lifestyle are closely related (17). Beliefs about health, diseases, and lifestyle are largely affected by culture and local values (18,19). Biological health can be focused on as the only measure of well-being if the role of cultural values in health is ignored. The potential of culture to become a key component in health care and development can be ignored (20).

This study aimed to evaluate the effectiveness of a psychoeducation program given to international nursing students to improve their healthy lifestyle behaviors and life satisfaction. There was a significant difference in the scores of the students who had cultural differences from the total Healthy Lifestyle Behaviors Scale, its subscales, and the Life Satisfaction Scale after the program ($p \leq 0.001$).

In this study, the total healthy lifestyle score of the students was 110.5±11.6 before the program. Vural and Bakır (2015) conducted a study with students in a school of health service (21). They reported the total scale score as 127.05±20.35, and Şemin and Tengiz (2016) reported as 136.79±17.80 in their study (22). Şimşek et al. (2012) found that the total score of medical students from the Healthy Lifestyle Behaviors Scale was 134.4±9.7(23). Aksoy and Uçar conducted a study with 281 nursing students and found the total scale score as 136.12±19.16 (9). The results of these studies, which were conducted with Turkish students, were higher than the mean scores of the students in our study. The students included in our study sample were the citizens of Afghanistan, Kyrgyzstan, Iran, Syria, and Saudi Arabia. This difference may have occurred because healthy life behaviors are largely affected by culture and local values (18). A study conducted in Qatar reported that socio-cultural factors influence women's decisions on participating in healthier lifestyles related to physical activity, healthy nutrition, and smoking (24).

In this study, the total Healthy Lifestyle Behaviors Scale score and subscale scores increased significantly after the program ($p \leq 0.001$). The difference between the pre-program and post-program scores obtained from the subscales of self-realization, health responsibility, exercise, nutrition,

interpersonal support, and stress management was strongly significant (p≤0.001). Şemin and Tengiz (2016) conducted a study to determine whether the health and life course affected the development of healthy lifestyle behaviors in students and to determine the most preferred education method and found the difference between the pre-and post-training has increased significantly (22). Some studies investigated the causal effect of education on health-related behaviors such as smoking, drinking alcohol, exercising, eating healthy food, and Body Mass Index (BMI). Some reported no causal correlation between education and health behaviors (25,26). Some reported a correlation (27-30). Kim et al. (2016) conducted a study with primary school students in South Korea and found that educational interventions aimed at changing health behaviors can be effective for primary school children (27). Brunello et al. (2013) emphasized that education had a protective effect on the BMI of women living in nine European countries and reduced the probability of being obese or overweight (28). In a study conducted in Indonesia to evaluate the effectiveness of training given to 7th – and 8th-grade students to prevent smoking, it was reported that students' knowledge about smoking and its harmful effects increased and that students showed more serious anti-smoking attitudes (29). Yazdani et al. (2010) reported that training given to nursing students on stress management reduced their depression, anxiety, and stress levels (30). These studies report that education is effective in developing healthy life behaviors and show similarities with the results of our study. This finding suggests that education programs should be benefitted to ensure students gain appropriate behaviors.

The difference in the mean scores of the students from the Life Satisfaction Scale before and after the program was significant (p≤0.001). Studies in the literature report a significant positive correlation between health behavior indicators and life satisfaction levels (31,32). Teker and Lüleci (2018) reported that there was a positive correlation between healthy lifestyle behaviors and quality of life and suggested that the improvement of the quality of life of individuals in the community can ensure they develop healthy lifestyle behaviors or improving healthy lifestyle behaviors can improve the quality of life (32). Gürsel et al. (2016) found that stress management, a subscale of the healthy lifestyle behaviors scale, was highly associated with the quality of life of instructors (33). In this study, students' mean healthy lifestyle scores and the quality of life scores differed significantly after the program.

Limitations of the Research: This study is limited to international students enrolled in the nursing department of a public university in the 2016-2017 academic year.

5. CONCLUSION

It was concluded that education given to international students is effective in ensuring them gain healthy lifestyle behaviors and that this situation affects life satisfaction positively. In light of these findings, considering that nursing students will become role models for society in the future, it is necessary to ensure nursing students adopt or develop healthy lifestyle behaviors with such psychoeducation programs. It is thought that it is necessary to ensure the continuity of psychoeducation programs to develop healthy lifestyle behaviors and life satisfaction of international nursing students.

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Clinical and Experimental Health Sciences

Reprocessing Cost Analysis of Specimens Rejected in Laboratory: Results from the Perspective of the Costs to the Hospital

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ABSTRACT

Objective: The objective of the study is to analyze the additional costs of reprocessing the specimens rejected in the laboratory to the hospital.

Methods: The data is acquired from the Düzce University Medical Application and Research Hospital (DUMARH) laboratories. 5-year (2015-2019) data was retrospectively reviewed and subjected to document analysis.

Results: The rate of the total rejected specimens has increased throughout the years. (2015, 0.88% – 2019, 2.12%). The most prominent rejection reasons are hemolysis specimen (32.9%), insufficient specimen (17.25%), clotted specimen (15.4%) and inaccurate examination request (10.64%). While the reprocessing cost of specimens was 12.085 dollars in 2015, it increased to 51.132 dollars in 2019. It is seen that the rejection rate has increased as the specimen number increased and the reprocessing costs have increased since the inflation in Turkey increased and the purchasing power of the hospital has decreased throughout the years.

Conclusion: In order to decrease and prevent the rejected specimen, there is a need for phlebotomy training, especially for nursing and other healthcare professionals, and strict quality control and standard operating procedures for the pre-analytical phase. These are the critical approaches that will improve the service quality of laboratories and patient safety.

Keywords: Laboratory, Rejected Specimen, Reprocessing, Cost Analysis.

1. INTRODUCTION

Today, diagnoses are mostly made by resorting to laboratory tests and depending on their results (1). Laboratory services play an important role in patient care, and laboratory data is estimated to affect 60-70% of the most important decisions regarding acceptance, discharge and medication. (2). Considering that approximately 80-90% of the diagnoses that doctors make to their patients are made according to laboratory tests, it is obvious that errors in the laboratory will decrease the chance of correct diagnosis. In addition, such mistakes increase adverse events and lead to an increase in costs (3).

Performing a laboratory test consists of three phases named as pre-analytical, analytical and post-analytical phases. The pre-analytical phase covers the process from the request of the test until the specimen is ready for analysis, the analytical phase includes the analysis process of the specimen, and the post-analytical phase covers the reporting and interpreting the test result (4).

Laboratory error is expressed as any defect that occurs during the entire testing process, from ordering tests to reporting results and in any way affecting the quality of laboratory services (4,5). One of the elements that make up the laboratory errors is the rejected samples.

Many studies in the last decade show that about 70% of errors causing rejected specimens occurred before the laboratory tests, that is, in the pre-analytical phase, and 30% in the analytical and post-analytical phase (6,7). In Turkey, it is found that the 96.33% of laboratory errors occur in the pre-analytical phase (8).

Most of the pre-analysis errors are caused by system defects and insufficient supervision of staff involved in sampling and processing. This results in an unacceptable number of unsuitable specimens due to hemolysis, clotting, insufficient volume, wrong container, misidentification and contamination (9). Patient specimens must be appropriate for laboratory results to be accurate and precise. Inappropriate specimens must be evaluated in the pre-analytical phase and faulty specimens must be rejected (10,11).

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During laboratory analysis, laboratory errors occur due to improper collection of specimens, carelessness, an unnecessary retake of samples and prolonged corrective-preventive actions and the test results are delayed. All of these errors result in the rejection of samples and repetition of the whole process for a rejected sample which causes a waste of time and resources in the laboratory (12).

In addition, these errors cause additional costs as they may require retaking of specimens, retesting and further investigation by laboratory staff. Also, erroneous results may cause many problems such as unnecessary treatment, complications of treatment, lack of proper treatment, delay incorrect diagnosis, and the remaking of additional and unnecessary diagnostic tests. These results lead to increased costs and inadequate patient outcomes due to time loss and staff effort.

It can be seen that costs are calculated in several ways when the studies about the costs of rejected specimens are examined: calculation according to the parameters determined by the health economy specialist (4), calculation by multiplying the numbers obtained from the hospital automation program with the material costs (13) calculation with a global survey taken from several countries (14), cost study made by calculating only the hourly wages of employees (15) and cost study only for a particular type of assay (such as INR…) (16) are the studies for major calculation techniques. The studies conducted for the reprocessing of rejected specimens that take strategic cost analysis tools, cost elements, cost distribution stages and key into account, could not be identified in PubMed, Scopus and Web of Science databases. The most original part of this study is the calculation of costs by using cost distribution keys in the process of direct raw materials and supplies, direct labor and general service production cost distribution in the reprocessing of rejected specimens.

The aim of the study is to provide useful information to the hospital management on taking the necessary precautions by calculating the number of specimens rejected for some reason in DUMARH* laboratories for the last 5 years (2015, 2016, 2017, 2018 and 2019), the cost of reprocessing of them for the hospital, by revealing the reasons for their rejections. With this study, useful information will be provided to the management to take necessary measures to eliminate the reprocessing costs of rejected specimens from activities that do not create added value to ensure efficient and effective use of hospital resources. In addition, this study aims to determine the reasons for the rejected samples, to reveal in which units they occur, and to contribute to taking the necessary administrative measures.

2. METHODS

The data of the study includes the 5 years (2015-2019) of specimen data from the Medical Biochemistry, Medical Microbiology, and Transfusion Center Blood Grouping (including lined and scuba) laboratories of Düzce University Medical Application and Research Hospital which is a tertiary 316-bed healthcare center located in Düzce, Turkey.

The research population consists of all the specimens coming to the laboratory of the hospital in question. Specimens coming to the laboratory are evaluated in terms of whether they are suitable for analysis or not and the ones that are not suitable are rejected by entering the reason for rejection in the hospital automation system. All specimens that were rejected for various reasons were studied.

Information about specimens accepted and rejected in the laboratory was obtained retrospectively through hospital automation and laboratory information management system. The financial data of the study were obtained from the managers and personnel working in the hospital's enterprise resource planning, administrative/financial affairs, accounting, and information processing departments and they are factual and primary data. Document analysis was performed during the data acquisition and cost analysis.

3. RESULTS

The total number of specimens, rejection rate, number of rejected specimens, reasons for rejection, rejection rates of each unit and reprocessing costs in the three laboratories belong to DUMARH (Medical Biochemistry, Medical Microbiology and Transfusion Center Blood Grouping laboratory) were examined in a way that will cover 2015-2019 (last 5 years). The tests such as Emergency-Routine Biochemistry Tests, Immunoassay Tests, Blood Gases, Urine, Fecal, Blood Count, Sedimentation, Coagulation, aCPT, Medical Microbiology and Transfusion Center Blood Grouping are all included in the analysis.

3.1. Data on Rejected Specimens

According to Table 1, the rejected total specimen rejection rates were determined to be lowest with 0.88% in 2015 and highest with 2.12% in 2019. It is remarkable to see that although the total number of samples increased by 5% in 2019 compared to the previous year, the rate of rejected samples increased by 14%.

According to Table 2, it is seen that among the most common reasons for rejection, hemolysis, insufficient specimen, clotted specimen and incorrect examination request have come to the fore especially in the last three years, although it varies according to years.

According to Table 3, Emergency Medicine (Adult) (33,1%) and Internal Diseases (13.84) have the most rejected specimen units when the units are examined separately. The rates of other units correspond to very small rates.

* Düzce University Medical Application and Research Hospital

Table 1. *Total specimens rejected and percentage of rejection*

Type	2015	2016	2017	2018	2019
Number of Rejected Specimens(including lined and scuba) (pieces)	41.390	62.180	107.613	122.754	139.706
Total Number of Specimens (pieces)	4.729.623	5.121.959	5.451.590	6.275.950	6.578.502
Rejection Rate (%)	0.88	1.21	1.97	1.96	2.12

Table 2. *Number and percentage of specimens rejected according to their reasons*

Reason of Rejection	2015		2016		2017		2018		2019	
	Amount	%	Amount	%	Amount	%	Amount	%	Amount	%
Hemolysis specimen	1502	15.36	1346	9.31	3462	**21.66**	4858	**25.76**	7703	**32.19**
Insufficient specimen	3001	**30.7**	3649	**25.24**	3232	20.22	3858	20.45	4128	17.25
Clotted specimen	1839	18.81	3218	22.26	2998	18.76	3576	18.96	3686	15.4
Inaccurate examination request	30	0.3	1326	9.17	1489	9.31	2289	12.13	2547	10.64
Wrong tube specimen	697	7.13	833	5.76	796	4.98	897	4.75	869	3.63
Inappropriate specimen	378	3.86	665	4.6	560	3.5	769	4.07	726	3.03
Excess specimen	501	5.12	343	2.37	43	0.26	64	0.33	64	0.2
Specimen that did not come to the laboratory	44	0.45	1	0.006	301	1.88	8	0.04	7	0.02
Other reasons	1783	18.24	3071	21.24	3096	19.37	2538	13.45	4196	17.53
TOTAL	9775	100	14452	100	15977	100	18857	100	23926	100

Table 3. *Number and percentage of rejected samples by requested units*

Units	2015		2016		2017		2018		2019	
	Amount	%	Amount	%	Amount	%	Amount	%	Amount	%
Emergency Medicine (Adult)	3354	34,48	3897	27,1	5382	33,78	6647	35,34	7892	33,1
Internal Diseases	1595	16,39	3041	21,15	2765	17,35	2645	14,0	3302	13,84
Nephrology, Urology, Dermatology, Orthopedics – Trav. and ENT Diseases	387	3,97	1147	7,97	1498	9,40	2284	12,14	2683	11,25
Obstetrics and Gynecology and Neon.	766	7,87	843	5,86	909	5,70	1.420	7,54	1813	7,6
Pediatry	607	6,24	1236	8,59	1219	7,65	1445	7,68	1636	6,86
Anesthesiology, Physical Medicine, Hematology, Hemodialysis	594	6,10	1175	8,17	1292	8,10	1190	6,32	1403	5,88
General Surgery, Gastroenterology and Endocrinology	286	2,94	612	4,25	525	3,29	505	2,68	905	3,79
Neurology and Neurosurgery	516	5,30	774	5,38	659	4,13	675	3,58	818	3,43
Chest Diseases and Surgery	245	2,51	342	2,37	545	3,42	608	3,23	742	3,11
Cardiology and Cardiovascular Surgery	305	3,13	389	2,70	432	2,71	678	3,6	751	3,14
Intensive Care and Infection Disease	937	9,63	595	4,13	343	2,15	316	1,68	402	1,68
Other Specializations	183	1,38	401	2,27	444	2,27	444	2,1	1579	6,27
TOTAL	9775	100	14452	100	15977	100	18857	100	23926	100

3.2. Cost Analysis Regarding the Reprocessing of Rejected Specimens

In determining the cost information of the study, all cost elements of the Dxxxxx Central-Emergency Laboratory for the last 5 years (2015-2019) were examined and cost analyzes were made. Unit costs are determined by calculating direct raw materials and supplies, direct labor and general service production expenses.

Costs are divided into two parts as direct and indirect according to the way they are loaded into the service costs. Since direct costs are the costs directly related to the laboratory unit, they are loaded without using the allocation key. Indirect costs such as general service production expenses were allocated with the help of various allocation keys according to their qualities.

Cost elements are allocated to the primary service production expense places, auxiliary service production expense places, auxiliary service expense places and operating expense places as the I. allocation. Then, as the second distribution, the costs collected in the auxiliary expense places are distributed to the main service production expense places according to various distribution methods (simple, graded, math and cross-distribution methods). As a final distribution, the costs collected in the main service production cost centers are calculated as unit cost according to the service quality measurement units (patient, day, number of examinations, minutes, etc.). In the laboratory unit cost distribution, auxiliary service is considered as production cost centers.

The dollar is used as the currency in cost calculations by taking the annual average exchange rate published by Central Bank of the Turkey Republic into account. Accordingly, the calculations were made taking the currency exchanges as 1 ₺= $2,72 in 2015, 1 ₺= $3,02 in 2016, 1 ₺=$3,65 in 2017, 1 ₺=$4,82 in 2018 and 1 ₺=$5,67 in 2019.

The list and price of the materials purchased by the Hospital's Revolving Fund Directorate, under the Public Procurement Law No. 4734; the gross salary, additional payment, revolving fund and duty fee expenses of the personnel working in the Central-Emergency Laboratory of the hospital and general service production expenses incurred in the researched laboratory are shown in Table 4.

Table 4. *Direct raw materials and supplies expenses, direct labor costs and general service production expenses ($-cent)*

Direct raw materials and supplies expenses ($-cent)						
Material Type		**2015**	**2016**	**2017**	**2018**	**2019**
Injector (5 cc, 10cc,20cc,50cc)		0.037	0.040	0.038	0.068	0.092
Edta/ gel tube/ Plastic Sterile Container		0.037	0.066	0.068	0.077	0.106
Glove		0.018	0.023	0.025	0.025	0.037
TOTAL MATERIAL EXPENSES PER UNIT ($)		0.092	0.129	0.132	0.170	0.235
Direct labor costs ($-cent)						
Direct Labor Elements		**2015 (11 people)**	**2016 (11 people)**	**2017 (14 people)**	**2018 (20 people)**	**2019 (20 people)**
Salary		93,156.57	92,303.98	101,847.45	78,129.07	73,209.75
Supplementary payment		37,770.26	40,794.43	43,184.56	37,819.80	36,470.90
Revolving Funds Payment		25,947.02	23,627.62	27,790.80	23,510.04	22,320.99
Duty fee		0.00	0.00	16,216.53	13,677.43	12,633.51
TOTAL FEE		156,873.86	156,726.03	189,039.33	153,136.35	144,635.15
FEES PER UNIT ($)		0.033	0.031	0.035	0.024	0.022
General service production expenses ($-cent)						
General Service Expense Items		**2015**	**2016**	**2017**	**2018**	**2019**
Indirect Personnel Expenses (Cleaning etc.)		1,100.00	1,288.08	1,144.11	987.58	1,075.84
Cleaning Material Expense		951.10	978,81	1,273.97	1,089.03	1,386.24
Hospital Automation Expense		2,786.63	2,885.31	3,660.52	3,083.00	2,749.56
Electricity Expense		9,502.25	9,164.14	8,579.05	6,753.11	6,095.59
Various Expenses		1,308.82	1,307.95	1,232.90	10,031.06	938.27
Accumulated Depreciation (Fixtures)		6,341.91	6,192.05	5,835.62	5,517.60	5,379.19
License, Document Editing and Licensing Expenses		3,583.27	3,414.24	1,949.86	1,839.23	2,833.42
Medical Waste Disposal and Transport Service Purchase Expenses		3,198.53	3,152.32	2,913.70	1,425.47	1,437.39
External Benefits and Services	Autoanalizer and HBA1C Kits	9,607.35	82,507.28	45,698.63	0.00	0.00
	Device for Microbiology and Sterilization Consumables and Kit	375,497.43	379,629.14	845,019.45	514,352.17	561,689.47
	Device for Biochemistry, Hormone Blood Gas and Urine Strip Kit	293,811.21	356,280.35	75,835.62	154,850.93	134,274.25
TOTAL ($)		789,688.51	846,799.67	993,143.43	699,929.18	717,859.23
GENERAL SERVICE PRODUCTION EXPENSE PER UNIT ($)		0.167	0.165	0.182	0.112	0.109

According to Table 4, despite the highest number of staff per unit (20 people) according to the total specimen, it is seen that the lowest labor expense was $ 0.022 in 2019 due to the lowest salary payment, and the highest with $0.035 in 2017 due to the highest salary payment. Despite the increase in the number of staff in 2018 and 2019 compared to previous years, the reason for the low salary per unit is the provision of employment based on personnel based outsourcing services in these years.

The examination of the specimens in the aforementioned laboratory is carried out by service procurement by tender through outsourcing. The service procurement subject to the tender is to purchase services in return for the results of the emergency-routine biochemistry test, immunoassay tests, blood gases, urine, stool, blood count, sedimentation, coagulation, aCPT, medical microbiology and Transfusion center blood grouping tests to be performed in the medical biochemistry, medical microbiology and transfusion center blood grouping laboratories of the hospital. These, the purchase of equipment in exchange for the kit, all calibrators for quality control, control, consumables, maintenance and spare parts costs of the devices, (in case of periodic or malfunction) belong to the company receiving the tender.

On the other hand, laboratory tests and cleaning are carried out by hospital staff. Materials for all disinfection processes (surface and hand etc.) related to cleaning, personal cleaning materials (paper towels, toilet paper, hand disinfectant, hand soap, etc.), all medical and domestic waste bags, cutting-piercing tools, medical waste buckets are covered by the hospital.

According to Table 5, when the reprocessing cost elements of the rejected specimens were analyzed by years, it was seen that although the common service production expenses were the most in 2015, 2016 and 2017, the direct raw materials and supplies expenses were the most in 2018 and 2019.

According to Table 6, during the period between 2015 and 2019, the unit costs of the samples increased by 26% in total, the rejected specimens increased by 151% and the total costs increased by 183%. The number of rejected specimens mostly increased by 73% in 2017, the total number of specimens mostly increased by 15% in 2018, unit costs mostly increased by 20% in 2019 and reprocessing costs increased by 85% in 2017, directly proportional to the highest number of rejected specimens.

According to Table 7, while the share of laboratory income in total revenue is 13% in 2015, 14% in 2016 and 2017, 12% in 2018, it decreased to 10% in 2019. Although the share of reprocessing cost in total revenue was 0.06% in 2015, 0.10% in 2016, 0.21% in 2017, 0.22% in 2018, this rate increased to 0.31% in 2019.

Table 5. *Reprocessing cost of rejected specimens*

Cost Elements	2015	2016	2017	2018	2019
Direct Raw Materials and Supplies Expenses	0.092	0.129	0.132	0.170	0.235
Direct Labor Expenses	0.033	0.031	0.035	0.024	0.022
General Service Production Expenses	0.167	0.165	0.182	0.112	0.109
TOTAL EXPENSES PER UNIT ($)	0,292	0,325	0,349	0,306	0,366
Rejected Specimen Number	41.390	62.180	107.613	122.754	139.706
REPROCESSING COST OF REJECTED SPECİMENS ($)	12,085.88	20,208.50	37,556.94	37,562.72	51,132.40

Table 6. *Change index of rejected specimens and costs compared to the previous year*

	2015		2016		2017		2018		2019	
	Unit	Change	Unit	Change	Unit	Change	Unit	Change	Unit	Change
Number of Rejected Specimens (pieces)	41.390	1	62.180	**0.50**	107.613	**0.73**	122.754	**0.14**	139,706	**0.14**
Total Number of Specimens (pieces)	4.729.623	1	5.121.959	**0.08**	5.451.590	**0.06**	6.275.950	**0.15**	6.578.502	**0.05**
Unit Cost ($)	0,292	1	0,325	**0.11**	0,349	**0.07**	0,306	**-0.12**	0,366	**0.20**
Reprocessing Cost ($)	12,085.88	1	20,208.50	**0.67**	37,556.94	**0.85**	37,562.72	**0.00**	51,132.40	**0.36**

Table 7. *The share of reprocessing costs in total income and expense*

Total Revenue ($)	**2015**	**2016**	**2017**	**2018**	**2019**
Reprocessing Cost	12.085,88	20.208,50	37.556,94	37.562,72	51.132,40
Revenue acquired from the Laboratory (SSI and Total Invoice Amount Including Paid)	2.663.528,38	2.820.884,05	2.556.195,46	2.149.564,05	1.581.053,16
Laboratory Total Cost of Production of Services	1.381.270,37	1.664.970,74	1.899.104,19	1.918.547,72	2.405.599,78
Laboratory Profitability	1.282.258,01	1.155.913,31	657.091,27	231.016,33	-824.546,62
Total Expenses of the Hospital	24.107.894,26	24.314.074,74	22.198.930,50	20.257.794,82	21.242.908,57
Total Revenue of the Hospital	20.500.785,56	19.942.879,45	18.113.571,04	17.254.345,34	16.524.800,34
Share of Laboratory Income in Total Revenue	0,13	0,14	0,14	0,12	0,10
Share of Reprocessing Cost in Total Revenue	0,0006	0,0010	0,0021	0,0022	0,0031
Share of Reprocessing Cost in Total Expense	0,0005	0,0008	0,0017	0,0019	0,0024

4. DISCUSSION

In the literature, there are many studies aimed at detecting faulty and rejected specimen rates in the laboratory. Association of Public Health Laboratories (17) set a specimen rejection rate of 2% or less as a monthly quality indicator. In similar studies on the subject, the specimen rejection rate was determined to be between 0.1% and 3.49% (17, 20). In this study, specimen rejection rates were determined to be between 0.08% and 2.12% between the years 2015 and 2019. On the other hand, although there is no standard threshold value in the world specified as an acceptable specimen rejection rate, the American College of Pathologists (CAP-College of American Pathologists) recommends each institution to compare its rejected specimen rates with references from multiple institutional studies (22). In a study on the reasons for rejection of laboratory specimens (12), improper packaging of specimens (84.2%), coagulation (15.8%), non-centrifuged specimens (46.9%), hemolysis specimens (19.8%) and wrong tube use (17.7 %) were found as the main reasons for rejection. In a similar study (3), the most common cause encountered was found to be the clotting of the sample with a rate of 43.8%, insufficient volume with 24% and hemolysis with 18%. In a study by Da Rin (2009) (2), the rate of inappropriate test request, sample collection and transport inadequate, misidentification of the patient, labelling errors was between 46-68.2% and the rate of equipment malfunction and sample mix-ups/interference was between 7-13% in the pre-analytical (outside&within the laboratory) phase. Besides the rate of failure in reporting and improper data entry was between 18.5-47% in the post-analytical phase.

Among the rejected specimens, although they vary by years, the most common reasons for rejection are hemolysis specimen, insufficient specimen and clotted specimen in general. In similar studies, the most common reasons for rejection in line with our findings with differences in the ranking. Insufficient specimen, hemolysis specimen and clotted specimen were reported as the reasons (19, 22).

When specimen rejection rates were evaluated on the basis of units, the highest rejection rate was determined in the adult emergency unit (34.48%; 27.1%; 33.78%; 35.34%; 33.1%) during the years subject to the study. This finding is in line with similar studies in the literature. When the reasons are examined, emergency services among all units stand out as the units where the number of patients is quite high and that require urgent intervention due to emergencies. Therefore, the risk of making mistakes and specimen rejects are more likely than other units (23,24).

Another issue is reprocessing costs. The share of these costs in the total expenses of the hospital increased for 0.05% – 0.08% – 0.17% – 0.19% and 0.24% during the 5-year period (Table 6). These rates are partially compatible with the literature. Indeed, in similar studies, reprocessing costs are estimated to represent 0.2% to 1.2% of total hospital costs. This is estimated to be approximately $ 1,199,122 per year for a 650-bed US hospital (4,15).

According to the results of the study conducted by Erdal et al. (2017) (14) at the global level in 2016 to determine the economic impact of rejected samples, the average annual cost (10,000 per tube; labour/materials included) of reprocessing laboratory-induced errors varies between $ 117 – $ 147 per year (Turkey), $ 32 – $ 67 (UK) and $ 294 – $ 417 (Italy). Again, in a similar study on this subject, the reprocessing cost per specimen 837,862 tubes was determined as $ 43,210 and the average cost as $ 21.9 (13). In our study, the total reprocessing cost was calculated as $ 12,058 for 2015 and $ 51,132 for 2019.

When the reprocessing costs are analyzed by years, it increased significantly by 67% in 2016 compared to the previous year and by 85% in 2017 compared to the previous year. The main reason for this increase, including the 7% increase in unit cost amount in 2017, is that there has been a serious increase in sample rejection rates such as 73% (Table 6).

In the study, it was determined that the number of rejected samples and unit costs affected the reprocessing cost of

rejected samples. In order to reduce the number of rejected samples, especially in the preanalytical stage, training of personnel, lean and six sigma methodology can be applied (26). In addition, in order to reduce the number of rejections, it is necessary to implement quality requirements, provide information, in-service training, share changing technological developments and increase communication (27).

Considering the unit cost factors, it has been determined that the general service production expenses were the biggest expenditure item until 2018, and as of 2018, raw materials and supplies expenses are the largest expenditure item in the laboratory expenses. Direct labour was observed as the smallest expense item (Table 5). Although the total specimen amount showed a steady increase between 2015-2019, the increase in rejected specimen amount was found to be disproportionate and irregular. Again, the rejected specimen amount, which increased at high levels until 2018, shows a smaller and regular increase as of 2018 (Table 6).

Although the total number of specimens of the hospital increased in 2019 compared to the previous year (5%), the number of rejected specimens (14%) increased more (9%). In addition, it was determined that there was a decrease of $ 568,510.89 in the income obtained from the laboratory in 2019 compared to the previous year (Table 6). Despite this decrease in revenues, there was an increase of 20% in unit costs and 36% in total costs (Table 6). In the same year, a 36% increase in costs, despite the 20.30% inflation in Turkey shows that the purchasing power of the hospital is not strong.

It can be also said that the total cost of reprocessing continues to increase every year as a result of the increase in unit cost. When investigated, the reasons for this situation can be determined as, inflation is being higher in the inputs of the health sector since 2018 although it has been 11% in Turkey over the years, movements in exchange rates and depreciation of the domestic currency against the dollar and the Euro. In addition, importing some of the devices and kits used in the laboratory causes prices to be highly affected by inflation and foreign exchange movements. Another reason for the increase in unit costs has been determined that the prolonged purchase times with the suppliers due to the decrease in the purchasing power of the hospital caused the increase in the purchase price levels due to the maturity differences.

The income from the laboratory has a considerable place in the total revenue of the hospital. In fact, in 2015, 2016 and 2017, laboratory revenues tended to increase in total revenue. The reason for this is that total specimen numbers increase year by year and there is no serious increase in unit costs. In 2018, however, it can be seen that although the revenue from the laboratory increased, the share of this income in total hospital revenue decreased (12%) (Table 7). The most important incomes of the hospital consist of invoice revenues issued in accordance with the Social Security Institution (SSI) in Health Implementation Communiqué (HIC). Despite the decrease in the purchasing power of the hospital, the fact that the HIC prices were not increased by the SSI caused a decrease in the total revenue of the hospital.

4.1. Limitations

In this study, cost items for the following items were not calculated. Cost for the re-examination of the patient due to rejected specimens, cost of improper treatments, the cost of prolonged hospital stay, deaths due to specimen errors and their costs, potential income losses due to dissatisfaction with health services were not included in the analysis. In addition, labor costs in the units where the specimens were taken again were not calculated. Labor costs in the laboratory, which is the unit where only reprocessing takes place, have not been calculated.

5. CONCLUSION

Due to the negative effects on patient safety and increased hospital costs, specimen rejections are an issue that must be considered regardless of their reason or ratio. The important thing is to eliminate these errors with minimum resources without compromising patient health. Laboratory tests, which are an important factor in patient diagnosis and treatment, need to be rejected and reprocessed due to some errors. Such errors and delays have the potential to endanger the health of patients, as well as to increase health care costs both directly and indirectly as they can also increase the length of hospital stay of patients. Considering the macro scale, sample rejections are a significant financial burden on hospitals and therefore on the state in terms of health economics.

In the face of these increasing costs, no additional payment is made to the hospitals by both SSI and patients for the samples that are reprocessed. Therefore, it is important to reduce the number of rejected samples and cost factors in the reprocessing of rejected samples. In order to reduce reprocessing costs, rejection rates must first be reduced. For this purpose, some preventive activities should be carried out by regularly monitoring sample rejection rates in hospitals. These activities include options such as phlebotomy training for nurses and other healthcare professionals, creation of a technological registration system, applying strict quality control and regular working procedures to laboratory workers in pre-analytical, analytical and post-analytical phases and regular inspections. In order to reduce unit costs, some measures can be taken such as finding alternative suppliers, using personnel more efficiently, actively using the financial resources allocated to the hospital and reducing borrowing costs due to maturity.

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Clinical and Experimental Health Sciences

Deglutition Disorders from the Perspective of Healthcare Professionals in Turkey

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ABSTRACT

Objective: Awareness of deglutition disorders is essential for prevention of deglutition-related complications and improving quality of care. The study examined the current knowledge, attitude and practice regarding deglutition disorders among healthcare professionals in Turkey.

Methods: Healthcare professionals who worked in hospitals and special education schools were included. A survey examining knowledge, attitudes, and practices regarding deglutition disorders, originally designed by Farpour and colleagues (2019), was adapted and administered to healthcare professionals working in hospitals and special education schools in Turkey.

Results: A total of 270 healthcare professionals were responded (72.7% response rate). 254 participants (94.1%) were familiar with the term deglutition disorders. 223 participants (82.6%) defined their professions as a management team member. All participants supported a multidisciplinary approach. 216 (80%) participants met a patient with deglutition disorders. 212 participants (78.5%) used at least one evaluation method to evaluate swallowing function, and 147 participants (54.5%) used at least one treatment method for treatment. Most participants (73.7%) were interested in attending a workshop about deglutition disorders.

Conclusion: The present study showed that knowledge about deglutition disorders is high among healthcare professionals in Turkey, and they believe the necessity of multidisciplinary approach in deglutition disorders. However, it is not understood if they follow an individualized and standardized evaluation and management procedures. Therefore, more detailed questionnaires especially focus on evaluation and management of deglutition disorders should be developed and healthcare professionals could be trained to improve management of deglutition disorders in Turkey.

Keywords: Deglutition, deglutition disorders, knowledge, attitude, dysphagia.

1. INTRODUCTION

Deglutition disorders, or difficulty swallowing may result from structural problems and/or neuromuscular disorders (1). Such disorders, which include oropharyngeal and esophageal swallowing disorders, are highly prevalent and can cause severe nutritional and respiratory complications, and decreased quality of life among patients and their caregivers (2,3).

A primary goal when working with patients with deglutition disorders is to prevent complications (3). There are many conditions that can cause deglutition disorders including structural deficits of the head or neck region (i.e., head and neck cancer and its treatments, head or neck injuries), damage to the brain or nerves (i.e., cerebral palsy, stroke, motor neuron diseases, multiple sclerosis, Alzheimer's disease), and functional causes (i.e., cricopharyngeal dysfunction). In some countries, researchers have conducted studies of the prevalence and incidence of deglutition disorders in various patient populations (4-12). The frequency of deglutition disorders varies with the patient characteristics, etiology of the disease, and its treatments (4-8). The prevalence of deglutition disorders is expected to rise with the increasingly aging population; therefore, it is an important healthcare issue, and one that is associated with enormous financial burden (13,14). As a result, it is important to evaluate swallowing function, define problems in swallowing function and prevent complications related to deglutition (9). However, deglutition disorders remain undiagnosed in most patients, and these patients do not receive any treatment and/or rehabilitation (10-12). Therefore, healthcare professionals must have sufficient awareness and knowledge and also appropriate attitudes to improve the management of deglutition disorders.

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National and international practices are important for identifying needs, raising awareness of best practices, and improving communication and quality of care (15-21). Most of the studies focused on the practices of speech and language therapists concluded that there are various patterns of practice in terms of assessment and management of patients with dysphagia (16-19,21). One study found poor agreement with regard to the treatment techniques used for patients with deglutition disorders, a variety of techniques were performed within a swallowing rehabilitation session, and evidence-based approach was not common (17). Another study showed that clinicians had agreement in their clinical or instrumental evaluation recommendations despite wide variability in clinical decision-making (19). In another study conducted in Australia, history taken, observation of swallowing and cranial nerve examination as clinical swallowing evaluation are mentioned as the components of best practice, and videofluoroscopic swallowing evaluation was reported to be important for clinical decision-making. Although exercised based training has been shown as the best practice, it has been reported that Australian practice was based on compensatory techniques (21). Because managing dysphagia requires a multidisciplinary approach, some studies also included a variety of other professionals to show their knowledge and attitudes regarding dysphagia (15,20). These studies also suggest the need for education, establishing a standardized approach, and multidisciplinary teamwork. Thus, it is important to investigate national practices to identify the areas that need improvement, reveal best practices, and establish both national and international guidelines. To our knowledge, there is no study that has addressed the current status of patients suffering from deglutition disorders in Turkey. In addition, no studies have investigated the awareness, knowledge, attitudes and practices of healthcare professionals in Turkey. Therefore, this study was aimed to (i) determine the current knowledge, (ii) identify the attitudes, and (iii) define practice regarding deglutition disorders among healthcare professionals in Turkey.

2. METHODS

The current study was performed at the Faculty of Physical Therapy and Rehabilitation at Hacettepe University. The Ethics Commission of the university approved the study protocol (Approval number = 35853172-050). Informed consent was obtained from the participants who participated in this study.

2.1. Participants

The participants were recruited from healthcare professionals who worked in universities, governmental and educational hospitals, and special education schools in Turkey. There are seven regions in Turkey; therefore, seven different members of the Dysphagia Research Society of Turkey were selected to coordinate the survey distribution across the country. The survey was sent electronically to potential participants using Google forms, and information regarding study details was provided before starting to fill the survey. All participants provided their informed consent when they clicked the start button of the survey.

2.2. Evaluation Procedures

A survey designed by Farpour et al. according to current dysphagia literature and authors' professional experiences was used in the study (15). The necessary permission was obtained from the corresponding author of the study. The forward-backward translation process was followed to translate the survey into Turkish language. Two bilingual Turkish physiotherapists translated the survey from English into Turkish for forward translation. Then, two translations were examined and converted into a single survey with a consensus for synthesis part. A native English-speaking language expert who also speaks Turkish translated the survey from Turkish into English for backward translation. The backward version was compared to the original by a committee consisting of a methodologist, a language professional and the entire translation team, and the Turkish version was finalized. The backward translation was presented to the corresponding author for their confirmation, and the translation process was completed.

After the translation process, the survey was also tested for content validity by five participants who were university-affiliated experts with a minimum of 10 years of practice in the area of dysphagia. The experts were asked to score each question as "necessary", "insufficient", or "unnecessary", and also instructed to include additional question if desired. The scores of the experts were used to calculate a content validity index. The critical value for the content validity index was 0.73 for the five experts (22). The questionnaire was then distributed in April 2019 via Google forms. Participants were asked to answer the questions so that their responses reflected their knowledge, attitudes and practices as best as possible. If the questionnaire was not returned, a follow-up inquiry was sent every four weeks. Twelve weeks after the initial posting, the survey was closed and replies were analyzed.

The survey included questions that requested descriptive information from the participants and 22 items with closed-ended and open-ended questions (15). The descriptive information included the participants' ages, occupational experience, in what regions of the country they lived, and types of hospitals with which they are associated. The survey had three subgroup items that related to knowledge (11 items), attitudes (4 items), and practices (7 items). In the knowledge section, participants were asked to state whether they were familiar with the term "deglutition disorders" (Q1), and also asked to define the term. The question that related to the definition of deglutition disorders was scored as "correct" or "incorrect" by two different dysphagia specialists with 10 and 20 years of experience. If both of them scored the answer as "correct", it was scored as "correct". This

section also had 10 statements that participants were asked to define as "correct" or "incorrect". The statements were related to the oral phase of swallowing (Q2), the esophageal phase of swallowing (Q3), the pharyngeal phase of swallowing (Q4), head and neck problems (Q5), aging (Q6), dehydration (Q7), pulmonary infections (Q8), modifications (Q9 and Q10), and quality of life (Q11). The attitude section included three statements that participants were asked to define as "correct" or "incorrect". The participants were asked whether their professions and other professions can help to improve swallowing functions and also whether a multidisciplinary approach is essential for improving deglutition disorders. There was one open-ended question that asked which other professions can help to improve deglutition disorders. The practice section contained one yes/no question and six open-ended questions. In this section, participants were asked questions such as whether they had encountered any patients with deglutition disorders and also to explain the underlying etiology of deglutition disorders, how to diagnose these disorders, and how to manage them. For open-ended questions in the attitude and practice sections, each answer was included in the calculations of the frequencies.

2.3. Statistical Analysis

The International Business Machines Corporation Statistical Package for the Social Sciences (IBM-SPSS) for Windows version 20 was used for statistical analysis. Descriptive statistics were calculated as a number/percent for qualitative data, and mean, standard deviation, minimum and maximum values for quantitative data.

3. RESULTS

No linguistic problems were identified with the translated survey, and every item on the final version found to match the original version. All questions were also found to be necessary by the experts, and a minor modification was made and one open-ended question related to the definition of the term 'deglutition disorders' was added to the first question of the knowledge section based on their feedback. The content validity index was determined to be 0.89.

A total of 371 healthcare professionals were invited to participate in the present study, and 270 healthcare professionals responded (72.7% response rate) to the survey. The mean age was 34.33±10.42 years (min=22, max=64) with a mean professional experience of 11.53±10.29 years (min=1, max=42). There were 8 various professions. Physicians constituted the majority of the study population (n = 119, 44.1%). The participants' characteristics are presented in Table 1.

3.1. Knowledge

A total of 254 participants (94.1%) reported that they were familiar with the term 'deglutition disorders'. 244 participants (90.4%) defined the term correctly. The mean knowledge score was 9.14±1.08 (min=3, max=10). The number of correct answers for each questions was as follows: Q2: 262 (97%), Q3: 260 (96.3%), Q4: 253 (93.7%), Q5: 263 (97.4%), Q6: 261 (96.7%), Q7: 255 (94.4%), Q8: 244 (90.4%), Q9: 233 (86.3%), Q10: 166 (61.5%), and Q11: 268 (99.3%).

Table 1. *The descriptive characteristics of participants*

	Mean (SD)	min – max
Age (year)	34.33±10.42	22-64
Occupational experience (year)	11.53±10.29	1-42
	n	**%**
Region of the country		
Aegean	17	6.3
Blacksea	19	7.0
Central Anatolia	148	54.8
Eastern Anatolia	15	5.6
Marmara	27	10.0
Mediterranean	26	9.6
Southeastern Anatolia	18	6.7
Hospital		
University hospital	143	53.0
Governmental hospital	33	12.2
Educational hospital	53	19.6
Special education school	41	15.2
Profession		
Medical doctor	119	44.1
Physiotherapist	82	30.4
Nurse	34	12.6
Speech-language pathologist	16	5.9
Dietitian	10	3.7
Dentist	5	1.9
Child development specialist	3	1.1
Psychologist	1	0.4

n:number;SD: standard deviation; min: minimum; max: maximum

3.2. Attitude

A total of 223 (82.6%) participants defined their professions as a management team member of deglutition disorders. They all believed that other disciplines also have an important role in the management of deglutition disorders and supported multidisciplinary approach (n=270, 100%). Table 2 illustrates the participant responses to the question asking which other professions can help to improve deglutition disorders.

3.3. Practice

A total of 216 (80%) of participants had interacted with a patient experiencing deglutition disorders. The reported underlying etiologies of deglutition disorders were neurological disorders (n=145, 67.1%), cancer (n=33, 15.3%), structural problems (n=30, 13.9%), and psychiatric disorders (n=8, 3.7%). 212 participants (78.5%) reported at least one evaluation method used for the detection of deglutition disorders. A total of 64 (30.3%) of participants reported using standardized tests to evaluate patients with potential

deglutition disorders. 147 participants (54.4%) reported at least one treatment method used for the management of deglutition disorders. The most used evaluation and treatment methods for deglutition disorders were shown in Table 3. A total of 170 (78.7%) participants referred their patients to other professionals.

199 participants (73.7%) were interested in attending in a workshop on diagnosis, assessment and management of deglutition disorders.

Table 2. *The percentages of other professions who can help improve deglutition disorders according to participants*

	Participants (n = 270)	
Profession	**n**	**%**
Physiotherapist	218	80.7
Medical doctor	195	72.2
Speech-language pathologist	82	30.4
Nurse	65	24.1
Dietitian	63	23.3
Psychologist	34	12.6
Dentist	30	11.1
Child development specialist	14	5.2
Occupational therapist	10	3.7

n:number

Table 3. *The most used evaluation and treatment methods for deglutition disorders*

	Participants (n = 270)	
Evaluation methods	**n**	**%**
History taken	162	60
Clinical swallowing evaluation	83	30.7
Videofluoroscopic swallowing evaluation	45	16.7
Fiberoptic endoscopic swallowing evaluation	14	5.2
Endoscopy	9	3.3
Treatment methods	**n**	**%**
Nutritional recommendations	78	36.1
Exercise based therapy	78	36.1
Surgery	41	19
Sensory stimulation	21	9.7
Electrical stimulation	12	5.6
Medical treatment	8	3.7
Kinesiotaping	5	2.3
Appliance application	3	1.4
Psychotherapy	1	0.5

n:number

4. DISCUSSION

Standard management guidelines, which are based on the best available evidence, provide improvement in the quality of healthcare to patients (23). There is a general guideline on diagnosis and management of deglutition disorders published in 2014, which provides a practical approach (24). Despite general guidelines, defining the awareness, knowledge, attitude and practice of healthcare professionals within countries is also important. Thus, we aimed to determine the current knowledge, attitude and practice patterns pertaining to deglutition disorders among healthcare professionals in Turkey. Our survey shows that healthcare professionals have sufficient knowledge about deglutition disorders, adopt the necessity of multidisciplinary approach, 78.5% of participants reported that they used at least one method to detect deglutition disorders, and 54.4% used at least one treatment method for management of deglutition disorders. The majority of participants were interested in attending in a workshop on diagnosis, assessment and management of deglutition disorders.

The study population consisted of participants from all regions of Turkey working in university, governmental, and educational hospitals, as well as special education schools. Of those who were invited to participate, 72.7% actually responded to the survey. The response rate is quite high, however the study population could be increased to represent the healthcare professionals currently practicing in Turkey because Turkey is a big country. The difficulty of reaching a sufficient number of participants that will represent the whole country is a common problem in survey research due to several reasons (25). For instance, absence of adequate sampling lists, and random population sampling are limitations for conducting survey research. Therefore, we tried to reduce this potential handicap by selecting seven persons from each region of the country to coordinate the survey distribution. It may also be a strength of the current study because including participants from all regions of the country may enable us to generalize the study results to entire country. As we expected, the majority of participants (approximately 55%) were from Central Anatolia, where the population density is high and the capital city is located. Another remarkable characteristic of our study population was being relatively young participants despite the age limit was up to 64 years. The reason may be the need for computer and internet usage (26).

Deglutition disorders are associated with a higher incidence of complications including malnutrition, dehydration, aspiration pneumonia, which may result in increased length of hospital stay, healthcare expenditure, decreased quality of life, and negative interaction between patients and caregivers (2,3). Awareness of deglutition disorders is essential for the prevention of complications in the early stages of such disorders (3). While understanding such disorders has been on the rise (15,27,28), our study results also show that participants have sufficient knowledge about deglutition disorders. The responses that were most commonly incorrect were related to the modifications suggested for patients with deglutition disorders (i.e., adaptive equipment usage, food consistency arrangement), of which the accuracy was above 60% for these questions. It is a remarkable finding because knowledge about the definition, physiology, and complications of deglutition disorders was consistent, with accuracy between 90% and 99% on these questions; however, healthcare professionals were not as knowledgeable

regarding modifications suggested for patients with deglutition disorders. Therefore, healthcare providers could likely benefit from training related to suggested modifications for such patients.

Consistent with the fact that healthcare professionals in Turkey supported a multidisciplinary approach to the treatment of deglutition disorders, they also reported physiotherapists, medical doctors, speech-language pathologists, nurses, dietitians, psychologists, dentists, child development specialists, and occupational therapists as team members who could help improve deglutition disorders. Of the participants, 78.7% reported that they referred their patients to other professionals. The top five professions mentioned as important in the management of deglutition disorders were physiotherapists, medical doctors, speech-language pathologists, nurses, and dietitians. Healthcare professionals in Turkey were aware of the importance of the role of therapists, nurses, and dietitians, in addition to medical doctors, in the management of deglutition disorders. This is a promising finding because not only diagnosis but also rehabilitation and care services are very important in management of deglutition disorders. The participants did not state the branch of physicians (i.e., otolaryngologist, gastroenterologist, pulmonologist) to which the participants referred their patients as a weakness of our study results.

The most common underlying etiologies of deglutition disorders among the participants' patients were neurological disorders and cancer. In general, the evaluation methods used to diagnose such disorders were taking a history and clinical swallowing evaluation. While an accurate history and clinical swallowing evaluation are useful, they are only the first steps in the clinical decision-making process (24), and can not replace instrumental swallowing tests to evaluate airway protection mechanisms (if necessary). However, the use of instrumental swallowing tests including videofluoroscopic and fiberoptic endoscopic swallowing evaluation is dramatically low according to the current study results. The possible reasons may be i) lack of knowledge about instrumental swallowing assessments, ii) insufficient accessibility to required assessment equipment, iii) lack of standardized protocol, iv) lack of trained professionals. Additionally, none of the participants mentioned an individualized evaluation protocol while answering this question. For instance, a step-by-step swallowing evaluation should be undertaken as part of the clinical decision-making process (12). After taking a history and performing a clinical swallowing evaluation, instrumental swallowing evaluation can be performed (if necessary). However, the current study results could not show if the participants follow an individualized and standardized evaluation protocol. Therefore, it could be suggested to use more detailed questions regarding swallowing evaluation procedure of healthcare professionals in future studies.

According to the answers to the last part of practice section, 54.4% of participants used at least one treatment method, with the most common methods being nutritional recommendations and exercise-based therapy. However, the participants did not mention individualized therapeutic approaches, a result which is similar to those from previous studies (15,17,28,29). One possible explanation is that an individualized management protocol relies on individualized evaluation processes and clinical decision-making requires sufficient evaluation to guide proper treatment decisions (30). Thus, the management process of deglutition disorders relies on an appropriate assessment process to plan optimal, individualized (patient-centered) treatment recommendations (24,31). Another possible reason is the variety of healthcare professionals who evaluate deglutition disorders and are responsible for clinical decision-making process. Therefore, training in terms of treatment is also essential because approximately half of the healthcare professionals did not perform any treatment, and the other half did not mention individualized and/or standardized treatment approaches.

One remarkable finding is the parallelism between the most commonly mentioned professions responsible for the management of deglutition disorders (i.e., physiotherapists, speech-language pathologists, and dietitians) and the most common methods used for the treatment of deglutition disorders (i.e., nutritional recommendations and exercise-based therapy). Therapists (physical and speech-language therapists) were mentioned as important professions in the management of deglutition disorders in Turkey. Also, exercise-based therapy is the most common treatment option according to study participants. This result is similar to the trends in deglutition rehabilitation in the literature (17). The rehabilitation of deglutition disorders previously focused on postures, maneuvers and strategies to improve the swallowing safety and efficacy (17,32); however, recent studies in the management of deglutition disorders have moved to exercise-based approaches, including oral motor exercises (33), head lift exercises (34), expiratory muscle strength training (35), biofeedback (36), and the proprioceptive neuromuscular facilitation technique (37). Dietitians are also now considered members of the deglutition management team. In addition to their role in assessment, they help develop oral, enteral, and parenteral feeding regimes, determine appropriate interventions related to diet, meal patterns, nutritional supplements, food texture and liquid consistency modifications, etc. (38).

As a promising finding, the majority of participants were interested in attending a workshop on the diagnosis, assessment and management of deglutition disorders. This important result shows the awareness of the participants regarding their lack of knowledge and practice related to the evaluation and management of such disorders. Therefore, educational programs and improvements in healthcare professionals' knowledge and practice could help facilitate early diagnosis and better treatment of deglutition disorders.

This current study has also some limitations. Turkey is a big country with approximately 1500 hospitals. Therefore, further studies with larger samples will be designed with more detailed questionnaires especially focus on evaluation

and management of deglutition disorders to expand the study results. In addition, to provide a more accurate understanding of professionals' knowledge regarding deglutition disorders, case scenarios could be used or focus group interviews may be designed to show the number of patients with deglutition disorders and their management practices to better identify their actual practice patterns. Another limitation is that our study population did not receive any standardized training regarding online questionnaire. An online training program for participants to explain the survey questions could be performed before future survey studies.

5. CONCLUSION

The present study provides an overview of deglutition disorders from the perspective of healthcare professionals in Turkey. In conclusion, knowledge about deglutition disorders is high among healthcare professionals in Turkey according to the survey answers, and they believe that deglutition disorders are related to many professions and require multidisciplinary approach. Approximately 80% of the participants reported to use at least one evaluation method to detect deglutition disorders, however over 50% used at least one treatment method. The individualized clinical decision-making process was not mentioned in the current study. Therefore, more detailed questionnaires especially focus on evaluation and management of deglutition disorders should be developed and healthcare professionals could be trained to improve the quality of care for deglutition disorders in Turkey.

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Clinical and Experimental Health Sciences

Dynamic Thiol/Disulphide Homeostasis a Promising New Marker in the Diagnosis of Acute Appendicitis in Children: A Case Control Study of Acute Appendicitis and Abdominal Pain

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ABSTRACT

Objectives: One of the most common emergency surgery in pediatric surgery is due to acute appendicitis (AA). The diagnosis of AA is usually made using with the clinical score using clinical signs, symptoms, and laboratory tests. But symptoms and signs are not always typical, and this situation put clinician in a compelling situation. The range of misdiagnosis of AA is between 28-57 % between 2-12 years old children. Thiol/ Disulphide homeostasis is an important indicator of oxidative stress and inflammation. This study is aimed to evaluate and compare the feasibility of thiol/disulphide levels in pediatric patients with AA and abdominal pain (AP).

Methods: In this case-control study three different group established with 25 healthy participants (NCG), 25 patients with abdominal pain (PCG), and 25 with AA (AAG). Demographics, white blood cell count, neutrophil-lymphocyte counts, hemoglobin, platelet, mean platelet volume, C-reactive protein, total thiol (TT), native thiol, (NT) and disulphide (DS) levels measure through blood samples.

Results: According to our result, the level of NT were significantly lower in AAG when compared with NCG and PCG ($p<0.001$). DS levels were significantly higher in AAG than in NCG ($p<0.001$). CRP levels were significantly higher in both PCG and AAG than those of NCG $p<0.001$).

Conclusion: Thiol/disulphide homeostasis is a valuable method to examine acute appendicitis in the pediatric patients. Fluctuations of thiol/disulphide homeostasis could be used as a marker in daily clinical practice for diagnosis of appendicitis.

Keywords: Thiol/disulphide homeostasis, appendicitis, pediatric population, pediatric appendicitis

1. INTRODUCTION

Acute appendicitis (AA) is the most common emergency surgery in pediatric surgery department (1). Although the diagnosis of AA is often made with a clinical approach, symptoms, and signs which are not always typical, and diagnosis can be difficult in these patients (2). While the misdiagnosis rate is between 28-57% in the age range of 2-12, this rate rises to 100% under the age of two (3). Delayed diagnosis and treatment increase the risk of perforation in AA, which is related to increased mortality and morbidity. Various clinical scoring systems have been developed for diagnosis of AA, but these scoring systems are not routinely used in clinical practice (4). In some cases, different scoring systems are not accurate enough for diagnosis in terms of sensitivity and specificity.

Delays in diagnosis may cause perforation, which is an important complication of AA. Mortality significantly increases with perforation of AA due to intra-abdominal abscess (1). Especially in young children, complications, and uncommon events may emerge rapidly (5). Diagnosis should be made quickly and accurately to avoid the undesirable consequences and complications of AA (6).

Along with imaging techniques such as ultrasonography and computed tomography, easily accessible and applicable tests such as leukocyte count, neutrophil ratio, C reactive protein (CRP) and bilirubin levels also evaluated for diagnosis of AA (7). On the other hand, there are studies in which different markers such as calprotectin and leucine-rich alpha glycoprotein are used other than standard tests.

Pathophysiology of AA has been defined in detail; however, the factors affect the AA remains unclear (8). The progression of AA has been related to oxidative stress markers by de

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Oliveira et al. (9). The potential role of oxidative damage also been investigated by other studies as well (8).

Plasma thiols have a crucial role in radical scavenging activities in the body and therefore serve as an antioxidant through various mechanisms. Thiol-Disulphide Homeostasis (TDH) plays an important role in antioxidant status, detoxification, signal transmission, apoptosis, and enzymatic activities (10). Abnormal thiol-disulphide homeostasis is known to play a role in the pathogenesis of various diseases such as diabetes (11), cancer (12), cardiovascular diseases (13), rheumatoid arthritis (14), chronic kidney diseases (15), AIDS (16), Parkinson, Alzheimer's, Multiple Sclerosis and Amyotrophic Lateral Sclerosis (17). This homeostasis is thought to play a role in the etiopathogenesis of AA. The aim of this study was to investigate dynamic thiol-disulphide homeostasis, as a promising biomarker for children with AA and in children with AP.

2. METHODS

In this prospective case control study involving healthy volunteers, AA and, AP. Patients with the same demographics, children between 5-14 years old who had AP and were diagnosed with AA included 25 children with appendicitis, 25 children with AP, and 25 healthy volunteers who admitted a university hospital in Istanbul, Turkey between August 2018 – February 2020. This study has been approved by local Ethics committee with the number of (13/20). An informed consent form signed by one of the parents/guardians of the children. Participants with acute appendicitis called AA group (AAG), participants with AP called positive control (PCG), and healthy participants called negative control group (NCG).

Participants' demographics were recorded. White Blood cell count, neutrophil ratio, leukocyte ratio, hemoglobin levels, platelet count, mean platelet volume, CRP levels, TT, NT, and DS levels were recorded in all groups. Patients diagnosed with any acute appendicitis and complaining abdominal pain have been included in contrary patients with a history of vitamins or any antioxidant substance, and not signed consent form was excluded from the study.

Patients with AA were diagnosed based on clinical symptoms, physical examination, WBC count, NLR, CRP, abdominal ultrasonography (used to measure the appendiceal diameter and wall thickness). Patients with an appendiceal diameter greater than 6 mm and wall thickness greater than 2 mm were considered to have appendicitis (18). All patients with AA were confirmed by examination of pathological specimens after the operation.

Venous blood samples were taken to measure thiol/disulphide homeostasis parameters of all participants who were included in the study. Blood samples were withdrawn after 8 hours of fasting to measure thiol/disulphide blood levels. Serum samples centrifugated at 2500 x rpm for 10 minutes and stored at – 80 °C. Then the serum samples tested for thiol/disulphide levels. Complete blood count, biochemistry, and CRP levels of all participants were measured at the time they were enrolled in the study. The reduced DS bonds were reduced to form free functional thiol groups according to Erel et al. (19). Both thiols either reduced or native thiol groups were determined. The amount of dynamic disulphide bonds was found by determining half of the difference between total thiol and native thiol groups. After calculating the amount of native, total thiol, disulphide, disulphide/total thiol ratio, native thiol/total thiol rates, and disulphide/native thiol ratios were determined.

DS levels ratios were compared between AAG, PCG, and NCG. Also, the clinical relationship between NT and NT/TT levels, DS, DS/NT and DS/TT levels and clinical manifestations also investigated.

Descriptive statistics are presented as frequencies and percentages. The normality of continues variables was assessed with Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables shown as numbers with percentages and normally distributed continues variables mean ± standard deviation and means (with interquartile range) used. Intergroup comparison between continues variables has been estimated with variance analyses, the ANOVA and student t-test. For the comparison of categorical variables we preferred chi-sguare or Fisher exact tests. For statistical analyses Jamovi, and the SPSS software (ver. 22.0; IBM SPSS Inc., Chicago, IL) was used. A p value < 0.05 was considered as statistical significance.

3. RESULTS

In this study 75 participants were included. The demographics, biochemical results, and the thiol/disulphide homeostasis parameters of the NCG, PCG, and AAG are summarized in Table 1. The ages of the participant were 9.56 ± 2.38, 9.72 ± 3.45, and 9.64 ± 3.16 for NCG, PCG, and AAG respectively (Table 1). No statistically significant difference observed among the groups in terms of age and sex ($p>0.05$). On the other hand, thiol ratios were found statistically significant with white blood cell count, neutrophil ratio, leucocyte ratio, hemoglobin levels, platelet number, mean platelet volume ($p<0.005$) (Table 1).

The mean results of WBC levels, neutrophil ratios, lymphocyte ratios, hemoglobin (Hg) levels, platelet (Plt) count, the mean platelet volume (MPV), CRP levels, among the groups were statistically different ($p<0.05$) (table 2 and figure 1).

TT levels associated with the antioxidant profile. The mean results of TT levels measured were NCG, PCG, AAG were 0.472 ± 0.0217, 0.470 ± 0.0237, 0.371 ± 0.01333 mmol/L respectively (Table 1) and a statistically significant difference observed between, NCG and AAG ($p<0.001$), PCG and AAG ($p<0.001$) (Table 2 and figure 3). On the other hand, measured NT levels were NCG, PCG, AAG was 0.340 ± 0.0304, 0.332 ± 0.0223, 0.197 ± 0.0288 mmol/L respectively and a statistically difference obtained ($p<0.05$) (Table 1, 2 and figure 3). The mean results of DS levels were NCG, PCG, and AAG 0.0664 ± 0.0150, 0.0676 ± 0.0159, 0.0876 ± 0.0159 mmol/L, respectively which given in table 1 and 2. Disulphide levels

were significantly different among the groups (p<0.001) (Table 2 and Figure 3). Our measurement showed that the NT/TT (%) ratio for NCG, PCG, and AAG were 72.1 ± 5.74 %, 71.2 ± 5.81 %, 53.1 ± 7.96 % respectively which given in table 1 and 2. Among the groups a statistically significant difference was present (Table 2) (p<0.001).

In this study, DS/NT(%) ratios for NCG, PCG and AAG were respectively 19.7 ± 5.37 %, 20.6 ± 5.49 %, 46.4 ± 15.7 % and a statistically significant difference were found (p<0.001) (Table 1, 2 and Figure 3). DS/TT (%) ratios for NCG, PCG and AAG were 13.9 ± 2.87 %, 14.4 ± 2.91 %, 23.5 ± 3.98 % respectively which given in table 1 and 2. In the comparison of DS/TT levels, a statistically significant difference has been obtained given in table 2 (p<0.001).

Table 1. *The demographic and laboratory findings of groups.*

	NCG	PCG	AAG	P
N	25	25	25	
Sex (n, M/F)	13/12	13/12	13/12	
Age	9.56 ± 2.38	9.72 ± 3.45	9.64 ± 3.16	
WBC (x10³/µL)	7.61 ±1.57	11.8 ± 3.46	24.1 ± 7.34	<0.001
Neut %	62.3 ± 8.26	70.5 ± 17.3	85.4 ± 16.6	<0.001
Lymph%	23.0 ± 5.16	33.6 ± 8.51	41.9 ± 7.81	<0.001
Hb (g/dL)	14.9 ± 1.77	13.3 ± 1.16	12.0 ± 1.51	<0.001
PLT (x10³/µL)	277 ± 51.6	261 ± 46.4	189 ± 11.2	<0.001
MPV (fL)	8.62 ± 0.697	8.21 ± 1.15	6.26 ± 1.14	<0.001
CRP (mg/dL)	0.237 ± 0.0943	0.628 ± 0.485	7.56 ± 2.92	<0.001
Total Thiol (mmol/L)	0.472 ± 0.0217	0.470 ± 0.0237	0.371 ± 0.01333	<0.001
Native Thiol (mmol/L)	0.340 ± 0.0304	0.332 ± 0.0223	0.197 ± 0.0288	<0.001
Disulphide (mmol/L)	0.0664 ± 0.0150	0.0676 ± 0.0159	0.0876 ± 0.0159	<0.001
Disulphide /Native Thiol (%)	19.7 ± 5.37	20.6 ± 5.49	46.4 ± 15.7	<0.001
Disulphide /Total thiol (%)	13.9 ± 2.87	14.4 ± 2.91	23.5 ± 3.98	<0.001
Native Thiol/Total Thiol (%)	72.1 ± 5.74	71.2 ± 5.81	53.1 ± 7.96	<0.001

NCG: Negative Control Group, PCG: Positive Control Group, AAG: Acute Appendicitis Groups, WBC: White Blood Count, Neut: Serum Neutrophil Ratio, Lymph: Serum Lymphocyte Ratio, Hb: Serum Hemoglobin Levels, MPV: Mean Platelet volume, PLT: Serum Platelet, CRP: C-Reactive Protein

Table 2. *One-way ANOVA (Welch's) of laboratory values and demographics.*

	F	df1	df2	p
Age	0.0187	2	46.7	NS
Sex	0.0000	2	48.0	NS
WBC	69.8762	2	38.4	<0.001
Neut %	19.5650	2	42.3	<0.001
Lymph%	52.2361	2	45.4	<0.001
Hb	18.1931	2	46.5	<0.001
PLT	58.6826	2	35.1	<0.001
MPV	39.1048	2	45.1	<0.001
CRP	84.2200	2	33.2	<0.001
Total Thiol	280.6810	2	44.6	<0.001
Native Thiol	202.2764	2	47.0	<0.001
Disulphide	14.1882	2	48.0	<0.001
Disulphide /Native Thiol	32.6414	2	44.2	<0.001
Disulphide /Total thiol	53.4055	2	47.2	<0.001
Native Thiol/Total Thiol	53.4055	2	47.2	<0.001

NCG: Negative Control Group, PCG: Positive Control Group, AAG: Acute Appendicitis Groups, WBC: White Blood Count, Neut: Serum Neutrophil Ratio, Lymph: Serum Lymphocyte Ratio, Hb: Serum Hemoglobin Levels, MPV: Mean Platelet volume, PLT: Serum Platelet, CRP: C-Reactive Protein

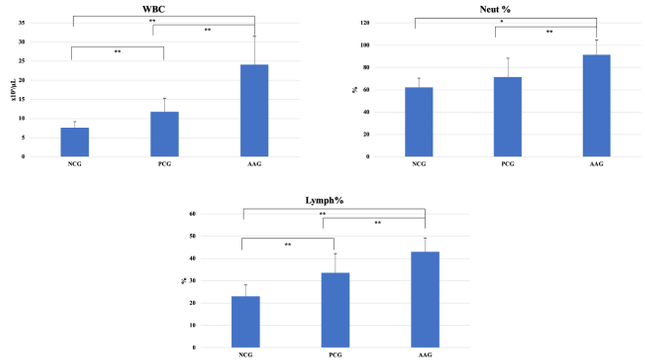

Figure 1. *Comparison white blood cell count, neutrophil ratio, and lymphocyte ratios. *p<0.05, **p<0.001. NCG: Negative Control Group, PCG: Positive Control Group, AAG: Acute Appendicitis Groups, WBC: White Blood Count, Neut: Serum Neutrophil Ratio, Lymph: Serum Lymphocyte Ratio.*

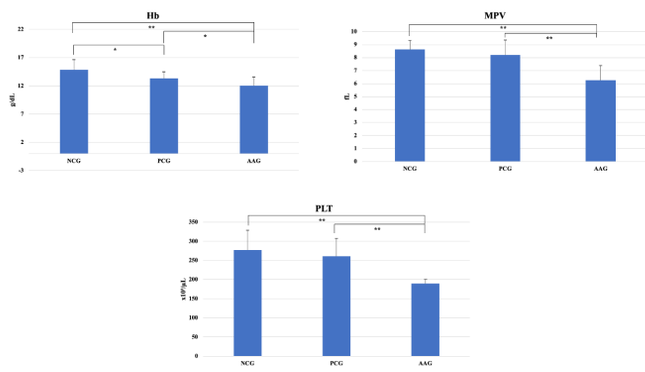

Figure 2. *Comparison serum hemoglobin, mean platelet volume, and platelet levels *p<0.05, **p<0.001. NCG: Negative Control Group, PCG: Positive Control Group, AAG: Acute Appendicitis Groups, Hb: Serum Hemoglobin Levels, MPV: Mean Platelet volume, PLT: Serum Platelet*

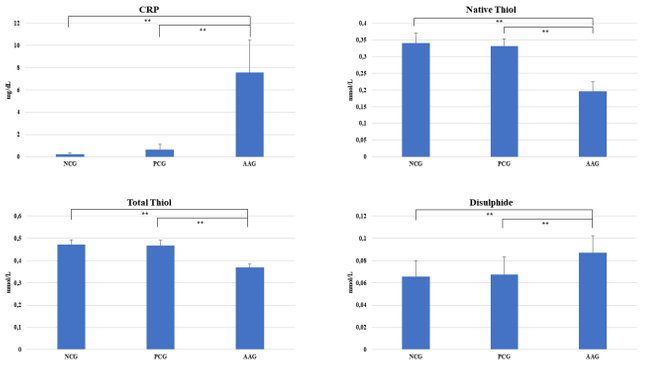

Figure 3. *Comparison serum CRP, native thiol, total thiol and introduction *p<0.05, **p<0.001. CRP: C-Reactive Protein, NCG: Negative Control Group, PCG: Positive Control Group, AAG: Acute Appendicitis Groups.*

4. DISCUSSION

In clinical practice, the diagnosis AA is still a big challenge for physicians. A definitive diagnosis would prevent unnecessary surgery (20-23). Even with sophisticated diagnostic methods, the rate of misdiagnosis of AA and abdominal pain in children varies between 28 % to 100 % (21). The importance of oxidative stress markers has an increasing interest in addition to inflammatory markers in AA diagnosis. Therefore, oxidative markers such as thiol and disulphide levels could be used as promising indicators for AA in children (24–26, 28-29).

In literature, some researchers have pointed out AA patients have decreased levels of thiol groups when compared with control (8,24,25,30). Oxidative stress causes an increase in DS levels and decrease in thiol levels. Recent studies investigated this change and compared with healthy individuals as a control group, which might be misleading. In this case control study of AA, AP, and control group, we tried to discriminate the difference of similar cases among 3 groups.

Elmas et al. has investigated the evolvement of thiol/disulphide ratio in AA group and control and found a significant difference between control and AA group (p<0.05) (30). Our findings were coherent with results presented by Elmas et al. (30). However, in our study, AP, and AA, were investigated through thiol/disulphide homeostasis perspective. Abdominal pain is one of the most common clinical findings of AA and discrimination of AP and AA is a challenge for physicians. According to our results, there is statistically significant difference between AP and AA groups in terms of thiols/disulphide levels (Figure 3).

Also, Yilmaz et al., Dumlu et al. and Ozyazici et al. reported that thiol/disulphide homeostasis was shifted towards disulphide side in AA patients (8,24,25). Our results showed that TT, NT, and DS levels were also impaired, and statistically significant difference has been present among the groups (p<0.001), which was favorable to findings in the literature.

Ozyazici et al. stated that increase of DS/NT ratio is related to the severity of inflammation, and it is possible to conclude that this ratio could be related with the progression of AA and could be used as a marker of AA together with other commonly used markers.

In our study the levels of NT and TT and the NT /TT ratio are lower in patients with AA as compared to AP and healthy individuals. Besides, it is also investigated for the first time that DS level and DS/NT and DS/TT ratios in AA, AP, and healthy patients. In other words, thiol/disulphide homeostasis was found to shift towards disulphide side in AA group.

There are several limitations to our work. We evaluated a relatively small sample size in one center. On the other hand, common diagnostic tools used for a scoring system such as procalcitonin, hs-CRP, ultrasonography, computerized Tomography, etc. have not been compared with thiol/disulphide assay. Studies which investigate the relationship between thiol/disulphide assays and other diagnostic tools should be accomplished for in future studies.

5. CONCLUSION

The early diagnosis acute appendicitis in pediatric population is hard to achieve in every cases due to the different feature of the disease. Novel instruments or biomarkers may prevent complications and give clinicians early notification about red flags. Our results revealed that thiol/disulphide homeostasis disturbed in children with AA. This shift towards the formation of disulphide may serve as a novel biomarker in AA. However, further studies are required to optimize this assay.

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Clinical and Experimental Health Sciences

Evaluation of Stress Levels of Dental Implants in Different Macrogeometry in Type 2 Bone: A Finite Element Analysis

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ABSTRACT

Objective: Implant geometry has an impact on the initial implant stability in the surrounding bone, stress distributions, and long-term success. The purpose of this finite element study was to measure and compare the stress values formed during the stepwise placement of conical and cylindrical implants in the Type 2 bone.

Methods: Conical and cylindrical implants (3.75-mm in diameter, 10-mm in length) were planned to be placed in the Type 2 bone. Stresses during insertion of the implants with clockwise torque of 450 N were measured 0.5-, 1-, and 1.5-mm distance from the implant and 2-10 mm depths between two millimeters apart. Maximum and minimum principal stresses and von Mises stresses in the cortical and trabecular bone were evaluated with a three-dimensional finite element analysis.

Results: The conical implant was created higher stress values than the cylindrical implant in the same condition, and the cortical bone showed higher stresses than the trabecular bone during the placement of both implants. Besides, the stress values were decreased as the depth increased and the distance from the implant decreased, as the depth increased from 2-mm to 10-mm and the distance from the implant decreased from 1.5-mm to 0.5-mm.

Conclusion: When the stresses generated in the cortical and trabecular bone surrounding the implant were evaluated, the cylindrical implant was found to be more advantageous than the conical implant of the same length and diameter.

Keywords: dental implant, dental implantation, dental stress analysis, finite element analysis

1. INTRODUCTION

The concept of osseointegration, which is a sign of implant success, was first described by Branemark and defines structural and functional linkage between living bone tissue and the surface of the implant (1-3).

Successful osseointegration depends on many factors. The first of which is the bony dependent factors such as bone quality and density, a width of the bone around the implant. Another factor is the macro-geometry of the implant because the implant geometry may influence the initial implant stability and stress distributions in the surrounding bone (4-8). The surgical technique is also an effective factor in successful osseointegration and plays a role in the success of osseointegration by acting in the implant placement process and final fixation. In addition to the surgical technique, the placement process of implants also plays a role in the success of osseointegration by affecting the stress distribution in the surrounding structures. It is very important to place the implants with controlled insertion torque in the implant slots. Because this process supports bone healing, helps to minimize stress distribution, and prevents bone fracture (9-13).

The stress in the cortical and trabecular bones around the implant is known to play an important role in the success of the implant. The response of bone healing or resorption is directly related to the stress within the bone, as stated in Wolf's theory (14,15). Low-stress levels around the implant may cause disuse atrophy; conversely, abnormally high-stress levels can cause pressure necrosis and failure of the implant due to this necrosis (16,17). Because of these facts, successful osseointegration can be achieved by optimization of stress and biomechanical interaction between bone and implant. The optimization of the stress in the surrounding bone during implant insertion was thought to increase clinical success. Damage to the bone at the microscopic level, along with increased stress, affects bone formation and remodeling, leading to bone resorption and decreased success of the osseointegration process, thereby reducing implant success (18). Understanding of relations between stress distribution in the surrounding bone, implant

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geometry, and osseointegration principles is so important for successful implant applications. In the literature, studies evaluating the stresses that occur during implant placement and the effects of different implant geometries on these stresses are insufficient (19,20).

The purpose of this this research was to measure and compare the stress values formed during the stepwise placement of conical and cylindrical implants in the Type 2 bone in mandibular posterior jaw models at each 2-mm depth and 0.5-mm to 1.5-mm distance from the implant, using three-dimensional finite element analysis (3D FEA). The hypothesis was: In implants of the same length and diameter applied to bones with the same properties, the implant with cylindrical macro-geometry will create less bone stress than the one with conical macro-geometry.

2. METHODS

In this experimental study, FEA was used to analyze stress around cylindrical and conical implants caused by placement in the mandible. Implants and bone structures were modeled on a personal computer (Intel Xeon® CPU 3.30 GHz, USA) using a 3D FEA program (ALGOR Fempro, ALGOR, Inc. USA) from computed tomography (CT) images. Data attainment for bone dimensions was based on CT images. According to the classification system of Lekholm and Zarb, a mandibular bone model representing Type 2 bone was selected (21). The jaw section modeled presented with a height of more than 10-mm and a width of more than 7-mm, representing the section of the mandibular molar region. Gingival soft tissue was not modeled. Trabecular bone was modeled as a solid structure in the cortical bone (Fig. 1a, 1b).

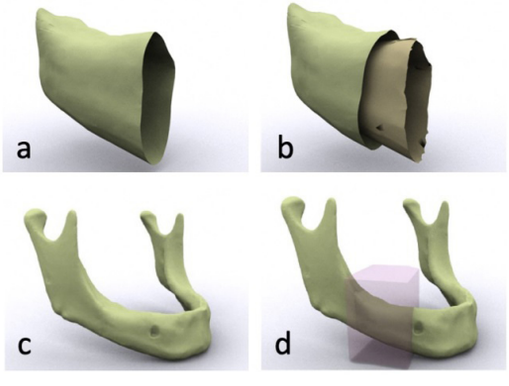

Figure 1. *a,b. Cortical and trabecular bone solid structures. c,d. Mandibular model and selection of the study model with Boolean operation*

The thickness of cortical bone created in the crestal region was 2.0-mm, and 1.0-mm in the buccal and lingual regions, with Rhinoceros 4.0 (Robert Mcneel & Associates, USA). The mesiodistal and inferior planes were not covered by cortical bone. When aggregating the components, Boolean operations were used to subtract the mandibular posterior region from the modeled mandible (Fig. 1c, 1d).

Implants were created with two different geometries. Using Rhinoceros 4.0, cylindrical and conical implant models were constructed, followed by meshing. The length (L) and diameter (D) of the implants were assumed to be L: 10 mm and D: 3.75 mm. For the implants, V-shaped threads were prepared, and the thread pitch was designed to be 0.6-mm. An initial cylindrical insertion cavity diameter was created less than the inner diameters of the cylindrical and conical implants.

All materials used in modeling were assumed to be isotropic, homogeneous, and linearly elastic (19,22-24). The elastic properties of the materials such as Young's modulus (E) and Poisson ratio (μ) were taken from literature, and these parameters were summarized in Table 1. After the materials data were defined in the system/software (Rhinoceros 4.0), models have mashed with 10-node-tetrahedron elements. A finer mesh was used around the implants. In cylindrical implant models 399 472 – 427 088 elements and 73 852 – 76 272 nodes, and in conical implant models 430 281 – 464 151elements and 79 315 – 82 497 nodes were used.

Table 1. *Material properties of materials used in the 3D FEM models.*

Materials	Young's modulus (Gpa)	Poisson ratio (μ)	References
Cortical Bone	13.0	0.3	(24)
Trabecular Bone	1.37	0.3	(18)
Titanium	102	0.3	(24)

An important criterion for simulating implant insertion technique is the boundary. The applied torque is positioned at the top of the implant. To analyze the model standing in space, it was fixed from peripheral points to prevent rigid body motions of assembly, and the boundaries were defined. The rigid implant was only allowed to rotate and move downward in the Z direction. A clockwise torque of 450 N mm was applied to the top of the implants. The insertion process was modeled in a step-wise manner with a torque applied to the implants that do not change with time.

After the torque application, stress values were measured at each depth of 2-mm and distances of 0.5-, 1-, and 1.5-mm from cylindrical and conical implants within the cortical and trabecular bone. These stress values were measured in the distal, mesial, buccal, and lingual aspects of the implant and evaluated by taking the average of these values. The analyses were made by von Mises, maximum (tensile stress), and minimum (compressive stress) principal stress in the cortical and trabecular bone around the implant system. Data were indicated numerically, color-coded, and compared among the models.

The descriptive statistic general linear model was used for the comparison of the stresses formed for both implants. Evaluations and comparisons of both implant systems were done with univariate analysis.

3. RESULTS

The von Mises stress, which is the maximum principal and minimum principal stresses for conical and cylindrical implants, were evaluated within the trabecular and cortical bone. Stress values were measured along with implants each 2-mm and three different distances from implants. The stress distributions within cortical and trabecular bone for each stage of insertion are shown in Figure 2 with color-coding.

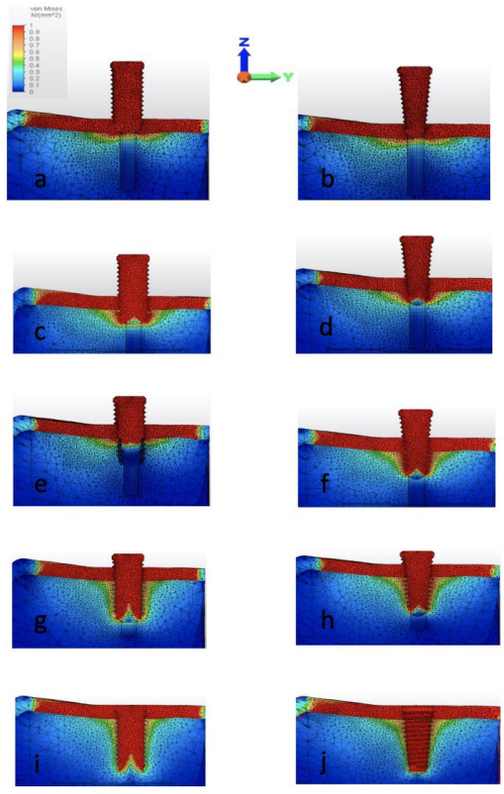

Figure 2. *von Mises stress with color coded projections of each 2-mm depth of cylindrical and conical implants. The stress distribution in the bone at a depth of 2-mm is (a) and (b), the stress distribution at the depth of 4-mm (c) and (d), the stress distribution in the bone at a depth of 6-mm is (e) and (f), the stress distribution in the bone at a depth of 8-mm is (g) and (h) and the stress distribution in the bone at a depth of 10-mm is (i) and (j)*

The implant design tended to obviously influence the bone stresses of both bone components. When comparing two different implant geometries, the conical implant created more von Mises stress than the cylindrical implant in the cortical bone at all depths. In the trabecular bone, although stress values fluctuate as the depth increases, at 10-mm depth, which is exactly located in the insertion hole, the conical implant was found to have more stress than the cylindrical implant. Maximum and minimum principal stress values also show similar results (Table 2 and 3).

The maximum stress values for both implants were observed in the cortical bone adjacent to the implant surface. The von Mises stress in the cortical bone is significantly higher than that in the trabecular bone for both implants (Table 2 and3). For instance, whereas the average stress value was 15.75 MPa when the conical implant was 2-mm in the cortical bone and 1-mm away from the implant, the stress value in the trabecular bone at the same conditions was 0.97 MPa. The highest average von Mises stress in the cortical bone concentrated at 0.5-mm away from the conical implant and the average value was 32.18 MPa. Similar results were obtained for maximum and minimum principal stress values (Table 3)

Table 2. *Average stress values during the placement of the cylindrical implant into the cortical and trabecular bone (MPa)*

	Distance from implant	2 mm	4 mm	6 mm	8 mm	10 mm
		von Mises stress				
Cortical bone	0.5 mm	21.84	17.70	17.56	15.29	16.03
	1 mm	11.18	9.63	9.70	8.52	9.67
	1.5 mm	6.60	5.88	5.97	5.22	5.74
	Maximum principal stress					
	0.5 mm	12.90	10.32	10.15	8.75	9.44
	1 mm	6.67	5.64	5.64	4.91	5.61
	1.5 mm	3.85	3.35	3.43	3.01	3.30
	Minimum principal stress					
	0.5 mm	-12.30	-10.10	-10.11	-8.89	-9.06
	1 mm	-6.44	-5.47	-5.55	-4.92	-5.49
	1.5 mm	-3.76	-3.42	-3.45	-3.00	-3.32
Trabecular bone	von Mises stress					
	0.5 mm	1.09	0.97	1.37	0.75	0.72
	1 mm	1.05	0.74	1.03	0.62	0.62
	1.5 mm	0.88	0.61	0.77	0.52	0.53
	Maximum principal stress					
	0.5 mm	0.64	0.58	0.77	0.43	0.41
	1 mm	0.61	0.43	0.59	0.35	0.36
	1.5 mm	0.51	0.35	0.44	0.30	0.30
	Minimum principal stress					
	0.5 mm	-0.61	-0.53	-0.80	-0.43	-0.42
	1 mm	-0.60	-0.42	-0.60	-0.35	-0.35
	1.5 mm	-0.50	-0.34	-0.20	-0.29	-0.30

Table 3. *Average stress values during the placement of the conical implant into the cortical and trabecular bone (MPa)*

	Distance from implant	2 mm	4 mm	6 mm	8 mm	10mm
		von Mises stress				
Cortical bone	0.5 mm	32.18	28.03	25.48	19.56	17.48
	1 mm	15.75	14.12	12.95	10.65	10.17
	1.5 mm	8.89	8.35	7.62	6.31	6.25
	Maximum principal stress					
	0.5 mm	25.79	16.42	14.70	11.33	10.04
	1 mm	11.91	8.22	7.59	6.12	5.85
	1.5 mm	6.31	4.84	4.46	3.60	3.63
	Minimum principal stress					
	0.5 mm	-17.92	-15.92	-14.69	-11.23	-10.13
	1 mm	-8.92	-8.07	-7.35	-6.17	-5.89
	1.5 mm	-5.13	-4.79	-4.33	-3.67	-3.58
Trabecular bone	von Mises					
	0.5 mm	1.04	1.29	1.01	0.90	0.77
	1 mm	0.97	1.02	0.82	0.74	0.67
	1.5 mm	0.86	0.80	0.66	0.61	0.56
	Maximum principal stress					
	0.5 mm	0.61	0.74	0.58	0.52	0.45
	1 mm	0.56	0.58	0.48	0.44	0.39
	1.5 mm	0.50	0.46	0.38	0.35	0.33
	Minimum principal stress					
	0.5 mm	-0.58	-0.75	-0.58	-0.51	-0.44
	1 mm	-0.56	-0.58	-0.47	-0.42	-0.38
	1.5 mm	-0.49	-0.46	-0.38	-0.35	-0.32

As the distance from the implant surface decreased, the stress values formed in both the cortical and trabecular bones diminished significantly. The highest stress values in three stresses obtained in the study were measured at a distance of 0.5-mm from the implant in cortical bone, and the stress values in the trabecular bone support this result (Table 2 and 3).

As the implant is placed into the insertion hole, that is, as the depth of the implant in the bone increases, the stress values affecting the trabecular and cortical bone decrease. This result was common for both implants and all types of stress. Values at a depth of 2-mm are significantly higher than values at 10-mm (Table 2 and 3). For instance, the average von Mises stress value in the cortical bone at 0.5-mm distance from the cylindrical implant was found to be 21.84 MPa when measured at 2-mm depth. At a depth of 10-mm, the value decreased to 16.03 MPa (Table 2). Similarly, Table 2 and 3 show that the maximum and minimum principal stress values decrease from 2-mm depth to 10-mm depth.

The minimum and maximum principal stress values, which express the compression and tension, were also high during the placement of the conical implant in the bone, similar to von Mises stress (Table 3).

4. DISCUSSION

Implant stability is explained by the concept of primary and secondary stability. Primary stability describes the mechanical connection between the bone-implant after implant placement and hinges on the implant's micro-mobility, bone density, implant placement, and implant design (25,26). Bone strains and stresses function in the threshold range of bone modeling, and modeling creates a stronger bone structure. On the other hand, strains and stresses surpass the range, micro damages and cracks in the bone matrix occur, and bone resorption occurs inevitably (26,28). Direct mathematical approaches, especially FEA is widely used as it has the advantage of measuring stress, strain, and deformation in bone structures (29,30).

To the best of our knowledge, few studies have used the FEA models to simulate dental implant insertion and the specific issue of primary stability (20,31). It has been stated that a torque of 300 to 500 N was observed to be suitable for implant placement. In the current study, similar to other studies, we planned for measurement and comparison of stresses occurring during cylindrical and conical implants with 450 N torque in type 2 bone. We can evaluate and compare the stress independently and objectively by keeping the diameter and length of implant constant.

The stress distribution in the bone is multifactorial and among these, macro-geometry is one of the most important factors (6,19,31,32). The understanding of the effects of different geometries in different bone qualities is important in the selection of implants and long-term success (16). The earlier implants were produced with a cylindrical shape. However, this design has not been yielded a successful result in all situations (7,8). Conical implants were introduced for immediate insertion into an extraction socket due to the capacity of engaging the bone walls and minimizing the need for bone graft procedures (33,34). Despite the developments of new implant models, the implants used today are gathered under two main designs, cylindrical and conical; and, minimizing the stress distribution they create in the bones is one of the main issues of dental implantology. Using FEA, the previous studies compared the von Mises stress concentrations of conical and cylindrical implant shapes at the site of implant entry into bone, and they reported that cylindrical implants were preferred to the conical implant (35,36). Patra et al. and Himmlova et al. also found similar results in their studies (37,38). As Siegele and Soltesz also compared cylindrical, conical, stepped, screw, and hollow cylindrical implant shapes, the researchers reported that

implant shapes lead to significant variations in stress distribution in the bone under loading (39). By evaluating the stress values of the two most commonly used implant geometries placed in type 2 bones in this study, we aimed to create a question mark in the minds of clinicians about the circumstances in which conical or cylindrical implants should be preferred. The results were found to be parallel to the previous studies that the conical implants had high values in von Mises stress compared with cylindrical implants into the bone.

There are many studies in the literature that optimize the shape of the implant surface and thread and change the fixture design in order to minimize crestal bone resorption by reducing the stress value in cortical alveolar crest (18,40,41). In most studies, it has been found that implant type and length do not affect the stress distribution in the cortical bone (19). Contrary to these studies, in the current study, the von Mises stresses during implant insertion into the cortical bone were significantly higher than in the trabecular bone for all models. In the cylindrical implant model, stress levels measured at a depth of 2-mm and a distance of 0.5-mm were found 21 times higher than the value of von Mises stress occurring in the cortical bone. This result may be due to the fact that the cortical bone has a higher modulus of elasticity (Young's modulus) than the trabecular bone and thus is stronger and more resistant to deformation (15,42,43).

In many finite element studies in the literature; It was determined that the highest von Mises stress values occurred in the bone region adjacent to the implant, while the stress values decreased in the apical region (19,24,38,42,44). Similar to previous finite element analysis studies, in the present study, the lowest von Mises stress values for both implant types were obtained from the apical region.

Up to 1.5-mm bone loss around osseointegrated implants within one year after implantation, and 0.2-mm bone loss within the following years were accepted within the physiological limits (45). In view of this amount of resorption and the physiological limitations of the bone feeding around the implant, the width of the implanted bone should be at least 2-mm greater than the implant diameter (3). One of the factors that can create the resorption process or disturb nutrition is the stress that occurs as a result of implant placement. Therefore, the stress values occurring at 0.5-, 1-, and 1.5-mm distance from the implant were measured and evaluated at all depths in this study. It was observed that in both cortical and trabecular bone, when the implant was removed from all depths, stress values decreased in all three types of stress. These results are similar to previous studies (32). Considering all these results, it has been understood that the width of the bone where the implant will be placed should be wider than the implant.

Clinically, bone height, width, and density are not standard in every patient. However, this study assumes that these parameters are the same for both implants. This assumption has brought the advantage of a clear understanding of the pressures created by the implants at different depths thanks to these constant parameters.

Since there is limited data in the literature about staged implant placement and stress measurement, the stress values measured at 2-mm to 10-mm depths during implant placement have been compared with previous studies investigating the implant length-stress relationship. Some of these studies have shown that the failure rate of short implants is higher than implants with a length of more than 10-mm (46). The previous researches reported that increased implant length reduced von Mises stress in both trabecular and cortical bone under loading (47,48). Steenberge et al. and Horiuchi et al. reported that an implant of at least 10-mm in length should be preferred for success (49). Based on these data, the stress results of 10-mm long implants were evaluated in the current study. Koca et al. (50) in their study evaluating the stress distribution of implants placed at five different bone levels (4-mm to 13-mm), determined the maximum stress value of von Mises at 4 – and 5-mm bone levels and the lowest stress level at 13-mm bone levels.

When the results obtained from the implant in two different geometries are examined in the current study, it has been observed that as the depth of the implant increases, the basic stress values decrease similarly to the previous studies. Although both implants show fluctuations in the trabecular bone strain and pressure strain during implantation, the stress value at a depth of 10-mm is less than 2-mm. In light of these results, the selection of the longest implants allowed by bone height is predicted to help minimize stresses and failures in the bones. For these reasons, modeling of the bone as a nonhomogeneous regenerative and anisotropic tissue that can respond to stress under load in future finite element analysis studies will enable those studies to present results closer to the clinical situation.

5. CONCLUSION

Within the limitations of these finite element analysis studies, when parameters such as the diameter of the implants, the length of the implant, and the density of the bone to which it is placed were kept constant, the following conclusions were obtained.

1. The conical implants caused more stress than the cylindrical implants.
2. The stress values decreased as the distance from the implant increased at all depths in the cortical and trabecular bone.
3. During the implantation of the conical and cylindrical implants in the bone, the stress value decreases as the depth increases at 0.5-mm to 1.5-mm distance from the implant.
4. In all the models, it was found that the stress in the cortical bone was more than that in the trabecular bone.

5. The highest stress values were observed in bone structures adjacent to the implant neck.

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Clinical and Experimental Health Sciences

Illness Perception of Turkish Patients Undergoing Hemodialysis and Peritoneal Dialysis: Similarities and Differences

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ABSTRACT

Objective: The aim of this study was to determine the illness perception of Hemodialysis (HD) and Peritoneal Dialysis (PD) patients having end-stage renal failure.

Methods: This cross-sectional study was carried out in Organ Transplantation and Dialysis Hospital. Data were collected between January-June 2016. The study was conducted with a total of 93 individuals including 45 patients undergoing PD and 48 patients undergoing HD between the indicated dates. An information form and Illness Perception Questionnaire-Revised (IPQ-R) were used as data collection instruments. Independent samples t test, one way anova and pearson correlation analysis were used to assess data.

Results: Among the patients, mean duration of disease was 81.4±77.7 (HD: 82.7±93.5, PD: 80.1+60.1) months, mean duration of dialysis was 57.7±58.3 (HD: 58.6±67.0, PD: 56.8±49.4) months and mean number of comorbid diseases was 1.4±0.6 (min: 1.0, max: 4.0). 93.5% of the patients had familial support (HD: 91.1%, PD: 95.8) and 69.9% (HD: 37.8%, PD: 100.0%) had taken a training about the disease and its treatment from healthcare professionals. It was also found that mean scores of PD patients from IPQ-R subscales including personal control, illness coherence and timeline acute/chronic were found to be significantly higher than HD patients ($p<0.05$).

Conclusion: As a result of this study, it was determined that HD patients perceived their illnesses as more challenging compared to PD patients. Therefore, especially HD patients may be given disease-related trainings with the onset of their treatment process and a psychological support may be recommended to accept their chronic diseases.

Keywords: Hemodialysis, illness perception, peritoneal dialysis, Turkish patients

1. INTRODUCTION

Illness Perception in Turkish patients undergoing Hemodialysis (HD) and Peritoneal Dialysis (PD) Chronic Kidney Disease (CKD) is a common public health problem both in the world and in our country. Renal replacement therapies are applied to patients who have been diagnosed with end-stage renal disease. According to 2018 summary report of Turkish Society of Nephrology, a total of 63.835 patients have received renal replacement therapies by the end of 2018; and among these patients, 60.643 were HD and 3.192 were PD patients, and these numbers were indicated to be increasing (1). CKD is a chronic disease requiring compliance to disease itself and to the adverse effects of treatment. This disease often affects daily lives and freedom of the individuals in a negative way. Some patients perceive their diseases negatively and they declare that their freedom is limited. Negative perception of illness causes experiencing psychological problems such as unhappiness and depression more intensely (2). Dialysis patients see themselves as dependent and their conditions as desperate due to the progressive nature of their diseases and difficult and restrictive treatment methods. Feeling of despair involves negative expectations for the future and it is closely associated with depression and suicidal ideation (3). Despite that, it was reported that positive perception of disease by CKD patients positively affected self-esteem and autonomy (4). Illness perception is defined as cognitive aspect of disease state. Patients try to explain their diseases in the light of their personal experiences, knowledge, values, beliefs and needs. Patients' individual interpretations regarding disease, their perception and evaluation and their emotional and behavioral responses are the factors determining their coping styles, their psychosocial stress and development of psychiatric disorder and their quality of life (5). Emotional responses shown towards the disease vary from individual to individual. Responses may show differences based on the meaning of affected organ or loss-of-function for the individual, type of disease, age of the individual, developmental period, nature of personality, beliefs and attitudes, defense mechanisms and coping patterns, their previous experiences and attitudes of their relatives regarding the disease (6). The course of disease was found to be better in individuals who had a high perception of internal control (5).

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Chronic Kidney Disease itself as a chronic disease and its treatment cause compulsory experiences in the lives of individuals (7). The differences between HD and PD treatments may lead patients to have different experiences in their illness perception and management skills (8).Recognition of these differences by the healthcare professionals may facilitate their understanding of patients, and it may be guiding while determining their approaches. Some preventive practices may be planned in order to protect mental health of dialysis patients by acquiring information about their illness perception styles (9). These practices are considered to affect life quality of dialysis patients and the course of disease in a positive manner.

In this study, it was aimed to identify the differences in illness perception styles of patients undergoing HD and PD and to shed a light on future protective mental health practices through these data.

Hypotheses:

H_0: There is no difference between illness perceptions of HD and PD patients.

H_1: There is a difference between illness perceptions of HD and PD patients.

2. METHODS

In this cross-sectional study, it was aimed to identify illness perceptions of HD and PD patients suffering from end-stage renal failure.

2.1. Sample

This cross-sectional study trying to reach the full course in the time in the drawing and taking the accepted study was carried out in the Organ Transplantation and Dialysis Hospital of a University Faculty of Medicine in Turkey. This Organ Transplantation and Dialysis Hospital is a district hospital and accepts patients from many cities within the Central Anatolia region. Thus, the common feature of these patients is that all of them were living in Central Anatolia region. In this hospital, HD patients generally undergo HD treatment 3 times a week. PD patients admit for control regularly every month. Data of the study were collected between January-June 2016. All HD patients who were registered during the indicated dates were reached during the study. Again, 45 PD patients, who had similar characteristics with the HD patients included during the same dates for age, sex, education level, disease duration, diagnosis time and the number of comorbid diseases, were included in the study. The number of PD patients registered in the hospital was 121. The study was conducted with a total of 93 individuals including 45 patients undergoing PD and 48 patients undergoing HD between the indicated dates. An attempt was made to reach all patient. 40% of the sample reached. One PD patient was not included in the study due to the lack of written consent.

Inclusion criteria of the study were being 18 years and older, being voluntary to participate in the study, not having any physical and mental disability that may prevent participation in the study and being able to read and understand Turkish. Data of the study were collected by a questionnaire form which was generated to identify descriptive and disease-specific characteristics of the patients and the Illness Perception Questionnaire-Revisedto measure perception of disease. Data were collected through face-to-face interviewing method. Interviews lasted for nearly 10 minutes.

2.2. Data Collection Instruments

Information Form: This form was composed of demographic characteristics of patients such as sex, age, marital status, education level, family type and employment status and the questions determining disease-related characteristics.

Illness Perception Questionnaire-Revised (IPQ-R):This questionnaire was developed by Weinmann in1996 and revised by Moss-Morris *et al.* in 2002. Turkish adaptation study and validity and reliability studies of the scale were carried out by Kocaman *et al.* (2007). IPQ-R involves three dimensions including illness identity, attributions concerning the disease and probable causes (5,10)

1) Illness Identity (Disease Symptoms): It involves 14 common disease symptoms (pain, sore throat, nausea, breathlessness, weight change, fatigue, stiff joints, sore eyes, wheeziness, headache, upset stomach, dizziness, sleeping difficulties, loss of strength). For each of these symptoms, the individuals are first asked whether "they experienced these since the onset of disease" and then, whether "they experienced these symptoms associated with their illness". This scale was arranged as giving a response for each symptom as yes/no. A high score of identity scale indicates a strong view of the patient on the presence of a high number of symptoms accompanying the disease.

2) Attributions concerning the disease (Illness Perception): This part is composed of 38 items including the views of the patient regarding the disease. A 5-point Likert-type grading (strongly disagree, disagree, neither agree nor disagree, agree, strongly agree) is used.

This scale involves seven subscales. These are called timeline (acute/chronic), timeline (cyclical), consequences, personal control, treatment control, illness coherence and emotional representations.

a. Timeline subscales investigate individual's perception regarding the duration of illness and it is grouped as acute/chronic and cyclical/episodic.
   A high score from timeline (acute/chronic) subscale indicates that the condition is chronic.

b. A high score from timeline (cyclical/episodic) subscale indicates that condition has a cyclic nature.

c. Consequences subscale investigates individual's views on the possible effects of the severity of disease on physical,

social and psychological functionality. A high score from consequences subscale indicates that the disease has negative outcomes.

d. Personal control investigates individual's internal control perception on the duration, course and treatment of the illness.

e. Treatment control investigates individual's views on the efficiency of the treatment given. A high score of personal and treatment control subscales indicates that the individual has positive views on his/her efficiency to control disease and treatment.

f. Illness coherence investigates individual's understanding of the disease. A high score from illness coherence indicates greater understanding of the condition.

g. Emotional representations investigate individual's emotions regarding the disease. A high score from emotional representations subscale indicates an increase in negative emotions provoked by the disease.

3) Probable Causes: It is composed of 18 items including probable causes in the formation of diseases. A 5-point Likert-type grading (strongly disagree, disagree, neither agree nor disagree, agree, strongly agree) is used. This dimension investigates individual's views on the probable causes of the illness and includes four subscales. These are psychological attributions (for instance; stressor worry, family problems, personality characteristics), risk factors (e.g. hereditary, smoking, alcohol and aging), immunity (e.g. a germ or virus and an altered body resistance) and accident or chance (e.g. accident, injury, bad luck).

2.3. StatisticalAnalysis

Statistical analysis of data was performed by using SPSS 21.0 (Statistical Packagefor Social Science) package program. Normality analysis of the data was carried out with Shapiro Wilk test. Independent samples t test, one way anova and pearson correlation analysis were used to assess data. Tukey analysis was used in post-hoc tests. $P<0.05$ was considered significant.

2.4. Ethical Consideration

The individuals undergoing peritoneal dialysis and hemodialysis in the study were informed about the aim of the study. Then, they provided written and verbal consents and signed informed consent form. Necessary permissions were taken from the Ethics Committee of Erciyes University. 2016/71-05.02.2016

3. RESULTS

Among 93 patients included in the study, mean age was 55.9±15.1 years old (min: 21.0, max: 86.0); mean duration of illness was 81.4±77.7 months (min: 3.0, max:468.0), mean duration of dialysis was 57.7±58.3 months (min: 3.0, max:264.0) and mean number of comorbid diseases was 1.4±0.6 (min: 1.0, max: 4.0). Out of all patients, 53.8% were males; 80.6%were married; 45.2% were elementary school graduates; 91.4% were unemployed; 67.7% had an income at a moderate level; and 74.2% had a core family (Table 1). 93.5% of the patients had family support (HD: 91.1%, PD: 95.8%), and 69.9% (HD: 37.8%, PD: 100.0%) had training from healthcare professionals regarding their illness and its treatment.

Table 1. *Descriptive characteristics of patients according to the dialysis modality*

Descriptive characteristics	HD n (%)	PD n (%)	Total n (%)
Sex			
Female	21(46.7)	22(45.8)	43(46.2)
Male	24(53.3)	26(54.2)	50(53.8)
Marital status			
Married	34 (75.6)	41 (85.4)	75 (80.6)
Single	11 (24.4)	7 (14.6)	18 (19.4)
Education			
Illiterate	3(6.7)	3(6.3)	6(6.5)
Literate	5(11.1)	4(8.3)	9(9.7)
Elementary	21(46.7)	21(43.8)	42(45.2)
Secondary school	8(17.8)	4(8.3)	12(12.9)
High school	5(11.1)	9(18.8)	14(15.1)
University	3(6.7)	7(14.6)	10 (10.8)
Employment status			
Employed	4(8.9)	4(8.3)	8(8.6)
Unemployed	41(91.1)	44(91.7)	85(91.4)
Monthly income			
Good	7(15.6)	13(27.1)	20(21.5)
Moderate	30(66.7)	33(68.8)	63(67.7)
Poor	8(17.8)	2(4.2)	10(10.8)
Family type			
Core	34(75.6)	35(72.9)	69(74.2)
Large	7(15.6)	10(20.8)	17(18.3)
Broken/ living alone	4(8.9)	3(6.3)	7(7.16)
Age (years) (Mean ± SD)	56.5±16.3	55.4±13.9	55.9±15.1
Duration of illness (months) (Mean ± SD)	82.7±93.5	80.1±60.1	81.4±77.7
Duration of dialysis (months) (Mean ± SD)	58.6±67.0	56.8±49.4	57.7±58.3
Number of comorbid diseases (Mean ± SD)	1.5±0.7	1.4±0.5	1.4±0.6

Abbreviation; HD: Hemodialysis, PD: Peritoneal Dialysis, SD: Standard Deviation

The presence of a high score in IPQ-R subscale of personal control represents a high positive belief that the individual can control his/her disease and its treatment. The increase in the mean score of illness coherence indicates that individual's level of understanding on his/her condition is enhanced. While timeline acute/chronic shows the way of individuals to perceive their diseases as acute or chronic, a high score shows that the condition is perceived as chronic. In this study, it was found that mean scores personal control, illness coherence and timeline acute/chronic of PD patients were found to be higher than HD

patients at a statistically significant level (p<0.05). No statistically significant differences were found in the other subscales of IPQ-R based on two dialysis modalities (p>0.05) (Table 2).

Table 2. *Comparison of IPQ-R subscales mean scores according to dialysis modality*

IPQ-R Subscales	HD Mean (SD)	PD Mean (SD)	Statistics*	p
Attributions concerning the disease (Illness Perception)				
Consequences	20.6(4.6)	19.9(5.2)	0.710	0.479
Personal control	20.6(4.0)	23.7(3.4)	**-3.936**	**0.000**
Treatment control	17.2(4.3)	17.1(3.4)	0.092	0.927
Illness coherence	17.1(4.9)	19.4(5.6)	**-2.078**	**0.041**
Timeline cyclical	13.0(3.5)	14.4(3.9)	-1.874	0.064
Emotional representations	21.2(5.4)	18.6(7.3)	1.916	0.058
Timeline acute/ chronic	22.6 (5.6)	25.4(5.2)	**-2.484**	**0.015**
Illness Identity (Disease Symptoms)	6.8(3.3)	6.6(3.3)	0.196	0.845

Abbreviation; HD: Hemodialysis, PD: Peritoneal Dialysis, SD: Standard Deviation

**Based on independent samples t-tests.*

Table 3. *Comparison of IPQ-R probable causes subscales mean scores according to dialysis modality*

PROBABLE CAUSES	HD Mean (SD)	PD Mean (SD)	Statistics*	p
Psychological attributions	14.68(4.95)	14.39(6.30)	0.250	0.803
Stress or worry	3.06 (1.40)	3.14 (1.66)	-0.247	0.805
My mental attitude e.g. thinking about life negatively	2.13 (1.28)	2.08 (1.51)	0.171	0.865
Family problems or worries	2.37 (1.33)	2.04 (1.50)	1.170	0.245
Overwork	2.84 (1.38)	2.60 (1.64)	0.760	0.449
My emotional state e.g. feeling down. lonely. anxious or empty	2.20 (1.15)	2.29 (1.50)	-0.328	0.744
Risk factors	15.55 (4.90)	14.35 (5.49)	1.110	0.270
Hereditary – it runs in my family	2.37 (1.45)	2.31 (1.67)	0.200	0.842
Diet or eating habits	2.57 (1.19)	2.31 (1.48)	0.943	0.348
Poor medical care in my past	2.0 (0.95)	1.97 (1.48)	0.080	0.936
My own behavior	2.40 (1.25)	2.68 (1.62)	-0.951	0.344
Ageing	2.33 (1.27)	2.02 (1.48)	1.086	0.280
Alcohol	1.71 (1.05)	1.29(0.98)	1.977	0.051
Smoking	2.15(1.31)	1.75(1.31)	1.488	0.140
Immunity	6.84 (2.52)	6.45 (3.13)	0.652	0.516
A Germ or virus	1.84 (0.79)	1.56 (1.04)	1.452	0.150
Pollution in the environment	2.08 (1.04)	2.02 (1.49)	0.253	0.801
Altered immunity	2.91 (1.37)	2.87 (1.74)	0.110	0.912
Accident or chance	4.24 (1.72)	3.54 (1.87)	1.877	0.064
Chance or bad luck	2.57 (1.30)	2.45 (1.71)	0.376	0.708
Accident or injury	**1.66 (0.79)**	**1.08 (0.45)**	**4.370**	**0.000**

Abbreviation; HD: Hemodialysis, PD: Peritoneal Dialysis, SD: Standard Deviation

**Based on independent samples t-tests.*

Table 4. *Comparison of IPQ-R subscales mean scores according to some variables*

Variables	IPQ-R Subscales	Statistics	p	Post-hoc***
Duration of illness	**Timeline acute/ chronic**			
less than a year	21.44(4.91)	**3.766****	**0.027**	**1-3 (0.025)**
2-4 year	23.50(6.72)			
5 year and above	25.40(4.76)			
Duration of illness	**Immunity**			
less than a year	8.11(2.54)	**3.173****	**0.047**	**1-3 (0.039)**
2-4 year	6.46(3.11)			
5 year and above	6.20(2.67)			
Duration of dialysis	**Timeline acute/ chronic**			
less than a year	21.86(4.51)	**3.468****	**0.035**	**1-3 (0.027)**
2-4 year	23.93(6.31)			
5 year and above	25.64(5.06)			
Sex	**Emotional representations**			
Female	21.65(6.60)	**2.491***	**0.015**	
Male	18.34(6.20)			
Sex	**Risk factors**			
Female	13.79(4.48)	**-1.992***	**0.049**	
Male	15.92(5.63)			
Maritial status	**Risk factors**			
Married	24.73(5.30)	**2.262***	**0.026**	
Single	21.50(6.01)			
Education	**Emotional representations**			
Illiterate	22.44(5.83)			
Literate	27.33(3.50)			**1-5(0.040)**
Elementary	19.61(6.45)	**2.698****	**0.026**	**1-6(0.020)**
Secondary school	19.66(6.42)			
High school	18.14(7.22)			
University	16.80(5.39)			

** Based on independent samples t-tests.** Based on one way anova test.*** Post-hoc test: Tukey*

Mean score of HD patients for accident or injury was found to be significantly higher than PD patients (p=0.000). There were no statistically significant differences in all other dimensions of IPQ-R probable causesbased on two dialysis modalities (p>0.05) (Table3).

In this study, mean IPQ-R and subscale scores of PD and HD patients and disease duration and diagnosis time were tested by one way anova analysis. Tukey post-hoc analysis was used to determine which group caused the difference between the mean scores. It was also found that there were statistically significant differences between the duration of diagnosis and mean scores IPQ-R timeline acute/chronic (F =3.766, p=0.27) and immunity (F =3.173, p=0.47). When the origin of difference was investigated in terms of the duration of diagnosis, mean score IPQ-R timeline acute/chronicof the ones whose duration of diagnosis was less than one year (21.4±4.9) was found to be significantly lower than the ones whose duration was 5 years and longer (25.4±4.7) (p=0.027).

Variables	IPQ-R Subscales							
	Attributions concerning the disease (Illness Perception)							Illness Identity
	Consequences	Personal control	Treatment control	Illness coherence	Timeline cyclical	Emotional representations	Timeline acute/ chronic	
Age (year)								r= – 0.213 p=0.040
Comorbid disease		r=-0.232 p=0.025	r=0.233 p=0.024				r=0.232 p=0.025	
Duration of illness							r=0.208 p=0.046	
Timeline acute/ chronic	r=0.271 p=0.009		r=-0.296 p=0.004					
Conseguences			r=-0.230 p=0.026	r=-0.362 p=0.000	r=0.402 p=0.000			
Treatment control		r=0.207 p=0.047						
Timeline cyclical				r=-0.355 p=0.000				
Emotional representations				r=-0.375 p=0.000				
Identity	r=0.295 p=0.004							
Psychological attributions	r=0.254 p=0.014							
Risk factors	r=0.237 p=0.022							
Chance or bad luck	r=0.287 p=0.005			r=-0.0222 p=0.032		r=0.222 p=0.032		

Besides, mean score IPQ-R immunity of the patients whose duration of diagnosis was less than one year (8.1±2.5) was found to be significantly lower than the ones whose duration was 5 years and longer (6.2±2.6) (p=0.047)

A statistically significant difference was found between the mean scores of IPQ-R timeline acute/chronic (F =3.468, p=0.35) and duration of dialysis (p=0.035). When the origin of difference was investigated in terms of the duration of dialysis, it was found that mean IPQ-R timeline acute/chronic score of the patients, whose duration of dialysis was less than one year (21.8±4.5) was significantly less than the ones whose duration of dialysis was 5 years and longer (25.6±5.0) (p<0.05).

A high score obtained from IPQ-R emotional representations subscale shows that negative emotions provoked by the disease are increased. In this study, IPQ-R emotional representations mean score of women (21.6±6.6) was found to be significantly higher than the mean score of men(18.3±6.2) (p=0.015). In addition to this, mean IPQ-R risk factors score of women (13.7±4.4)was found to be significantly lower than the mean score of men (15.9±5.6) (p=0.049).The comparisons between mean IPQ-R scores and sex variable were analyzed by independent samples t test.

In this study, patients' mean scores of IPQ-R and its subscales and marital status and education level were assessed by one way anova analysis. Tukey post-hoc analysis was used to determine which group created the difference between the means. Timeline acute/chronic mean score of the participants, who were married (24.7±5.3), was found to be significantly higher than the single individuals (21.5±6.0) p=0.026).

Moreover, it was found that there was a statistically significant difference between education level of the participants and mean IPQ-R emotional representations score (F =2.698 p=0.026). Mean score of the illiterate participants (27.3±5.8) was found to be significantly higher than the ones who were graduates of high school (18.1±7.2) and university (16.8±5.3) (p=0.026).

In this study, it was also found that there were not significant differences between the participants in both groups based on their employment states, monthly income, family type, state of getting support with IPQ-R mean score(p>0.05).

The increase in mean IPQ-R illness coherence score shows that individual's level of understanding concerning his/her condition is enhanced. The increase in the mean score of treatment control subscale indicates that the beliefs of

individuals on that their diseases can be kept under control and the treatment is effective are increased.

The increase in the mean score of IPQ-R consequences subscale shows that individuals believe that the disease has negative consequences on their physical, social and psychological functions. According to the results of pearson correlation analysis in the study, negative and significant correlations were found between consequences and treatment control (r=-0.230, p=0.026) and illness coherence (r= – 0.362, p<0.001). Again, consequences dimension was found to have positive and significant correlations with timeline cyclical (r= 0.402, p=0<0.001), emotional representations (r= 0.550, p=0.000), identity (r= 0.295, p=0.004), psychological attributions (r=0.254, p=0.014), risk factors (r= 0.237, p=0.022), immunity (r=0.230, p=0.026) and accident or chance (r= 0.287, p=0.005).

Moreover, there were positive and significant correlations between timeline acute/chronic and duration of diagnosis (r=0.208, p=0.046) and consequences (r=0.271, p=0.009) whereas there was a negative and significant correlation between timeline acute/chronic and treatment control (r=-0.296, p=0.004).

The number of comorbid diseases was found to be positively correlated with timeline acute/chronic (r=0.232, p=0.025) whereas it was found to have negative and significant correlations with personal control (r=-0.273, p=0.008) and treatment control (r=0.233, p=0.024).

Furthermore, accident or chance was found to have negative and significant correlations with illness coherence (r=-0.222, p=0.032) and emotional representations (r=-0.222, p=0.032). Similarly, illness coherence was found to be negatively correlated with emotional representations (r=-0.375, p<0.001) and timeline cyclical (r= – 0.355, p<0.001). In addition, there was a negative and significant correlation between age and identity (r= – 0.213, p=0.040); and treatment control and personal control was found to be positively correlated (r= 0.207, p=0.047).

4. DISCUSSION

According to the studies investigating the relationship between illness perception and disease outcomes, the course of disease is better in individuals whose internal control perceptionis high (5). In the study by Iskandarsyah *et al*. which was carried out in 2014, it was determined that patients, whose illness perception was good, had a better treatment compliance (11). In order to enhance treatment compliance, patients with a poor illness perception may be identified and they may be oriented to individualized treatment for depression or anxiety. In this study which was conducted to determine and evaluate illness perception in dialysis treatment used in CKD, mean age of 93 patients was 55.97 years old, mean duration of disease was 81.4±77.7 months and mean duration of dialysis was 57.7±58.3 months. In the study by Jansen *et al*., mean age was found to be 64 years old.In their study with HD patients, Karabulutlu *et al*. found mean age as 52 years old, mean duration of disease as 75 months and duration of HD treatment as 64 months (12). Also in the study by Krespi *et al*.,dialysis patients stated that they experienced loss of strength, they could not do the things they could previously, they had to get rest more often and they got tired in a short time (13). Symptoms associated with disease and its treatment such as weakness and fatigue may affect compliance of patients negatively (14).

In this study, mean scores of IPQ-R attributions concerning the disease (Illness Perception) subscales including personal control, illness coherence and timeline acute/chronic among PD patients were found to be significantly higher than the scores of HD patients. In this study, illness perception was found to be more positive in PD patients compared to HD patients in three dimensions; and thus, H_1 hypothesis was accepted and H_0 hypothesis was rejected. While patients are dependent on the machines and healthcare staff in HD treatment, patients can perform treatment on their own at home environment and more independently in PD (15). In other words, patients can use PD alternative since they have cognitive and physical capacity to take their own responsibility. Considering that HD patients do not have these features, more positive perception of PD patients for the disease and its treatment compared to HD patients was not evaluated as a surprising finding. Thus, HD patients may feel a loss of control on their bodies and lives since they can not undertake their own care responsibilities; and may perceive the condition more negatively.

This may be derived from the fact that it is necessary to choose conscious patients, who have a good sociocultural level, for PD. Feelings of personal control are important for the life quality of dialysis patients (16,17). As similar to our results, Jansen *et al*. reported that mean scores of dialysis patients were 6.3 in “anxiety” dimension and 4.9 in “personal control” dimension (18). In the study by Karabulutlu *et al*. which was conducted with HD patients, mean scores of emotional representations, timeline (acute/chronic) and personal control were found to be higher than the other subscales (12). Moreover, the results of the study by Alharbi *et al*. indicated that PD patients perceived their illnesses as less chronicand managed disease better as similar to our study (19).

It has been reported that dialysis patients with a high personal control had a better compliance to treatment, they had a high quality of life and less experienced psychiatric problems such as anxiety and depression (16,20). In the study by Cvengros *et al.,* it was shown that low control perception of patients decreased treatment compliance (21). It was also found that mean accident or injury scores of HD patients were significantly higher than PD patients. This can be considered as HD patients have difficulties in controlling disease and they see disease like bad luck as a defense mechanism. In addition to this, Karabulutlu *et al*. reported the causes of disease as risk factors and psychological attributions mostly. It was observed that patients stated probable causes as

accident or chance at the least (12). Cultural tendencies are also important in the perception of illness besides disease-related individual perceptions. When causes of disease were evaluated in general, they were reported as stress, distress and anxiety as a reflection of culture in Turkish society (12).

Dialysis process, that is carried out besides medications in dialysis patients, is a phenomenon causing time consumption in the patients' lives at a significant level (12). It was found that there were significant differences between the duration of diagnosis and IPQ-R timeline and immunity mean scores of the participants. When the origin of this difference was examined, it was found that IPQ-R timeline acute/chronic mean score of the participants who had a duration of diagnosis less than one year was lower than the ones whose duration was 5 years and longer. This situation may be due to that patients begin to perceive their conditions as chronic since they accept the condition and lose the hope for recovery as the duration of diagnosis progresses. IPQ-R immunity mean score of the individuals whose duration of diagnosis was less than one year was found to be significantly lower than the ones whose duration was 5 years and longer.The reason of this situation may be that individuals are not yet hopeless and exhausted at the onset of disease. Depletion of power later in the treatment process may cause a decrease in the score.

A significant difference was found between the duration of dialysis and IPQ-R timeline acute/chronic mean score of the participants. When the reason of this difference was examined, it was found that IPQ-R timeline acute/chronic mean score of the participants whose duration of dialysis was less than one year was significantly lower than the ones whose duration was 5 years and longer. This may due to the fact that patients begin to perceive disease as chronic since they accept the condition and lose the hope for recovery as the duration of treatment increases. Also in the study by Karabulutlu *et al*.,it was found that the majority of patients had opinions such that the disease would last long, it was permanent rather than being temporary and they would spend the rest of their lives with this disease (12).

IPQ-R emotional representations mean score of women was found to be higher than men at a statistically significant level. This high score might be derived from the condition that women are more sensitive in emotional terms. In addition to this, IPQ-R risk factors mean score of women was found to be significantly lower than men. The reason may be that habits such as alcohol and smoking are seen mostly amongmen in Turkish society.

Timeline acute/chronic mean score of the married participants was found to be higher than single ones. This situation may be derived from the fact that married individuals have more roles within the society (such as father, spouse or mother), and change in these roles may affect individuals more.

A significant difference was found between education level of the participants and their mean scores of IPQ-R emotional representations. Mean score of illiterate patients was found to be significantly higher than high school and university graduates. The reason may be that it may be easier to investigate better and to find out ways of compliance as education level increases. Educated individuals may understand disease and treatment better and integrate them into normal life.

5. CONCLUSIONS

There are studies in the literature investigating illness perceptions of the patients in several chronic diseases; but, there is a limited number of studies examining illness perception among dialysis patients in our country. One limitation of our study was the limited number of patients included in the study. Sample size was small but the results are guiding since the number of HD and PD patients were close to each other. Besides being instructive as is, this study may be guiding for many studies when it is conducted with a large sample size.

As a result of this study, it was determined that HD patients perceived their illnesses as more challenging compared to PD patients. Therefore, especially HD patients may be given disease-related trainings with the onset of their treatment process and a psychological support may be recommended to accept their chronic diseases.

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Clinical and Experimental Health Sciences

Is There a Correlation Between Benign Paroxysmal Positional Vertigo and Indirect Sinus Lifting?

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ABSTRACT

Objective: The aim of this study is to inform surgeons regarding benign paroxysmal positional vertigo (BPPV) after indirect sinus lifting procedures and to assess its relationship with age, gender, residual alveolar bone height (RAB), and cortical thickness of the sinus floor.

Methods: This study included 138 patients presenting for evaluation and management of BPPV after indirect sinus lifting. Patients with RAB lengths of 5–8 mm had been taken for indirect sinus lifting. Preoperative RAB length and cortical thickness of the sinus floor had been determined by cone beam computed tomography (CBCT) in each patient. The patients diagnosed with BPPV were promptly treated by an otolaryngologist. Data were assessed by descriptive statistical methods (mean ± standard deviation). Results were evaluated at the $p<0.05$ significance level, in 95% confidence interval (95% CI).

Results: Totally 4 out of 138 of the patients showed BPPV. There was no statistically significant difference between the mean ages and gender ratio between the patients with BPPV [BPPV(+)] and without BPPV [BPPV(-)] groups. It was found that BPPV is 2.48 times more prevalent in patients with RAB criterion values <5.9 mm than in patients with criterion values >5.9 mm. BPPV is 4.54 times more prevalent in patients with a criterion cortical thickness value >0.8 mm than in patients with a criterion value <0.8 mm.

Conclusion: Based on the results of this study, patients with cortical thickness values >0.8 mm should be informed before undergoing surgery, and patients exhibiting postoperative symptoms associated with vertigo should be treated promptly.

Keywords: Benign paroxysmal positional vertigo, maxillary sinus, osteotomy, Schneiderian membrane

1. INTRODUCTION

Pneumatization of the maxillary sinus occurs after tooth loss. In cases with 5–8 mm residual alveolar bone (RAB) height, indirect sinus floor elevation should be performed for prosthetic rehabilitation [1-3]. However, there are many complications associated with the closed sinus lifting procedure [4,5]. A complication that is not well known, but is not uncommon, is osteotomy-related benign paroxysmal positional vertigo (BPPV). It is a common vestibular and organ disorder characterized by short-lived recurrent episodes of vertigo associated with rapid changes in head position. BPPV is sometimes masked by postoperative complaints such as pain, swelling, and inadequate liquid consumption [6-9]. Some patients do not consider the vertigo to be related to the implant surgery, and thus, do not inform their clinicians of this symptom.

The purpose of this study is to inform patients and surgeons about vertigo after indirect sinus lifting procedures performed with osteotomes. The authors hypothesized that postoperative BPPV is related to indirect sinus lifting trauma. As such, the aim of this study was to assess the complication of BPPV as a complication of indirect sinus lifting procedure using age, gender, RAB height, and cortical thickness of the sinus floor as predictor variables.

2. METHODS

2.1 Study Design / Sample

The study was approved by İstanbul Medipol University University Clinical Ethics Committee with the protocol number of 194140909. The study population was composed of all patients presenting for evaluation and management of BPPV after indirect sinus lifting between September 2014 and April 2015. Patients who needed dental implant therapy in one quadrant (right or left) were included in the study sample. Patients were excluded as study subjects if they had previous vertigo attacks, acute or chronic sinusitis, viral

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infections, or any history disease that might lead to vertigo (e.g., Ménière's disease).

2.2 Variables

In this cohort study, the predictor variables were age, gender, preoperative RAB height, and cortical thickness of the sinus floor determined by cone beam computed tomography (CBCT); the outcome variable was presence of postoperative BPPV. All variables were obtained from the patients' case histories.

2.3 Data Collection Methods

The CBCT examinations were performed using a ProMax 3D Mid machine (Planmeca Oy, Helsinki, Finland). CBCT scan assessments were performed directly on a 23" 1920x1080 pixel Acer Monitor and an HP Reconstruction PC. A Planmeca Romexis Viewer (Roselle,IL,USA) was used to measure the distance between the sinus floor membrane and the alveolar crest (RAB height) and the cortical thickness of the sinus floor. All measurements were performed by the same specialist (Figure 1).

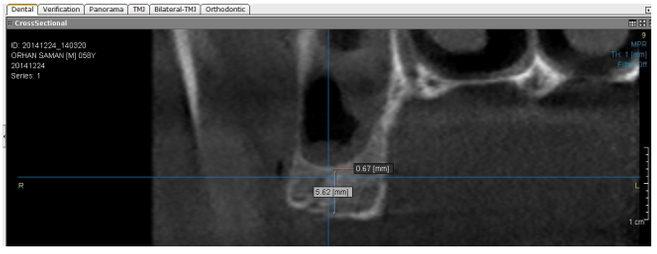

Figure 1. *An example of the measurement from a radiologic image*

The data of the patients with BPPV included the duration times of the vertigo episodes. These patients had been referred to an otolaryngologist for diagnosis and treatment, in keeping with the department's protocols; the Dix–Hallpike test was used to diagnose BPPV. After a diagnosis of BPPV was made, the Epley maneuver was performed immediately for recovery [6].

The BPPV patients had been re-called after one week and one, three, and six months to control for recurrence. The archives were scanned for any neurovegetative symptoms associated with the autonomic nervous system, such as nausea and vomiting, and the data were recorded.

To achieve standardization, the same osteotome set (2.0, 2.5, 3.0, and 3.5 mm diameters) had been used in all of the operations. According to the literature, patients with RAB heights of 5–8 mm had been taken for indirect sinus lifting [1,2].

2.4 Data Analyses

Statistical analyses were performed using NCSS 2007 software (Number Cruncher Statistical System/ Kaysville, UT, USA). Data were assessed by descriptive statistical methods (mean ± standard deviation). An independent samples t test was used for paired group comparisons, and Fisher's exact test was used for qualitative analysis. Logistic regression analysis was used as the statistical method for determining the factors affecting the presence of BPPV. Results were evaluated at the $p<0.05$ significance level, in 95% confidence interval (95% CI).

3. RESULTS

The study included 138 healthy patients (79 women and 59 men) with an average age of 47.2 years (range, 35–68 years). Four of the 138 patients (2.89%) were diagnosed with BPPV, using the Dix–Hallpike test. Severe vertigo associated with neurovegetative symptoms, such as nausea, occurred in one of the 138 patients. This patient, who was diagnosed six weeks later, was a 72-year-old female with a RAB height of 5.6 mm and a cortical thickness of 1.2 mm. This delay in the diagnosis prolonged the duration of the complication. The other three BPPV patients were diagnosed promptly with the Dix–Hallpike test and treated with the Epley repositioning maneuver by the same otolaryngologist. Three additional patients experienced dizziness the day after the operation, and BPPV two days later: a 39-year-old female with a RAB height of 5.9 mm and cortical thickness of 1 mm, a 57-year-old man with a RAB height of 5.2 mm and cortical thickness of 1 mm, and a 40-year-old female with a RAB height of 5.3 mm and cortical thickness of 1.1 mm). The second patient who had BPPV (39-year-old female) was diagnosed in the first postoperative week. The third patient (57-year-old man) presented to the clinic five days after the operation and was diagnosed promptly with BPPV. The fourth patient (40-year-old female) had not informed the clinicians of any complications at the first week, but presented at the clinic in the second week with the complication of nystagmus, which was diagnosed as BPPV. None of the 134 remaining patients experienced any neurovegetative symptoms associated with BPPV.

In the statistical analysis, the patients with BPPV were designated as BPPV(+) and the patients without BPPV were designated as BPPV(-). There was no statistically significant difference between the mean ages of the BPPV(-) and BPPV(+) groups ($p=0.279$). There was no statistically significant difference in gender ratio between the BPPV(-) and BPPV (+) groups ($p=0.466$). The average RAB value of the BPPV(+) group was found to be statistically lower than that of the BPPV(-) group ($p=0.019$). The average cortical thickness value of the BPPV(+) group was found to be statistically higher than that of the BPPV(-) group ($p=0.0001$) (Table 1).

In the logistic regression analysis, while cortical thickness was determined to be the main factor, RAB height variable lost value ($p=0.011$) (Table 2). Calculations of the areas

under the receiver operating characteristic (ROC) curve were performed for RAB and cortical thickness parameters for the diagnosis of BPPV. The area under the ROC curve was found to be 0.743 (0.662–0.814) for RAB and 0.988 (0.952–0.998) for cortical thickness. The aim of this calculation is to define which parameter is the determining factor for presence of vertigo (Table 3). The area for cortical thickness was found to be statistically higher than that of RAB height (p=0.022), suggesting that cortical thickness is a better diagnosis parameter than RAB height for predicting BPPV (Table 4).

For the RAB parameter, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (+LR), and cutoff value (criterion) were found to be 99.50, 59.70, 16.9, 99.54, 2.48, and 5.9, respectively. These results indicate that BPPV is 2.48 times more prevalent in patients with criterion values <5.9 than in patients with criterion values >5.9.

For the cortical thickness parameter, the sensitivity, specificity, PPV, NPV, +LR, and criterion values were found to be 99.87, 77.97, 23.5, 99.92, 4.54, and 0.8, respectively. These results indicate that BPPV is 4.54 times more prevalent in patients with criterion values >0.8 than in patients with criterion values <0.8 (Table 5).

Table 1. *Correlation of age, gender, RAB and cortical thickness parameters with BPPV (-) and BPPV (+) group*

		BPPV (-) n:134		BPPV (+) n:4		p
Age		58.83±12.29		52±15.68		0.279
Gender	**Man**	58	43,30%	1	25.00%	
	Woman	76	56.70%	3	75.00%	0.466
RAB		6.14±0.74		5.5±0.32		**0.019**
Cortical Thickness		0.56±0.2		1.08±0.1		**0.0001**

BPPV (+): patients with benign paroxysmal positional vertigo
BPPV (-): patients without benign paroxysmal positional vertigo

Table 2. *Logistic regression analysis of RAB and cortical thickness parameters*

	B	S.E.	p	Exp(B)	95% CI	
					Lower Limit	Upper Limit
RAB	-2.20	2.12	0.301	0.11	0.00	7.12
Cortical Thickness	5.69	4.16	**0.011**	72.45	17.47	113.90

Table 3. *Area under ROC curve (AUC), standard error (SE) and 95% confidence interval of RAB and cortical thickness parameters*

	AUC	SE	95% CI
RAB	0.743	0.102	0.662 – 0.814
Cortical Thickness	0.988	0.039	0.952 – 0.998

AUC: area under ROC curve
SE: standard error
CI: confidence interval

Table 4. *Pairwise comparison of ROC curves of RAB and cortical thickness parameters*

Pairwise comparison of ROC curves	p
RAB / CorticalThickness	0.022

Table 5. *Criterion (cut off point), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (+LR) in the analysis*

	Criterion	Sensitivity	Specificity	PPV	NPV	+LR
RAB	<5.9	99.50	59.70	16.9	99.54	2.48
Cortical Thickness	>0.8	99.87	77.97	23.5	99.92	4.54

4. DISCUSSION

In the cases of increased pneumatization of the maxillary sinuses, the rehabilitation of the region is very challenging [10]. The uncommon complication of BPPV is very difficult for surgeons to describe to patients after these operations.

As such, the purpose of this study was to inform patients and surgeons about vertigo that occurs after indirect sinus lifting procedures performed with osteotomes. It was hypothesized that postoperative BPPV is related to indirect sinus lifting trauma. The aim of the study was to assess the complication of BPPV by means of age, gender, RAB height, and cortical thickness of the sinus floor. Only four patients in this retrospective study had experienced BPPV. In the statistical analysis, while cortical thickness was determined as the main factor, the RAB height variable lost value. BPPV is seen 4.54 times more often in patients with a cortical thickness criterion >0.8 mm than in patients with a criterion value <0.8 mm. According to the statistical analysis of the present study, if cortical bone thickness is >0.8 mm, there is a risk potential for BPPV formation. In the indirect sinus lifting procedure, surgeons should apply more force to lift the sinus floor if cortical bone is dense and thick.

In cases with 5–8 mm of RAB height for indirect sinus lifting, only 0.8–1 mm of total alveolar height is formed by the cortical plate, which means that RAB thickness is mainly formed by spongious bone in indirect sinus lifting cases. Cortical bone is more resistant than spongious bone, and it accumulates and transmits more vibratory forces. On the other hand, spongious bone, which has more plastic deformation, absorbs vibratory forces [11]. The results of this retrospective study reflect those characteristics.

There are several reports of BPPV after sinus floor elevation with osteotomes [6-9, 12-14]. A previous study reported that four of 146 patients who underwent osteotome sinus floor elevation developed BPPV one or two days after the surgical procedure, which was promptly resolved with the Epley repositioning maneuver [6]. In a randomized clinical trial, it was found that three of 98 patients who underwent sinus floor elevation with osteotome and gentle tapping of a mallet developed BPPV while none of 98 patients who underwent sinus floor elevation with a screwable osteotome (without tapping with a mallet) developed BPPV. The researchers

surmised that the percussive forces of the osteotome and mallet are capable of detaching otoliths [9]. Furthermore, the patient's head position (hyperextended and tilted to one side) favors the entry of these free-floating particles into the semicircular canal [12]. Our results regarding BPPV complication triggered by closed sinus floor elevation procedure (2.89%) were similar to case series evaluations that reported percentages of 2.43% (6) and 3.06% (9). All patients presenting with BPPV in our sample were treated with the Epley repositioning maneuver, which has proven to be very effective in treating the disorder [15,16].

According to the previous studies, the factors that act simultaneously in triggering positional vertigo following this surgical procedure are the percussive forces exerted on the upper maxilla by the osteotomes, the vibratory forced exerted by the implant drill, and the hyperextended head position [6,8,17,18]. In our clinic, all operations involving the maxilla are performed while the patients' heads are hyperextended. For this reason, we think one of the reasons we encountered vertigo is the positioning of the head during the operation. The other factor that provokes BPPV is the percussive forces, which are capable of detaching the otoliths. When performing dental implants, both the osteotomes tapped on with mallets and drilling procedures might create percussive forces.

There is only knowledge about the incidence of idiopathic BPPV in patients 50–70 years of age, although the condition is found in all age groups. The incidence of idiopathic BPPV ranges from 11 to 64 per 100,000 per year [19], and it increases by approximately 38% per decade of life [16]. BPPV was not found to be related to age in the present study.

In the literature, vertigo after closed sinus floor elevation with osteotomes is seen more often in women than in men (1:1.5) [16]. In some studies, sex distribution is nearly equal for post-traumatic and post-vestibular neuritis [20,21]. In our study, there was no statistical difference between genders. Our findings showed that cortical thickness seems to be a better diagnosis parameter than RAB height for predicting BPPV. The posterior maxillary alveolar ridge consists of mostly spongious bone, and it can deform easily while absorbing the osteotomy strokes. On the other hand, a thick cortical sinus floor transmits most of the osteotomy forces to the posterior semicircular canal via cranial buttresses, thus inducing BPPV. Many studies have shown the relationship between BPPV and closed sinus lifting procedure but there is no study showing a relationship between the presence of vertigo and cortical thickness of the sinus floor [6,7,8,9]. The authors in the present study state that the findings should help the clinicians determine about possible complications which may occur postoperatively.

Studies regarding this complication have been performed mainly by otolaryngologists. In the present study, the authors are mainly oral and maxillofacial surgeons who had performed the surgical operations and estimated this complication. In addition, the presence of BPPV was assessed by means of the parameters of age, gender, RAB height, and cortical bone thickness, which is unique in the literature. However, there were only four cases of BPPV in the present study; therefore, more case follow-ups are needed in order to obtain dependable statistical data. Other factors that require attention in order to produce more accurate results are cortical bone density, which varies among patients, and determination of the forces exerted by the osteotomes used in these procedures.

5. CONCLUSION

Our results indicate that although BPPV has been considered to be a rare complication following indirect sinus lift procedures, it is highly disruptive to patients if not diagnosed correctly and treated properly. The phenomenon of BPPV was found to be mainly associated with the parameter of preoperative cortical thickness value. We suggest that in particular, patients with cortical thickness values >0.8 mm should be informed before undergoing surgery and referred to otolaryngologists when faced with any neurovegetative symptom associated with vertigo. We also recommend that implant surgeons add this complication to their informed consent forms for sinus lifting procedures.

In future studies, we recommend testing a broader sample and including the operation duration, cortical bone density, number of osteotomy strokes, measurement of stroke force for each blow, and force variances among different sized implants to evaluate other possible factors that may cause BPPV.

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Clinical and Experimental Health Sciences

Follow-up of Geriatric Patients With Pressure Ulcers By Plastic, Reconstructive and Aesthetic Surgery in Intensive Care Conditions

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ABSTRACT

Objective: The aim of this study was to define the Follow-up results and the observation of relationship between the clinical features and wound conditions of geriatric patients with pressure ulcers treated in the intensive care unit by Plastic, Reconstructive and Aesthetic Surgery (PRAS)

Methods: The research was carried out at Evliya Çelebi Training and Research Hospital of Kütahya University of Health Sciences between January 2018 and January 2020. All pressure ulcers on set of our patients was observed during hospitalization. Study was conducted on 215 patients hospitalized in neurology and general intensive care units. Ulcer diagnosis was performed by European Pressure Ulcer Advisory Panel (EPUAP) and National Pressure Ulcer Advisory Panel (NPUAP). Patient data were collected and evaluated by surgical care nurse and PRC surgeon together during the visit. The confidentiality and personal rights of each patient were respected.

Results: There were 215 patients with pressure injuries, 45.6% were hospitalized in the neurology intensive care unit and 42.5% were with the diagnosis of cerebrovascular disease, 41.6% of patients state of consciousness was evaluated as confused. Gender prevalence were 52.2% were female with mean age 72.5 ± 2.4. There are 43.2% of the ulcers were in the sacral area, 52% were in stage 2, all patients had fecal / urinary incontinence.

Conclusion: Awareness and education of the care professionals working in intensive care units in terms of preventive measures can save patients from pressure ulcers and avoid patients from the difficult and risky surgical interventions.

Keywords: Geriatrics, Intensive care, pressure ulcer

1. INTRODUCTION

Pressure ulcer is a condition of skin injury and necrosis caused by pressure alone or a combination of pressure and laceration/ friction which progress to complete closure or cessation of circulation of blood vessels in localized skin and / or subcutaneous tissues, usually occurring on bone protrusion areas (1,2).

Pressure ulcers are frequently seen in Intensive Care Units (ICU) where physical activity and mobilization are limited due to the sedative, analgesic and muscle relaxant drugs used. Patients in ICU are also frequently applied with mechanical ventilation because of loss of consciousness or general condition disorders. A prolonged stay in ICU can lead to ventilation disorders, incontinence, malnutrition, inflammation and hypoalbuminemia which in turn leads to excessive risk for pressure ulcers (3).

Pressure ulcers develop most often in the elderly, intensive care patients, and those who are long-term bed ridden. They are usually seen where there are bone protrusions and have a negative effect on quality of life, as they result in a slower healing process, prolonged hospital stay, increased risk of developing complications, may even be life-threatening and there by increase the cost of care (3,4,5).

If this commonly seen pathology is not treated, it can lead to infection and sepsis, and ultimately death. A multidisciplinary approach to treatment is important. For successful treatment, the branches of plastic surgery, general surgery, orthopedics, internal medicine, endocrinology, infection, neurology, physical therapy and rehabilitation are required to work incollaboration, with the inclusion of nurses and all health care professionals (6).

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Although the risk of pressure ulcers may be high, they can be prevented by taking the appropriate measures, and thus, length of hospital stay, treatment cost, nosocomial infections and mortality rates can be reduced (3).

This research was planned to define the clinical features of geriatric patients and the pressure ulcers that developed during their hospital stay and to discuss clinical experiences.

The aim of this study was to define follow-up results and the observation of relationship between the clinical features and wound conditions of geriatric patients with pressure ulcers treated in the intensive care unit by Plastic, Reconstructive and Aesthetic Surgery (PRAS).

2. METHODS

The research was conducted at Evliya Çelebi Training and Research Hospital, Kütahya University of Health Sciences between January 2018 and January 2020. Approval for this retrospective study was granted by the Ethics Committee of Okan University (Decision No: 14 / 22.01.2020). All the study procedures were in accordance with the 2008 regulations of the Helsinki Declaration. The study included a total of 215 patients hospitalized in the Neurology and General Intensive Care Units with the onset of pressure ulcers observed during hospitalization. The laboratory findings obtained on the day of PRAS consultation and on each patient visit were evaluated and measures were taken to eliminate the pressure effects. These measures included changing the position of the patient every 2 hours, the use of airbeds to ensure an even distribution of the patient's weight at all points, and the application of a silicone cushion with a central hole to the body parts corresponding to the bone protrusions. Systemic treatment (correction of anemia, hypoproteinemia and hypoalbuminemia) and local ulcer care were applied. If the ulcer was infected, parenteral antibiotic treatment was started as soon as possible according to the tissue culture and antibiogram test results evaluated by the infectious disease specialist. If the ulcer was clean, a prophylactic broad spectrum antibiotic was given 1 hour before the operation and was continued as needed. The necrotic tissues were debrided by tangential excision in each dressing. The patients were made ready for surgery within 2 to 3 weeks. Patients were accepted as suitable candidates for surgical treatment when the general health condition was stable, necrotic tissue was completely eliminated from the ulcers, the ulcer edges had started to contract and hemoglobin with total protein returned to normal limits. Surgery was performed with the consent of the patient's relatives. Conservative treatment was applied when surgical treatment could not be performed for any of the stated reasons.

Inclusion criteria:

– Age>70 years

– Hospitalised in Intensive Care Unit (ICU)

– Patients with an ASA score of 3

– Patients taking anticoagulants

– Pressure ulcer developed during hospitalisation

– Informed consent for participation in the study was obtained from relatives of the patient (PRC).

Exclusion criteria:

-Age <70 years

-Inpatients other than in ICU.

–Pressure ulcer developed before hospitalization

-Consent was not obtained from relatives of the patient for participation in the study.

Ulcer diagnosis was made according to the pressure ulcer classification system defined by the European Pressure Ulcer Advisory Panel (EPUAP) and National Pressure Ulcer Advisory Panel (NPUAP). Data and patient information were collected from the ulcer diagnosis and follow-up form of the Ministry of Health. Systemic diagnosis (consciousness, physical competence) and body mass indexes of the patients were evaluated according to the standards of the Ministry of Health. Patient data were collected by a nurse with a master's degree in surgical care nursing and a PhD in public health nursing and the PRA surgeon together during the patient visits and the patient evaluations were made in collaboration. The confidentiality and personal rights of each patient were respected. The data collection took approximately 20 minutes per patient. Conservative treatment consisted of daily washing of the pressure ulcers, necrotic areas with gauze and applying saline wet dressings. For severely affected patients, debridement was performed bedside with local anesthesia and for those with mild form of disease debridement was performed in the operating room under spinal or general anesthesia. Surgical closure of the pressure ulcer was made with flap surgery and skin grafting. Skin grafting could be applied to well granulated pressure ulcers in the trochanteric or heel regions, which were not in continuous contact with the bed and bore no patients weight. Flap surgery was performed in ischial, sacral and gluteal weight bearing regions. The surgical method to be chosen in the treatment of pressure sores varied according to the anatomical localization of the wound. The flaps we preferred in the sacral region were; the gluteus maximus muscle-skin rotation flap, bilateral gluteal V-Y advancement flap (Fig 1), unilateral V-Y advancement flap (Fig 2), transverse lumbosacral f lap, and limberg flap. In the trochanteric region, tensor fascia lata muscle-skin transposition flap, tensor fascia lata VY advancement flap, posterior gluteal thigh flap, vastus lateralis muscle flap, and subcutaneous pedicle tensor fascia lata myocutaneous island flap is preferred.

Data obtained in the study were analysed statistically using IBM SPSS Statistics software (SPSS IBM, Turkey). Conformity of the data to normal distribution was evaluated. Descriptive statistical methods (mean, standard deviation, frequency) were used

Figure 1. *Pressure Ulcer Repair with Skin Advancement Flap*

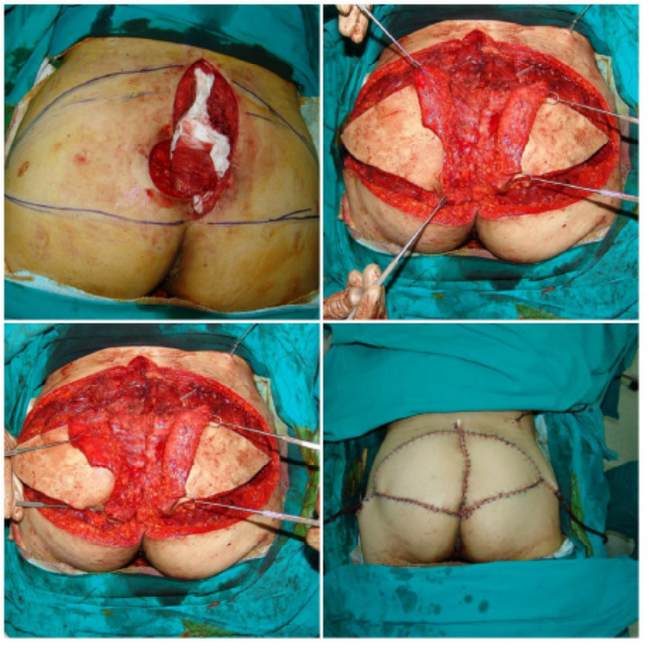

Figure 2. *Pressure Ulcer Repair with Bilateral V-Y Flap*

3. RESULTS

During our study, the number of hospitalizations in intensive care units was 1150 in two years, and bedsores developed in 215 of the hospitalized patients. this rate was determined as 18.69% of hospitalized patients. The 215 patients with pressure ulcers comprised 52.2% females and 47.8% males with a mean age of 72.5 ± 2.4 years, and mean body mass index of 20.1 ± 1.8. Of the total patients, 45.6% were hospitalized in the Neurology ICU and 42.5% had a diagnosis of cerebro vascular disease. Respiration with a mask was applied to 40.4%, 26.9% were intubated, and 33% had no comorbidity other than hypertension. It was determined that 73.9% of the cases were dependent on physical activity evaluation, and 36.2% were fed via enteral routes (nasogastric, gastrostomy, jejunostomy). In the evaluation of state of consciousness, 41.6% were confused. The ulcers were in the sacral area in 43.2% of the patients, at stage 2 in 52%, and stage 1 in 22.3%. All the patients had fecal / urinary incontinence (Table 1). According to the laboratory findings on the day of PRAS consultation and per patient visit, mean hemoglobin values were 10.3 ± 1.04 mg / dl, mean albumin values were 2.4 ± 0.2gr / dl, and mean hematocrit values were 32.7% ± 2.77. Surgery was applied to 58 geriatric patients whose ulcers developed in the hospital (Table 2). Vacuum-assisted dressing was used in 17 patients of which 15 recovered. Conservative treatment was applied to 140 patients with recovery recorded in 120. Successful recovery was seen in 80% of the treated patients. In patients with low albumin, hemoglobin and hematocrit values, the ulcers healing process was observed to be much faster after replacement. Ulcer lines were renewed and re-sutured was performed in three of our patients who developed separation of the suture lines as a complication. In a case who developed wound infection, the signs of infection were dressing and regressed with medical treatment without the need for additional intervention. Venous congestion developed six hours after the operation in a patient whose sacral defect was closed with a superior gluteal artery perforator island flap. Due to partial necrosis, a second operation was performed to advance the existing flap and the defect was closed. Other complications such as total flap loss, hematoma, and seroma were not observed in any of the cases. The mean hospital stay was found to be 16.26 (2-52) days.

Table 1. *Sociodemographic characteristics and clinical features of the geriatric patients in the study*

FEATURE	N	%
INTENSIVE CARE		
General IC	117	54.4
Neurology IC	98	45.6
GENDER		
Female	112	52.2
Male	103	47.8
MEDICAL DIAGNOSIS		
Cerebrovascular Event	92	42.5
General condition disorder	57	26.5
Pneumonia	39	18.5
Chronıc Obstructıve Pulmonary Dısease (COPD)	27	12.5
STATE OF CONSCIOUSNESS		
Confused	88	41.6
Coma	62	28.7
Conscious	42	19.5
Stupor	23	10.2
RESPIRATORY SUPPORT		
Mask	87	40.4
Nasal cannula	70	32.7
Intubation	58	26.9
PHYSICAL ACTIVITY		
Dependent	159	73.9
Semi-dependent	56	26.1
ADDITIONAL DISEASE		
Hypertension	71	33.0
Diabetes	68	31.8
COPD	32	14.8
Pneumonia	30	13.9
Diabetes Hypertension +	14	6.5
NUTRITION		
Enteral	78	36.2
Oral	71	33.2
Parenteral	66	30.6
PRESSURE ULCER REGION		
Sacrum	93	43.2
Coccyx	39	18.1
Trochanter	31	14.4
Heel	30	13.9
Scapula	22	10.4
PRESSURE ULCERSTAGE		
Stage 2	112	52.0
Stage 1	48	22.3
Stage 3	42	19.5
Stage 4	13	6.2
Total	215	100.0

Table 2. *Laboratory values of the geriatric patients in the study*

FEATURE	Value
Meanage (years)	72.5±2.4
Body mass index average	20.1±1.8
Average hemoglobin values	10.3±1.04mg/dl
Average albumin values	2.4±0.2gr/dl
Average hematocrit values	32.7±2.77

4. DISCUSSION

Despite the advances in patient care in recent years, the care, treatment and post-treatment rehabilitation of pressure ulcers are among the most difficult surgical problems. Recurrence of pressure ulcers is a common problem regardless of the treatment method used (7). Ultimately, attempts to prevent pressure ulcers and patient education should be part of the treatment of every patient (8,9). The anatomic localization of pressure ulcers is important as it can help in preventive interventions. Although ulcers can develop in any localisation under pressure, the most common areas in the current study were seen to be the sacrum, heels, ischium and trochanter. In a study of 200 patients, Dansereau and Conway identified the anatomic distribution of compression ulcers as 28% ischial, 19% trochanteric, 17% sacral and 36% other regions (heel, malleolus, knee, etc.). (9). In a series of 108 cases studied by Ercocen et al., pressure ulcers were detected as 47% sacral, 27% trochanteric, 15% ischial and 11% other regions (heel, malleolus, elbow and back) (10). Similar findings have been found in many studies (11,12). In the current cases, the most common localisation of pressure ulcers was sacral at 43.2%, followed by the coccyx region at 18.1%, and the trochanter region at 14.4%. In Western societies, pressure ulcers are more common in the ischial region, because of better rehabilitation with the patient sitting up earlier. In the current study, it was seen that the patients spent more time in the supine or lateral position due to the longer rehabilitation and poor adaptation to daily life because of low educational and economic levels. This explains why sacral pressure ulcers were so frequently seen in the current cases.

In a previous study of ICU patients in Turkey, the frequency of pressure ulcers was found to be 28.6%, with average patient age of 56.2 years (12). The incidence of pressure ulcers in intensive care units has been reported between %11 and %29 in different studies (13), and our results of frequency of pressure ulcers were found as %18.69 were found to be in agreement with the literature findings. In a study from Macedonia of 2099 ICU patients, the frequency of pressure ulcers was found to be 12.19%, with an average age of 76.38 years (13). In a study conducted in Italy, the frequency of pressure ulcers was found to be 22.7%, and the average age was 83.7 ± 7.8 years for those without pressure ulcers, and 85.6 ± 6.9 years for those with pressure ulcers (14). In the current study of 215 patients with pressure ulcers, 45.6% were in Neurology ICU, 52.2% were female, the mean age was 72.5 ± 2.4 years, and 42.5% were hospitalized with the diagnosis of cerebrovascular disease. During the 2 year

period of the study, 2774 patients were admitted to the Neurology and General ICUs, of which 215 (7.75%) met the inclusion criteria of this study.

According to the results of the current study survival analysis, the mean BMI of patients who developed pressure ulcers was 20.1 ± 1.8. While ulcers developed in all cachectic patients, approximately one-tenth of patients who were over weight developed an ulcer. According to the current study findings, it can be said that cachexia and excess weight are important factors in the development of pressure ulcers. In weak individuals, ulcers development is facilitated by adipose tissue resulting from changes in negative nitrogen balance. Being over weight causes the adipose tissue to deteriorate and the underlying tissues to be come more susceptible to ischemic damage (15,16). In a study by Neloska et al (2016), it was reported that 70.28% of cachectic patients developed pressure ulcers (13). Another study also stated that the rate of pressure ulcers was higher in cachectic and obese elderly patients compared to other groups (17).

The mean albumin value of the current study patients was 2.4 ± 0.2 gr/dl. It was observed that ulcer healing was faster when the albumin level was within the normal referenceranges. Previous studies have indicated that there is a positive relationship between pressure ulcer prevalence and low albumin level (18,19). In a study by Neloska et al. (2016), a significant correlation was determined between the presence of hypoalbuminemia and pressure ulcer development (13). Jaul and Menzel (2014) also reported that albumin level is a statistically significant factor in pressure ulcer development (17).

The mean hemoglobin values of the current study patients was 10.3 ± 1.04 mg/dl. In patients with low hemoglobin values, the risk of developing pressure ulcers is high. Ulcer healing was observed to be faster when the hemoglobin level was within the normal referenceranges in the current study patients. In a study by Hanonu (2014), the hemoglobin value of patients who developed pressure ulcers was determined to be 9.76 ± 1.71 g/dl (20). In a study of 2099 patients, Neloska et al. (2016) reported that patients with low hemoglobin developed pressure ulcers (13). Neiva et al (2014), reported that the mean hemoglobin value of patients who developed pressure ulcers was 10.5 ± 1.3 g / dl and a significant relationship was determined between low hemoglobin level and pressure ulcer development (21). The current study results can be seen to support the findings of previous studies showing that low hemoglobin level is a risk factor for pressure ulcer development.

Since relapse is frequently seen following the surgical treatment of pressure ulcers, especially in compression pressure ulcers, care should be taken not to damage adjacent flap areas while planning flaps in surgical treatment. Debridement is the first step in the surgical treatment of pressure ulcers (22). After debridement, the defect exposed is covered by appropriate skin or muscle-skin flaps. Small, superficial pressure ulcers localized in the sacral region can be closed with local cutaneous flaps (22). Musculocutaneous flaps should be preferred for wide and deep sacral compression ulcers. The most preferred muscle is the gluteus maximus muscle (23). In patients with a wide, deep cavity in the current study, the first choice was a gluteus maximus muscle-skin flaps. In trochanteric pressure ulcers, Foster et al. used a tensor fascia lata flap in 73 cases, and reported flap success rate of 93% and complication rate of 15% (24). In the current study cases, the first option was the tensor fascia lata muscle-skin flap. In one case, subcutaneous pedicle tensor fascia lata flap was applied, but partial necrosis developed in the flap. In trochanteric ulcers that destroy deep tissue and bone, a vastus lateralis muscle-skin flap with better blood supply and volume is preferred instead of a tensor fascia lata flap, which is a thin flap. This flap was used in 3 cases and no complications were encountered after the operation. Ischial pressure ulcers are the region with the highest incidence of relapse despite successful reconstruction. The recurrence rate for flaps used to close localized pressure ulcers in this region has been reported as 27.8% for fasciocutaneous flaps and 63% for musculocutaneous flaps (24). Among the flap options, gluteal thigh flap, which is fed from the descending branch of the inferior gluteal artery, is used most often. This flap can be prepared as a muscle-skin flap or a fasciocutaneous flap. Other flap options are inferior gluteus maximus muscle-skin flap and biceps femoris V-Y advancement flap (23). The lower half of the gluteus maximus muscle is carried with the skin on it in the form of a rotation flap. Hamstring muscles individually or collectively, gracilis or tensorfascia lata muscle-skin flaps are other muscle-skin flaps which are preferred to close ischial pressure ulcers. If the defect is large, as in the current study cases was ischial pressure injuried, gluteal muscle-skin flaps were preferred because of the good blood supply and sufficient cushioning. Medium-sized defects were covered with posterior gluteal thigh flaps.

5. CONCLUSION

As health care professionals working in ICU, providing daily care to patients are the first link directly witnessing primary changes in pressure ulcers, they have to be aware of preventive measures, the algorithm for effective intervention to additional problems in the early period, and the effective and timely prevention of malnutrition. Thus, the clinical problem of pressure ulcers can be resolved before reaching the difficult and risky surgical intervention stage. It should be kept in mind that surgical treatment of pressure ulcers is the last step and resolution of the basic problem can be achieved effectively with raised levels of awareness and education programs. More attention should be given to patients over the age of 70 years as the risk of pressure ulcer development is much higher in this patient group.

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Clinical and Experimental Health Sciences

Antimicrobial Effect of Polyhexanide on Denture Base and Soft Lining Materials

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ABSTRACT

Objective: Polyhexanide (PHMB; polyhexamethylene biguanide) is a well-known antiseptic agent; however, no data exist for its application on denture base and lining materials. In the present in vitro study, the aim was to compare viable bacterial or fungal cell numbers and their adhesion on different types of denture base and lining materials in diverse concentrations of PHMB.

Methods: Light-activated urethane dimethacrylate (UDMA), heat-polymerized polymethyl methacrylate (PMMA), heat-polymerized polydimethylsiloxane, and autopolymerizing polyethylmethacrylate discs were prepared for each group (n = 10). 1×10^8 CFU/mL of all the tested species were appended separately to discs, and they were immersed into different PHMB suspensions (0.5%, 1%, 2%, and 5%) for 10 minutes. The antimicrobial activity and number of adherent species on the surface were evaluated.

Results: In the PMMA group, all studied species except *C. albicans, L. acidophilus*, and *S. aureus* were decreased in various concentrations ($p < 0.05$), and all studied species presented a significant decrease in every concentration of PHMB in the UDMA group ($p < 0.01$) in comparison to the control. *N. sicca, K. pneumoniae, S. pyogenes, S. sanguis, C. pseudotuberculosis*, and *S. aureus* ($p < 0.05$) were reduced in the heat-polymerized polydimethylsiloxane group, while all tested species except *B. subtilis* were decreased in the autopolymerizing polyethylmethacrylate group in comparison to the control ($p < 0.01$). Among all tested materials and species, no significant difference was detected in adherent cell number ($p > 0.05$).

Conclusion: PHMB suspension, in various concentrations, can reduce some species of bacterial and yeast cells.

Keywords: Disinfectant, bacterial growth, denture adhesive, denture base.

1. INTRODUCTION

Removable prostheses are still a treatment of choice in cases of edentulism, especially in the older population. Sometimes the fundamental rules may not be sufficient for ideal denture retention and stability, and soft denture lining materials are identified as a viable option to overcome this problem (1). Inadequate oral hygiene related to biofilm formation and plaque accumulation is one of the major problems for denture base and soft lining materials (2). These materials are easily colonized by microorganisms, including pathogenic and opportunistic bacteria and fungi (3,4). The biofilm formation and adhesion of microorganisms on denture base and soft lining materials depend on several factors, including surface roughness, free energy, and hydrophobicity (5,6). This formation and accumulation may lead to tissue inflammation in the oral mucosa and is identified as denture-related stomatitis, which can be associated with a burning sensation, bleeding, unpleasant taste, and halitosis (7).

To overcome this problem, prostheses can be cleaned mechanically, chemically, or through a combination of both (8). Mechanical cleaning may not be as effective as demanded due to the irregular surface texture of the dentures and the limited hand manipulation of the senior population (8,9). According to the literature, different chemical agents have been studied to disinfect denture base and soft materials; however, none of them has demonstrated superiority over any other (10-14). Furthermore, some adverse effects, including allergic reactions and oral mucosal tissue irritations, due to toxic ingredients of related disinfectants have been reported. These toxic ingredients could become incorporated into the denture base and lining materials (15,16).

Polyhexanide (polyhexamethylene biguanide; PHMB) is a biocidal cationic polymer (17). It is an antiseptic agent that has been used for many years in different applications in medicine for its broad antibacterial and antifungal activity (17-19). It has been commonly accepted that the antimicrobial activity is due to the ability of PHMB to perforate the bacterial phospholipid membrane, leading ultimately to bacterial death (20). It is one

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of the most promising agents with low cytotoxicity and high tissue compatibility (20,21). Studies have indicated that PHMB inhibits plaque regrowth and reduces oral bacterial count, thus it may be a good option for preventive applications (22,23). To the best of the author's knowledge, despite the advantages of PHMB, no data currently exists in the literature regarding its application as a disinfectant agent on denture base and lining materials. In the present in vitro study, the aim was to compare viable bacterial or fungal cells and their adhesion on different types of denture base and lining materials in diverse concentrations of PHMB. The null hypothesis that PHMB has a reduced tendency for viable cell number and the adhesion of bacterial or fungal microorganisms on denture base and soft lining materials was tested.

2. METHODS

In this study, light-activated urethane dimethacrylate (UDMA) denture base material (Eclipse, Dentsply Trubyte, York, PA, USA), heat-polymerized polymethyl methacrylate (PMMA) denture base material (Meliodent, Bayer Dental, Newbury, UK), heat-polymerized polydimethylsiloxane (Molloplast® B, Detax GmbH & Co., Ettingen, Germany) soft lining material, and autopolymerizing polyethylmethacrylate (Visco-gel, Dentsply Trubyte, York, PA, USA) soft lining material were tested.

2.1. Specimen preparation

Specimens for each material were fabricated by investing wax patterns (12 × 12 × 3 mm) in a cylindric-shaped stone mold. The heat-cure PMMA resin specimens were prepared within a dental flask and cured in a manner similar to that used in conventional denture construction according to the manufacturer's instructions.

UDMA specimens were preheated for 2 minutes in a special oven (Eclipse Conditioning Oven, Dentsply Trubyte, York, PA, USA) to 55 ºC. A separating agent (Al-Cote, Dentsply Trubyte, York, PA, USA) was then applied onto the stone mold, and the warmed resin was adapted into the mold by using finger pressure. After cooling, specimens were removed from the mold, and remnants were removed. To prevent inhibition of polymerization by oxygen, the specimens were warmed in a 55 ºC oven (Eclipse Conditioning Oven, Dentsply Trubyte, York, PA, USA) for 1 hour, and coated with an air barrier coating (Eclipse ABC, Dentsply Trubyte, York, PA, USA). Then, specimens were processed in a light-processing unit (Eclipse Processing Unit, Dentsply Trubyte, York, PA, USA) for 10 minutes. At the end of polymerization, any excess resin was removed using finer grades of silicon carbide paper (320, 600, and 1200 grit), and the polishing was performed with a felt wheel and diamond paste.

Soft lining material samples were prepared according to the manufacturer's instructions. To explain briefly, a separator was applied where bonding was not desired. Temporary soft denture liners were packed into molds and closed under pressure. Polymerization was achieved, in a water bath at 100 ºC for 2 hours for heat-polymerized polydimethylsiloxane, and proximately for 2 or 3 minutes from the start of mixing for the autopolymerization of polyethylmethacrylate. Undesired excess resin was trimmed by sharp instruments. Polyhexanide (Fagron GmbH & Co. KG, Hamburg, Germany) was diluted in water of standardized hardness (WSH; according to DIN EN 1040) to the final test concentrations. All further dilutions were prepared with 40% DMSO/WSH. The suitability as solvent of 40% DMSO/WSH regarding inefficacy was demonstrated using the quantitative suspension test as well as the microdilution test, according to Koburger et al. (24).

2.2. Cell culture and adherence assay

In order to assess bacterial and fungal adhesion, denture base and soft lining disc specimens (n = 10) were sterilized with ultraviolet light and kept in Petri dishes. The bacterial and fungal strains used in this study are presented in Table 1. In the present study, the cell culture and adherence assays were modified and performed according to Pavan et al.'s technique (25). Briefly, bacterial strains were grown onto Mueller Hinton agar (CM337, Oxoid Deutschland GmbH, Wesel, Germany) plates at 37 ºC. Fungal strains were grown onto Sabouraud dextrose agar (CM41, Oxoid Deutschland GmbH) at 30 ºC. 0.5 McFarland suspensions corresponding to $1x10^8$ CFU/mL of all the tested bacteria and fungi were appended separately to all test discs. Discs were placed into the incubators (EN400, NÜVE, Ankara, Turkey) at 90% humidity and 37 ºC. For fungal suspensions, each disc was incubated at 90% humidity and 30 ºC. After 12 h, 24 h, and 36 h of incubation, discs were immersed into PHMB suspensions of 0.5%, 1%, 2%, and 5% concentrations for 10 minutes. The disks were removed from the PHMB suspensions and transferred to microtubes containing sterile saline, and after vortexing, the suspensions were diluted and plated into the blood agar base (Merck KGaA, Darmstadt, Germany) to define the number of bacteria or fungi, and their quantity was determined by counting the colonies.

Moreover, 0.5 McFarland suspensions of all the tested bacteria and fungi were placed into the remaining discs, and then kept in the incubator for 6 h. To remove the loosely adherent cells, the specimens' surfaces were gently rinsed with 1 mL of phosphate-buffered saline (PBS; Sigma-Aldrich, St. Louis, MO, USA) at a distance of 10 cm for 1 min. Adherent micro-organisms on the surface of the specimens were counted in blood agar plates (Merck KGaA).

Table 1. *The tested bacterial and fungal strains in present study*

Number	Names	Codes	Gram Stain	Morphology
1	*Neisseria sicca*	ATCC-9913	Gr (-)	Diplococcus
2	*Streptococcus mutans*	ATCC-21752	Gr (+)	Coccus
3	*Klebsiella pneumoniae*	ATCC-10031	Gr (-)	Bacillus
4	*Bacillus subtilis*	ATCC-6633	Gr (+)	Bacillus
5	*Streptococcus pyogenes*	ATCC-19615	Gr (+)	Coccus
6	*Candida albicans*	ATCC-10231	Gr (+)	Yeast
7	*Lactobacillus acidophilus*	ATCC-11975	Gr (+)	Bacillus
8	*Streptococcus sanguis*	ATCC-10557	Gr (+)	Coccus
9	*Proteus vulgaris*	ATCC-7829	Gr (-)	Bacillus
10	*Corynebacterium pseudotuberculosis*	ATCC-19410	Gr (+)	Bacillus
11	*Escherichia coli*	ATCC-11229	Gr (-)	Bacillus
12	*Candida tropicalis*	ATCC-750	Gr (+)	Yeast
13	*Staphylococcus aureus*	ATCC-25923	Gr (+)	Coccus

2.3. Statistical analysis

In the post-hoc power analysis, the alpha error was accepted as 0.05 in order to control Type I error, and the power ranged from 77.1% to 99.9%. This analysis was performed by G* Power 3.0.10 Franz (Faul, Universitat Kiel, Kiel, Germany). Statistical analysis was performed using one-way analysis of variance (ANOVA), and wherever appropriate, subsequent post-hoc analysis was performed using the Tukey test (a = 0.05). Log-transformed values were used due to positively skewed distribution. Statistical data were processed using IBM SPSS 24.0 software (Armonk, NY, USA) for Windows. The statistical significance was set as 0.05.

3. RESULTS

The viable cell number of related microorganisms on the denture base and soft lining materials, after immersion in different concentrations of PHMB suspensions, are presented in Tables 2 through 5. To state the results briefly, in PMMA samples, the number of *Candida albicans*, *Lactobacillus acidophilus*, and *Staphylococcus aureus* species did not demonstrate any significant difference in suspensions of PHMB with different concentrations ($p > 0.05$). In contrast, in UDMA samples, the viable cell number of all studied microorganisms presented a significant decrease in every concentration of PHMB suspension in comparison to the control samples ($p < 0.01$). Among the dental liner specimens, in heat-polymerized polydimethylsiloxane, different concentrations of PHMB suspension reduced the number of *Neisseria sicca* ($p < 0.05$), *Klebsiella pneumoniae* ($p < 0.05$), *Streptococcus pyogenes* ($p < 0.05$), *Streptococcus sanguis* ($p < 0.05$), *Corynebacterium pseudotuberculosis* ($p < 0.05$), and *Staphylococcus aureus* ($p < 0.05$). PHMB suspensions with different concentrations decreased all tested microorganism species except *Bacillus subtilis* in autopolymerizing polyethylmethacrylate samples in comparison to the control suspension ($p < 0.01$). No significant difference was observed between the different concentrations of PHMB suspensions in the reduction of viable bacteria and yeast numbers on tested denture base and soft lining materials ($p > 0.05$).

Table 2. *Viable cell number of related microorganisms on PMMA samples that immersed into PHMB suspensions of 0.5%, 1%, 2%, 5% concentration for 10 minutes.*

	PMMA n:10														
	12h					24h					36h				
	0.5 %	**1%**	**2%**	**5%**	**C**	**0.5%**	**1%**	**2%**	**5%**	**C**	**0.5%**	**1%**	**2%**	**5%**	**C**
N. sicca	10^6	$\mathbf{10^3}$	$\mathbf{10^2}$	**0**	$\mathbf{10^5}$	10^4	$\mathbf{10^2}$	$\mathbf{10^2}$	**0**	$\mathbf{10^5}$	10^4	$\mathbf{10^1}$	$\mathbf{10^1}$	**0**	$\mathbf{10^6}$
S. mutans	10^6	$\mathbf{10^2}$	$\mathbf{10^2}$	**0**	$\mathbf{10^5}$	10^5	$\mathbf{10^2}$	$\mathbf{10^2}$	**0**	$\mathbf{10^5}$	10^4	$\mathbf{10^1}$	$\mathbf{10^1}$	**0**	$\mathbf{10^6}$
K. pneumonia	10^7	10^6	10^5	$\mathbf{10^2}$	$\mathbf{10^5}$	10^6	10^5	10^4	$\mathbf{10^1}$	$\mathbf{10^6}$	10^5	10^4	10^3	$\mathbf{10^1}$	$\mathbf{10^7}$
B. subtilis	$\mathbf{10^7}$	$\mathbf{10^6}$	$\mathbf{10^1}$	$\mathbf{10^1}$	$\mathbf{10^4}$	$\mathbf{10^2}$	$\mathbf{10^2}$	$\mathbf{10^1}$	$\mathbf{10^1}$	$\mathbf{10^4}$	$\mathbf{10^2}$	$\mathbf{10^1}$	**0**	**0**	$\mathbf{10^7}$
S. pyogenes	10^6	$\mathbf{10^2}$	$\mathbf{10^2}$	**0**	$\mathbf{10^4}$	10^5	$\mathbf{10^2}$	$\mathbf{10^2}$	**0**	$\mathbf{10^5}$	10^4	$\mathbf{10^1}$	$\mathbf{10^1}$	**0**	$\mathbf{10^6}$
C. albicans	10^5	10^2	10^2	0	10^3	10^1	0	0	0	10^3	0	0	0	0	10^7
L. acidophilus	10^6	10^3	10^2	0	10^3	10^2	10^2	10^2	0	10^3	10^2	10^2	10^1	0	10^6
S. sanguis	10^6	10^6	**0**	**0**	$\mathbf{10^4}$	10^4	10^4	**0**	**0**	$\mathbf{10^4}$	10^2	10^2	**0**	**0**	$\mathbf{10^7}$
P. vulga	10^7	10^7	$\mathbf{10^5}$	**0**	$\mathbf{10^6}$	10^6	10^5	**0**	**0**	$\mathbf{10^7}$	10^5	10^4	**0**	**0**	$\mathbf{10^7}$
C. pseudotuberculosis	10^7	10^5	10^5	$\mathbf{10^2}$	$\mathbf{10^5}$	10^6	10^4	10^4	$\mathbf{10^1}$	$\mathbf{10^6}$	10^5	10^4	10^3	$\mathbf{10^1}$	$\mathbf{10^7}$
E. coli	$\mathbf{10^5}$	$\mathbf{10^3}$	$\mathbf{10^2}$	$\mathbf{10^2}$	$\mathbf{10^6}$	$\mathbf{10^5}$	$\mathbf{10^2}$	$\mathbf{10^2}$	$\mathbf{10^2}$	$\mathbf{10^7}$	$\mathbf{10^4}$	$\mathbf{10^2}$	$\mathbf{10^2}$	$\mathbf{10^2}$	$\mathbf{10^7}$
C. tropicalis	10^5	$\mathbf{10^3}$	$\mathbf{10^2}$	$\mathbf{10^2}$	$\mathbf{10^4}$	10^5	$\mathbf{10^3}$	$\mathbf{10^2}$	$\mathbf{10^1}$	$\mathbf{10^5}$	10^4	$\mathbf{10^2}$	$\mathbf{10^2}$	$\mathbf{10^1}$	$\mathbf{10^6}$
S. aureus	10^5	10^4	10^4	10^2	10^4	10^5	10^4	10^4	10^2	10^5	10^3	10^3	10^3	10^2	10^5

PMMA: Heat-polymerized polymethyl methacrylate; PHMB: Polyhexanide; C: Control; h: Hours. Numbers with bold indicate statistically significant difference in comparison to control (p<0.05).

Table 3. *Viable cell number of related microorganisms on UDMA samples that immersed into PHMB suspensions of 0.5%, 1%, 2%, 5% concentration for 10 minutes.*

	UDMA n:10														
	12h					24h					36h				
	0.5 %	1%	2%	5%	C	0.5%	1%	2%	5%	C	0.5%	1%	2%	5%	C
N. sicca	10^3	**10^1**	**0**	**0**	**10^3**	10^1	**0**	**0**	**0**	**10^3**	10^1	**0**	**0**	**0**	**10^4**
S. mutans	**10^1**	**0**	**0**	**0**	**10^3**	**0**	**0**	**0**	**0**	**10^3**	**0**	**0**	**0**	**0**	**10^4**
K. pneumonia	**10^2**	**10^1**	**0**	**0**	**10^3**	**10^1**	**0**	**0**	**0**	**10^3**	**0**	**0**	**0**	**0**	**10^4**
B. subtilis	10^2	**10^1**	**10^1**	**0**	**10^3**	**10^1**	**10^1**	**10^1**	**0**	**10^3**	**10^1**	**10^1**	**0**	**0**	**10^4**
S. pyogenes	**0**	**0**	**0**	**0**	**10^3**	**0**	**0**	**0**	**0**	**10^3**	**0**	**0**	**0**	**0**	**10^4**
C. albicans	**10^2**	**10^1**	**0**	**0**	**10^4**	**10^2**	**0**	**0**	**0**	**10^5**	**10^1**	**0**	**0**	**0**	**10^6**
L. acidophilus	**10^2**	**10^1**	**0**	**0**	**10^3**	**10^1**	**10^1**	**0**	**0**	**10^3**	**10^1**	**10^1**	**0**	**0**	**10^4**
S. sanguis	**10^1**	**0**	**0**	**0**	**10^3**	**0**	**0**	**0**	**0**	**10^3**	**0**	**0**	**0**	**0**	**10^4**
P. vulga	**10^2**	**10^1**	**0**	**0**	**10^3**	**10^1**	**0**	**0**	**0**	**10^3**	**0**	**0**	**0**	**0**	**10^4**
C. pseudotuberculosis	10^3	**10^2**	**0**	**0**	**10^3**	10^2	**10^1**	**0**	**0**	**10^3**	10^1	**0**	**0**	**0**	**10^4**
E. coli	10^5	10^4	**0**	**0**	**10^4**	10^4	10^3	**0**	**0**	**10^5**	10^3	10^2	**0**	**0**	**10^6**
C. tropicalis	**10^2**	**10^1**	**0**	**0**	**10^4**	**10^1**	**10^1**	**0**	**0**	**10^4**	**10^1**	**0**	**0**	**0**	**10^5**
S. aureus	**10^2**	**10^2**	**0**	**0**	**10^3**	**10^2**	**10^1**	**0**	**0**	**10^4**	**10^1**	**10^1**	**0**	**0**	**10^5**

UDMA: light-activated urethane dimethacrylate; PHMB: Polyhexanide; C: Control; h: Hours.
Numbers with bold indicate statistically significant difference in comparison to control (p<0.01).

Table 4. *Viable cell number of related microorganisms on Heat-Polymerized Polydimethylsiloxane samples that immersed into PHMB suspensions of 0.5%, 1%, 2%, 5% concentration for 10 minutes.*

	Heat-Polymerized Polydimethylsiloxane n:10														
	12h					24h					36h				
	0.5 %	1%	2%	5%	C	0.5%	1%	2%	5%	C	0.5%	1%	2%	5%	C
N. sicca	10^5	10^5	10^4	**10^4**	**10^5**	10^4	10^4	10^4	**10^3**	**10^5**	10^4	10^4	10^3	**10^2**	**10^6**
S. mutans	10^4	10^4	10^3	10^3	10^3	10^3	10^3	10^2	10^2	10^4	10^1	10^1	0	0	10^5
K. pneumonia	**10^4**	10^4	10^4	10^3	**10^4**	**10^3**	10^3	10^3	10^2	**10^5**	**10^2**	10^2	10^2	10^1	**10^6**
B. subtilis	10^4	10^4	10^3	10^3	10^3	10^3	10^3	10^2	10^2	10^4	10^2	10^2	10^1	0	10^5
S. pyogenes	10^4	10^4	10^3	**10^2**	**10^3**	10^3	10^3	10^2	**0**	**10^4**	10^2	10^2	0	**0**	**10^5**
C. albicans	10^3	10^3	10^3	10^2	10^3	10^2	10^2	10^2	0	10^4	10^1	10^1	0	0	10^5
L. acidophilus	10^3	10^3	10^2	10^1	10^2	10^2	10^2	10^1	0	10^3	10^1	0	0	0	10^4
S. sanguis	10^2	**10^2**	**10^1**	**0**	**10^2**	10^1	**10^1**	**0**	**0**	**10^3**	10^1	**0**	**0**	**0**	**10^4**
P. vulga	10^3	10^3	10^2	10^2	10^3	10^2	10^2	10^1	10^1	10^4	10^1	0	0	0	10^4
C. pseudotuberculosis	10^3	10^3	**10^2**	**10^1**	**10^3**	10^2	10^2	**10^1**	**0**	**10^4**	10^1	10^1	**0**	**0**	**10^4**
E. coli	10^4	10^4	10^3	10^3	10^3	10^3	10^3	10^2	10^1	10^4	10^2	10^2	10^1	0	10^4
C. tropicalis	10^3	10^3	10^3	10^2	10^3	10^3	10^3	10^2	10^2	10^4	10^2	10^2	10^1	0	10^4
S. aureus	10^4	**10^3**	**10^2**	**10^1**	**10^3**	10^2	**10^2**	**0**	**0**	**10^4**	10^1	**0**	**0**	**0**	**10^4**

PHMB: Polyhexanide; C: Control; h: Hours. Numbers with bold indicate statistically significant difference in comparison to control (p<0.05).

Table 5. *Viable cell number of related microorganisms on Autopolymerising polyethylmethacrylate samples that immersed into PHMB suspensions of 0.5%, 1%, 2%, 5% concentration for 10 minutes.*

	Autopolymerising polyethylmethacrylate n:10														
	12h					24h					36h				
	0.5 %	1%	2%	5%	C	0.5%	1%	2%	5%	C	0.5%	1%	2%	5%	C
N. sicca	10^3	**10^2**	**10^2**	**10^2**	**10^4**	10^3	**10^2**	**10^1**	**10^1**	**10^4**	10^2	**10^1**	**10^1**	**0**	**10^5**
S. mutans	**10^3**	**10^2**	**10^2**	**10^1**	**10^4**	**10^3**	**10^2**	**10^2**	**0**	**10^5**	**10^2**	**10^1**	**10^1**	**0**	**10^5**
K. pneumonia	10^5	10^4	**10^3**	**10^3**	**10^4**	10^5	10^4	**10^2**	**10^2**	**10^5**	10^4	10^3	**10^2**	**10^2**	**10^5**
B. subtilis	10^3	10^3	10^3	10^3	10^3	10^3	10^3	10^2	10^1	10^4	10^3	10^2	10^1	10^1	10^5
S. pyogenes	10^4	**10^3**	**10^3**	**10^1**	**10^4**	10^3	**10^3**	**10^3**	**0**	**10^5**	10^3	**10^2**	**10^2**	**0**	**10^5**
C. albicans	10^3	10^3	**10^2**	**10^1**	**10^3**	10^2	10^2	**10^2**	**0**	**10^4**	10^1	10^1	**10^1**	**0**	**10^5**
L. acidophilus	**10^2**	**10^2**	**10^2**	**10^1**	**10^3**	**10^2**	**10^2**	**10^2**	**0**	**10^4**	**10^2**	**10^1**	**10^1**	**0**	**10^4**
S. sanguis	10^4	10^3	**10^1**	**10^1**	**10^3**	10^4	10^2	**10^1**	**0**	**10^4**	10^3	10^1	**10^1**	**0**	**10^4**
P. vulga	10^3	**10^2**	**10^1**	**0**	**10^3**	10^3	**10^2**	**10^1**	**0**	**10^4**	10^2	**10^1**	**10^1**	**0**	**10^4**
C. pseudotuberculosis	**10^3**	**10^2**	**10^1**	**0**	**10^4**	**10^1**	**10^1**	**10^1**	**0**	**10^5**	**10^1**	**10^1**	**0**	**0**	**10^5**
E. coli	10^4	**10^3**	**10^3**	**10^1**	**10^4**	10^4	**10^3**	**10^2**	**10^1**	**10^5**	10^3	**10^3**	**10^1**	**10^1**	**10^5**
C. tropicalis	**10^4**	**10^2**	**10^1**	**0**	**10^5**	**10^3**	**10^1**	**0**	**0**	**10^5**	**10^2**	**0**	**0**	**0**	**10^6**
S. aureus	**10^4**	**10^3**	**10^3**	**0**	**10^5**	**10^4**	**10^3**	**10^3**	**0**	**10^5**	**10^3**	**10^3**	**10^2**	**0**	**10^6**

PHMB: Polyhexanide; C: Control; h: Hours. Numbers with bold indicate statistically significant difference in comparison to control ($p<0.01$).

Among the adherent cell numbers of studied microorganisms on denture base and soft lining specimens, after rinsing with 1 mL of phosphate-buffered saline, no significant difference was detected between the different concentrations of PHMB suspensions and the control ($p > 0.05$).

4. DISCUSSION

In the present study, the null hypothesis was partially accepted due to the PHMB of various concentrations affecting only the viable cell number of different microorganisms on the denture base and soft lining materials. According to our findings, the number of adherent microorganisms was not responsive to PHMB.

In this in vitro study, to determine the viable cell numbers after the incubation period and treatment with different PHMB suspensions, the culture method (CFU/mL) was appointed. This method is sensitive enough to allow for exclusive detection of surviving microorganisms under favorable conditions (26). Budtz-Jorgensen et al. stated that the build-up of denture plaque was initially rapid but then slowed down (27). In their study, the number of bacteria and yeasts were similar in 2-day-old and 7-day-old plaque (27). In the present study, PHMB suspensions were prepared in concentrations of 0.5 to 5%. These amounts were determined according to a study from Koburger and colleagues (24). They indicated that the minimum inhibitory concentration and minimum bactericidal concentration of PHMB varied from 0.5 mg/L to 4 mg/L and from 1 mg/L to 32 mg/L, respectively. They determined the comparable concentrations for the minimum inhibitory concentration (MIC_{48}) and minimum bactericidal concentration (MBC_{24}).

Disinfectant solutions are good options to achieve proper hygiene in denture base and/or reline materials. According to the literature, sodium hypochlorite (10), chlorhexidine digluconate (10), sodium perborate (11), glutaraldehyde (13), and different natural ingredients (12,14) have been tested. Despite the significant reduction in bacteria and *Candida* spp. counts, none of these agents has demonstrated superiority to the others. On the other hand, PHMB has been marketed as a disinfectant solution in western countries for many years (28). Successful outcomes have been achieved using PHMB in wound treatments, mouthwash formulations, and soft lens care solutions (17,19,23). PHMB is also well known for its broad antimicrobial spectrum against gram positive and negative bacteria and yeasts (29,30). However, in 2013, the European Chemicals Agency classified PHMB as ''fatal if inhaled,'' so it should be used with caution (31). In the present study, we did not check the amount of coated and residual PHMB content on the surface of the samples after incubation and subsequent washing, and we consider this as a limitation of the study. To best of our knowledge, however, there is no described safety threshold value for PHMB as a denture disinfectant agent, and future studies are warranted related to this issue. In our study, 6 different species of bacillus (3 gram positive and 3 gram negative), 4 different species of gram positive coccus, a gram negative diplococcus, and 2 different species of yeasts were tested. These microorganisms exist in oral microbiota and play a role in plaque accumulation and pathogenesis of denture stomatitis (32). According to our results, PHMB of various concentrations was able to decrease the number of viable cells only in some of the tested microorganisms that were incubated on different types of denture base and soft lining materials in comparison to the control samples, and any significant difference was observed between the different concentrations of PHMB suspensions. These findings were in accordance with the antibacterial effect of PHMB on different surfaces, objects, and instruments (28,29).

In the present study, the remaining adherent cell number of the studied microorganisms on the denture base and

soft lining materials did not demonstrate any significant difference. Adhesion of microorganisms depends on the type of material. Increased surface roughness, free surface energy, and wettability are influential factors of bacterial adhesion (5,6). For instance, bacteria strains with a high free surface energy, such as *Streptococcus mutans*, can adhere preferentially to hydrophilic substrates that exhibit high free surface energy (6). These indicators may explain the diverse number of viable cells on tested materials with different concentrations of PHMB. In this study, these factors were not tested, and this can be considered a limitation of our study. In line with present outcomes, PHMB seems to be a potential disinfecting agent for removable prostheses; however, well-designed clinical studies that consider the possible effects of saliva, intra-oral pH, and temperature as well as the material characteristics are warranted.

5. CONCLUSION

Within the limits of our study, PHMB suspension, of various concentrations, can reduce some species of bacterial and yeast cells. Any significant difference was observed between the different concentrations of PHMB suspensions regarding their antimicrobial effect. Clinical application, optimal level of concentration, and oral tissue response of PHMB need to be tested with further studies.

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Clinical and Experimental Health Sciences

The Risk Factors for Preoperative and Postoperative Deep Vein Thrombosis in Surgical Patients

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ABSTRACT

Objective: This paper investigated the risk of preoperative and postoperative deep vein thrombosis (DVT) in surgical patients.

Methods: The sample consisted of 377 patients of the general surgery, orthopedics and traumatology, neurosurgery, and cardiovascular surgery clinics of a university hospital. Data were collected using a demographic characteristics questionnaire, the Deep Vein Thrombosis Diagnostic Criteria Form, the Autar Deep Vein Thrombosis Risk Assessment Scale, the Caprini Risk Assessment Model, and the Padua Prediction Score. The data were analyzed using descriptive analysis.

Results: According to the Autar Deep Vein Thrombosis Risk Assessment Scale, most participants were in the "low risk" category in the preoperative period (91%), and more than a quarter of the participants were in the "high risk" category in the postoperative period (30%). According to the Caprini Risk Assessment Model, less than half of the participants were in the "moderate risk" group in the preoperative period (39%), and more than half the participants were in the "high risk" group in the postoperative period (70.6%). According to the Padua Prediction Score, most participants were in the "low risk" category in the preoperative period (82.2%), and more than half the participants were in the "high risk" group in the postoperative period (52.8%). More than half the participants who used graduated compression stocks in the preoperative period misused them (62.7%). A bit more than half the participants who used graduated compression stocks in the postoperative period used them correctly.

Conclusion: The results show that surgical patients are at a higher risk for deep vein thrombosis in the postoperative period than in the preoperative period.

Keywords: Surgical nursing, patient care, deep vein thrombosis, thromboembolism.

1. INTRODUCTION

Deep vein thrombosis (DVT) is a health problem that causes preventable deaths (1). It is a type of venous thromboembolism (VTE), a major risk factor for most hospitalized persons. Half a million cases of DVT and 300.000 cases of pulmonary embolism (PE) are reported annually in six European countries (2). According to the USA national database, the prevalence of DVT is 7.1 cases per 1.000 (3). The prevalence of VTE in postoperative Korean patients is 20.9 cases per 1.000 (4). There is no dataset on VTE in Turkey, but Acun (2012) reported its prevalence and incidence in postoperative patients in Turkey as 0.8% and 1.3%, respectively (5).

Deep vein thrombosis is generally caused by regional trauma, hypercoagulability, and the narrowing of the blood flow in the vascular wall of the lower extremities. It can suddenly burst and result in a blood clot (1). Although DVT generally presents with local pain, swelling, discoloration, and warm skin, different methods (USG and venography) should be used to diagnose it. Deep vein thrombosis can cause long-term posttraumatic syndrome or chronic venous insufficiency, reducing the quality of life and increasing health costs (6, 7).

Age, stroke or paralysis, a history of DVT, immobility, cancer treatment, obesity, cardiac dysfunction, varicose veins, the presence of a central venous catheter, inflammatory bowel disease, pregnancy, estrogen use, and nephrotic syndrome are risk factors for DVT. However, the primary cause of DVT in the lower extremities is major surgical interventions (hip, leg, pelvic fracture, etc.) (8, 9).

Patients should start receiving pharmacological and mechanical prophylaxis at least 24 hours before surgery to

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minimize the risk factors for DVT (10). Early mobility and anti-embolism stockings are the postoperative interventions of choice for low-risk patients. In addition to those interventions, intermediate-risk patients should undergo intermittent pneumatic compression (IPC) and anticoagulant medication therapy. High-risk patients should receive pharmacological treatment (8).

Surgical nurses play a critical role in preventing DVT (7, 11, 12). Healthcare professionals should identify the risk factors for DVT in the first admission and apply medication when necessary. The Safe Surgery Checklist in the Operating Room assesses whether DVT prophylaxis is necessary "before the surgical incision" (13). In the postoperative period, nurses monitor the signs and symptoms of DVT, help patients with early mobility, get them to do deep breathing and coughing exercises, and teach them how to use elastic compression stockings and IPC devices (14).

There are many national and international guidelines for identifying, preventing, and managing the risk factors for DVT (14, 15). Healthcare professionals should use valid and reliable tools to determine the risk level of DVT (14, 16-18).

Nurses should use various scales to identify the risk factors for DVT because it is one of the major complications among surgical patients. This study aimed to identify the preoperative and postoperative risk factors for DVT in surgical patients. We believe that the results will help us better understand the condition and provide further guidance.

1.1. Research Questions

1. What are the individual risk factors for DVT in surgical patients?
2. What are the surgery-related risk factors for DVT in surgical patients?
3. What is the preoperative risk level of DVT in surgical patients?
4. What is the postoperative risk level of DVT in surgical patients?

2. METHODS

2.1. Study Design and Sample

This descriptive study aimed to identify the preoperative and postoperative risk factors for DVT in surgical patients of a state university hospital.

The study population consisted of all patients of the general surgery, orthopedics and traumatology, neurosurgery, and cardiovascular surgery clinics of a state university hospital because they are, in general, at a higher risk of developing DVT (9, 21). A total of 20.605 patients underwent surgery in those clinics in 2017. Participants were recruited using stratified sampling (22). The sample consisted of 377 patients who met the inclusion criteria and agreed to participate (Table 1).

Table 1. *Stratified sampling by clinic*

Stratum No	clinic	Number of Patients (Ni)	Stratum Weight Ni/N=Ai	Number of Patients in the Sample
1	General surgery clinic	7643	7643/20.605=0.37	140
2	Orthopedics and traumatology Clinic	6179	6179/20.605=0.29	113
3	Neurosurgery clinic	4601	4601/20.605=0.22	84
4	Cardiovascular surgery clinic	2182	2182/20.605=0.1	40
	Total	20.605	1.00	377

The inclusion criteria were (1) agreeing to participate, (2) being literate, (3) being over 18 years of age, (4) having no communication problems, (5) undergoing surgery, and (6) staying at the clinic for at least one day before and one day (24 hours) after surgery.

2.2. Data Collection Tools

Data were collected using a demographic characteristics form, a deep vein thrombosis diagnostic criteria form (DVT-DCF), the Autar deep vein thrombosis risk assessment scale (ADVTRAS), the Caprini risk assessment model (RAM), and the Padua Prediction Score (PPS).

The demographic characteristics questionnaire was based on a literature review conducted by the researchers. The questionnaire consisted of three subscales and 33 items (5, 6, 19, 23). The questionnaire elicited information on sociodemographic characteristics and the preoperative and postoperative periods.

The Autar deep vein thrombosis risk assessment scale (ADVTRAS) was developed by Ricky Autar (1996) and revised in 2003 (8, 24). The scale consists of seven categories: age groups, body mass index (BMI), mobility, special risk category, trauma risk category, surgical intervention, and high-risk diseases. The total score ranges from 0 to 31, with higher scores indicating a higher risk for DVT (0-10=low risk, 11-14=moderate risk, 15-32=high risk). Büyükyılmaz, Şendir, Autar, and Yazgan (2015) adapted the scale to Turkish and found its Cronbach's alpha (α) as 0.78 to 0.90 (25). Cronbach's alpha value was found to be 0.37 in the study.

The Caprini risk assessment model (RAM) was developed by Joseph A. Caprini (2005) to determine the risk level for VTE in internal medicine and surgical patients (26). The model assesses age, BMI, type of surgery, mobility, central venous access, sepsis, acute myocardial infarction (MI), hip, pelvis, leg fracture, stroke, or trauma history. The model consists of five categories scored as 1, 2, 3, or 5, with higher scores indicating a higher risk for VTE (0=very low risk, 1–2=low risk, 3–4=moderate risk, and ≥5=high risk). The scale in

the National Venous Thromboembolism Prophylaxis and Treatment Guidelines published by the Turkish Society of Cardiology in 2010. It has been translated into Turkish. The use of RAM is recommended for surgical patients (15). In Aydın's (2014) medical specialty thesis, RAM was used in the Turkish patient population (27).

The Padua Prediction Score (PPS) was developed by Barbar et al. (2010) at the University of Padua, Italy (28). The scale evaluates 11 risk factors; age, active cancer, previous VTE, reduced mobility, already known thrombophilic condition, recent trauma, heart and/or respiratory failure, acute infection and/or rheumatologic disorder, acute MI and/or ischemic stroke, obesity, and ongoing hormonal treatment, each of which is scored on a scale of 1 to 3 (< 4=low risk, ≥ 4=high risk). The Turkish version of the PPS has been published in the National Venous Thromboembolism Prophylaxis and Treatment Guidelines (15). Also PPS was used in the a medical specialty thesis with Turkish patient population (27).

The deep vein thrombosis diagnostic criteria form (DVT-DCF) was based on a literature review conducted by the researchers (5, 7, 19, 23). The form assesses leg pain, edema, tenderness, rising body temperature, loss of motor functions, limitation of motion, sensory loss, change in leg circumference, and Homan's sign (calf pain on dorsiflexion of the foot with the knee straight). Leg pain is scored on a scale of 0 to 10.

2.3. Data collection

The study was conducted between January 1 and March 30, 2018, in two stages: preoperative and postoperative. The researchers informed the patients about the research purpose and procedure and obtained informed consent from those who agreed to participate. Afterward, they asked participants to fill out the demographic characteristics questionnaire. In the postoperative period, the researchers filled out the ADVTRAS, RAM, PPS, and DVT-DCF and obtained lab test results from patient files during evaluation. The data were collected through face-to-face interviews. The researchers conducted the interviews outside of treatment hours in the patients' rooms at their convenience in the absence of distractions (pain, dressing, mobilization, etc.). Data collection took 20-25 minutes.

2.4. Data Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows, IBM, version 18.0). Descriptive statistics (number, percentage, mean and standard deviation) were used for analysis.

2.5. Ethical Considerations

Before data collection, the study was approved by the Ethics Committee of the university (Decision No/Date: 2017-433/14.11.2017). Written permission was obtained from the university hospital. Verbal informed consent was obtained from patients who agreed to participate. The study was carried out according to the ethical principles outlined by the Declaration of Helsinki.

3. RESULTS

Of all participants, 31.8% had a primary school degree, 35.3% were housewives, 83% were married, 69% were living in the city center, 75.6% had a neutral income (income equals expenses), and 37.1% were general surgery patients, 30% were orthopedics and traumatology patients, 22.3% were neurosurgery patients, and 10.6% were cardiovascular surgery patients.

Participants (176 female and 201 male) had a mean age of 57.20±17.20 years. Of all participants, 38.5% had a normal BMI, 57.3% had a chronic disease (36.9% hypertension), 55.4% were on medication (35.8% antihypertensive drugs), 19.1% were smokers, 17% were exercising regularly, 89.7% had sedentary jobs, and 20.4% had to travel long distances (92% by bus) (Table 2).

The mean duration of surgery was 137.87 ± 5.26 minutes. Of the participants, 30.3% underwent orthopedic surgery (below waist level), 73.5% were under general anesthesia, 64.7% had had surgery before, and 97.3% had no history of DVT (Table 3).

According to the ADVTRAS scores, the majority of the participants (91%) were in the low-risk category in the preoperative period, while less than half were in the moderate (39.2%) or high-risk (30%) categories in the postoperative period. According to the RAM scores, less than half the participants (39%) were in the moderate-risk category in the preoperative period, while more than half (70.6%) were in the high-risk category in the postoperative period. According to the PPS scores, most participants (82.2%) were in the low-risk category in the preoperative period, while a bit more than half the participants (52.8%) were in the high-risk category in the postoperative period (Table 4).

Two hundred and thirty-five (62.3%) participants did not use graduated compression stockings in the preoperative period. More than half of the participants (62.7%) misused them. Most participants (81.2%) were on anticoagulant drugs. In the postoperative period, two hundred and fifty-six participants (67.9%) used graduated compression stockings, more than half of them (55.9%) used the stockings correctly, and more than half of the participants (57.3%) were on anticoagulant drugs. Participants were able to stand on their two feet about 14.85 ± 12.06 hours after surgery, while one hundred and forty-five participants (38.5%) did it in the first eight hours after surgery (Table 5).

The researchers used the DVT-DCF to evaluate the preoperative and postoperative risk factors for DVT. The three most common symptoms of DVT in the preoperative period were leg pain (40.1%), limitation of motion (32.4%), and sensory loss in the leg (10.3%). The three most common symptoms of DVT in the postoperative period were

limitation of motion (47.2), leg pain (35%), and change in leg circumference (9.8%).

Table 2. *Distribution of individual risk factors for DVT (n=377)*

Demographic Characteristics	n	%
Age ($\bar{x}$±SD: 57.20±17.20, **Min-Max:** 18-91 years)		
18-30	36	9.5
31-40	42	11.1
41-50	36	9.5
51-60	81	21.6
61-70	92	24.4
≥71	90	23.9
Gender		
Female	176	46.7
Male	201	53.3
BMI ($\bar{x}$±SD:26.91±5.54, **Min-Max:** 15.24±49.95)		
Underweight (<18.5 kg/m^2)	13	3.4
Normal (18.5-24.9 kg/m^2)	145	38.5
Overweight (25-29.9 kg/m^2)	126	33.4
Obese (30-39.9 kg/m^2)	85	22.6
Morbidly obese (≥ 40 kg/m^2)	8	2.1
Chronic Illness		
Yes	216	57.3
No	161	42.7
Type of Chronic Illness*		
Hypertension	139	36.9
Diabetes mellitus	79	21.1
Malignant (active cancer)	58	15.4
Chronic obstructive pulmonary disease	19	5.1
Coronary artery disease	16	4.2
Others (Cirrhosis, Crohn's disease, acid reflux, hypothyroidism, rheumatoid arthritis, etc.)	14	3.7
Regular Use of Medication		
Yes	209	55.4
No	168	44.6
Type of Medication*		
Antihypertensives	135	52.9
Antidiabetics	77	30.2
Bronchodilators	17	6.7
Heart diseases and anticoagulants	17	6.7
Others (proton pump inhibitors, antipsychotics, hormone therapy)	9	3.5
Smoking		
Yes	72	19.1
No	305	80.9
Regular Exercise		
Yes	64	17.0
No	313	83.0
Sedentary Work Style		
Yes	39	10.3
No	338	89.7
Having to Travel Long Distance		
Yes	77	20.4
No	300	79.6
Means of Transportation		
Bus	347	92.0
Plan	26	6.9
Train	4	1.1

$\bar{x}$:Mean, SD:Standard deviation, Min:Minimum value, Max:Maximum value, BMI:Body Mass Index

** Percentages were based on n as more than one option was marked*

Table 3. *Distribution of surgery-related risk factors for DVT (n=377)*

Characteristics	$\bar{x}$±SD	Min.-Max.
Duration of Surgery (minute)	137.87±5.26	15-600
	n	%
Type of Surgery		
Minor <30 minute	12	3.2
Planned major	24	6.4
Emergency	40	10.6
Abdominal	104	27.2
Neurosurgery (brain and nerve)	84	22.3
Orthopedic	113	30.3
Type of Anesthesia		
General Anesthesia	277	73.5
Local Anesthesia	100	26.5
History of Surgery		
Yes	244	64.7
No	133	35.3
History of DVT		
Yes	10	2.7
No	367	97.3

$\bar{x}$: Mean, SD:Standard deviation, Min:Minimum value, Max:Maximum value, DVT: Deep vein thrombosis

Table 4. *Preoperative and postoperative ADVTRAS, RAM and PPS Scores (n=377)*

Scales	Preoperative Period		Postoperative Period	
	n	%	n	%
ADVTRAS				
Low risk (≤ 10)	343	91.0	116	30.8
Moderate risk (11-14)	34	9.0	148	39.2
High risk (15 ≥)	-	-	113	30.0
RAM				
Very low risk (0-1)	92	24.4	2	0.5
Low risk (2)	33	8.8	24	6.4
Moderate risk (3-4)	147	39.0	85	22.5
High risk (5 ≥)	105	27.8	266	70.6
PPS				
Low risk (<4)	310	82.2	178	47.2
High risk (4≥)	67	17.8	199	52.8

ADVTRAS:Autar deep vein thrombosis risk assessment scale, RAM:Caprini risk assessment model, PPS:Padua Prediction Score

Table 5. *Prophylactic measures for the prevention of preoperative and postoperative DVT (n=377)*

Measures	n	%
Using graduated compression stockings in the preoperative period		
Yes	142	37.7
No	235	62.3
Using graduated compression stockings correctly in the preoperative period (n=142)*		
Yes	53	32.3
No	89	62.7
Being on anticoagulant medication in the preoperative period		
Yes	71	18.8
No	306	81.2
Using graduated compression stockings in the postoperative period		
Yes	256	67.9
No	121	32.1
Using graduated compression stockings correctly in the postoperative period (n=256)*		
Yes	143	55.9
No	113	44.1
Being on anticoagulant medication in the postoperative period		
Yes	161	42.7
No	216	57.3
The first time to stand up on two feet after surgery (hours) (n=356)* $\bar{x}$**±SD:**14.85±12.06 **Min.-Max.:** 0-72		
≤ 8	137	38.5
>8	219	61.5

x̄:Mean, SD:Standard deviation, Min:Minimum value, Max:Maximum value
**Percentages were based on n as more than one option was marked.*

4. DISCUSSION

Deep vein thrombosis is a severe complication that causes mortality and morbidity in surgical patients. Nurses should use accurate measures to identify the risk factors for DVT as early as possible. This study identified the preoperative and postoperative risk factors for DVT in surgical patients of a university hospital.

Healthcare providers should identify the risk factors for DVT before administering prophylaxis to surgical patients. Most of our participants were over 60 years of age (48.3%) and male (53.3%) (individual risk factors for DVT). Deep vein thrombosis occurs at all ages, but the risk is higher after 60 years of age, because aging causes muscle weakness, venous insufficiency, endothelial dysfunction, fragility, reduced mobility, and systemic diseases (32).

More than half of the participants (58.1%) were above normal BMI. Measures for DVT risk identification regard a BMI of > 25 (24, 26) or > 30 as a risk factor (30). Ageno et al. (2008) found that obese individuals were about twice as likely to develop both PE and DVT as normal-weight individuals (23). However, Wang et al. (2015) detected no difference in the incidence of VTE between normal-weight and obese general surgery patients and stated that surgeons should be more careful only when performing abdominal hernia repairs on obese individuals (33). Özkaya et al. (2013) found that the most common individual risk factors for DVT encountered by surgeons in Turkey were a history of DVT and obesity (34).

More than half of the participants (57.3%) had a chronic disease, mainly hypertension, and diabetes mellitus (58%), damaging the endothelial layer of the blood vessels and increasing the risk of DVT (23).

According to the ADVTRAS scores, 91% were in the low-risk category in the preoperative period, whereas 39.2% were in the moderate-risk category in the postoperative period. Büyükyılmaz et al. (2015) reported that patients were in the moderate DVT risk category after orthopedic surgery (25). Özbaş and Karadağ (2020) found that 89.3%, 40.7%, and 11.4% of orthopedic patients were in the low-, moderate-, and high-risk categories in the postoperative period, respectively (35).

According to the RAM scores, 39% of our participants were in the moderate-risk category in the preoperative period, while 70.6% were in the high-risk category in the postoperative period. Bahl et al. (2010) evaluated the RAM scores of 8216 general surgery, cardiovascular surgery, and urology patients and found that 52.1%, 36.5%, 10.4%, and 0.9% were in the very high, high-, moderate-, and low-risk categories, respectively (36). Kim et al. (2020) conducted a study on 750 general surgery patients and reported that 48.9% were in the low – or moderate-risk category, while 43.8% and 7.3% were in the high – and very high-risk categories, respectively (37). Olufemi-Aworinde et al. (2018) also determined that one in every two patients (n=820) was in the moderate-risk category in the postoperative period (38).

According to the PPS scores, 82.2% of our participants were in the low-risk category in the preoperative period, while 52.8% were in the high-risk category in the postoperative period. However, Yormaz et al. (2019) found that patients who underwent bariatric surgery (n=270) were in the low-risk category in the preoperative and postoperative periods (29). Elias et al. (2017) reported that patients with and without VTE had a PPS score of 7.7 and 4.9, respectively (39).

Some studies have compared RAM and PPS scores (16-18). Zhou et al. (2018) concluded that both scales could identify the risk factors for DVT but that RAM was more comprehensive than PPS (18). However, some studies indicate that RAM is better at identifying the risk factors for DVT in hospitalized patients than PPS (16, 17). Our results showed that ADVTRAS, RAM, and PPS categorized the same patients into different risk groups. To develop a professional language, healthcare professionals should use one assessment tool customized to clinics.

Mechanical and pharmacological methods can prevent the development of DVT (14). Özkaya et al. (2013) found that most physicians (72%) used mechanical methods for DVT prophylaxis (34). Özbaş and Karadağ (2020) reported that physicians applied mechanical prophylaxis to 2.9% and 58.6%

of orthopedic patients in the preoperative and postoperative periods, respectively (35). Graduated compression stockings are a mechanical measure commonly used to prevent DVT. Most of our participants did not use compression stockings in the preoperative period, but more participants used them in the postoperative period. However, most participants misused the stockings. The Turkish Guideline for the Treatment of Venous Thromboembolism Prophylaxis suggests that healthcare professionals teach patients how to use graded compression stockings (Evidence level A) (15). Research also shows that patients do not know how to use graduated compression stockings (35, 40). Serpici and Gürsoy (2018) reported that surgical patients trained by nurses were more informed of DVT and were more likely to adhere to interventions to prevent DVT (41). However, Dirimeşe, Yavuz, and Nurulke (2012) reported that most patients knew how to use compression stockings but had difficulty using them (42). According to our clinical observations, patients misused the compression stockings because they were informed only orally and were provided no written material.

Pharmacological measures can also be used to prevent DVT. Of our participants, 81.2% were on anticoagulant medication in the preoperative period, while 57.3% were on anticoagulant medication in the postoperative period. Ferreira et al. (2017) reported that 67.2% of Portuguese patients (n=2747) received thromboembolic prophylaxis, most of whom (88.3%) were on low-molecular-weight heparin therapy (43). Özkaya et al. (2013) determined that 74% of physicians used pharmacological measures to prevent DVT (34). Özbaş and Karadağ (2020) found that the overall pharmacological thromboprophylaxis rate in the preoperative and postoperative periods was 12.9% and 86.4%, respectively (35). The Safe Surgery Checklist, which is mandatory for all patients undergoing surgery in Turkey, has a clause determining whether DVT prophylaxis is necessary or not (13).

Participants were able to stand on their two feet about 14.85 ± 12.06 hours after surgery. Çebi and Tanrıverdi (2009) reported that immobility was the most common risk factor for DVT (52.3%) (44). Özbaş and Karadağ (2020) found that mobilization 17-24 hours after orthopedic surgery was 68.6% (35). Early mobility, especially in the first 24 hours after surgery, is critical for preventing DVT (10). The national guideline in Turkey suggests that healthcare professionals encourage patients for early mobility in the postoperative period (Evidence level A). According to the guideline, surgical patients with a low risk for VTE do not require any prophylactic measure other than early and frequent mobility (very strong recommendation) (15).

4.1. Limitations of the study

This study had one limitation. The results were sample-specific, and therefore, not generalizable to the whole population.

5. CONCLUSION

Most surgical patients have chronic diseases (hypertension and diabetes mellitus) and individual DVT risk factors (advanced age and gender). Most surgical clinic patients have risk factors for DVT due to surgery (long operation, surgery below waist level, general anesthesia, surgical history, etc.). Surgical patients are at a higher risk of developing DVT in the postoperative period than in the preoperative period. Different scales yield different results concerning the risk factors for DVT when applied to the same patient population. Moreover, patients should be trained on how to use graduated compression stockings.

The following are recommendations based on the results:

- Healthcare professionals should use a standardized scale to identify the risk factors for DVT in clinical patients.
- Authorities should develop evidence-based nursing guidelines, algorithms, checklists, and interventions to identify the risk factors for DVT and monitor whether healthcare professionals use them.
- Medical schools should provide nursing students with training in DVT risk assessment and prophylaxis.
- Nurses should be provided with in-service training in DVT risk assessment and prophylaxis.
- A national database on DVT risk assessment and prophylaxis should be developed.
- Multicenter research on DVT risk assessment and prophylaxis should be conducted.

Conflict of Interest: None

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Clinical and Experimental Health Sciences

Analysis of Saliva and Gingival Crevicular Fluid Immunoglobulin a in Adults Having Different Caries Status

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ABSTRACT

Objective: The aim of the study was to compare the salivary IgA and gingival crevicular fluid IgA levels in caries active and caries free subjects.

Methods: The study was carried out on 40 subjects divided into two groups, Group I caries free, (DMFT =0) and Group II caries active, (DMFT >10). Saliva and gingival crevicular fluid samples were obtained and plaque index, gingival index, gingival crevicular fluid volume and salivary flow rate were determined. The levels of S. mutans and lactobacillus were determined by culture. IgA concentrations of saliva and gingival crevicular fluid samples were determined using the ELISA. Data were analyzed using the Mann-Whitney U and $\chi 2$ tests ($\alpha = 0.05$).

Results: Gingival crevicular fluid volume, plaque index and gingival index values of group II were significantly higher than group I ($p< 0.05$). Although lactobacillus counts of group II were higher than group I, no statistically significant differences were observed for microorganism counts ($p>0.05$). Salivary flow rate, gingival crevicular fluid-IgA and saliva-IgA levels were no statistically significant between the groups ($p>0.05$).

Conclusion: The present study showed that microorganism counts in the saliva did not by themselves influence the DMFT index. There is no dependence between secretory immunity and dental caries in subjects.

Keywords: Dental caries, gingival creviculer fluid, immunoglobulin, saliva.

1. INTRODUCTION

Dental caries is a multifactorial disease and microorganisms play the most important role in the formation and development of caries. Streptococcus mutans are often isolated from cavitated carious lesions and Streptococcus mutans to be considered a primary pathogen in caries due to the fact that it produces glucan for bacteria to adhere to the tooth surface, is acidic and aciduric (1). Lactobacilli are colonized later, so they do not play an active role at the initiation of caries, but they are effective in the development of caries after the lesions progress. Since the level of lactobacilli in saliva is associated with a high consumption of carbohydrates, it can be a useful indicator for a cariogenic diet (2).

Human saliva is a clear, slightly acidic (pH 6.0 to 7.0) liquid consisting of 98% water and 2% electrolytes, mucus, antibacterial compounds, and various enzymes (2). Saliva also contains many proteins involved in maintaining oral tissue, such as lysozyme, lactoferrins, lactoperoxidase, albumin, mucin, histatins, defensins, and immunoglobulins (3). In addition, saliva is also a mixture of salivary gland secretions, gingival crevicular fluid (GCF), bronchial and nasal secretions, bacteria and bacterial products, desquamation epithelial cells, and other cellular oral fluids (2). Gingival crevicular immune mechanism involves both cellular and humoral immunity (4).

Saliva immunoglobulins are the first line of defense against pathogenic bacteria and their secretions (5). Salivary IgA (S-IgA) prevents adhesion of bacteria to the tooth surface. S-IgA does this by neutralizing bacterial toxins and enzymes by blocking the binding of bacteria to cell receptors (5).

Numerous studies have reported the protective role of S-IgA against dental caries in both children and adults (6, 7). These studies investigated the correlation between total salivary S-IgA concentrations and caries susceptibility as recorded by an index of decayed, missing, or filled teeth (DMFT) or surfaces (DMFS). However, the results differ; while some studies showed positive or negative correlation between S-IgA and dental caries, in some studies, no correlation was reported. Therefore, the protective mechanism of S-IgA against dental caries is still unclear.

For this reason, the aim of the present study was to quantify the microbiological and immunological profiles of caries active and caries free subjects and to identify the active

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cariogenic factors that can be used to predict dental caries in susceptible populations.

The null hypotheses of the study, there is no significant difference between immunological and microbiological profiles of in caries active and caries free subjects.

2. METHODS

2.1. Subjects and Study Design

This study was carried out with the ethical approval of Ataturk University Faculty of Dentistry Ethics Committee (16.10.2012/012) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study. The study was carried out on 40 subjects (20 females and 20 males) aged 15–40 years, who attended the Department of Restorative Dentistry, Faculty of Dentistry, Ataturk University. Inclusion criteria are systemically healthy, anti-inflammatory drugs have not been used within the previous 2 months, and no antibiotic therapy has been taken in the past 6 months. The exclusion criteria were tobacco consumption, diabetes, pregnancy, breastfeeding, medication intake that caused a decrease in saliva flow, use of antibiotics within 6 months or dental or periodontal treatment that continued 12 months before the beginning of the study (8). Dental caries examination was performed according to the World Health Organization criteria using traditional dental chairs, artificial light, flat mirror and explorer (9). Subjects were divided into 2 groups as Group I DMFT = 0 caries-free group and DMFT> 10 caries active group.

Saliva and GCF samples were collected from participants in the study. Saliva flow rate, Streptococcus mutans and lactobacillus levels and Salivary IgA were analyzed in saliva samples. Plaque index (PI), gingival index (GI) GCF volume and GCF-IgA analysis were performed on GCF samples.

2.2. Saliva Sampling

Subjects were asked to brush their teeth and not eat or drink for 2 hours before sampling. All procedures were performed in the same order to reduce the effect of circadian rhythm on saliva flow and content (8). Subjects were seated in dental chairs and 2 cc of unstimulated saliva was collected in especial tubes according to Scully method (10), (In this method, subjects were asked to spit in the tubes once a minute for ten minutes). All samples were collected between 09:00 and 11:00, and the time spent for each procedure was set to a maximum of 30 minutes (11). The average salivary flow rate (SFR) was measured from the total volume according to Krasse (12). After collection of 0.5mL of salivary sample, it was transferred immediately to the laboratory at a temperature of –80ºC.

2.3. Periodontal Examination and GCF Sampling

Plaque index (PI), gingival index (GI) and GCF volume were determined. The same trained examiner recorded PI and GI using a periodontal probe according to Löe and Silness (13). Four different sampling areas were created in the mouths of the subjects in the premolar molar region. Plaque and gingival index were evaluated on the facial, lingual / palatinal, mesial and distal surface of the teeth to be examined. According to these results, a separate score was given for the four surfaces of the tooth and the total score was divided into four and the score of the tooth was found.

GCF was collected from the mesial or distal surface of the respective teeth. Following the evaluation of the PI, the supragingival plaque was removed and the areas to be sampled were isolated using cotton rolls. Saliva absorber was used to prevent saliva contamination. A paper strip (Periopaper, ProFlow Inc., Amityville, USA) was inserted intracreviculer 1 mm below the gingival margin and left in place for 30 s. The procedure was repeated three times. A total of 3 strips of paper were sampled and the strips of paper were transferred to a chairside electronic gingival fluid meter (Periotron 8000, Oraflow Inc., Plainview, USA) for volume determination. The paper strips were then immediately placed into three labeled Eppendorf tubes (Microcentrifuge tubes, ISOLAB, Wertheim, Germany) containing 100 µl of 0.9% of physiological saline solution, isolated with ParafilmH M, (SPI Supplies Inc., West Chester, USA) to avoid evaporation and sent to the laboratory. The samples were stored at – 80°C for subsequent assays (14).

2.4. Microbiological Tests

S. mutans and Lactobacilli analysis in the saliva of the subjects were carried out according to the Koga-Ito(15) method in the Microbiology Laboratory of Ataturk University Medical Faculty. Within 3 h after sampling, saliva samples were diluted to 10^{-1} and the following tests were performed:

2.4.1. Mutans streptococci Counts

Diluted saliva samples from subjects were planted in Mitis salivarius Bacitracin sucrose agar (Difco, Detroit, Mich., USA) and incubated at 37 ° C in candle jars for 72 hours. S. mutans colonies formed at the end of this period were counted, and amounts over 100,000 CFU / mL were considered the high risk group and those below were considered the low risk group.

2.4.2. Lactobacilli Counts

Diluted saliva samples from subjects were planted in Rogosa agar (Difco, Detroit, Mich., USA) under aerobic conditions for 72 hours at 37 ° C. Lactobacilli colonies formed at the end of this period were counted and amounts above 10,000 CFU / mL were considered as the high-risk group and those below were considered the low-risk group.

2.5. S-IgA and GCF-IgA Analysis

S-IgA and GCF-IgA analysis were performed using commercial ELISA kits (Human Secretory Immunglobulin A ELISA Kit, East Biopharm, LOT NO: 201408) according to manufacturer's recommendations at the Ataturk University, Faculty of Medicine Microbiology Laboratory. Firstly, solutions were prepared for the test. The samples were homogenized by shaking and centrifuge at 2000 rpm for 20 minutes and supernatants were removed. For test procedure 40 µL sample,10 µL S-IgA-antibody and 50 µL Streptavidin-HRP were added to test wells and incubated 60 minutes at 37°C. At the end of incubation plates were washed five times. After washing procedure, 50 µL chromogen A and 50 µL chromogen B solutions were added to each well and mixed gently. Plates were incubated 10 minutes at 37°C away from light. After this period, 50 µL stop solution was added into each well to stop the reaction. Finally measurements were made optical densit (OD) under 450 nm wavelenght within 15 minutes after adding stop solution. A standard curve was obtained and salivary SIgA levels were calculated and expressed in µg/mL.

2.6. Statistical Analysis

Statistical analysis was performed using SPSS 20 (IBM, Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine the distribution of the data. The Mann-Whitney *U* test was used to compare the parameters between caries free and caries active group. In addition, χ2 test was used to compare the mutans and lactobacillus levels of groups. The value of $p<0.05$ was considered as statistically significant.

3. RESULTS

The clinical and laboratory data obtained from caries free and caries active subjects and the statistical comparison results are given in Table 1. SFR is within normal limits in both groups and there is no statistically significant difference between them (p=0,056). GCF volume, GI and PI values of caries active group were significantly higher than caries free group (p< 0.05). But, GCF-IgA and S-IgA levels were no statistically significant between the groups (p>0.05).

In addition, lactobacillus counts of caries active group were higher than caries free group but no statistically significant differences were observed for microorganism counts between the groups (p>0.05) (Table 2).

Table 1. *Clinical and laboratory values and Mann-Whitney U test results between the groups*

GROUPS			DMFT	PI	GI	GCF (µL)	SFR (mL/min)	GCF-IgA (µg/mL)	S-IgA (µg/mL)
CF (n=20)	Median		0.00	0.64	0.29	0.03	0.40	5.56	6.40
	Minimum		0	0.00	0.00	0.02	0.13	4.16	3.00
	Maximum		0	1.71	1.71	0.08	5.00	9.04	12.71
	Percentiles	25	0.00	0.33	0.073	0.03	0.28	4.82	4.38
		50	0.00	0.64	0.29	0.03	0.40	5.56	6.40
		75	0.00	1.00	0.68	0.048	0.62	6.13	8.11
CA (n=20)	Median		14.00	1.50	0.71	0.05	0.88	5.21	5.77
	Minimum		9	0.29	0.12	0.03	0.05	4.12	3.72
	Maximum		25	3.43	2.43	0.10	2.50	6.82	20.70
	Percentiles	25	11.00	0.71	0.43	0.04	0.46	4.82	4.41
		50	14.00	1.50	0.71	0.05	0.88	5.21	5.77
		75	15.00	2.50	1.07	0.07	1.36	5.87	8.18
p			0.001*	0.002*	0.011*	0.002*	0.056	0.579	0.978

**p<0.05, CF: Caries free, CA: Caries active, SFR: Saliva flow rate, PI: Plaque index, GI: Gingival index, GCF: Gingival crevicular fluid, GCF-IgA: Gingival crevicular fluid IgA, S-IgA: Salivary IgA*

Table 2. *Distribution of Streptococcus mutans and lactobacillus levels in the subjects' saliva and their statistical comparisons*

	CF n(%)	CA n(%)	χ2	p
S. mutans				
≤ 10^5 CFU/mL	19 (95)	19 (95)	0.00	1.00
> 10^5 CFU/mL	1 (5)	1 (5)		
Lactobacilli				
≤ 10^4 CFU/mL	14 (70)	8 (40)	3.64	0.06
> 10^4 CFU/mL	6 (30)	12 (60)		

**Data are presented as n (%). CF: Caries Free; CA: Caries Active; CFU = colony-forming units.*

4. DISCUSSION

Studies in recent years have shown that antibodies are valuable components in preventing dental caries. Research on immunology has indicated that bacterial products modulate the immune response (16). Saliva components that can affect bacterial proliferation and plaque ecology have been described and have been reported to form caries resistance mechanisms (16). Three effective mechanisms have been described in the pathogenesis of caries. These are S-IgA and other antibodies, serum antibodies and cellular immunity. Especially S-IgA is known to play an important role in preventing caries (16).

One of the antibacterial properties of saliva is that it has secretory immune system components. Saliva has an important role in maintaining oral health. It has been proved to be a credible diagnostic aid in detecting different biomarkers (3). Gingival crevicular fluid is a biological fluid originating from blood plasma, which has different compositions in the gingival sulcus and has the properties to determine the ecology of the gingival sulcus. Cellular components, electrolytes, bacterial-metabolic products, cytokines, host and bacterial enzyme and enzyme products-inhibitors and immunoglobulins in the GCF content are characteristic of the liquid (14). Therefore, in the present study, salivary and GCF immunoglobulins and S. mutans and lactobacilli status in saliva were investigated in caries free and caries active subjects. According to our research, although IgA studies in adults' saliva are few, no study investigating IgA in GCF has been found. There are a few and inadequate studies on adult's salivary IgA and only the studies by Koga-ito (17) and Gornowicz (18) involved adults. Therefore, it is necessary to conduct research on this subject. In the present study, GCF and S-IgA levels were no statistically significant between the groups ($p>0.05$). In addition, lactobacillus counts of caries active group were higher than caries free group but no statistically significant differences were observed for microorganism counts between the groups ($p>0.05$). Therefore, the hypothesis was accepted.

In the present study, dental carries index was used to assess the relationship with S-IgA. Many previously conducted studies used decay-missing-filled (DMF) index (19). In this study, clinical parameters such as PI, GI, GCF volume and saliva flow rate were also determined. The salivary flow determination was performed according to Krasse (12) and the results were classified as follows: normal (up to 1 ml/min), reduced salivary flow (lower than 0.7 ml/min) and xerostomia (values below 0.1 ml/min). In this study, it was found that the saliva flow rates of caries free and caries active subjects were in the range of 0.98 and 1.00 ml / min and these values were within normal limits in both groups. Saliva flow rate was not statistically significant between the groups ($p>0.05$), because all subjects were selected among clinically healthy individuals who did not take any medication that could affect saliva flow rate.

GCF is an exudate from the blood plasma in the gingival sulcus between the tooth and the gingival edge or in the periodontal pocket. In fact, there is very little GCF in the healthy sulcus, and when the gum is healthy, this liquid is in the form of a transudate or serum exudate in the sulcus. With the increase of inflammation in the gingiva, transudate turns into inflammatory exudate, which contains molecules derived from high amounts of gingival tissues, vascular cellular components of inflammation and serum-derived molecules. Increased GCF volume is positively associated with the degree of gingival inflammation (20). In the present study, GCF volume, GI and PI values of caries active group were significantly higher than caries free group ($p< 0.05$). As a result, in the present study, a moderate inflammation can be mentioned in the caries active group according to the system of Löe and Silness. This may be due to exclusion of individuals with periodontal disease from the study, since only the effect of caries on IgA level was examined.

There is no consensus on the S-IgA concentration in caries free and caries active subjects in different studies, despite the fact that immunological factors seem to play an important role in microorganism colonization and dental caries. Although some studies demonstrated high concentrations of S-IgA in a lower caries activity (3, 17, 21, 22), other studies showed high levels of S-IgA with an increase in caries activity (4, 11, 18, 23-25) . However, there are studies that have not observed any correlation between S-IgA and dental caries (17, 26-29).

Shetty et al.,(3) found that IgA decreased with increase in caries prevalence. According to the authors, this may be due to the high specific binding ability of the immunoglobulins to the microbial species and their neutralizing effect. Thus, it protects against dental caries by preventing bacterial adhesion and colonization on the tooth surface. Gregory et al., (21) also reported similar results and explained this difference in IgA levels may be due to increased production of IgA antibodies against Streptococcus mutans in caries free than caries active childrens. Koga-ito (17) and Kuriakose (22) indicated in their studies that the amount of S-IgA reduced following the increase in the number of decayed teeth and according to their conclusion, this reduction could be as a result of body defence mechanism.

Nawaz et al.,(4) found that S-IgA was raised in patients with dental caries compared to healthy controls and the authors stated that this may be due to the protective mechanism of immunoglobulins against dental caries to reduce and control caries severity. Ranadheer et al. (25) and Amoundi et al. (23) have also detected an increased level of IgA in patients of dental caries**.** In similar to the results of the study, Gornowicz and Fidalgo indicated higher levels of S-IgA in people with more decayed teeth (18, 24) As the results of the study showed, there was a positive correlation between high levels of dental caries and salivary levels of IgA. The result is confirmed by Bagherian (11) that revealed a weak inverse correlation between the variables.

Interestingly, some studies showed no correlation between dental caries and IgA levels. A study by Camling and Kohler (26) demonstrated no clear evidence for the protective role

of salivary IgA antibodies against Streptococcus mutans colonization. Zengo et al., (29) and Fukuda et al., (27) stated that the difference between caries free and caries active groups did not reach statistical significance in terms of immunoglobulins in parotid saliva. The results of these studies are similar to the findings of our study. Studies conducted by Koga et al. and Shifa et al. supported this hypothesis (17, 28).

These differences as a result of studies may be due to variations in sampling size, different conditions in collecting saliva samples, different criteria applied in subject selection, differences among individuals in terms of oral hygiene and diet. In addition, immunoglobulin concentrations may vary depending on saliva flow rate, hormonal factors, physical activity and emotional state (30).

The limitation of this study is that it was conducted with a small number of participants.

5. CONCLUSION

Within the limits of this study, it may be considered that caries status may not affect S-IgA and GCF-IgA levels. However, further studies with larger sample sizes will provide a better understanding of the subject.

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Clinical and Experimental Health Sciences

The Possible Useful Effectiveness of Sinapic Acid on Sepsis-Induced Secondary Organ Damage in Rats

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ABSTRACT

Objectives: In this study, we investigated the possible useful effectiveness of Sinapic acid on rat kidney and lung tissues in an experimental cecal ligation puncture (CLP) model.

Methods: CLP model was created for the rats in the CLP group. 20 mg/kg of Sinapic acid was given in the CLP-Sinapic acid group. At the end of the experiment, lung and kidney tissues were collected and biochemical analyzes were evaluated.

Results: For the lung and kidney tissue samples; antioxidant levels decreased, and oxidant levels increased in the CLP group. When the immunohistochemical parameters were evaluated, IL-1β, caspase-3, and TNF-α immunopositivity were severe levels in CLP group. But immunopositivity of these parameters have been observed as attenuated in CLP-Sinapic acid group compared to CLP group.

Conclusion: The results of our study showed that Sinapic acid has useful effectiveness on the sepsis model caused by CLP in the lung and kidney tissues.

Keywords: Cecal ligation puncture, sinapic acid, lung, kidney, rat.

1. INTRODUCTION

Sepsis, a systemic inflammatory response to infection, is a life-threatening health problem (1). Surgery or surgical operations are accepted as one of the most common reasons of sepsis (2). The cecal ligation and puncture (CLP) sepsis model is considered to be the most striking experimental procedure for sepsis-related studies because it is reasonable, repeatable and applicable (3). CLP results in widespread peritonitis leading to contamination of the abdominal area and initiation of the systemic inflammatory response and even sepsis (4). The pathophysiology of sepsis is important for diagnosis, prognosis, and determination of appropriate treatment. Sepsis causes many different physiopathological processes. Basically, free oxygen radicals create damage causing denaturation in cellular proteins, injury to DNA, and peroxidation in membrane lipids (5, 6). Under normal physiological conditions, small amounts of free oxygen radicals have an important function in on cellular activity protecting. However, when the concentrations of these free radicals increased, this leads to fatal damage in the cell (7, 8). Some studies have shown the positive results of antioxidant agents which were applied to relieve the effects of free oxygen radicals in experimental sepsis models (9, 10). The incidence of sepsis-related organ failure is variable due to the definition criteria of organ failure. Respiratory insufficiency is accepted as one of the organ deficiencies at the early stage of sepsis and also, acute renal failure is a common cause of sepsis and worsening prognosis. In addition, coagulopathy, liver, central nervous system and gastrointestinal system pathologies are other situations that can be seen frequently and increase mortality (11, 12).

Phenolic compounds in foods originate from one of the main classes of secondary plant metabolites (13). They act as an antioxidant and protect living plants, and nutrients from oxidative rancidity at a low concentration (14). Sinapic acid (SA) is a hydroxycinnamic acid-derived polyphenol with 3,5-dimethoxy and 4-hydroxyl replacements in the phenyl group of cinnamic acid. SA can be completely acquired from various vegetables, rye and fruits, and it has strong antioxidant, anti-hyperglycemic and anti-inflammatory effects as in vitro and in vivo studies (15-18). Hitherto, it has been proved that SA has protective properties against oxidative damage in a

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large number of experimental animal studies by using different models (17-19). It has not been found any experimental study which researches the effects of SA on kidney and lung in animal experiments with abdominal sepsis. For this purpose, we planned this study to evaluate the effects of SA on lung and kidney in the CLP-induced sepsis model.

2. METHODS

2.1. Laboratory Conditions and Drugs

This study was carried out in Atatürk University Experimental Animal Research and Application Center. University Experimental Animals Local Ethics Committee (27.04.2018-103) has approved the study All rats were kept in a laboratory environment a 12-night/12-day, with a humidity of 55% and a mean temperature of 21 °C. The experimental animals were fed with standard pellet feed and tap water. However, all rats were starved before 12 hours from the experiment., but free to reach water. Ketamin (Ketalar®, Pfizer, Istanbul), Xylazin (Rompun®, Bayer, Istanbul), and SA (Sigma-Aldrich Co, USA) were used during the experiment.

2.2. Groups and Experimental Model

In this study, 24 Wistar albino male rats (weighing 200±10 g) were used and divided into 3 groups. In the sham-operated group (n=8), anesthesia was applied with a 60/10 mg/kg ketamine/xylazine mixture (20). After the anesthesia, rats' abdomen was shaved, and a vertical midline incision was made in the abdomen through skin and facia, then it was closed with no CLP model. In the CLP group (n=8), a midline laparotomy was done. The cecum was brought outside the body. The cecal ligation was applied to the rats and two through-and-through punctures were made on the antimesenteric face of the cecum with an 18-gauge needle and thus, CLP-induced polymicrobial sepsis model was established. The cecum was replaced into the abdominal cavity and the abdominal incision was closed via 3-0 silk thread. 1% lidocaine solution was applied on the wound for analgesia to the animals. In the CLP+SA group, in addition to the CLP model, 20 mg/kg single dose intraperitoneal (i.p.) SA was given. In this study, the preferred effective dose of SA was selected from the previous studies (21, 22). In the 18th hour after the application of CLP, rats were sacrificed under high dose (23) anaesthesia. Then, the kidney and lung tissues were removed. Tissue samples were stored at – 80 ° C.

2.3. Biochemical Analysis of Kidney and Lung Tissues

After the kidney and lung tissue samples have been homogenized, all biochemical analyses were made for the homogenized tissues. Malondialdehyde (MDA) levels were measured according to the method presented by Ohkawa et. al, to define the lipid peroxidation status (24). The results were given as µmol/g protein. It was analyzed using the superoxide dismutase (SOD) activity specification protocol detected by Sun et al (25). Superoxide dismutase (SOD) activity results in tissue samples were given as U/mg protein. Myeloperoxidase (MPO) activity was measured using a method improved by Bradley et al (26). The results of MPO activity on tissues were presented as U/g protein. Total oxidant status (TOS) measurement was made with the commercially available kit (Rel Assay Diagnostics, Product Code: RL024). Total antioxidant status (TAS) value was evaluated with the commercial kit (Rel Assay Diagnostics, Product Code: RL0017). TAS and TOS results were presented as nmol/L. The ratio of TOS to TAS was accepted as the oxidative stress index (OSI). OSI value was detected as follows: OSI=[(TOS, µmol H_2O_2 equivalent/L)/(TAS, mmol Trolox equivalent/L)×10] (27, 28).

2.4. Immunohistochemical Staining

Detection of kidney and lung tissues from euthanized rats was carried out in neutral formaldehyde solution for 1 day and formaldehyde was removed by washing with tap water. The tissues were blocked in the paraffin through the routine alcohol-xylol follow-up process. After the deparaffinization of the tissues on the polylysine lam, they were kept in 3% H_2O_2 for 10 min to inactivate endogenous peroxidase activity and they were washed in PBS. Later, the samples were stored in antigen retrieval solution for 10 min at 500W to remove antigens and they were washed in PBS again. Sodium citrate buffer (Santa Cruz Biotechnology, Cat. No: sc-294091, 10 mM, pH 6.0) was used as antigen retival solution. Protein block solution was added to prevent nonspecific binding and washed in PBS. Cleaved caspase-3 (Novus Biological, Cat. No: NB600-1235, Dilution:1/100), tumor necrosis factor-alpha (TNF-α) (Novus Biological, Cat. No: NBP1-19532, Dilution:1/100), and interleukin-1 beta (IL-1β) (Bioss, Cat. No: bs-0812R, Dilution:1/100) were applied to the sections as primer antibodies and washed with phosphate buffer solution (PBS). Finally, it was followed the procedure described by the expose mouse and rabbit specific HRP/DAB detection IHC kit (Abcam: ab80436). 3,3'-diaminobenzidine chromogen was used, and contrast stained with hematoxylin. Immunopositivity was examined at 20x magnification in the light microscope according to the severity of positive staining.

2.5. Statistical Analysis

The results obtained from the experiments were given as mean ± standard deviation. *P-values* below 0.05 were considered statistically significant. The comparisons between groups were done according to One-Way ANOVA and Bonferroni test. In the immunohistochemical study, the immunopositivity observed in the kidney and lung tissues were evaluated as severe immunopositivity +++, moderate immunopositivity ++, mild immunopositivity +, and negativity – (29, 30). The Kruskal Wallis test was used to determine the difference among the groups, and the Mann-Whitney U test was used for identification of the groups that produced the differences

3. RESULTS

3.1. Biochemical Results of Kidney and Lung Tissues

The results of this research obviously showed that CLP caused an important increase in the levels of TOS, MDA, OSI values, and MPO activities compared with the Sham group on kidney and lung tissues (*P-values*<0.05) (see Table 1). On the other hand, it was detected that these parameters significantly decreased in the group treated by SA compared with the CLP group (*P-values*<0.05). However, treatment with SA caused significant changes on kidney and lung tissues. TAS values and SOD activities were compared in all groups. TAS values and SOD activities increased due to treatment with SA in comparison with untreated CLP group (see Table 1).

Table 1. *Efficacy of Sinapic acid on kidney and lung, total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI) in sepsis induced by cecal ligation puncture (CLP) in rats.*

		Sham-operated	CLP	CLP-Sinapic acid
Lung	TAS (mmol Trolox equivalent / L)	0.61±0.05[a]	0.25±0.01[a,b]	0.56±0.06[b]
	TOS (μmol H_2O_2 equivalent / L)	6.25±0.69[a]	8.11±0.32[a,b]	6.59±0.42[a,b]
	OSI	1.02±0.15[a]	3.26±0.28[b]	1.18±0.15[b]
Kidney	TAS (mmol Trolox equivalent / L)	2.12±0.21[a]	1.17±0.17[a,b]	2.09±0.20[b]
	TOS (μmol H_2O_2 equivalent / L)	5.80±0.48[a]	7.43±0.78[a,b]	5.84±0.53[a,b]
	OSI	0.27±0.03[a]	0.63±0.08[b]	0.28±0.04[b]

a(P-values<0.05); Between the Sham-operated and CLP groups statistically significant.
b(P-values<0.05); Between the CLP and CLP – Sinapic acid groups statistically significant.

Table 2. *Quantification of Caspase-3, IL-1β, and TNFα immunopositive cells in the CLP and sinapic acide treated rats in kidney tissue.*

Groups/Immunopositivity	Caspase 3	IL-1β	TNFα
Sham	0.12±0.12[a]	0.25±0.16[a]	0.12±0.12
CLP	2.75±0.16[b]	2.50±0.26[b]	2.37±0.41
CLP+Sinapic acide	1.62±0.37[c]	1.25±0.25[c]	1.12±0.39

Immunopositivity data are expressed as mean ± SEM (n = 8). Different superscript letters(a,b,c) show the difference among groups.

3.2. Immunohistochemical Results of Kidney Tissue

Immunohistochemically, differences between groups were determined in terms of caspase 3, IL-1β and TNFα immunopositivity (p<0.05, Table 2). Immunohistochemical staining for apoptosis did not show caspase-3 immunopositivity in the sham group (Fig. 2A). Caspase-3 immunopositivity was found as the most intensive in tubular epithelial cells and glomeruli in the CLP group (Fig. 2B). In the CLP+SA, Caspase-3 immunopositivity was observed only in the tubular epithelial cells (Fig. 2C). Immunohistochemical staining for inflammatory reaction did not show IL-1β immunopositivity in the sham group (Fig. 3A). IL-1β immunopositivity was most intensively seen in the intertubular area and glomeruli in the CLP group (Fig. 3B and Table 2). In the CLP+SA group, IL-1β immunopositivity was found in the tubular epithelial cells and intertubular area (Fig. 3C and Table 2). TNF-α immunopositivity was not found in the sham group (Fig. 4A). TNF-α immunopositivity was most abundant in the tubular epithelial cells and intertubular area in sepsis (CLP) group (Fig. 4B and Table 2). In CLP+SA group, a mild TNF-α immunopositivity was found in the intertubular area and glomeruli (Fig. 4C and Table 2).

3.3. Immunohistochemical Results of Lung Tissue

Immunohistochemical staining for apoptosis did not show caspase-3 immunopositivity in the sham group (Fig. 5A). Caspase-3 immunopositivity was found as the most intensive in the inflammatory cells of peribronchiolar lymphoid hyperplasia field in the CLP group (Fig. 5B). In the CLP+SA group, there was a mild Caspase-3 immunopositivity around the bronchiole (Fig. 5C). Immunohistochemical staining for inflammatory reaction did not show IL-1β immunopositivity in the sham group (Fig. 6A and Table 3). IL-1β immunopositivity was most intensively seen in the inflammatory cells of peribronchiolar lymphoid hyperplasia field in the CLP group (Fig. 6B and Table 3). In the CLP+SA group, it has been observed that IL-1β immunopositivity decreased although there was peribronchiolar lymphoid hyperplasia intensity (Fig. 6C and Table 3). TNF-α immunopositivity was not found in the sham group (Fig. 7A and Table 3). TNF-α immunopositivity was most abundant in the inflammatory cells of peribronchiolar lymphoid hyperplasia field in the CLP group (Fig. 7B and Table 3). In CLP+SA group, there was a moderate TNF-α immunopositivity in the inflammatory cells around the bronchial (Fig. 7C and Table 3).

Table 3. *Quantification of caspase 3, IL-1β, and TNFα immunopositive cells in lungs of the CLP and sinapic acide treated rats in lung tissue*

Groups/Immunopositivity	Caspase 3	IL-1β	TNFα
Sham	0.00±0.00[a]	0.12±0.12[a]	0.12±0.12[a]
CLP	2.62±0.18[b]	2.37±0.32[b]	2.25±0.41[b]
CLP+Sinapic acide	1.75±0.36[c]	1.12±0.29[c]	1.00±0.32[c]

Immunopositivity data are expressed as mean ± SEM (n = 8). Different superscript letters(a,b,c) show the difference among groups.

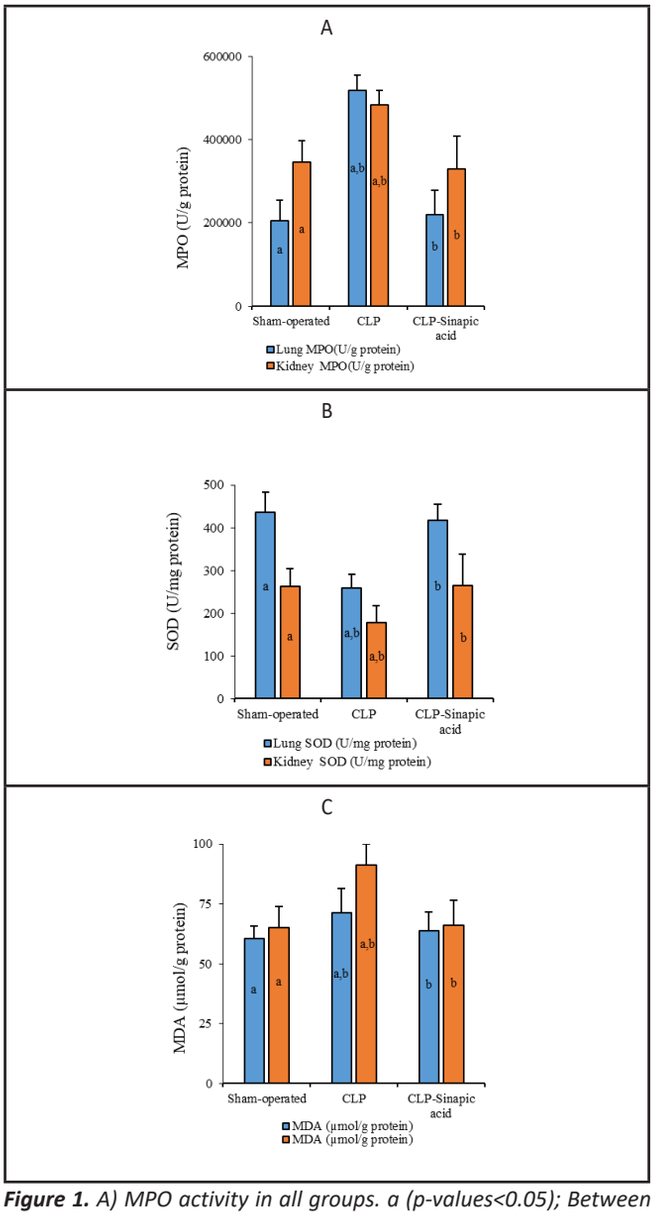

Figure 1. *A) MPO activity in all groups. a (p-values<0.05); Between the sham-operated and CLP groups statistically significant. b (p-values<0.05); Between the CLP and CLP+SA groups statistically significant. B) SOD activity in all groups. a (p-values<0.05); Between the sham-operated and CLP groups statistically significant. b (p-values<0.05); Between the CLP and CLP+SA groups statistically significant. C) MDA levels in all groups. a (p-values<0.05); Between the sham-operated and CLP groups statistically significant. b (p-values<0.05); Between the CLP and CLP+SA – Sinapic acid groups statistically significant.*

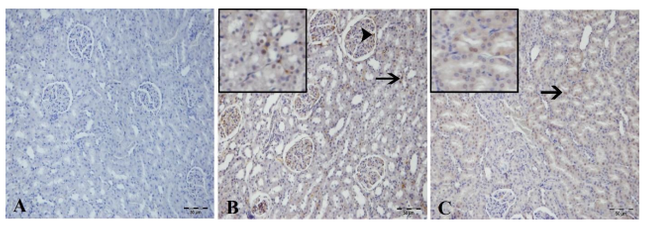

Figure 2. *A) Sham-operated group, B) CLP group, intense caspase-3 immunopositivity in the tubule epithelium (arrow) and glomerular structure (arrow head), C) CLP-Sinapic acid group, caspase-3 immunopositivity in the tubular epithelial cells (arrow).*

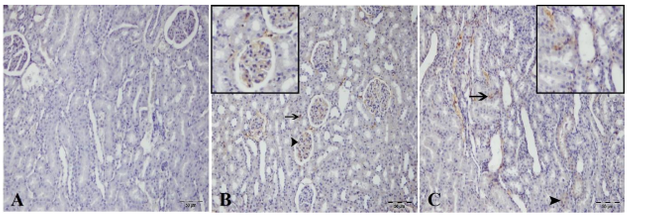

Figure 3. *A) Sham-operated group, B) CLP group, intensive IL-1β immunopositivity in the intertubular area (arrow) and glomerular structure (arrow head), C) CLP-Sinapic acid group, IL-1β immunopositivity in the intertubular area (arrow) and tubule epithelial cells (arrow head).*

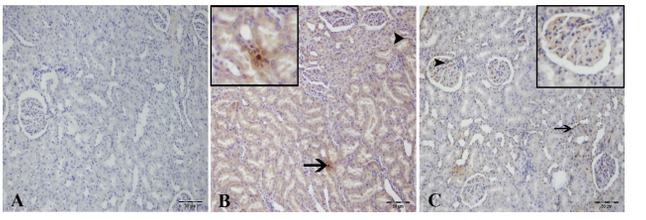

Figure 4. *A) Sham-operated group, B) CLP group, intensive TNF-α immunopositivity in the intertubular area (arrow) and tubule epithelial cells (arrow head), C) CLP-Sinapic acid group, TNF-α immunopositivity in the intertubular area (arrow) and glomerulus (arrow head).*

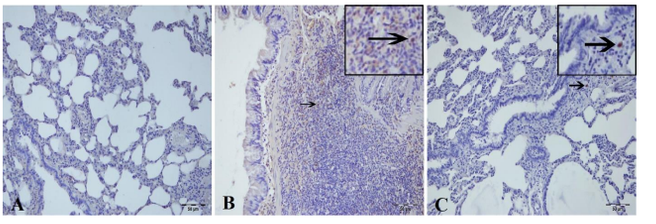

Figure 5. *A) Sham-operated group, B) CLP group, intense caspase-3 immunopositivity in the inflammatory cells of peribronchiolar lymphoid hyperplasia area (arrow), C) CLP-Sinapic acid group, mild caspase-3 immunopositivity in the inflammatory cells around the bronchiole (arrow).*

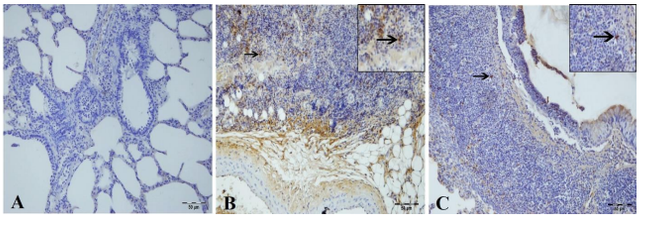

Figure 6. *A) Sham-operated group, B) CLP group, intense IL-1β immunopositivity in the inflammatory cells of peribronchiolar lymphoid hyperplasia area (arrow), C) CLP-Sinapic acid group, decreased IL-1β immunopositivity in the peribronchiolar lymphoid hyperplasia area (arrow).*

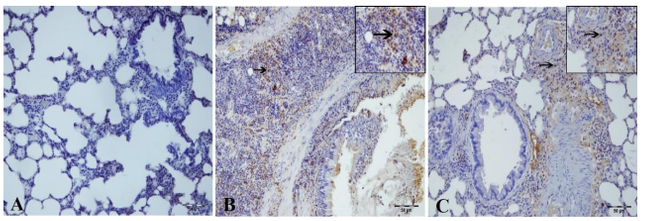

Figure 7. *A) Sham-operated group, B) CLP group, intense TNF-α immunopositivity in the inflammatory cells of peribronchiolar lymphoid hyperplasia area (arrow), C) CLP – Sinapic acid group, mild TNF-α immunopositivity in the inflammatory cells around the bronchiole (arrow).*

4. DISCUSSION

Despite the advances in pathogenesis, pathophysiology, diagnosis and treatment methods, sepsis is a lethal process which still maintains its importance today. The incidence of sepsis, the consequences of which change over time, and having limited information about epidemiology make it a remarkable health problem. It ranks 10th among the causes of death in the USA. It is estimated that 1400 people die every day, and about 500,000 people die per year due to sepsis worldwide (31, 32). The basis of physiopathological events that occur in the sepsis, is an initiation of the immune system response against the toxins and the antigenic structures of the microorganisms entering the body. Sepsis develops if the inflammatory response grows and goes out of control. The inflammatory and procoagulant responses caused by sepsis lead to diffuse endothelial dysfunction, endovascular injury and even multiple organ failure. Factors such as inflammatory-anti-inflammatory, procoagulant-anticoagulant, oxidant-antioxidant, apoptotic-antiapoptotic mechanisms which play a crucial role in maintaining of homeostasis balance, trigger irreversible damage and organ failure in sepsis (33-35). Despite improvements in the treatment of sepsis-induced CLP, the incidence of multiple organ failure and mortality rates are high. It is believed that excessive production of oxygen free radicals, activated by immune system cells, cause oxidative damage and it takes an important role in the pathogenesis of sepsis (36, 37). The lungs are the most affected organs during the multiple organ failure. Poor prognosis in sepsis is often responsible for the lung complications (38). Major systemic and local mediators, neutrophil-endothelium interactions, microvascular thrombosis, renal hypoperfusion and reperfusion injury have been accepted as responsible for the pathogenesis of acute renal failure which is another important organ damage in sepsis. Renal cell death in acute renal failure depends on necrosis as well as apoptosis (39). In the early phase of sepsis, activated phagocytes release large quantities of granular enzymes and produce uncontrolled oxygen free radicals. Goode et al. enounced that oxidative damage is important in the pathogenesis of sepsis and antioxidant therapy can play a protective role against sepsis and its complications (36). The formation of superoxide radical increases depending on a number of factors such as inflammation, radiation, aging, chemical substances and medicines. Superoxide radicals affect all important compounds in cells such as lipids, proteins, DNA, and carbohydrates. Free radicals are highly reactive and short-lived (40, 41). Therefore, it is difficult to measure them directly. To determine the increase in free radical production, measurement of the final products of peroxidation such as MDA, last product of lipid peroxidation, is the most widely used method. In our model, the antioxidant feature is the main protective effect of SA. Inhibition of oxidative stress in the treatment of CLP-induced sepsis model is one of the important mechanisms that prevent organ damage. Other antioxidants such as glutathione (GSH), melatonin, and vitamin E modulate reactive oxygen species (ROS) in cells and inhibit the tissue damage (42, 43). MDA is one of the extremely reactive metabolic products, resulting from lipid peroxidation, which is caused by free oxygen radicals on the tissues (44).]. MDA levels increased significantly on the tissues as a result of lipid peroxidation with liver and kidney toxicity due to CLP, which was given formerly in the literature (9, 45, 46). SOD acts as a supportive antioxidative enzyme that provides protective defence against ROS (47). Viewed incompatible with the finding of Xie et al. (2012), Abd El-Latif et al. (2016) and other studies indicate an important decrease in the activities of SOD in the liver and kidney of CLP-applied animals (9, 48). In our study, MDA level and MPO activity of lung and kidney tissues increased significantly in the sepsis model. However, the SA treatment changed the results markedly and the oxidative stress response reduced. The definition of TOS value provides an important mark of lipid peroxidation and oxidative stress. TAS, as an antioxidant, can maintain the tissue against the oxidative damage through scavenging free radical species. OSI is a parameter that demonstrates whether the oxidant and antioxidant balance is improved on the oxidant side or on the antioxidant side. It is detected by proportioning total oxidants into total antioxidants. The use of OSI is more precious than the use of oxidants and/or antioxidants alone. Increased OSI value due to increased oxidants or reduced antioxidants, initiates uncompensated free radicals, which is lead to peroxidation of lipids, oxidation of proteins and DNA damage (20). In this study, we measured TAS, TOS and OSI values of lung and kidney tissues in the CLP-induced sepsis.

The regulation of apoptosis in cells have conducted by caspases. Until today, 14 different members of the caspase family have been defined, which form two categories. One included in the activation of other caspase family members, caspases such as caspase-1, caspase-2, caspase-4, caspase-5, caspase-8, caspase-9, and caspase-10, and the others mainly interceding apoptosis, involving caspase-3, caspase-6, caspase-7, and caspase-14. Caspase-8 and caspase-9 activate caspase-3 to start apoptosis (49, 50). In this study, as it was in a previous study [39], it was exposed caspase-3 activities and found that CLP promoted caspase-3, indicating that both the programmed cell death receptor and mitochondria-related pathways were involved in apoptosis in the CLP model induced by sepsis of renal and lung cells. Sepsis occurs via a

network of pro-inflammatory cytokines, such as TNF-α and interleukin, which are extremely produced due to the diverse harmful situation, for example, infections. This intensified inflammatory response in the kidney is considered to be a crucial part of the pathophysiology of sepsis (51). Similar to the findings of many studies (52, 53), TNF-alpha and IL-1b levels increased in renal and lung tissues due to sepsis induced by the CLP method. This condition indicates that an intense apoptosis was triggered in kidney and lung tissues. But proinflammatory cytokine levels reduced due to SA treatment and inflammation severity decreased.

5. CONCLUSION

As a conclusion, TAS value declined in lung and kidney tissues but TOS and OSI values increased in the CLP group. On the other side, both TOS and OSI values diminished and TAS value increased due to SA treatment. numerous studies were performed to reduce the complications that may occur during sepsis (4, 9, 54, 55). As a result of these studies, many new drugs have been developed in the treatment of sepsis and it is still debated which drug is more effective. It was detected in many studies in literature that SA protects against oxidative damage of heart tissue in ischemic reperfusion injury, has a protective effect on lysosomal dysfunction in ischemic heart damage caused by isoproterenol, is effective against cisplatin-induced nephrotoxicity, is effective against kainic acid-induced hippocampal neuronal damage, is protective against oxidative kidney damage caused by gentamicin, and also is effective against arsenic-induced toxicity (15-17, 56, 57). In our study, the effects of SA on kidney and lungs were investigated by creating a sepsis model via CLP in rats. This study indicated that SA with antioxidant efficacy may be a potential treatment for sepsis. further researches are imperative through clinical human studies whether SA can be used clinically and to elucidate the mechanisms of the presented therapeutic efficiency of SA.

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Clinical and Experimental Health Sciences

The Antiepileptic and Antidepressant-Like Effects Of Dexpanthenol in Female Swiss Albino Mice

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ABSTRACT

Objective: Oxidative stress is one of the main mechanisms of epilepsy and depression. Based on our information, behavioral effects of dexpanthenol in animals have not yet been demonstrated. Dexpanthenol itself is a topical medicine to restore skin barrier against infections caused by microorganisms which also stimulates the peristaltic movements in the gut when administered parenterally; however since it is cheap and easy to use with minor side effects, the main idea of the current research was to evaluate whether dexpanthenol has an antiepileptic and/or antidepressant-like effects.

Methods: A group of female Swiss albino mice (25-30 g) were injected with dexpanthenol (ip, N = 8) or saline (ip, N = 8), and 30 min later pentylenetetrazole (65 mg/kg, ip)-induced convulsions were determined for 30 min. In addition, another group of mice were again injected with dexpanthenol (500 mg/kg, ip, N = 8) or saline (ip, N = 8) and immobility time were evaluated in the forced swim test. Finally, mouse righting reflex test was used to assess the possible changes in motor coordination.

Results: Our data showed that dexpanthenol, at the dose of 500 mg/kg displayed significant antiepileptic and antidepressant-like effects without affecting motor behavior.

Conclusions: A common low-cost topical drug for various skin disorders that can also be given parenterally for motility regulation has an antiepileptic and antidepressant-like activity in mice.

Keywords: Epilepsy, Depression, Dexpanthenol, Mice

1. INTRODUCTION

Dexpanthenol, a precursor and alcohol analogue of D-pantothenic acid is a commonly used topical medicine to restore skin barrier against infections caused by microorganisms (1). There are several mechanisms how dexpanthenol shows its pharmacological activity, but the most common mechanisms are that dexpanthenol promotes cell proliferation and protects epithelium (2) which may contribute to inhibit oxidative stress (3, 4) and show anti-inflammatory activity (5). Moreover, dexpanthenol is readily oxidized to pantothenic acid in the mammalian cells which in turn stimulates the peristaltic movements in the gut. Thus, it has been a treatment option for adynamic ileus (6).

Epilepsy is a complex and one of the most common neurological disorders characterized by recurrent seizures; which affects approximately 70 million people worldwide (7). Even though there are various cellular mechanisms to understand the seizure susceptibility in mammals, one of the main mechanisms of epilepsy is the imbalance between excitatory and inhibitory neurotransmitter systems in the brain (8). Besides, more than 20% of the patients with epilepsy are refractory to current therapy options (9-11); therefore it is crucial to investigate new drugs and/or bioactive chemicals that have potential antiepileptic features with low adverse effects.

In addition to epilepsy, depression is one of the leading psychiatric and social problems in developing countries. Most patients with depression have been treated by classical antidepressant drugs, however 30% of the patients do not respond to those treatments (12), and yet the mechanisms underlying depression are still unclear (13). It is likely that, epilepsy is also related to depression since there are several

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reports which clarify the emotional responses are much higher in patients with epilepsy (14, 15).

It has been well documented that sex hormones may change the effects of the drugs. For example, women are more susceptible to the analgesic effect of morphine, as well as the dermatological adverse effects of antiepileptic drugs; such as rash (16). Furthermore, women have higher risks for anxiety and depression (17, 18). Also, there are few studies showing the sex differences in seizure susceptibility in mice (16, 19, 20).

Based on our information, behavioral effects of dexpanthenol have not yet been investigated. Thus, the main idea of the current research was to evaluate whether dexpanthenol has an antiepileptic and/or antidepressant-like effects in young female *Swiss albino* mice.

2. METHODS

2.1. Animals

Female *Swiss albino* mice (25-30 g) purchased from the Experimental Medicine Research and Application Center (SUDAM) at the University of Selcuk were used in the experiments. They were randomly divided into 4 groups (1: saline + PTZ; 2: dexpanthenol + PTZ for epilepsy study; 3: saline alone and 4: dexpanthenol alone for depression study) and housed in a vivarium. Food and water were ad libitum. The ethical statement was approved by the University of Selcuk Animal Care and Use Committee (Protocol Number 2020/3).

2.2. Anticonvulsant-like Effects: The Pentylenetetrazole (PTZ)-induced Seizures

The GABA-A receptor antagonist PTZ has been a widely used chemoconvulsant for decades in rodent models of epilepsy (21). A single dose of PTZ (65 mg/kg, ip) (22) was injected in mice 30 min after dexpanthenol (500 mg/kg, ip) or saline administration. The effective dose of dexpanthenol was selected according to our previous studies and literature (5, 23, 24). After PTZ administration, mice were observed for 30 min and the onsets of myoclonic and clonic convulsions and the occurrence of tonic hindlimb extension were recorded. After the observation period, mice were euthanized by high dose of ketamine anesthesia.

2.3. Motor Behavior: The Righting Reflex

The mouse righting reflex test was performed just before the forced swim test whether dexpanthenol at the dose of 500 mg/kg altered motor behavior in mice. The test was modified from the protocol as previously described in detail (25). Briefly, 30 min after the dexpanthenol treatment, mice were put on supine position and observed for righting reflex within 5 sec for 3 consecutive episodes.

2.4. Antidepressant-like Effects: The Forced Swim Test

The forced swim test was carried out by using the protocol described previously (26, 27). Concisely, mice were individually placed into glass cylinders (19 x 15 x 9 cm) which contain 23–25 °C tap water 30 min after dexpanthenol injection. During the 6 min period, immobility behaviors were recorded. A decrease in the duration of immobility was considered as an antidepressant-like effect.

2.5. Drugs

Dexpanthenol (Bepanthen® 500 mg / 2 ml) was purchased from Bayer Pharmaceuticals (Turkey) and dissolved in saline. Intraperitoneal injections were given 30 min before behavioral tests in a volume of 0.1 ml / 10 g body weight.

2.6. Statistical Analysis

Results were presented as means ± S.E.M. Statistical analyses were performed by SPSS statistical software (Version 14.0, SPSS Inc., Chicago, Il). A non-parametric Mann-Whitney U test was used for analyzing the data. Significance was set at $P < 0.05$.

3. RESULTS

3.1. Effects of Dexpanthenol in PTZ-induced Seizures

The effects of dexpanthenol in PTZ-induced seizures are shown in Table-1. At the dose of 500 mg/kg, dexpanthenol significantly prolonged the onset of myoclonic (control: 42.50 ± 8.41 sec; dexpanthenol: 116.42 ± 14.68 sec, N = 8 for each group, $P < 0.05$; Mann-Whitney U test) and clonic convulsions (control: 71.13 ± 11.34 sec; dexpanthenol: 226.57 ± 28.35 sec, N = 8 for each group; $P < 0.05$, Mann-Whitney U test) respectively. None of the mice were died during the seizures, as well as none of them showed usually fatal tonic hind-limb extensions.

Table 1. *The onset of myoclonic and clonic convulsions in saline control and dexpanthenol groups*

Groups	Onset of Myoclonic Convulsions (sec)	Onset of Clonic Convulsions (sec)
Saline (N = 8)	42.50 ± 8.41	71.13 ± 11.34
Dexpanthenol (N = 8)	116.42 ± 14.68*	226.57 ± 28.35*

Dexpanthenol significantly prolonged the onset of the seizures ($P < 0.05$, Mann-Whitney U test) and showed antiepileptic-like activity.*

3.2. Effects of Dexpanthenol on Righting Reflex

Dexpanthenol, at the dose of 500 mg/kg, did not alter motor behavior. Righting reflexes were within 2 and 3 sec for all groups. Data not shown.

3.3. Effects of Dexpanthenol in Forced Swim Test

While the duration of immobility was found 161.13 ± 18.24 sec in control group, at the dose of 500 mg/kg, dexpanthenol significantly reduced the duration of immobility to 82.59 ± 10.18 sec and showed antidepressant-like effect (Table-2); P < 0.05, Mann-Whitney U test. Eight mice were used in each group.

Table 2. *The duration of immobility in saline control and dexpanthenol groups.*

Groups	Duration of Immobility (sec)
Saline (N = 8)	161.13 ± 18.24
Dexpanthenol (N = 8)	82.59 ± 10.18*

Dexpanthenol significantly reduced the duration of immobility (P < 0.05, Mann-Whitney U test) and showed antidepressant-like activity.*

4. DISCUSSION

Dexpanthenol, namely Bepanthen® has been widely used for various diseases since 1950s such as systemic lupus erythematosus (28), chronic bronchitis (29), dermatological lesions (30, 31), chronic constipation (6, 32), postoperative ileus (33), testicular atrophy (34), acute rhinitis (2) and pattern alopecia (3). It is a stable alcoholic analog of D-pantothenic acid which in turn metabolized to pantothenic acid in the cells (35). Because of its antioxidant activity, dexpanthenol could reverse the hepatotoxic and ototoxic effects of cisplatin, a commonly used anticancer drug (36, 37). Recently, the metabolite pantothenic acid has been shown to enhance glutathione and coenzyme A levels as well as ATP synthesis in the cells that are the major defense systems against oxidative stress (38).

In the present study, we investigated the anticonvulsant and antidepressant-like effects of dexpanthenol in the mouse pentylenetetrazole and forced swim tests, respectively. To our knowledge and literature, this is the first pharmacological and behavioral study which has revealed the neurological effects of dexpanthenol. Briefly, dexpanthenol, at the dose of 500 mg/kg, ip showed promising effects in epilepsy and depression without altering motor coordination. And, it is a low cost drug with minor side effects.

It has been well documented that oxidative stress plays a major role in epilepsy (39) and depression (40). Epilepsy-related mitochondrial dysfunction and brain damage were attributed to oxidative stress and neuroinflammation in animal studies (41, 42) which might be primary mechanisms for dexpanthenol. Unlike epilepsy, oxidative stress plays a dual role in depression. While it may cause depression, depression itself may cause oxidative stress (43). Evidence showed that dexpanthenol has an anti-inflammatory activity and significant effects for reducing oxidative stress markers (44). Therefore, our current data support the idea of the inhibition of oxidative stress-induced activity by dexpanthenol in the brain. In addition, few studies showed that oxidative stress associated pharmacological and physiological effects were higher in females (45, 46), however in an age-related sex differences in antioxidant activity study, it has been found that women show efficient antioxidant activity (47). Since there are main differences responding to oxidative stress between sexes, we decided to study with young female mice.

5. CONCLUSION

Our data suggest that dexpanthenol may be involved in central nervous system antioxidant activity and could be a potentially novel low cost antiepileptic and/or antidepressant agent. However further studies are needed to understand the cellular mechanisms of these effects.

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Clinical and Experimental Health Sciences

The Effect of Ultrasonic Surgery Tool in the Treatment of Tonsillolithiasis

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ABSTRACT

Objective: This study aimed to reveal the effects of the ultrasonic surgical tools in tonsillolith treatment alongside its complaints as an office-based surgical procedure.

Methods: Forty-four patients included in this study who were aware of the white-yellowish lesions on their tonsils concurrently complained of either halitosis and/or the foreign body sensation. Patients were asked to mark their pain scores on the visual analog scale for the pain on the 1st day after the procedure. Halitosis and foreign body sensation were questionnaired before the procedure. The surgical procedure was performed under local anesthesia with the probe of the ultrasonic surgical tool after the tonsilloliths were removed. Tonsils were examined again, also halitosis and foreign body sensation were questionnaired on the postoperative 6th and 12th month period.

Results: There was a statistically significant improvement in the patients' halitosis complaint on the postoperative 6th (p=0.001) and 12th (p=0.000) month when compared to first attendance to the clinic. The foreign body sensation in the throat also had a statistically significant decrease in the postoperative 6th (p=0.000) and 12th month (p=0.000). Results showed that there is a statistically significant improvement of tonsilloliths on the postoperative 6th month (p=0.000) and 12th month (p=0.000).

Conclusion: The use of ultrasonic surgical tools in the treatment of tonsilloliths can be a favorable one-day office procedure. With its short duration of application, the lower pain scores, the day to return a normal diet, and its satisfactory results this procedure can be carried out easily and safely.

Keywords: Tonsillolithiasis, ultrasonic energy, halitosis

1. INTRODUCTION

Tonsil stones (tonsilloliths) are calcifications that can occur in enlarged tonsillar crypts and develop by the sedimentation of food debris and exfoliation of the crypt mucosa. This conglomerate can gradually calcify from a soft, gel-like mass to hard "stones" (1,2). Tonsilloliths are mostly smaller structures that are in 3-4 mm size, and prevalence is given as 16% to 46.1% in the literature (3,4). Although tonsilloliths are asymptomatic, they may cause chronic bad breath, dry cough, swallowing disorders, otalgia, foreign body sensation, or a bad taste in the mouth (5-7). Due to the recurrent inflammatory stages in the crypts, it is assumed that bacteria and epithelial deposits accumulate along with food debris. Calcification occurs through the storage of dissolved inorganic substances in saliva (8).

Asymptomatic tonsil stones do not require any treatment after the patient is informed besides symptomatic tonsilloliths can be either curetted or surgically removed with various techniques under local or general anesthesia (9,10,11). If clinical treatment with topical antiseptics and oral antibiotics does not provide relief, surgical removal of the tonsils is indicated. Laser and radiofrequency are already used powered instruments in the treatment of tonsillolith and its concurrent complaints (12,13,14), yet this is the first study in the literature in which we aimed to reveal the effect of ultrasound energy in the tonsillolith treatment.

2. METHODS

This study data obtained from patients who were presented to our Ear Nose & Throat (ENT) clinic between the 2017 – 2020 years. Our regular procedures in clinical evaluation and follow up was conducted for the patients with tonsilloliths. The approval for the research was obtained from the Local Ethics Committee (Approval Number: 2020/85-1196). The patients included in this study were aware of the white-yellowish lesions on their tonsils, concurrently complained of either halitosis and/or the foreign body sensation. The

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participants were selected over 18 years old patients and questioned for their medical history. All patients went through a complete ENT examination. The ones with acute or chronic periodontal, gastrointestinal, sinonasal, oropharyngeal, pulmonary diseases, and who had uncontrolled gag reflex were not included in the study. Patients were questioned subjectively whether they have halitosis and foreign body sensation before the procedure and on the 6th and 12th-month follow up visits. Patients were asked to mark their pain scores on the visual analog scale (VAS), which was evaluated over 100 point, for the pain on the 1st day after the procedure. The day in which patients' pain is ended up and the day that they return to normal eating habits were also noted. Tonsils were examined again and noted whether if tonsillolths were still present on postoperative the 6th and 12th-month period.

2.1. Surgical Procedure

This procedure was performed under local anesthesia with 2% lidocaine injection (Jetokain simplex; Adeka İlaç San, Samsun, Turkey) on the tonsillar pillars and on the tonsil crypt surface, 10 minutes after the application of 10% lidocaine pump spray (Vemcaine; Vem İlaç San, Tekirdag, Turkey). After the gag reflex disappear tonsilloliths (Figure 1) were removed from the crypts with the help of forceps by applying pressure on the tonsil. First, the non-activated ultrasound probe (D&A UltraSurg II; Diamant Medical Equipment Ltd, Thessaloniki, Greece) was inserted deep into the cleared crypt (Figure 2). This powered instrument generates vibration between 20.000 and 60.000 Hz. At the 85% power setting, by using a foot pedal the apparatus was activated in 10 seconds for each application. The probe was drawn back with minimal circular movements to provide contact with the periphery of the crypt. The tissue gets blanched and the probe was also placed on the outer surface of that crypt (Figure 3). The process was finalized with the control of bleeding.

Figure 1. *The view of the tonslillolith in the right tonsil crypt*

Descriptive statistics were performed with Statistical Package for Social Sciences version 17.0 (SPSS Inc; Chicago, IL, USA). In the statistical analyses Chi-square test, Wilcoxon signed-rank and independent t-tests were used. A p-value of less than 0.05 was statistically chosen as the level of significance.

Figure 2. *Placement of the probe into the cleared crypt of the right tonsil*

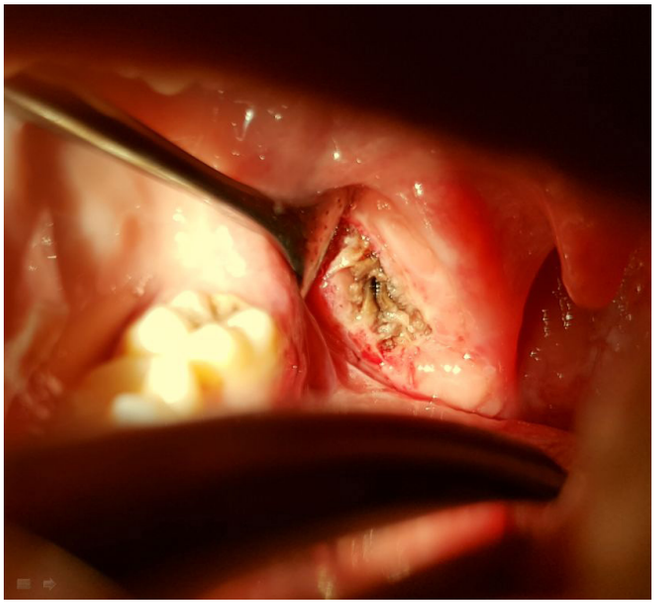

Figure 3. *The blanched right tonsil after the appliance of ultrasonic surgical tool*

3. RESULTS

There were 44 patients (24 women and 20 men) with a mean age of 32.18 ± 5.81 that existed in the study. 18 of them had

on the right, 16 on the left, and 10 of them had bilateral tonsilloliths. The region in which tonsilloliths were mostly seen as the upper pole of the tonsils (38.7%), the bottom of the tonsils was the area where the tonsilloliths were seen less frequently (9.1%). The patients who were smoking were in the percent of 63.6% (n=28). The patients who had halitosis and foreign body sensation in the throat, before the tonsilloliths were removed, were 77.3% (n=34) and 79.5% (n=35) consecutively. In VAS score mean value of pain was 18.72 ± 14.26 on the 24th hour of the procedure. The mean of the time when the pain was disappeared found as 1.54 ± 1.17 days. The mean time when the patients were started a normal diet was 1.88 ± 0.86th day.

19 of the 34 patients had complain of halitosis on the 6th month. The number of patients who had halitosis on the 12th month were 13. There was a statistically significant improvement in the patients' halitosis complaint on the postoperative 6th (p=0.001) and 12th (p=0.000) month when compared to first attendance to the clinic. When compared the 6th and 12th month the decrease in halitosis complaint was also found to be statistically significant (p=0.014). 14 of the 35 patients had complain of halitosis on the 6th month. The number of patients who had halitosis on the 12th month were 9. The foreign body sensation in the throat also had a statistically significant decrease in the postoperative 6th (p=0.000) and 12th month (p=0.000). When compared to the 6th month and 12th month there is also a statistically significant decrease in the foreign body sensation in the throat. (p=0.025). There was no correlation found between the day to start on a normal diet, and postoperative VAS scores (p=0.204). Although postoperative VAS score and the day in which pain set to zero was found statistically related to each other (p<0.001), the day that pain was completely disappeared showed no statistically significant correlation with the day on which normal diet was started (p=0.280). There was a statistically significant relation between the non-smoking patients and the day in which pain ends completely. (p=0.003)

10 patients had undergone the second procedure on the 6 months period due to tonsillolith reoccurance. Among these patients, 5 of them had tonsilloliths on the 12th month period also. Except them, also 1 patient had tonsilloliths on the 12th month period, so that total number of patients who had tonsilloliths on the 12th month period was 6. The tonsil sides were the same in the 4 patients and different in the 6 patients in the postoperative 6th month period. 12th month period only in 6 patients tonsilloliths became visible again and 4 of them had on the same side, 2 of them on the different tonsil sides. These results showed that there is a statistically significant improvement of tonsilloliths in the postoperative 6th month (p=0.000) and 12th month (p=0.000). But there is no significant change was observed between the 6th and 12th month (p=0.219). No complications were seen in any patient.

4. DISCUSSION

The tonsilloliths are most commonly found within the crypts of the palatine tonsils but there are few reports in which these calcified stones can be found in the lingual tonsil, adenoid and pharynx also (15-18). As the tonsillectomy and tonsillotomy techniques are evolved, various choices arose in handling the tonsilloliths. In the treatment of these calcifications several methods of cryptolysis which means the destruction of the tonsil crypts, have been used with different types of surgical instruments. Studies in recent years showed that ultrasonic surgery tools have been used efficiently for head and neck, general surgery, gynecology, cardiovascular and thoracic surgery procedures. Most commonly these tools are used in chronic tonsil diseases, oral cavity and neck oncology in otorhinolaryngology department (19). Ultrasonic energy converts into mechanical energy via transducer which lets acoustic waves to induce the tip of the probe and provides mechanical vibration. These vibrations denaturate the collagen fibers and as well coagulate vessels with lower thermal energy. It was found that only one study used this device for tonsillotomy in the literature, apart from that in each study ultrasonic energy were used for tonsillectomy. The tonsillectomy with ultrasonic surgery tools showed a significant reduction in operative time, intraoperative blood loss and rehospitalization due to secondary bleeding and was associated with early restoration of the nutritional routine (20).

Laser tonsil cryptolysis (LTC), radiofrequency (RF), coblators, and tonsillectomy are the most current procedures (12,13). Tonsillectomy is also one of the preferred procedures but mostly in patients who have chronic caseous tonsillitis, hypertrophic tonsils, and with large tonsil stones. When compare tonsillectomy to intracapsular techniques, it has higher rates of bleeding, prolongation in the duration of postoperative pain, and later progression to normal dietary habits. In the literature review we couldn't encounter any research which investigate the effects of ultrasonic surgery tools in tonsillolithiasis treatment, in this regard we discussed our results with the studies which used the other surgical tools for tonsillolith.

RF application with bipolar and monopolar rods have been studied several times. RF cryptolysis targeted to destruct the epithelium with the formation of fibrosis which tends to close the crypt openings (10,14,21,22). Vogt et al reported that the RF cryptolysis is a day case procedure that is minimally invasive with lower complaint rates, bipolar RF cryptolysis can cause less pain than the monopolar technique also. In several studies, it is indicated that laser cryptolysis has higher costs though it has a faster healing period with less postoperative pain, immediate return to normal dietary habits, and fewer complication rates (10,22). RF ablation costs are reported as less than laser cryptolysis and suggested as it can be more appropriate for the patients who have insufficient mouth opening and too much gag reflex (14). Our patients showed no significant gag reflex after applying lidocaine spray and

injection so we can manage to place an ultrasonic probe inside and around the crypts in which calcification was found.

In LTC, crypts are vaporised with thermal energy, and scar tissue occurs with the new formation of collagen tissue (14,23). LTC is also reported as one of the effective treatment methods for tonsilloliths and halitosis in patients. Hashemıan et al (10) compared LTC to RF ablation and reported that they are both effective although LTC has a faster healing period. Though LTC can have serious complications such as burning in the mouth, face, and even in the respiratory system, also it can affect the retina. Moreover, as the cost of laser equipment is known to be higher than other instruments that are used in the treatment of tonsil diseases, it can be difficult to provide (24).

Several researches studied halitosis in patients with tonsilloliths. Rio et al.reported that chronic caseous tonsillitis can be a risk factor for halitosis moreover CO2 laser cryptolysis help the improvement of halitosis and clearance of the tonsilliths (11,25). Hashemihan et al suggested that either with the radiofrequency or with the CO2 laser there is an improvement on tonsilloliths foreign body sensation and halitosis complaint of the patients (10). Finkelstein et al concluded that laser CO2 cryptolysis is an effective treatment for halitosis which requires repetitive second procedures at a low rate (21). In another laser cryptolysis study, which Krespi et al performed, the repetitive procedure rate was found as 1.16 procedures per patient (22). Similar to these studies we do have a rate of second procedure 1.22 per patient and also we have significant improvement in halitosis and foreign body sensation in the throat.

Chang et al. proposed that coblation cryptolysis also have satisfactory results in tonsillolith treatment with the tonsil resurfacing opportunity (24). In our study, we also benefit from this idea of resurfacing the tonsils, with ultrasonic energy. The harmonic scalpel (HS) which uses ultrasonic energy is one of the tonsillectomy/tonsillotomy techniques (26,27,28). In this study, we used a type of harmonic scalpel tool which differs by the operating instrument probe. Ultrasonic waves utilizes minimal thermal energy by providing simultaneous cutting and coagulation in the surrounding tissue with the vibration. The waves of the vibration form low pressure in the intracellular area which causes the explosion of cell and tissue separation. As a result, connective scar tissue occurs which seals the crypt. The tissue harm is reduced with the lower temperature heat (50-100°C) when compared to electrocautery (over 400ºC). Despite these Modi et al showed that harmonic scalpel, coblators, and electrocautery have a similar thermal injury in the tonsillar fossa during a tonsillectomy. The mean depth of thermal injury with ultrasonic tools was reported as 0.68 mm (29). Accordingly we supposed that the low postoperative pain scores can be related with this minimal thermal injury in our study. In the literature review there was only one study in which intracapsular tonsillotomy was performed with the same ultrasonic surgical instrument that we used. Khalaf AQ et al (26) reported satisfying results in chronic tonsillitis and tonsillar hypertrophy with this surgical tool. Several studies support that ultrasonic energy decreases pain scores with the least postoperative discomfort in tonsillectomy (27,28). Similar to these ultrasound energy performed a significant decrease in patient's complaints and also helps the elimination of the tonsilloliths in our study. However, some studies indicated that HS, coblator, and electrocautery have no difference in post-tonsillectomy pain (30).

In our study we discussed our results with other treatment modalities in the light of the literature. Comparing ultrasonic surgical tools with other procedures which are commonly used at the treatment of tonsillolith and performing objective methods for halitosis in the research might strengthen our results. These two subjects can be the shortenings of our study.

5. CONCLUSION

The use of ultrasounic surgery tools in the treatment of tonsilloliths can be a favorable one-day office procedure. With its short duration of application, the lower pain scores, the day to return a normal diet, and its satisfactory results this procedure can be carried out easily and safely. In the English literature review, there are no studies exist related to the ultrasound energy in the treatment of tonsilloliths. It is the first study that brings out the ultrasound as an alternative technique in tonsilloliths and the complaints that it caused. Nevertheless, there should be further studies have to be conducted to understand its tissue effects, halitosis management, and cost-effectiveness and also to determine the safety.

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Clinical and Experimental Health Sciences

The Comparison of Physical Activity, Fatigue and Quality of Life in Different Age Groups

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ABSTRACT

Objective: The purpose of this study is to compare the levels of physical activity, fatigue, and quality of life of healthy individuals belonging to different age groups.

Methods: A total of 107 healthy individuals participated in the study, of which 39 were young (aged between 18 and 39), 42 were middle-aged (aged between 40 and 64), and 26 were elderly (over 65 years old). While physical activity was measured using the International Physical Activity Questionnaire, fatigue level was evaluated using the Fatigue Assessment Scale, and quality of life with the World Health Organization Quality of Life Instruments.

Results: A statistically significant difference has been detected between three groups with regards to the levels of physical activity, fatigue, and quality of life ($p<0.05$). The physical activity levels of the elderly individuals were lower than those of the middle-aged individuals, while their fatigue levels were higher. The quality of life which was related to physical health and social relationships of the young and the middle-aged were similar and higher than those of the elderly individuals. Middle-aged individuals had a higher psychological health-related quality of life than elderly individuals, but their environment – and physical health-related quality of life was higher than both young and elderly individuals.
Conclusion: It has been concluded that elderly age group is associated with the lowest levels of physical activity and quality of life and the highest level of fatigue. We think that by getting elderly to adopt habit of exercise, the decrease in levels of physical activity and quality of life, and increase in fatigue level can be prevented.

Keywords: Age, physical activity, fatigue, quality of life.

1. INTRODUCTION

Physical activity is ''defined as any movement of the body that requires energy expenditure'' (1). Physical activities positively affect the physical and mental health of individuals, is useful in both the prevention and treatment of diseases, and refers to a linear relationship with health (2,3). Besides reducing the risk of developing many diseases, physical activities have psychological benefits such as alleviating depression, stress, and anxiety, as well as positively affecting socialization (4). Considering its prevalence and impacts on health and inactivity; which have serious and far-reaching outcomes in the economic, environmental, and social realms of life and is one of the leading five crucial risk factors in terms of chronic diseases and global mortality, should be regarded as a pandemic (5). It is believed that physical inactivity is the main cause of about 30% of ischemic heart diseases, 27% of diabetes cases, and approximately 21 to 25% of breast and colon cancer cases (6). Studies show that physical activity, as well as mass and muscle strength decrease with age (7). After the age of 30, muscular strength starts to decrease at the rate of 10 to 15% every decade, and this process accelerates after the age of 50. Despite being not life-threatening, the loss of muscle mass makes daily activities difficult and causes the level of physical activity to decrease (8).

Fatigue is a significant symptom in various medical and neurological disorders (9). Fatigue, defined as muscle fatigue, is a symptom commonly noticed during exercise activities; however, it can also manifest itself as a secondary symptom of many diseases and health conditions during daily activities (10). Studies in the literature suggest that physical inactivity predisposes to increased fatigue (10), while physical activity contributes to the ability of both healthy individuals and patients of all ages to resist fatigue by increasing muscle strength and functionality (11,12). Findings regarding the relationship between age and fatigue are precarious (13). While some studies state that there is no relationship between age and fatigue (14), some others concluded that

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the level of fatigue increases by aging (15). It was also found in some studies that older people have lower levels of fatigue (16).

Quality of life is defined ''as the perception of an individual's goals, expectations, standards and concerns regarding her/his sociocultural status'' (17). It is observed in all relevant studies that physical activity greatly affects the quality of life. It is an ordinary result of the studies in the literature that regular physical activity provides to be physically stronger, to own a better quality of life, and to be better physically and psychologically (18).

It is highly expected to encounter many studies in the literature investigating the change in the levels of physical activity, fatigue, and quality of life with age, but there are no studies that compare the levels of physical activity, fatigue, and quality of life among healthy individuals of different age groups, as far as we know. Therefore, this study intent to compare young, middle-aged, and elderly individuals in terms of their levels of physical activity, fatigue, and quality of life.

2. METHODS

2.1. Individuals

A total of 107 individuals who live in various cities in Turkey, of which 39 were young (between the ages of 18 and 39), 42 were middle-aged (between the ages of 40 and 64), and 26 were elderly (over the age of 65), included in the study. Each participant was enlightened about the content of the study, the consent form for their voluntary participation in the study was read online, and the approvals of the participants were obtained. The approval from the ethics committee of Sivas Cumhuriyet University was obtained with the decision dated 18.11.2020 and numbered 2020-11/17. Evaluation forms and questionnaires were performed with participants using the online questionnaire method. The demographic information of the individuals (age, height, body weight, gender was recorded, and those with a body mass index (BMI) of over 35 kg/m^2 and having any systemic, neurological, or orthopedic disorders limiting physical activity were excluded from the study.

2.2. Measurements

The International Physical Activity Questionnaire-Short Form (IPAQ-SF) was used to evaluate the level of physical activity. This questionnaire evaluates the physical activity levels of individuals in the last seven days in four categories of vigorous activities, moderate activities, walking, and sitting. The total weekly MET-min/week score is counted by multiplying the metabolic equivalent of task (MET) values (vigorous = 8 MET, moderate = 4 MET, walking = 3.3 MET), the period of the activities (minutes), and the frequency of the activities (number of days) (19).

The fatigue levels were assessed using the Fatigue Assessment Scale (FAS). The FAS questionnaire is a one-dimensional scale for fatigue testing and consists of 10 statements, of which five examine physical fatigue and the other five examine mental health. The intensity of fatigue, presented by the total score, is between 10 and 50 (20,21). The FAS includes 10 statements with 5 options, ranging between "1 = never" and "5 = always." Except for statements 4 (I have enough energy for everyday life) and 10 (When I am doing something, I can concentrate quite well), the remaining 8 statements are negative. Thus, the scores of the options chosen for statements 4 and 10 are reversed before the analysis of the data ("1 = always" and "5 = never") (21,22).

The World Health Organization Quality of Life Instrument, Short Form (WHOQOL-BREF) was employed to ascertain the quality of life (19). The WHOQOL-BREF scale measures the quality of life in four basic dimensions: physical health, psychological health, social relationships, and environmental health (19,23). This scale consists of 26 items and has a 5-point rating type, with answers ranging from "1 = Not Satisfied at all" to "5 = Very Satisfied." High scores indicate a high quality of life. In the Turkish adaptation of the form, another question related to the environment was added, so it includes a total of 27 questions (24).

2.3. Statistical Analysis

Statistical analysis of the study was carried out using the "Statistical Package for Social Sciences" (SPSS) Version 22.0 (SPSS inc., Chicago, IL, USA) software. The normal distribution of the data was analyzed using visual (histograms and probability graphs) and analytical methods (Kolmogorov–Smirnov Test and Shapiro–Wilk Test). The Kruskal–Wallis Test was conducted to discover the differences between three different age groups. In the analysis of the statistical significance, the type 1 error level was taken as 5%. Pairwise comparisons were analyzed using the Mann Whitney U Test. Bonferonni correction was applied and the p significance value to be used for pairwise comparisons was determined as 0.017.

3. RESULTS

Although there was a statistically significant difference between the three groups in terms of body weight and BMI ($p<0.05$, Table 1), no significant difference was detected in terms of height ($p>0.05$, Table 1). The difference in body weight between the groups was resulting from the difference between the young and the elderly participants ($p = 0.001$), the body weight of the elderly of which was higher than those of the younger participants. The difference in the BMI was due to the difference between the young and elderly participants ($p<0.001$) and the difference between the middle-aged participants and elderly participants ($p = 0.010$). Accordingly, the BMIs of the elderly participants were higher than those of the young and the middle-aged participants.

As for the difference between the physical activity levels in the three groups, there were a statistically difference between them (p<0.05, Table 2). This stemmed from the difference in the levels of physical activity between the middle-aged and the elderly participants (p = 0.009). So, the physical activity levels of the elderly participants were found to be lower than those of the middle-aged participants.

Table 1. *Demographic information of the participants.*

		Young (n=39)	Middle-aged (n=42)	Elderly (n=26)	p
Body weight (kg) (Median /IQR)		65 (58 /80)	75 (68 / 80)	80 (73 / 86)	**0.002*** ¥
Height (cm) (Median /IQR)		167 (160/ 174)	167 (160 /173)	166.5 (161/174)	0.884
BMI (kg/cm^2) (Median /IQR)		24.2 (22.6/27.3)	25.65 (24.1/27.7)	28.15 (26/30.5)	**<0.001*** ¥ Φ
Gender	**Female (%)**	27 (69.2)	23 (54.8)	10 (38.5)	
	Male (%)	12 (30.8)	19 (45.2)	16 (61.5)	

*Significance of the difference between * the three groups, ¥ young and elderly, Φ middle-aged and elderly (* Kruskal–Wallis Test, ¥ – Φ – ¶ Mann Whitney U Test); BMI: Body Mass Index; IQR: interquartile range, n: number.*

A statistically significant difference was observed between the three groups in terms of fatigue levels (p<0.05, Table 2). This difference was caused by the difference in fatigue levels between the middle-aged participants and the elderly participants (p = 0.001). Fatigue levels of elderly individuals were found to be higher than those of the middle-aged individuals.

Table 2. *Comparison of physical activity level, fatigue level and quality of life by age groups.*

		Young (n=39)	Middle-aged (n=42)	Elderly (n=26)	p
IPAQ-SF (Median /IQR)		570 (231/2140)	693 (396 / 1080)	396 (198 / 594)	**0.035*** Φ
FAS (Median /IQR)		22 (20 / 28)	21 (14 / 24)	25.5 (22 / 29)	**0.003*** Φ
WHOQOL-BREF (Median/ IQR)	**PH**	15.42 (13.14/16.57)	15.14 (13.71/17.14)	12.57 (10.85/14.28)	**<0.001*** ¥ Φ
	PS	14 (12/16)	15.67 (13.33/17.33)	12.66 (11.33/14.66)	**0.002*** Φ
	SR	13.33 (12/16)	14.66 (13.33/16)	11.33 (9.33/12)	**<0.001*** ¥ Φ
	EH	13.5 (12.5 /14.5)	15 (13 / 16.5)	12.75 (11 /14.5)	**0.006*** ¶ Φ

*Significance of the difference between * the three groups, young and middle-age, ¥ young and elderly, Φ middle-aged and elderly (* Kruskal–Wallis Test, ¥ – Φ – ¶ Mann Whitney U Test); IPAQ-SF: International Physical Activity Questionnaire – Short Form; FAS: Fatigue Assessment Scale; WHOQOL-BREF: World Health Organization Quality of Life Instrument, Short Form; PH: physical health; PS: psychological health; SR: social relationships; EH: environmental health; IQR: interquartile range.*

According to scores obtained from quality of life questionnaire, it was observed that there was a significant difference between the three groups in the sense of the four sub-parameters (p<0.05, Table 2). The difference in terms of the WHOQOL-physical health was due to the difference between the values obtained for the young and the elderly participants (p<0.001) as well as the middle-aged and the elderly participants (p<0.001). Therefore, it was seen that the young and the middle-aged participants had similar levels of physical health-related quality of life, which is higher than those of the elderly participants. In terms of the WHOQOL-psychological health, the results obtained for the middle-aged and the elderly participants were different (p = 0.001). Accordingly, the middle-aged participants were observed to have higher levels of psychological health-related quality of life than those of the elderly participants. The difference in terms of the WHOQOL-social relationships was due to the difference between the values obtained for the young and the elderly participants (p<0.001) and the middle-aged and elderly participants (p<0.001). So, it was discovered that young and middle-aged participants had similar levels of social relations-related quality of life, which is higher than those of the elderly participants. As for the difference in terms of the WHOQOL-environment, it was due to the difference between the values obtained for the young and the middle-aged participants (p = 0.016) and the middle-aged and elderly participants (p = 0.004). Consequently, it was observed that the environment-related quality of life of the middle-aged participants was higher than those of the young and elderly participants.

4. DISCUSSION

As a result of this study, where we compared individuals in different age groups on the basis of physical activity, fatigue level, and quality of life; it was proved that there were differences in the levels of physical activity, fatigue, and quality of life of young, middle-aged, and elderly individuals. All in all, it was found that older individuals had lower levels of physical activity and quality of life, and higher levels of fatigue.

Physical activity is a body movement with any skeletal muscle that occurs with energy expenditure (25). Hall et al. (26) explained that the level of physical activity decreased with increasing age. This study showed that age-related differences in physical activity were clear in most of the 10-year age bands for both sexes. The most outstanding age-related differences in activity appeared in groups over 60 and over 70 years of age. Each age group was significantly different from the previous one (26). In our study, it was noticed that the physical activity levels of the middle-aged individuals were higher than the physical activity levels of elderly individuals. In this respect, our findings conform to the findings of the relevant studies in the literature.

Fatigue is defined as not being able to gather the energy needed to perform a task or not having enough resources

for a task (27). The consequences of studies in the literature examining the change of fatigue with age are precarious (13). A study carried on by Cathébras et al. (28) observed no significant relationship between age and fatigue. A study by Tibblin et al. (29) found that older people had lower levels of fatigue. Researchers think that this is because individuals who are 65 years old are at the retirement age and can start living comfortably (29). In a research done by Fuhrer et al (30), it was observed that the level of fatigue increased with age. In our study, parallel to the study of Fuhrer et al., it was found that elderly participants had higher levels of fatigue than middle-aged participants. This increase in fatigue levels with age may have emerged as a result of decreasing physical activity.

According to the World Health Organization, quality of life is described as the way individuals perceive their own situation, their goals and expectations, as well as the standards within their own culture and value system (23). The concept of quality of life is multidimensional, can show a change over time, and is related to the expectations and lives of individuals (31). In the study of Onat et al. (32), it was pointed out that there was a significant linear relationship between age and quality of life, and an increase in age caused a decline in the quality of life score. In the same direction with this study, in the present study, it was seen that the elderly group emerged as the one with the lowest physical health-related, psychological health-related, social relations-related, and environment-related quality of life.

In a research done by Arslantas et al. (33) into individuals over 65 years of age, it was found that when the domain score averages of the WHOQOL-BREF Scale increased, the quality of life decreased significantly in all areas except the social relationships domain. In their study, Isıklı et al. (34) evaluated the quality of life of individuals aged 35 and over, and found that the quality of life domain with the highest score regarded as the social relationships domain and the one with the lowest score regarded as the environment domain. When we look at the mean domain scores in our study, the highest score in the young age group was captured in the physical health domain and the lowest score was captured in the environment domain. In the middle age group, the highest score was seized in the physical health domain and the lowest score was seized in social relationships domain; in the elderly group, the highest score was grasped in the physical health domain and the lowest score was grasped in the social relationships domain. The most important reason for the changes in the average domain scores may be due to the differences in age and lifestyle of the participant groups. The COVID-19 pandemic can be shown as the reason why the social relationships domain is the one with the lowest score. Despite the different results found in the literature, the consensus remains that quality of life scores decrease with age.

The fact that sufficient communication could not be established with the elderly participants due to their educational and cultural backgrounds as the questionnaires were processed in the online environment, can be regarded as a limitation for our study. This is also the reason why the number of elderly individuals who took part in the study is fewer than that of the other groups.

5. CONCLUSION

It has been found as a conclusion of this study comparing individuals of different age groups in terms of levels of physical activity, fatigue, and quality of life that the age group with the lowest physical activity level and quality of life and the highest level of fatigue is held by the elderly individuals. The findings of this study reveal the fact that the levels of physical activity, quality of life, and fatigue, which were also stated in previous studies to be associated with age, differ in elderly individuals compared to other age groups. Individuals of all ages, especially the elderly, should be reminded that the most important and effective way to prevent the decrease in physical activity and quality of life, as well as to reduce the feeling of fatigue is to make exercise a habit. Thanks to adopting the habit of exercise, both the expected decrease in the levels of physical activity and quality of life, and the increase in fatigue can be prevented.

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Clinical and Experimental Health Sciences

Investigation of the Effects of Amlodipine on Paracetamol-Induced Acute Kidney Toxicity in Rats

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ABSTRACT

Objective: Paracetamol is an analgesic and antipyretic agent that widely used throughout the world. The increase of the usage and its easy accessibility brings along the toxicity risk. Paracetamol toxicity may result in drug induced hepatotoxicity and nephrotoxicity. Anti-inflammatory and antioxidant effects of amlodipine which creates vasodilatation by blocking L-type calcium channels and its usage in elderly for renoprotective purposes, ponders that it might be favorable in cases with inflammation such renal damage inducted with paracetamol. Thus, aim of our study is to analyze effects of amlodipine, one of L-type calcium channel blockers, in acute renal damage inducted with paracetamol.

Methods: 30 male rats consisting of 5 groups were used in our study. Groups; I: Health Control group. 2 ml Phosphate-buffered saline (PBS) oral was administered. II: 10 mg/kg Amlodipine III: Paracetamol (2g/kg) IV: 5 mg/kg Amlodipine + paracetamol V: 10 mg/kg Amlodipine + paracetamol. Rats were sacrificed after 24 hours following paracetamol administration.

Results: Serum levels of creatinine and blood urea nitrogen (BUN) were increased in paracetamol group, those parameters improved in amlodipine groups. While superoxide dismutase (SOD) activity and glutathione (GSH) levels measured in kidney decreased in paracetamol group, amlodipine has significantly corrected these parameters. Meanwhile malondialdehyde (MDA) quantities increased in paracetamol group, it has been seen that in the amlodipine administered groups quantities of increased MDA have statistically significantly decreased

Conclusion: This study showed that amlodipine has protective effects against paracetamol toxicity in kidney. Amlodipine revealed its protective effects by suppressing the oxidative damage and improving antioxidant activity. Amlodipine can be drug of choice in hypertensive patients with analgesic nephropathies.

Keywords: Amlodipine, kidney, paracetamol, rat, toxicity.

1. INTRODUCTION

Paracetamol is the most commonly used analgesic and antipyretic drug worldwide for the past 50 years, with few unwanted side effects when taken at therapeutic doses. Paracetamol is widely available over-the-counter or prescription. Increased use and easy accessibility bring with it the risk of toxicity (1, 2). Paracetamol taken at a dose of 200 mg/kg at one time in children over 6 years of age or 10 grams in total within 24 hours, and 200 mg/kg and above in a child under 6 years of age. leads to acute poisoning. In cases of increased sensitivity to paracetamol toxicity such as alcoholism, long-term fasting and isoniazid use, the toxic dose of paracetamol is 4 g per day or 100 mg/kg (2). Paracetamol toxicity may be asymptomatic, but it was shown in the early 1960s to cause drug-induced hepatotoxicity or more severe and fatal acute hepatic injury (3).

Paracetamol is ordinarily metabolized in the liver with conjugation reactions to achieve water soluble sulfate or glucuronic acid complexes. 2-4% of therapeutic doses of paracetamol is metabolized by the cytochrome p450 enzyme (CYP) to a toxic metabolite called N-acetyl p-benzoquinone (NAPQI). NAPQI is a highly reactive electrophilic molecule and bio-inactivated by binding with glutathione in the liver and then excreted in the urine (4, 5). When taken in toxic doses that is about 10-fold of therapeutic dose, the amount of NAPQI occurred exceeds the binding capacity of glutathione and this excess amount of NAPQI result in liver and kidney damage (6).

Paracetamol is converted to p-aminophenol metabolite in renal cortex, which is a selective nephrotoxic compound and causes necrosis at renal cortex by de-acetylation. P-aminophenol formed in therapeutic doses is conjugated with glutathione and excreted as inactive glutathione conjugates. In chronic use or at high doses, when glucuronide and sulphate conjugation pathways are saturated, glutathione stores are depleted and toxic NAPQI and p-aminophenol metabolites accumulate. The binding of NAPQI to the hepatocyte membrane and sulfhydryl proteins causes liver

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damage. P-aminophenol binds to renal macromolecules by covalent bonds, causing kidney damage. Acetaminophen also has damaging effects on kidney medulla and papilla through prostaglandin (PG) synthase enzyme inhibition.

The calcium ion, which is generally responsible for the contraction relaxation responses in the body, is involved in all smooth and striated muscle functions. Calcium shows its cellular effects through calcium channels and many different calcium channels (L,T,P,Q etc.) have been defined according to its location. Amlodipine is one of the main antihypertensive agents that cause vascular dilatation by blocking L-type calcium channels (7). It is known that calcium blockers are preferred in diabetic patients to benefit from their kidney protective effects and because they increase cerebral blood flow in the elderly. Today, one of the most important effects of calcium channel blockers is its relaxing effect on vascular smooth muscle cells (8). This effect leads to increased renal circulation rate and glomerular filtration level. Unlike other vasodilators, calcium channel blockers do not cause water and salt retention. They also increase diuresis and natriuresis. It has been reported that these drugs prevent the drop-in glomerular filtration rate in hypertension and renal failure. Furthermore, promising results have been reported regarding its protective effects on acute tubular necrosis and acute renal failure due to renal ischemia or nephrotoxis (9). In previous studies, amlodipine's antihypertensive and renoprotective effects, as well as potent antioxidant and anti-inflammatory effects were reported (10-13). The fact that amlodipine has anti-inflammatory and antioxidant effects and is used for renoprotective purposes in the elderly is a condition with inflammation such as paracetamol-induced kidney damage. It suggests that it can also be useful in this situation.

In the light of above-mentioned literature, this study aimed to determine the effect of amlodipine, one of the L-type calcium channel blockers, in acute renal injury induced by paracetamol.

2. MATERIALS AND METHODS

2.1. Animals

A total of 30 Wistar Albino male rats, weighing 200-215 grams, obtained from the experimental animal laboratory within the Atatürk University Experimental Research and Application Center were used. During the experiment, the rats were given enough (ad libitum) water and pellet food. Animals were housed at normal room temperature (22 C ^{0}) in the laboratory and fed in groups before the experiment. All phases of our work have been approved by the Atatürk University Animal Experiments Local Ethics Committee (24.02.2012/2-26).

2.2. Experiment Plan

In the study, 5 animal groups each containing 6 rats, a total of 30 rats were used. All groups were fasted for 24 hours prior the experiment. Fasted animals were divided in the in the following groups:

Group I: Control group. 2 ml of 1X Phosphate-buffered saline (PBS) (containing 1% carboxymethyl cellulose-CMC) was administered orally by oral gavage.

Group II: Paracetamol solution prepared in 2 ml 1X Phosphate-buffered saline (PBS) (containing 1% carboxymethyl cellulose-CMC) at a dose of 2 g/kg was administered orally by gavage.

Group III: 1 hour after oral administration of 10 mg/kg amlodipine, 2 ml 1X Phosphate-buffered saline (PBS) (containing 1% carboxymethyl cellulose-CMC) was administered orally by oral gavage.

Group IV: 5 mg/kg amlodipine (2 ml of 0.9% NaCl prepared in solution) after 1 hour after oral administration of 2 g/kg dose of 2 ml paracetamol solution gavage was administered orally with.

Group V: 1 hour after oral administration of 10 mg/kg amlodipine, 2 ml paracetamol solution at a dose of 2 g/kg was administered orally by gavage.

All paracetamol doses administered in the study were adjusted according to the relevant literature (14). 4 hours after paracetamol administration, the rats in the whole group were given enough water (ad libitum) and feed until the end of the experiment.

The experiment was terminated by euthanasia with high dose thiopental (50 mg/kg) 24 hours after the administration of paracetamol to all groups. The kidneys and blood samples of the animals in all groups were taken. Part of the kidney removed was separated for biochemical analysis and placed in phosphate buffer and stored in a – 80 ˚C freezer. The remaining kidney histological studies % for 4s neutral was determined by placing the formaldehyde solution. The collected bloods were centrifuged and their serums were obtained and the serums were stored in a freezer – 80 °C.

2.3. Biochemical Studies

2.3.1. Analyzes Performed on Kidney Tissue

After the kidney tissues collected were stored at deep freezer and at the day of experiment they were homogenized with help of liquid nitrogen. 1 ml Phosphate-buffered saline (PBS) was added on 50 mg of kidney tissue and the mixture was homogenized in liquid nitrogen with Tissue Lyser II (Qiagen). Grounded tissue samples were centrifuged and supernatants were used for following analyses. Superoxide dismutase (SOD) activity (15) (Cayman Chemical Superoxide Dismutase Assay Kit Item Number 706002) glutathione (GSH) (16) (Cell Biolabs OxiSelect Total Glutathione (GSH) Assay Kit STA-312) and malondialdehyde (MDA) (17) (Cell Biolabs OxiSelect TBARS Assay Kit (MDA Quantitation) STA-330) levels were measured twice according to the modified methods with multi well plate reader in the light of the kit protocols (18, 19). Data were presented as the mean ± standard deviation

results per milligrams of protein. Total protein levels were analyzed by the Lowry Method (Sigma Aldrich, TP0300).

2.3.2. Analyses performed on Serum

The blood samples were taken into the tube without anticoagulant and centrifuged at 4000 g for 10 minutes. After the separated serum samples were transferred to Eppendorf tubes, they were placed in the device to be analyzed in the "Cobas C-501" auto analyzer. Renal function analyses were performed via commercial kits (BEN Biochemical Enterprise). Creatinine (Ref: Cr280) and BUN (Ref: BK151) levels were evaluated with multi well plate reader (20).

2.4. Statistical analysis

Results from the experiments were given as mean ± standard deviation, and P values below 0.05 were considered statistically significant. One – way variance analysis (ANOVA) following post-hoc "Duncan" test was used to determine significant differences between the groups.

3. RESULTS

3.1. Serum BUN and creatinine findings

As seen in Figures 1 and 2, the mean levels of BUN and creatinine levels in the serum of healthy rats were 14.4 ± 3.05 U/L and 0.25 ± 0.09 U/L, respectively, while in the control group given 2g/kg paracetamol, these levels were 27.25 ± 7.07 U/L and 0.65 ± 0.15 U/L, respectively. It was determined as L. In the control group given only 10 mg/kg amlodipine, BUN and creatinine levels were determined as 14.22 ± 2.49 U/L and 0.21 ± 0.13 U/L, respectively. The mean BUN and creatinine levels in rats given paracetamol + amlodipine 5 mg/kg were measured as 20.69 ± 4.26 U/L and 0.52 ± 0.06 U/L, respectively. BUN and creatinine levels in rats given paracetamol + amlodipine 10 mg/kg were measured as 18.25 ± 7.21 U/L and 0.4 ± 0.12 U/L, respectively.

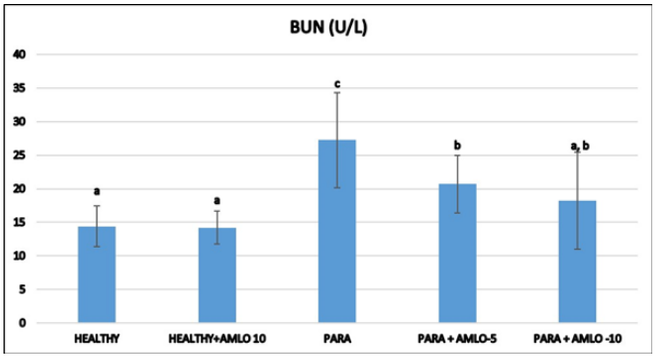

Figure 1. *Comparison of serum BUN levels according to groups Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

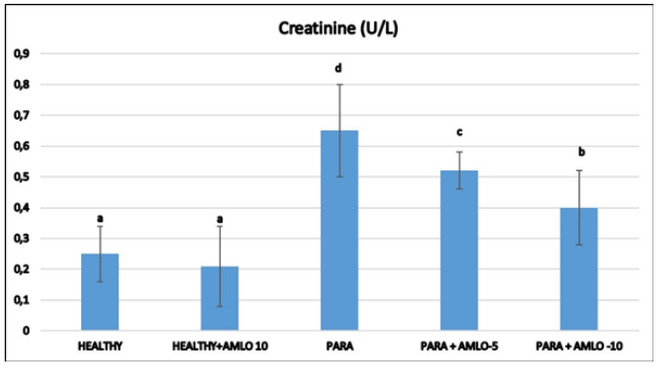

Figure 2. *Comparison of serum creatinine levels by groups Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

It was observed that the BUN value was significantly higher in the paracetamol group then the health rat group. It was observed that the BUN value in the PARA + AMLO5 group was lower than the paracetamol group and had approximately the same BUN values with the PARA + AMLO10 mg/kg and AMLO10 mg/kg groups.

When the creatinine levels were examined, it was observed that this value was significantly higher in the paracetamol group and there was a statistically significant difference compared to the other groups. Although there was no statistically significant difference between the PARA+AMLO 5 mg/kg, PARA+AMLO 10mg/kg and AMLO 10mg/kg groups, the best improvement in creatinine values were determined in the AMLO 10 mg/kg group.

3.2. Kidney SOD, GSH and MDA findings

As seen in Figures 3, 4 and 5, the mean levels of SOD, GSH and MDA in kidney tissue of intact rats were 30.33 ± 2.48 U/mg protein, 3.21 ± 0.57 nmol/mg protein and 1.42 ± 0.39 nmol/mg protein, respectively, while 2 g/kg paracetamol was given to the control group. These levels were determined as 14.52 ± 3. 94 U/mg protein, 1.21 ± 0.30 nmol/mg protein and 3.4 ± 0.86 nmol/mg protein, respectively. In the AMLO 10 group, these values were measured as 31.96 ± 4.40 U/mg protein, 3.26 ± 0.58 nmol/mg protein and 1.47 ± 0.32 nmol /mg protein, respectively. SOD, GSH and MDA levels in the PARA + AMLO 5 mg / kg group were 21.12 ± 4.72 U/mg protein, 2.26 ± 0.54 nmol/mg protein and 2.54 ± 0.43 nmol/mg protein, respectively, in the PARA + AMLO 10 mg/kg group. respectively 25.63 ± 5:56 U / mg protein, 26 ± 0.73 nmol / mg protein and 2.17 ± 0:33 nmol / mg protein was detected.

It was observed that there was a statistically significant difference in the SOD value in the paracetamol group and the other groups, and this value was significantly reduced. No significant difference was found between the PARA + AMLO 5 mg/kg and the PARA + AMLO 10 mg/kg groups.

GSH values measured in the paracetamol group were statistically significantly lower than the other groups. There was no significant difference in increasing GSH levels between

two different doses of amlodipine. The increase in GSH level observed in all treatment groups was parallel. Significantly, it was observed that AMLO application was quite effective in increasing GSH levels.

MDA level increased significantly in the paracetamol group. MDA levels significantly improved in the PARA + AMLO 5 and PARA + AMLO 10 treatment groups. The greatest improvement in terms of MDA level belonged to AMLO 10 mg/kg group.

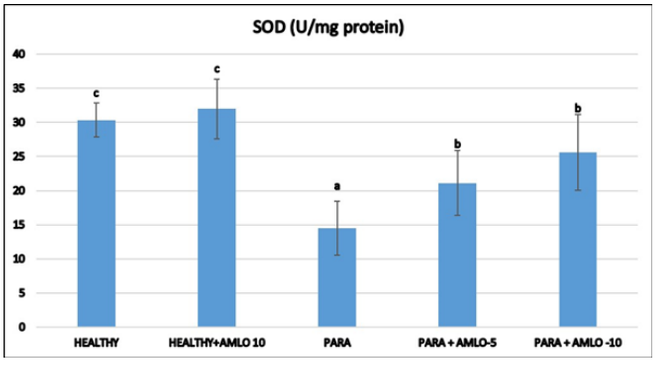

Figure 3. *Comparison of SOD levels in kidney tissue according to the groups. Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

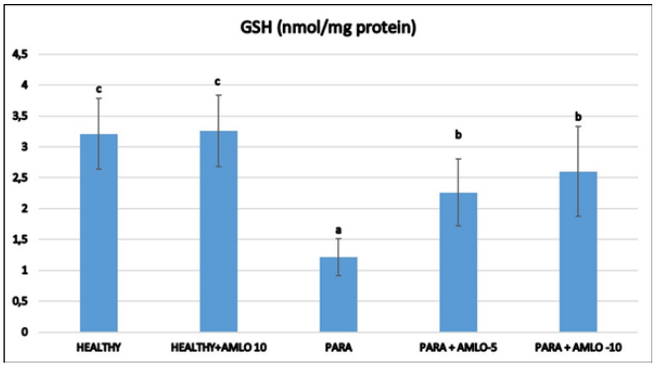

Figure 4.Comparison *of GSH levels in kidney tissue according to the groups. Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

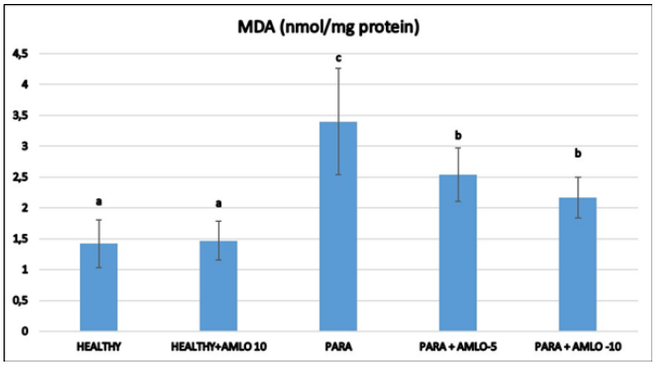

Figure 5. *Comparison of MDA levels in kidney tissue according to groups. Different letters in the columns indicate that the difference is significant (P <0.05) according to the Duncan test. *** AMLO: Amlodipine, PARA: Paracetamol*

4. DISCUSSION

In this study, the effects of dihydropyridine derivative amlodipine, one of the L-type calcium channel blockers, on paracetamol toxicity induced experimentally in rat kidneys were demonstrated. For this purpose, BUN and CREATIN values, which are routine parameters of toxicity, and SOD, GSH and MDA values, which are oxidative stress and antioxidant system parameters, were examined.

Paracetamol is an analgesic and antipyretic drug and it is commonly used; even as an over the counter product. 90-95% of paracetamol, which administered at therapeutic concentrations, is conjugated to glucuronic acid, sulfuric acid, cysteine in the liver. Small amounts of hydroxylated and deacetylated metabolites of paracetamol it is excreted directly in the urine (21). A small part of paracetamol is transformed into n-acetyl-p-benzoquinone (NAPQI) by cytochrome-p mediated N-hydroxylation. NAPQI is a reactive intermediate, eliminated from the kidney by hepatic glutathione and detoxifying to the non-toxic acetaminophen-mercapturate compound. Paracetamol overdose causes severe hepatotoxicity as it is primarily metabolized in the liver. The kidneys, on the other hand, are affected in the advanced stages of liver damage or rarely alone, without liver damage (22).

Acute tubular necrosis can occur due to paracetamol overdose, and it has been found that approximately 1-2% of patients exposed to paracetamol overdose may develop renal failure (23). The mechanism of toxicity caused by paracetamol in the kidney has not been fully elucidated. In case of overdose, the cytochrome P-450 enzyme system is activated as a result of the saturation of glutathione and sulfation reactions. CYP2E1 isoenzyme is involved in biotransformation in the kidney. With the action of prostaglandin synthetase and N-deacetylase enzymes and cytochrome P-450 enzyme systems, toxic metabolites such as NAPQI and p-aminophenol are formed (2, 4). All of these metabolites cannot be detoxified and form conjugates with sulfhydryl and glutathione in cellular proteins. Glutathione depletion by these conjugates themselves or caused is thought to cause oxidative stress (24). It is thought that this situation leads to the activation of lysosomal enzymes and/or caspases, resulting in apoptosis or programmed cell death. As a result, hemostasis is disrupted, causing tissue damage, leading to impaired renal functions.

Measurement of BUN and creatinine levels in blood samples taken from patients has become routine in clinical evaluation of renal functions. In experimental studies, while evaluating kidney functions, BUN and creatinine levels were measured from animal sera, and the nephrotoxicity model created was evaluated and the effects of the drugs administered on kidney functions were examined (25, 26).

Naguib et al.(27) examined the fungus type Pleurotus ostreatus in hepatorenal damage caused by paracetamol. They observed that serum BUN and creatinine levels increased in the paracetamol group compared to the control group. In yet

another study, Das et al.(28) studied the effect of taurine on paracetamol-induced nephrotoxicity in mice. In evaluating the effects of oxidative damage on kidney functions, they based on BUN and creatinine levels and observed that these values increased. In our study, we used serum BUN and creatinine values to evaluate renal functions. We observed a statistically significant increase in serum BUN and creatinine levels 24 hours after the paracetamol group when compared with the healthy group. Based on this, we can say that our toxicity model occurs when we compare it with the healthy group. We see that amlodipine application, which we use as a treatment, improves kidney functions over these two values.

In a study conducted by Li et al.(29) the effects of amlodipine and nifedipine on gentanicin-induced kidney damage in rats were examined and both drugs were shown to reduce gentamicin-induced damage. Thus, the increased protein and N-acetyl-beta-D-glucosaminidase levels in the urine of rats and the increased amount of creatinine and BUN in the serum were decreased by these drugs. In the study, the authors examined both oxidative stress parameters and apoptosis pathways.(30) The beneficial effects of amlodipine in a kidney stone model made by Albayrak et al. Supports its protective effects in renal failure and damage (31). However amlodipine rat mesangial cells Smad6 and Smad7 upregulation with Adriamycin the toxicity overlapping studies and our findings inhibition of amlodipine supports the protective effect on kidney tissue (29).

NAPQI caused by the effect of CYP-450 enzyme systems is held responsible for paracetamol-induced kidney damage. During the detoxification of this electrophilic intermediate, different conjugates are formed with sulfhydryl and glutathione moieties in cellular proteins (4). It has been reported that these conjugates increase oxidative damage and this may be one of the toxicity mechanisms (24). In parallel with the increase in oxidative stress, the consumption of antioxidant defense systems is also important in paracetamol-induced kidney damage. The main reason for our study of amlodipine is its previously reported powerful antioxidant properties. Therefore, in our study, SOD and GSH were investigated as antioxidant parameters, and MDA, the biomarker of lipid peroxidation, as an oxidative parameter.

While SOD protects cells from the harmful effects of superoxide ion, GSH protects cells from oxidative damage by reacting with free radicals and peroxides. Abdul Hamid et al.(32) investigated the role of Zingiber zerumbet extract in paracetamol-induced nephrotoxicity and evaluated the resulting oxidative damage with the decrease in SOD and GSH levels. In our study, when we compared the SOD activity and GSH levels we used to evaluate oxidative damage, we observed a statistically significant decrease in the Paracetamol group compared to the healthy group. We see that our treatment group, the PARA + Amlodipine 5 and 10 mg/kg groups, showed a statistically significant increase compared to the paracetamol group. Considering our antioxidant parameters, we can say that amlodipine administration significantly reduces oxidative damage especially at a dose of 10 mg/kg.

Amlodipine and other dihydropyridine derivative calcium channel blockers are known for their powerful antioxidant effects (33). It has been shown in previous studies that amlodipine increases the amount of reduced glutathione in kidney tissue and increases the activity of superoxide dismutase enzymes (30). In another study, the protective effects of amlodipine, nifedipine, and nitrendipine on doxsurobicin – induced kidney damage were examined and only amlodipine was found to be effective. Amlodipine given at a dose of 5 mg/kg in the study improved the BUN and creatinine levels and also increased the GSH, SOD and GST values significantly (34). When these studies and our findings are evaluated together, it is clearly seen that amlodipine increases antioxidant parameters such as SOD and GSH in preventing kidney damage.

Superoxide radical and hydroxyl radical initiate lipid peroxidation in membranes of different cell organelles such as endoplasmic reticulum, nucleus, mitochondria and cytoplasm. MDA occurs in the peroxidation of fatty acids. MDA is found in blood and urine and correlates well with the degree of lipid peroxidation (35). Therefore, it is used in experimental studies. Aycan et al.(36) evaluated the effect of timoquinone on nephrotoxicity caused by paracetamol. They observed that lipid peroxidation decreased in the treatment group as a result of the measured MDA values. Also, previous studies demonstrated antioxidant effects of carvacrol and thymolare important against paracetamols harmful effects (37). As a result of our study, we observed that the MDA values in the paracetamol group increased significantly when compared to the healthy group. In the PARA + AMLODIPIN 5 and 10 mg/kg groups, the MDA level was close to the values of the healthy group. Considering the MDA levels in the PARA + AMLO 10 mg/kg group, we can say that it reduces lipid peroxidation and regresses it to an almost healthy level.

Li et al.(29) investigating the effects of amlodipine in a gentamicin-induced kidney injury model in rats, also demonstrated the contribution of amlodipine to decrease the amount of MDA in kidney tissue in preventing renal tubular damage. Again, the fact that amlodipine administration decreased kidney MDA levels in doxsurobicin-induced kidney toxicity supports the antioxidant effect of amlodipine and the protective effect of this effect on the kidneys (29).

5. CONCLUSION

In conclusion, in this study, we can say that amlodipine reduces paracetamol-induced kidney damage and this reduction is mediated by reducing oxidative stress and supporting antioxidant systems.

This finding suggests the use of amlodipine as an additional alternative to existing therapies, especially in the emergency treatment of paracetamol-induced renal toxicity. Also we can recommend amlodipine as a drug of choice in hypertensive

patients with analgesic nephropathies. However, more detailed experimental and clinical studies are needed to determine the current mechanism of action.

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Clinical and Experimental Health Sciences

Validity and Reliability of Turkish Version of the Scale on Community Care Perceptions (Scope) for Nursing Students

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ABSTRACT

Objective: The purpose of study was to conduct a study on validity and reliability of Turkish version of the "Community Care Perceptions for Nursing Students".

Methods: This methodological study was conducted in two of the universities located in Istanbul with 386 students between the dates May and December in 2019. During the designation of the Turkish version of the scale back-translation method was utilized for the language adaptation. Validity was assessed as content and construct validity and the reliability was assessed as internal consistency, test-retest analysis. Content validity was evaluated with expert views, construct validity with confirmatory factor analysis, internal consistency with Cronbach's Alpha coefficient, test-retest results with Pearson's Correlation analysis.

Results: Cronbach's Alpha coefficient was found as .94 and sub-dimensions ranged between .65-.88. Item total correlation was found over .20 excluding 26th, 28th items, test-retest correlation was calculated as .72. Content validity index was determined as .99. Confirmatory factor analysis was approved the structure of scale consisting of 33 items and 3 factors.

Conclusions: Nursing Students' Community Care Perceptions Scale was found to be valid and reliable. It may be used to assess community care perceptions of nursing students taking the course of community care nursing in Turkey.

Keywords: Community, perception, scale, nursing.

1. INTRODUCTION

Public health nursing is defined by American Nurses Association (ANA) as "the practice of promoting and protecting the health of populations using knowledge from nursing, social, and public health sciences" (1). Public health practices are general and comprehensive not limited to a certain disease or age groups. It is a consistent and dynamic process. Public health nursing is responsible for protection and development of health, health education, management, collaboration as well as the management and maintaining the education provided to groups families and individuals in community in the light of holistic approach (2, 3).

At present time, health care services changing to provide caring services at an institutional setting into providing caring services at home setting of the patients (4). Even though caring perception transforms into a societal form, it is not the same for nursing students, because nurses prefer working in hospitals to societal caring settings (5, 6). Hospitals present an attractive working environment for nurses with their equipment resources and technological infrastructure. Thus, the interest of nurses to societal care remain rather low compared with hospital care settings (7).

Students consider community health care as a placement requiring limited clinical skills and the patients never become healthy again (7). Community health care perceptions of students do not reflect the roles, responsibilities of public health nurses and realities of this field appropriately (6). Additionally, practice placements in community care are regarded as challenging because such placements are required to be innovative and creative in problem-solving and establishing relations (8). Thus, this placement is needed certain strategies aiming to increase awareness and realization (6). Internship during training provides students experience in variety of health fields to help them focus a future career. Even though students experience various

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internship opportunities, career process is rather complex and effected by great number of variables (9). Obtaining information about how community care perceptions of students develop during education as well as the factors effecting this development will be useful to understand the assumptions laying beneath the community care placement's being less popular. Educators might re-design the curriculum accordingly effecting the willingness of students to work in community care services positively and hindering the unrealistic expectations and misunderstandings (10).

It is absolutely crucial that educational institutions should describe students' perceptions on different health fields at early stages of their education in order to help students to make logical choices. Various studies exist in literature focusing on career preferences of nursing students on different fields of health care services (11, 12, 13). The studies conducted on this issue include some scales majority of which related to working with old and mentally disordered patients whereas not any scales exist assessing the perceptions of nursing students on community-based caring. As the importance of community-based care increased, a scale is needed to assess the perception of students and consider community care as a career option. Scale on Community Care Perceptions (SCOPE) for nurse students was developed by Van Iersel et al. in 2018 (14).

The aim of this study was to determine validity and reliability of the Turkish form Scale on Community Care Perceptions for nursing students.

2. METHOD

This methodological study was conducted with students of two of the universities located in Istanbul between the dates 2018-2019 spring and 2019-2020 fall semesters. The study population included nursing students taking the course of Public Health Nursing. Students in both of the universities realize internship on community health practices for eight hours a week, 14 weeks and 112 hours total in a year. It is recommended for scale adaptation studies that each item of the scale should involve 10-20 participants and confirmatory factor analysis should include at least 300-500 participants (15). Data were collected from 386 participants.

For pilot test, data collection tools were implemented to 20 students in total. As the result of pilot test recommendations, an expression "In my opinion, working in the field of community health nursing is a ..... profession" was added for a better understanding of the scale.

2.1. Measurement

The data were collected based on self-report in class environment following the Public Health Nursing course's practice section. Two weeks later retest was administered with 50 participants. Personal Information Form and Scale on Community Care Perception for Nursing Students were utilized for data collection.

2.2. Personal Information Form

This form prepared compatible with the relevant literature consisted of six personal questions including "age, gender, education of parents, having a relative working in community care center, having a condition requiring a community health care service for themselves or family members"

2.3. The Scale on Community Care Perception (SCOPE) for Nursing Students

The scale was developed by Margriet van Iersel et al. in 2018 having three sub-dimension and 33 items in total and additional last two items examining the reasons of a health field selection. The first 11 items were intended to identify community care, the next five items (12^{th}-16^{th}) community care for practice placements and the last 17 ones (17^{th}-33^{rd}) community care as a future profession. Community care perception sub-dimension was divide into two sub-groups as: *Enjoyment* (1^{st}-6^{th}, 10^{th}-11^{th} items) and *Utility* (7^{th}-9^{th} items). Community care perception subscale measures the affective component of community care as a whole. "Enjoyment" refers to how working in the field of public health is a work for students. "Utility" can be seen as altruism, the meaning students give to caring for the needs of person. Community care for practice placement sub-dimension had two sub-groups as: *learning possibilities* (13^{th},15^{th} and 16^{th} items) and *personal satisfaction* (12^{th} and 14^{th} items). "Learning possibilities" reflects the importance students give to learning activities. "Personal satisfaction' is represented by freedom of action and the ability to perform in the role of nurse." Community care as a future profession sub-dimension covered four sub-groups as: *caregiving* (17^{th}, 22^{nd}, 25^{th}, 28^{th} and 32^{nd} items), *complexity and workload* (18^{th}, 21^{st}, 26^{th} and 27^{th} items), *collaboration* (19^{th}, 20^{th}, 24^{th} and 31^{st} items), *Professional development* (23^{rd}, 29^{th}, 30^{th} and 33rd items). Placement and future profession subscales measure cognitive attitudes of a placement as student, and of a profession as graduate in community care. "Caregiving" can be perceived as independent roles. "Collaboration" reflects the importance students place on the diversity of people they work with in the context of practice. "Complexity and workload" refers to the perceived stressful work situations encountered or to be encountered in community nursing. "Professional development" refers to the importance students place on high nursing status, diversity in care, and nursing skills. The items were scored between 1 (negative expressions) and 10 (positive expressions). The expressions in Community care sub-dimension were placed randomly. Some negative expressions were placed in the left side of the questionnaire whereas some of them in the right. Positive expressions in 2^{nd}, 5^{th}, 7^{th}, 8^{th} and 10^{th} items of the scale were placed in the left side (positive expression was coded as 1). Thus, scores of the items were reversed during the analysis. Sub-dimensions of the scale can be used separately.The lowest score that can be taken from the scale is 33 and the highest score is 330. This scale has no cut off point. A high scale score indicates that students have high perceptions of

community care. The SCOPE items are available in Turkish form (see supplementary material 1).

Language Equivalence-Cultural Adaptation and Content Validity

In the language adaptation process of Community care Perception Scale for Nursing Students, two linguists with full command on both language (Turkish-English) translated the scale from English (the original language of the scale) into Turkish. Turkish version of the scale was examined by the researchers and put into the final form. The views of 10 Public Health Nursing professionals were received in order to ensure content validity. Both qualitative and quantitative opinions were received from experts for content validity. As quantitative opinions, the content validity of the scale was evaluated with the Content Validity Index (CVI) both on an item basis and in terms of the overall scale. The CVI for each item was found by dividing the number of specialists who rated the scale as 3 or 4 by the total number of specialists. CVI on the scale level was found by finding the arithmetic mean of the item CVI scores. The professionals were asked for scoring the appropriacy and comprehensibility of each item in the scale [*1 point: Not appropriate-4 points: Very appropriate].* Qualitative opinions were received from experts to evaluate the cultural adaptation of the scale. Necessary arrangements were realized in the light of views of professionals. Following the ensuring of content validity, the scale was translated into back to English by two other linguists. Back translated forms of the scale were united by the third linguist.

2.4. Statistical Analysis

The data were assessed using a statistical programs (SPSS 20 and LISREL 8.8). Content and construct validity analysis for the validity and internal consistency and test-retest analysis for reliability of the scale were held by the researchers. Average, percentage and standard deviation parameters were utilized in the analysis of descriptive findings. In the validity and reliability of the scale, Content Validity Index for content validity; Confirmatory Factor Analysis for construct validity; Cronbach's Alpha Coefficient for internal consistency; Pearson's Correlation Analysis for item analysis and test-retest were benefited ($p < 0.01$).

2.5. Ethical Considerations

The permission from the owner of the scale was obtained for the use of Community Care Perception Scale for Nursing Students via e-mail. Prior to implementation of the study Ethical Committee approval (18.02.2019-42) and permission from universities were obtained. Students were requested to sign the written informed consent forms and students' and universities' names were not mentioned in the study.

3. RESULTS

The mean ages of participants were 22.37±1.88 and 81.1% of them were females. 76.9% of them studied in public university. 40.5% of their mothers and 31.1% of their fathers were primary school graduate. 56.5% of them reported that they worked in a public health center and 26.9% of them stated a relative worked there. 19.4% of them were identified as having a condition requiring community care for themselves or a family member (Table 1).

Table 1. *Demographic characteristics of students (N=386)*

Characteristics		Min. – Max.	Mean±Sd
Age		20-39	22.37±1.88
		n	%
Gender	Female	313	81.1
	Male	73	18.9
Mother's education	Illitarete	46	11.9
	Literate	23	6.0
	Primary school	156	40.5
	Middle school	55	14.3
	High school	65	16.9
	University and +	40	10.4
Father's education	Illitarete	10	2.6
	Literate	15	3.9
	Primary school	120	31.1
	Middle school	87	22.5
	High school	99	25.6
	University and +	55	14.2
Having family relative working in the community care center	Yes	104	26.9
	No	282	73.1
Having a condition requiring a community health care service for themselves or family members	Yes	75	19.4
	No	311	80.6

3.1. Results on Validity

Content Validity

Some minor corrections were made in 1st, 19th and 21st items in accordance with professionals' views. According to scores stated by 10 professionals the mean item Content Validity Index score was found .90-1.00 and it was .99 for the scale in total.

Construct Validity

The construct of the scale was confirmed by Confirmatory Factor Analysis. When the general fit indices related with original version were examined, Comparative Fit Index (CFI), Non-Normed Fit Index (NNFI) were identified as perfect, Standardized Root Mean Square Residual (SRMR), Root Mean Square Error of Approximation (RMSEA) as good and Goodness of Fit Index (GFI), Adjusted Goodness of Fit Index (AGFI), Root Mean Square Residual (RMR) as weak. χ2/Degree of Freedom (χ2/df) was determined as moderate fit (Table 2).

3.2. Results on Reliability

Cronbach's Alpha coefficient was indicated as .91 for community care sub-dimension; .80 for community care for practice placement sub-dimension; .87 for community care as a future profession sub-dimension and it was .94 for the SCOPE of the scale. Test-retest correlation of the scale ranged between .49-.72 (p<.001). The mean scores of the sub-dimensions were assessed as 7.71±1.61 for community care sub-dimension; 7.33±1.80 for community care for practice placement sub-dimension and 6.50±1.39 for community care as a future profession sub-dimension (Table 3).

Table 2. *Confirmatory factor analysis fit indices*

Fit indices	Reference *	Result
χ2/degrees of freedom	5 ↓=Medium fit 3 ↓=Excellent fit	1674.75/467=3.5
P value	p<0.05=Non-fit p>0.05=Excellent fit	
Goodness of Fit Index (GFI)	0.90 ↑=Good fit 0.95 ↑=Excellent fit	.79
Adjusted Goodness of Fit Index (AGFI)	0.90 ↑=Good fit 0.95 ↑=Excellent fit	.75
Comparative Fit Index (CFI)	0.90 ↑=Good fit 0.95 ↑=Excellent fit	.96
Non-Normed Fit Index (NNFI)	0.90 ↑=Good fit 0.95 ↑=Excellent fit	.95
Root Mean Square Residual (RMR)	0.10 ↓=Weak fit 0.08 ↓=Good fit 0.05 ↓=Excellent fit	.36
Standardized Root Mean Square Residual (SRMR)	0.10 ↓=Weak fit 0.08 ↓=Good fit 0.05 ↓=Excellent fit	.067
Root Mean Square Error of Approximation (RMSEA)	0.10 ↓=Weak fit 0.08 ↓=Good fit 0.05 ↓=Excellent fit	.082
Reference: (Cokluk, Sekercioglu, Buyukozturk, 2012)		

Table 3. *Reliability analysis of the scale on community care perceptions*

	Subscale	Item	Mean ±Sd		Item-total r	Item-subscale r	Test-retest r	Cronbach alpha
Community Care	Enjoyment	1	6.38±2.16	7.12±1.59	.62	.62	.68*	.87
		2	6.60±2.35		.49	.60		
		3	7.16±2.27		.69	.80		
		4	7.09±2.32		.67	.76		
		5	7.41±2.33		.27	.32		
		6	7.20±2.28		.61	.61		
		10	7.36±2.14		.55	.61		
		11	7.78±1.87		.65	.71		
	Utility	7	8.29±2.12	8.28±1.91	.58	.78	.49*	.88
		8	8.13±2.16		.62	.78		
		9	8.44±2.10		.65	.75		
	Subscale total	-	-	7.71±1.61	-	-	.58*	.91
Placement	Personel satisfaction	12	7.74±2.38	7.51±2.16	.57	.54	.63*	.70
		14	7.28±2.55		.65	.54		
	Learning possibilities	13	7.52±2.37	7.17±1.88	.55	.50	.66*	.73
		15	6.74±2.42		.55	.62		
		16	7.20±2.26		.63	.54		
	Subscale total	-	-	7.33±1.80	-	-	.72*	.80
Profession	Caregiving	17	7.57±2.35	6.96±1.52	.65	.50	.54*	.70
		22	6.98±2.41		.59	.53		
		25	7.13±2.30		.63	.50		
		28	6.07±2.02		.19	.20		
		32	6.91±2.31		.55	.54		
	Complexity and Workload	18	4.71±2.62	5.56±1.77	.21	.44	.53*	.67
		21	7.16±2.51		.67	.37		
		26	5.22±2.34		.14	.45		
		27	5.13±2.50		.41	.56		
	Collaboration	19	7.22±2.43	6.76±1.73	.55	.55	.54*	.65
		20	6.13±2.69		.42	.34		
		24	7.06±2.35		.57	.50		
		31	6.61±2.46		.46	.34		
	Professional development	23	6.78±2.69	6.59±1.89	.62	.52	.65*	.75
		29	6.60±2.21		.56	.57		
		30	6.95±2.37		.56	.50		
		33	6.04±2.71		.57	.62		
	Subscale total	-	-	6.50±1.39	-	-	.62*	.87
	Total			7.21±1.36			.72*	.94

Test retest Pearson's correlation. * $p < 0.01$

4. DISCUSSION

In order to administer a scale in a different language and culture, an adaptation process is needed to realize. As the language and cultural differences between the country where the scale was developed originally and the target country get bigger, assessment process gains more importance. Following the translation of the scale from source language into target language by taking language and cultural issues into consideration, it should be tested to prove its reliability and validity within the community. At present study, the validity of the Community Care Perceptions Scale was tested through content and construct validity and reliability was evaluated with total item correlation and internal consistency.

Validity is defined as the degree to which a tool measures what it claims to measure. (16, 17). The validity of the present study was assessed with content validity and confirmatory factor analysis.

Content validity is shaped by the views of 5-10 professionals on related field. The scale should be re-designed in accordance with those professionals' views (16). Literature suggests on the issue that 80% of the scores by the professionals

should be over 3 and the content validity index score should be at least .83 (18, 19). In our study, minor changes were made in the light of views of professionals in three of the items. Our study indicated that a consensus existed among professionals in terms of content validity, items of the scale were compatible with the culture and the scale represented the structure what it claimed to measure.

Confirmatory factor analysis is a type of validity analysis used while developing a scale or adapting a certain scale into another culture. Confirmatory factor analysis is assessed via fit indices and variety of fit indices exist in Literature (20). Among the most common fit indices are χ2/df, GFI, AGFI, CFI, RMSEA, RMR and SRMR. Not any consensus exists in Literature on which of the indices are to be used (21). At present study, GFI, AGFI, RMR were identified as weak fit. GFI and AGFI were developed as an alternative to χ2 for the assessment of model-data fit independently from sample size (20). Although AGFI is indicated that it is not affected by the size of sample, some studies claimed the opposite (21). Thus, GFI and AGFI's having weak fit in our study does not necessarily suggest non-confirmation in our study as χ2/ Degree of Freedom presented moderate fit. Instead, other fit indices were identified as CFI, NNFI perfect; SRMR, RMSEA good fit and χ2/Degree of Freedom moderate fit. Overall, the original construction of the scale was confirmed by Confirmatory Factor Analysis.

The concept of Reliability is defined as the degree to which a measurement instrument gives the same results each time that it is used, assuming that the underlying thing being measured does not change (17). The reliability is assessed through internal consistency, item total correlation and test-retest methods in our study.

Internal consistency is an assessment of how reliably survey or test items that are designed to measure the same construct actually do so. Alpha coefficient is one of the most common methods to test internal consistency reliability (22). The alpha value is recommended to be >.70 however >.60 is considered to be acceptable (23). At present study, the Cronbach's Alpha value was found .94 and it ranged between .65-.88 sub-dimensions that shows a good level of reliability as in the original scale. Cronbach's Alpha coefficient was indicated as .86 for community care sub-dimension; .70 for community care for practice placement sub-dimension; .81 for community care as a future profession sub-dimension and it was .89 for the SCOPE of the original scale (14).

Item-total correlation is used to observe strong and weak relations between items and to determine inter-item consistency (22). The items having a value below .20 are recommended to be removed from the scale (24). At present study, total item correlation values for all items except for 26th and 28th were identified over .20. The subscale correlation coefficients of those two items were found ≥.20 and they were not removed in order not to change the original structure of the scale.

Test-retest reliability is the degree to which test scores remain unchanged when measuring a stable individual characteristic on different occasions. Literature suggests at least two at most four weeks interval between the tests (25) and test-retest correlation coefficient is recommended to be ≥.40 in literature. In our study, test-retest correlation was found as good in terms of remaining unchanged in time.

Study Limitations

The results of the study are restricted to students studying in a district of Istanbul province.

5. CONCLUSION

To conclude; Turkish version of Community Care Perception Scale developed by Margriet Van Iersel et al was deduced as reliable and valid. It might be used to assess the community care perceptions of nurses having received the practice section of Public Health Nursing course.

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Clinical and Experimental Health Sciences

Difficulties Experienced by a Group of Nursing Students during Pandemic Process and Their Coping Strategies: A Qualitative Research

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ABSTRACT

Objective: This phenomenologic study aims to investigate the difficulties experienced by a group of nursing students during the pandemia process thoroughly and to explain coping strategies.

Methods: This research was carried out using the phenomenological method, which is one of the qualitative research methods, to examine the views of nursing students on their pandemic experiences and their coping strategies "Information Form" and "Questionnaire Form" were sent to the students online, and forms that were filled out completely and sent back were included in the content analysis.

Results: Participants mean age was 21.19±1.06. Of the participants, 77.00% were female, 34.4% stated that they live in a metropolis during the pandemia process, while 83.6% mentioned that they were with their family, 31.1% did not leave their homes unless it is necessary. As a result of data analysis, the main themes of difficulties/stressors, stress/anxiety increasing factors, and coping strategies were reached.

Conclusion: Student nurses experience more than one difficulty regarding the pandemia process; some students state that the pandemia process has changed their perception of their profession, and they mostly use positive methods to cope with these difficulties.

Keywords: Pandemic, difficulties, coping, nursing students.

1. INTRODUCTION

The Novel Coronavirus Disease, which was officially announced as the COVID-19 by WHO, has become a pandemic affecting all countries of the world (1). During pandemics, it is possible to experience the following responds: anxieties of individuals about their own health and the health of their relatives, fear of transmission, changes in sleeping pattern or diet, difficulty in attention and concentration, ingravescence of chronic diseases (if any), and increased alcohol or substance use. In a study carried out in China with healthy individuals in the 18-30 age group, 52.1% of participants stated that they felt terrified and anxious due to the COVID-19 outbreak (2). Wang et al. (2020) reported that being a female, being a student, having symptoms similar to COVID-19, negative health perception, high anxiety and depressed mood are risk factors for mental health (3).

Covid-19 pandemic is accompanied by mental symptoms and emotional problems that appear as fear, anxiety, panic, insecurity, and overstress. In the pandemic, "vulnerability" has replaced the perception of "robustness" in the collective consciousness of societies. A large part of the society, particularly the elderly, those with chronic diseases and healthcare professionals, have had to face stressors that emphasize the weakness in the face of the pandemic, such as quarantine, social distancing, avoiding the virus, and strict hygiene procedures (4).

It is stated that being a healthcare worker during outbreaks creates high levels of biopsychosocial stress, even if not traumatic (4,5). The tools that healthcare workers expressed to be effective in coping with the difficulties that accompany the pandemic process are: using individual positive coping strategies, positive reframing, social support getting from colleagues and family, and positive feedback and support from authorities (6). Identifying the coping strategies of healthcare workers and candidates receiving health education, and making attempts that can improve them could be important in preparing for possible future calamities. Li and Peng (2020) determined that cognitive coping, emotional coping, and social support can significantly reduce anxiety in university students in coping with the anxiety associated with the Covid-19 pandemic; they also stated that social support is

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the most effective coping strategy, and behavioral coping significantly predicts anxiety (7).

Coping strategies can be regarded as certain cognitive or behavioral respond towards stressors beyond individual capacities.[7] Individuals to use effective coping strategies in all stressful life events is a protective factor for mental health. In its most generally accepted classification, coping strategies can be defined as positive (functional) and negative (non-functional) coping, and positive strategies reduce the destructive effect of stress (8).

The first COVID-19 case in Turkey was confirmed on March 10, 2020. University students were asked to evacuate their dormitories, so they had to return to their families or friends' homes, and many of them could not even take their personal belongings, on the other hand, student dormitories have been used for quarantine purposes. During this period, face-to-face lectures were postponed for an indefinite time, clinical applications have been delayed indefinitely, and education and training activities have been carried out through online courses (by reducing the hours of many lessons). Besides, curfews have been imposed in many provinces of Turkey, especially in metropolitan areas, on weekends, travel restrictions have been imposed in provinces where the infection is spreading rapidly, and quarantine enforcement has been implemented at different times in many settlements.

This process can be perceived as more stressful considering the similar situations that nursing students may encounter after graduation. Due to the fact that they will work in contact with infected people for a long time in similar situations and because of the fears they might have, it was considered important to clarify the experiences and coping strategies regarding the pandemic. This rapid change will cause stress for nursing students. Although they do not work actively in this process, it is thought that nursing students may experience fears about similar situations they may encounter in their future professional lives. Since they are the occupational group that will work in contact with infected people for the longest time, determining their experiences regarding the pandemic and their strategies of coping with stress may provide evidence for their further attempts. Except for a study focusing on coping strategies of professional nurses and nursing students during the pandemic process (9) and a study on coping with anxiety (10), no qualitative study was found in the literature. Defining student nurses' personal experiences and perspectives and evaluating their coping strategies and their effectiveness can provide evidence to strengthen students in vocational training.

This study was planned to investigate the difficulties experienced by nursing students during the pandemic process thoroughly and to explain their coping styles. In this study, the following questions were sought:

- What are the difficulties experienced by nursing students during the pandemic process?
- What have nursing students done to cope with these difficulties?

2. METHODS

2.1. Research design and participants

This research was carried out using the phenomenological method, which is one of the qualitative research methods, to examine the views of nursing students on their pandemic experiences and their coping strategies. The main purpose of phenomenological research is, by departing from the experiences and feelings of individuals, to search for truth in narratives related to a particular phenomenon and to produce in-depth explanations for this phenomenon (11). The phenomena dealt with this method may appear in various forms such as events, experiences, perceptions, orientations, concepts and situations in the world we live in. Phenomenology provides a suitable research base for studies aiming to investigate the phenomena that are not completely unfamiliar to us, and which we do not fully understand (12).

At the state university where the research was conducted, the students of the faculty of health sciences nursing department take the "coping with stress" course, as an elective course (the student chooses the course if he/she wishes). While the first author of the article was conducting the coping with stress courses face-to-face for three weeks (two hours per week) before the pandemic, the author conducted this course online for eleven weeks (one hour per week) during the pandemic. For this reason, all students taking this course formed the population of the research (N=83). In the study, the sample size was not determined, the "Information Form and Questionnaire Form" prepared by the researchers was sent online to the group e-mail addresses of the students taking the course and the forms sent back constituted the sample of the research (N=61). Concepts of stress, stressor, coping and methods of coping with stress constituted the content of the course in question, after the pandemic started, a two-hour "Recommendations on protecting mental health in the pandemic" subject was added to the course content.

2.2. Data Collection Tools

In this study, the "document review method", one of the phenomenological techniques, was used. "Information Form" and "Questionnaire Form" were sent to the students online, and forms that were filled out completely and sent back were included in the content analysis. The data in the study were collected after the completion of students' final exams, and thus, it was aimed to prevent students from feeling obliged to participate in the study.

The information form consists of 10 multiple-choice items questioning the students' sociodemographic characteristics and daily life, such as age, gender, with whom and where

he/she lives, and where and with whom he/she is in the pandemic process.

The questionnaire form consists of 2 open-ended items that question the difficulties in the pandemic process and the ways to cope with them, and these questions are:

- What difficulties have you experienced during the pandemic process?
- How did you cope with the difficulties in this process?

2.3. Ethical Approval

Prior to the research, ethics committee approval was obtained from the Noninvasive Clinic Ethical Committee of the Faculty of Health Sciences at Marmara University (Decision no:47, dated:25.06.2020). After ethics committee approval, institution approval of the study was obtained from the Faculty of Health Sciences at Marmara University (Decision no:183271, dated: 06.07.2020).

2.4. Data Analysis

Data analysis in qualitative phenomenology research is aimed at revealing lives and senses. In the content analysis made for this purpose, there is an effort to conceptualize the data and reveal the themes that can define the phenomenon. The phenomenon is defined within the framework of concepts and themes, and is presented in a descriptive narrative by writing through direct quotations. Besides, the results obtained within the framework of emerging themes and patterns are explained and interpreted (13). In this study, the data analysis process was carried out with the six-step thematic analysis method proposed by Braun and Clarke: 1) Becoming familiar with the data; 2) Creating codes; 3) Find common themes; 4) Review of themes; 5) Defining and naming definitive themes; 6) Reporting (14).

In this study, the researcher applied the variation method in order to increase the validity and reliability (15), all forms from students were read over and over by both researchers independently, two researchers coded separately, and then researchers created themes by linking the codes together. In addition, to increase the validity of the results, the peer debriefing technique conveyed by Başkale was also used (16). Asking people with general knowledge of the research subject and specialized in qualitative research methods to examine the research in various dimensions is called peer debriefing.

Together with the student statements, the coding made in the research and the themes linked with these coding were sent to an experienced independent expert who previously conducted a qualitative research, and expert opinion was obtained. In addition, descriptive data obtained from the information forms were reported numerically.

3. RESULTS

Participants were at the age group of 19-24 and their mean age was 21.19±1.06. Of the participants, 77.00% were female, 34.4% stated that they live in a metropolis during the pandemia process, while 83.6% mentioned that they were with their family, 31.1% did not leave their homes unless it is necessary. 3.3% of the participants had received a diagnosis of Covid-19, while 41.9% stated that someone from their family or acquaintance was infected with Covid-19. 54.1% of the participants underlined that the "coping with stress" course they took for eleven weeks in this process was "very useful" (Table 1). The answers to the question of "What difficulties have you experienced during the pandemic process?" formed two main themes as "Difficulties/Stressors and Stress-Increasing Factors".

Table 1. *Sociodemographic Characteristics of Students*

Sociodemographic Characteristics		Min-max	Mean±SS
Age		19-24	21.19±1.06
		n	**%**
Gender	Male	14	23.0
	Female	47	77.0
Where you live during the pandemic process	Metropol	21	34.4
	Small city	24	39.3
	Town	11	18.0
	Village	5	8.2
People living together during the pandemic	Family	51	83.6
	Kin	5	8.2
	Friend	5	8.2
Frequency of leaving the house in a pandemic	Every day	2	3.3
	A few times a week	20	32.8
	Once a week	20	32.8
	Never	19	31.1
Her/his state of getting Kovid-19 infection	Yes	2	3.3
	No	59	96.7
The status of one of her/his family to be infected with Kovid-19 infection	Yes	25	41.9
	No	36	59.9
The usefulness of the stress coping lesson in dealing with negative emotions during the pandemic process	Not at all useful	—	-
	Partially useful	1	1.6
	Quite useful	27	44.3
	Very useful	33	54.1
Total		61	100

Sub-themes of "Difficulties/Stressors" main theme were as follows: Educational difficulties 49.18% (n=30), Emotional difficulties 45.90% (n=28), Fear of transmission/infection with Covid-19 49.18% (n=30), Uncertainty 39.44% (n=24), Being stuck at home/being in quarantine 26.22% (n=16), and Change in professional perception/anxiety 24.59% (n=15) (Table 2). Some statements about themes were presented below:

Table 2. *Theme and sub-themes*

Theme	Sub-themes	%
Difficulties/ Stressors	Educational difficulties	49.18
	Emotional difficulties	45.90
	Fear of transmission/infection with Covid-19	49.18
	Uncertainty	39.44
	Being stuck at home/being in quarantine	26.22
	Change in professional perception/anxiety	24.59
Stress/Anxiety Increasing Factors	Domestic Conflicts	27.86
	Social Media Posts	40.98
	Negative Interactions in a close relationship	32.18
Coping Strategies	*A-Positive Coping Strategies*	
	Physical strategies	45.90
	Hobbies	39.34
	Humor	32.78
	Stopping	24.59
	Organizing time	19.67
	Taking exact information	14.75
	Awareness exercises	14.75
	B-Negative Coping Strategies	13.11
	Overeating	18.03
	Increasing smoking/use of alcohol	

** Participants have multiple expressions of difficulties, factors that increase stress, and coping..*

Educational Difficulties

"…When the course is given online and if there is an internet connection cut off or any other problem in the connection, then, I will not be able to get the efficiency I want from the exam; what if we fail the exams?" (K14)

"…I was thinking a lot about what will happen next. Since I could not bring my computer with me, I was unable to continue online lessons. On the other hand, I could not get a straight answer from my university for the next term…." (K11)

"Since I could not attend my internships, I will be unqualified in terms of practice. When I get assigned in the future to a department related to my internships that I was unable to attend, I will probably get in a quandary." (K44)

Emotional Difficulties

"…It's so hard to be apart from my beloved ones, to lose my independence, to feel like I'm losing control, to abide by enforced rules!" (K55)

"…The fear of losing! They say it's very hurtful, that is it is! I'm not talking about the fear of financial loss here. I am talking about the losses of family members…" (K26)

"…We have lost our close relatives. You feel sorry for them, you mourn, most importantly you want to be with them. But you're not able to do anything since you're tied hand and foot. You feel very helpless…" (K12)

Fear off Transmission/Infection with Covid-19

"…Everyone is likely to get this disease. The possibility of transmission is a challenge in itself. When that hour comes (the time when new cases are announced by the health minister), I feel intense fear while waiting for the new number of cases and deaths to be announced..." (K5)

"…The fear of "Will I be infected on the way?", or when I came home, "Have I been infected on the way?"; the fear of trying to stay away from mom and dad as possible…Fears seemed to dominate me…" (K8)

Uncertainty

"… 'When will we return to our old lives?' or 'Could we live a life like before?'; these questions run in my head. I give way to despair of the fact that 'We cannot get rid of this virus!'" (K3)

"…The virus that entered our lives suddenly and still uncertainty about how long we will live with this virus… nothing is known!" (K19)

Being Stuck at Home/Being in Quarantine

"…The house has become a stressor in itself after a while; staying at home continuously and compulsorily, not being able to leave the house easily whenever you want, these are very difficult situations to endure!" (K5)

"Being at home all the time, being unable to spend your energy, being unable to stay alone, the feeling of being in a place like a box all the time, these were both demoralizing me and constantly putting a damper on my desire to do something." (K25)

Change In Professional Perception/Anxiety

"Struggling with such a biological war in my student life has worried me about my future. I can't help thinking about my job. Do I want this job anymore?" (K32)

"…Finally, it was about my perspective on the nursing profession. Keep doing this job despite all the risks? If I hadn't learned the coping strategies we covered in class, I would probably think I was helpless and cry every day!" (K6)

"…Since I'm studying nursing, as if I knew the cure for all diseases, in even the smallest incident, people ask me why. This profession has already stressed me out…" (K16)

Another main theme formed by the statements of the nurse students participating in the study was "Stress/Anxiety Increasing Factors". Sub-themes under this main theme are as follows: Domestic Conflicts 27.86% (n=17); Social Media Posts 40.98% (n=25), and Negative Interactions in A Close Relationship 32.78% (n=20) (Table 2).

Domestic Conflicts

"When the whole family is all at home together, we are experiencing a lot of arguments at home. We were having trouble understanding my adolescent brother before, now we do not understand him at all, he has gotten ill-tempered." (K12)

"…We all have difficulties since we have to share the same environment for a long time. Even the presence of the coronavirus did not worry my mother as much as ours…" (K29)

Social Media Posts

"…Not only fake news, watching the minister of health talking every day, and following the table he presents, the increasing number of cases and deaths every day, especially at the beginning of the quarantine process…"(K19)

"The fact that the matter in question is always the same or the fact that everyone talks about this matter carelessly; seeing foolish behaviors of people on the internet, who could not understand the importance of the situation we are in, who endanger not only themselves but everyone…" (K28)

Negative Interactions in a Close Relationship;

"My father is the only employee in our house and the economic needs of everyone in our home are under my father's responsibility. My father also has many chronic illnesses but still has to go to work. My mother always cries when she finds out some things! It seems like we all make each other worse." (K39)

"The stressors of people with whom we are in the same environment inevitably affect us, too. It is quite difficult for me to resist this." (K61)

"…My boyfriend is a worrywart person. He has been experiencing fear and stress at the highest level since the first day of the pandemic. He hardly ever goes out on the street, he will drive us crazy too…" (K53)

The answers to the question of "How did you cope with the difficulties in this process?" were discussed under the main theme of "Coping Strategies", and these responses were grouped into positive and negative coping strategies. These sub-themes are as follows: Physical strategies (breathing exercises, regular diet and sleep, physical exercise, etc.) 45.90% (n=28), Hobbies 39.34% (n=24), Humor 32.78% (n=20), Stopping Negative Thinking 24.59% (n=15), Organizing time %19.67 (n=12), Taking exact information 14.75% (n=9) and Awareness exercises 14.75% (n=9).

In terms of breathing exercises among the physical strategies, three students (K5,17, 31) stated that "focusing on breathing causes anxiety as it reminds shortness of breath, which is one of the symptoms of Covid-19." The negative coping strategies, on the other hand, covers the following: Overeating 13.11% (n=8) and Increasing smoking/use of alcohol 18.03% (n=11) (Table 2).

Positive Coping Strategies

"…Actually, it is quite reasonable that the right breathing is effective in managing the intense stress we experience. When I used this method I was able to think calmly." (K21)

"Thanks to regular diet and sports, I began to return to my previous weight and this started to affect my mental health positively." (K11)

"I like to draw a caricature. I'm trying to get over this period, at least mentally, with little damage, by drawing funny cartoons and making jokes about many subjects." (K5)

"I always tried to be busy with something not to think about negative things. I was involved in acts such as painting, reading, singing, and cooking." (K60)

"It is our nation that ridicule the most coronavirus. So indeed it is, funny videos are everywhere. Watching these videos makes me happy. Those in my family also watch these videos and we all laugh together. Laughter really has a healing effect!" (K39)

"I already love humor, and good humor can make you forget everything these days."(K51)

"I pondered over awareness. We attended online education and this made me very comfortable in this regard." (K1)

"Stopping negative thinking was the most effective method. It made me think smarter and calmer." (K27)

"I chose the method of using the time well because the reason for my stress was my days to get monotonous and not knowing how to use my time. Therefore, I started my day by making a plan, abiding by my routine." (K16).

Negative Coping Strategies

"I always made dessert. It used to be like spending time, but gradually I started to feel that I relieve while eating dessert. I gained weight, quite a lot." (K60)

"Although I know it increases the risk of Covid-19, I light a cigarette after cigarette. Then I feel guilty, moreover, I am a nursing student." (K55)

4. DISCUSSION

The Covid-19 pandemic has deeply affected all humanity, both physically and spiritually, and it has shaken our perception of security. Each person felt restricted to different levels and has given his own behavior-specific reactions. In this study, the difficulties experienced by nursing students during the pandemic process and their coping strategies were discussed from their own perspectives, and the main themes of difficulties, stress/anxiety increasing factors, and coping were reached; meanwhile, one of the most striking results was the point of "Change in professional perception/ anxiety", which expresses the change in student nurses' professional perceptions.

It was thought that "change in professional perception/ anxiety", among the difficulties experienced by student nurses, may be related to the fact that healthcare professionals are occupational groups that are active in the pandemic and in a high-risk group. Healthcare professionals around the world have been exposed to physical and mental threats that vary to the extent of the prevalence of pandemic, moreover, there have been healthcare professionals who died due to the Covid-19 infection. In all of the outbreaks such as SARS, Ebola, MERS-CoV infections with fatal consequences that

were experienced recently and Covid-19 that we are still experiencing, it was the healthcare professionals who affected most and at risk of harm (3-5). Therefore, the concern stated by student nurses in this theme is quite understandable and this may indicate the necessity of studies in this field.

The theme of "educational difficulties" obtained from the statements of the participants is related to online education. Although online education has some advantages compared to face-to-face education, it has also led to a lifestyle change for university students. For the group who comes together in their classes during the day and who uses the social facilities of university campuses, going back to their families and missing out the activities they do with groups of friends may have increased the difficulty experienced. Similarly, Baloran (2020) reported that also Philippine students had difficulties with online education. States and universities should produce practical solutions in reducing students' educational difficulties (17).

Although epidemics cause a wide variety of emotional responses, the difficulties are not the same for everyone (9). In this study, students stated that they experienced "emotional difficulties" such as anxiety, fear, and sadness. In a study conducted with a sample of university students, 82.98% of the students stated that they were afraid of the pandemic (18). Similarly, Baloran (2020) reported that most of the students experienced anxiety (17). In a study addressing the psychological effects of a pandemic in the general population in China, it was reported that 16.5% of the participants had moderate and severe depression, 28.8% had moderate and severe anxiety, and 8.1% had moderate and severe stress symptoms, and that being a student was effective at higher levels of anxiety, depression, and stress (3). Another difficulty experienced by nursing students is the anxiety of transmission, the majority of the students stated that they did not leave the house either only once a week or at all. In a study conducted in Turkey with medical school students, students stated that they are afraid of being infected with the Covid-19 (19). Similar to these studies, Roy et al. (2020) and Wang et al. (2020) reported that individuals get anxious about themselves and their families during the ongoing pandemic (3,20).

"Uncertainty", another difficulty determined, can be explained by the rapid spread of the Covid-19 infection in a form not encountered before or by the fact that no vaccine or effective treatment has yet been found and by the lack of clear data on the course of the pandemic. As it is quoted from Tönbül (2020); the fact that the threat in the Covid-19 pandemic has been perceived uncertainly and continuously can cause the fear felt to become chronic; while the emotion felt by individuals at most was anxiety, the thought of what I would do if this disease is transmitted to me, my child or my parents was the most common thought (21). Emotions such as fear, unhappiness, despair, and helplessness that combined with uncertainty and disease anxiety cause intense difficulty (22). Considering these themes altogether, the necessity of preventing mental influences as well as physical influences during the pandemic becomes prominent.

In the study, the theme of "being stuck at home/being in quarantine" was another difficulty. By his nature, the human is a social being, and youth is perhaps one of the periods when sociability becomes the most important. Socialization is one of the most important and integral parts of life for young people, therefore, the obligation to stay at home, which is compelling for everyone, can be even more challenging for teens. Polizzi et al. (2020) stated that "separation" is a necessity for all people to survive in the COVID-19 outbreak and that this is related not only to feeling lonely but also to being deprived of many activities for relaxation (going to parties, movies/theater, sports halls, etc.) (23). In the struggle with the difficulty stated in this theme, it is necessary to underline, via media, the fact that the distance experienced is "physical", not "social"; and that there is a need to promote the maintenance of social contact on online platforms as much as possible.

Another main theme formed by the statements of the nurse students participating in the study was the "stress/anxiety increasing factors", and sub-themes were: domestic conflicts, social media posts, and negative interactions in close relationships. The fact that university students had to stay at home with their families may have caused pushing the mental limits as well as the physical ones. Staying in the same house all the time may turn into a situation that pushes close relationships and triggers conflicts. On the other hand, emotions associated with stress and anxiety can be transmitted from individuals to each other in these relationships. In social media, unnecessarily following the pandemic-related posts with negative content may increase stress and anxiety. Bozkurt et al. (2020) reported that being exposed to the flow of unfounded information via social media posts and watching programs on the pandemic for long hours on the internet and televisions increase anxiety and panic (24).

The last main theme in this study is the "Coping Strategies", while its related two sub-themes were "positive" and "negative" coping strategies. The functional strategies used by nursing students were as follows: physical strategies (breathing exercises, regular diet and sleep, physical exercise, etc.), hobbies, humor, stopping negative thinking, organizing time, taking exact information, and awareness exercises. Another interesting result of the study was the fact that, in terms of breathing exercises among the physical strategies, three students mentioned that "focusing on breathing causes anxiety as it reminds shortness of breath, which is one of the symptoms of Covid-19." It may be thought that breathing exercises should be addressed in this pandemic and studies with large samples should be conducted on this subject.

Negative coping strategies used by students in this study were overeating and increasing smoking/use of alcohol. Almost all of the nursing students stated that coping with stress course they took was very useful in coping with negative emotions during the pandemic process. Zhi et al. (2020) found that

the information that student nurses received on epidemic prevention and treatment reduced their stress and this positively affected the perception of occupational identity (25). Li and Peng (2020) determined that cognitive coping, emotional coping, and social support were effective in coping with anxiety experienced by university students during the Covid-19 pandemic process and that social support is the strongest protective coping strategy and behavioral coping also predicts anxiety (7).

Perng et al. (2020) suggested that listening to music (75,2%) is the most popular among the various stress-reducing strategies, which was followed by talking to a friend (72,3%) and sleeping (%61,3) (26). Savitsky et al. (2020) stated that the use of humor was effective in reducing anxiety associated with the pandemic (10), while Huang et al. (2020) reported that for nursing students, only problem-focused coping strategies affect anxiety and fears and they suggested that nurses should receive better training in coping strategies (9).

Rajkumar et al. (2020) recommended psychological support programs and psychoeducation to cope with health-related anxiety during the pandemic period and they stated that these attempts can provide more accurate and realistic information by choosing positive strategies instead of negative ones (1). Polizzi et al. (2020) suggested using multiple-coping strategies (e.g. behavioral activation, acceptance-based coping, awareness practice, affectionate favor practices) to reduce stress and promote well-being, and they reported that these strategies would help individuals create meaning, develop tolerance, increase social support, develop an insight into deep human devotion, and carry out target-driven value-oriented actions in the midst of the COVID-19 pandemic (13). Considering that developing positive coping strategies is one of the protective factors in many mental disorders; it can be said that there is a need for studies on this subject in struggling with the pandemic.

4.1. Limitations

Our research was performed only in one nursing school. For this reason, it does not represent all nursing students. Due to the absence of students from different faculties in the sample of this study, especially from departments other than the health department, the study was limited to representing the experiences of young people who were not educated in health/disease/epidemic issues. Besides, since students in this study have taken the “coping with stress course”, this may have an effect on their coping strategies.

5. CONCLUSION

Within the scope of this study, we can list the difficulties experienced by students as educational difficulties, emotional difficulties, fear of transmission/infection with Covid-19, uncertainty, being stuck at home/being in quarantine, change in professional perception/anxiety; while domestic conflicts, social media posts, and negative interactions in a close relationship, on the other hand, constitute stress/anxiety increasing factors. Although the students mostly used more than one positive coping strategies, some of them stated that they also used negative coping strategies such as overeating and increasing smoking/use of alcohol. Departing from this information; when we consider that it will be the nursing students who will be front-line professionals in the fight against future social health problems, the development of positive coping strategies may be suggested. Besides, the young people’s difficulties and coping strategies during the pandemic who were studying different departments other than health sciences and whether there is a change in the professional perceptions of students who receive education in health sciences during the pandemic process are recommended to be discussed in future studies.

Conflict of interest

The authors do not have any conflict of interest to disclose

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Clinical and Experimental Health Sciences

Exploring Problem Areas of Elderly Patients with Diabetes and the Support Provided by Their Family

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ABSTRACT

Objective: Diabetes increases problems in emotional areas particularly among the elderly patients by aggravating negative emotions such as loss, anxiety and fear and makes these patients need higher level of family support. This study aims at exploring problematic areas of the elderly diabetic patients and their family support levels.

Methods: The data of this descriptive study were collected by the researcher by conducting a face to face interview with 218 elderly diabetic patients who presented to Endocrine Polyclinics of State Hospital between October 2015 and October 2016. To collect the data, "Patient Information Form", "Problem Areas in Diabetes Scale (PAID)" and "Hensarling's Diabetes Family Support Scale (HDFSS)" were used.

Results: Although problem areas among the patients were found to be fewer than expected; it was found that there were significant differences between problem areas and "sex, diabetes time, treatment type, length of oral antidiabetic medicine use and insulin use, development of diabetes-related complication and hospitalization due to these complications in the recent year" ($p<0.05$). Besides, the family support levels of the elderly patients were below the moderate level, and "the number of individuals the patients live together with", "the number of people receiving support due to diabetes" and "the number of people who received support from their spouses because of diabetes" was a significant variable that affected HDFSS total score and the subscale scores ($p<0.05$).

Conclusion: For a better diabetes management, sex and diabetes related variables should be taken into consideration while delivering health services and increasing family support levels can make positive contributions to the mood of the elderly patients.

Keywords: Affective symptoms, aged, diabetes mellitus, family, nursing,

1. INTRODUCTION

Diabetes is a metabolic disease that requires continuous medical care; it is characterised by chronic hyperglycaemia, in which the organism cannot sufficiently benefit from carbohydrates, fats and proteins owing to the lack of insulin or disorders that affect insulin secretion (1). According to the ninth Diabetes Atlas, this condition has a high incidence in the elderly; there are 135.6 million patients with diabetes aged 65–99 years in 2019, whereas this number is expected to reach 276.2 million 2045 (2).

It has been reported that physical damage caused by diabetes and its complications adversely affect psychological well-being of elderly, and these feelings trigger the progression of diabetes complications (3,6). In order to minimize complications and to maximize quality of life among the elderly who are the main target group in diabetes care; the elderly should be supported, accepted and understood (7,8). In the management and control of chronic diseases, the importance of family support on the health status of the elderly rural population should be taken into account. Family support has a major impact on a patient's ability to self-manage their chronic condition. Family support can improve health by affecting the daily behavior of the elderly, and loss of support can negatively affect health. (9,10). Regardless of the presence of a chronic disease, ageing, physical and psychosocial changes, decrease in psychomotor skills, need for help in performing daily life activities and decrease in emotional and social relations occur. Due to increasing risk of mortality in the elderly who are trying to adapt to the period of these losses, providing elderly individuals with a strong family support is essential (11-13). After the diagnosis of diabetes, vital regulations such as diet, activity,

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and health control create anxiety, fear, guilt and emotional stress in elderly individuals. Emotional stress is an important cause of increased blood sugar in older people.Therefore, a comprehensive approach to the management of diabetes is required. Family support in the diabetes care of the elderly has an important effect on protecting the health of the elderly by reducing complications and emotional stress (7).

Allowing the elderly to express feelings such as anxiety, guilt, fear and pessimism caused by diabetes and expressing that these feelings are correctly understood by a family member are assurance that the individual can be provided with empathetic support by the family. Therefore, it is important for the family members to monitor blood sugar, remind the elderly to take their medicines on time, encourage them to undergo routine health checks for complications and support them (9,14,15).

The family's support to the elderly in the care and treatment of diabetes, such as purchasing nutritional supplements for their diet, encouraging them to exercise and assisting them in taking their medicines, was identified as facilitating factors for the elderly to cope with diabetes. Family members should share responsibilities in providing assistance so that the elderly can avail appropriate health services (7,10,13,14).

A better understanding of the emotional problems of patients is necessary to guide healthcare initiatives in improving the treatment and monitoring of diabetes and in strengthening support systems. In the literature, it has been shown that many health workers cannot detect and evaluate psychological problems and thus do not provide the patients with the support they need (16).

For the complex nature of diabetes and effective management of the disease, the participation of nurses with multiple roles in providing care is very important. Diabetics are often in serious contact with the healthcare system, and most of their direct contact is with nurses. In a variety of settings at all levels of the healthcare system, from routine clinical visits to inpatient care, nurses play a central role in the care of diabetic patients. One of the important roles of nurses stated in the literature in the care of diabetes is to support diabetic patients with their emotional problems (17). This study determines the emotional problems experienced by elderly patients with diabetes and the variables affecting them; determining the family and other variables, which are the most important sources of support that can help the elderly, will contribute to the nurse's fulfillment of this role. The aim of this study is to identify the problem areas of diabetes mellitus patients, their levels of family support and the variables that affect them; it also aims to the planning and implementation of appropriate nursing interventions by creating awareness.

2. METHODS

Ethics committee approval was obtained for this descriptive study from the Scientific Research Ethics Committee of Karadeniz Technical University Faculty of Medicine with the decision dated 19.10.15 and numbered 24237859-602. The universe of the study consisted of 500 patients aged 65 years and above who applied to State Hospital Endocrine Polyclinic with the diagnosis of Type 2 diabetes, with reference to January 2014–January 2015 data. The sample of the study was determined by the formula used to determine the number of individuals in the sample in cases where the number of individuals in the universe was known, and 218 patients who matched the research criteria were found to represent the universe (18). More than 50% of the patients was reached with the sample of the study. The inclusion criteria for this research are as follows: individuals aged 65 years and above; individuals diagnosed with diabetes; individuals who can communicate verbally; individuals without psychiatric disorder requiring treatment; individuals who are oriented to person, place and time; and individuals accepting to participate in the study were identified.

2.1. Data Collection Tools

2.1.1. Patient Information Form

This form was made by the researcher through a literature review, and this form was used for the patient sociodemographic interface (age, gender, education level, marital status, number of children, family type) and diabetes mellitus (the duration of diabetes, the duration of diabetes treatment, the duration of oral antidiabetic drugs, insulin use, the cause of diabetes hospitalization in the past year, including complications to diabetes) and family (the number of people living at home, helping family members due to diabetes) it includes related questions (4,19,20).

2.1.2. Problem Areas in Diabetes Scale (PAID)

The PAID Scale was developed in 1995 by Polonsky and friends (21). In studies abroad, the internal consistency of the PAID Scale was found to be 0.90, the Turkish validity and reliability of the scale was reported in a study by Yilmaz with a Cronbach's alpha value of 0.80. This scale is a 20-item test that questions the areas of emotional stress of patients with diabetes and long-term diabetes treatment. Emotional stress areas are hate, guilt, depressive mode, anxiety and fear. Scoring of the scale is between 0 and 100. Low scores indicate minimal emotional problems. In our study, PAID Cronbach's alpha internal consistency coefficient was calculated as 0.79.

2.1.3. Hensarling's Diabetes Family Support Scale (HDFSS)

This scale was developed by Janice Hensarling (14); HDFSS measures perceived family support, especially for adults with Type 2 diabetes. HDFSS showed an item–item correlation mean of 0.52, an item–total score correlations between 0.49 and 0.87 and measurements supporting internal consistency of Cronbach's alpha value of 0.96. Pearson's correlation coefficient examined the relationship between the factors. These factors were within the expected range (0.50–0.79) for the dimensions of the concept Diabetes Family Support.

The validity and reliability study of the scale in Turkish was performed by Akin, and the Cronbach's alpha value was found to be 0.79–0.96. The total score of HDFSS is between 0 and 96. The higher the total score obtained from this scale, the higher the family support the individual perceives. In our study, Cronbach's alpha internal consistency coefficient total is 0.90 for HDFSS; 0.88 for empathetic support; 0.75 for encouragement support; 0.67 for facilitative support and 0.58 for participative support.

2.2. Data Collection

The questionnaire forms were given to patients aged 65 and above who applied to State Hospital Endocrine Polyclinic between October 2015 and October 2016 with the diagnosis of Type 2 diabetes.

2.3. Statistical Analysis

In evaluating the findings of the study, SPSS (Statistical Package for Social Sciences) Windows 18.0 programme was used. Continuous variables were presented as mean and standard deviation, and categorical variables were presented as number (percentage). When the parametric test assumptions are provided, the analysis of variance, which tests the significance of the difference between two averages, was used to compare independent group differences; when the parametric test assumptions were not provided, Mann–Whitney U test and Kruskal–Wallis Variance Analysis were used to compare the independent group differences. The results were evaluated at 95% confidence interval, and p value < 0.05 was considered significant.

3. RESULTS

61.0% of the patients included in the study were female (n = 133), 77.1% were in the 65-74 age group (n = 168), 41.7% were primary school graduates (n = 91), 73.4% were married (n = 160), 47.7% have five or more children (n = 104), 75.2% are core families (n = 164), 84.4% received help due to diabetes (n = 184). The mean PAID score of the patients was 37.46 ± 9.53. There was statistically significant difference between PAID mean scores and gender and family type (p<0.05) (Table 1). Table 2 shows the duration of diabetes, type of treatment, oral antidiabetic drug (OAD) used, duration of insulin use and diabetic complications (p<0.05); a significant difference was found between the mean PAID scores and hospitalisation (p<0.0001) in the last year due to these complications. In Table 3, the mean HDFSS score of the patients was 57.13 ± 13.75; the highest mean score in the sub-dimensions was 23.01 ± 6.11 for empathetic support. The mean scores for HDFSS, empathetic and encouragement support were significantly higher in patients who received diabetes education (p<0.05). The mean score for empathetic support (p<0.05) was found to be high in the diabetic elderly who developed diabetes-induced hypoglycaemia, whereas the mean scores for empathetic support (p<0.01), facilitative support (p<0.05) and total HDFSS (p<0.01) in the elderly who developed diabetic foot or neuropathy were found to be significantly low. As a result of these complications, the mean score for encouragement support, facilitative support, participative support and total HDFSS were significantly lower in hospitalization caused by diabetic foot/neuropathy in the last one year (p<0.05) (Table 4). There was a significant difference in the mean number of patients with the home together with empathetic support, encouragement support, facilitative support, participative support and total HDFSS (p<0.0001; p<0.01). There were significant differences in the empathetic support, facilitative support, participative support and total HDFSS mean scores of elderly patients who were helped by their spouses. In addition, there were significant differences in the empathetic support, encouragement support, participative support and total HDFSS mean scores of elderly patients who were helped by their child (p<0.05; p<0.01) (Table 5).

Table 1. *Average PAID scores of the elderly diabetic patients and average PAID scores according to socio-demographic characteristics*

PAID†		X̄ ± SD	Med (Min – max)	
Total		37.46±9.53	37.50 (14 – 65)	
	n	**%**	**PAID† X̄ ± SD**	**Test Value**
Gender				
Female	133	61.0	39.01±9.66	t=3.048
Male	85	39.0	35.05±8.87	p=0.003
Age				
65-74	168	77.1	37.76 ±9.38	t=0.830
75 years and above	50	22.9	36.48±10.07	p=0.407
Educational status				
Illiterate	88	40.4	38.17±9.37	
Literate	24	11.0	35.58±9.38	KW=3.991
Primary education	91	41.7	37.66±10.30	p=0.262
High school/ University	15	6.9	35.13±4.64	
Marital status				
Married	160	73.4	37.63±9.54	t=0.431
Unmarried	58	26.6	37.00±9.58	p=0.667
The Number of the children				
No	9	4.1	36.11±7.01	
1-2	18	8.3	38.06±8.19	F=0.368
3-4	87	39.9	38.17±9.72	p=0.776
5 and above	104	47.7	36.88±9.83	
Family type				
Core	164	75.2	36.51±9.18	t=-2.601
Broad	54	24.8	40.35±10.07	p=0.010
Receiving help due to diabetes				
Yes‡	184	84.4	37.54±9.31	t=0.288
No	34	15.6	37.03±10.80	p=0.773

† *Problem Areas in Diabetes Scale* ‡ *Doing activities of daily living, transportation to hospital, measuring blood glucose.*

Table 2. *Average PAID scores of the elderly diabetic patients according to diabetic features*

	n	%	PAID† X̄ ± SD	Test Value
Length of diabetes				
Less than 1 year	8	3.7	30.63±11.07	KW=10.403 p=0.034
1-5 years	47	21.5	35.11±9.52	
6-10 years	61	28.0	37.39±10.24	
11-15 years	39	17.9	39.85±9.84	
More than 16 years	63	28.9	38.68±7.80	
Type of diabetes treatment				
OAD‡ + diet	69	31.6	35.04±10.13	F=3.810 p=0.024
Insulin + diet	85	39.0	39.24±8.39	
OAD‡ + insulin + diet	64	29.4	37.72±9.89	
Length of OAD‡ use				
Less than 1 year	7	5.3	24.43±12.16	F=3.897 p=0.005
1-5 years	42	31.5	35.20±8.57	
6-10 years	39	29.1	37.72±10.66	
11-15 years	21	16.0	40.33±9.66	
More than 16 years	24	18.1	35.96±8.96	
Length of insulin use				
Less than 1 year	28	18.8	33.00±8.35	F=4.654 p=0.001
1-5 years	60	40.3	39.05±9.03	
6-10 years	32	21.5	41.56±8.11	
11-15 years	14	9.3	38.00±10.09	
More than 16 years	15	10.1	42.33±6.84	
Presence of complication caused by diabetes (n=198) §				
Yes‖	198	90.8	37.92±9.30	t=2.268 p=0.024
No	20	9.2	32.90±10.8	
Hospitalization caused by diabetes in the last one year (n=110)§				
Yes¶	110	50.5	39.68±9.25	t=3.560
No	108	49.5	35.20±9.32	p=0.0001

†Problem Areas in Diabetes Scale ‡Oral antidiabetic drug §Multiple answers ‖ Hyperglycemia, cardiovascular disease ¶Hyperglycemia, diabetic foot, retinopathy

Table 3. *Average total score and average subscale scores of HDFSS of the elderly diabetes patients*

HDFSS†	X̄ ± SD	Med (Min – Max)
Empathetic support	23.01±6.11	24 (5-36)
Encouragement support	14.00±4.96	14 (1-27)
Facilitative support	14.25±3.68	14 (3-23)
Participative support	5.87±1.90	6 (1-8)
Total HDFSS*	57.13±13.75	57 (10-92)

†Hensarling's Diabetes Family Support Scale

Table 4. *Average total score and average subscale scores of HDFSS of the elderly diabetes patients in terms of their diabetic characteristics*

		n	%	HDFSS† X̄ ± SD	Test Value
Status of receiving diabetes education					
Empathetic support	Yes	147	67.4	23.63±5.92	t=2.170 p=0.031
	No	71	32.6	21.73±6.34	
Encouragement support	Yes	147	67.4	14.62±4.96	t=2.688 p=0.008
	No	71	32.6	12.72±4.74	
Facilitative support	Yes	147	67.4	14.38±3.55	z=-0.278 p=0.781
	No	71	32.6	13.99±3.94	
Participative support	Yes	147	67.4	5.83±1.94	z=-0.321 p=0.748
	No	71	32.6	5.94±1.84	
Total HDFSS†	Yes	147	67.4	58.46±13.84	t=2.070 p=0.040
	No	71	32.6	54.38±13.24	
Complications caused by diabetes					
Hypoglycemia					
Empathetic support	Yes	143	65.6	23.62±5.98	t=2.021 p=0.044
	No	75	34.4	21.87±6.23	
Encouragement support	Yes	143	65.6	14.04±4.79	t=0.172 p=0.864
	No	75	34.4	13.92±5.30	
Facilitative support	Yes	143	65.6	14.33±3.47	z=-0.359 p=0.720
	No	75	34.4	14.11±4.07	
Participative support	Yes	143	65.6	5.97±1.94	z=-1.417 p=0.156
	No	75	34.4	5.67±1.82	
Total HDFSS†	Yes	143	65.6	57.96±13.39	t=1.225 p=0.222
	No	75	34.4	55.56±14.38	
Diabetic foot / neuropathy					
Empathetic support	Yes	22	10.1	19.77±5.85	z=-2.596 p=0.009
	No	196	89.9	23.38±6.05	
Encouragement support	Yes	22	10.1	12.45±4.38	t=-1.545 p=0.124
	No	196	89.9	14.17±5.00	
Facilitative support	Yes	22	10.1	12.14±4.23	z=-2.524 p=0.012
	No	196	89.9	14.49±3.55	
Participative support	Yes	22	10.1	5.55±1.95	z=-0.925 p=0.355
	No	196	89.9	5.90±1.90	
Total HDFSS†	Yes	22	10.1	49.91±13.16	t= – 2.634 p=0.009
	No	196	89.9	57.94±13.61	
Hospitalization caused by diabetic foot/neuropathy in the last one year					
Empathetic support	Yes	8	3.7	18.88±7.30	z=-1.496 p=0.135
	No	210	963	23.17±6.03	
Encouragement support	Yes	8	3.7	10.50±3.38	z=-2.152 p=0.031
	No	210	96.3	14.13±4.97	
Facilitative support	Yes	8	3.7	10.25±4.71	z=-2.478 p=0.013
	No	210	96.3	14.40±3.56	
Participative support	Yes	8	3.7	4.50±1.20	z=-2.148 p=0.016
	No	210	96.3	5.92±1.90	
Total HDFSS†	Yes	8	3.7	44.13±13.88	z=-2.537 p=0.011
	No	210	96.3	57.63±13.53	

†Hensarling's Diabetes Family Support Scale.

Table 5. *Average total score and average subscale scores of HDFSS of the elderly diabetic patients in terms of their characteristics related to their families*

		n	%	HDFSS† $\bar{X}$ ± SD	Test Value
The number of the individuals with whom patients lived at home					
Empathetic support	Alone	21	9.6	17.43±6.8	F=7.142
	1-2	82	37.6	23.83±5.72	p=0.0001
	3-4	53	24.4	23.70±5.69	
	5 and above	62	28.4	23.24±5.88	
Encouragement support	Alone	21	9.6	10.33±4.62	F=4.618
	1-2	82	37.6	14.12±4.84	p=0.004
	3-4	53	24.4	14.74±4.63	
	5 and above	62	28.4	14.45±5.08	
Facilitative support	Alone	21	9.6	10.62±4.21	KW=20.512
	1-2	82	37.6	14.78±3.42	p=0.0001
	3-4	53	24.4	15.19±2.61	
	5 and above	62	28.4	13.98±3.91	
Participative support	Alone	21	9.6	4.57±2.25	KW=11.515
	1-2	82	37.6	5.96±1.81	p=0.009
	3-4	53	24.4	6.34±1.78	
	5 and above	62	28.4	5.77±1.83	
Total HDFSS†	Alone	21	9.6	42.95±15.09	F=9.568
	1-2	82	37.6	58.70±12.89	p=0.0001
	3-4	53	24.4	59.96±10.90	
	5 and above	62	28.4	57.45±14.02	
Family members that give assistance due to diabetes‡					
Spouse					
Empathetic support	Yes	111	50.9	24.29±5.86	t=3.202
	No	107	49.1	21.69±6.11	p=0.002
Encouragement support	Yes	111	50.9	14.55±4.62	t=1.672
	No	107	49.1	13.43±5.25	p=0.096
Facilitative support	Yes	111	50.9	14.85±3.26	z=-2.072
	No	107	49.1	13.64±3.99	p=0.038
Participative support	Yes	111	50.9	6.18±1.66	z=-2.103
	No	107	49.1	5.54±2.08	p=0.035
Total HDFSS†	Yes	111	50.9	59.86±12.50	t=3.044
	No	107	49.1	54.30±14.46	p=0.003
Children					
Empathetic support	Yes	69	31.7	24.45±5.52	z=-2.071
	No	149	68.3	22.35±6.27	p=0.038
Encouragement support	Yes	69	31.7	15.00±4.25	t=2.197
	No	149	68.3	13.54±5.21	p=0.029
Facilitative support	Yes	69	31.7	14.93±2.94	z=-1.310
	No	149	68.3	13.94±3.95	p=0.190
Participative support	Yes	69	31.7	6.25±1.91	z=-2.342
	No	149	68.3	5.69±1.87	p=0.019
Total HDFSS†	Yes	69	31.7	60.62±11.13	t=2.846
	No	149	68.3	55.52±14.56	p= 0.005

†Hensarling's Diabetes Family Support Scale ‡Doing activities of daily living, transportation to hospital, measuring blood glucose.

4. DISCUSSION

In our study, the scale of the problem areas that help assess the quality of life of patients with diabetes, who are sensitive to emotional distress and can benefit more from psychological help, has been used, and it has been found that the problem areas of elderly diabetes patients are not as high as expected (3). In the literature, it was found that elderly patients perceived emotional problems less than younger patients included in the studies (3,4,16,22,23). This situation has been associated with increased acceptance and adaptability with ageing. Elderly diabetes patients were found to need more family support, and empathic support was more likely to be higher than other sub-dimensions; however, it was found that older people are more likely to express feelings such as anxiety, guilt, fear and pessimism caused by diabetes (14).

In our study, it was determined that older women experienced more problems related to diabetes than men. In the literature, it is stated that women have higher diabetes load, have more power with diabetes and have more problems compared with men (3,16,20,23). Traditionally, women have more roles in the family and society to carry out their care and coordination duties, and it is stated that women are more fragile and their welfare levels are worse (16).

When considering gender in evaluating family support, the significantly higher share of participative support in older women is related to the need for more help from a family member in accessing health services than men (14). It has been determined that the problem areas of the elderly with large families are significantly higher than the elderly with small families. It has been found that for the elderly with extended families, the members of the family have experienced confusion in sharing responsibilities, and thus support in the care of the elderly becomes insufficient.

While the emotional problem areas of the elderly with diabetes duration of up to 15 years have increased, it has been observed that the emotional problem areas decreased 16 years and after. This situation has been associated with the fact that the negative meaning given to the disease in the first encounter may prevent the individuals to cope with the problems, but this meaning can be perceived more positively in the following periods. For less than a year, the elderly using OAD and insulin has been found to be significantly less problematic. In the elderly, the increase in the duration of diagnosis; long-term use of medication; difficulty in accessing drugs; dementia, depression and cognitive dysfunctions; neglecting treatment or not and the use of multiple medications, increase the development of retinopathy and neuropathy. Due to these negativities, older people need more support from someone else since these factors disrupt compliance with treatment and increases problem areas. For the elderly who received diabetes education, a significant increase in total HDFSS, empathetic and encouragement support sub-dimensions shows that the family also supports the elderly in attending diabetes education. In this study, total HDFSS, empathetic and encouragement support levels

including monitoring blood glucose levels, reminding them to take medication on time and encouraging to them to undergo routine health checks were found to be high. In this case, elderly patients with diabetes education are presumed to have families that are supportive of managing and adapting to diabetes. In addition, it is stated that the participation of the family in the diabetes education of elderly diabetes patients will increase the empathy ability of the family (14,19). In our study, the problem areas of the elderly with complications were found to be significantly higher. Studies have shown that many patients with diabetes are suffering not only from depression but also from emotional distress related to diabetes, and patients develop serious complications that may be caused by diabetes such as serious emotional problem (4,5).

In our study, participative support was found to be significantly higher in the elderly with diabetes complications. High level of participative support suggests that the elderly with complications develop more awareness on accessing health services in order to control diabetes by educating their families about diabetes and its complications. Hospitalisation was evaluated as an indicator of non-adherence in all age groups and especially in the elderly (24). In our study, it was found that in the last year, a high degree of significance in the problem areas of the hospitalised elderly was observed. In the literature, it is often stated that being in a hospital environment causes fear and anxiety with regard to the disease; not knowing what to do and uncertainty of recovery from the disease are the causes of anxiety to the patient and his or her family (25). This information suggests that hospitalisation may cause intense stress in elderly patients, may make them feel aloof, may cause anxiety and may increase problem areas related to diabetes. The fact that the empathetic support is significantly higher in the elderly who have diabetes-induced hypoglycaemia shows that the family feels empathy and supports the elderly because the hypoglycaemia requires urgent intervention.

The total HDFSS, empathetic and facilitative support levels of the elderly who developed diabetic foot were significantly lower than those who did not develop diabetic foot. In elderly patients hospitalised due to diabetic foot, total HDFSS, encouragement, facilitative and participative support levels were found to be significantly lower than those who were not hospitalised. This situation shows that if the family support, which is the most important part of social support, is low or insufficient; moreover, it can increase the development of diabetic foot, which may cause fear, worsen the quality of life, cause organ dysfunction, and lead to recurrent hospitalisations. In the literature, it has been reported that financial and moral support provided by the spouse, family members and friends are important resources in dealing with the psychosocial problems brought about by the old age as well as other diseases (26,27). In our study, family support in terms of total HDFSS, empathetic and facilitative support scores were found to be significantly low for elderly patients living alone compared with the other groups living with one or more family members. In a previously conducted study, the social support from spouses was higher in married elderly individuals (27); in another study, it was found that the social support perceived by the elderly, friends and private people in the nursing home was lower than that of the elderly living in their own homes (28).

According to the elderly who received help from the family due to diabetes those who did not receive help from the family total HDFSS and empathetic, encouragement and participative support scores were found to be significantly higher. Baykal and Orak discussed that patients with diabetes who have received spousal and/or child help were found to have significance in family support (8). The family is an important source of support, particularly in the elderly, where health deterioration and associated physical and psychosocial problems can be overcome with minimal damage and may enable the elderly to adapt to the new situation (28). In our study, total HDFSS, empathetic, facilitative and participative support were found to be significantly higher than the support received from their spouses due to diabetes. Polat and Kahraman have found that social support of the elderly living with their spouses is higher (26). When the relationships within the family are further privatised , in other words, when the marital relationship is examined, spouses often get a different importance than the other sources of social support. The fact that spouses deal with each other, solve problems together and give mutual support to each other emotionally, financially and mentally is the most important factor in maintaining physical and psychosocial health of spouses (29). Total HDFSS, empathetic, encouragement and participative support scores of elderly with diabetes were found to be significantly higher in those who received help from their child. Children who are the support sources in old age and who have increased their role and importance have a positive effect on the physical and psychological health of the elderly; support from children also provides positive feelings such as respect for the elderly, high morale, life satisfaction and positive coping with stressful events (30).

5. CONCLUSIONS

It has been observed that the problem areas related to diabetes are low in elderly diabetic patients, but as the duration of diabetes, the type of treatment and complications increase, the emotional problems related to diabetes increase in the elderly. Family support has a great role in the management of some complications such as diabetes and hypoglycemia and neuropathy in the elderly. Families need to be informed that women experience more emotional problems with diabetes and need more family support. Since the elderly are more sensitive to emotional problems in the early years of diabetes, it is of great importance to address diabetes-specific problems. The help of family members, especially spouses and children, in protecting the health of the elderly shows the importance of the family in the management of diabetes. It is necessary to strengthen family ties and ensure that family members understand their role in controlling diabetes. The family members are told which

behaviors help the management of diabetes, and that they should have supportive behaviors rather than controlling behaviors. In order to understand and reach both sides in the management of diabetes, information should be collected from both patients and their family members, and periodic training programs should be implemented.

Limitations

Our study has some limitations. The limitations of this study are that elderly patients have low sociocultural levels and have difficulties in expressing themselves. Also, our research represents part of the universe. Therefore, the results cannot be generalized to all elderly diabetic patients.

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Conflict of interest

The authors declare no conflict of interest.

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Clinical and Experimental Health Sciences

An Assessment of Menstrual and Genital Hygiene Behaviours among Adolescent Females at Gazimağusa, Northern Cyprus

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ABSTRACT

Objective: Inadequate menstrual and genital hygiene behaviours are common and important problems for adolescent health. This study aims to determine menstrual and genital hygiene behaviours and the affecting factors among female students enrolled in high schools located in Gazimağusa, Northern Cyprus.

Methods: This school-based, cross-sectional, and descriptive study was conducted in three high schools in the Gazimağusa town borders in Northern Cyprus with 379 students. Data were collected through the Socio-demographic Form and the Genital Hygiene Behaviours Scale.

Results: The scale mean score was found 79,28±6,80 (min:47 / max: 112). The factors affecting menstrual and genital hygiene behaviours were found to be the type of schools the students were enrolled (X2: 14,771 / P: 0,001), the education level of the mothers (X2: 9,806 / P: 0,020), and the education level of the fathers (X2: 15,879 / P:0,001).

Conclusions: The participants of this study had an above-average level of right genital hygiene behaviours. Genital hygiene behaviours were found to be affected by the type of school, the education level of the mothers, and the education level of the fathers.

Keywords: Adolescents, behaviour, female, hygiene, menstruation

1. INTRODUCTION

Puberty is a key process of human development into adulthood, involving the most rapid physical growth the human undergoes except for prenatal and neonatal growth (1). Therefore, it is necessary to carefully investigate adolescents' reproductive health specific to adolescence and to organize services for these (2). These services become even more important when it is considered that adolescents consist of approximately one-fifth of the world population (1.2 billion) (3, 4). Reproductive health problems that require particular attention include anaemia, dysmenorrhea, urinary tract infections (such as bacterial vaginosis), sexually transmitted diseases (STD) and HIV, unwanted pregnancies, unhealthy miscarriages, birth-related injuries and death, and female genital mutilation (2,5,6). Another important health problem concerning the adolescence period is poor perineal and menstrual hygiene behaviours (1,3,6,7) because it is known that genital hygiene behaviours (GHB) and incorrect and inadequate hygiene practices in women disrupt the vaginal flora and cause many health problems (8). Besides, the development of menstrual and GHB at a young age through accurate information becomes an important attitude and behaviour for protecting women's health in the long term (9)

Factors that have effects on the formation of menstrual and GHB are reported to be gender perception, cultural norms, taboos, level of access to resources, parent effect, personal preferences, socio-economic factors, and education (1,3,6,10). On the other hand, the beginning of menstruation causes extra difficulty in terms of perineal hygiene for adolescents who tend to accept less support from their parents (3). The most frequently encountered inadequate menstrual and GHB include cleaning the genital area wrongly (from back to front), leaving the genital area moist after cleaning, using nonhygienic clothes in the menstrual period, wearing nylon textile fabric underwear, having a bath and washing hands in inadequate frequency, etc. (11-14). Genito-urinary infections threatening woman's health and becoming a silent epidemic every day are also closely associated

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with inadequate genital hygiene practices (15-17). Some girls' trying new practices disrupting the natural flora such as genital sprays, wet wipes, vaginal shower, powder, bath foam, etc. could cause vulvar contact dermatitis (3). When it is considered that practices about genital hygiene are learned at a young age, the identification of risk behaviours among young women is important in terms of taking precautions to improve genital hygiene. In this way, it could be possible to prevent many negative consequences that could emerge in the further life periods (7).

Teaching correct GHB is important in terms of preventing health problems; it also contributes to the early diagnosis and treatment by increasing individual awareness about potential changes (19). Despite this, current studies conducted in different countries of the world indicate that adolescent females have different levels of inadequate menstrual and GHB (12,14,20-25). In fact, in all periods of their life, all women have the right to learn menstrual and GHB and to access the necessary materials that could affect their genito-urinary health. Therefore, although it is not explicitly mentioned, menstrual and GHB are associated with the 3rd, 4th, 5th, 6th, and 8th goals of the Millennium Development Goals (17). In this regard, the GHB of adolescents should be investigated as a women's and children's health right, and support should be provided in light of the knowledge gained. The cultural and socio-economic environment where women live have effects on shaping genital hygiene behaviours (1,3,6,10). Therefore, researchers tried to report the current situation of genital hygiene behaviours in their own society (12,14,20-25). On the other hand, no studies in the literature were found to define genital hygiene behaviours of adolescent females in Northern Cyprus. This study aims to contribute to the literature about genital hygiene behaviours of adolescent females in Northern Cyprus.

Research Questions

- What are the genital hygiene behaviours of female students enrolled in schools located in Gazimağusa?
- Do genital hygiene behaviours of female students enrolled in schools located in Gazimağusa demonstrate differences according to their socio-demographic characteristics?

2. METHODS

2.1. Research Design and Sample

This school-based, cross-sectional and descriptive study was conducted between 02.12.2019 and 01.04.2020 in three high schools located in Gazimağusa, Northern Cyprus. The types of schools were public college, public (general) high school, and vocational high school. Public college students were accepted through an exam conducted nationwide. Unlike the other two schools, the education system of the school aimed to prepare students for universities in other countries, primarily England. As to public (general) high schools, they accepted students without exams, using point averages, and the majority of these students aimed at national universities and universities in Turkey. Vocational high schools did not require any prerequisites and accepted students who wanted to acquire a profession after high school. The reason for conducting the study in these schools was due to factors such as the recommendation of the Ministry of National Education, cooperation of the school administration for the study, and crowded classrooms. The universe of the study included a total of 482 female students who were enrolled in these schools when the study was conducted (Public college: 157/ public (general) high school 182/ vocational high school:143). No sampling was performed; the study aimed to access all the target population. However, 103 students who did not have parent's consent, who did not want to fill in the questionnaire despite having parent's consent, and who did not complete the questionnaire and/or who were not at school during the time data were collected were excluded from the study, and the study was completed with 379 participants who met the sampling criteria. Hence, approximately 78,6% of the target population (482) was accessed. The inclusion criteria were being enrolled in any one of the schools selected when the study was conducted, being a female, and having both parent and personal consent to participate in the study.

2.2. Data Collection Tools

Data were collected through the Socio-demographic Form and the Genital Hygiene Behaviours Scale. The Socio-demographic Form was developed by the researchers in line with the literature to collect data about the socio-demographic characteristics that might have effects on perineal hygiene (7,13,14,19). The form included 14 questions regarding the participants' demographic characteristics such as the type of school they were enrolled in, grade level, age, family structure, economic condition, etc. as well as support and source of knowledge about genital hygiene.

The Genital Hygiene Behaviours Scale (GHBS) is a measurement tool that aims to identify women's genital hygiene practices. Reliability and validity of the scale, which was developed by Karahan in Turkish in 2017, were performed with high school students. The scale is composed of 23 items and three sub-scales. The sub-scales include "General Hygiene Habits (first 12 items)", "Menstrual Hygiene" (13th to 20th items)", and "Abnormal Finding Awareness" (21st to 23rd items). The items are responded on a 5-point Likert Scale that ranged from "I strongly agree" to "I strongly disagree". Items 7, 14, 19, 20, and 23 are scored reversely. The scores to be obtained from the scale range between 23 and 115; higher scores indicate positive genital hygiene practices. The scale is a self-report scale, and it can be responded by students themselves in 10 to 15 minutes. Cronbach's Alpha value of the whole scale was found 0,80 (7). This study found Cronbach's alpha value of the whole scale as 0,76.

2.3. Data Collection Process

Collaboration was made with school administrations in the data collection phase. One week before the data were collected, the school administrations sent information and consent forms to parents and students. Data were obtained by self-report from students who gave informed consent to participate in the study during the time and place indicated by the psychological counseling unit of the schools.

2.4. Statistical Analyses

Data were analysed using Statistical Package for Social Sciences 24 software. The participating students' demographic characteristics were identified using frequency analysis. Descriptive statistics were utilized for the scores obtained from the GHBS. Normality distribution of the students' GHBS scores was analysed using the Kolmogorov-Smirnov test, and since the data did not distribute normally, the study used nonparametric hypotheses tests. Hence, the Mann-Whitney U test was utilized when the independent variable was composed of two groups and the Kruskal-Wallis H test was utilized when it was composed of more than two groups.

2.5. Ethical Considerations

Before the study was conducted, ethics committee approval was obtained from the Eastern Mediterranean University ethics committee (Date:21.10.2019 – ETK2019/23-12). Written permission was obtained from the Ministry of National Education (Date: 26.11.2019 – GOÖ.0.00-223/02-19/E.10085), and verbal approval was obtained from the school administrations. In addition, parents and students filled in the consent forms prepared in line with the Declarations of Helsinki.

3. RESULTS

Of all the participants, 68% were aged 14-16, 41,6% were enrolled in public (general) high schools, 81,0% had a nuclear family, 63,8% lived in a village or town, and 72,3% perceived their income equal to expenses. Besides, mothers of 40,1% and fathers of 42,4% were high school graduates.

This study investigated students' support factors and sources of knowledge about genital hygiene behaviours. The analyses showed that 90,2% of the students (n= 342) received support for genital hygiene practices. Support sources were indicated as their mother by 84,2 % (n=319), other female relatives by 22,2% (n= 84), friends by 9,2% (n=35), and nurses or teachers by 1,1 % (n=4) respectively. The ratio of the students who reportedly searched about genital hygiene was 98,9% (n=375), and the sources of research were indicated as their mother and other female relatives by 82,8% (n=314), internet by 56.5 % (n=214), friends by 15.8% (n=60), and lastly teachers or nurses by 1.8% (n=7).

Table 2 demonstrates students' GHBS total and sub-scale mean scores. The GHBS total mean score was found 79.28 ± 6.80 in this study.

Table 1. *Socio-demographic characteristics of the students (n=379)*

	(n)	(%)
Type of School		
Vocational High School	114	30,08
Public Collage	107	28,23
Public (General) High School	158	41,69
Grade Level		
9th Grade	97	25,59
10th Grade	101	26,65
11th Grade	102	26,91
12th Grade	79	20,84
Age Group ($\bar{x}$ *=15,83±1,20***)**		
14-16	261	68,87
17-19	118	31,13
Place of Living		
Village/Town	242	63,85
City	137	36,15
Education Level of the Mother		
Primary School	83	21,90
Secondary School	63	16,62
High School	152	40,11
University	81	21,37
Education Level of the Father		
Primary School	70	18,47
Secondary School	76	20,05
High School	161	42,48
University	72	19,00
Economic Condition of the Family		
Income less than expenses	19	5,01
Income equal to expenses	274	72,30
Income more than expenses	86	22,69
Family Type		
Nuclear Family	307	81,00
Extended Family	28	7,39
With one parent only	44	11,61

Comparison of the total mean scores of the GHBS according to the socio-demographic characteristics of the students are demonstrated in Table 3. It was determined that the type of school, education level of the mother and the father were effective on students' genital hygiene behaviours ($p<0,05$), but age, grade level, place of living, economic status of the family, and family type were not effective ($p>0,05$).

Table 2. *Students' Genital Hygiene Behaviors Scale scores*

	n	$\bar{x}$	s	Min	Max
General Hygiene Habits	379	43,99	4,75	23	60
Menstrual Hygiene Habits	379	27,08	2,92	17	40
Abnormal Finding Awareness	379	8,66	2,20	3	15
Genital Hygiene Behaviours Scale	379	79,28	6,80	47	112

Table 3. *Comparison of the Total Mean Scores of the Genital Hygiene Behavior Scale According to the Socio-Demographic Characteristics of the Students*

Variables		General Hygiene Habits Subdimension Score X ± SD	Menstrual Hygiene Habits Subdimension Score X ± SD	Abnormal Finding Awareness Subdimension Score X ± SD	Genital Hygiene Behaviours Scale Total Points X ± SD
Age Group	14-16	43,90±4,95	27,01±2,96	8,64±2,22	79,08±7,01
	17-19	44,18±4,31	27,22±2,83	8,73±2,15	79,74±6,32
		Z: – 0,1280 p: 898	Z: – 0,417 p: 0,676	Z: – 0,331 P: 0,741	Z: – 0,170 p: 0,865
Type of School	Vocational High School[1]	42.56 ±5.32	27,03±3,48	8,89±2,52	78,01±8,22
	Public College[2]	44,72±4,20	26,72±2,11	8,75±2,11	79,89±5,93
	Public High School[3]	44,53±4,47	27,35±2,94	8,45±1,99	79,80±6,11
		X²:14,771 **P: 0,001*** **Diff**:1-2,1-3	**X²**:1,611 p: 0,447	**X²**:4,530 p:0,104	**X²**:5,823 p: 0,054
Grade Level	9th Grade	43,54±4,81	26,99±3,12	8,49±2,14	78,44±6,90
	10th Grade	43,26±5,42	26,57±2,90	8,81±2,26	78,08±7,54
	11th Grade	44,62±4,76	27,48±2,68	8,65±2,10	80,54±6,41
	12th Grade	44,67±3,47	27,30±2,95	8,71±2,34	80,24±5,82
		X²: 4,285 p:0,232	X²: 3,325 p:0,344	X²: 1,187 p: 0,756	X²: 5,637 p: 0,131
Place of Living	Village/Town	44,09±4,57	27,16±2,93	8,60±2,09	79,45±6,60
	City	43,81±5,08	26,93±2,91	8,77±2,38	78,99±7,17
		Z:-0,497 p: 0,620	Z: – 0,473 P: 0,636	Z: – 0,936 p: 0,349	Z: – 0,998 p: 0,318
Education Level of the Mother	Primary School [1]	42,82±4,62	27,17±2,87	8,53±2,37	78,60±6,00
	Secondary School[2]	44,21±4,00	27,16±3,21	8,32±2,35	78,84±6,62
	High School[3]	44,30±4,83	26,91±2,80	8,95±2,05	79,62±6,79
	University[4]	44,44±5,16	27,22±3,01	8,54±2,14	79,70±7,74
		X²: 9,806 **p: 0,020*** **Diff**:1-3,1-4	X²: 1,312 p:0,726	X²: 4,805 p:0,187	X²: 7,214 p:0,065
Education Level of the Father	Primary School [1]	42,29±4,59	26,63±2,62	8,43±2,40	77,04±6,09
	Secondary School[2]	44,18±4,26	27,97±3,12	8,70±2,26	79,72±5,84
	High School[3]	44,39±4,55	27,07±2,92	8,84±1,96	80,01±6,57
	University[4]	44,54±5,52	26,57±2,83	8,47±2,44	79,39±8,42
		X²: 15,879 **p: 0,001*** **Diff**:1-2, 1-3,1-4	X²: 8,818 **p:0,032*** **Diff**: 1-2,2-4	X²: 1,536 p:0,674	X²: 16,364 **p: 0,001*** **Diff**:1-2,1-3,1-4
Economic Status of the Family	Income less than expenses	43,95±3,03	27,53±2,41	8,63±2,17	79,84±5,15
	Income equal to expenses	43,88±4,60	27,12±2,92	8,64±2,13	79,30±6,51
	Income more than expenses	44,34±5,51	26,84±3,04	8,77±2,43	79,10±8,00
		X²: 1,688 p: 0,430	X²: 1,331 p: 0,514	X²: 0,861 p: 0,650	X²: 0,282 p: 0,869
Family Type	Nuclear Family	44,17±4,66	26,85±2,85	8,67±2,24	79,36±6,83
	Extended Family	44,04±4,58	28,04±3,74	8,54±2,13	79,50±7,02
	With one parent only	42,68±5,37	28,05±2,59	8,68±1,93	78,64±6,58
		X²: 1,688 p: 0,430	X²: 1,331 p: 0,514	X²: 0,861 p: 0,650	X²: 0,282 p:0,869

*Z: Mann-Whitney U test, X2: Kruskal-Wallis H, Diff: Difference, *p<0,05*

4. DISCUSSION

The majority of adolescents' sources of knowledge about genital hygiene included parents (16, 20, 21, 24, 26,27), close friends, and media (28). In line with the literature, this study also found that students mostly consulted a woman in their family, particularly their mother, about menstrual and GHB. Receiving no support from fathers is considered to result from the traditional view, which indicates that generally parents having the same gender with their children deal with gender-specific care. The finding indicating low ratios of receiving information and consultation from health professionals is also parallel to the related literature (20,21, 23, 27, 29,30). This finding is considered to be the indicator of the lack of school nursing practices in the country as well as the failure of protective health services in accessing adolescents.

This study found the participating students' GHBS general mean score as 79.28. When it is considered that the scores to be obtained from the scale range between 23 and 115 and higher scores indicate right genital hygiene behaviours, the participants in this study are considered to have right hygiene behaviours. In their similar study, Göger and Tuncay (2021) reported the GHBS total mean score of female high school students staying in a hostel as 85.3 (31). In their study conducted with midwifery department students, Kartal et al. (2020) found the GHBS total score as 95.2 (32).. Another study conducted with women who received education in the field of health sciences reported the GHBS total scores of the first – and second-year students 93.77 and 95.16 respectively (33). A study conducted with female high school students in Ethiopia reported the hygiene behaviours ratio as 53.6%; another study conducted in the same country reported it 46.1% (34,35). This ratio was reported to be 63.3% in Indonesia (36). The findings obtained from this study are similar to the findings in the study conducted with high school students in Turkey, which might result from the fact that the two societies have a common culture and similar socio-demographic characteristics. On the other hand, students who received education in the health sciences, due to their age and education, received the highest scores in this study, which was an expected finding. When compared to the studies in Ethiopia and Indonesia, despite not being at the desired level, genital hygiene behaviours of female adolescents in Northern Cyprus were higher.

This study also investigated whether students' genital hygiene behaviours were affected by socio-demographic characteristics or not. Adaptation to menstrual periods and perineal hygiene are reported to be insufficient in the early periods of adolescence, but healthy menstrual and genital hygiene habits are reported to increase with the increase in age and experience (9,26,33,34,35). On the other hand, Göger and Tuncay (2021), like in this study, reported no difference between high school female students' age and genital hygiene behaviours (31). This might result from the fact that the students' age was close to each other.

Education and health are the primary development and improvement components of societies, and the relationship between them is known, continuous, and positively strong (37). The majority of the studies on GHB conducted with adolescents indicated that the students' hygiene behaviours were affected by the education level of mothers positively or negatively (25, 28, 31, 32, 34,38). On the other hand, some studies reported that the education level of the mother did not affect students' GHB (33,39). In line with the general literature knowledge, this study found that students with low mother education level had worse general hygiene habits. The most remarkable finding of this study is that the education level of fathers was low among students who had low scores in the GHBS general and general hygiene and menstrual hygiene sub-scales. A study conducted in Lebanon also reported a similar finding (38). Based on this study and literature examples, both parents' education levels were found to be the most important variable that affects students' GHB.

Education institutions have a fundamental purpose of producing and disseminating culture at different levels and transmitting the cultural heritage of society from generation to generation (40). Therefore, schools, where adolescents spend most of their time, affect students' health and behaviours (41). The literature includes contradictory results on the effects of students' menstrual hygiene behaviours (34, 38). This study found that the type of school affected students' genital hygiene behaviours. Hence, general hygiene behaviours of adolescents in technical high schools were poorer than other schools. There are no specific regulations and education on this issue in the schools where the study was conducted, and since no school nursing service was provided, this difference was considered to result from the profile of students who applied to these schools. The reason was that while students were accepted to the schools at public college status with exams, they were accepted to the general high schools with point averages. There was no prerequisite for being accepted to the technical high school; students who did not have a university plan and had low achievement scores applied to these schools to acquire a profession.

The difference between these student profiles is considered to affect the study results. The literature includes studies showing that healthy GHB increased with the increase in grade level as well as other studies showing no differences (31,34,38,42). This study found that, like in the age factor, the grade level did not affect genital hygiene behaviours.

Just like in education, income level and family structure are among factors affecting women's health status. Studies investigating adolescent females' GHB showed that adolescent females who had a nuclear family (43) and those who had high income had better GHB (9, 25, 44). However, this study found that both factors did not affect GHB.

The distance of women's place of living to service centres such as schools and hospitals and communication sources affect their social status and health (45). Some studies reported that genital hygiene behaviours of young women were poorer because they had low economic income and

education level, and they had problems about access to health institutions and hygiene products (9, 42). However, like in this study, there are some other studies that showed that the place of living did not affect women's genital hygiene habits (34, 43). As for Northern Cyprus, the biggest places of living are towns, and villages are close to town centres and are quite developed. Therefore, this study assumed that students who lived in villages or towns and those who lived in city centres had similar resources and thus had similar GHB.

This study contributed to the literature about GHB of females living in a region where the issue was not investigated much so far. Adolescent females' above-average knowledge on the issue indicates their vulnerability. The identification of high-risk groups is one of the most important responsibilities of protective health services. This aspect of the study contributed to protective health services. On the other hand, health professionals were found to have almost no contribution to the education and consultancy needs of adolescents about GHB, and education was found to be the most important factor affecting GHB. This finding indicates the need to integrate health services into education services through implementations like school nursing.

5. CONCLUSION

This study showed that the participants had above-average knowledge of right genital behaviours. Factors affecting GHB were found to be the type of school, education level of the mother, and education level of the father. Due to the clear effect of education on GHB, health professionals working in the field of community health are recommended to be included in the programs specific to the issue and then they should be provided with structured trainings for students, parents, and teachers. Researchers interested in the issue are recommended to conduct studies that evaluate students' urogenital symptoms and genital hygiene behaviours in tandem and randomized controlled studies that could assess the effect of structured training for parents, teachers and students.

Informed Consent

Written informed consent was obtained from the students and their parents.

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Statement of Conflict of interests

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Clinical and Experimental Health Sciences

Time Difference Between Onsets of Lateral and Medial Hamstring Muscles During Gait in Patients With Patellofemoral Pain: A Preliminary Study

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ABSTRACT

Objective: Early activation of lateral hamstrings (LH) relative to medial hamstrings (MH) has been thought to be the cause of abnormal knee abduction and external rotation of the tibia, which affects the orientation of patellar tendon and increases lateral patellofemoral compression. Therefore, early activation of LH relative to MH is considered to have a role in the patellofemoral pain (PFP). The aim of this study was to investigate the time difference between MH and LH onsets in patients with PFP during gait.

Methods: Thirteen patients with bilateral PFP (mean age 28.73±7.44 years) and 13 asymptomatic subjects (mean age 30.47±6.22 years) were recruited in the study. Gait analysis was performed using the ELITE system (BTS, Milano-Italy) with video cameras (TVC, BTS, Milano-Italy). Participants were requested to walk at a self-selected speed on a force platform, and EMG data were recorded from MH and LH muscles for 10 initial contacts by using TELEEMG (BTS, Milano-Italy). Time difference between the onsets of the MH and LH was calculated for each initial contact by using moving averaging method, then their mean was obtained for each participant.

Results: The time difference between onsets of MH and LH was – 26.9±22.2 ms for PFP subjects and – 11.2±14.2 ms for control subjects, and LH mainly became activated earlier compared to MH in most of the subjects in both groups. There was a statistically significant difference between the time differences of the groups (p=0.041).

Conclusion: Our findings suggest that LH displayed an earlier activation in subjects with PFP compared to control subjects during gait.

Keywords: Hamstrings, Surface EMG, Patellofemoral Pain, Gait., Time Difference

1. INTRODUCTION

Patellofemoral pain (PFP) is a common complaint experienced by physically active adults and adolescents (1), however its etiology has remained unclear (2). PFP is thought to be a result of abnormal patellar tracking and increased patellofemoral reaction forces that cause increased joint forces over the lateral patellar facets (1). Both altered knee and hip muscles activations were considered to be responsible for abnormal patellar tracking (2). Studies regarding activation timing on PFP have been mostly carried out on Vastus Medialis Obliques (VMO) and Vastus Lateralis (VL) muscles because of their crucial role in the patellofemoral kinematics (3). It was found that the relationship between timing of VMO and VL had changed in the patients with PFP (3). In addition, increased Gluteus Maximus activity (4) and delayed onset of the Gluteus Medius relative to the VMO during the weight bearing activities were reported (5,6). However, most of the studies focused on the contribution of knee extensor muscles to PFP and the knee flexor group muscles received less attention (7-9).

Although hamstring muscles are primarily related to the tibiofemoral joint mechanics, they are considered to have effect on the patellofemoral joint as well. Experiments carried out on the effect of hamstring contractions on the patellar stability have provided evidence supporting the claim. It has been shown that contraction of the hamstring muscles causes posterior translation and external rotation of tibia, which affects the orientation of the patellar tendon (10-11). In an in vitro study, Elias et al. (2011) found that loading the hamstrings increased the patellar flexion, lateral tilt and lateral shift by 1°, 0.5° and 0.2°, respectively. Total contact force also increased at each flexion angle by 5% (12). Si-hyun et al. (13) measured activity of the medial and lateral

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hamstring in standing position and suggested that dominant muscle contraction of lateral hamstring (LH), relative to medial hamstring (MH), may contribute to increased tibial rotation (13). As excessive tibial rotation is evident in patients with PFP clinically, this suggestion supports the clinical observations. In addition, it is generally agreed that an uneven onset of hamstrings can induce increased external tibial rotation with a preceded onset of LH in patients with PFP. To the authors' knowledge, there are only two published studies which directly investigated the relationship between the onsets of the LH and the MH in PFP (7,8). In one of these studies, the EMG activities of MH and LH hamstring muscles were assessed during voluntary isometric contraction in sitting position (7). According to the results of this study, the LH contracts earlier than the MH (7) compared to the control group. Dieter et al. (2014) investigated the muscle activation patterns of trained cyclists during cycling and they found significant difference between PFP and healthy groups in onset time of MH and LH muscles during cycling. Besides, they observed that LH activation occurred earlier than MH. Since PFP is a problem that aggravates mainly during dynamic activities, it is important to assess hamstring activity in dynamic activities. To this date, the study performed by Dieter et al. (2014) has been the only study investigating the activation onsets of MH and LH muscles during dynamic activity (8).

Therefore, we aim to investigate the time delay between the LH and MH in patients with PFP while they walk at a self-selected speed and compare them with healthy asymptomatic control subjects in order to elicit the role of hamstring muscles on the PFP. We hypothesized that patients with PFP would display greater time difference between MH and LH muscles, with the LH displaying an earlier activation than MH when compared to healthy control levels.

2. METHODS

The study was carried out at Gait Analysis Laboratory of Department of Orthopedics and Traumatology in University. This study was conducted in accordance with the rules of the Declaration of Helsinki. Written informed consent was obtained from each participant. The study was approved by the Ethics Committee of Hacettepe University (Approval number: GO14/646-31; Date:21.01.2015).

2.1. Subjects

Thirteen patients with bilateral PFP for the PFP group (8 females and 5 males; age: 30.46±6.22 years, height: 167.87±7.81 cm, weight: 67.87±13.4 kg, BMI: 23.84±2.84 kg/cm^2) and 13 asymptomatic, healthy subjects for the control group (10 females and 3 males; age: 28.73±7.43 years, height: 169.73±7.09 cm, weight: 67.46 ±14.31 kg, BMI: 23.15 ±3.31 kg/cm^2) were recruited in this study. As there was no available literature on the time delay between the onset of MH and LH during gait, we were unable to calculate a sample size. We decided to conduct this preliminary study with 13 participants in each group.

Patients with PFP were screened to rule out other knee pathologies, and radiologic examination consisting of AP, lateral, and tangential radiograms was performed.

The patients who met the following criteria were included in the patient group: [1] bilateral pain arising from the patellofemoral articulation; [2] a pain intensity level of at least 3/10 point according to the Numeric Analog Scale (NAS) experienced while performing at least two of the following functional activities commonly associated with PFP: ascending or descending stairs, squatting, prolonged sitting, or kneeling, [3] a history of pain lasting longer than 2 months (14,15), [4] (4) being between 18-40 years of age and [5] body mass index <25.

The exclusion criteria were: [1] a history of knee surgery, [2] a history of patellar instability, or [3] neurological conditions that would affect gait (14).

All patients had bilateral complaints and the most severely affected leg was chosen for assessment. The participants in the control group had no knee pathology, existing knee pain or effusion that would affect their gait. The leg to be tested was chosen randomly for this group. None of the subjects in either group had played sports professionally at any point in their life. Demographic data, standing Q angle (16) and anthropometric measurements were recorded for all participants. Self-administered Kujala patellofemoral pain scale was used by PFP patients to determine their knee functions (17).

2.2. Experimental Set-up and Procedure

Silver/silver chloride, pre-gelled surface EMG electrodes (Ambu Blue Sensor, Denmark) were used to record the EMG signal while walking. Skin preparation and electrode placement were performed according to Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) criteria. The skin under the electrodes was cleaned by a skin preparation gel (NuPrep, Do Weaver and Co, USA) until the electrical impedance of the skin was less than 5 KΩ by using an impedance meter (Noraxon USA, INC, impedance meter) (). For the electrode placement, the participants were positioned prone on the table with their knee slightly flexed (less than 90^o). The electrodes were placed at 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia while thigh in slight lateral rotation for LH (Biceps Femoris) muscles while they were placed at 50% on the line between the ischial tuberosity and the lateral epicondyle of the tibia while the thigh in slight lateral rotation for MH (Semitendinosus) muscle. Interelectrode distance was 20 mm between centers. A ground electrode was placed over the tuberositas tibia. Portable 8 channel TeleEMG (BTS, Milan, Italy) with built-in x10 amplifications, 10-450 Hz bandpass filter and 1000 Hz sampling rate were used to record EMG signals.

Six high-speed video cameras and 2 force platforms were synchronized with the surface EMG electrodes. The ELITE system (BTS, Milano, Italy) and video cameras (TVC, BTS, Milano, Italy) were used for gait analysis. Force platforms (Kistler Instruments, Winterthur, Switzerland) were buried in the middle of the walkway to record the ground reaction force, and detect the stance and swing phases used in the calculation of the onset of the initial contact (IC). Kinematic data were acquired and digitized with 100 Hz sampling rate.

Retroreflective spherical markers were placed according to Davis protocol over the bony landmarks to determine the joint centers and segment axis (Figure 1) (18). Next, the participants were invited to attend to a familiarization session to ensure their participation in the experiments since many wires would be placed on their bodies, which might result in discomfort while walking. The real recording sessions were initiated when the verbal start command was given. The participants were requested to walk at their self-selected speed on the 10 m long walkway. The procedure was repeated until the ICs of the evaluated side on the force platform were 10 records. The subjects were not informed of the existence of the force platform.

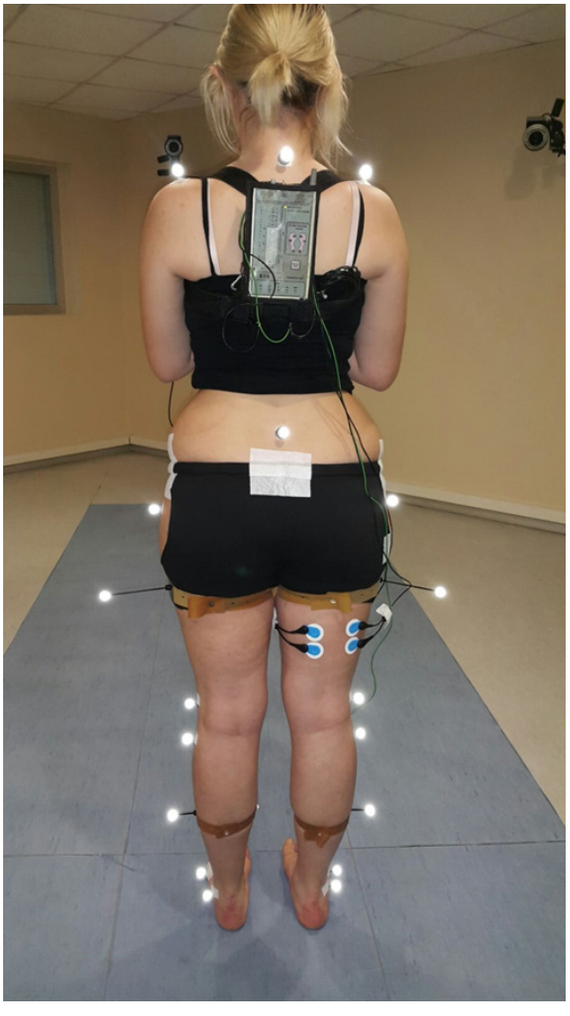

Figure 1. *The participant ready for EMG recording*

2.3. Data Processing

A custom prepared program written by MatLab (R2011) was used to detect the onsets of the LH and MH muscles. The raw EMG data for each epoch was full wave rectified and low pass filtered at 50 Hz (6^{th} order Butterworth Filter). Then, it was averaged over a window of 20 ms, moving with a step of one sample. The onset of the EMG was identified as the point at which the signal deviated by more than three times the standard deviation of the baseline for a minimum of 25 ms (Figure 2) (19, 20). In addition, all data were also visually checked to ensure the onset time and there was no signal noise, which was possibly caused by movement artefacts (20). Then, the time delay between LH and MH was calculated as the difference between the onsets of EMG signals from LH and MH. A negative value meant that the onset of the LH occurred before the onset of the MH muscle. The mean of the time delays for 10 contractions was calculated for each participant.

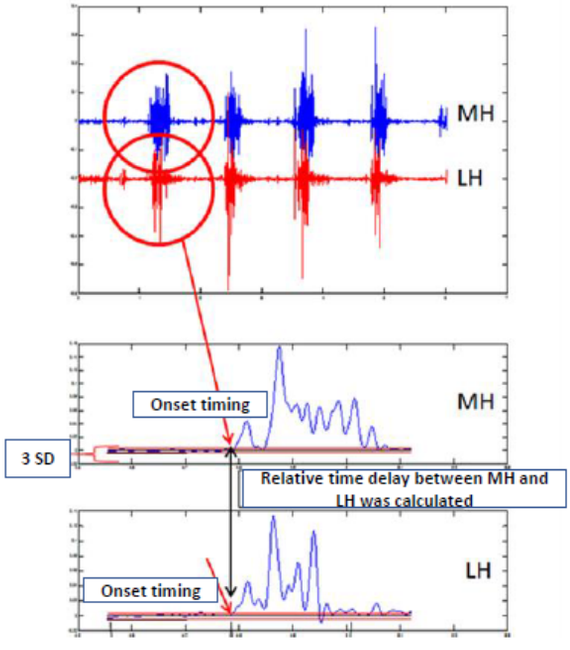

Figure 2. *Calculation of the relative time delay between MH and LH. Calculation of the onset times for MH and LH muscle.*

The following parameters were evaluated for the gait analysis: mean velocity (m/s), swing velocity (m/s) and kinematic evaluation of knee flexion angles at initial contact (IC) (°). Mean velocity (m/s) was assessed to ensure that any kinematic differences between groups were not due to differences in walking speed. Swing velocity was defined as the distance covered during the swing/swing duration and was assessed as hamstring's onsets were started just before initial contact. The knee flexion angle at IC (°) was evaluated as it might affect the onset of hamstring muscles.

2.4. Statistical Analysis

The data of this study were analyzed with the SPSS 20 for Windows (IBM, Armonk, New York). The normality was confirmed by Shapiro-Wilk testing with α set at 0.05. The independent sample-t test was used to determine the difference between the PFP and control groups. Statistical significance was set at $p< 0.05$.

3. RESULTS

There were no significant differences between the groups in age (p=0.494), height (p=0.499), weight (p=0.938) and BMI (p=0.605). There was no significant difference (p=0.614) in Q angle between the PFP (15.13°±1.59°) and control group (14.86°±1.24°). The mean Kujala patellofemoral pain score was found to be 81.2 (±12.1) in the PFP group.

It was observed that onset of the activity of the MH and LH muscles prior to initial contact varied between individuals. In the control group, the LH muscles of 10 participants contracted earlier than the MH muscles, while the opposite result was found in the remaining 3 participants. In the PFP group, the LH muscles contracted before the MH muscles in 12 individuals, and the MH muscles contracted before the LH muscles in 1 individual (Table 1).

Table 1. *Time difference between onsets of lateral and medial hamstring muscles. Time difference between LH and MH was computed by subtracting the onset time of MH from the onset time of LH (negative value means onset of LH started before the onset of the MH muscle)*

PFP LH-MH (ms)	Control LH-MH (ms)
-19.8	-27.1
-26.5	-11.7
-34.5	-5.4
-33.8	– 19.4
-16	-11.3
-23.7	15.9
20.1	-10.5
-69.1	-21.4
-12.2	2.2
-13.6	13.0
-22.6	-27.2
-37.4	-18
-60.7	-24.1

For the PFP group, the mean (±SD) time delay between the onsets of MH and LH was – 26.9 (±.22.2) ms whereas for the control group it was – 11.2 (±14.2) ms. There was statistically significant difference in the time delays between the groups (p=0.041).

There were no statistically significant differences between the groups for mean velocity, swing velocity and IC knee flexion degree (p=0.366, 0.198 and 0.964, respectively) (Table 2).

Table 2. *Comparison of the mean velocity, swing velocity and IC knee flexion degrees of the control and PFPS groups.*

	Control (n=15) mean±SD	PFPS (n=15) mean±SD	p value
Mean Velocity (m/s)	1.12 ± 0.10	1.17 ± 0.13	0.366
Swing Velocity (m/s)	2.79 ± 0.21	2.92 ± 0.29	0.198
IC knee flexion (º)	3.898 ± 4.86	3.942 ± 5.46	0.964

4. DISCUSSION

This case-control study reveals that there was statistically significant time delay difference between the activation onsets of the LH and MH in patients with PFP when compared to healthy subjects during gait.

While walking, the long head of the biceps femoris is activated in the last part of the swing phase, aiming to decelerate both hip flexion and knee extension, and it also prepares the lower limb for the IC, resulting in load absorption. In IC, plantar flexion occurs, controlled by eccentric contraction of tibialis anterior and increased flexion of the knee joint, followed by knee extension (21). At that stage during IC, the knee absorbs load and shows symptoms in case of any pathology caused either by an internal derangement or imbalance of the musculoskeletal dynamics. That is why we defined the IC as a reference point in time in our study and investigated which part of the hamstrings (medial or lateral) was activated first before this reference point. If LH or MH displays an altered onset time, it is expected to observe altered rotational moments affecting the knee kinematics and lead to the maltracking of the patella.

There is limited number of studies in the literature which primarily focused on investigating timing of hamstring muscles in PFP in comparison to asymptomatic subjects. In Patil et al.'s (2011) study, the subjects were asked to perform maximal voluntary isometric contraction while sitting on an adjustable chair with their hip at 90˚ flexion and their knee at 45˚ flexion. While the time delay between onset times of LH and MH was found as 62±73.1 ms in the control group, it was found 8.2±80.9 ms in the PFP group and, the results revealed that LH was activated earlier than MH (7). However, when subject is sitting, testing the hamstrings will reveal results about selective activation of these muscles since the hip is relatively well stabilized and all moments from other parts of the body are ignored . Since PFP is a problem that is aggravated mainly during dynamic activities, it is important to assess hamstring activation in dynamic activities.

In another study, Dieter et al. (8) investigated the muscle activation patterns of LH and MH muscles in cyclists with and without PFP. The results of this study showed that cyclists with PFP exhibited altered temporal characteristics in their muscle activation patterns compared to those without PFP. The average onset of LH muscle occurred 39±44 ms after MH muscle onset in control group, whereas the LH onset occurred 111±78 ms before MH onset in the PFP group.

According to our results, in both PFP and control groups, LH was activated earlier than MH: for the PFP group, LH was activated 26.9 (±22.2) ms earlier while in the control group, LH was activated 11.2 (±14.2) ms earlier than MH. However, the time difference between the onsets of LH and MH was statistically significant. Therefore, our results support previous studies (7,8).

One of the parameters which may affect EMG data and kinematic parameters is speed of walking. In our study, the participants were asked to walk at their self-selected speed since walking at comfortable speed improves repeatability of EMG data (2). In their systematic review, Barton et al. (2009) (22) concluded that velocity is one of the temporaspatial gait characteristics which shows trend towards reduction in PFP patients, and only in one study, significant reductions in knee flexion angle were found at IC in the sagittal plane (23). In our study, there were no statistically significant differences between the mean velocity, swing velocity of the gait and IC knee flexion angles of the groups.

Another parameter which may affect the results is the symptom severity. According to Crossley et al. (2004) (24), a Kujala score of 70 implies moderate pain and disability. In our study, the mean Kujala score of the PFP subjects was 81.2 which is higher than the threshold that Crossley et al. (2004) (24) stated. As the higher score means more disability, the time difference between the onsets could be higher if the participants with PFP were more severely affected.

To our knowledge, this is the first study that assessed the time difference between the onsets of MH and LH muscles during gait. However, this study has some limitations that should be highlighted. We could not perform priori sample size analysis as there was no data to use for calculation. To inform future studies, we performed post-hoc sample size estimation to find out how many participants would be required to adequately conduct a future study to detect differences between the groups in medial–lateral hamstring timing. This calculation was carried out with a significance level of 0.05, 80% power, and using the mean and standard deviations of the groups. The calculation showed an estimated sample size of 22 for each group. Further research with a larger sample size is therefore recommended.

5. CONCLUSION

This study was conducted to find out whether the time delay between the activation onsets of the MH and the LH differs in patients with PFP when compared to healthy subjects. Although there were large variations between the subjects, significant difference was found in the time delays between the groups. The results showed that the time difference between the onsets of MH and LH changed in PFP patients compared to the healthy participants and LH displayed an earlier activation than MH.

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Conflict of interest: There is no conflict of interest for this study.

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Clinical and Experimental Health Sciences

The Relationship Between Emotional Labor, Organizational Loyalty, and Turnover Intention in Nurses

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ABSTRACT

Objective: This study aimed to determine the relationship between nurses' perceptions of emotional labor, organizational loyalty, and their turnover intention.

Methods: This study was conducted in a private hospital in Ankara and two hundred and seven nurses participated. Correlation analysis was used to determine the relationships between variables. Multiple linear regression analysis was used to measure the effect of emotional labor and organizational loyalty on turnover intention. The data were obtained using the Emotional Labor Scale, the Organizational Loyalty Scale, the Turnover Intention Scale, and an information form developed by the researchers to inquire about the personal and professional characteristics of the nurses.

Results: Nurses' perceptions of organizational loyalty had a negative effect (-0.664) on their turnover intention. Twenty percent of the change in nurses' turnover intention is explained by organizational loyalty and the dimensions of emotional labor, namely, superficial acting, deep acting, and natural emotions.

Conclusion: It was found that the emotional labor and organizational loyalty perceptions of the nurses were at a moderate level, whereas their turnover intention was low. It was found that only organizational loyalty had a significant effect on nurses' turnover intention.

Keywords: Organizational loyalty, emotional labor, turnover intention, nurse

1. INTRODUCTION

Healthcare is part of a service sector where the highest rate of face-to-face interaction and communication occurs. Nurses, who make up the majority of healthcare workforce and are at the forefront (1), are those who play the most important role in patient care (2). The attitudes and behaviors expected from nurses, who are in charge of the complex structure of today's healthcare institutions, are that they perform their duties meticulously and successfully even when they are tired, stressed, and unhappy. Most of the nurses exhibit these behaviors during their professional life, without feeling a sense of obligation, due to the nature of the profession, which causes them to make extra effort physically, mentally, and emotionally. Humans are emotional beings; therefore, emotional labor is the most important element in this effort (3).

The concept of emotional labor, which is based on emotion, expresses the effort spent during the expression or control of emotions; and also it was defined as employees' displaying socially desired and expected emotions during their interactions and relationships in the workplace (4). In addition, emotional labor is the employees' effort to regulate and manage real emotions, such as the feeling obliged to hide the emotions they actually feel and fake the emotions they do not actually feel (5). During the emotion regulation process, individuals control the process with or without being aware of their emotions (6). The concept of emotional labor has been examined by some researchers and various dimensions of the concept have been revealed. Hochchild (1983) discussed the concept of emotional labor in two dimensions, namely surface acting and deep acting, according to the behaviors employees assume in expressing their emotions. Ashforth ve Humphrey (1993) examined the concept of emotional labor in three dimensions: surface behavior, deep behavior, and natural emotions (7). In other studies, there is a difference in naming the dimensions and in the number of sub-dimensions (8, 9). Surface acting is defined as individuals' effort to show emotions that they do not really feel during work, in other words they act (4, 10). Deep acting, on the other hand, is

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defined as the individuals' making efforts for the emotional expression they actually want to show (7). Individuals, mostly working in the service sector, act deeply in order to generate feelings and reactions appropriate for working conditions (11). The concept of natural emotions refers to employees' display of certain behaviors that they actually feel without any effort. In this respect, natural emotions are based on spontaneous and real emotions (7, 12). Patients and patient relatives are not the only people with whom nurses interact and communicate. Nurses have to communicate and interact with healthcare professionals and their colleagues. Nurses' relations with their colleagues are expected to be within the framework of the principles and rules of the institution. This is also related to the management of emotions, the perception of professional identity, and the sense of loyalty to the organization. Kang et al. (13) defined the concept of organizational loyalty as member behaviors that involve increasing the interests of the organization rather than self-interests, and showing behaviors appropriate to these interests. The feeling of loyalty, which is the last stage of the feeling of belonging to an organization/institution, is a psychological and behavioral trait. Loyalty means sincere and firm friendship, sincere devotion, control in feelings and emotions, non-betrayal, and conformity to the truth, and it also refers to being attached to an institution or organization as an ideal team member (14). The common point between commitment and loyalty is that both contain a sense of belonging to an institution or organization (15).

Nursing is a challenging profession because it involves strong emotional states. Emotionally intense jobs and intense interpersonal interactions involve emotional labor behaviors that can lead to burnout (16, 17). This also triggers the turnover intention, which is a result of an emotional exhaustion (18). Nurses' turnover intention has been the focus of many studies. Many factors, such as workload, burnout, decreased job satisfaction, and emotional labor, have been identified as potential factors and important predictors of nurses' turnover intention (19-21).

2. METHODS

2.1. Purpose and Design of The Research

The study was conducted to examine the relationship between emotional labor, organizational loyalty perceptions, and turnover intention in nurses. The study had a descriptive design for the purposes of determining the relations between variables and to make generalizations.

2.2. The Research Questions

The research questions generated in research purposes are as follows:

- Which level of nurses' emotional labor, organizational loyalty, and turnover intentions?
- Is there a relationship between nurses' emotional labor, organizational loyalty and turnover intentions?
- Have any affect nurses' perceptions of emotional labor on turnover intentions?
- Have any affect nurses' perceptions of organizational loyalty on turnover intentions?

2.3. Study Population and Sampling

This research was conducted in a private hospital in Ankara. In the study, no sample selection was made, and 376 nurses working in the hospital constituted the population of the study. Nurses who worked in the hospital for at least one year were included in the study. One hundred and twenty-four nurses with less than one year of experience were not included in the study. Data were collected between April and June 2020. The participation was on voluntary basis of the questionnaires distributed to 250 nurses, 207 were eligible for examination. Forty-three questionnaires were not filled partly or completely due to the increasing workload of nurses because of the COVID-19 pandemic.

2.4. Data Collection Tools

The data were obtained using the Emotional Labor Scale, the Organizational Loyalty Scale, the Turnover Intention Scale, and an information form developed by the researchers to inquire about the personal and professional characteristics of the nurses.

Information Form: A form consisting of 11 items was created in order to determine the socio-demographic characteristics of the nurses.

Emotional Labor Scale: The Emotional Labor Scale developed by Diefendorff, Croyle, and Grosserand (2005) was used to measure the nurses' emotional labor perception (22). It was adapted to Turkish by Basım and Beğenirbaş in 2012 (23). It consists of 13 statements in three dimensions: surface acting (6 items), deep acting (4 items), and natural emotions (3 items). The items in the scale are of five-point Likert type (1 = Never, 5 = Always): "I act in order to be able to deal with customers appropriately", "I exhibit emotions to my customers different than I really feel", and "The emotions I show to the customers arise spontaneously". Basım and Beğenirbaş (2012) reported the Cronbach Alpha coefficient of the scale as .80. They also stated that the scale was valid and reliable. In this study, the Cronbach Alpha reliability coefficient of the scale was calculated as .86.

Organizational Loyalty Scale: In order to measure the organizational loyalty perceptions of the employees, Uygur and Koç used the Organizational Loyalty Scale in their 2010 study (15). The scale consists of 14 statements. The scale includes 5-point Likert type items (1 = I don't agree at all, 5 = I totally agree). The scale was later used by Aşkın (2014). The Cronbach Alpha coefficient of the scale was reported by

Aşkın (24) as .89. In this study, the Cronbach Alpha reliability coefficient of the scale was calculated as .87.

Turnover Intention Scale: The Turnover Intention Scale developed by Mobley, Horner, and Hollingsworth (25) was used to measure the level of employee turnover intention. The scale has a total of three 5-point Likert type items (1 = Strongly disagree, 5 = Strongly agree). The scale was taken from the study conducted by Örücü and Özafşarlıoğlu in 2013 (26). They found the Cronbach Alpha coefficient of the scale as .90. They also stated that the scale was valid and reliable. In this study, the Cronbach Alpha reliability coefficient of the scale was calculated as .92.

2.5. Data Analysis

In this study, frequency, percentage, mean, and standard deviation values (as descriptive statistics) were used in order to determine the levels of emotional labor, organizational loyalty, and turnover intention. Correlation analysis was used to determine the relationships between variables. Multiple linear regression analysis was used to measure the effect of emotional labor and organizational loyalty on turnover intention.

2.6. Ethical Considerations

Approval for the study was obtained from the Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (Decision No: 2020/004 and #2020001). Written permission was obtained from the hospital administrations where the study was conducted. The nurses invited to the study were informed about the study, and those who gave consent and volunteered included in the study. The identity information of the nurses was not written on the data collection forms.

3. RESULTS

It was found that 75.4 of the nurses participating in the study were female, 71% were single, 78.3% were health vocational high school graduates, 37.2% were service nurses, 58.9% were between the ages of 21 and 30 years, 70.5% of them had less income than their expenses, 37.2% were employed in the intensive care unit, 64.7% had less than 5 years of professional tenure, 79.2% had less than 5 years of institutional tenure, 60.4% of them worked on 12-h shifts, and 79.2% of the nurses had no children (Table 1).

Table 1. *Nurses' socio-demographic information (n=207)*

Socio-Demographic Information	Frequency	Percentage	Socio-Demographic Information	Frequency	Percentage
Sex			***Marital Status***		
Female	156	75.4	Married	60	29.0
Male	51	24.6	Single	147	71.0
Education Status			***Responsibility***		
Vocational Health High School	162	78.3	Service Nurse	77	37.2
Associate Degree	27	13.0	ICU Nurse	76	36.7
University Degree	17	8.2	Nurse-in-Charge	19	9.2
Graduate Degree	1	0.5	Other	35	16.9
Age Group			***Income Level***		
<20 years	58	28.0	Income less than expense	146	70.5
21-30 years	122	58.9	Income equals Expense	49	23.7
>31 years	27	13.1	Income more than expense	12	5.8
Unit Employed			***Duration of Professional Tenure***		
ER	8	3.9	< 5 years	134	64.7
OR	19	9.2	5-10 years	44	21.3
Surgery	41	19.8	11-15 years	18	8.7
Internal Medicine	42	20.3	>16 years	11	5.3
Polyclinics	10	4.8	***Duration of Institutional Tenure***		
ICU	77	37.2	< 5 years	164	79.2
Other	20	4.8	5-10 years	36	17.4
Shift Type			11-15 years	7	3.4
Always Day Shift	65	31.4	>16 years	-	-
Always Night Shift	13	6.3	***The number of Children***		
Rotating 12-h Shifts	125	60.4	None	163	78.7
Rotating 8-h Shifts	3	1.4	1	22	10.7
8-h Day Shift; 24-h Night Shift	1	0.5	2	19	9.2
			>3	3	1.4

In interpreting the mean scores of the employees, the studies in the literature were reviewed and an interpretation was made based on this review (Soh et al., 2010: 549; Akbolat et al., 2014: 89; Çankaya, 2017: 277). Accordingly, the values between 1.00 and 2.33 in the mean scores were considered as "low level participation"; values between 2.34 and 3.66 were considered as "medium level participation"; and values between 3.67 and 5.00 were considered as "high level of participation". In line with this information, it was determined that the emotional labor and organizational loyalty perceptions of the nurses were at a medium level. When the dimensions of the Emotional Labor Scale were examined, it was seen that the results differed between dimensions. Nurses' surface acting perceptions were low, deep acting perceptions were medium, and natural emotion perceptions were high. On the other hand, it was found that the nurses' turnover intention was at a low level (Table 2).

Table 2. *Min-max, mean and standard deviation and correlation values*

Scales	Min-Max Values in the Study	Mean ± Standard Deviation	Scale Min-Max Values
Emotional Labor Scale	1.00-5.00	3.52±0.83	1.00-5.00
Surface Acting Domain	1.00-5.00	2.19±1.21	1.00-5.00
Deep Acting Domain	1.00-5.00	3.33±1.23	1.00-5.00
Natural Emotions Domain	1.00-5.00	4.22±0.90	1.00-5.00
Organizational Loyalty Scale	1.00-5.00	3.57±0.87	1.00-5.00
Turnover Intention Scale	1.00-5.00	1.96±1.10	1.00-5.00

The relationships of the variables with each other and the direction and degree of these relationships were examined by the Pearson correlation analysis. Pearson correlation analysis results are shown in Table 3.

Table 3. *Correlation analysis regarding the variables*

Scales	1	2	3	4	5
Surface Acting	1				
Deep Acting	0.380**	1			
Natural Emotions	-0.089	0.312**	1		
Organizational Loyalty Scale	0.337**	0.310**	0.201**	1	
Turnover Intention Scale	-0.039	-0.035	0.023	-0.443**	1

Organizational loyalty had a weak positive correlation with surface acting (0.337) and deep acting (0.310). On the other hand, organizational loyalty had a weak positive and significant relationship with natural emotions (0.201). There was no significant relationship between the dimensions of emotional labor and turnover intention. Finally, a weak negative significant relationship was found between organizational loyalty and turnover intention (-0.443) (Table 3).

Multiple linear regression analysis was conducted to examine the effects of emotional labor and organizational loyalty perceptions of the nurses on their turnover intention. Analysis results are presented in Table 4.

According to the analysis results, nurses' perceptions of organizational loyalty had a negative effect (-0.664) on their turnover intention. Finally, it can be said that 20% of the change in nurses' turnover intention is explained by organizational loyalty and surface acting, deep acting, and natural emotions (Table 4).

Table 4. *Multiple linear regression analysis*

Variables	Unstandardized coefficients					95% confidence interval	
	B	Std. Error	*β*	t	p	Min Limit	Max Limit
Coefficient	3.286	0.400	-	8.211	0.000	2.497	4.075
Surface Acting	0.124	0.065	0.137	1.906	0.058	-0.004	0.253
Deep Acting	0.031	0.065	0.035	0.481	0.631	-0.097	0.159
Natural Emotions	0.159	0.083	0.130	1.912	0.057	-0.005	0.322
Organizational Loyalty	-0.664	0.086	-0.526	-7.702	0.00**	-0.833	-0.494

3.1. Limitations of the Study

The results obtained in the present study are limited to the views of the nurses working in the private hospital where the study was conducted in Ankara, and therefore, they are not generalizable to all nurses. Furthermore, the gap in the literature regarding the concept of organizational loyalty in nurses has constrained our ability to compare our research results with those of other studies. This study may be considered as a stepping stone in studying the relationship between organizational loyalty and emotional labor and its effect on nurses' turnover intention.

4. DISCUSSION

The present study was conducted to examine nurses' emotional labor, organizational loyalty, and turnover intention, and it was found that the perceptions of nurses' emotional labor and organizational loyalty were at a moderate level. On the other hand, it was found that the nurses' turnover intention rate was low. In a similar study, the relationships between emotional labor, burnout, and turnover intention in nurses in six different hospitals in Korea were investigated, and it was reported that emotional labor was associated with turnover intention; and, burnout played a mediating role in this outcome (18). Considering the effect of emotional labor on turnover intention, it can be predicted that the sense of organizational loyalty is also low in these individuals.

An analysis of the emotional labor scale sub-dimension scores of the nurses showed that the nurses' perception of the surface acting (2.19 ± 1.21) was low, deep acting (3.33 ± 1.23) was moderate, and that of natural emotions (4,22 ± 0.90) was high. Therefore, it may be stated that the feelings nurses experience during patient care and treatment are natural feelings, and that nurses sincerely share the pain and joy of patients during care and treatment because nurses are prone to emotional labor behavior due to the nature of the profession. The fact that nurses are more successful in exhibiting natural and sincere behaviors affects them positively in emotional terms. In this case, nurses are expected to have a higher motivation and organizational loyalty with low turnover intention.

In a similar study by Özkol Kılınç et al. (27), nurses received a mean score of 2.80 ± 0.68 from the emotional labor scale. Among the scale sub-dimensions, they received the highest score from deep acting (3.29 ± 0.88). Deep acting, which is an effort to harmonize the feelings that nurses have to show to their patients with their real emotions, may cause harmful consequences for various aspects of psychological well-being in nurses (20). It can be said that emotional disharmony experienced in this situation may cause high emotional exhaustion, low job satisfaction, and high turnover intention (20, 21).

Baksi and Edeer (28) found that the status of loving the profession ($\beta = 0.185$, $p < 0.05$) was a significant predictor of the deep acting sub-dimension of emotional labor in nurses working in an intensive care unit. In a study conducted in nurses working in an intensive care unit, it was stated that emotional labor refers to nurses' actions used to maintain order and encourage more positive interpersonal interactions (29). In this case, it can be said that the emotional labor exerted is related to the effort to carry out the duties effectively, resulting from organizational loyalty. In general, it is possible to talk about the positive effect of such an effort on reducing the nurses' turnover intention.

The ever-increasing number of confirmed and suspected cases and heavy workload in the COVID-19 process puts nursing services under intense pressure (30). Yang et al. (2021) report that there are studies showing that Covid-19 increases the intention to leave (31). For example, a cross-sectional survey conducted among front-line nurses in the Philippines revealed that fear of COVID-19 enhanced turnover intention (32). Similarly, the perceived threat of COVID-19 increased turnover intention among Pakistani nurses (33).

As the pandemic continues, an important consideration is that frontline nurses work in a specific work environment, facing a heavy workload while combating a highly contagious disease (34-36). Guixia and Hui (37) found that the incidence of nurses' burnout in COVID-19 period was high, which was correlated with anxiety and depression. The mental health problems of nurse should not be underestimated. Both managers and nurses themselves should pay attention to the burnout. Nurses with symptoms of anxiety and shorter working time are the focus of attention and intervention.

According to the results of the multiple linear regression analysis, it was found that the only significant effect on the nurses' turnover intention was organizational loyalty. Nurses' perceptions of organizational loyalty have an expected negative effect (-0.664) on their turnover intention. Çınaroğlu et al.(38) found that the most important factor determining the level of loyalty in nurses is job satisfaction. Job satisfaction in work environment increases organizational loyalty, and decreases turnover intention.

Twenty percent of the change in nurses' turnover intention was explained by organizational loyalty, surface acting, deep acting, and natural emotions. Work overloads, high performance expectations, and emotional incompatibilities in relationships with patients cause nurses to show more emotional labor (39). This situation reduces the sense of organizational loyalty and negatively affects turnover intention. However, more evidence is needed on this result. Discussing the relationship between emotional labor factor and organizational loyalty will clarify the effect of emotional labor on nurses' turnover intention.

5. CONCLUSION

In this study, which was conducted to examine the effect of nurses' perceptions of emotional labor and organizational loyalty on turnover intentions, the perceptions of nurses' emotional labor and organizational loyalty were first examined. Accordingly, it was found that the emotional labor and organizational loyalty perceptions of the nurses were at a moderate level. On the other hand, it was found that the nurses' turnover intention was low. According to the results of multiple linear regression analysis, it was determined that only organizational loyalty had a significant effect on nurses' turnover intention. According to the results of the research, organizational loyalty perceptions of the nurses had a negative effect (-0.664) on their turnover intention. Twenty percent of the change in nurses' turnover intention was explained by organizational loyalty and superficial acting, deep acting, and natural emotions.

Guidance should be offered via trainings that will enable nurses to recognize their emotional state and its effects on patient care and job performance. Strategies should be developed to increase the sense of organizational loyalty that may affect the delivery of nursing care and services. It is thought that this will affect the performance of health institutions positively.

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Clinical and Experimental Health Sciences

Evaluation of Forensic Medical Cases During COVID-19 Pandemic

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ABSTRACT

Objective: Investigating the effects of the coronavirus disease pandemic on forensic medical cases admitted to emergency department (ED).

Methods: This was a retrospective study conducted between March and August 2019 (prepandemic period), and March and August 2020 (pandemic period). All the patients admitted to the ED that required a forensic medical examination were investigated.

Results: A total of 4527 forensic cases were investigated (prepandemic period: 2937, pandemic period: 1590). There was a male predominance among the patients (prepandemic period: 62.1%, pandemic period: 67.7%). During both periods, the most common forensic complaints were the same, and assaults, motor vehicle accidents, and penetrating injuries were in the top three, respectively. During pandemic number of motor vehicle accidents decreased significantly ($p < 0.001$); on the other hand number of suicide attempts did not change ($p= 0.83$).

Conclusion: When compared to the prepandemic period, the number of forensic cases decreased by half during the pandemic period. Number of motor vehicle accidents significantly decreased during the pandemic, which might have been a consequence of the stay-at-home orders. There was no increase in the in the number of suicide attempts; however, the psychological effects of the pandemic can be long-lasting and might lead to increases in rate of suicide attempts in the long-run.

Keywords: Forensic, Pandemic, COVID-19, Motor vehicle collision, Suicide

1. INTRODUCTION

With the declaration of the coronavirus disease 2019 (COVID-19) outbreak as a pandemic by the World Health Organization (WHO) to prevent the rapid spread of the disease, officials advised people to stay at home and governments imposed a series of lockdowns, wherein social gatherings were limited, travel became difficult and non-essential businesses closed for several weeks (1). All of these life-style modifications have caused significant psychological and social effects on society.

Studies have indicated that the pandemic led to the exacerbation or development of psychiatric disorders and an increased rate of suicide attempts that thought to be the result of anxiety, uncertainty, social isolation, chronic stress, economic difficulties and fear of contagion (2). On the other hand, as a consequence of stay-at-home orders and social distancing, the overall trauma admissions, especially for motor vehicle collisions, have decreased significantly (3). Pandemic-related modifications in the social structure have also affected criminal activity (4). Miyar et al. demonstrated a decrease in crimes related to violence, and assault and battery, however organized crimes remained steady (5).

This study aimed to investigate the effects of the pandemic on forensic medical events. The distribution of forensic patients admitted to the emergency department (ED) during the pandemic and pre-pandemic periods, and their differences were analyzed.

2. METHODS

The study was conducted with the approval of Keçiören Training and Research Hospital Clinical Studies Ethical Committee with file number 2012-KAEK-15/2214 at 12.01.2021 in a third degree hospital caring for pandemic patient. Files of the patients who had forensic medical examination records in the hospital data registration system between March and August 2020 (pandemic period), and March and August 2019 (pre-pandemic period) were

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retrospectively investigated. All of the patients who required a forensic examination for any reason admitted to the adult ED were included in this study.

Files with forensic records in the hospital system could be accessed independently of the diagnosis. After the forensic files were determined, ICD codes were checked and there were records with different ICD codes for similar clinical conditions. In order to make the analysis of the data more accurate, the ICD codes describing similar clinical conditions were re-coded according to the forensic complaint. Files with missing data were excluded. Variables such as demographic findings, forensic complaints at admission and ED outcomes of the patients were examined.

2.1. Statistical Analyses

The statistical analysis was performed using IBM SPSS Statistics for Windows 22.0 (IBM Corp. Armonk, NY, USA). Continuous variables were described in terms of the median and interquartile range (IQR) (25%–75%) after assessing distribution of normality. The categorical variables were defined as numbers and frequencies. To determine the differences between the groups Mann-Whitney U test and chi square tests were used. The results were also represented in a graph. Statistically, p level less than 0.05 was considered as significant.

3. RESULTS

The number of patients with forensic complaints investigated was 4527. Applications made during the pre-pandemic period was nearly two times more than the applications at the pandemic period (n = 2937 and n = 1590, respectively). Total number of patients admitted to ED during pre-pandemic were 155381 and forensic cases were 1,89 percent of all; during pandemic number of total ED admissions were just 61054 but forensic cases were 2,6 percent of total (Table 1). During both periods, the number of forensic cases had the tendency to increase during summer. The number of cases were significantly decreased during the early pandemic period (Figure 1).

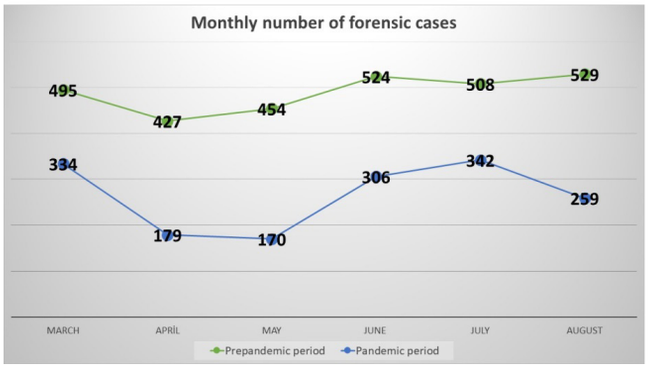

Figure 1. *Monthly number of forensic cases at prepandemic period (2019) and pandemic period (2020)*

The median age of the forensic patients admitted to the ED during the pre-pandemic period was 28 (IQR: 20–40) which was 30 during pandemic (IQR: 22–41, P < 0.001). When gender distribution was investigated, it was shown that the number of female forensic patients decreased significantly during the pandemic period (P < 0.001). The majority of the patients were Turkish citizens during all study periods (P = 0.09; Table 1).

Table 1. *Characteristics of forensic cases admitted to emergency department.*

	Prepandemic period (n=2937)	Pandemic period (n=1590)	P value
Total number of emergency department admission	155381	61054	
Percentage of forensic cases	%1,89	%2,6	
Age	28 (IQR 20 – 40)	30 (IQR 22 – 41)	**<0.001**
Gender			**<0.001**
Female	1113 (37.9%)	513 (32.3%)	
Male	1824 (62.1%)	1077 (67.7%)	
Nationalities			0.09
Turkish Republic	2860 (97.4%)	1534 (96.5%)	
Others	77 (2.6%)	56 (3.5%)	

**Variables were defined as median (ınter quartile range 25-75) and number (percentages in column).*

The complaints that requires forensic medical examination were suicide attempts, motor vehicle accidents, assaults, intoxications, penetrating injuries, gunshot wounds, falling from heights, drug abuse, burnings, animal bites, and electrical shocks. During both periods, the most common forensic complaints were the same. Assaults, motor vehicle accidents, and penetrating injuries were in the top three, respectively. When the subgroups were analyzed, it was shown that there was a significant decrease in the number of motor vehicle accidents during the pandemic period (P < 0.001). While comparing the severity of the clinical situations of the forensic cases, it was shown that both the percentage of life threatening conditions and the percentage of patients who could not be treated with simple medical interventions were increased at the pandemic period (P = 0.003 and P < 0.001, respectively). Correlated with this data, the number of patients who transferred to another center because of intensive care unit necessity increased during the pandemic period. However, in general, more than 90% of the patients were discharged from the ED during both periods. (Table 2).

When patients with suicide attempt were examined further, there was not a significant increase in the number of suicide attempts during pandemic period. Although there was a general male predominance among the forensic patients, the number of female patients who had attempted suicide was nearly two times higher. The majority of the suicide

attempts were drug-related and the most commonly used drugs for suicidal intervention were paracetamol, non-steroid antiinflammatory drugs, antibiotics, antipsychotics, and multi-drug combinations (Table 3).

Table 2. *Distribution of forensic complaints upon admission, severity of the clinical situation and outcomes at emergency department.*

	Prepandemic period (n=2937)	Pandemic period (n=1590)	P value
Complaints			<0.008
Assault	1135 (38.6%)	635 (39.9%)	0.39
Motor vehicle	834 (28.4%)	380 (23.9%)	**<0.001**
accident	285 (9.7%)	150 (9.4%)	0.76
Penetrating injuries	228 (7.8%)	133 (8.4)	0.83
Suicide attempt	455 (15.5%)	292 (18.4%)	
Others			
Life-threatening situation	84 (2.9%)	72 (4.5%)	**=0.003**
Yes	2853 (97.1%)	1518 (95.5%)	
No			
Be cured with simple medical intervention	2577 (87.7%)	1297 (81.6%)	**<0.001**
Yes	360 (12.3%)	293 (18.4%)	
No			
Outcome at ED			
Discharged at ED	2708 (92.2%)	1459 (91.8%)	
Hospital admission	72 (2.5%)	14 (0.9%)	
ICU admission	21 (0.7%)	7 (0.4)	
Transferred to other	42 (1.4%)	85 (5.3%)	
centers	6 (0.2%)	1 (0.1%)	
Death at ED	88 (3%)	24 (1.5%)	
Unauthorized leave			

** Variables were defined as number (percentages in column).** Abb: ED: emergency department, ICU: intensive care unit*

Table 3. *Characteristics of forensic cases admitted due to suicide attempt*

	Prepandemic period (n=228)	Pandemic period (n=133)	P value
Age	29.50 (IQR 23 – 37)	27 (IQR 22 – 37)	0.44
Gender			0.92
Female	152 (66.7%)	93 (69.9%)	
Male	76 (33.3%)	40 (30.1%)	
Drug related suicide attempt	200 (87.7% of all)	99 (74.4% of all)	
Commonly used drugs for suicidal interventions	24 (12%)	5 (5.1%)	
	23 (11.5%)	16 (16.2%)	
Paracetamol	16 (8%)	7 (7.1%)	
NSAID	54 (%27)	11 (11.1%)	
Antibiotics	38 (19%)	26 (26.3%)	
Antipsychotics			
Multi-drug combinations			

**Abb: NSAID: non-steroid anti-inflammatory drug*

4. DISCUSSION

This study demonstrated that comparing with the pre-pandemic period; during the pandemic total number of forensic cases decreased nearly to half; but on the other hand ratio of forensic cases to total ED admissions were increased. Although the top three forensic complaints, which comprised assaults, motor vehicle accidents, and penetrating injuries, were the same during both periods, there was a significant decrease in the number of motor vehicle accidents during the pandemic. On the other hand, there was no increase in the number of suicide attempts, which was contrary to expectations.

After the announcement of the pandemic the number of ED admissions showed a sharp decrease with the impact of many factors, such as curfews and the fear of viral contamination (6). Şan et al. demonstrated that comparing to the pre-pandemic period; additionally to other medical conditions, there has been a significant decrease also in forensic events, such as suicide attempts (25.7%) and traffic accidents (47.7%) during the pandemic (7). Similarly, in the current study, the number of forensic medical admissions during the pandemic were just nearly half that of the previous year. Although there seems to be a proportionally increase in forensic cases during pandemic, this might because of people had to apply to the ED in forensic medical events, on the other hand unnecessary green zone admissions, an important determinant of total ED admissions, had decreased significantly during pandemic (6). For this reason it should be more accurate to analyze the forensic case groups among themselves, rather than ratios.

Current studies have reported a male predominance in forensic medical patients (8, 9). In this study, it was observed that this difference in favor of men became more pronounced during the pandemic period. This might have been a consequence of the behavioral and social factors of the pandemic, which have different impacts between the genders.

When the impact of the pandemic on crime rates was investigated, it was observed that despite a marked decline in general, in the number of homicides remained unchanged and the incidence of domestic violence has increased (10). Assaults and penetrating injuries (stabbing) also constituted an important part of the forensic events in this study. One reason for the lower rate of females in the forensic medical cases might have been that the female victims of domestic violence may not have been able to seek medical help.

During the COVID-19 pandemic, overall trauma admissions, especially motor vehicle collisions were significantly decreased (11). When the subgroups were analyzed, our results also showed a significant decrease in only the number of motor vehicle accidents. Stay-at-home orders and so fewer drivers on the road might be the most important factors contributing this decrease (12). Another important factor might have been the reduction in alcohol-impaired driving. Closure of bars and nightclubs aimed to maintain social distancing, prompted people to consume alcohol at home

instead, and thus reduced the incidence of alcohol-related vehicle collisions (12).

In addition to its effects on physical health, the pandemic has resulted in many psychological disorders. Pandemic caused an increase at the prevalence of anxiety, stress and depression in society (13). At a study from Turkey, authors demonstrated that being female was a risk factor for pandemic-associated psychological disorders (14). Stress-related psychiatric conditions are associated with suicidal behaviors (2). Although suicide attempts were higher among the women in this study, there was no significant increase in the number of suicide attempts when compared to the pre-pandemic period. However, the mental health consequences of the pandemic are likely to present for a long time and a peak in suicide attempts might be seen later than during the actual pandemic (2, 15).

Limitations

First limitation of this study was, as a consequence of its retrospective design, it could not be possible to obtain the details of the examination findings and so understanding the severity of the patients and the types of injuries clearly. Second, external validity could not be determined because this was a single-centered study.

5. CONCLUSION

In conclusion, when compared to the pre-pandemic period, the number of forensic cases decreased by half during the pandemic period. The most common forensic complaints were assaults, motor vehicle collisions, and penetrating injuries, respectively. There was a significant decrease in the number of motor vehicle accidents during the pandemic period, which might have been a consequence of the stay-at-home orders. Contrary to expectations, there was no increase in the in the number of suicide attempts. However, the psychological effects of the pandemic can be long-lasting and might lead to increases in the rate of suicide attempts in the long-run.

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Conflict of interest

The Authors declare that there is no conflict of interest

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Clinical and Experimental Health Sciences

Factors Associated with Nurses' Attitudes Towards Evidence-Based Practice in Turkey

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ABSTRACT

Objective: Nurses' attitudes related to Evidence-Based Practices (EBP) have been widely studied in Western countries, on the other hand, few studies have examined nurse attitudes and practices related to evidence-based practice in Eastern European and Middle Eastern countries. Therefore, we investigated Turkish nurses' attitudes towards evidence-based practice and the socio-demographic factors associated with it in Turkey.

Methods: This is a descriptive study using a sample of 290 nurses employed by three hospitals in Turkey. Participants completed the Evidence-Based Nursing Attitude Questionnaire and a demographic survey to measure 13 personal, occupational, and professional variables. The analysis included descriptive statistics, t-tests, and ANOVA.

Results: The results of the study showed that nursing education, ability to use professional nursing standards, and conference attendance were significantly associated with higher evidence-based practice. Nurses who had a membership in a professional organization reported higher scores in the cognitive subscale. Younger nurses who have least length of nursing experience stated higher scores in the affective subscale. Moreover, nurses who use professional nursing standards in practice told higher scores in the behavioral subscale.

Conclusion: There are several factors associated with greater evidence-based practice among nurses, those are identified as higher nursing education, professional organization membership, conference attendance, and more satisfaction with income. Results suggest providing in-service education for older and experienced nurses in the benefits and processes of evidence-based practice, supporting activities that promote professionalism.

Keywords: evidence-based practice, evidence-based nursing, nurse attitudes, professional nursing practice, nursing, Turkey.

1. INTRODUCTION

The demand of delivering high-quality patient care has been rising internationally (1). Evidence-based practice (EBP), which is one of the fundamental provisions of quality health care, has been emphasized internationally; thus, EBP movements have received significant attention and resource commitments in healthcare (1). EBP approach guides healthcare providers' decisions to apply the best available scientific evidence with clinical expertise and patient's unique preferences (2). Implementing EBP is a basic responsibility of all healthcare providers (3-4). Nursing is the largest profession in health care and can affect the health care quality significantly (5). Professional nursing requires nurses to base their interventions on scientific knowledge instead of traditional customs, intuition, and habits. When nurses use evidence and research to guide their practice, they transform their role from being "care assistants" to "care professionals" (1).

The benefits of evidence-based practices can be listed as decrease in the health care cost, improvement in the health outcomes, and increase in the autonomy of nurses, which contributes to the professionalization of nursing (6-8). Many clinical nurses, however, are sceptical about using EBP recommendations because they believe that academic nurses, who perform theoretically-based research, are far removed from clinical realities and that research has limited clinical application (9-12). In the study of Upton and Upton, some nurse researchers reported that their research is not utilized in patient care settings and that clinical nurses do not base their interventions on evidence (13). Nurses' attitudes related to EBP have been widely studied in the international

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nursing literature, especially in western countries (Australian, western European and North American countries), leading to an EBP movement (4, 13-15). These studies indicate that many nurses recognize the importance of EBP in enhancing patient outcomes, even when they have little knowledge about how EBP is developed and implemented (4, 6). However, little attention has been paid to the EBP movement among nurses in Eastern European and Middle Eastern countries such as in Saudi Arabia (16), Jordan (17), Iran (18), and Oman (19).

EBP is not widely used in the clinical setting in Turkey, where is a Eastern European country (20). Until relatively recently, Turkish nurses prefer to base their practice on long-standing traditions, customs, habits, and personal and peers' experiences rather than on scientific sources of information (20, 22). Even if they believe the benefits of using EBP, those nurses reported that they cannot fully incorporate it in their practice (21). Moreover, nursing education did not emphasis EBP and primarily focused on training nurses in the psychomotor skills necessary for task-oriented patient care (5). Only beginning in 2010, Turkish nursing regulations emphasized the importance of EBP: "In every environment, a nurse specifies the health-related needs of families and society that can be met by nursing attempts. She/he plans, applies, evaluates, and monitors the nursing care *based on evidence* in the context of the needs specified during the process of nursing diagnosis." (23). After the government regulations in 2010, nurse educators encourage nursing students to ground their thinking and care in the latest evidence and research recommendations when developing care plans for their patients (24).

By better understanding nurses' current attitudes about EBP in Turkey, we take an important step towards elucidating how nurses and their leaders can enhance EBP throughout Eastern Europe. Although several Turkish nurse researchers have begun to investigate EBP in Turkey (5, 25-26), there are limited studies conducted in that area. This study builds upon their initial work.

The aims of this study were: 1) to investigate the cognitive, affective, and behavioral attitudes of nurses towards EBP in Turkey, and 2) to understand relationships between these attitudes and nurses' demographic characteristics (personal, occupational and professional factors).

2. METHODS

2.1. Study Design and Sample

The study utilized a descriptive study design to investigate Turkish nurses' cognitive, affective, and behavioral attitudes towards EBP and the demographic factors associated with them. A convenience sample of registered nurses was recruited from the pool of 340 nurses employed by three hospitals in a city in Turkey. Inclusion criteria were being 1) a registered nurse, 2) older than 18 years, and 3) able to read in Turkish. We recruited the sample from different types of nursing units during their staff meetings. A power analysis was used to calculate a minimum required sample size based on the following parameters: small to medium effect size (0.35), statistical power of 0.8, probability level of 0.05, predictor number of 28. A minimum sample size of 217 was determined.

2.2. Data Collection Tools

The study used two tools to collect data – the *Evidence-Based Nursing Attitude Questionnaire* (*EBNAQ)* and a demographic survey we developed specifically for this study.

Evidence-Based Nursing Attitude Questionnaire (EBNAQ). The EBNAQ was developed and psychometrically-tested to measure Spanish-speaking nurses' attitudes towards EBP (27). Ayhan and colleagues (2015) translated the *EBNAQ* into Turkish, establishing the scale's validity and reliability for Turkish nurses. Cronbach's alpha reliability coefficient for the whole scale was 0.90 while the coefficients of the three sub-dimensions 1) cognitive, 2) affective, and 3) behavioral were 0.86, 0.69, and 0.71 respectively (26).

The *EBNAQ* consists of 15 statements. The subject responds to each statement using a 5-point Likert scale. The range of scores varies from 15 to 75, with higher scores indicating a higher positive attitude towards EBP. A nurse's knowledge, feelings, and intentions are all important considerations in understanding the process of nurse adoption of EBP (27). Therefore, the 15 items of the *EBPNQ* measure three dimensions of EBP attitudes:

1) cognitive factors, which examine the knowledge a nurse has about EBP;

2) affective factors, which explore the nurse's feelings about EBP; and

3) behavioral factors, which signify the nurse's intention to apply evidence into their nursing practice.

Demographic Survey. In order to determine factors that are associated with different attitudes about EBP, we developed a form to gather personal, occupational, and professional information from each of the subjects. *Personal data* included age, gender, and nursing education program. Four types of educational programs prepare Turkish nurses for practice: medical-high-school (4-year secondary school basic nursing degree); associate degree (2-year nursing degree); BSc Nursing (4-year bachelor degree) and graduate (master's) degree. *Occupational data* included years of nursing experience, satisfaction in income, ability to practice professionally (i.e. using nursing standards and principles to guide practice) and the nurse's practice role (nurse manager [administrative and leadership roles], clinical nurse [basic nursing care] and specialized nurse [advanced training in emergency, operating or intensive care]). *Professional data* included information about the nurse's certification in an area of nursing practice, subscription to a professional nursing journal so far, frequency of reading academic/professional nursing journals so far, membership in a professional organization, and participation in professional conferences and symposiums so far.

2.3. Ethical Consideration

The study was reviewed and approved by Kastamonu University's Scientific Research and Publishing Ethics Committee with [2007/1] approval number. This study was approved according to Declaration of Helsinki guidelines. The proposal was also submitted to the three clinical facilities where the research was conducted, who likewise gave permission. Informed consent was obtained from all participants prior to participation. The confidentiality and privacy of the nurses were protected. The nurses were informed that their participation was completely voluntary, and they might choose not to participate in the study. All collected information in this study was anonymous.

2.4. Data Analysis

The responses to the paper based *EBNAQ* and *Demographic Survey* instruments were entered into SPSS (IBM Corp, Armonk, NY) version 25.0 statistical software. Only completed surveys were used in the analysis. Descriptive statistics were computed to describe the frequencies and distribution of each of the variables measured. *T*-test and one-way analysis of variance (ANOVA) tests were used to analyse the difference in means between the nurses' personal, occupational, and professional characteristics and their cognitive, affective, and behavioral attitudes towards EBP. After performing the ANOVA test, we ran the Scheffe test as a complementary post-hoc analysis of the significant findings to differentiate between nurses' attitudes and the demographic variables (personal, occupational, and professional characteristics). Confidence intervals (95%) were calculated at the $p < .05$ significance level.

3. RESULTS

Out of the original pool of 340 nurses, 290 (85%) nurses completed the instruments. *Table 1* shows the sample was primarily female and middle-aged nurses. The sample was representative of all educational levels with high-school, associate degrees, and baccalaureate degrees each compromising roughly 1/3 of the sample. Only 4% had master's degrees. *Table 2* shows years of experience was well represented in each of the three categories. Only about a 27% of the nurses were fully satisfied with their incomes, and only about 32% felt that they were fully able to practice professionally in using nursing standards and principles to guide practice. Finally, almost half of the sample practiced as clinical nurses and about 45% as specialized nurse. In *Table 3,* which highlights indicators of professionalism, we see that around 65% of sample never read academic article or attended professional conferences. Moreover, almost 98% of nurses do not have academic journal subscription. While 27% of the sample had professional certification, only 13% had membership from a professional organization.

Table 1. *Distribution of Evidence-based Nurses' Attitudes Questionnaire Score by Personal Characteristics (N= 290)*

Demographic Characteristics	n(%)	Cognitive Mean (SD)	Affective Mean (SD)	Behavioural Mean (SD)	Total Score Mean (SD)
Age					
18-25	63 (21.7)	27.6 (2.82)	16.1 (1.78)	15.3 (2.07)	59.0 (5.48)
26-40	153 (52.8)	27.3 (3.74)	15.6 (2.82)	14.4 (2.61)	57.2 (7.97)
41+	74 (25.5)	27.1 (4.41)	15.0 (2.72)	14.4 (2.84)	56.5 (8.34)
t/F (p – value)		0.259 (0.073)	2.783 (0.059)	3.359* (0.001)	1.918 (0.06)
GenderType equation here.					
Female	242 (83.4)	27.4 (3.70)	15.6 (2.59)	14.6 (2.60)	57.6 (7.52)
Male	48 (16.6)	26.8 (3.96)	15.3 (2.82)	14.3 (2.52)	56.4 (8.15)
t/F (p – value)		1.001 (0.472)	0.581 (0.34)	0.893 (0.432)	0.995 (0.444)
Nursing Education					
Medical-high-school	88 (30.3)	27.6 (3.49)	15.9 (2.23)	14.9 (2.46)	58.5 (7.05)
Associate (nursing college)	92 (31.7)	26.8 (4.11)	14.9 (2.95)	14.1 (2.81)	55.7 (8.17)
BSc Nursing	98 (33.8)	27.1 (3.43)	15.7 (2.47)	14.5 (2.43)	57.3 (7.08)
Master in Nursing	12 (4.2)	30.4 (3.87)	16.9 (2.91)	16.1 (2.78)	63.4 (8.37)
t/F (p – value)		3.647* (0.025)	3.940* (0.018)	3.219* (0.038)	4.680* (0.002)

*$p < 0.05$.

Table 1 provides an overview of nurses' personal characteristics with the three *EBNAQ* subscales. There was a significant difference in mean behavioral (intent-to-practice) scores within age. Behavioral scores of the youngest nurses' (18-25 years old) was statistically significantly higher than the score of the oldest nurses (over 41 years old) (p<.05). Similarly, there was a significant difference in mean cognitive (knowledge), affective (feelings), and behavioral (intent-to-practice) *EBNAQ* scores within nursing education (p<.05). Masters-prepared nurses had the highest total *EBNAQ* mean scores, while associate degree nurses had the lowest.

Table 2 indicates several significant differences in the mean scores of the three *EBNAQ* subscales within nurses' occupational characteristics. A significant difference was found in the mean affective (feelings) scores within nurses' years of experience (p<.05). Nurses working the shortest amount of time had the highest scores, while nurses with the most experience had the lowest. Nurses who were satisfied with their nursing incomes had significantly higher affective (feelings) scores (p<.05). The ability to practice professionally – using professional nursing values, processes and standards – was significantly different in nurses' cognitive (knowledge), behavioral (intent-to-practice), and total EBP scores (p<.05).

Table 3 demonstrates an overview of professional practice characteristics with the three *EBNAQ* subscales. Nurses who had achieved professional certification and nurses who were members of professional organizations had significantly higher EBP cognitive scores than those who had not achieved these indicators of nursing professionalism (p<.05). There was significant difference in mean cognitive, affective, and total EBP scores within attending professional conferences (e.g. symposia, congresses) (p<.05). Finally, subscribing to professional journals and/or reading academic journals were not significantly different in any EBP scores.

Table 2. *Distribution of Evidence-based Nurses' Attitudes Questionnaire Score by Occupational Characteristics (N= 290)*

Demographic Characteristics	n (%)	Cognitive Mean (SD)	Affective Mean (SD)	Behavioural Mean (SD)	Total Score Mean (SD)
Years of Nursing Experience					
0-10	122 (42)	27.2 (3.36)	15.9 (2.36)	14.8 (2.36)	57.9 (6.94)
11-20	93 (32)	27.7 (3.63)	15.7 (2.70)	14.6 (2.60)	58.0 (7.74)
20+	75 (26)	27.0 (4.43)	14.8 (2.84)	14.2 (2.90)	56.0 (8.44)
t/F (p – value)		0.778 (0.553)	3.792* (0.033)	1.152 (0.102)	1.726 (0.063)
Income Level					
Yes	77 (27)	27.13 (3.48)	15.23 (2.64)	15.99 (2.25)	58.35 (7.38)
No	117 (40)	27.24 (4.27)	14.15 (2.78)	15.30 (2.89)	56.68 (8.42)
Partially	96 (33)	27.53 (3.26)	14.57 (2.19)	15.46 (2.54)	57.56 (6.75)
t/F (p – value)		0.276 (0.699)	4.196* (0.011)	1.665 (0.122)	1.136 (0.180)
Uses Professional Standards					
Yes	93 (32)	27.3 (3.52)	15.9 (2.33)	15.1 (2.45)	58.4 (7.41)
No	66 (22.8)	26.4 (4.49)	15.3 (3.06)	13.9 (2.84)	55.6 (9.06)
Partially	131 (45.2)	27.8 (3.41)	15.4 (2.57)	14.5 (2.49)	57.7 (6.86)
t/F (p – value)		3.287*(0.03)	1.608 (0.273)	4.258* (0.001)	2.675* (0.023)
Practice Role					
Nurse Manager	17 (5.8)	28.5 (3.63)	16.7 (2.97)	15.2 (2.46)	60.5 (7.92)
Clinical Nurse	144 (49.6)	27.0 (3.27)	15.3 (2.36)	14.4 (2.46)	56.7 (6.80)
Specialized Nurse	129 (44.6)	27.4 (4.21)	15.7 (2.81)	14.7 (2.73)	57.8 (8.35)
t/F (p – value)		1.355 (0.248)	2.577 (0.396)	1.331 (0.296)	2.270 (0.303)

**p < 0.05.*

Table 3. *Distribution of Evidence-based Nurses' Attitudes Questionnaire Score by Professional Practice Characteristics (N= 290)*

Demographic Characteristics	n (%)	Cognitive Mean (SD)	Affective Mean (SD)	Behavioural Mean (SD)	Total Score Mean (SD)
Professional Certification					
Yes	78 (26.9)	28. (4.62)	15.7 (2.98)	14.6 (3.01)	58.2 (9.16)
No	212 (73.1)	27.0 (3.35)	15.5 (2.49)	14.6 (2.42)	57.1 (6.98)
t/F (p – value)		1.777* (0.023)	0.772 (0.146)	0.047 (0.790)	1.120 (0.158)
Journal Subscription					
Yes	7 (2.4)	30.0 (2.94)	16.4 (1.90)	15.9 (2.55)	62.3 (6.47)
No	283(97.6)	27.2 (3.74)	15.5 (2.64)	14.5 (2.59)	57.3 (7.62)
t/F (p – value)		1.935 (0.060)	0.913 (0.427)	1.327 (0.318)	1.715 (0.128)
Reading Academic Article					
Never	190 (65.5)	27.2 (3.90)	15.4 2.63)	14.4 (2.61)	56.9 (7.85)
1-3	87 (30)	27.5 (3.38)	15.8 (2.52)	15.0 (2.41)	58.3 (6.86)
4+	13 (4.5)	28.3 (3.79)	16.2 (3.03)	14.6 (3.23)	59.2 (8.87)
t/F (p – value)		0.709 (0.691)	1.534 (0.126)	1.457 (0.090)	1.343 (0.142)
Conference Attendance					
Yes	110 (37.9)	28.1 (4.37)	15.9 (2.83)	14.8 (2.92)	58.8 (8.63)
No	180 (62.1)	26.9 (3.24)	15.3 (2.47)	14.4 (2.36)	56.6 (6.84)
t/F (p – value)		2.687** (0.000)	1.957* (0.027)	1.153 (0.312)	2.385* (0.015)
Professional Organization Membership					
Yes	36 (12.4)	28.9 (4.07)	15.6 (3.12)	14.5 (2.69)	58.9 (8.63)
No	254(%) (87.6)	27.1 (3.65)	15.5 (2.55)	14.6 (2.58)	57.2 (7.51)
t/F (p – value)		2.690* (0.010)	0.051 (0.877)	0.119 (0.738)	1.285 (0.246)

**p < 0.05. **p < 0.001.*

4. DISCUSSION

This study examined Turkish nurses' cognitive, affective, and behavioral attitudes to EBP and its' relationship to various personal, occupational, and professional factors. One of the most encouraging findings is that, nurses who worked in Turkey received an average of *EBNAQ* total scores (55.61 to 63.42; range = 15-75), which was relatively high, indicating reasonably positive attitudes towards EBP. This finding is congruent with other studies that indicate Turkish nurses generally believe EBP enhances the quality of care (7, 21, 26), even though nurses perceive barriers to implementing EBP (25).

The results reflect the previous studies, finding similar associations of EBP with gender, nursing education, income satisfaction, use of professional standards, professional certification, conference attendance, and professional organization membership. However, our findings related to age, years of experience, practice role, journal subscription, and reading academic articles fail to support findings from previous studies. We attempt to explain these discrepancies below. One of the most noteworthy findings of our study is that younger nurses (18-25) have higher behvioral *EBNAQ* scores, means intent to practice EBP, compare to mature nurses (> 41 years) that is concurrent with previous studies (4, 22). On the other hand, Dikmen and colleagues (2014) and Goris and colleagues (2014) found that in Turkey older nurses exhibit higher professionalism (and presumably positive EBP attitudes are an important element of professionalism) compared to younger nurses (7, 21). This contradictory finding may be related to EBP attitudes being only one attribute of professionalism. According to Ghadirian and colleagues (2014), there are a multitude of attributes associated with professionalism (28). Older nurses may have acquired many of these other attributes, demonstrating their professionalism, but positive EBP attitudes may not be one of them.

Consistent with our previous findings from Turkey (7, 21, 29), highly educated nurses are more likely to have knowledge, have positive feelings, and have commitment to practice EBP. In Turkey, although EBP is not in the nursing curriculum yet, recently nurse educators started to teach and increase nursing students' awareness about EBP(24). Additionally, nursing students read professional journals, attended scientific meetings, and reported higher desire for research (20, 24). Therefore, it is likely that more recently educated younger nurses have received better education about the importance of EBP. Older nurses who have been in the profession longer

may not have had the advantage of a good introduction to the benefits and processes of EBP. Although experienced nurses expected to mentor newer nurses, they have difficulty implementing EBP into their own nursing practices (30). Newly graduated nurses reported fewer barriers to use EBP and had greater desire for EBP (31).

The findings related to age were consistent with two other studies from Turkey (7, 29), as we found nurses with the least experience (0-10 years) had higher affective scores than nurses with the most experience (>20 years), which are consistent with findings by two other studies from Turkey (7, 29). The reason might be the less experienced nurses have recently graduated and have had the benefit of EBP training.

Nurses who were satisfied with their incomes had higher affective scores than their colleagues who were either dissatisfied or partially satisfied with their incomes. We also found that nurses who felt that they could practice using the values, processes and standards associated with professional nursing practice had higher cognitive, behavioral, and total *EBNAQ* score averages. Karamanoğlu and colleagues (2009) also found that nurses who reported they were able to practice their nursing knowledge, values, and skills had higher professional attitude scores (32). Thus, it seems that nurses who feel satisfied with their incomes and their ability to practice professionally have more knowledge and motivation for EBP compare to nurses who are discouraged with their jobs.

Our findings related to nursing role (manager nurse, clinical nurse, specialty nurse) did not support the results reported by other Turkish studies (7, 21, 32). They found that manager nurses had higher professional attitude scores than nurses in other roles. Even though our findings lacked significance, nurse managers in our study had the highest scores in all the *EBNAQ* subscales and total scale. This undoubtedly reflects their interest in enhancing the quality of healthcare and the professionalism of nursing services within their organizations.

In the demographic survey, the factors included in the *Professional Practice Characteristics* section are activities that are associated with the concept of nurse professionalism (28). Nurses who engage in these activities tend to be more "professional" and more interested in nursing research than nurses who do not engage (7, 21, 26). Our findings validate these findings only partially because only professional certification, conference attendance, and professional organization membership reached significantly similar results. For instance, nurses who had professional certification and professional organization membership received higher cognitive scores, means had more knowledge about EBP. Also nurses who attended conferences received higher cognitive, affective and total *EBNAQ* scores, means had more knowledge and positive feelings about EBP. According to Al Mutair (2015), nurses who join professional organizations also extend their commitment beyond the needs of patients to the needs of the profession, engaging in additional professional and political activities (16).

In this study, subscribing to journals and reading academic articles – other indicators of professionalism – did not reach significance, but the mean scores consistently showed higher *EBNAQ* scores for nurses who engaged in these activities than those who did not. Thus, it still seems correct to conclude engaging in these professional activities helps nurses increase their knowledge about, enhance their opinions towards, and their commitment to EBP. Engaging in professional development activities of all kinds provides exposure to research and scientific programs, increasing nurses' positive attitudes towards them.

One professional activity that we did not include in our survey is participating in nursing research projects. Dalheim and colleagues (2012) found that nurses who participated in research projects developed positive attitudes and skills towards research and EBP (33). The opportunity to participate in research seems to be an important avenue for enhancing EBP attitudes.

5. CONCLUSION

In this study, factors associated with significantly higher EBP attitudinal scores included being single, more highly educated, more satisfied with income, and ability to practice using professional standards. Being younger and less experienced were also associated with higher EBP attitudinal scores. Other factors associated with higher EBP scores included being certified, being a member of a professional organization and attending professional conferences.

Implications

The results of our study suggest several recommendations for enhancing nurse attitudes about and commitment to EBP:

Provide in-service education for older and experienced nurses. Because the population of older, experienced nurses have *EBNAQ* scores lower than younger less experienced nurses, their deficit may be related to a lack of formal EBP education that was not available during their nurse training. Inservice education about EBP and its purpose, processes, and applications may increase these nurses' commitment to EBP.

Support job satisfaction. Since nurses who are dissatisfied with their jobs have less interest in EBP, nursing leaders at healthcare organizations should give attention to indicators of job satisfaction, creatively addressing them. For instance, even if salaries can't be raised, other benefits, such as scheduling flexibility, may increase job satisfaction.

Support professional practice. Nurses who feel like professionals, whose knowledge and skills are valued and incorporated into patient care, are more engaged in EBP. Nurse leaders at healthcare facilities should promote a culture that facilitates professional nursing practice. They can inventory the strengths and weaknesses of their organizations and gradually take steps to improve the value

placed on nursing values, standards and processes, such as interdisciplinary rounding.

Support educational advancement. Since higher education is associated with positive EBP attitudes, organizations should consider policies that help and reward advanced education and degrees. Enhancing the knowledge and skills of the nursing workforce is likely to increase nurse commitment to EBP and the quality of care the healthcare organization provides to its patients.

Support professional activities. Since professional activities such as certification, professional organization membership, conference attendance and journal subscription and reading are associated with positive EBP attitudes, these activities should be valued by and monetarily supported by clinical organizations. Nurse researchers can advance nursing science and its application to patient care by conducting studies relevant to clinical nurses. They can provide clinical nurses with opportunities to see how the research process identifies patient care problems, tests new interventions, critically evaluates these interventions, implements research findings, and builds new research on previous research problems (11).

Limitations

Generalization of this study to other nurses should be done cautiously, since the study has several methodological limitations. First, as a descriptive study, we used primarily associative rather than predictive methods. Second, the tools used in the study were self-administered and self-reported, which are subject to validity concerns. Third, the sample was taken from one city in Turkey, and may not be generalizable to other cities or countries. Finally, we wished we had included "opportunities to participate in the research process" in the demographic survey, and recommend that this factor be included in further research about factors that could influence EBP.

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Clinical and Experimental Health Sciences

Comparative Analysis of Service Costs In Intensive Care Unit, Length of Stay and Mortality Rate Before and During the COVID 19 Pandemic

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ABSTRACT

Objective: The aim of the present study was to compare the average length of stay, mortality rates and service costs in intensive care unit provided to patients during October-November-December 2019 (pre-pandemic), with the average length of stay, mortality rates and service costs in intensive care unit during October-November-December 2020 (pandemic).

Methods: This was a retrospective cross-sectional comparative, single-center study. The demographic data (age, gender), average length of stay, mortality and hospital costs of intensive care patients during October-November-December 2019 (pre-pandemic) were compared using the hospital records with the same data of patients in the same intensive care unit during October-November-December 2020 (pandemic), and the factors affecting the cost were investigated.

Results: Of the 437 patients included in the study, 233 were hospitalized in pre-pandemic period and 204 in pandemic period. Pre-pandemic period mean age was 65.04 ± 17.0, and pandemic period mean age was 68.07 ± 15.1 years. The majority of the cases in both periods were male (57.9% and 63.2%). Length of stay, cost and mortality rates were significantly higher in the pandemic group (p: 0.000). There was a significant positive correlation between length of stay and cost (p: 0.000).

Conclusion: It was found that intensive care costs increased considerably during the COVID 19 period, along with the increases in the length of stay and mortality rates. Advanced age and increase in length of stay were found to be correlated with mortality, but only length of stay was correlated with cost.

Keywords: COVID – 19, Length Of Stay, ICU Cost, Mortality

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) has affected every continent in the world and is considered the biggest infectious disease outbreak of the 21st century, with over 125,507,698 cases and 2,755,212 deaths as of March 27, 2021. (1)

The COVID-19 pandemic is observed to have a detrimental impact on global health systems and affect every aspect of human and economic life. A major concern with the COVID-19 pandemic is the high financial burden on healthcare systems. To fully understand the economic burden of COVID-19 and assist decision makers in planning future investments in COVID-19 prevention and treatment strategies, specific data describing the healthcare costs of hospitalized COVID-19 patients is needed. A cohort study in Saudi Arabia reported that the average healthcare cost of COVID 19 patients admitted to the intensive care unit (ICU) per patient was $ 21,178.21 ± 14,839.38. This cost was higher in patients undergoing mechanical ventilation. (2) Similarly, Wang et al. reported the estimation of average medical cost for COVID-19 patients to be $ 6,500 in their modeling studies. (3)

However, to the best of our knowledge there is no study investigating how much these costs have changed compared to a year ago, neither in the world nor in our country. The present study aimed to compare the length of stay (LOS), mortality rates and costs between patients in the intensive care unit during the last quarter of 2019 and the same period of 2020.

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2. METHODS

The study was planned as a retrospective cross-sectional comparative study. The study was initiated after obtaining the approval of the Clinical Research Ethics Committee of S.B.U Kocaeli Derince Research And Training Hospital (Ethics committee approval number: 2021/14). (ClinicalTrials.gov ID: NCT04748614)

From the electronic records of our hospital, the demographic data (age, gender), the average length of stay, mortality rates and hospital costs of the patients who were admitted to the intensive care unit during October-November-December 2019 (pre-pandemic) were compared with the demographic data (age, gender), the average length of stay, mortality rates and hospital costs of the patients who were admitted to the intensive care unit during October-November-December 2020 (pandemic), and the factors affecting the costs were investigated.

Since the first COVID 19 case in our country was detected on March 11, 2020, the last quarter of 2019 was determined as the Pre-Pandemic period.

The primary objective of this study was to compare the healthcare costs of ICU patients before the COVID 19 outbreak (Pre-Pandemic) and during the Pandemic.

Secondary objective was to compare these two periods in terms of length of stay and mortality rates, and to determine the factors affecting the costs.

2.1. Statistical Analysis

The results were presented for categorical variables as numbers and percentages, for continuous variables as mean ± standard deviation. Comparison of the categorical variables between groups was done using Chi-square or Fisher exact test. The normality of distribution for continuous variables was confirmed with the Kolmogorov–Smirnov test. For comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. To evaluate the correlations between measurements, Pearson's correlation coefficient was used. p value of 0.05 was considered statistically significant for all tests. Statistical analysis was performed using the IBM SPSS ver. 22 package software (IBM Software, New York, United States).

3. RESULTS

A total of 448 patients were screened in this study comparing patients in intensive care in the last quarter of 2019 and the last quarter of 2020. 11 of these patients (3 pre-pandemic; 8 pandemic) were excluded from the analysis because cost information was not available. Of the 437 patients included in the study, 233 were hospitalized in the pre-pandemic period and 204 in the pandemic period. Pre-pandemic period mean age was 65.04 ± 17.0; pandemic period mean age was 68.07 ± 15.1 years. Although there was no statistical difference in terms of gender, the majority of the cases were male (57.9% and 63.2%) in both periods. LOS, cost (average, daily, per patient) and mortality rates were significantly higher in the pandemic group (p: 0.000) (Table 1, Figure 1).

Table 1: *Comparative Analysis of Groups*

	Pre-pandemic	pandemic	P
n (437)	233	204	
Age (year)	65.04 ± 17.0	68.07 ± 15.1	0.051
Sex (f/m)(n)	98/135	75/129	0.281
LOS (day) (1-99 day)	6.1 ± 9,2	8.8 ± 9,8	0.003*
Cost (Turkish Liras (TL))	14.703 ± 15.019	26.967 ± 21.295	0.000*
Cost per patient (TL)	63	132	0.000*
Daily cost (TL)	2.410 ± 1.632	3.064 ± 2.172	0.000*
Discharge (n)	156 (% 67,0)	71 (% 34,8)	0.000*
Death (n)	77 (% 33,0)	133 (% 65,2)	

Chi-Square Tests(LOS: length of stay*

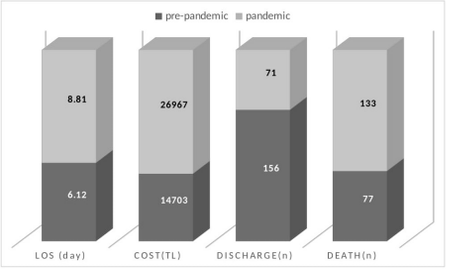

Figure 1. *Comparative Analysis of Groups*

When the factors affecting the cost were examined, there was a significant positive correlation between length of stay and cost (p: 0.000). It was observed that as age and length of stay increased, mortality increased, but they were not correlated with cost (Table 2).

CONSORT 2010 Flow Diagram

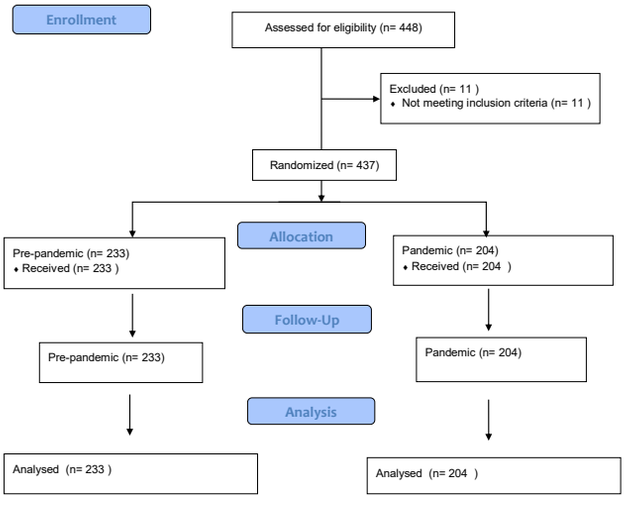

Figure 2: *CONSORT 2010 Flow Diagram*

Table 2. *Correlation of Cost, Age, LOS And Mortality Between Groups:*

			Cost	Age	LOS	DEATH
Pre-Pandemıc	Cost (TL) (14.703 ± 15.019)	Pearson Cor.	1	-,088	**,576****	,049
N:233		Sig.		,181	**,000**	,453
	Age (Year) (65.04 ± 17.0)	Pearson Cor.	-,088	1	,025	**,206****
		Sig.	,181		,706	**,002**
	LOS (Day) (6.1 ± 9,2)	Pearson Cor.	**,576****	,025	1	,195**
		Sig.	**,000**	,706		,003
	Death [77 (% 33,0)]	Pearson Cor.	,049	**,206****	**,195****	1
		Sig.	,453	**,002**	**,003**	
Pandemic	Cost (TL) (26.967 ± 21.295)	Pearson Cor.	1	-,118	**,773****	-,054
N:204		Sig.		,092	**,000**	,444
	Age (Year) (68.07 ± 15.1)	Pearson Cor.	-,118	1	-,038	**,217****
		Sig.	,092		,591	**,002**
	LOS (Day) (8.8 ± 9,8)	Pearson Cor.	**,773****	-,038	1	-,038
		Sig.	**,000**	,591		,585
	Death [133 (% 65,2)]	Pearson Cor.	-,054	**,217****	-,038	1
		Sig.	,444	**,002**	,585	

***. Correlation is significant at the 0.01 level (2-tailed). LOS: lenght of stay; TL: Turkish Liras*
*** pearson correlation levels:*
0.01 – 0.29 low correlation
0.30 – 0.70 moderate relationship
0.71 – 0.99 high level correlation

4. DISCUSSION

In this study, where pre-COVID 19 intensive care costs and COVID 19 period intensive care costs were compared, it has been determined that, during the COVID 19 period, the costs of hospitalization increased considerably, along with the increases in length of stay and mortality rate. While advanced age and increase in length of stay were correlated with mortality, only length of stay was correlated with cost.

Patient characteristics, clinical outcomes, and resource use of hospitalized COVID-19 patients have been described in several US studies. (4-6) However, limited data are available describing direct healthcare costs associated with hospital resource use among hospitalized COVID-19 patients. (7) A study in Saudi Arabia (2) determined a cost of $ 21,178.21 ± 14,839.38 per patient among those admitted to the ICU, and a study in USA (7) stated that this cost increased up to $ 54,402. Similarly, a simulation study by Sarah et al. (8) determined the cost of a patient requiring hospitalization as $ 14,366. While the cost analysis results of our study were in line with the literature (TL 26,967 ± 21,295), they were additionally compared with the pre-pandemic values, and it was observed that the cost increased almost two-fold compared to the pre-pandemic period (pre-pandemic: TL 14,703 ± 15,019 and pandemic: TL 26,967 ± 21,295). This situation highlights the scale of resources required to manage COVID-19 cases.

It has been shown in various studies that the mean age of patients in intensive care due to COVID 19 is high. A study by Fusco et al. (7) reported median (mean) age as 63 (61) years, among hospitalized COVID-19 patients (N = 173,942). Similarly, Haase et al. (9) found that average age was 68 (59-75). In the present study, mean age in the pandemic period was 68.07 ± 15.1. Although it increased compared to the pre-pandemic period, this increase was not statistically significant. In addition, our study determined that, advanced age was correlated with increased mortality, which was in line with the literature(7), but not correlated with increased costs. This situation is not in line with the literature because according to Sarah et al., the cost increases as the age increases. (8) We believe that this difference is due to the fact that the mentioned publication is based on a simulation software, and that our study has been a single-center study and included only intensive care patients.

In our study, there was no difference between the genders in the comparison of the two periods, however it was observed that the male gender was at risk in terms of admission to intensive care (pre-pandemic: 57.9% and pandemic: 63.2%). Our findings are in line with the literature. (2, 7, 9, 10)

It is anticipated that, the length of stay will increase during the pandemic period because the treatment and complications of COVID 19 disease are not yet fully elucidated. However, previous studies comparing patients who were followed up in the hospital wards and who were admitted to intensive care,

reported that median length of stay was 4 days for patients who were not admitted to ICU and did not undergo invasive mechanical ventilation (IMV), while it increased to 15 days for patients who were admitted to ICU or underwent IMV.(7) It also followed a course that increased with age (≥50 years: 6 days). (7) In a study by Khan et al. the median LOS was 7.93 days, and the maximum LOS was 43 days. (2) Unlike these studies, our study includes LOS values before and during the pandemic and is in line with the literature with LOS values of 6.1 ± 9.2 days for the pre-pandemic period, and LOS values of 8.8 ± 9.8 days during the pandemic period. In addition to the literature, cost was found to be correlated with the increase in LOS.

COVID 19 patients in intensive care unit have an increased risk of mortality. Mortality rates ranging from 0% to 84.6% can be found in the literature (11); however, this review found the ICU mortality rate as 35.5% (31.3-39.9%) as a result of quantitative analysis of all these studies. This study also stated that the highest mortality rate was in the Middle East when viewed on a regional basis. (61.9% (52.5–70.5%)). In our study, mortality rate was 65% in the pandemic period in parallel with the literature, but a two-fold increase in mortality was found compared to the pre-pandemic period. In addition, in line with the literature, mortality was correlated with age (7), but no correlation was found between increased mortality and cost.

The results of this study should be interpreted in the context of various limitations. First, the study data only represent the ICU inpatient environment and focused directly on medical costs, therefore the full clinical and healthcare economic burden of patients hospitalized for COVID-19 such as the indirect costs incurred by patients due to hospitalization for COVID-19 (for example, employment income losses, family travel expenses, childcare costs, etc.); are largely unknown and not evaluated in this study. In addition, as the significant proportion of hospitalized COVID 19 patients are transferred to other care facilities and those who are discharged home may require additional care outside of the inpatient setting, additional studies need to be conducted in other care settings. Second, the scarcity of critical supplies can increase costs, as suppliers can increase prices (for example, hospitals pay up to fifteen times the normal price for personal protective equipment and medical supplies). Third, our analysis does not include impacts such as indirect medical costs, or reduced income due to reductions in elective procedures, or potential cost increases resulting from worse disease outcomes due to delays in preventive care and diagnosis.

Although this is a single-centre study, it provides valuable information regarding economic burden of COVID 19 patients, who were admitted to the ICU due to COVID 19, on hospitals. The findings of our study provide the first insights regarding the economic burden on hospitals with regard to providing healthcare to COVID-19 patients hospitalized in Turkey. Such cost data will be useful as input for future studies assessing the economic burden of healthcare services for COVID 19 pandemic in Turkey, and for developing cost-effectiveness models to evaluate the potential impacts of COVID 19 prevention and treatment efforts.

5. CONCLUSION

In our study comparing pre-pandemic and pandemic periods, all three values of patients in intensive care during pandemic, length of stay, hospital costs, and mortality rates increased by almost two-fold compared to the pre-pandemic period**.** The findings of this study support the need for urgent implementation of effective interventions, including safe and effective vaccines.

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Ethical considerations: The study was initiated after obtaining the approval of the Clinical Research Ethics Committee of S.B.U Kocaeli Derince Research And Training Hospital (Ethics committee approval number: 2021/14). (ClinicalTrials.gov ID: NCT04748614)

Conflicts of interest: None

Authorship statement: IK, MYK: Conceptualization, Methodology, Data curation, Writing – Original draft preparation, Visualization, Investigation, Supervision, Reviewing and Editing,

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Clinical and Experimental Health Sciences

Dental Anxiety and Cardiovascular Response Changes In Multiple Implant Surgery – An Observational Study

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ABSTRACT

Objective: The aim of the study is to observe the level of anxiety and its relationship with cardiovascular changes in each implant in the patients with a high number of implants applied in a single session.

Methods: In the prospective observational study, 100 patients, who had undergone 4 or more implant surgeries in the same session electively, were included in the study. Demographic data of each patient were recorded. After Corah Dental Anxiety Scale (C-DAS) was applied to the patients 10 minutes before the surgery, standard heart rate (HR), saturation, systolic (SAP), and diastolic (DAP) blood pressure monitorization were performed and the measured values were recorded during surgery and 30 minutes after the end of the procedure, and the surgery period were recorded.

Results: It was determined that the mean age of the cases was 52.0±11.7 and the number of implants was 5.8±1.5, and the surgery periodwas 53.7 ± 18 minutes. There was a positive correlation between HR and CDAS at all times and as the number of implants increased, SAP and DAP were added to this correlation ($p < 0.05$). As the number of implants increased, HR, SAP and DAP also increased ($p < 0.05$). As the surgery period increased, postoperative anxiety increased ($p < 0.05$).

Conclusion: It was found that anxiety levels of patients and accordingly the HR, SAP and DAP increased as the number of implants increased in the patients who underwent 4 or more implant surgeries in the same session.

Keywords: Dental anxiety, cardiovascular response, implant surgery

1. INTRODUCTION

Anxiety about dentist and dental treatment is considered as one of the common concerns of people. Dental anxiety includes fears of varying intensity, such as not liking going to the dentist, worrying, being afraid, showing symptomatic symptoms (excessive sweating or feeling unwell as if you have a physical illness).

Anxiety is a consciously perceived emotional response that intensifies the activity of the autonomic nervous system. The sympathetic nervous system promotes the release of epinephrine and norepinephrine. Activation of this system results in changes in heart rate (HR), breathing and blood pressure patterns, and responses such as discomfort, tremor, and increased sweating. Blood pressure and heart rate may also change in dental treatments (1).

In developed countries, great importance is attached to the diagnosis and treatment of dental anxiety. Therefore, there are many scale-development studies oriented at measuring dental anxiety and fear in these countries (2). Dental Anxiety Scale, developed by Corah et al. (3), in 1969, is one of the most commonly used scales (Corah Dental Anxiety Scale – C-DAS).

Corah Dental Anxiety Scale (CDAS) is a scale consisting of 4 items for measuring how people feelconcerned and anxious during dental interventions. The highest score of the scale is 20 and the lowest score is 4. A high score indicates that the person has high anxiety. Total dental anxiety score obtained by adding the scores given to the four questions is rated in two groups as low anxiety (4-11 points) and high anxiety (12-20 points). In general, the patients having a total score of 12 and above are considered to be anxious and those having

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a score of 15 or above are considered as those with high anxiety.

It has been concluded that Turkish adaptation of C-DAS is valid and reliable for all age groups (4).

To the best of our knowledge, there are no studies evaluating the number of implants and the effect of each implant on anxiety and cardiovascular responses separately. The hypothesis of this study is to test that as the number of implants increases, pre-procedural anxiety and therefore heart rate and blood pressure increase.

2. METHODS

The study was designed as a prospective observational study. It was started after the ethics committee approval was obtained from Erzincan Binali Yildirim University Clinical Trials Ethics Committee and written consents of the patients were obtained (33216249-604.01.02-E.22014). ClinicalTrials.gov ID: NCT04037930. The study was carried out in accordance with the Helsinki Declaration.

One hundred patients over the age of 30 who will undergo elective dental implant surgery were included in the study. Inclusion criteria were four or more implant surgeries in the same session, being literate, good general health, and not using any medication that could cause cardiovascular changes. Exclusion criteria were defined as patients with syndromic disease, systemic disease, cardiac problems, who had undergone other oral or maxillofacial procedures in the last 6 months, who used drugs that could cause changes in heart rate, who used a pacemaker or implantable cardioverter defibrillator (ICD).

Demographic data of each patient (age, gender, medical history, drug use, etc.) were recorded after informed consent was obtained. C-DAS questionnaire (Table 1) was applied to the patients 10 minutes before the operation and preoperative scores were recorded. Preoperative heart rate, peripheral oxygen saturation and non-invasive blood pressure monitoring of each patient were performed, the measured values were recorded and the measurements were continued during the peroperative period. From these measurements; values were included during local anesthesia, at the time of incision, at the beginning of each implant, at the suture stage after the procedure, and 30 minutes after the end of the procedure. In addition to the physiological values at all these times, the CDAS questionnaire was repeated and recorded. When an implant was finished, the surgeon informed the patient for the CDAS questionnaire, a CDAS questionnaire was administered by the dental technician, the results were recorded, and the surgeon moved on to the next implant. This cycle was repeated for each implant throughout the operation. In addition, operation times were also recorded, as anxiety values were examined. The change over time of all values, including CDAS, was determined as the main point of the study.

Infiltration anesthesia with getocaine was performed 10 minutes after the preoperative records. The records at this time were recorded as “anesthesia”. As an operation, the flap was removed, the socket was prepared, the implant was placed and an envelope flap was applied. Bone volume and quality were chosen to suit all patients. None of the patients required advanced surgical procedures. Nucleoss T6 of Turkish origin and a South Korean megagen anyridge implant were applied in our hospital.

A senior oral and maxillofacial surgeon was familiar with the purpose of this study. All the implants were performed by the same surgeon.

The primary aim of this study was to observe the level of anxiety in patients with a large number of implants and its relationship with cardiovascular changes in each implant.

TABLE 1.The *Corah’s Dental Anxiety Scale that formed part of the study questionnaire*

1. If you had to go to the dentist tomorrow, how would you feel?

(1) Look forward to it as a reasonably enjoyable experience

(2) I wouldn’t care one way or the other

(3) I would be a little uneasy about it

(4) I would be afraid that it would be unpleasant and painful

(5) I would be very frightened of what the dentist might do

2. When you are waiting in the dentist’s office for your turn in the chair, how do you feel?

(1) Relaxed

(2) A little uneasy

(3) Tense

(4) Anxious

(5) So anxious that I sometimes break out in a sweat or almost feel physically sick

3. When you are in the dentist’s chair waiting while he gets his drill ready to begin working on

your teeth, how do you feel?

(Same alternatives as Q.2)

4. You are in the dentist’s chair to have your teeth cleaned. While you are waiting and the

dentist is getting out the instruments which he will use to examine your teeth around the

gums, how do you feel?

(Same alternatives as Q.2)

2.1. Statistical Analysis

Results were presented as mean ± standard deviation for continuous variables. Chi-square or Fisher's exact test was used to compare categorical variables between groups. Student's t-test or Mann-Whitney U test was used to compare independent continuous variables between the two groups. Similarly, paired samples t-test or Wilcoxon signed-rank test was used for dependent continuous variables. Pre-post measurements or percentages of difference were used when comparing dependent groups. Pearson correlation coefficient was used to evaluate correlations between measurements. The statistical significance level was accepted as 0.05 for all tests. Statistical analysis, IBM SPSS ver. 19 packages of software (IBM Software, New York, United States).

3. RESULTS

3.1. Demographic Data

One hundred patients aged over 30 years are included in the study. It was determined that mean age of the patients was 52.0 ±11.7, number of implants was 5.8 ±1.5; surgery periodwas 53.7 ±18 minutes. Number of men/women was 58 / 42. Table 2 shows the mean score of CDAS levels based on time. According to this table, preoperative anxiety levels are "low (4)" in multiple implant patients, and anxiety levels gradually decrease over time.

When examining the cardiovascular changes and CDAS correlation that is the aim of the study, it was observed that there was a positive correlation between heart rate and CDAS at all times, and systolic and diastolic artery pressures were also added in this correlation as the number of implants increased. As can be seen in this table, heart rate increases as anxiety level increases, or heart rate decreases as anxiety level decreases, but the correlation between anxiety and blood pressure becomes correlated as the number of implants increases and the duration of the operation increases. Heart rate change seems to reflect anxiety level better than blood pressure (Table 3).

When the conditions affecting the anxiety levels were examined, it was observed that gender, age, and number of implants, surgery period did not affect the anxiety levels (Table 4).

Table 2. *Descriptive Statistics*

	N	Mean	Std. Deviation
Age	100	52.0	11.7
Number of implants	100	5.8	1.5
4	27		
5	14		
6	31		
7	16		
8	6		
9	3		
10	3		
Surgery period	100	53.7	18.0
Gender			
Male	58		
Female	42		
CDAS Preop	100	8.07	3.1
CDAS Anesthesia	100	7.20	2.9
CDAS 1stImplant	100	7.20	2.9
CDAS 5thImplant	72	6.97	2.7
CDAS Final Implant	100	6.19	2.1
CDAS Postop	100	5.49	2.0

CDAS: Corah Dental Anxiety Scale

Table 3. *Cardiovascular changes and CDAS correlation based on time*

Heart rate (HR)	n	Mean ± SD	Sig.	SAP	Mean ± SD	Sig.	DAP	Mean ± SD	Sig.	CDAS
Preop	100	78.1±10.9	**0.027***	preop	135.4±15.4	0.218	preop	79.4±11.6	0.179	**8.07**
anesthesia	100	83.9±10.3	**0.020***	anesthesia	140.7±14.1	0.932	anesthesia	83.4±10.1	0.003	**7.20**
1st implant	100	80.0±9.8	**0.001***	1st implant	138.0±14.9	0.691	1st implant	82.9±9.9	0.903	**7.20**
5thimplant	73	78.4±9.8	**0.018***	5thimplant	139.1±15.4	0.853	5thimplant	81.5±10.2	0.557	**6.97**
Postop	**100**	**79.1±10.4**	**0.000***	**postop**	**137.6±13.2**	**0.508**	**postop**	**82.8±10.0**	**0.367**	**5.49**
6th implant	59	77.3±10.8	**0.001***	6th implant	143.5±13.9	0.572	6th implant	82.4±10.8	0.635	**6.40**
7th implant	28	79.4±7.4	**0.005***	7th implant	142.0±13.3	0.771	7th implant	84.0±13.0	**0.012***	**6.11**
8th implant	**12**	**84.2±11.2**	**0.018***	**8th implant**	**144.9±14.9**	**0.047***	**8th implant**	**87.5±11.5**	**0.585**	**7.25**
9th implant	**6**	**87.8±9.2**	**0.000***	**9th implant**	**158.5±2.8**	**0.003***	**9th implant**	**93.8±3.9**	**0.001***	**8.17**

**Correlation is significant at the level of 0.05 (2-tailed). CDAS: Corah Dental Anxiety Scale, HR: heart rate, SAP: systolic artery pressure, DAP: diastolic artery pressure*

Table 4. *Factors affecting anxiety*

Gender	CDAS Preop 1	CDAS Anesthesia 1	CDAS 1st Implant	CDAS 5th Implant	CDAS Final Implant	CDAS Postop 1
Male	8.03	7.41	7.41	7.39	6.41	5.52
Female	8.12	6.90	6.90	6.42	5.88	5.45
P (Sex)	0.975	0.279	0.376	0.153	0.150	0.796
P (Age)	0.292	0.163	0.163	0.458	0.054	0.081
P (No. of implants)	0.209	0.098	0.084	0.911	0.167	0.917
P (Operation period)	0.984	0.806	0.188	0.272	0.268	0.052

** logistic regression, **Correlation is significant at the level of 0.05 (2-tailed). CDAS: Corah Dental Anxiety Scale*

4. DISCUSSION

In this study, in which the effect of multiple dental implant surgery on anxiety and cardiovascular system was investigated, it was determined that both anxiety levels and HR, SAP and DAP increased as the number of implants increased.

Pain, anxiety and irritability associated with dental treatment cause acute changes in autonomic nerve activity, resulting in complications such as blood pressure and vagal reflex(5). Therefore, monitoring the changes in autonomic nerve activity during dental treatment may be useful in preventing the complications. According to the study by Nagao et al. (6), in 2002, that is the only study in the literature that investigated autonomic nerve activity in implant surgery (6), heart rate, systolic arterial pressure, and diastolic arterial pressure increased as the number of implants and surgery period increased. In the present study, a correlation was detected between the number of implants and HR, SAP and DAP and as the number of implants increased, HR, SAP and DAP also increased.

The diagnosis and treatment of dental anxiety in developed countries are emphasized with great importance. There are both subjective and objective ways to measure dental anxiety. While objective measurements include blood pressure, heart rate, and respiratory rate (7-9), there are numerous scales that are developed and tested for subjective measurements. Corah Dental Anxiety Scale (CDAS) is one of scales that are tested and proved to be reliable (10, 11). In the present study, it was aimed to demonstrate the association of anxiety and cardiovascular system using both objective and subjective scales. Accordingly, HR levels were correlated with the anxiety level at all times of the study. High anxiety was associated with high HR. SAP and DAP showed correlation only with CDAS as the number of implants increased.

Dental anxiety is expected to decrease after the procedure (12). In a study by Muğlalı et al.(12), the anxiety levels measured immediately after the operation were found to be significantly lower than the preoperative levels, and in our study postoperative anxiety levels decreased in all the patients compared to preoperative levels.

Dental anxiety has several reasons. Early-onset dental anxiety develops in childhood as a result of direct experiences and by observing the parental examples (7). Anxiety with late onset develops typically when adult patients have tooth cavity (if cavities disturbintraoral appearance) or they have undergone more dental treatments due to tooth cavity about the average in their adolescence or other dental problems (13). In another study, some additional causes of anxiety were listed. If a patient is afraid of suffocation, obstruction, injection, vision, or even thought of blood, they are more likely to experience dental anxiety (14). Other sources of anxiety are caused by the concerns about the numbness via local anesthetics, and low pain tolerance and lack of trust to the dentist are also among the causesof anxiety. However, these studies indicated that age and gender were not specified among the reasons of anxiety. There are also other studies in the literature specifying that age and gender do not affect anxiety (15, 16). In the present study, no correlation was found between age and gender, and anxiety.

In the present study, it was found that the number of implants or operation period and anxiety were not correlated. In fact, it was found that anxiety levels decreased when the operation was completed, regardless of the duration of the operation or the number of implants.

There are some limitations in the present study. First limitation is that the number of implants was not proportional. Since 7 or more implants are very rare, some statistical calculations could not be performed and the results cannot be generalized to this group of patients. Second limitation is that many other factors affecting the reasons of anxiety (educational level, previous dental procedure experiences, etc.) were not included in the study. The results of the present study should be supported by the studies including all of them and more homogeneous groups.

5. CONCLUSION

In the present study, it was found that anxiety levels of patients and accordingly the heart rate and blood pressure increased as the number of implants increased in the patients who underwent 4 and more implant surgeries in the same session. And, when the operation is over, it has been found that anxiety levels decrease regardless of the duration of the operation or the number of implants.

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Clinical and Experimental Health Sciences

Predictors of 30-Day Re-hospitalization After Total Hip and Total Knee Arthroplasty: A Orthopedic Ward Perspective

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ABSTRACT

Objective: The study was aimed to elucidate risk factors identifiable from ward-derived data of thirty-day re-hospitalization among patients undergoing total hip and total knee arthroplasty.

Methods: The study was designed as a cross-sectional and prospective study. The data of the study were collected through the Patient Sociodemographic Form, the Nurse Physical Assessment and Observation Form, the Charlson Comorbidity Index (CCI), and the Katz Activities of Daily Living (ADL) Scale.

Results: Patients were scored using this CCI system and grouped as high (high CCI group >2, n = 49) and low CCI (low CCI group ≤2, n = 78) with a cut-off score of 2. The 30-day re-hospitalization rate was 14.2%, and the most common reason for re-hospitalization was a surgical infection. Surgical risk, Activities of daily living dependency, and comorbidities index scores of the patients were not significantly additive effects on re-hospitalization (p> 0.05). The results indicate that surgical infection was often the cause of higher rates of re-hospitalization among patients with total knee and total hip arthroplasty.

Conclusions: Orthopedic nurses should close observation of surgical site infection and design an effective discharge following-up order to the prevention of re-hospitalization in patients with"high risk".

Keywords: Re-hospitalization, rates, causes, knee, hip, arthroplasty.

1. INTRODUCTION

Hip and knee arthroplasty surgery has been one of the most frequently required orthopedic surgery procedures in recent years. Epidemiologic analyses indicate that total hip arthroplasty rates increased by 30% between 2000 and 2015, while knee arthroplasty almost doubled (1). Total hip and total knee arthroplasty are most often implemented in patients in old age; patients with cardiovascular diseases and chronic liver diseases have a higher incidence of post-surgical complications (2). Comorbidities are defined as diseases or medical conditions which do not relate causally to the primary diagnosis but coexist with it. Elderly patients generally have more comorbidities but the effects of comorbidities on the results of arthroplasty need to be further studied (3). In a medical environment, classifying comorbidities using value-based metrics can help improve pre-surgical counseling, decrease potential complications and allow for perioperative resources to be properly assigned. Orthopedists commonly use the American Society of Anesthesiologists' physical status classification (ASA-PSC) or the Charlson Comorbidity Index (CCI) (4). The CCI is also utilized as a predictor for postoperative adverse cases, revision surgery, and re-hospitalization in post-operative arthroplasty (5).

Re-hospitalization rates increase in the first 30 days after surgery, indicating that the risk of re-hospitalization in the early postoperative stage is highest (6). Re-hospitalization forms a great part of health costs. The re-hospitalization of a patient within a month of discharge is a serious problem for the healthcare system (7). The 30-day re-hospitalization rate reported in orthopedic surgery alone is around 2-14% (8), and it has been predicted that 12% will be re-hospitalized for potentially preventable causes (7). According to a systematic review and meta-analysis study, the reasons for the 30-day rehospitalization of orthopedic patients include three categories: In the Wound related category; surgical site infection (32.2%), non-infected wound (14%), cellulitis (9%), seroma (6.5%), and hematoma (4.2%), in the Surgical category; fixation failure (9.4%), pain (7.7%) and dural tear (4.1%), and in the Medical category; medical complication

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(26.4%), deep vein thrombosis (DVT) (3.5%) (8). Reducing unscheduled re-hospitalizations significantly improves the quality of health care and lowers costs. Some healthcare systems thus use re-hospitalization rates as a quality criterion to calculate health service payments (8).

Also, osteoarthritis or hip fracture severely restrain an individual's ability to perform daily life activities, so patients with joint disorders are the most likely to need help from unofficial caregivers while waiting for surgery or after surgery (9). In the period following arthroplasty, it should not be forgotten that the "inability to cope" in the home environment can be an important factor leading to re-hospitalization and that the patient is physically restricted and at risk of comorbidity after an early discharge (10).

In clinical practice, nurse assessment tools can consistently produce data about a person's potential health status. Value-based nurse assessment tools translate organic misery and signs of risk into an understandable language (11). Such tools are one of the chief ways of understanding patients to better provide high-quality patient care. Family members may not always be present at a patient's bedside to offer help. However, nurses continuously evaluate their patients and they endeavor to understand and interpret their needs from different perspectives. The nurses who work at a hospital and the assessment tools they routinely use are the best sources of information about a patient. Those nurses who know the patient best, and who have all the available data from patient follow-ups, play a vital role when it comes to detecting the factors affecting 30-day unscheduled re-hospitalization (12). In re-hospitalization, various social and medical factors, such as the patient's age, the severity of the disease, functionality, and comorbidities, are critical (3). However, there are too few studies specifying the variables that may affect re-hospitalization rates among patients who have had arthroplasty. These studies mainly focus on the effects of the patients' demographic and clinical characteristics, the surgical procedure, and the comorbidity index score on re-hospitalization (7,13). There is too little information about the relationship of nurses' follow-up data or daily life activity to re-hospitalization (14). Consequently, the current study included as variables the nurse assessment tools (pain, pressure sore, risk of fall, system examination criterion), comorbidity risk index (ASA, CCI), and the patients' daily activity levels, in addition to predictive variables like age, surgical procedure, lengthy hospitalization. It sought to provide a broader perspective concerning the 30-day re-hospitalization of the patients who had total hip arthroplasty and total knee arthroplasty. The aim was to analyze the effects of the clinical condition and comorbidity risk levels of patients who had had hip and knee arthroplasty on ADL 30-day unscheduled re-hospitalization.

2. METHODS

2.1. Participants

The study was conducted in a 500-bed urban hospital with a 20-bed orthopedics and traumatology clinic, whose staff consisted of 12 nurses, seven orthopedics and traumatology specialists, and ten junior doctors. A descriptive prospective design was used to analyze the patient-related factors affecting the 30-day unscheduled re-hospitalization of patients who had had total hip arthroplasty and total knee arthroplasty. Inclusion criteria: (a) patients aged 20 and above; (b) indication of elective primary total knee and hip arthroplasty; (c) patients who did not have a communication problem (speech, hearing, foreign language); (d) volunteering for the research. Exclusion criteria: (a) patients aged under 20; (b) who had not had total hip and knee arthroplasty; (c) patients who did not volunteer to participate; (d) patients with who it was not possible to communicate. The universe of this study consisted of 307 patients aged 18 years and over and who underwent total hip or knee replacement surgery in the orthopedics and traumatology clinic between June 2019 and January 2020. The cluster sampling method was used in this study. The sample size was determined using the simple sampling method (15). To determine the sample size of the research, the suggested formula for quantitative research (n=N.s2.Zα2 /[(N-1). d2+s2. Zα2) was used (16). Accordingly, the standard deviation was taken to be s=1, and the significance level as 0.05 (95% confidence level), the corresponding theoretical value Z0.05=1.96, and influence quantity giving a sampling error of d=0.15. According to the formula, the sample size was calculated as 113. During the study, a total of 180 patients who did not suitable for the criteria of the study, were excluded from the study. Considering that the number of questionnaires returned may be low due to incomplete, inaccurate, or low-suitability questionnaires, a total of 127 patients were included. There was no data loss because all of 127 patients voluntarily in the research.

2.2. Data Collection Tools

The data of the patients were obtained through the Patient Introduction Form, the Nurse Physical Assessment and Observation Form, the Charlson Comorbidity Index (CCI), and the Katz Activities of Daily Living Scale.

Patient Introduction Form: This form includes 10 questions about patients' data (5) and their hospitalization-related data in the orthopedic ward where they were the length of stay (5). 30-day re-hospitalization data were obtained through the hospital information system and by telephone by the orthopedic nurse researchers.

Nurse Physical Assessment and Observation Form: This is a form routinely used by the nurses to monitor the inpatients' medical records and follow-ups. It includes a history of the patient, a nurse physical examination form, vital signs, Visual Analog Scale (VAS), Braden Risk Assessment Scale, and ITAKI

fall risk scores, as well as observation notes. We collected patient's clinical data from these forms. In this study, the Numeric Rating Scale of VAS was used as a measurement method for the intensity of pain. The patients were asked to mark their pain levels on a horizontal line with a 0-10 scale (0= "no pain" and 10= "worst possible pain") (17). The Braden Risk Assessment Scale is composed of six dimensions that reflect sensory perception, skin moisture, activity, mobility, friction and shear, and nutritional status. Braden risk scores of 12 or less are defined to be at high risk of pressure ulcers development, those with a score between 13-14 are defined to be at moderate risk and those with a score between 15-16 are defined to be at low risk. The validity and safety study for this scale was made by Oguz in Turkey and the reliability and the validity of the scales were found to be quite high (18). The ITAKI Fall Risk Scale consists of a total of 19 risk factors that may cause patient falls. Two risk levels, low and high, were determined over the total score obtained as a result of the evaluation of risk factors. If the total score is below five, the risk of falling is considered low, and if it is five or more, the risk of falling is considered high (19).

Charlson Comorbidities Index: The CCI was developed in a New York hospital in 1987 as a measurement of one-year mortality risk and a load of disease. It involves 19 medical diagnoses and the index is scored from 1 to 6 points. In clinical practice, a single numerical score is given to the medical diagnoses included in the CCI. Comorbidities are given points from 1 to 6 for the mortality risk and severity of the disease. These scores are added up to obtain the total index score. One point is added for the age of 40 and every ten years above 40. The lowest score obtainable is "0" and the highest is "37". As the score increases, so does the predicted mortality rate increases (20).

ASA Physical Condition Classification System: This is an assessment system in which the patient is preoperatively classified and the medical comorbidities of a patient before anesthesia are evaluated. The classification system alone does not predict perioperative risks. Determining the ASA level is a clinical decision based on multiple factors. The physical condition can be classified at various times during the patient's pre-surgical evaluation, but the final evaluation is done by an anesthetist on the day of anesthesia (21).

Katz ADL: The Katz ADL Scale scores six activities (bathing, dressing, toilet, movement, excretion, nutrition). The validity and reliability studies of the Turkish version of the scale were conducted by Pehlivanoğlu et al. in 2018. Every activity on the Katz ADL Scale includes three options: dependent (1 point), semi-dependent (2 points), and independent (3 points). In the Katz ADL index, scores of 0-6 are evaluated as the patient being dependent, 7-12 as the patient being semi-dependent, and scores of 13-18 as the patient being independent (22). The Cronbach's alpha for the Turkish version of the KATZ ADL scale was found to be 0.83 (22). In the present study, Cronbach's alpha for the Turkish version of KATZ was found to be 0.87.

2.3. Procedure

The data was obtained by the researcher through face-to-face meetings with the patients. The researcher met each patient on the day of hospitalization and the day of discharge. On the first day of hospitalization, the patient's vital signs, Braden Pressure Ulcer Risk Tool, ITAKI Fall Risk Tool, VAS, CCI, ASA, and Katz ADL evaluations were conducted by the researcher. Finally, the researcher met the patients on the day of discharge and recorded again the patient's vital signs, Braden Pressure Ulcer Risk Tool, ITAKI Fall Risk Tool, VAS and ASA follow-ups.

2.4. Data Analysis

The data were analyzed using the Statistical Package for Social Sciences program (SPSS-22). Numbers, percentages, arithmetic means, and standard deviation was used for the analysis. To compare the variables, non-parametric Chi-square tests, and Univariate Logistic Regression, and Pearson Correlation and Multicollinearity Regression Analysis were applied. The statistical significance of the alpha level was accepted as $p < 0.05$.

2.5. Ethical Considerations

After approval had been obtained from the Clinical Trials Ethics Committee (date: 05.07.2019 and no: 2019/245), the descriptive and prospective data of patients who had had elective total hip or knee arthroplasty were collected between June 2019 and January 2020. The institutions to which each writer belonged approved the human protocol for this research and all the research was conducted according to ethical principles. The patients were informed about the study and were obtained written and verbal consent.

3. RESULTS

The mean age of the patients was 63.35 (SD=9.67). Most of the total hip and knee arthroplasty patients were women. 14.2% of the patients were re-hospitalized within 30 days. The most frequent reason for unscheduled re-hospitalization was surgical infection (Table 1).

3.1. Patients' CCI, ASA, Katz ADL, and Nurse Follow-up Assessments

Almost all of the patients (91.6%) had medium systemic disorders according to the ASA classification. The ADL levels of 58.3% of the patients were "semi-dependent". According to the patients' CCI scores, 61.4% had a one-year mortality risk score of ≤2; 38.6% had a score of>2, and the mean CKI score was 2.59±2.411 (Table 1).

The vital signs and risk scores (including the nurse follow-ups) for the patients' hospitalization and discharge days are given in Table 2. The VAS mean scores of the patients were 1.09±1.211 during hospitalization and 1.06±1.194 during discharge. The

ASA mean scores were 1.06±1.194 during hospitalization and discharge. According to the Braden Risk Assessment Scale, risk mean scores were respectively 21.023±1.887during hospitalization and 21±1.881 during discharge. The ITAKI fall risk mean scores were 8.692±2.961duringhospitalization and 9.189±2.402 during discharge.

3.2. Predictors Affecting Re-hospitalization

According to the sociodemographic characteristics of the patients, there was no significant difference at the p<0.001 significance level (Table 3). In Table 4, the Exp (β) values show ODDS rates. The ODDS rates show how many times more or how many times less the probability arises of observing two events studied alongside one another. When the β coefficients for the independent variables are negative, the ODDS rate as Exp (β) is interpreted as decreasing by considering the negative relationship. According to this, 16.2% were women and the Total Knee Arthroplasty (TKA) was 38.4%. As the Braden risk and ASA scores decrease, this also contributed to re-hospitalization but this was not statistically significant (p>0.05).

Table 1. *Patients' sociodemographic and clinical characteristics (n=127)*

Variables		Number (n)	Percent (%)
Gender	Female	101	79.5
	Male	26	20.5
Length of stay (day) (Mean±SD)	9.34±7.92	Min:3 Max: 65	
Age (years) (Mean±SD)	65.35±9.679	Min:24 Max: 82	
Age group (years)	≤50	11	8.7
	51-60	22	17.3
	61-70	51	40.2
	≥71	43	33.8
Level of education	Illiterate	34	26.8
	Primary	79	62.2
	Secondary	6	4.7
	Higher Education	8	6.3
Caregiver	Partner	23	18.1
	Daughter	51	40.2
	Son	16	12.6
	Relative	37	29.1
Prosthesis type	Total Hip Arthroplasty	26	20.5
	Total Knee Arthroplasty	101	79.5
30-day rehospitalization	Yes	18	14.2
	No	109	85.8
Rehospitalization clinic	Orthopedic and traumatology	11	61.1
	Physical therapy and rehabilitation	6	33.3
	Neurology	1	5.6
Causes of rehospitalization	Surgical infection	9	50.0
	Physiotheraphy	6	33.3
	Change in consciousness	1	5.5
	Dislocation	2	11.1
ASA classification	ASA 1	12	9.4
	ASA 2	77	60.2
	ASA 3	38	30.4
Katz ADL	Dependent	2	1.5
	Partially dependent	74	58.3
	Independent	51	40.2
Katz ADL (Mean±SD)	12.606±3.21	Min:3	Max:18
CCI	≤2 (equal to the one-year relative risk)	78	61.4
	>2 (higher to Relative risk 2 times)	49	38.6
CCI (Mean±SD) 2.59±2.411		Min:0	Max:19

ASA: American Society of Anesthesiologists; Katz ADL: Activities of Daily Living; CCI: The Charlson comorbidity index; SD: Standart Deviation

Table 2. *Clinical data of patients*

Variables	Hospitalization day		Day of discharge	
Vital signs	Mean±SD	Min – Max	Mean±SD	Min – Max
Pulse	83.78 ± 12.453	56 – 130	83.464±7.985	62-102
Body temperature (°C)	36.349 ± 0.247	36 – 37	36.440±0.240	36-36.9
Systolic blood pressure (mmHg)	119.763±11.715	100 – 160	119.527±7.648	100-140
Diastolic blood pressure (mmHg)	72.440±9.147	60 – 90	73.464±8.579	60-90
SPO_2	92.866±2.917	89 – 98	93.362±1.858	90-98
VAS	1.09±1.211	0-6	1.060±1.194	0-6
ASA classifications	2.20±0.618	0-3	2.200±0.618	0-3
Braden Pressure Ulcer Risk Tool	21.023±1.887	16-23	21.000±1.881	16-23
Itaki Fall Risk Tool	8.692±2.961	1-15	9.189±2.402	6-15

SPO2: Oxygen saturation; VAS: Visual Analogue Scale; ASA: American Society of Anesthesiologists; SD: Standart Deviation

Table 3. *Individual data of the patients with bivariate relationships to 30-day rehospitalization (yes/no)*

		30-day re-hospitalization			
		Yes n(%)	No n(%)	X^2;	p
Gender	Female	14 (11.0)	87 (68.5)	0.843;	0.528
	Male	4 (3.1)	22 (17.4)		
Age (year)	≤60	3 (2.4)	30 (23.6)	0.947;	0.331
	≥61	15 (11.8)	79 (62.2)		
BMI (kg/m^2)	≤24,9	1(0.8)	8(6.2)	0.075;	0.626
	≥25	17(13.4)	101(79.6)		
Prosthesis type	Total Hip Arthroplasty	16 (12.6)	85 (66.9)	1.129;	0.235
	Total Knee Arthroplasty	2 (1.6)	24 (18.9)		

BMI: Body Mass Index; CCI: The Charlson comorbidity index X2: Chi-Square test; p<0.001

Table 4. *Logistic regression analysis of some clinical data about patient-related conditions and 30-day rehospitalization*

							95% C.I. EXP (βp)	
	β	Standard error	Wald	df	p	Exp(β)	Alt	Üst
Constant	5.95	6.68	0.781	1	0.377	366.870		
Age group	-0.048	0.044	1.218	1	0.270	1.04	0.874	1.038
Female	0.162	0.702	0.053	1	0.818	1.175	0.297	4.648
TKA	0.384	0.264	2.123	1	0.145	1.468	0.876	2.462
Katz ADL	-0.057	0.107	0.289	1	0.591	1.051	0.766	1.164
CCI	0.055	0.162	0.116	1	0.734	1.057	0.770	1.450
Braden risk score	-0.127	0.182	0.487	1	0.485	1.135	0.617	1.258
ITAKI Fall risk score	0.076	0.105	0.522	1	0.470	1.079	0.878	1.327
ASA mean score	-0.591	0.589	1.009	1	0.315	1.805	0.175	1.755

TKA: Total Knee Arthroplasty; Katz ADL: Activities of Daily Living; CCI: Charloson Comorbid Indeks; ASA: American Society of Anesthesiologists

4. DISCUSSION

This study aimed to analyze the effects of the social and medical conditions of patients who had had total knee and hip arthroplasty on re-hospitalization; the results of the study are here discussed in the light of the relevant literature.

4.1. Sociodemographic Characteristics of the Patients

In a meta-analysis, it was emphasized that osteoarthritis generally affects the knees and that it shows an increasing incidence with age, especially in women (3). In the literature, the variable mean age for arthroplasty was found to be 66.5 ± 6.2 (3). The mean ages of the patients who had had surgery and who were observed in this study were similar to those in other studies, including international populations.

4.2. Re-hospitalization of Patients and Potential Predictors

In the literature, it is observed that the re-hospitalization rates of the patients vary depending on the patient profile and the specialty of the service provided. 30-day re-hospitalization rates in orthopedics alone are around 2-14% and the most common reason is surgical site infection (8,23-26). In a meta-analysis conducted by Kurtz et al. (2016) it was found that the 30-day re-hospitalization rate in the patients who had had total hip arthroplasty varied between 0% and 22% (median: 4.9%). In the current study, the 30-day re-hospitalization rates of the patients who had had arthroplasty were found to be close to the highest level. The reason for the high rate of re-hospitalization in the first 30 days after the surgical procedure: it may be an indication that patients are not ready for discharge, do not fully understand the instructions and directions for discharge or receive inadequate post-operative discharge training (6). The most common reason for re-hospitalization was surgical site infection, in line with the literature (7,8,13), which shows that focus should be placed on the training and follow-up of this patient group. To determine the increasing cost of the hospitalization of patients who have had total hip and knee arthroplasty, it is important to evaluate the rates of re-hospitalization, when that occurs, and the reasons for it. Taking measures against the most common reasons for re-hospitalization can be effective in reducing the cost (26). Hospital nurses should develop new strategies for educating patients who have had arthroplasty.

The ASA classification is commonly used in orthopedics studies. This classification divides patients into subgroups according to the severity of the associated diseases (21). In this study, most of the patients had systemic diseases according to these classifications. It was thought that knowing the ASA score would be beneficial in determining the connection between re-hospitalization. Patients with high ASA scores were expected to have serious comorbidities and high needs in the postoperative period. However, the ASA classification was not found to be related to re-hospitalization. In analyzing the ODDS rates, it was found that women who had poor scores in the ASA classification and for Braden risk were more likely to be re-hospitalized.

The study evaluated the comorbidity index scores of the patients who had had hip and joint arthroplasty. The patients were graded with the CCI system and were divided into groups: high CCI group > 2, n = 49; low CCI group ≤2, n = 78. The CCI mean score was 2.59±2.411. The findings of the study are compatible with the findings of previous studies (4,27). The findings also showed that there was no correlation between the age and gender of the patient, prosthesis site, comorbidity index, Katz ADL, Braden risk score, and fall risk score and re-hospitalization. Nevertheless, in the analysis of the ODDS rates, it was found that the women patients with pressure ulcers risk according to the Braden score had a high risk of re-hospitalization. Although this information has minimal value prospectively in managing re-hospitalization, we can prospectively conclude that a patient with pressure ulcers risk according to the Braden score will likely be more intensive re-hospitalization either from high infection risk or a long stay. This is particularly significant for re-hospitalization in patients of total hip and knee arthroplasty are age, gender, hypertension, obesity, and the characteristics of the hospital. As Braden Score includes an assessment of chronic comorbidities, and poor baseline in the patients with pressure ulcers risk according to the Braden score could account for all of these associations. According to the nurse follow-ups during the hospitalization and discharge of the patients, there was no significant change in the medical characteristics of patients and this was not correlated with re-hospitalization. In similar studies, it was observed that the age and gender of patients who had arthroplasty were not related to re-hospitalization (28). In contrast, in some studies, the age of the patient, the preoperative body mass index, the ASA 3 classification, the number of comorbidities, and the duration of hospitalization were defined as predictors of re-hospitalization in the patients who had had total knee arthroplasty (29,30). The evidence for risk factors for 30-day re-hospitalization in total hip and knee arthroplasty patients shows inconsistencies for some sociodemographic factors such as age, gender, and ASA classification, which includes the comorbidity burden.

Strengths and Limitations

Some limitations should be taken into consideration when discussing the effect of the independent variables on re-hospitalization. The reliability of the results is limited to the answers of the patients. The other limitation is the prospective collection of data during a short period of research in one university hospital in one region. The results cannot, therefore, be generalized, although they can provide an idea of how similar patient groups might function. The error rate of the data based on criteria within independent variables seems to be acceptably low. More than one criterion was used, so it can be thought that almost all the aspects of each patient were reached.

5. CONCLUSION

The 30-day re-hospitalization rate was high after hip and knee arthroplasty. Re-hospitalization often occurred due to surgical site infections. Surgeons and nurses should thus focus on educating and following up with this patient group. The assessment tools used in this study, including the CCI, the ASA, and the ADL, were found not beneficial as predictors of adverse cases related to re-hospitalization or surgical site infection.

We also suggest that the CCI, ASA, ADL be used to identify "high-risk" patients because each of these tools relates to a specific aspect of a patient's health condition. While the ASA and CCI provide a limited picture of each patient's risk (4), the goal of this study was to form a complete image by using additional risk assessment tools. It was found that surgical site infection was the main cause of the 30-day re-hospitalization of patients who had arthroplasty. Close observation of surgical site infection is thus of vital importance to prevent re-hospitalization. Identifying "high-risk" patients using value-based metrics can help to decrease the incidence of re-hospitalization. Patients and family caregivers should be seen as part of the rehabilitation process and they should be given training on infections, dislocation, mobilization, exercise.

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Conflict of Interest

The authors declare no potential conflict of interest.

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Clinical and Experimental Health Sciences

Evaluating the Styles of Coping With Stress of Individuals With Multiple Sclerosis During the Covid – 19 Pandemic

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ABSTRACT

Objective: Multiple sclerosis (MS)is among the most influential environmental factors. Quarantine days during Covid-19 outbreak can cause conditions such as anxiety, isolation stress, financial and long-term economic stress, including health concerns.The descriptive study was planned and applied with the aim of examining the impacts of Covid-19 pandemic on the styles of coping with stress of individuals with multiple sclerosis.

Methods: The study was carried out on 246 volunteer individuals during April2020-May2020 following the approval of the Turkey MS Association and the briefing provided to the individuals.The data were acquired via Personal Information Form and The Styles of Coping with Stress Scale.

Results: The mean age of individuals with MS was 39.41±9.06 years. Statistically significant increase was found in the sub-dimensions of optimistic and helpless approach with gender, submissive approach with marital status, helpless and submissive approach with education status, helpless, submissive and seeking social support sub-dimensions with working status ($p<0.0$, $p<0.05$).

Conclusion: It was determined that individuals with MS use the helpless approach and submissive approach most frequently in coping with stress during the Covid-19 pandemic.It was determined that those living with their families mostly use the optimistic approach and self-confident approach.It is thought that MS associations will be effective in coping with stress in reducing symptoms and social and physical support through informative meetings, home visits, psychotherapies, yoga and organized trainings.

Keywords: covid 19, multiple sclerosis, stress, coping style

1. INTRODUCTION

Coronavirus disease 2019 (Covid-19) is a global viral pandemic that emerged in Eastern Asia and rapidly spread out all over the world. Multiple sclerosis(MS) is a demyelinating disease of unknown etiology caused or triggered by the virus. Different viruses including herpes viruses are considered as environmental, etiological agents or risk factors that result in relapse in the course of MS (1).

Stress is among the environmental factors that has the greatest impact on Multiple sclerosis (MS). It has been reported in various studies that there is a relationship between stress and MS(2). Mohr et al. (2004) reported more relapse after stressful life events. It is considered that stressful life events during infection may lead to immunosuppression and problems in the removal of the pathogen in addition to MS advancement (3).

Although there are studies dealing with different forms of coping with stress, individuals with secure attachment styles tend to find more effective coping styles; There is a consensus that individuals with anxious and avoidant attachment styles use ineffective coping styles (4-5). In one study, securely attached individuals showed styles of active planning, external help seeking, religious indulgence, acceptance, and cognitive restructuring; apathetic-avoidant attachment style of active planning; Fearful-avoidant individuals, on the other hand, stated that they frequently use coping styles such as escaping, isolating, denying the problem and dealing with other things (6).

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The quarantine procedures that went into effect during the Covid – 19 pandemic may lead to stressful situations including health concerns as well as anxiety, isolation stress(7). It is known that anxiety, depression and stress may trigger attacks in individuals with MS together with other symptoms (8). It is also known that relationships between individuals with MS and their social networks including families, friends, peers, colleagues, professional organizations are among the primary features for coping with stress. Various studies have put forth that interpersonal and social interactive relations have positive impacts on knowledge, trust, social support, clinical results, behaviors, decision making and self-care(9-10).

2. METHODS

2.1. Aim and Type of the Study

The study was planned and carried out in a descriptive style for examining the impact of the Covid-19 pandemic on the styles of coping with stress of individuals with Multiple sclerosis.

Study Questions

1. What are the styles of coping with stress of individuals with MS?

2. What are the styles of coping with stress of individuals with MS with regard to their sociodemographic characteristics?

2.2. Place and Time of the Study

The study was carried out on individuals with MS registered to the Turkey MS Association during the dates of April 2020-May 2020.

2.3. Study Population and Sample Group

The study population was comprised of individuals registered to the Turkey Multiple Sclerosis Association, whereas the sample group was comprised of 246 individuals with who volunteered to take part in the study. There are 1100 individuals with MS registered to the association. Turkish Multiple Sclerosis Association; To introduce the disease to patients, their relatives and the society, to increase national/international cooperation opportunities and to raise awareness about MS, to contribute to scientific research on the diagnosis and treatment of the disease, to represent our country in international platforms, to carry out mutual information flow, to be with the patients at every stage of the disease, to provide medical treatment places, to increase the quality of life of patients and their relatives, to organize activities to enrich their social lives, to contribute to their personal development in the fields of education and art, and to provide rehabilitation and psychological counseling services.

2.4. Data Acquisition Tools

2.4.1. Information form

Prepared by the researchers in accordance with the related literature, comprised of 7 questions on the individuals with MS (age, gender, education status, marital status, employment status, social security status) and individuals they live with.

2.4.2. The styles of coping with stress scale (CSS):

The Styles of Coping with Stress Scale is a 4-point Likert type developed by Folkman and Lazarus (1985) and consists of 30 items. The reliability and validity study was carried out in our country by Şahin and Durak (1995). The scale has two dimensions as problem-focused effective methods and emotion-focused ineffective methods. These two dimensions are reflected in 5 factors known as “self-confident”, “optimistic”, “helpless”, “submissive” and “seeking social support”. It was adapted to Turkish society by Şahin and Durak (1995) (11). The Cronbach Alpha internal consistency coefficient for the 5 sub-scales of CSS was calculated as 0.74. When the coronbach alpha values of the scale sub-dimensions were examined in our study, it was determined as Optimistic approach .83, Self-confident approach .85, Helpless approach .84, Submissive approach .85, Seeking social support .83. The sub-scales and the minimum and maximum scores vary as:

- Optimistic approach (items 2,4,6,12,18), 0 – 15 score
- Self-confident approach (items 8,10,14,16,20,23,26), 0 – 21 score
- Helpless approach (items 3,7,11,19,22,25,27,28), 0 – 24 score
- Submissive approach (items 5,13,15,17,21,24), 0 – 18 score
- Seeking social support (items 1,9,29,30). 0-12 score.

The scale comprised of 30 items in total provides a scoring that varies between 0-3 (0 = not used, 1 = used a little, 2 = used, 3 = used too much). Items 1 and 9 of the seeking social support sub-scale are scored reversely. Scores of each factor are calculated separately and the total score is not calculated.

2.5. Data Acquisition Method

The data were acquired by sending the informed consent form including information on the study and the online questionnaire form to individuals with MS isolated at their homes by taking the approval of the Turkey MS Association and with their support. Face-to-face interviews could not be carried out with the participants due to the Covid-19 pandemic and informed consents were received. They were

asked to answer the questions by taking their conditions during the previous month after the onser of the Covid-19 pandemic in Turkey.

2.6. Data Evaluation

The data were presented in the form of percentages, mean or median values. Kolmogorov Smirnov analysis was carried out to determine whether the data are distributed normally or not. Independent t test was used for comparing more than two independent groups during the analysis of data with normal distribution, where One Way ANOVA test was used for determining the difference between more than two independent groups and Post hoc Tukey test was used for determining the group or groups with differences. Statistical significance was evaluated as $p<0.05$.

2.7. Limitation of the Research

No sample selection was made in the study and the results can be generalized to this group.

2.8. Ethical Aspect of the Study

Approval was taken from the Turkey MS Association and informed consent forms were taken from the participants in order to carry out the study. Ethics Council approval was obtained from the University Ethics Council (FBU/2020-005).

3. RESULTS

Table 1 presents the results on the styles of coping with stress of individuals with MS who participated in the study with regard to their descriptive characteristics. Mean age of the individuals with MS who participated in the study was 39.41±9.06(min:20, maks:63), 71.1% (n:175) were women, 62.6% (n:154) were married, 55.7% (n:137) had an education level of university and above, 46.3% (n:114) were employed, 93.1% had health insurance, 61.8% (n:152) were living with their nuclear family.

Mean score of he sub-dimensions of the MS patients coping styles scale according to gender were compared, and the increase in the optimistic approach ($p<0.01$) in men and helpless approach ($p<0.05$) sub-dimension in women was statistically significant. It was determined that men showed a more optimistic approach ($p<0.01$), while women showed a desperate approach (Table 1).

The sub-dimensions of the MS patients coping styles scale and their mean score according to marital status were compared, and the submissive approach ($p<0.05$) of married people was found to be statistically significant compared to singles (Table 1).

The sub-dimensions of MS patients coping styles scale and their educational status mean score were compared and it was found to be statistically significant in the helpless approach and submissive approach sub-dimensions ($p:0.001$, $p<0.05$). Primary school graduates from university or higher education level; On the other hand, secondary school graduates were found to have a more desperate approach than those with a university or higher education level ($p:0.001$). It was found that secondary school graduates showed a more submissive approach than university and higher education levels (Table 1).

The sub-dimensions of coping styles and working status of MS patients were compared and it was found statistically significant in the sub-dimensions of helpless approach, submissive approach and seeking social support ($p<0.01$, $p:0.01$). It was determined that those who did not work were more helpless and submissive than others, and those who were employed more sought social support than those who did not work (Table 1).

The sub-dimensions of coping styles and health insurance scores of MS patients were compared and the helpless approach and seeking social support sub-dimensions were found to be statistically significant ($p<0.05$, $p:0.01$). The mean score of helpless approach was found to be significantly higher in those who did not have health insurance ($p<0.05$), and it was determined that those with health insurance applied to social support more than those without health insurance (Table 1).

The sub-dimensions of coping with stress styles of MS patients and the mean scores of the people they live with were compared and the sub-dimensions of optimistic approach, self-confident approach and seeking social support were found to be statistically significant ($p<0.05$). It was determined that the optimistic approach and self-confident approach score averages of those living with a nuclear family were higher than the others ($p<0.05$), and those living with a nuclear family were more likely to seek social support than those living with an extended family (Table 1).

The mean scores of individuals with MS from the sub-dimensions of the stress coping style scale are optimistic approach 9.00±3.05, self-confident approach 14.35±4.27, helpless approach 11.60±4.40, submissive approach 6.90±3.12, seeking social support 5.79±1.59 was determined(Table 2).

Table 1. *The Styles of Coping with Stress Scale According to the Descriptive Characteristics of Patients (N:246)*

		The Styles of Coping with Stress Scale				
		optimistic approach	self-confident approach	helpless approach	submissive approach	seeking social support
Introductory Features	N; (%)	Mean±SD	Meant±SD	Mean±SD	Mean±SD	Mean±SD
Gender						
Woman	175 (%71.1)	8.65±2.85	14.07±4.27	11.92±4.24	6.84±3.18	5.76±1.56
Man	71 (%28.9)	9.90±3.25	14.70±4.20	10.64±4.56	7.08±4.00	5.88±1.65
Test value and p		t:-2.722;**p: 0.007****	t:-1.440;p: 0.151	t:2.096;**p:0.037***	t:-0.608;p:0.544	t:-0.483;p:0.629
Marital Status						
Single 92(%37.4)		8.65±3.15	13.65±4.41	11.76±4.32	6.30±3.18	5.73±1.47
Married 154(%62.6)		9.25±2.95	14.70±4.13	11.44±4.40	7.26±3.00	5.85±1.65
Test value and p		t:-1.489;p:0.138	t:-1.803;p:0.073	t;-0.414;p: 0.679	t:-2.239;**p: 0.026***	t:0.414;p:0.597
Education status						
[a]Primary school	18(%7.3)	9.05±3.05	14.91±4.76	14.32±4.16	7.14±2.52	6.03±1.20
[b]Middle School	16(6.5)	8.60±2.75	15.12±3.92	14.16±3.76	8.70±2.82	5.19±1.77
[c]High school	75(30.5)	9.45±3.30	14.03±4.27	11.84±4.80	7.26±3.54	5.55±1.47
[d]University and↑	137(%55.7)	8.85±2.90	14.00±4.27	10.80±4.00	6.48±2.88	6.00±1.65
Test value and p		F:0.683;p: 0.563	F:0.689;p: 0.553	F:6.080;**p:0.001**** a>d; b>d	F:3.155;**p:0.026*** b>d	F:2.188;p:
Working status						
[a]Working	114(%46.3)	8.95±3.15	14.00±4.13	12.32±4.24	7.08±3.06	6.15±1.53
[b]Not working	79(%32.1)	8.55±2.60	14.28±4.13	12.72±4.56	7.44±3.30	5.40±1.59
[c]Retired	42(%17.1)	9.95±3.40	14.98±4.90	11.28±4.16	5.94±2.76	5.64±1.53
[d]Other (free, not working regularly)	11(%4.5)	9.50±2.55	15.33±4.06	8.32±2.32	4.80±2.22	5.85±1.74
Test value and p		F: 2.010;p:0.113	F:0.741;p: 0.528	F:4.337;**p:0.005**** b>d	F:4.080;**p:0.008**** b>d	F:3.885;**p: 0.010*** a>b
Health assurance						
Yes	229(%93.1)	9.00±3.25	14.21±4.27	11.36±4.40	6.78±3.12	5.88±1.56
No	17(%6.9)	9.10±2.90	15.33±3.85	13.92±3.44	8.22±3.12	4.83±1.77
Test value and p		t:-0.096;p:0.924	t:-0.993;p:0.321	t:-2.277;**p:0.024***	t:-1.774;p:0.077	t:2.612;**p: 0.010***
People they live with						
[a]Nuclear family	152(%61.8)	9.30±2.85	14.70±4.13	11.12±4.56	6.96±3.00	6.00±1.56
[b]Extended family	20(%8.1)	8.60±2.90	14.70±3.85	12.48±5.60	7.50±4.50	5.01±1.59
[c]Only	20(%8.1)	9.90±3.55	15.19±4.55	11.52±3.12	6.00±2.40	6.03±1.41
[d]Other (friends, neighbors etc.)	54(%22.0)	8.05±3.15	12.81±4.48	12.40±3.60	6.78±3.06	5.49±1.62
Test value and p		F:2.930;**p:0.034*** a>d	F:2.905;**p:0.035*** a>d	F:1.441;p:0.232	F:-0.826;p:0.481	F:3.270;**p:0.022*** a>b
Age 39.41±9.06 (min:20, max:63)		r:0.171;p:0.007**	r:0.048;p: 0.458	r:-0.010;p:0.870	r:-0.023;p:0.722	r:0.054;p:0.403

**p<.05; **p<.01; ***p<.001*

Table 2. *The Styles of Coping with Stress Scale (N:246)*

Scale Sub-Dimensions	Minimum Maximum Values that can be taken	Minimum-Maximum Values Patients Receive	Mean ± Standard Deviation
Optimistic Approach	0-15	1-15	9.00±3.05
Self-Confident Approach	0-21	2.03-21	14.35±4.27
Helpless Approach	0-24	2-23.04	11.60±4.40
Submissive Approach	0-18	0-16.98	6.90±3.12
Seeking Social Support	0-12	0.75-9	5.79±1.59

4. DISCUSSION

In this section, research and literature findings are discussed according to the findings of the study. The mean age of individuals with MS in our study was 39.41±9.06(min:20, maks:63), with 71.1 % (n:175) women, 62.6 % (n:154) married, 55.7 % (n:137) with education levels of university. Kiwi et al. (2019) put forth that the mean age of individuals with MS is 33.59 ± 8.70 (age interval: 18-57 years), that 67.8 % are women, 67.1 % are married(12).

Mean scores of men were observed to be higher at a statistically significant level compared with those of women in the optimistic approach sub-dimension($p<0.01$); whereas the mean scores of women in the hopeless approach sub-dimension were determined to be higher compared to men($p<0.05$). Dişçi et al. (2019) determined in their study that even though the difference between the ways of coping scale sub-dimensions and mean gender scores was not statistically significant; mean scores of women for self-confident approach, hopeless approach and seeking social support were determined to be higher than those of men; while the mean scores of men for optimistic approach and submissive approach were determined to be higher than those of women(13). Aung et al. (2018) reported in their study that individuals with MS mostly use self-confident approach(2.09±0.66), followed by optimistic approach(1.86±0.68), while the submissive approach is the least preferred approach(1.15±0.58). Individuals with MS strive to provide confidence and analyze their conditions in order to cope with stress and continue their lives like other people (14). In our study, it is thought that gender differences have an effect on coping with stress.

It was determined in our study as a result of examining the relationship between the ways of coping scale sub-dimensions and mean marital state scores that there is a statistically significant increase in the submissive approach sub-dimension mean scores($p<0.05$). Dişçi et al.(2019) put forth that optimistic approach, helpless approach, submissive approach and seeking social support are higher for married individuals compared to single individuals while also indicating that the self-confident approach is higher for single individuals(13). Öz et al.(2019) reported in their study that marred individuals who are receiving support experience more stress at a statistically significant level compared with single individuals(15). It was determined in our study as a result of evaluating the relationship between the ways of coping style sub-dimensions for individuals with MS and their education state mean scores that there is a statistically significant difference for the helpless approach and submissive approach sub-dimensions($p:0.001$, $p<0.05$). Dehghani (2020) reported in their study that university or higher education graduates adopt self-confident approach more that high school graduates at a statistically significant level($p<0.05$) (9). Aung 2018 indicated in the study on coping methods that the effectiveness of coping with stress increases with increasing education level (14). In our study, it is thought that the higher mean scores of married people compared to singles in coping with stress is the psychological and moral support provided by the spouses to each other.

The relationship between ways of coping sub-dimensions for individuals with MS and their employment state mean scores was examined as a result of which a statistically significant difference was observed in the helpless approach, submissive approach and seeking social support sub-dimensions($p<0.01$, $p:0.01$). Okanlı et al. (2017) carried out a study as a result of which it was indicated that psychosocial adaptation is closely related with effective coping strategies for individuals with MS (16). It has been put forth that cognition and stress establish an indirect connection between depression and anxiety in MS(17-18). Kobelt et al. (2017) carried out a study as a result of which it was reported that the submissive approach is used more by unemployed individuals (18). It has been stated in another study that MS has an adverse impact on the careers of 54 % of individuals with MS. It has been set forth that unemployed individuals use submissive approach more, that MS results in a decrease in income, loss of employment-status-career resulting in early retirement and negative impacts on career plans(19).

The increase observed in our study between the ways of coping scale sub-dimensions of individuals with MS and health insurance mean scores was observed to be at a statistically significant level in the helpless approach and seeking social support sub-dimensions($p<0.05$, $p:0.01$). Kiropoulos et al. (2020) indicated that factors that have an adverse impact on the quality of life of individuals with MS such as stress, anxiety, fatigue, pain, sleep disorders, insufficient social support, economic problems increase symptoms and attacks (20).

It was determined as a result of examining the relationship between the ways of coping scale sub-dimensions for individuals with MS and the mean scores of the individuals they live with that there are statistically significant differences in the optimistic approach, self-confident approach and seeking social support sub-dimensions($p<0.05$). It was determined as a result of a study carried out in Turkey on 50 patients diagnosed with MS that the majority of the patients use the self-confident and helpless approaches.The coping behavior of MS patients has been determined to be related with social support and especially the support from family, friends or MS patients(21-22). There is a negative relationship between coping strategies and nuclear family and social behaviors.

5. CONCLUSION

Individuals with Multiple Sclerosis(MS) mostly use helpless and submissive approaches in coping with stress during the Covid-19 pandemic.It was determined that the men display a more optimistic approach than women, while it was also determined that the women use the helpless approach more than men.It was put forth that the married individuals use the submissive approach more than the single individuals, while the primary school graduates use the helpless

approach more than the university.Unemployed individuals use the helpless and submissive approaches more than the others, while the employed individuals use the seeking social support style more than the unemployed.While those without health insurance use the helpless approach more, those with health insurance use the seeking social support style more.It was determined that those living with their nuclear families generally use the optimistic and self-confident approaches more.Hence, special trainings should be provided to individuals with MS for improving their ways of coping.Briefing meetings at MS associations, home visits, psychotherapies, various activities such as yoga etc. will have a positive impact on adaptation to symptom management and will also have a positive impact on coping with stress when the activities of the associations are able to provide social and physical support to the individuals. Support should be provided by the association to use stress coping methods more frequently for those who are primary school graduates and married and do not have social support. Due to the fact that individuals with MS remain closed at home during the pandemic process, services such as education and counseling can be planned online and support can be provided to individuals.

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Conflict of Interest

No conflict of interest has been declared by the author(s).

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Clinical and Experimental Health Sciences

Analysis of Glial Fibrillary Acidic Protein and Ubiquitin C-Terminal Hydrolase L1 in Postmortem Serum and Cerebrospinal Fluid in Traumatic Cerebral Deaths

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ABSTRACT

Objective: There is a growing body of research aimed at identifying biological markers that could indicate traumatic cerebral deaths such as traumatic brain damage in the postmortem period. In the event of astrocytic and neuronal injury, glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase L1 (UCH-L1) are released into cerebrospinal fluid and blood. In the postmortem identification of traumatic brain injury, the present research explores the ability of GFAP and UCH-L1.

Methods: Cerebrospinal fluid and blood samples were obtained from medicolegal autopsies, 17 cases with severe head trauma, 9 cases with the non-lethal head trauma group and 18 control cases. UCH-L1 and GFAP levels in postmortem cerebrospinal fluid and serum were determined from an enzyme-linked immunosorbent assay (ELISA).

Results: GFAP level in cerebrospinal fluid and serum was 2.68±0.67 ng/ml and 0.79±0.92 ng/ml in the lethal head trauma group, 2.74±0.64 ng/ml and 1.05±0.68 ng/ml the non-lethal head trauma group and 2.49±0.55 ng/ml and 1.05±0.89 ng/ml in the control group, respectively. UCH-L1 level in cerebrospinal fluid and serum was 3.02±0.68 ng/ml and 2.69±0.77 ng/ml in the lethal head trauma group, 3.34±0.70 ng/ml and 2.59±0.65 ng/ml the non-lethal head trauma group and 3.28±0.33 ng/ml and 2.74±0.34 ng/ml in the control group, respectively. Elevated cerebrospinal fluid and serum UCH-L1 and GFAP levels were observed in all cases, although absence of statistically significant difference between the trauma and control groups ($p>0.05$).

Conclusion: Further studies are needed to assess whether postmortem serum and CSF GFAP and UCH-L1 concentrations increase regardless of the cause of death.

Keywords: Traumatic brain injury, glial fibrillary acidic protein, ubiquitin C-terminal hydrolase L1, autopsy

1. INTRODUCTION

Traumatic brain injuries (TBI) are considered among common causes of mortality and morbidity. The majority of cases are associated with falls and traffic accidents (1). Deaths from traumatic injuries to the head, occurring particularly during traffic accidents and falls, hold an important place in the practice of forensic medicine (1). The primary tissue damage sustained during a head trauma may cause brain contusion, laceration, intracranial hematoma and skull fracture. A diffuse axonal injury can also occur as a result of the stretching and rupture of brain tissue and vessels following rapid acceleration-deceleration. Ischemia and hypoxia, which may not result directly from the trauma, brain edema, increased intracranial pressure and cellular changes caused by posttraumatic inflammatory processes, can lead to secondary damage (2,3). The effectiveness of various biomarkers has been investigated in the detection of TBI that occurs in patients after sustaining a head trauma. The identification of a biomarker that can indicate brain damage has been challenging due to the multitude of enzymes and proteins that are released into circulation, the complex structure of the brain and the diversity of the cells affected by trauma (4). Studies have identified such biomarkers as glial fibrillary acidic protein (GFAP) for astrocytic injuries; Alpha-II spectrin, c-TAU and phosphorylated neurofilaments (p-NF) for axonal injuries; and neuron-specific enolase (NSE) and ubiquitin c-terminal hydrolase isozyme L1 (UCH-L1) for neuronal injuries (5). These biomarkers can be detected in both blood and cerebrospinal fluid (CSF) following a traumatic brain injury (6). Recent studies have evaluated biomarkers of brain injury and their ability to identify traumatic brain injury in the postmortem period (3,7,8).

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GFAP is the main protein in the astroglial cytoskeleton. Under physiological conditions, GFAP is typically not detectable in the plasma of healthy individuals (9,10). GFAP levels have been reported to be detectable in the CSF and serum within the first hour, particularly in patients with serious to extreme TBI, as well as increased levels in ischaemic cell death and in ischaemic and hypoxic conditions resulting in necrosis (11,12).

The ubiquitin C-terminal hydrolase L1 enzyme is involved in the marking of both ubiquitin precursors and ubiquitinated proteins. UCH-L1 is specifically expressed at high levels in the neurons, and is estimated to account for 1–2% of the soluble proteins in the brain (13,14,15). It has been suggested, due to its abundance in neurons, that UCH-L1 could be used in clinical practice as a neuron-specific biomarker of traumatic brain injury. UCH-L1 levels in cerebrospinal fluid and serum starts increasing shortly after an injury, as does GFAP (4,16). The mechanisms by which biomarkers such as GFAP and UCH-L1 are released into the bloodstream remain unclear, although it has been proposed that cerebrospinal and interstitial fluid exchange, also known as the glymphatic system, and blood-brain barrier disturbance may be due to this (17,18,19). The blood UCH-L1 levels are also low in healthy subjects (4,20). In clinical trials, Diaz-Arrastia et al accepted the upper limit of normal for serum UCHL1 as 0.244 ng / ml (4).

Previous postmortem studies have demonstrated that GFAP can be found in the postmortem brain samples of both humans and gnawers (21,22). Recent studies have reported postmortem GFAP measurements in CSF and serum (7,8), and postmortem UCH-L1 measurements in CSF (23). However no postmortem measurements of UCH-L1 in the serum have been previously reported. The objective of this research is to carry out a postmortem review of the levels of UCHL-1 and GFAP in human serum and cerebrospinal fluid by means of an enzyme-linked immunosorbent assay (ELISA) and to determine the potential of these biologic markers as indicators of postmortem traumatic brain injury. These biomarkers were selected because UCHL-1 and GFAP measured different molecular events and began to increase shortly after injury.

2. METHODS

2.1. Subjects

This project was conducted after obtaining the approval of the Non-interventional Clinical Trials Ethics Committee with the number 60116787-020 / 81511. A total of 44 cases that underwent a medicolegal autopsy in the department of forensic medicine were included in this cross – sectional study. There were 17 cases in the lethal head trauma group, 9 cases in the non-lethal head trauma group, and 18 cases in the control group. In all cases, deaths had occurred at the scene. None of the 44 cases received cardiopulmonary resuscitation and were not hospitalized. Since lethal head trauma and non-lethal head trauma cases died at the scene, they were evaluated according to the investigation records and pathological findings during autopsy and were estimated to be acute death with a short survival time. The control cases were evaluated as acute death since they consisted of sudden cardiac deaths such as acute myocardial infarction. None of the cases had a history of neurodegenerative disease.

2.2. Collection and Storage of Samples

CSF and blood samples were obtained within 24 h of death in the routine forensic autopsies. A 5-ml blood sample obtained from the femoral vein by puncture and centrifuged at 3000 rpm for 15 minutes. A 3–4 ml CSF sample was collected using suboccipital puncture from the same cases and centrifuged at 4000 rpm for 10 minutes to separate it from the blood cells. Before taking the samples, the skin was decontaminated with a 90% ethanol solution. Hemolyzed samples were excluded. Centrifugation process was done according to Teunissen et al (2009) protocol standardization (24). Blood and CSF samples were directly stored at – 80°C freeze in Eppendorf tubes to protect the sample quality and minimize the impact of putrefaction after sample collection and centrifugation process. Later, samples were shipped on dry ice.

2.3. Human GFAP and UCH-L1 ELISA

The GFAP levels in CSF and serum samples were analyzed using a human GFAP ELISA kit (YL Biont Human glial fibrillary acidic protein (GFAP) ELISA Kit; Catalog number: YLA1905HU); and the UCH-L1 levels were determined using a human UCH-L1 ELISA kit (YL Biont Human Ubiquitin Carboxyl Terminal Hydrolase L1 (UCH-L1) ELISA Kit; Catalog number: YLA0790HU). The calibration range was reported to be 0.05 ng/ml→15 ng/ml and the sensitivity was 0.026 ng/ml for GFAP and the calibration range was reported to be 0.1 ng/ml→38 ng/ml and the sensitivity was 0.05 ng/ml for UCH-L1. The intra-assay precision was <8% and inter-assay precision was <10%. The tests were performed using a sandwich-based ELISA method, and all procedures were performed as per the manufacturer's protocol.

2.4. Human GFAP/UCH-L1 ELISA Test Protocol

The GFAP and UCH-L1 levels in the CSF and serum samples were determined using the ELISA kit protocols. Sufficient microwell strips were prepared for the standards, blinds and the number of samples to be tested, and each sample was studied in duplicate in standard, blind and control wells. The microwell strips were washed twice with 400 µl of Wash Buffer per well and the fluid remaining in the wells after washing was withdrawn. The Wash Buffer sat in the wells for 10–15 sec before being withdrawn. The standards were prepared as per the kit protocol. A 100-µl Sample Diluent solution was added to the wells spared for the blinds and a 50-µl Sample Diluent solution was added into the wells spared for the samples. A 50-µl sample was added to the relevant wells, and a 50-µl Biotin-Conjugate solution was added to all wells. The plate was covered with an adhesive film and incubated at room temperature for 2 hours. The adhesive film was removed and the wells were emptied and washed. A 100-µl Streptavidin-HRP solution was added to

all wells. The plate was covered with an adhesive film and incubated at room temperature for 1 hour. The adhesive film was removed and the wells were emptied and washed. A 100-µl TMB Substrate Solution was added into all wells. The strips were incubated at room temperature for 10 minutes. A 100-µl Stop Solution was added to all wells. The absorbance of each well was read at a primary wavelength of 450 nm using a spectrophotometer.

2.5. Statistical Analysis

Continuous variables were expressed in number and percent as mean ± standard deviation (SD), median (minimum-maximum values) and categorical variables. The Shapiro-Wilk Test was used to verify the normality of the distribution of data. The Kruskal-Wallis Variance Analysis was used to compare independent groups if parametric test conditions were not met. The Spearman correlation analysis was used to evaluate the relationships between continuous variables. The Chi-square analysis was used to investigate the discrepancies between categorical variables. The data was analyzed using the SPSS 25.0 software package. In all analyses, a p value less than 0.05 was considered statistically significant.

3. RESULTS

Of the 44 cases, 33 were male and 11 were female, with a mean age of 46.32±15.02 years (Median: 45, Min: 18–Max: 72). Of the cases with a lethal head trauma, eleven had sustained a motor vehicle crash and six had sustained falls. Their injuries included fractures to cranial bones, subarachnoid hemorrhages, subdural hemorrhages and brain contusions. Of the non-lethal head trauma cases, seven had sustained a motor vehicle crash and two had sustained falls, and these cases had suffered only abrasions and lacerations to the scalp. Death of the nine cases was attributed to chest and abdominal traumas. The cause of death was sudden cardiac death in cases in the control group, none of which had sustained a head trauma. In the control group, the causes of death were acute myocardial infarction in 15 cases, hypertrophic cardiomyopathy in 1 case and heart failure in 2 cases. Demographic data for all cases included in the study were shown in table 1.

The mean GFAP level in CSF was 2.68±0.67 ng/ml (range 1.91 – 4.41) in the lethal head trauma group, 2.74±0.64 ng/ml (range 2.05 – 3.89) in the non-lethal head trauma group, and 2.49±0.55 ng/ml (range 1.64 – 3.82) in the control cases. No statistically significant difference between the groups was observed (p=0.447) (Figure 1A).

The mean GFAP level in the serum samples was 0.79±0.92 ng/ml (range 0.06-4.02) in the lethal head trauma group, 1.05±0.68 ng/ml (range 0.05 – 3.88) in the non-lethal head trauma group and 1.05±0.89 ng/ml (range 0.36 – 2.61) in the control cases. No statistically significant difference between the groups was observed (p=0.279) (Figure 1B).

Table 1. *Demographic and pathological characteristics of all cases*

	All of cases (n= 44)	Lethal head trauma group (n= 17)	Non-lethal head trauma group (n= 9)	Control group (n= 18)
Sex				
Female	11	2	2	7
Male	33	15	7	11
Mean age, yrs (SD)	46.32±15.02	41.41±16.55	51.22±15.66	48.5±12.48
Postmortem interval, h (SD)	10.77±6.05	8.7±3.6	11.55±7.47	12.33±6.87
Mechanism of injury				
Motor vehicle crash	18	11	7	-
Fall	8	6	2	-
Cause of death				
Macroscopic cerebral hemorrhage	17	17	-	-
Macroscopic brain contusion	9	9	-	-
Fractures to cranial bones	11	11	-	-
Hemotorax	9	2	7	-
Macroscopic lung contusion	7	3	4	-
Intraabdominal hemorrhage	4	1	3	-
Intraabdominal solid organ lacerations	4	1	3	-
Acute myocardial infarction	15	-	-	15
Hypertrophic cardiomyopathy	1			1
Heart failure	2	-	-	2

The mean UCH-L1 level in CSF was 3.02±0.68 ng/ml (range 1.04 – 3.91) in the lethal head trauma group, 3.34±0.70 ng/ml (range 2.36 – 4.75) in the non-lethal head trauma group and 3.28±0.33 ng/ml (range 2.28 – 3.76) in the control cases. No statistically significant difference between the groups was observed (p=0.428) (Figure 2A).

The mean UCH-L1 level in serum was 2.69±0.77 ng/ml (range 1.32 – 4.80) in the lethal head trauma group, 2.59±0.65 ng/ml (range 1.85 – 4.11) in the non-lethal head trauma group and 2.74±0.34 ng/ml (range 2.27 – 3.48) in the control cases. No statistically significant difference between the groups was observed (p=0.545) (Figure 2B).

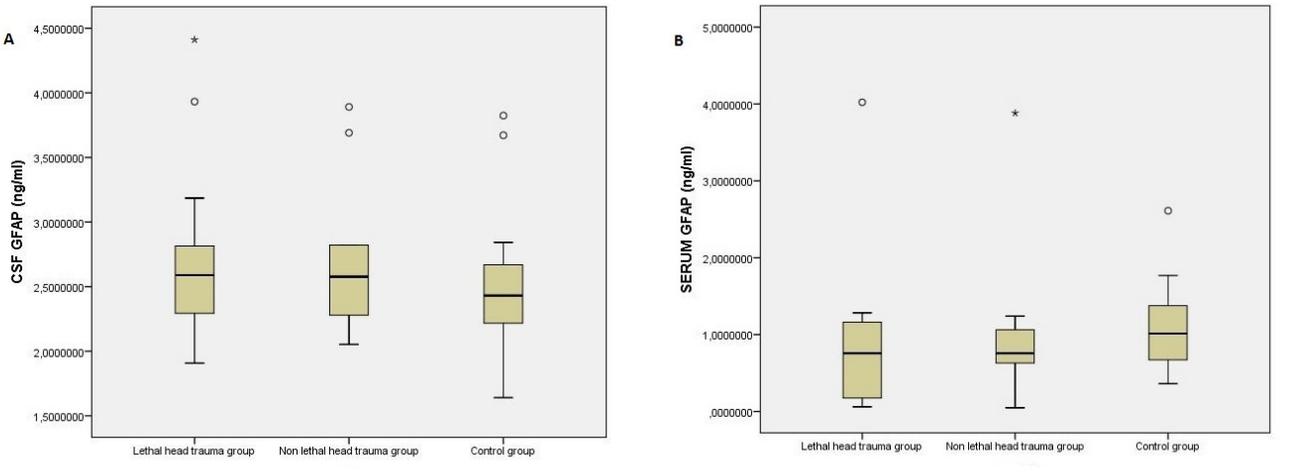

Figure 1. *A; GFAP concentrations in cerebrospinal fluid in the lethal head trauma group, the non-lethal trauma group and the control group. There was no statistically significant difference between the groups (Kruskal Wallis test, p>0.05). B; GFAP concentrations in serum in the lethal head trauma group, the non-lethal trauma group and the control group. There was no statistically significant difference between the groups (Kruskal Wallis test, p>0.05).*

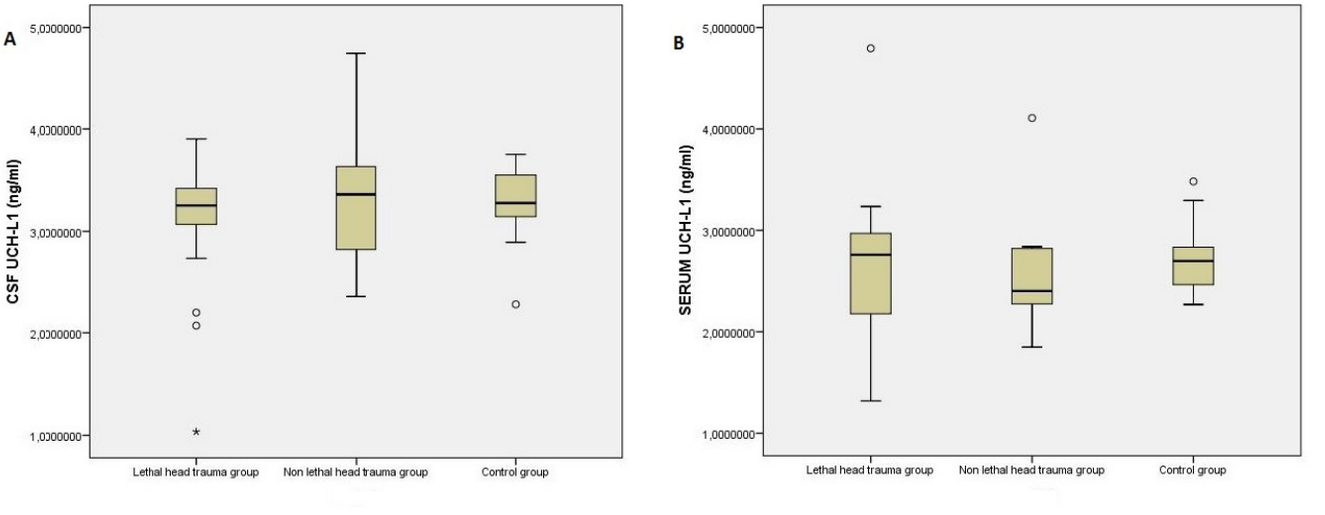

Figure 2. *A; UCH-L1 concentrations in cerebrospinal fluid in the lethal head trauma group, the non-lethal trauma group and the control group. There was no statistically significant difference between the groups (Kruskal Wallis test, p>0.05). B; UCH-L1 concentrations in serum in the lethal head trauma group, the non-lethal trauma group and the control group. There was no statistically significant difference between the groups.*

When the changes within each group are examined; there was no statistically significant difference between CSF and serum UCH-L1 concentrations in the lethal head trauma group (p> 0.05); CSF UCHL-1 concentrations were statistically significantly higher than serum UCH-L1 concentrations in the non-lethal head trauma group and the control group (p <0.05). The GFAP levels in CSF than serum was higher significantly in all groups was statistically significant (p <0.05) (Table 2).

We didn't observe correlation between CSF GFAP, serum GFAP, CSF UCH-L1, serum UCH-L1 levels and postmortem interval (Spearman's correlation coefficient r<0.20; p>0.05).

Table 2. *Serum and CSF UCH-L1 and GFAP concentrations*

		Mean	Standart Deviation	P value
Lethal head trauma group	CSF UCH-L1	3.02	0.68	0.176
	Serum UCH-L1	2.69	0.77	
	CSF GFAP	2.68	0,67	<0.001*
	Serum GFAP	0.79	0,92	
Non-lethal head trauma group	CSF UCH-L1	3.34	0.70	0.029*
	Serum UCH-L1	2.59	0.65	
	CSF GFAP	2.74	0.64	0.008*
	Serum GFAP	1.05	0.68	
Control group	CSF UCH-L1	3.28	0.33	<0.001*
	Serum UCH-L1	2.74	0.34	
	CSF GFAP	2.49	0.55	<0.001*
	Serum GFAP	1.05	0.89	

*GFAP: Glial fibrillary acidic protein; UCH-L1: Ubiquitin c-terminal hydrolase isozyme L1; CSF: Cerebrospinal fluid. *p<0.05 statistically significant*

4. DISCUSSION

In this study evaluating the potential of biological markers, such as GFAP and UCH-L1, in the prediction of traumatic brain injury in the postmortem period in patients with head trauma, GFAP and UCH-L1 levels could be measured by ELISA in the postmortem CSF and serum samples. It was found in the present study that CSF and serum GFAP and UCH-L1 concentrations are increased both in cases with lethal head trauma and in those who died of non-cerebral causes; however, the discrepancy was not statistically relevant between the groups. These results suggest that the changes in postmortem CSF and serum GFAP and UCH-L1 concentrations are independent of the underlying neurological disorder.

There have been only a few studies in literature evaluating postmortem GFAP concentrations in CSF and serum (7,8). In the study by Olzack et al (2018) the mean GFAP concentration in the CSF was found to be 2346.75±1312.33 pg/ml in head trauma cases and 201.21±66.65 pg/ml in control cases, showing a significantly higher concentrations in the head trauma cases. On the other hand, Breitling et al (2018) evaluated postmortem serum GFAP concentrations and found no statistically significant difference between deaths due to primary cerebral causes and non-cerebral deaths in terms of GFAP concentrations (8). Similar to the findings of Breitling et al (2018), no significant difference was identified in the present study CSF and serum GFAP concentrations between cases who died of head trauma and deaths related with non-cerebral causes. It was hypothesized in the present study that GFAP and UCH-L1 levels will be elevated particularly in severe traumatic brain injuries, and that these markers could be useful in the postmortem diagnosis of traumatic brain injury. The present results reveal, however, that postmortem GFAP and UCH-L1 levels were high regardless of the cause of death, suggesting that other mechanisms could exist that are responsible for this increase. Breitling et al (2018) suggested that increases in postmortem GFAP concentrations in non-cerebral deaths could be attributable to perimortem pathophysiological events that trigger GFAP release (8). Clinical studies report that hypoxia and ischemia may lead to an increase in GFAP concentrations in the CSF and serum by causing a breakdown of astroglial cells and a disturbance of the blood-brain barrier (25,26). In patients who have suffered non-traumatic out-of-hospital cardiac arrest, GFAP levels have been shown to be high (25). An increase in GFAP levels due to hypoxia has also been reported in the patients with neonatal hypoxic ischemic encephalopathy (26). In this study, as the control group consisted of cases of acute cardiac death (such as acute myocardial infarction) that did not receive cardiopulmonary resuscitation and were not hospitalized, an increase in these markers may be due to cardiac death-induced hypoxia.

As a neuron-specific cytoplasmic enzyme, UCH-L1 has been researched as a marker of neuronal injury in the clinical trials of TBI and brain ischemia (4,16,27). It has been reported that UCH-L1 becomes detectable within a couple of hours of trauma (28). The mechanisms by which UCH-L1 is transported from the brain compartments into the circulatory system are yet to be clearly understood, although it has been suggested that it is released into the circulatory system due to neuronal damage and increased permeability of blood-brain barrier (27,29). In the present study, postmortem UCH-L1 concentrations in CSF and serum were found to be increased both in cases with lethal head trauma and in those who died of non-cerebral causes. Other stress factors in the perimortality phase and under hypoxic and ischemic conditions may be affecting UCH-L1 secretion and concentrations, independently of neurological disorders. Clinical studies have indicated increased UCH-L1 concentrations resulting from hypoxic brain injury and disruption of the blood-brain barrier in pediatric patients that survived cardiac arrest, and in patients in whom cardiac arrest was induced for the repair of an aortic aneurysm (30,31). In a postmortem study, Piette et al (2011) reported that a relationship could exist between ubiquitin immunoreactivity in locus coeruleus and the duration of agony (32).

The relatively low number of cases can be considered a limitation of the present study. Since the cases have a short survival time, biomarker release due to mechanical cell trauma may not have been realized at level to distinguish it from other causes of death. The fact that it is high in acute myocardial infarction may be due to the fact that the process of agony is accompanied by a certain extent of cerebral hypoxia. We believe further research is needed with a larger sample in this topic. Different from other studies, however, the simultaneous investigation of the biomarkers of trauma both in the blood and cerebrospinal fluid is one of the strengths of the present study.

5. CONCLUSIONS

In this study postmortem serum and CSF UCH-L1, and GFAP levels, were high in deaths resulting from both traumatic cerebral and non-cerebral causes. Since there are studies in the literature that report different results in this topic, it is thought that other studies to be performed by classifying them according to survival time after trauma are needed. In addition, immunohistochemical studies may be useful to see the effect of hypoxic and agonal processes on biomarker release.

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Conflicts of interest

The authors declare that they have no competing interests.

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Clinical and Experimental Health Sciences

Development of Triamcinolone Acetonide Loaded Poly(lactic-co-glycolic acid) Dry Powder Inhaler Formulations for the Treatment of Asthma

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ABSTRACT

Objective: The objective of this study was to develop triamcinolone acetonide (TAA) loaded poly(lactide-co-glycolic acid) (PLGA) dry powder inhaler (DPI) formulations by using spray dryer and to characterize the formulations with reference to their appropriateness for pulmonary drug delivery.

Methods: PLGA dry powder inhalers containing TAA were produced in two stages. In the first step, PLGA microparticles were prepared by emulsion-solvent evaporation method and the DPI formulations were produced by the spray-drying process using mannitol and leucine. TAA loaded PLGA DPI was classified physicochemical properties. The in vitro dissolution test was carried out using modified USP apparatus 2. Aerosol performance was identified with next generation impactor.

Results: This study has demonstrated that TAA loaded PLGA DPI were effectively prepared. Scanning electron microscope illustrates the spherical shape, particle size (D50) was established to be between 2.7-3.1 µm and all formulations charged negatively. Special chemical interaction in the DPI was not observed by FT-IR. The in vitro aerosol performance study represented DPI formulations have the proper aerodynamic properties for targeting the lungs. The in vitro TAA release from DPI formulations decreased with increasing of PLGA concentration.

Conclusion: Developed PLGA dry powder inhaler formulations containing TAA have shown suitable aerodynamic characteristics to be administered to the lungs thereby could improve in the management of asthma by increasing TAA residency in the lungs for a prolonged period of time.

Keywords: Triamcinolone acetonide, pulmonary drug delivery, dry powder inhaler formulations, poly(lactide-co-glycolic acid), spray dryer

1. INTRODUCTION

Asthma is an illness caused by chronic inflammation of the large and small airways resulting in airway hyper-responsiveness and excessive mucous secretion. It is considered by various levels of symptoms of wheezing, shortness of breath and airflow obstruction (1). According to Global Initiative for Asthma (GINA) report 2021, GINA recommends that all adults and adolescents with asthma should obtain inhaled corticosteroids (ICS) containing controller treatment, to lessen the risk of severe exacerbations. However, there are side effects associated with this treatment, such as dysphonia and oral candidiasis. Up to 58% of patients report dysphonia at the same time as using inhaled corticosteroids (2).

The most crucial parameter defining the site of deposition of aerosol drugs within the respiratory tract is the particle characteristics of the aerosol. Good distribution all the way through the lung entails particles with an aerodynamic diameter between 1 and 5 µm (3). The inhaled corticosteroid formulation contains a particle size larger than 5 µm, triggering local side effects. Subsequent to the inhalation, more or less, 10–60% of the inhaled dose is deposited in the lungs. The fraction of ICS (40–90%) deposited in the oropharynx can result in local oropharyngeal side effects (4). Triamcinolone acetonide (TAA) is an effective corticosteroid used as first-line treatment of asthma in preventing asthma exacerbation. The local infections of the oropharynx with *Candida albicans* came about as a side effect in the commercial item for consumption containing TAA. The basis for this is that only 26% of the active substance reached the lungs in administration devoid of using spacer (5, 6).

Presently, DPI prepared with polymeric materials that endow with sustained release for local targeting is of great interest. Poly(lactic-co-glycolic acid) (PLGA) is a non-toxic, biodegradable and biocompatible polymer approved by Food and Drug Administration (FDA) and European Medicines

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Agency for drug delivery applications that have been expansively used in the encapsulation of drug molecules to augment their clinical efficacy (7).

The aim of the study was to develop and evaluate TAA loaded PLGA DPI for high pulmonary delivery, to increase the deposition and absorption of TAA in the deep lungs, thereby increasing the therapeutic efficacy. It is the first time demonstrated PLGA DPI formulation of TAA intended to pulmonary route. PLGA DPI containing TAA were characterized with respect to their morphology, particle size and size distribution, in vitro release and aerodynamic behaviour.

2. METHODS

2.1. Materials

TAA, leucine, polysorbate 80, polysorbate 20 and sodium lauryl sulphate (SLS) were obtained from Sigma-Aldrich (Poole, U.K). PLGA (50:50) was purchased from Boehringer Ingelheim (Ingelheim Rhein, Germany). Mannitol was purchased from Roquette (Lestrem, France). Polyvinyl alcohol (PVA) (MW 20.000–30.000) was purchased from Acros (Geel, Belgium). Solvents were HPLC analytical grade (Merck, Darmstandt, Germany).

2.2. Determination of TAA by HPLC

An Agilent 1100 Series HPLC system (Santa Clara, CA, USA) equipped with thermostated column compartment and a UV absorbance detector were used for determination of TAA. The column temperature was controlled at 25 °C. The detection wavelength was set at 236 nm. Chromatographic separation was carried out on the Thermo Scientific Hypersil ODS column (250x4.6 mm, 5 µm). The mobile phase was a mixture of water and acetonitrile [60:40] (8) and the retention time for TAA was 6.85 min. The method was validated according to the guideline Q2 (R1) of ICH.

2.3. Preparation of PLGA Microparticles Containing TAA

TAA loaded PLGA microparticles were prepared by emulsification solvent evaporation technique. TAA and PLGA were dissolved in 2 mL acetone as internal phase and this organic solution was added to 20 mL external aqueous phase containing PVA (1% w/v) as a stabilizing agent. The resulted suspension was homogenized at 20.000 rpm using a high-speed homogenizer (Ultra-Turrax, IKA T-18, Germany) for 2 minutes. Once the emulsion was formed, it was kept under constant agitation for 2 hours in order to remove the organic solvent by evaporation. The microparticles formed were separated by centrifugation at 30.000 rpm (Optima MAX-XP Beckman Coulter, California, USA) for 1 h and the precipitated microparticles were washed twice by deionized water, using centrifuge (15.000 rpm for 15 minutes) to eliminate remained PVA. In conclusion, the obtained microparticles were dried at room temperature for 1 day and weighted. (9).

2.4. Determination of Entrapment Efficiency

TAA content in the PLGA microparticles was assessed by dispersing 3 mg of microparticles in 5 ml in pH 7.4 PBS with 1% SLS. The dispersion was shaken for 24 hrs. Then, it was centrifuged at 15.000 rpm for 30 min and the amount of TAA in the supernatant was analyzed by HPLC. The entrapment efficiency expressed in percentage were calculated according to Equation 1 (n=6) (10).

Drug entrapment efficiency (%) = (calculated drug concentration/ theoretical drug concentration) × 100.....(1)

2.5. Preparation of PLGA Dry Powder Inhaler Formulations Containing TAA

Microparticles (30%), Mannitol (50%) and leucine (20%) were suspended in 50 mL deionized water then was spray-dried with constant stirring using a Büchi Nanospray dryer B-90 (Büchi Laboratory-Techniques, Flawil, Switzerland) under the following conditions: Nozzle: 5.5 µm mesh, inlet temperature 80°C, outlet temperature 40-42°C, gas flow rate 116-120 L/ min, Pressure: 31-36 mBar. The resultant spray dried powders were collected and yield percentage was calculated by the following Equation 2 (11).

Spray-drying yield = weight of collected powder / total mass of all ingredients of each formulations.....(2)

2.6. Characterization of the Formulations

Differential scanning calorimetry Analysis

Differential scanning calorimetry (DSC) of PLGA was performed using DSC-8000 (Perkin Elmer, Waltham, Massachusetts) equipped with a thermal analysis data acquisition software. The sample (between 3 – 6 mg) was heated in an aluminum pan using dry nitrogen as the effluent gas. The analysis was performed at a rate 10 °C /min from 25 °C to 300 °C temperature range under nitrogen flow of 20 mL/min.

Thermogravimetric Analysis

Thermogravimetric analysis (TGA) of the formulations was performed using a Perkin Elmer (TGA-4000, Waltham, Massachusetts) instrument. A ceramic pan was loaded with sample and heated from 25 to 250°C at a rate of 10°C/min under dry nitrogen flowing at rate of 40 mL/min.

Fourier-Transform Infrared Spectroscopy

Fourier-transform infrared (FT-IR) spectra of the samples were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer attached with an attenuated total reflectance accessory (Perkin Elmer Spectrum 100, Waltham,

Massachusetts) with wave numbers ranging from 4000 cm^{-1} to 650 cm^{-1}, using four scans with a resolution of 4 cm^{-1}.

Particle Morphology

The surface morphology of the formulations was evaluated using scanning electron microscopy (SEM, Quanta 250 FEG, Hillsboro, OR) at 15 kV, with magnifications of 10.000 × and 25.000×.

Particle Size Distribution and Surface Charge

The size of the particles was determined by laser diffraction with a dry sample dispersion system (Mastersizer 3000, Aero S, Malvern instruments, UK). D50 represent the equivalent diameters at 50% cumulative volume of the particles. The size distribution Span was calculated according to Equation (3). Zeta potential (ZP) of formulations were measured by photon correlation spectroscopy (Nano ZS, Malvern Instruments, UK) (n=3).

Span = D90-D10/D50.....(3)

2.7. Aerodynamic Particle Size Analysis

The aerodynamic particle size whose allocation has been identified was analyzed by using a Next Generation Impactor (NGI, Copley Scientific Ltd., Nottingham, UK) and a standard pharmacopeial procedure was used (USP 39 (601). A dry powder having an inhalation apparatus (Aerolizer®, Novartis, Switzerland) was filled with a No. 3 hydroxypropyl methylcellulose capsule (Capsugel, France). The flow rate was adapted to a pressure drop of 4 kPa, resulting in a flow rate of 100 L/min for 2.3 s. Following aerosolization progression, the disseminated powders remained in the capsule and the powder deposited in the entire the parts of NGI were gathered using mobile phase and analyzed by HPLC. The fine particle fraction (FPF), emitted dose (ED), respirable fraction (RF), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were determined. The emitted dose (ED), fine particle fraction (FPF), and respirable fraction (RF) were calculated as follows (Equation (4,5,6):

Emitted dose (ED%) = (Initial mass in capsules – Final mass remaining in capsules)/ Initial mass in capsules × 100%..... (4)

Fine particle fraction (FPF%) = Mass deposited on stages 2 through 7/ Initial particle mass loaded into capsules × 100%.....(5)

Respirable fraction (RF %) = Mass deposited on stages 2 through 7/ Initial particle mass on all stages × 100%.....(6)

2.8. Solubility Studies

The solubility of TAA was determined in: deionized water, phosphate buffer (PB) pH 7.4 and modified PB pH 7.4 which contained 1% (w/v) sodium lauryl sulphate (SLS), 2% (w/v) polysorbate 80 and 2% (w/v) polysorbate 20. The excess amount of TAA were added to 5 mL solutions and shaken for 24 hrs at room temperature. Samples centrifuged at 10.000 rpm for 10 min (n=6). The amount of TAA in the samples was analyzed by HPLC.

2.9. In Vitro Dissolution Studies

Dissolution testing was performed on 15 mg spray dried powders using "paddle over disc" method previously described (12). For the dissolution test, NGI was run to ensure that sufficient formulation dose was accumulated at stage 2-3. After dose collection was completed, part of the dissolution cup was removed and a 55 mm diameter pre-soaked polycarbonate membrane was placed over it. 300 ml phosphate buffer pH 7.4 containing 1% (w/v) of SLS was used as dissolution media. Dissolution testing was performed in accordance with sink conditions, at 37 ±1 °C with a paddle rotating speed of 75±2 rpm. Six samples from each formulation (F1, F2 and F3) were studied. 1 ml of sample was withdrawn at each time interval and replaced with fresh dissolution medium to maintain the sink condition. Samples (1 mL) were analyzed by HPLC.

2.10. Statistical Analysis

For drug release data one-way analysis of variance (ANOVA) and post hoc Tukey-Kramer multiple comparisons were performed (GraphPad Prism 5, La Jolla, USA). Data were shown as mean ± standard error of mean (S.E.M.) and $p<0.05$ was accepted as statistically significant.

3. RESULTS

3.1. Preparation and Physicochemical Properties of PLGA Dry Powder Inhaler Formulations Containing TAA

TAA loaded PLGA microparticles were prepared effectively by emulsion-solvent evaporation method and the DPI formulations were formed subsequent to spray-drying process using mannitol and leucine as DPI carriers. Unclustered and comparatively monodisperse TAA loaded PLGA DPI were attained. SEM images of DPI formulations displayed almost spherical structures with smooth surfaces devoid of pores or voids (Fig. 1). As given in Table 1, the entrapment efficiency of PLGA microparticles increased in conjunction with augmenting polymer concentration. The entrapment efficiency for all microparticle formulations was greater than 41% and the uppermost entrapment efficiency was noted down in the F1 formulation with 54.5%.

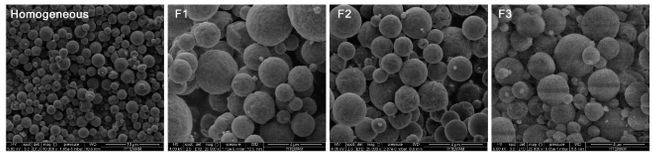

Figure 1. *SEM micrographs of DPI formulations.*

It has been confirmed that gathering microparticles by spray drying is proficient and convenient, and furthermore, it increases the percent yield (13). The process yields for DPI formulations were between 48.7% and 64.6%, processing of fewer polymers given higher percent yield.

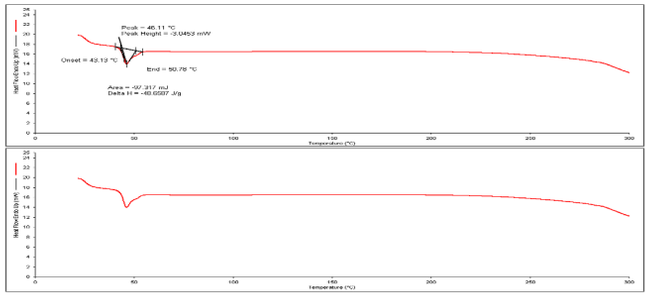

Figure 2. *DSC thermogram of PLGA*

Figure 2 shows the DSC thermogram of PLGA and the amorphous nature of PLGA indicated an endothermic peak at 46.11 °C corresponding to the polymer transition temperature (Tg). The water content of DPI formulations was 2%–2.3% indicating that water was removed during the spray-drying process.

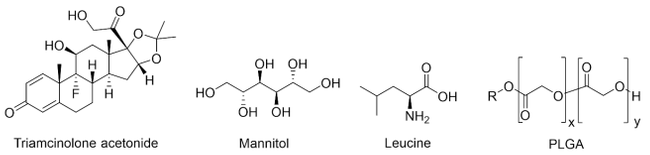

Figure 3. *Chemical structures of the compounds used in the DPI formulations*

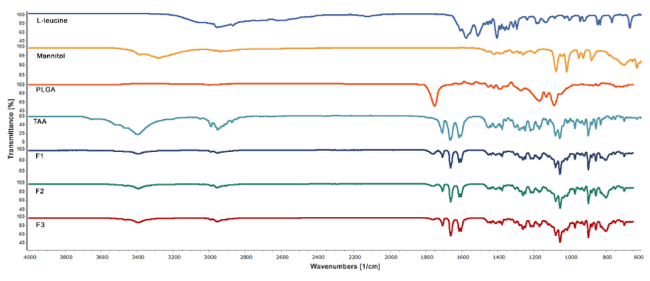

Figure 4. *FT-IR spectra of the formulations and formulation components*

The chemical structures of the compounds (Fig. 3) were assessed by using FT-IR analysis (Fig. 4). The FT-IR spectra of PLGA displayed a carbonyl stretching band at 1750 cm^{-1}, C(=O)-O stretching band at 1172 cm^{-1} and O-C-C stretching band at 1086 cm^{-1} thus indicating the presence of ester functional group. Other bands observed at 2999-2952.2, 1423 and 1386 cm^{-1} can be assigned as C-H stretching, C-H asymmetric and symmetric bending bands respectively. The FT-IR spectra of mannitol exhibited a hydroxyl group stretching band and an out of plane – OH bending band at 3283 cm^{-1} and 700.99 cm^{-1}, respectively. The C-O stretching bands for mannitol were also observed as two sharp bands at around 1080 and 1020 cm^{-1} region. Additionally, two bands observed at around 1419 and 1350 cm^{-1} region are a result of the coupling vibrations between OH in-plane bending and C-H wagging vibrations which can be confirmative for primary and secondary alcohol groups in mannitol structure. The observed – $NH3^{+}$ stretching bands (3062 cm^{-1}), asymmetric (1605 cm^{-1}) and symmetric – $NH3^{+}$ bending vibrations (1512 cm^{-1}), asymmetric (1575 cm^{-1}) and symmetric (1405 cm^{-1}) C=O stretching bands in FT-IR spectra of leucine were in agreement with the literature C=O stretching bands in FT-IR spectra of leucine were in agreement with the literature (14). The latter also displayed C-N stretching, O-H out of plane bending and N-H rocking bands at 1296, 920 and 666 cm^{-1}, respectively. TAA, has – OH stretching band at 3395 cm^{-1} and C-H stretching bands at 2991.7-2873.5 cm^{-1} as expected. The dioxole residue of the molecule yielded with a C-O-C asymmetric stretching band at 1055 cm^{-1} whereas tertiary and secondary alcohol groups produce C-O stretching and O-H out of plane bending vibrations at 1218, 1079 and 700 cm^{-1}, respectively.

The particle size distribution and ZP values of the DPI formulations were presented in Table 1. All formulations exhibited relatively narrow range distributions of <5 µm and with spans in the range of 2.19±0.13 –2.73±0.39, which were appropriate for DPI formulations. Zeta potential measurements make available information about particle stability in the formulation. The higher value indicates better stability due to repulsion between particles and homogeneity of the system on account of reducing aggregation. ZP values were negative and varied between – 19.4±0.39 and – 25.4±2.7. The result showed that increasing of TAA in the formulation increased the negative zeta potential. Similar results were reported by Yildiz et al. (15).

Table 1. *Physical characterization of formulations.*

Code	TAA:PLGA	D50±SD (µm)	Span	ZP±SD (mV)	Process yield±SD (%)	Entrapment efficiency±SD (%)	Water content±SD (%)
F1	10:1	3.1±0.3	2.73±0.3	-19.4±2.6	48.7±2.9	54.5±2.2	2.3±0.4
F2	20:1	2.8±0.4	2.34±0.2	-22.6±1.8	59.4±3.2	47.9±2.8	2±0.6
F3	30:1	2.7±0.1	2.19±0.1	-25.4±2.7	64.6±2.1	42.3±1.4	2.1±0.2

TAA: triamcinolone acetonide; PLGA: Poly (lactic-co-glycolic acid); ZP: zeta potential, SD: standard deviation.

3.2. Aerodynamic Particle Size Analysis

The aerodynamic characteristics of the formulations analyzed with NGI are shown in Table 2. MMAD assessment of between 1 and 5 µm is preferable for targeting the respiratory region of the human lung (16). MMAD and FPF varied from 2.46±0.4 to 4.1±0.3 µm and 39.42±1.4 to 54.17±1.3%, respectively. Despite the fact that all formulations were executed beneath the similar spray-drying circumstances, F1 showed the smallest MMAD. Likewise, FPF of FI was considerably superior to that of F2 and F3. Even though the quantity of polymer is declined by half, RF values of F1 and F2 was near to each other. ED uniformity for all formulations was in the high range (93.68±1.28–98.31±1.77%) for pulmonary route. The GSD (1.73 to 1.91) values of formulations pointed out that the formulations are suitable for pulmonary delivery (17).

Table 2. *The aerodynamic characteristics of DPI formulations measured by NGI.*

Formulations	FPF±SD (%)	ED±SD (%)	RF±SD (%)	MMAD±SD (µm)	GSD± SD
F1	54.17±1.3	98.31±3.9	78.51±2.7	2.46±0.4	1.73±0.2
F2	43.39±2.3	97.24±2.4	78.06±3.4	3.77±0.8	1.91±0.5
F3	39.42±1.4	93.68±2.8	70.92±2.9	4.1±0.3	1.83±0.4

FPF: fine particle fraction; ED: emitted dose; MMAD: mass median aerodynamic diameter; GSD: geometric standard deviation, SD: standard deviation.

3.3. Solubility Studies

Solubility studies aimed to determine the appropriate dissolution media that provides sufficient sink conditions for the release of TAA from DPI formulations. PB pH 7.4 + 1% (w/v) SLS exhibited maximum solubility for TAA. Results are depicted in Table 3.

Table 3. *Solubility of TAA in different dissolution media.*

Dissolution media	Solubility (µg/mL) ± SD
Deionized water	17.28±0.7
Phosphate buffer pH 7.4	18.76 ±1.1
Phosphate buffer pH 7.4 + 1% (w/v) sodium lauryl sulphate	833.41± 12.9
Phosphate buffer pH 7.4 + 2% (w/v) polysorbate 80	162.23 ±7.4
Phosphate buffer pH 7.4 + 2% (w/v) polysorbate 20	51.32 ±3.6

SD: standard deviation.

3.4. In Vitro Dissolution Studies

Figure 5 illustrates in vitro release profiles of TAA from DPI formulations. All formulations showed a biphasic release profile with an initial burst release followed by slower release (18). The release percentages of TAA were 37.6% for F1, 46.01% for F2, and 62.93% for F3 at 12 hrs.

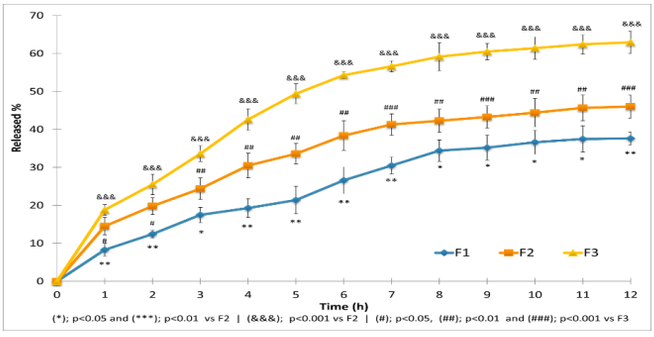

Figure 5. *In vitro release profiles of TAA in phosphate buffer, pH 7.4 + 1% SLS.*

4. DISCUSSION

Images were acquired using an SEM, as provided in Fig. 1, DPI formulations were fairly spherical, smooth, and regular. The drug: polymer concentrations of which the formulations did not radically affect the morphologic properties. In addition, the outlet temperature of spray dryer was below the glass transition temperature of PLGA (Tg ≈ 47 °C) hereby, the structural forms of the microparticles were preserved and prevented from accumulating on the wall by softening of microparticles (19). PLGA concentration in the oil phase is a key factor having an effect on the entrapment efficiency of PLGA microparticles containing TAA. Microparticles were prepared using PLGA by altering concentration as given in Table 1. Increase in concentration of polymer led to an improvement in drug entrapment efficiency (from 42.3% to 54.5%) (20). Panyam et al. (21) indicated that as PLGA amount increases in the formulation, hydrophobic drugs will mix with PLGA more and thus higher drug entrapment efficiency will be achieved. The percentage of water content results was about to each other in all formulations. Generally, low moisture is expected in the spray-dried powders as a high amount of moisture can decrease particle dispersion by the formation of interparticle forces. One of the reasons for the low moisture content in formulations is that mannitol has a lower moisture absorption capacity than lactose and glucose, improving the flow properties of powders for inhalation (22).

Considering the IR spectra of all formulations, the overlapping of carbonyl enlarging band of PLGA, leucine and TAA yielded with a broad band at around 1700 cm^{-1}. Conversely, N-H rocking and C-O-H in plane bending vibrations were probative for leucine, while vinyllic stretching bands and out of plane bending of – OH were confirmative for TAA and mannitol, respectively. In brief, the FT-IR spectra of the three PLGA matrix (F1, F2, F3) unveiled the predictable vibrational bands and didn't demonstrate any supplementary or unexpected absorbsions thus suggesting physical entrapment of TAA within the PLGA matrix. The FT-IR analysis was employed as to accumulate information about the probable interactions

of the compounds utilized for the formulations of the study. Since TAA loaded PLGA DPI didn't exhibited any additional vibration bands in the FT-IR spectra, that there wasn't any molecular interaction between the compounds used for the formulation can be concluded.

It is well known that particles less than 5 µm can be dispersed deep into the smaller airways and the penetration concerned correlates well with a good quality clinical necessity to a treatment which is found locally. All DPI formulations possessed small D50 values with narrow span in particle size distribution which was suitable for inhalation. The SEM images were confirmed by the results obtained. Moreover, increasing the concentration of PLGA will enlarge the particle size of microspheres. The increase in the amount of PLGA increases the viscosity of the solutions, resulting in the formation of larger particles. Similar results established by Han et al. (23). The charge on the respiratory system is negative owing to mucin (24). Negative charge on the respiratory system and negative charged DPI microparticles could repulse each other and microparticles can advance to the deep lung region without collapsing in the upper airway. In a similar study, Mali et al. (25) studied on budesonide DPI formulation which has shown negative surface charge of −17.5 mV.

It is essential to assure that the microparticles might be potentially delivered to the pulmonary route as the target organ. Thus, FPF is an eminent parameter for identifying the aerodynamic behavior of spray dried particles (26). In the present study, an augmented lung deposition of F1was observed as measured up to F2 and F3. This may be correlated to the presence of higher polymer ratio, which reduced the agglomeration of the particles. F1 was easily dispersed to aerosols characterized by high FPF. This situation is additionally confirmed by the data taken from FPF of F3. As FPF of F3 value was the lowest among formulations, indicating strong cohesiveness between the particles by reason of having the lowest amount of polymer. Furthermore, presence of L-leucine in formulations brings about decline in particles interaction and augment in fine particle fraction. The motive why l-leucine is able to efficiently increase the aerosolization performance of the spray dried powders might be attributed to its anti-adherent and surface active properties, consequently affecting the aerosolization properties of the powders (27). Besides the fine particle fraction for lung deposition of a drug formulation, another important factor is mass distribution of the MMAD. Likewise, MMAD of F3 value was higher than F1 and F2. Devrim et al. (28) suggested that the increase in the MMAD values was related to the aggregate formation by the particles during the aerosolization because of the effect of cohesive forces. GSD values above 1.5 all powders can be regarded as polydisperse, which is typical for most pharmaceutical aerosols (29). The GSD values were in the range of 1.73 to 1.91, all formulations showed low GSD values, which indicated that the aerosolized particles were narrowly distributed in size. Based on the experimental data, the zeta potential of formulations has less impact on FPF. F1 formulation has the highest FPF and lowest MMAD and GSD values among all formulations. The present results indicate that F1 could reach the lungs in high amounts.

According to solubility studies, TAA was most dissolved in phosphate buffer pH7.4+ 1% SLS, therefore, phosphate buffer pH7.4+ 1% SLS was used as dissolution media to ensure the sink condition. FDA has allowed some surfactants, such as SLS and polysorbates, to be used as dissolution enhancers. However, FDA has approved the use of SLS up to 2% in dissolution media (30). Considering in vitro dissolution study, two stages could be determined according to the rate of drug release; phase I is defined as burst release and phase II shows sustained release (31). Owing to TAA released from the pores near the particle surface, burst release could have occurred within 2 hours in all formulations. F1, F2 and F3 showed an initial drug release of 12.46±1.01%, 19.82±2.2% and 25.5±2.7% respectively. Thereafter, the drug release rate depends on the molecular diffusion rate in the polymer matrix or erosion from the particle matrix and this is attributed to phase II. During this stage, TAA encapsulated inside the PLGA microparticles could be released out slowly. The rate of release of the drug from each DPI formulation differed owing to the amount of PLGA in formulations. The rate limiting step is the amount of PLGA in the formulations. As expected, the release rate slowed down as the PLGA ratio in the formulations increased (32). Hence, F3 with the lowest PLGA ratio reached the highest drug release (62.93±2.86%) among formulations. In other words, TAA was hardly released from F1 because the degradation rate of PLGA in F1 was slower than F2 and F3. Also, one of the reasons leading to slow diffusion of TAA from polymeric matrix might be low swelling of the polymer in the dissolution medium. Among the formulations, F1 has the highest polymer concentration and increasing the polymer concentration in the formulation causes a decrease in the swelling rate. Since the amount of polymer in the F3 formulation is the least compared to the F1 and F2 formulations, it is thought that the F3 formulation has the highest swelling capacity in the dissolution medium, so the release pattern is quite different from the F1 and F2 formulations. As observed, there was a significant rise in the release rate of F3 among formulations.

In terms of statistical analysis, at all time points, the drug release was different from each other, which was statistically higher in the F3 formulation than in the F2 and F1 formulations, and in the F2 formulation than in the F1 formulation.

5. CONCLUSION

TAA-loaded PLGA DPI prepared and evaluated in this study could provide prolonged drug delivery to the lungs, by which it will not only increase the therapeutic efficacy as decreasing the therapeutic dose but also endow with a useful inhaler dosage form for patients suffering from asthma.

Conflict of Interest

The author stated that there are no conflicts of interest regarding the publication of this article.

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Clinical and Experimental Health Sciences

Breast Cancer in Men: Risk Factors, Treatment Options, Quality of Life: Systematic Review

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ABSTRACT

Objective: The aim was to systematically examine the risk factors that have a role in the development and prognosis regarding the breast cancer among men and patients' survival rate, and the studies performed to determine the treatment methods and patients' quality of life.

Methods: The databases of PubMed, Scopus, Cochrane Library, OVID-LWW, Medline Complete, Science Direct, Taylor&Francis, ULAKBIM, Ethos, OpenThesis, Open Dissertation, ProQuest Dissertations & Theses Global, and National Center of Theses were used to screen the literature. Case-control and cohort studies published between 2000 and 2020 were included. Following the screening activity, 14 studies were included in the systematic review.

Results: This study involved seven cohort and seven case-control studies. Most of the patients were followed with invasive carcinoma diagnosis. These studies aimed to examine the genetic mutations and impacts of environmental, anthropometric and hormonal factors in regard to the risk factors. The factors such as the molecular classification of cancer, presence of genetic mutation, cancer stage and treatment methods affected the prognosis and survival rate. Mastectomy was used as the first treatment option, and this process had adverse impacts on patients' quality of life physically, mentally and emotionally.

Conclusion: This study indicated that many risk factors played a role in the development and prognosis of breast cancer among men and their survival rate, that mastectomy was the primary treatment option, and that patients' quality of life was adversely affected during/following the disease.

Keywords: male breast cancer, risk factors, treatment, quality of life.

1. INTRODUCTION

Breast cancer is the most frequent type of cancer among women but is quite rare among men. Although the prevalence of breast cancer among men was 1% or less, this rate has been increasing in recent years (1,2)). According to 2020 estimations made by the American Cancer Society, 2620 people in United States of America will be diagnosed with this disease, and 520 of them will lose their lives (3). Although many aspects of breast cancer have been understood due to various reasons such as high number of studies conducted with women or effective operation of screening programs, informational deficiencies are experienced as the number of cases among men is limited, samples of these studies are limited or relevant studies are retrospective. Thus, diagnoses are generally made at a later period (2,4,5). Moreover, the amount of information on the ethology of male breast cancer is quite limited compared to the information on breast cancer among women (6,7). The literature indicates genes, age, hormones boosting the estrogen level, factors related to lifestyle or environmental factors (1,8,9)). The treatment methods used on women are also used on men. However, while lumpectomy is often preferred for women while mastectomy is the procedure performed on men (4). The treatment method is shaped by different factors such as tumor type, stage, or hormone receptor (10)). The presence of informational deficiency in the society may direct people to believe that men do not have breast tissue and thus they cannot suffer from breast cancer (11)). Therefore, people diagnosed with breast cancer may suffer from concerns related to embarrassment and stigma, which may affect their quality of life (1).

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This study aimed to systematically examine and present the data of the studies reviewing the risk factors which have a role in the development and prognosis regarding the breast cancer among men and patients' survival rate, and the results of studies performed to determine the treatment methods and patients' quality of life following the diagnosis.

2. METHODS

The systematic review was carried out in accordance with the PICOS format. It was determined as: P (population): Male breast cancer patients, I (Intervention): Not applicable, C (Comparator(s)): Men that didn't have breast cancer, O (Outcome(s)): risk factors, prognostic factors, treatment options, quality of life, S (Study design): case-control and cohort studies. This systematic review was conducted from PubMed, Scopus, Cochrane Library, OVID-LWW, Medline Complete, Science Direct, Taylor&Francis, ULAKBIM databases and Ethos, Open Thesis, Open Dissertation, ProQuest Dissertations & Theses Global, and National Center of Theses databases. The screening was performed using the Turkish and English keywords. To determine the English keywords, Medical Subject Headings (MeSH) were used, and to determine the Turkish keywords, Turkish Science Terms Dictionary (TBT) was utilized. Then, the keywords of "male breast cancer", "male breast tumors", "male breast neoplasm", "risk factors", "treatment", "life quality", "quality of life" and "health-related quality of life" and relevant combinations were used, and screening was performed between January and April 2020. The last screening activity was performed at 5 April 2020. The flow chart regarding the literature screening is presented in Figure 1. The case-control and cohort studies were included as the number of cases was limited. The protocol of the study was registered by PROSPERO (ID: CRD420.201.78399).

The inclusion criteria were as follows:

- Samples containing people aged 18 years or older,
- Publication in English or Turkish,
- Publication between 2000 and 2020,
- Accessibility to the full text,
- Breast cancer as the primary diagnosis among men.

Manuscripts with, qualitative studies, systematic review, meta-analyses, case reports, editorial reports, short reports and descriptive, or cross-sectional study designs were excluded.

Ethic Consideration

This study was a systematic review; no ethics committee approval was required. The researcher also declares that there was no conflict of interest in this study.

Risk of Bias in Individual Studies

Two researchers independently reviewed full texts. Newcastle Ottawa Scale used to evaluate the study criteria. The scale is scored between 0-9 and the higher the score, the higher the quality of the study (12). Total quality scores were shown in Table 1 and Table 2.

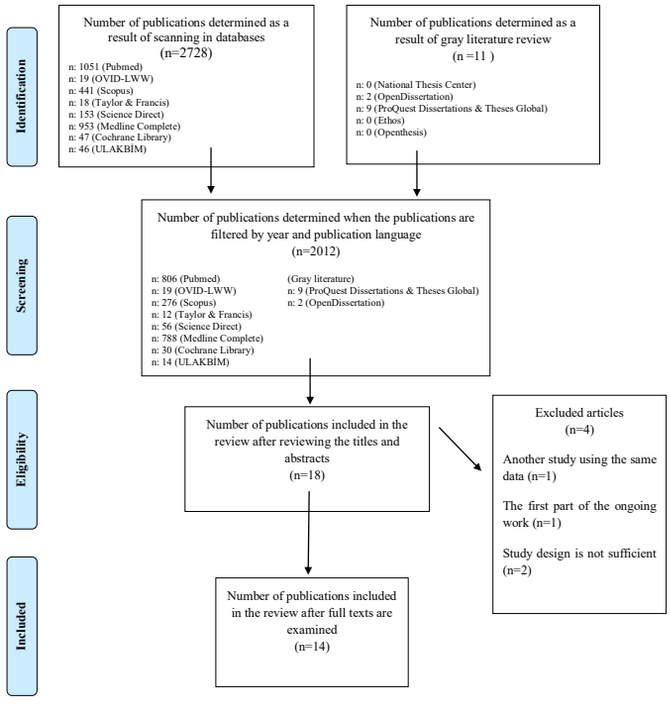

Figure 1. *PRISMA chart regarding the literature screening*

Table 1. *Properties of the reviewed cohort studies*

Author/year and country	Study objective	Sample	Duration of monitoring	Age*	Cancer type	Main results	Newcastle Ottawa Scale Score (0-9)
André et al. (2019) Portugal	Determining the parameters used to define the treatment and characterization of male breast cancer and assessing the relationship between these parameters and healthy and general survival	196	Mean 84.9 months	Diagnostic age: 66.5 (min-max: 31-89) of the patients, 55.1% were aged between 40 and 69 years maximum	of the patients, 39.2% were diagnosed with invasive carcinoma	Forty-four patients were assessed in terms of BRCA mutation and 15 had BRCA2 mutation. A relationship was found between BRCA2 mutation, family history, bilateral cancer, high Ki-67 presence, PR (progesterone receptor)-(negative), and Luminal B-like tumors. A relationship was found between Luminal B-type, BRCA2 mutation, high Ki-67 presence, second and third stage, short and healthy survival and general survival period. Moreover, a relationship was found between the ages below 70 years and low survival rate. The treatments performed on patients included; • Surgical (90.3%) / 4.6% lumpectomy • Radiotherapy (63.3%) • Hormonotherapy (60.2%) • Chemotherapy (37.2%)	8
Keinan Boker, Levine, Leiba, Derazne & Kark (2018) Israel	Assessing the relationship between the body mass index of adolescent men aged between 16 and 19 years and male breast cancer	1,382,093 people were monitored. Breast cancer was found in 100 male people.	21.3±12.5 years on average	17.3±0.4 at the early stages of monitoring 38.6±12.6 at the end of monitoring 46.9±8.7 years as the diagnostic age	of the patients, 75% were diagnosed with infiltrative ductal carcinoma	People with excessive weight and obesity were found to have a higher risk of breast cancer compared to those with normal weight. Minimal risk among adolescents was seen among those with a body mass index of 21.0 kg/m^2; the risk was found to be significantly high among the adolescents with a body mass index higher than 24.2 kg/. European people had higher risk compared to Asians, Africans and Israelis.	7
Rugo et al. (2013) USA	Assessing the demographic characteristics of black and Caucasian people diagnosed with HER-2 (human epidermal factor receptor) positive metastatic breast cancer, treatment methods and clinical results	919 Caucasian: 793 Black: 126	Duration of monitoring for Caucasian people: 28.4 months Duration of monitoring for black people: 21 months	Caucasian: 54 (min-max: 22-92) Black: 50 (min-max: 20-90)	61% of Caucasian people and 50.8% of black people had stage 1-3 for more than 12 months following the first diagnosis Cancer type not specified	Compared to the Caucasian people, black people had; • breast cancer at an earlier age • higher obesity prevalence • diabetes at a rate higher than two times • and a co-morbid cardiovascular disease higher than two times. Adjuvant systematical treatment was performed in both races (Caucasian: 75.4%, black: 66.7). Transtuzumab was used as the preliminary medication for both people before the first progression. ER/PR (estrogen receptor/progesterone receptor) was negative for most black people, but it was positive for most of the Caucasian people. As hormonotherapy could not be preferred as a treatment method, number of those who received chemotherapy was higher compared to Caucasian people. In addition, the progression-free survival duration of black people was shorter than that of Caucasian people, and black people had a higher mortality risk. The regional metastasis risk was higher among black people, and only the bone or bone-breast metastasis development rate was higher among Caucasian people.	8

Author/ year and country	Study objective	Sample	Duration of monitoring	Age*	Cancer type	Main results	Newcastle Ottawa Scale Score (0-9)
Turashvili et al. (2018) USA	Assessing the relationship between the 21-gene recurrence score of male patients with ER+(positive)/ HER2-(negative) breast cancer and treatment type.	38	34 months (1.05-133.3)	70 (min-max: 40-84)	Diagnosis of invasive ductal carcinoma for 63.2%	21-Gene recurrence score; • Low in 26 cases (<17) • Moderate in 9 cases (18-30) • High in 3 cases (≥31). Total mastectomy was performed for all patients. Radiotherapy was administered to a patient thereafter. As a hormonal therapy; • 31 patients received tamoxifen • Three patients received aromatase inhibitor. Five patients were treated with adjuvant chemotherapy along with the hormonal treatment (moderate recurrence score for three patients, and high recurrence score for two patients) Consequently, only one patient experienced distant metastasis 29 months after the monitoring, but other patients showed no distinctive symptoms.	8
Zhou et al. (2010) China	Determining the changes in the treatment methods used for male breast cancer patients and effectiveness of radical mastectomy and modified radical mastectomy	70 patients in total Two groups Cohort A (1969-1997): 35 Cohort B (1998-2009): 35	3-391 months (median 55 months) **Cohort A** 1969-1997 **Cohort B** 1998-2009	Of all patients: 61 (min-max: 27-90) Cohort A: 60 (min-max: 27-90) Cohort B: 62 (min-max: 32-80)	of the patients, 81.4% were diagnosed with infiltrative ductal carcinoma	Cohort A • Multidisciplinary treatment was performed for 26 patients (74.3%). • Adjuvant chemotherapy was not conducted for 23 patients (65.7%). • Radiotherapy was not conducted for 25 patients (71.4%). • Hormonal treatment was not performed for 26 patients (74.3%). • Radical mastectomy was performed for 26 patients (74.3%) Cohort B • Multidisciplinary treatment was performed for 33 patients (94.3%). • Adjuvant chemotherapy was conducted for 23 patients (65.7%). • Radiotherapy was not conducted for 31 patients (88.6%). • Hormonal treatment was conducted for 23 patients (65.7%). • Radical mastectomy was performed for 19 patients (54.3%). No difference regarding the five-year survival rates was found between the groups that underwent radical mastectomy and modified mastectomy. The treatment methods were monitored in ten-year periods and modified radical mastectomy was found to be preferred more in the last 10 years. Therefore, both methods were found to be equally effective. Presence of axillary node involvement, advancement of cancer stage and performing post-operative radiotherapy were found as the potential factors that may adversely affect the five-year survival rate.	8

Author/year and country	Study objective	Sample	Duration of monitoring	Age*	Cancer type	Main results	Newcastle Ottawa Scale Score (0-9)
Zongo et al. (2018) Burkina Faso (Western Africa)	Determining the diagnostic stages, treatment models and five-year survival rates of male patients with breast cancer	51	1990-2009	60.9±8.4	Of the patients, 91.1% were found to have epithelial tumors (ductal and lobular carcinoma)	The disease stage was three and four for 88.8%. Surgery was the primary treatment method. 31 patients were operated. Of the patients who underwent surgery, 80.6% underwent mastectomy with axillary dissection, 12.9 had mastectomy and 6.5% had lumpectomy. 15 patients (29.4%) underwent chemotherapy while 11 received (21.6%) hormonal treatment. Radiotherapy was performed in two cases. The five-year survival rate was found to be 49.9%. The survival duration of stage one and two patients was found to be longer than five years while the survival rate of stage three and four were found to decrease from 54 months to 36 months.	7
Son et al. (2012) Korea	Determining the BRCA1/2 mutation prevalence among the patients of high-risk, non-familial breast cancer	758 patients in total Female: 741 Male: 17	May 2007-May 2010	Not specified	Not specified	65 out of 758 patients (8.6%) had mutation in BRCA1/2 genes. None of 17 patients had BRCA1 gene mutation, while only one of them had BRCA2 mutation. BRCA1/2 mutation prevalence was found to be higher than 10% for the people with a history of cancer diagnosis before the age of 35 years, bilateral breast cancer, and personal breast and ovary cancer.	7

**Median (min-max); Mean±Standard deviation (SD)*

Table 2. *Properties of the reviewed case-control studies*

Author/year and country	Study objective	Sample	Age*	Cancer Type	Main Results	Newcastle Ottawa Scale Score (0-9)
Andrykowski (2012) USA	Determining the physical and mental states of men following the development of breast cancer and specifying their medical behaviors	Case: 66 Control: 198	Case: 66.2±15.9 Control: 65.9±15.8	Not specified	Data were collected using Behavioral Risk Factor Surveillance System (BRFSS) The duration after the diagnosis was made was found to be 12±10.9 years. Compared to the control group, the case group; • had more co-morbid disease history • had less satisfaction from their lives • had poor general, mental and physical health statuses in the last month • Due to the physical, mental and emotional problems, they had more limitations in their activities. 16 indicators were assessed in regard to medical behaviors. No significant different was found between the medical behaviors of the case group, with only one exception that case group had less exercising time in the last month.	8
Guenel et al. (2004) Denmark, France, Germany, Italy, Sweden	The role of alcohol consumption for male breast cancer was examined.	Case: 74 Control: 1432	Not specified Patients aged between 35 and 70 were included	-	Alcohol consumption varied between 30.2 to 46.9 g/day within the case groups; Regarding the control groups, this rate ranged from 19.8 to 38.3 g/day, meaning the case group had higher alcohol consumption rate. Alcohol consumption of 60g/day significantly increased the risk for cancer. In cases where this rate was higher than 90 g/day, the risk was found to increase by six times. In addition to alcohol consumption; gynecomastia, diabetes, male factor fertility problems, injuries to head and every 1 kg/m^2 increase in body mass index had a significant relationship with the cancer risk. A daily alcohol consumption routine of 10g was found to increase cancer risk by 16%.	8
Orr et al. (2011) England	Determining whether the single nucleotide polymorphism changes within 2q35, 5p12, 6q25.1, 10q26.13 and 16q12.1 chromosomes, which create breast cancer among women, cause the development of male breast cancer.	Case: 433 Control: 1569	Median diagnostic age 65.5 (Interquartile range: 59-72)	of the patients, 92% were diagnosed with invasive carcinoma	A significant relationship was found between five single-nucleotide polymorphism and male breast cancer. These are • rs13387042 (2q35) • rs10941679 (5p12) • rs9383938 (6q25.1) • rs2981579 (FGFR2) • rs3803662 (TOX3) A comparison between the male breast cancer risk rates and published risk rate for women indicated a significant difference regarding genders withinthree polymorphism. These are • rs13387042 (2q35) (riskier for men than women) • rs3803662 (TOX3) (riskier for men than women) • rs6504950 (COX11) (riskier for women than men)	8

Author/year and country	Study objective	Sample	Age*	Cancer Type	Main Results	Newcastle Ottawa Scale Score (0-9)
Ottini et al. (2014) Italy	Assessing the impact of the changes within the Arg213His [638G(A)], a functional polymorphism of sulfotransferase 1A1 (SULTH1A1) enzyme that plays a key role in estrogen metabolism, on the development of male breast cancer	Case: 394 Control: 786	Not specified	-	A significant difference regarding the SULT1A1 Arg213His genotype distributions was found between the case and control groups. SULT1A1 Arg213His variant could be a risk factor with low penetration for male breast cancer. Moreover, a significant relationship was found between SULT1A1 risk genotype and HER2.	8
Palli et al. (2007) Italy	Determining the relationship between BRCA2 N372H variant and male breast cancer risk.	Case: 99 Control: 261	Case: 67.9±11.8 Control: 55.9±6.9	-	Of the people in case group, eight (8.1%) were found to have BRCA1/BRCA2 gene mutations. Six (6.1%) had BRCA2 mutation while two (2.0%) were found to have BRCA1 mutation. No significant difference was found between the BRCA2 N372H genotypes and case and control groups. In addition, people over the age of 60 years had increased cancer risk rate. HH homozygote genotype was found to increase the risk for the men aged over 60 years.	7
Silvestri et al. (2018) Italy	Assessing the FANCM mutation on male breast cancer	Case: 506 (negative BRCA1 and BRCA2 mutations) Control: 854	Mean diagnostic age: 61.5 (min-max: 22-90)	of the patients, 80.2% were diagnosed with invasive ductal carcinoma	Two FANCM mutations, c.1432C>T (p.Arg478Ter) and c.1972C>T (p.Arg658Ter), were found in two people from the case group. Although the frequency of mutation was higher in the case group, no significant difference was found between both groups. FANCM c.5101C>T mutation was not be found in the case group, but FANCM c.5791C>T mutation was seen in two people in the control group. In addition to these two mutations, other rare partial mutations could play a role in increasing the sensitivity to cancer.	7
Villeneuve et al. (2018) Denmark, France, Germany, Italy, Sweden	Assessing the role of environmental chemicals and profession on the male breast cancer	Case: 104 Control: 1901	Not specified.	-	• Cancer risk was high for wood processing sector, paper manufacturers, • machinists of motor vehicles, • painters, • paper manufacturers, • people of wood crafting sector, • medical and social service staff • and those who sell and repair motor vehicles. Risk rate increased for every ten year or longer for the machinists of motor vehicles, and the risk was found to decrease for farmers and agricultural workers, despite being not significant. A significant relationship was found between the alkyl phenolic compounds, which are environmental chemicals, and risks. The risk could increase for the machinists of motor vehicles due to petrol, petrol solvents or polycyclic hydrocarbons.	8

**Median (min-max); Mean±Standard deviation (SD)*

3. RESULTS

Keywords were used in the first section of the literature screening activity, and 2739 studies were found. Within the second section, studies were filtered based on the year of publication and language. Consequently, 2012 studies were found. These studies were systematically organized examining the relevant titles and abstracts and using Mendeley reference management program to review 18 full study texts with suitable study designs. Following the quality assessment, 14 studies were included in the systematic review (Figure 1). Moreover, seven cohort and seven case-control studies were found among these studies. The characteristics of cohort studies are present in Table 1 while the qualities of case-control studies are provided in Table 2.

3.1. General Properties of Cohort Studies

Cohort studies were found to have been published in 2010, 2012, 2013, 2018 and 2019. Of these studies, two were conducted in the United States of America (USA) while others were conducted in Portugal, Israel, China, Burkina Faso and Korea. The number of people monitored in those studies varied between 38 and 1,382,093, and the duration of monitoring ranged from 21 to 391 months. The patients within those studies were mostly diagnosed with invasive carcinoma (Table 1). A cohort study examining the quality of life was not found. Cohort studies included one study that reviewed the risk factors directly affecting the development of breast cancer. The study by Keinan Boker et al. (2018) indicated that people with obesity or extra weight had a higher risk of developing breast cancer compared to the people with normal weight. Moreover, European people had a higher risk of developing breast cancer compared to Asian, African and Israeli people (2). In the study by Son et al. (2012) who assessed the gene mutation prevalence of BRCA1/2 in terms of the risk factor after developing breast cancer, only one out of 17 patients in the sample of 758 patients (both genders) had BRCA2 mutation. In addition, BRCA gene mutations were found to be capable of having a greater role for the patients who developed cancer before the age of 35 years and had bilateral breast cancer, breast and ovary cancer histories (13).

Other cohort studies reviewed the factors that affected prognosis and/or survival rate. André et al. (2019) examined 196 people for 84.9 months and found a relationship between Luminal B type cancer, BRCA2 mutation, high Ki-67 value, age over 70 years, advanced cancer stage and survival rate (4). Rugo et al. (2013) examined 917 people for racial differences and found that prognosis of black people was worse than that of Caucasian people, and that black people's survival rate was lower (14). Zhou et al. (2010) conducted a study on 70 people to compare treatment options and activities for breast cancer among men and found that presence of axillary node involvement, implementation of postoperative radiotherapy and failure to perform hormonal treatment adversely affected prognosis and/or survival (15).

The treatments performed in the studies indicated that mastectomy was used as the first treatment option and that surgical procedure were assisted with radiotherapy, hormonotherapy and chemotherapy. Turashvili et al. (2018) found in their study that mastectomy was initially performed on almost all patients (n=38), and that surgical procedure was assisted with hormonotherapy rather than radiotherapy (5). André et al. (2019) found that 90.3% of 196 patients underwent a surgical procedure, followed by radiotherapy, hormonotherapy and chemotherapy, respectively (4). Zhou et al. (2010) found in their study where they compared the treatment options for 70 patients with breast cancer that multidisciplinary treatment methods were mostly used and that there was no difference between radical mastectomy and modified radical mastectomy (15). Zongo et al. (2018) revealed that 31 patients out of 51 underwent a surgical procedure, and that 80.6% of these patients underwent mastectomy along with axillary dissection mastectomy while 12.9% underwent mastectomy and 6.5% experienced lumpectomy. Moreover, within the same study, 15 patients (29.4%) underwent chemotherapy while 11 received (21.6%) hormonal treatment (16).

3.2. General Characteristics of Case-control Studies

Case-control studies were published in 2004, 2007, 2011, 2012, 2014 and 2018. Of these studies, three were conducted in Italy, two were performed in more than one country (Denmark, France, Germany, Italy and Sweden), and the others were conducted in England and USA. The number of participants in case groups ranged from 66 to 506, and the number of people in control groups were between 198 and 1901. Regarding the risk factor, four studies reviewed the genetic factor while one examined the alcohol consumption, and one investigated the professional factors (Table 2).

Regarding the studies examining the genetic factors, Orr et al. (2011) found that there could be a relationship between the single-nucleotide polymorphisms of rs13387042 (2q35), rs10941679 (5p12), rs9383938 (6q25.1), rs2981579 (FGFR2), rs3803662 (TOX3) and development of breast cancer, while Ottini et al. (2014) indicated that variant of sulfotransferase 1A1 (SULTH1A1) enzyme SULT1A1 Arg213His could have a relationship with the development of breast cancer, and Silvestri et al. (2018) revealed that there could be a relationship between two partial FANCM mutations of c.1432C>T (p.Arg478Ter) and c.1972C>T (p.Arg658Ter) and development of breast cancer (8,17,18). The study conducted by Palli et al. (2007) to examine the relationship between BRCA2 N372H variant and breast cancer development risk for men indicated that there was no significant difference regarding the mutations between the case and control group but people younger than 60 had higher cancer risk and HH homozygote genotype could increase the risk for the men younger than 60 (7).

Two articles on the relationship between men's habits, current diseases, professions and cancer development were examined, and among them, the study by Guenel et al. (2004)

on the impact of alcohol consumption on breast cancer development found that an alcohol consumption rate of >60 g (gram)/day increased the risk significantly (a 16% increase in the risk for every increase on 10 g in the consumption). In cases where this rate was higher than 90 g/day, the risk was found to increase by six times. In addition to alcohol consumption; gynecomastia, diabetes, male factor infertility problems, injuries to head and every 1 kg/m^2 increase in body mass index were found to have a significant relationship with cancer risk (6). Villeneuve et al. (2018) performed a risk assessment based on professional groups and found that people working in wood processing sector, machinists of motor vehicles, painters, paper manufacturers, people of wood crafting sector, medical and social service staff, and those who sell and repair motor vehicles had higher cancer development risk (19).

Treatment methods were not included in these studies, but one study was found to have examined the quality of life. The study conducted by Andrykowski (2012) to assess patients' physical and mental statuses following the diagnosis of breast cancer found that general, mental and physical statuses of those in the case group were not good compared to those of the control group, that they had more limitations in their activities due to physical, mental or emotional problems, and that their quality of life was poor (1).

4. DISCUSSION

The results of this systematic review that examined the risk factors, treatment options and quality of life which play a role in the development and prognosis of male breast cancer and men's survival rate will be compared to the information in the literature.

This review indicated that many genetic and environmental factors, excessive weight or obesity, and variables such as alcohol consumption, diabetes, age or cancer stage affected the development/prognosis of breast cancer, thus the survival rate, which was also mentioned in the results section (2,4,18,19,6–8,13–17). Brinton et al. (2014) examined the anthropometric and hormonal risk factors that played a role in the development of male breast cancer and found that body mass index was the most important factor in regard to the risk and that conditions that create hormonal changes such as Klinefelter syndrome, gynecomastia, diabetes, cryptorchidism or orchid could create risks related to the breast cancer (20). Moreover, another study by Brinton et al. (2008) that examined the risk factors found that family history and obesity significantly increased the breast cancer risk and that alcohol consumption had no relationship with the risk, which contradicts with the relevant result in this compilation (21). The study conducted by Ewertz et al. (2001) revealed that cancer history in the family, obesity that started ten years before the diagnosis, and use of digoxin and methyldopa could be a risk factor for the development of male breast cancer (22). Regarding the studies examining the factors that had an impact on the prognosis and/or survival rate, Ravi et al. (2012) found that advanced age, high cancer stage and increased tumor size adversely affected the prognosis (23). Yadav et al. (2020) similarly indicated that advanced age, black race, and increase in tumor grade and disease stage adversely affected the prognosis, and therefore reduced survival rate (24).

According to the studies examined within the review, the first method preferred for the treatment of male breast cancer was mastectomy. Moreover, lumpectomy was found to be performed less, and treatment methods such as radiotherapy, chemotherapy and hormonotherapy were used as supportive treatment methods (4,5,15,16). The studies examining the treatment methods used for the male people diagnosed with breast cancer included the study by Ravi et al. (2012) who found that modified radical mastectomy was used as the standard treatment method and that radiotherapy, chemotherapy and hormonotherapy were performed as the post-surgical adjuvant treatment methods (23). Another similar study by Yadav et al. (2020) found that 71.3% of the patients underwent total mastectomy and 23.7% had lumpectomy (24). Rushton et al. (2014) examined 73 female and 73 male patients and found that all of men underwent mastectomy while 38 out of 73 women had this procedure (25). The retrospective study conducted by Wan et al. (2018) to examine 161 male patients found that 88.8% of them had a surgical procedure, and the most frequent surgical procedure was mastectomy (93%) (26).

Result of one study reviewed about of the quality of life following the breast cancer development was stated that people's physical, mental and emotional health statuses were not good and that people had limitations in their activities due to the their problems (1). The study by Ruddy et al. (2013) evaluated the quality of life of the male patients who survived the breast cancer and found that patients had hormonal and sexual problems and that these problems affected their quality of life (27). Moreover, another study examining the quality of life collectively assessed the women and men with breast cancer and compared their results with the results of healthy male population. That study found that men with breast cancer had higher scores from the physical function, role function-physical, pain, vitality, social function, role function-emotional and mental health subdimensions of quality of life compared to the women with the same disorder, meaning men had higher quality of life than women in these subdimensions. Results of men with breast cancer indicated that they gained lower scores from all subdimensions compared to the scores of healthy male population and male population aged between 61 and 70 years, meaning the quality of life of men with breast cancer was lower (28).

The limitation of our review is that we excluded all studies that did not report cohort and case control, another limitation of the review process may lead to a restriction (English, Turkish).

5. CONCLUSION

This systematic review was found that many factors such as age, body mass index, occupation, alcohol consumption, genetic factors (mutations), hormonal factors, diabetes, injuries to head and fertility had a role in the development of male breast cancer. Moreover, factors such as the molecular classification of cancer, presence of genetic mutation, cancer stage and treatment method affected the prognosis and survival rate. Although the treatment type varied by the factors such as cancer type, tumor size and stage, and axillary lymph node involvement, the main treatment method was surgery. Mastectomy was generally performed as the surgical procedure, but lumpectomy was preferred less. Regarding the quality of life, development of breast cancer adversely affected patients' physical, mental and emotional statuses.

Due to the fact that there is an informational deficiency regarding the male breast cancer in the literature, awareness of the risk factors and treatment methods to be used and supporting the people bio-psychosocial so that they are affected from this period to the lowest degree are important. Therefore, multi-centered prospective studies are needed to increase the sample size.

Conflict of interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript

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Clinical and Experimental Health Sciences

Current Approach to Spermatogonial Stem Cells in Vitro Maturation

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ABSTRACT

The studies conducted to determine the stage of its usability in prospective fertility restoration of testicular tissues taken from prepubertal patients undergoing oncology treatment were screened. In addition, the current status of spermatogonial stem cell cultures, testicular tissue cultures, and testicular organoid research and their potential in fertility restoration were examined.

Spermatogonial stem cells are only found in prepubertal testicular tissue. Germinal serial cells are not found. Since spermatozoa are not produced in this period, spermatogonial stem cells are stored by freezing in the form of testicular tissue pieces or testicular cell suspension. It is not yet clear how to ensure the maturation of freeze-thawed or fresh spermatogonial stem cells for fertility reconstruction when it is necessary. The spermatogonial stem cells can be placed in their original niche by maintaining the vitality of the seminiferous tubules in vitro. Then, it can be transplanted to the recipient.

Many hypotheses suggested that that maturation can be achieved via such as two-dimensional, three-dimensional tissue cultures. To ensure differentiation and proliferation of spermatogonial stem cells in three-dimensional cultures, it is necessary to ensure the long-term viability of the seminiferous tubules in vitro or solve creating an environment similar to the seminiferous tubules niche.

In this review article, spermatozoa could be obtained in three-dimensional culture. However, the application of this system in different laboratories and the provision of the setup involves various difficulties.

Standard organoids and organoid scaffolds that can be developed for three-dimensional cultures seem to be more preferable.

Keywords: In vitro maturation, three-dimensional culture, testicular organoid, seminiferous tubules niche.

1. INTRODUCTION

The spermatogonial stem cells (SCC) of patients who will undergo oncology treatment in the prepubertal period can be stored by slow freezing and vitrification. Currently, 1033 testicular tissues belonging to boys between the ages of 3 months and 18 years are stored in the cryobank for future use in centers in Europe and North America (1).

Reaching 80% of survival with the treatment methods developed in childhood cancer diseases necessitates the development in the use of prospective SCC in fertility restoration (2). Can mature spermatozoa be obtained from SCC in vitro? Can spermatogenesis be achieved? Can meiosis occur in immature testicular tissue? It requires answering these questions. In the future, it is not clear how the SCC can be used for fertility restoration and how their maturation can be achieved. The testicular tissue of oncology patients in the prepubertal period contains not only SCC but cancer cells. Therefore, some problems need to be overcome, such as SCC isolation from cancer cells, cryopreservation, transplantation, and maturation of these cells. Here, we examined current developments in the stage of in vitro maturation applications with two-dimensional (2D) and three-dimensional (3D) cultures applied to testicular tissues used in fertility restoration with a literature review.

Some researchers have sought solutions that have been sought by experimental autologous, homologous, or xenotransplantation applications of fresh or frozen-thawed tissues (3, 4, 5).

In order to ensure full spermatogenesis in vitro, providing microenvironment conditions suitable for SCC is seen as

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the target solution. The real microenvironment should be provided in culture, and in vivo maturation (differentiation and proliferation) of the SCC should be realized. Therefore, in fertility restoration, some researchers have tried to ensure in vitro maturation of the SCCs by keeping the seminiferous tubule tissue alive in vitro and preserving its viability (6). Furthermore, in vitro culture studies of fresh or freeze-thawed SCCs are ongoing, and 2D and 3D cultures, organoids, organoid scaffolds are tried to be developed. They try to provide in vitro maturation of SCCs on the organoid scaffold, which can best imitate morphological and physiological in vivo conditions (7, 8). Developments in this subject will also shed light on the treatment of adults with maturation arrest. Advances will significantly contribute to the treatment of fertility restoration for prepubertal oncology patients and adults with maturation arrest.

1.1. Niche of Spermatogonial Stem Cells In Seminiferous Tubules

For in vitro maturation to occur, it is necessary to know the change and development of the SCCs and the morphological and physiological conditions of the niche where these cells are located. Male reproductive cells undergo a very complex process until they pass through the embryonal, fetal, postnatal, and pubertal periods and become mature spermatozoa. Stem cells migrate from the seminiferous tubules lumen to the base in the gonocyte stage and settle on the basement membrane. Reproductive cells located on the basement membrane form spermatogonium (9, 10).

Spermatogoniums form SCCs that can renew and differentiate themselves through mitosis (11). Sertoli cells are somatic host cells lined up on the basement membrane in the seminiferous tubules.

While the gonads develop between 4-8 weeks in the organogenesis phase during the embryonal period, the surface begins to form within the gonadal cords made by the mesodermal epithelium. Sertoli cells act as a bridge between the vascular area and the germ cells. SCCs are lined up along the lateral surfaces of Sertoli cells from the basal to the lumen. Therefore, it actively manages spermatogenesis and provides nutrition. SCCs have settled in a special micro-environment within the seminiferous tubules, whose control and testis balance. The survival, proliferation, and differentiation of SCCs take place in this microenvironment (12). The SCC niche can be defined as a micro-environment that fixes the SCCs to preserve their origins. Tissue architecture is essential for the differentiation and proliferation of SCCs. Niche is a microenvironment that includes morphology and physiological function together.

It is a local tissue microenvironment that directly protects and regulates all cells of the germinal series (13). Somatic Sertoli and Leydig cells and peritubular myoid cells direct this niche, located in the basal compartment required for spermatogenesis. Sertoli and peritubular myoid cells provide the adhesion molecules that allow SCCs to bind to the basement membrane (14). Although Leydig cells and peritubular myoid cells do not directly contact SCC, they control the SCC niche through Sertoli cells (15). The contact and molecular interaction of somatic cells with each other is the main factor that enables stem cells to differentiate into haploid mature cells (12). In transplantation studies, it is seen how effective Sertoli cells and germ cells are in proliferation and differentiation. This is confirmed by the occurrence of spermatogenesis when normal Sertoli is transplanted to recipient infertile mutant testicles with Sertoli cell defects (16, 17).

Moreover, increasing the number of Sertoli cells in the recipient testis also increases niches (18). So we can say that disruption of communication between somatic cells and niche will naturally impair spermatogenesis. SCC niche performs proliferation and differentiation via endocrine and paracrine signals. Glial cell-derived neurotrophic factor (GDNF), one of the cytokines secreted by Sertoli cells and peritubular cells, plays a key role in this arrangement in the niche. GDNF provides SCC's proliferation by affecting surface receptor-complex of A single, A paired, A aligned cells (19). It has been shown that GDNF and fibroblast growth factor 2 (FGF2) are found in mouse Sertoli cells (20). Likewise, GDNF is also produced by peritubular myoid cells (21). The proliferation of SCCs is also provided by the cytokine colony-stimulating factor1 (CSF1) produced by peritubular myoid cells and Leydig cells in the interstitial area outside the tubules (22).

The tight junction complexes between Sertoli cells form the blood-testis barrier. This barrier divides the area of the seminiferous tubules into two parts as basal and adluminal compartments. The formation of these compartments plays an important role in the differentiation of germ cells. In addition, the blood-testis barrier provides a selective flow between interstitial fluid and adluminal fluid. This situation creates an immune-privileged environment for haploid germ cells in the adluminal compartment in the seminiferous tubules (23). Thus, identifying the details of SCC niche components in mammalian testicles is important to understanding the basis of sustained spermatogenesis.

1.2. Transplantation of Spermatogonial Stem Cells

Spermatogonial stem cell transplantation was first performed in 1994 by Brinster RL et al. (24). They isolated SCC from 4-12 day old mice, applied chemotherapy (busulfan), and transplanted into adult mice that developed azoospermia. They performed spermatogenesis in 70% of the recipients 35 days after transplantation. They found that the recipient testicular Sertoli cells were sufficient for structuring.

In ongoing studies, they obtained offspring eight months after transplantation of SCCs from mice of different age groups to the recipient (25). Spermatogenesis was performed with autologous orthotopic and ectopic transplantation of SCCs in primates (4). In monkeys, spermatozoa and embryos could be formed by autologous transplantation of SCCs (3).

In other ongoing studies, spermatogenesis was performed with the transplantation of SCCs in primates after freezing and thawing, and offspring could be obtained with these cells after three months, five months, and 99 days (26, 27, 28). Offspring could also be produced in some farm animals by donor transplantation (29, 30). However, problems such as the long time required for the cells to settle and become productive after transplantation, the low number of SCCs in the fresh testis, and the presence of numerical insufficiency in transplantation require the short-term culture of the SCCs (31). Since it is known that 4096 mature spermatozoa can be obtained (32) from a single SCC in rats where SCCs can reproduce numerically with the self-renewal feature (28, 33), fertility restoration requires at least 40-80 SCCs. In addition, the use of germinal stem cell lines seems appropriate in terms of solving the numerical problem.

Another problem is that the recipient testicle is older than the donor and requires more stem cells. Ensuring in vitro maturation of the SCCs in culture will solve the problems (5, 34). In addition, the application of Invitro maturation will eliminate the problem of contamination with cancer cells when the testicular tissue/suspension is transplanted.

1.3. Two-Dimensional Testis Cell Culture

In recent years, in vitro spermatogenesis of adult primate testicular cells has been attempted to achieve, but haploid cells could not be formed although it has reached the meiotic phase**.** Spermatocytes survived for about four weeks without separating into spermatids (35). Culture studies have also been conducted in adult men with maturation arrest for infertility treatment. Tesarik et al. reported that in vitro culture of adult human testicular cells with maturation arrest at the level of primary spermatocyte can be achieved spermatogenesis and can be obtained haploid cells and born alive baby by providing fertilization with these cells (36). In a similar situation, in vitro culture could reach the round spermatid stage (37). Lee et al. 2D cell cultures prepared from spermatogenic arrest and Sertoli cell-only in adult human testicles could reach microinjectable round spermatids (38). Spermatogenesis could not be completed in co-cultures with/without Leydig cells with Sertoli cells obtained from non-obstructive azoospermia adult human testicles (39). 2D culture media did not reflect the body environment, as the cells were grown in a single layer on plastic surfaces. Making 2D and, as an advanced stage, 3D cultures on brain-dead adult human germ cells K.Gholami et al. showed that 3D cultures were more efficient and successful in colony formation, proliferation, and differentiation than 2D culture (40). Prepubertal testicular cultures are seen as more complex applications compared to adult maturation arrest testicles. Prepubertal cultures are applications for the realization of two stages of spermatogenesis, including spermatocytogenesis and spermiogenesis. The small prepubertal testicular tissue and the small amount of SCC, the cells being in the gonocyte and spermatogonium stages, and the expectation that these cells perform both spermatocytogenesis and spermiogenesis reveal the complexity of the situation. The searches have been continued by carrying out various co-culture applications to provide the in vivo niche environment of adult mouse SCCs in vitro culture environment (41).

1.4. Tree-Dimensional Seminiferous Tubules Tissue / Organ Culture

It is necessary to develop testicular tissue culture and 3D culture research to overcome the deficiency of 2D cultures. When 3D culture was applied in a collagen matrix to adult human testicular cells with nonobstructive azoospermia with spermatocyte arrest, development was also achieved until the haploid round spermatid stage (42). With the applications made, moving to the advanced stage from spermatid was a serious problem in front of the researchers.

Sato T. et al. managed to overcome the challenge by developing a 3D in vitro culture method in the newborn mouse testis (43). They did in vitro organ culture of newborn mouse testis containing only gonocytes and primitive spermatogonia. They showed that spermatogenesis could occur in in vitro organ culture in more than two months. They were able to obtain spermatids and mature spermatozoa in testicular seminiferous tubules organ culture. They obtained offspring by microinjection with the produced spermatid and spermatozoa. This development positively contributed to elucidating the molecular mechanisms of spermatogenesis and the development of new diagnosis and treatment techniques in male infertility. They showed that spermatogenesis is possible even without in vivo circulation, and the method can be applied in mammals. Their ongoing studies proved that spermatogenesis error caused by microenvironment disorder in the original testis could be overcome by in vitro culture (44). They showed that by providing physiological conditions in mammals, spermatozoa could be obtained from germinal serial cells in about six weeks, and this culture can be applied (45). They stated that in vitro organ culture developed by adapting serum-free culture medium to old culture systems could be a simple and easily applicable method. They also developed spermatids and spermatozoa from freeze-thawed prepubertal testicular tissue by in vitro culture and obtained healthy offspring by microinjection. They showed that healthy offspring could be created with this method after treating childhood cancers (46, 47).

Komeya et al. developed this system a little further and adapted micro-fluid millipore membrane technology to seminiferous tubules organ culture (48). By creating a culture environment more suitable for physiological homeostasis, they provided spermatogenesis in the newborn mouse testis for a long period of six months. Thus, seminiferous tubules preserved their function in the culture environment for months. At the same time, they provided endocrine function by releasing luteinizing hormone and testosterone with this system. As a result, they obtained offspring with the formed spermatids and spermatozoa. Working differently, Michele et al. were able to preserve the integrity of the seminiferous

tubules by applying organotypic culture to human prepubertal testicular tissue (49). They saw that Sertoli cell maturation took place, and testosterone was produced in 139 days. However, a progressive loss of spermatogonium occurred, and differentiation into a haploid cell could not occur. Thus, the desired success could not be achieved. In human prepubertal testicles, failure to achieve in vitro spermatogenesis can be explained by the reasons such as the prepubertal process taking longer in humans compared to rodents, the need for different molecules, and the presence of unknown points about the niche.

1.5. Testicular Organoids

It is seen that the microenvironment must be provided in vitro for the SCCs to survive and transform into a haploid cell that will gain the ability to proliferate, differentiate and fertilize the oocyte (50). For in vitro maturation, Zhang et al. tried to reconstruct the testicles from newborn mouse testicular cells in a 3D culture medium (51). Although limited, they obtained seminiferous tubules formation and blood testicular barrier formation. They made the differentiation happen from spermatogonium to the primary spermatocyte stage. Mincheva M. et al. showed that somatic cells tend to form tubule-like structures in adult human in vitro primary testicular somatic cell culture and that Sertoli and myoid cells interact (52). 3D models have been useful in tracking the types of cellular interferences that induce in vitro cellular events and mechanisms. 3D models have been useful in tracking the mechanisms that create cellular interactions that induce these events in vitro.

In this area, an in vitro system is tried to be produced that fully models and mimics the testicular microenvironment and SCC niche. Organoids and organoid scaffolds may also be useful in in vitro 3D testicular tissue culture and providing the microenvironment to mimic the organism. Problems of SCC maturation can be overcome by using the testicular organoid augmentation method. Organoids are three-dimensional structures composed of multiple cell types that recapitulate the cellular architecture and functionality of natural organs. Organoids can be used as a physiologically feasible model system to study intercellular interaction, development, and tissue morphogenesis (7). In cell biology, the organoid niche can determine the epigenetic modification associated with signals, stem cell differentiation, and reprogramming of somatic cells. Organoids derived from stem cells are opening new avenues for modeling human diseases and regenerative medicine. However, many difficulties have to be overcome for stem cells to be applied versatilely in clinics. Stem cells, which build all the structural and functional units in the human body, can solve hematological, heart, nervous and digestive system diseases, cancer (53), and fertility restoration. With this in mind, some researchers working in male reproductive biology began to establish and characterize testicular organoids.

Alpes-Lopes et al. succeeded in creating a blood-testicular barrier by making 3D organoid culture from rat testicular cell suspension (8, 54). In addition, they developed the “Three Layer Gradient System”. This model contributed to the in vitro niche formation by showing the germ cell-somatic cell relationship and forming round tubular structures similar to the seminiferous tubules. It also created a new platform to investigate unknown factors in SCC proliferation and differentiation.

Pendergraft et al. used three adult human testicular tissues with brain death (55). They added a human testicular extracellular matrix to the culture medium. They added Sertoli, Leydig cells, which were obtained from the testis and immortalized, to the culture together with the SCCs. They obtained a testicular organoid. They were able to generate post-meiotic germ cells, albeit at a low rate. They provided a valuable model for germ cell biology. They have shown that human testicular organoids will be useful in the formation of the invitro niche.

On the other hand, Sakib et al. developed a pyramid-shaped microwells culture system suitable for the special architectural structure of the testicle (56, 57). They tried to create testicular organoids by placing prepubertal testicular cells in microwells by centrifugation. They created multicellular 3D testicular organoids from mammalian testicular tissues such as humans, pigs, mice, and monkeys. They showed that vitrified testicles could also be used to create testicular organoids. They showed that thousands of homogeneous organoids could be produced in this way.

Topraggaleh et al. produced testis-derived macropore scaffolds from mouse testicular extracellular matrix (58). They enabled the SCCs to differentiate until the post-meiotic period in culture. Furthermore, they showed that it could provide a new platform for testicular tissue engineering and in vitro spermatogenesis.

2. CONCLUSION

In general, 2D culture studies were able to reach the spermatid stage. Then, it is seen that spermatogenesis can be achieved in 3D cultures. However, the completion of in vitro meiosis and spermatogenesis, the production of haploid cells from SCCs under culture conditions, and the provision of niche seem to be a difficult practice. In vitro seminiferous tubules, tissue/organ culture, and testicular habitat maintenance require great skills and conditions to be overcome. Extracellular testicular matrix, testicular organoids, and organoid scaffolds supported with various substances appear to be a new and developing strategy for in vitro maturation. Organoid and organoid scaffolds will contribute to fertility restoration in prepubertal children and adult spermatogenic arrest, Sertoli cell-only patients. However, more work is needed to optimize the systems by developing and standardizing them with tissue engineering.

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Clinical and Experimental Health Sciences

ERRATUM TO:

Determination of Quality of Life of Individuals Before and After Bariatric Surgery: Prospective Study with 1 Year Follow-Up

DUE TO A TECHNICAL PROBLEM, THE ARTICLE WAS PUBLISHED WITHOUT TABLES AND FIGURES:

Missing tables and figures are given below. You can find original article (doi: 10.33808/clinexphealthsci.862544) at
https://dergipark.org.tr/tr/pub/clinexphealthsci/issue/65525/862544

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Table 1 *Characteristics of individuals (n=40)*

Characteristics	Mean±SD	Median (min-max)			Total score of QoL after OS					
Age	37.37 ± 9.18	36 (28 – 58)	Total score of QoL before OS		1st month		3rd month		1st year	
		n(%)	Mean± SD	Median	Mean± SD	Median	Mean± SD	Median	Mean± SD	Median
Gender	Female	30(75)	88.50±5.94	88.00	89.13±5.90	89.00	95.63±3.57	96.00	97.53±3.34	98.00
	Male	10(25)	94.90±6.93	93.50	91.00±7.13	87.50	94.60±3.13	95.00	95.70±2.98	95.50
	TEST p		F=.011 .007*		F=.909 .416		F=.000 .420		F=.828 .132	
Marital status	Married	30(75)	89.63±7.31	89.00	89.80±6.44	89.50	95.40±3.77	96.00	97.06±3.61	96.00
	Unmarried	10(25)	91.50±4.55	91.50	89.00±5.64	87.00	95.30±2.40	95.50	97.10±2.38	98.00
	TEST p		F=1.690 .454		F=.166 .728		F=1.596 .938		F=2.371 .978	
Education status	Primary education	6(15)	88.17±6.11	89.00	90.83±5.81	90.50	96.83±3.19	97.00	96.33±2.66	96.00
	High school	25(62.5)	89.84±6.57	89.00	88.56±6.22	89.00	95.72±3.71	96.00	97.28±3.80	97.00
	University	9(22.5)	92.11±7.75	91.00	91.67±6.34	88.00	93.44±2.07	94.00	97.00±2.29	98.00
	TEST p		F=.657 .524		F=.971 .388		F=2.191 .126		F=.192 .826	
Chronic illness	Yes	15(37.5)	91.33±7.37	93.00	90.20±6.60	87.00	95.73±3.45	95.00	97.07±2.46	97.00
	No	25(62.5)	89.36±6.34	89.00	89.24±6.04	89.00	95.16±3.51	96.00	97.08±3.78	98.00
	TEST p		F=.099 .376		F=.497 .641		F=599 .618		F=.123 .990	
How many years have been obese	5 years	9(22.5)	91.22±3.31	91.00	91.22±5.93	91.00	95.00±2.29	95.00	96.89±3.06	98.00
	5 to10 years	21(52.5)	87.76±6.45	88.00	89.33±7.18	88.00	95.43±3.92	96.00	97.76±3.56	98.00
	10 years and over	10(25)	94.00±7.93	94.50	88.70±4.06	88.50	95.60±3.56	96.00	95.80±2.86	95.50
	TEST p		F=3.465 .042*		F=.421 .659		F=.073 .930		F=1.218 .308	
Type of surgery	Sleeve gastrectomy	15(37.5)	90.73±7.27	90.00	90.13±3.36	89.00	94.80±2.70	95.00	97.73±3.55	98.00
	Roux-en-Y gastric by – pass	25(62.5)	89.72±6.50	90.00	89.28±6.20	89.00	95.72±3.85	96.00	96.68±3.17	96.00
	TEST p		F=.030 .650		F=.050 .679		F=.264 .422		F=.125 .337	

**p<0.05 (QoL: Quality of life, OS: Obesity surgery, SD, standard deviation)*

Table 2. *Correlation between follow-up times of individuals and total quality of life scores (n=40)*

		Total score of QoL before OS	Total score of QoL after OS		
			1st month	3rd month	1st year
	QoL before OS	1			
Total score of QoL after OS	1st month	.313* p=.025	1		
	3rd month	.049 p=.382	.098 p=.273	1	
	1st year	-.218 p=.089	-.052 p=.375	.427* p=.003	1

**p<0.05 (QoL: Quality of life; OS: Obesity surgery)*

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Table 3. *Simple lineer regression analysis between body mass indeks and total quality of life according to follow-up time (n=40)*

		Total score of QoL before OS	Total score of QoL after OS																		
			1st month					3rd month					1st year								
		B	SE	β	t	model (p)	B	SE	β	t	model (p)	B	SE	β	t	model (p)	B	SE	β	t	model (p)
BMI before OS		-0.119	0.650	-0.102	-0.183	.856	1.581	0.558	1.474	2.835	.008*	0.402	0.336	0.671	1.195	.240	0.622	0.308	1.084	2.018	.051
BMI after OS	1st month	-1.262	0.839	-0.997	-1.504	.141	-2.533	0.719	-2.173	-3.521	.001**	0.053	0.434	0.081	0.122	.904	-0.020	0.398	-0.032	-0.050	.960
	3rd month	1.446	0.601	-1.106	2.406	.022*	0.601	0.516	0.499	1.165	.252	-0.222	0.311	-0.330	-0.713	.480	-0.616	0.285	-0.955	-2.159	.038*
	1styear	-0.069	0.569	-0.033	-0.122	.903	0.071	0.488	0.037	0.145	.886	-0.157	0.294	-0.146	-0.533	.597	0.126	0.270	0.122	0.468	.643
	R	0.416					0.531					0.403					0.484				
	F	1.827					3.444					1.694					2.678				
	p	.146					.018*					.173					.048*				

**p<0.05 **p≤0.001 (BMI: Body mass indeks, QoL: Quality of life, OS: Obesity surgery)*

Table 4. *Average score of subscale of SF-36 according to tho follow-up times (n=40)*

SF_36			Mean±SD	Median	TEST (t)	p
PH						
		pre-OS	19.75±5.52	20.50	22.618	.000**
	post-OS	1st month	19.87±3.85	19.00	32.641	.000**
		3rd month	29.30±1.84	30.00	100.574	.000**
		1st year	30.00±0.00	30.00	-	-
RP						
		pre-OS	5.52±1.93	4.00	18.062	.000**
	post-OS	1st month	6.45±1.95	8.00	20.948	.000**
		3rd month	8.00±0.00	8.00	-	-
		1st year	8.20±1.26	8.00	41.000	.000**
BP						
		pre-OS	3.77±1.58	4.00	15.141	.000**
	post-OS	1st month	4.90±2.18	5.00	14.206	.000**
		3rd month	2.35±0.83	2.00	17.830	.000**
		1st year	2.17±0.55	2.00	25.035	.000**
GH						
		pre-OS	19.62±1.99	20.00	62.184	.000**
	post-OS	1st month	16.75±1.86	17.00	56.834	.000**
		3rd month	14.25±1.17	14.00	76.949	.000**
		1st year	15.32±1.18	15.500	81.785	.000**
VT						
		pre-OS	13.57±2.09	14.00	41.150	.000**
	post-OS	1st month	13.65±1.62	14.00	53.096	.000**
		3rd month	13.00±1.28	13.00	64.182	.000**
		1st year	12.82±1.26	13.00	64.449	.000**
SF						
		pre-OS	6.17±1.13	6.00	34.570	.000**
	post-OS	1st month	6.10±1.19	6.00	32.311	.000**
		3rd month	6.10±0.78	6.00	49.595	.000**
		1st year	5.50±0.51	5.50	68.695	.000**
RE						
		pre-OS	4.27±1.45	3.00	18.649	.000**
	post-OS	1st month	4.97±1.33	6.00	23.660	.000**
		3rd month	6.15±0.95	6.00	41.000	.000**
		1st year	6.15±0.95	6.00	41.000	.000**
MH						
		pre-OS	17.40±2.71	17.50	40.524	.000**
	post-OS	1st month	16.90±2.18	16.50	48.996	.000**
		3rd month	16.22±2.05	16.00	49.893	.000**
		1st year	16.90±2.18	16.50	48.996	.000**

***p<0.001 (SF-36: Short Form 36, PH: physical health, RP: role limitations because of physical health problems, BP; bodily pain, GH: general health perceptions, VT: vitality, SF: social functioning, RE: role limitations because of emotional problems, MH: general mental health, SD: standard deviation) (OS: obesity surgery)*

Table 5. *Simple lineer regression analysis between Characteristics of individuals and subscale of SF-36 according to follow-up time (n=40)*

SF-36 β		Gender		Marital Status		Education Status		Chronic İllness		How Many Years Have Been Obese		Type Of Surgery				
		model(p)	β	model(p)	β	model(p)	β	model(p)	β	model(p)	β	model(p)	R	F	p	
PH																
pre-OS	0.450	.004*												0.450	9.642	0.004*
RP																
post-OS 3rd month										,143	.043*			0.372	0.883	.518
BP																
post-OS 1st year										-,325	,043*			0.279	3.215	0.081
GH																
pre-OS												-,434	,033*	0.305	3.886	0.056
SF																
post-OS 1st month								,382	,037*					0.110	0.461	0.501
RE																
pre-OS								-,978	,046*					0.140	0.757	0.390

**p<0.05 (OS: obesity surgery, SF-36: Short Form 36, PH: physical health, RP: role limitations because of physical health problems, BP; bodily pain, GH: general health perceptions, SF: social functioning, RE: role limitations because of emotional problems) Note: Only statistically significant data are written in this table.*

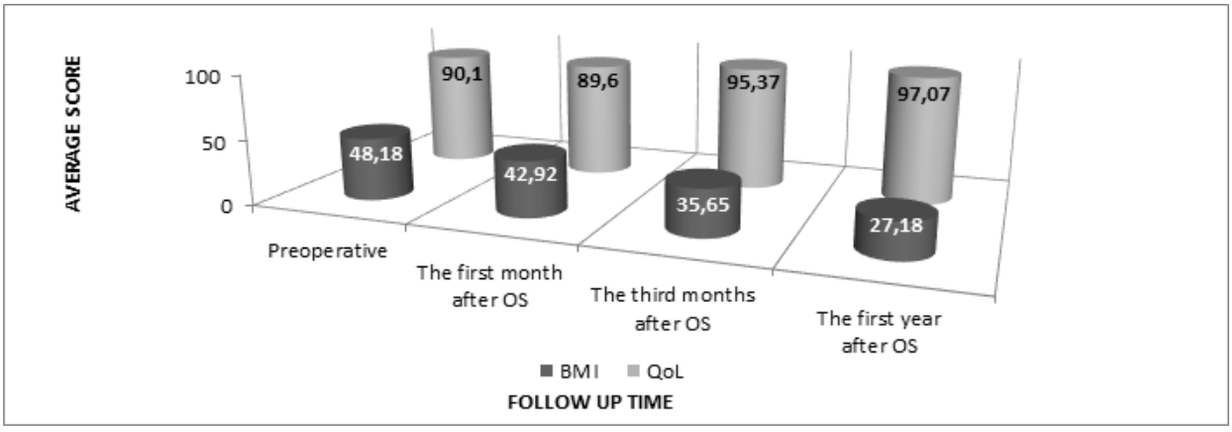

Figure 1. *The relationship between body mass index and quality of life according to individual follow-up times (n=40) (BMI: Body mass indeks, QoL: Quality of life, OS: Obesity surgery)*