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Research Article

The Effects of Pregnant Obesity in Newborn

Yeni Doğanlarda Hamile Obezitesinin Etkileri

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Abstract

Aim: In the present study it was aimed to evaluate the correlation between Body Mass Index (BMI) of pregnant women and the anthropometric measures of their newborn babies.

Materials and Methods: BMI of four hundred pregnant women who were followed up in Beykoz district between January 2011 and June 2020 and the records of the height, weight and head circumference measurements of their babies were retrospectively analyzed. During the follow-up, the study group consisted from pregnant women with a Body Mass Index (BMI) of 30 and above, and the control group among the pregnant women with a Body Mass Index (BMI) of <30. Both groups were compared in terms of neonatal outcomes

Results: A total of 347 pregnant women were included in the study. When birth weights of newborns of obese pregnant subjects and non-obese pregnant controls were compared; It was observed that babies of obese pregnant women were significantly heavier than non-obese (3424.63±510.46 vs 3105.45±397.07; p<0.001). Height and head circumference of the newborns were similar in both groups (49.54±2.46 vs 49.68±2.66 p = 0.840 and 34.71±1.85 vs 34.65±2.05 p=0.735, respectively).

Conclusion: It was shown in our study that obesity, which is an important health problem in pregnant women, also affects the newborn weight.

Keywords: Pregnancy, obesity, body mass index, newborn

Öz

Amaç: Bu çalışmada gebelerin Beden Kitle İndeksi (BKİ) ile yeni doğan bebeklerinin antropometrik ölçümleri arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Araştırmamızda Ocak 2011 ve Haziran 2020 tarihleri arasında Beykoz İlçesinde takip edilmiş ve doğum yapmış gebelerin, Beden Kitle İndeksleri (BKI) ile bebeklerinin boy, kilo ve baş çevresi ölçümlerine ait kayıtlar retrospektif olarak incelendi. İzlemler sırasında Beden Kitle İndeksi (BKİ) 30 ve üzerinde olan gebelerden (Obez) çalışma grubu, aynı tarih aralığında izlem yapılmış BKİ<30 olan gebelerden (Non-obez) ise kontrol grubu oluşturuldu. Her iki grup neonatal sonuçlar açısından karşılaştırıldı.

Bulgular: Toplam 347 gebe çalışmaya dahil edildi. Obez gebeler ile non-obez gebelerin bebeklerinin doğum ağırlıkları karşılaştırıldığında; obez gebelerin bebeklerinin non-obezlere kıyasla anlamlı oranda daha ağır oldukları gözlendi (3424.63±510.46 vs 3105.45±397.07;p<0.001). Yenidoğanların boy ve baş çevreleri ise her iki grupta benzer bulundu (sırasıyla 49.54±2.46 vs 49.68±2.66; p=0,840 ve 34.71±1.85 vs 34.65±2.05 p=0,735).

Sonuç: Gebelerde önemli bir sağlık problemi olan obezitenin, yenidoğanların doğum ağırlıklarını etkilediği çalışmamızda gösterilmiştir.

Anahtar kelimeler: Gebelik, obezite, vücut kitle indeksi, yenidoğan

INTRODUCTION

Obesity in pregnancy is defined as Body Mass Index (BMI) ≥30 according to the World Health Organization (WHO) criteria (1).

Keeping the Body Mass Index at a certain level during pregnancy significantly prevents the early and late complications of the pregnancy processes and the similar complications that may occur in newborns. Approximately 30-40 percent of adult women living in industrialized countries have obesity problems.

Obesity is a health problem that affects the daily routine practices and the quality of life is significantly impaired in obese women (2). Similar to the global trend, in our country the obesity rate is increasing also among women of reproductive age and pregnant women. Maternal obesity can cause serious short- and long-term complications for

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both the mother and the newborn.

Weight gain during pregnancy is a considerable issue. It is closely related to the health of the mother and the newborn from the beginning to the end of pregnancy. As women get older, more women become pregnant while they're overweight or obese. Excess weight gain during pregnancy is associated with increased birth weight of the newborns and inability to lose weight postpartum. Recommendations regarding weight gain during pregnancy aim the best outcome of pregnancy for the mother and the newborn.

MATERIAL AND METHOD

In our study, BMI of 347 pregnant women who were followed up and gave birth in Beykoz District between January 2011 and June 2020, and the records of the height, weight and head circumference measurements of the newborns were analyzed retrospectively. The study group consisted of pregnant women with BMI>30 and above during the follow-ups and the control group was pregnant women with BMI <30 who were followed up within the same period. Both groups were compared in terms of neonatal outcomes.

Mothers who gave birth at term and their newborns were included in the study.

Those who gave birth below 37 weeks (premature births) and those with multiple pregnancies were not included in the study.

The data were analyzed using the SPSS 25.0 package program. The distribution of the data was evaluated with the Kolmogorov Smirnov test. In addition to descriptive statistical methods (mean, standard deviation, frequency), Chi-Square test was used for parametric data. The results were evaluated at 95% confidence interval and 5% significance level.

RESULTS

A total of 347 pregnant women were included in the study.

The mean age of the pregnant women in the study group was 27.50±5.08 (17-44) years. 34.5% of the women were in the age group of 24 years and below, 31.7% were in the age group of 25-29 years and 33.7% were in the age group of 30 years and over. 43.5% of the participants had primary education or below, 89.9% did not work in any income-generating job, and 60.5% described their income as medium (Table 1).

There was no significant difference between the obese and non-obese groups in terms of weight gain during pregnancy regardless of duration of pregnancy (p=0.703 and p=0.615) (Table 2).

Table 1. Distribution of Pregnant subjects by Socio-Demographical Characteristics

Socio-Demographical Characteristics	Number (n=347)	%
Age		
≤ 24 years	120	34.5
25- 29 years	110	31.7
≥ 30 years	117	33.7
Education status		
Primary school and below	151	43.5
Middle School	60	17.2
High school	110	31.7
University	26	7.49
Working status		
Working	35	10.1
Not working	312	89.9
Family income status		
High	113	32.5
Middle	210	60.5
Low	24	6.91

Table 2. Comparison of weight gain and duration of gestational period during pregnancy

Weight gain during pregnancy	Obese (n=52)		Non-obese (n=295)		P value*
	n	%	n	%	
Weight gain<9kg	15	28.8	136	46.1	
Weight gain 9-14kg	26	50.0	77	26.1	0.703
Weight gain >9kg	11	21.2	82	27.8	
Gestation period	**Obese (n=52)**		**Non-obese (n=295)**		**P value***
	n	**%**	**n**	**%**	
Gestation period<39 weeks	21	40.4	91	30.9	0.615
Gestation period≥39 weeks	31	59.6	204	69.1	

*Fisher Exact Test

HbA1c levels were statistically significantly higher in obese pregnant women (p<0.001).

Total cholesterol and LDL levels in obese pregnant subjects were significantly lower than in non-obese pregnant controls (p=020 and p=002) (Table 3).

The mean birth weight of the babies born to mothers in the study group was 3424.6(±510.46) gr, and for the control group mean birth weight of the babies was 3105.45(±397.07) gr (p<0.001). When the head circumferences, heights, laboratory values and delivery types of the babies of both groups were compared, no significant difference was found (Table 4).

Table 3. Comparison of Laboratory Characteristics of the Groups

Laboratory Parameters	Obese (n=80)	Non-Obese (n=80)	P-value*
Glucose (µmol/L)	84.89±10.12	85.50±11.86	.726
HbA1C	4.91±0.38	4.26±0.32	<.001
Total Cholesterol	266.78±44.63	203.44±44.16	.020
HDL	61.19±12.84	64.74±11.85	.071
LDL	203.44±44.16	135.05±34.03	.002
VLDL	51.43±19.57	46.46±15.48	.077
Triglyceride	257.15±97.86	232.27±77.41	.077
Hemoglobin	12.25±1.36	12.22±1.27	.905
Platelets	224.58±60.71	215.63±65.92	.373

*Independent T-Test

Table 4. Comparison of the Newborns' Characteristics

		Obese (n=52)	Non-Obese (n=295)	P-value*
Newborn Birth Weight (Kg)		3424.63 ±510.46	3105.45 ±397.07	<.001
Newborn Head Circumference (cm)		34.71 ±1.85	34.65 ±2.05	0.735
Newborn Height (Cm)		49.54 ±2.46	49.68 ±2.66	0.840
Neonatal Hemoglobin		11.2±3.24	11.6±2.54	0.540
Mode of delivery	Normal vaginal delivery	21 (40.3%)	194 (65.7%)	0.196**
	Caesarean	31 (59.6%)	101 (34.2%)	
Gender of the newborns	Female	25 (48.0%)	145 (49.1%)	0.077**
	Male	27 (51.9%)	150 (50.8%)	

*Independent T Test * **Fisher Exact Test

DISCUSSION

In our study, the prevalence of obesity in pregnant women was found to be 15.0%. In a retrospective study of 1038 people, the prevalence of obesity was 2.9%, (1). In the study of İrge et al. conducted on 202 pregnant women living in the city center of Malatya province, the rate of overweight and obese women was 27.2% (2). In their retrospective study Aydın et al. found the prevalence of obesity as 13.3%, in gynecology and obstetrics clinic of İzmir Atatürk Training and Research Hospital (3). In a study conducted with pregnant women who applied to the Erciyes University Medical Faculty Hospital gynecology and obstetrics clinic, Gürel et al. found that prevalence of obesity before the pregnancy as 13.6% (4). In their study, Taşdemir et al. determined that 47.3% of pregnant women were obese and the remaining 52.6% were non-obese before delivery (5).

In the study of Driul et al., the prevalence of obesity before pregnancy was 5.5% (6), in the study of Baeten et al. 10.1% (7), in the study of Khashan and Kenny obesity was 16.9% and morbid obesity was 1.85% (8). In the study of 349 pregnant women done by Ugwuja et al. obesity was 17.2% and morbid obesity was 5.4% (9), in a study conducted with pregnant women in England in 2006 the prevalence was 18.5%, and in the study of Susan et al. in New York and other 26 states, it varied between 13.9% and 28.9% (10). In a study by Hull et al., which examined the effects of maternal body weight on newborns, it was found that 46% of pregnant women were normal weight and 54% were obese (11). In their study, Sewel et al. also found the prevalence of obesity in pregnant women to be 38.9% (12). When these results are evaluated, it is suggested that prevalence of obesity in pregnant women may vary according to the selected sample, lifestyle and demographic characteristics of the individuals in the sample.

In the Obesity and Physical Activity guide of The Turkish

Ministry of Health at least 30 minutes of daily exercise is recommended (13). ACOG supports exercise if there are no obstetric and medical complications during pregnancy (Evidence A) (ACOG, 2015). Walking is an appropriate form of exercise for many women. In addition, swimming, physical exercises and water exercises may easily be done during pregnancy (14).

In the studies of Jain et al. and Glaser et al., it was observed that the risk of giving birth to a macrosomic baby, GDM and stillbirth risks decreased in women who lost weight between two deliveries (15,16). In our country, in a study investigating whether women receive recommendations according to the 2009 IOM guideline about weight gain during pregnancy, it was stated that approximately half of the women talked about weight gain in the prenatal period during their pregnancy follow up, but only one out of every five women received the right weight gain recommendations that is in line with this guideline. Appropriate prenatal weight gain charts (Prenatal Weight Gain Grid), which are widely used in many countries, should be used to ensure appropriate weight gain during pregnancy (17).

In our study, it was determined that the newborns of obese pregnant subjects were more overweight than the newborns of those who are non-obese. However, no significant difference was observed in terms of head circumference and height. Taşdemir et al. also found the rate of LGA newborns to be 22% in obese pregnant women and 7% in non-obese pregnant women (5). Leddy et al. also reported that the newborns of women who are obese during pregnancy are also at risk of becoming obese (18). Larsen et al. and Hull et al. in their study conducted in a USA cohort also found that obese pregnant women had larger babies (19). This relationship was similarly observed in European cohorts. For example, in Austria, Kirchengast and Hartmann found a positive relationship between BMI before the pregnancy and birth weight of the newborns (20). In the Swedish sample, Rossner and Ohlin found that maternal weight gain and initial maternal body weight were positively associated with infant birth weight (21). As a result, it is observed that there is a positive relationship between maternal obesity and birth weight of newborns in different cohorts.

In the literature, it is suggested that maternal obesity is associated with abnormal fetal growth. Heavier women are less likely to have a small for gestational age infant or a pregnancy complicated by intrauterine growth retardation, but this protective effect disappears when maternal BMI reaches the obesity level (>30 kg/m²). The most important concern in obese pregnant women is fetal macrosomia, which is defined as an estimated fetal weight of 4500g or more and it seems to increase 2 to 3 times in obese pregnant women (22). Beyond that, it is stated that there is a direct correlation between maternal obesity and fetal macrosomia. In a meta-analysis study conducted on this subject, the prevalence of fetal macrosomia was 8.3% for the control group with normal weight compared to 13.3% and 4.6% for obese and morbidly obese women, respectively (23). Moreover, there are several studies in which results have been obtained that fetal macrosomia in obese women is not only associated with an increase in the absolute size of the fetus, but also with a change in body composition (24). Sewell et al.31 found that newborns of mothers with a normal body mass index (<25kg/m²) had an average fat mass (334 g and body fat composition 9.7%) (25). The average fat mass of the newborns of women with BMI>25kg/m² was 416 g, and the body fat composition was 11.6%. It is stated that a large part of this effect is a result of weight gain during pregnancy.

In our study, it was observed that there was no relationship between the size of the baby (height and head circumference) and maternal obesity. In the literature, Hull et al. found that the newborns of obese pregnant women were 1.1cm shorter on average than the newborns of non-obese pregnant women in their study conducted in a USA cohort (11). In our study, although there was no significant difference, the newborns of pregnant women with normal maternal body weight were found to be taller (mean 0.14cm). Depending on our study, we may suggest that maternal obesity does not have an effect on newborn height and head circumference.

CONCLUSION

Overall, it is considered that it will be beneficial for obese pregnant women to gain an appropriate weight within a program starting from the prenatal period, and in this context, it is important to have an adequate and balanced diet during pregnancy.

Family Health Centers (FHCs) have an important role in preventive medicine in regulating diet and preventing obesity in pregnant women.

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Research Article

Investigation of the Relationship between Fertility Adjustment and Spousal Support in Women with Infertility

İnfertil Olan Kadınlarda Fertilite Uyumu Ve Eş Desteği Arasındaki İlişkinin İncelenmesi

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Abstract

Aim: The study aims to determine the relationship between fertility adjustment and perceived spousal support in women with infertility.

Material and Methods: The correlational, descriptive type this research was conducted in eastern Turkey between December 2019 and September 2020. The study sample consisted of infertile women registered in five Family Health Centers, selected by cluster sampling method (n:139). The data were collected using the Participant Information Form prepared by researcher the Fertility Adjustment Scale (FAS), and the Spousal Support Scale. In addition to descriptive statistics, correlation and regression analyses were used in the data analysis.

Results: In the study, it was found that the mean score of women in the FAS was 23.30±1.35, and the mean score in the Spousal Support Scale was 65.41±10.41. In the correlation analysis performed between fertility adjustment and spousal support in the study, a negative, weak, but significant relationship was found, and the regression analysis showed that total spousal support, financial support, and appreciation dimension explains fertility adjustment by 11%, 13%, and 10%, respectively ($p<0.001$). In the study, it was found that there was a statistically very weak significant relationship between emotional support, which is one of the sub-dimensions of spousal support, and fertility adjustment, and the regression analysis showed that emotional support explains fertility adjustment by 0.06% ($p<0.05$).

Conclusion: In the study, it was found that fertility adaptation increases as spousal support increases, and the advanced analysis showed that spousal support explained fertility adjustment by 11%. It is recommended that counseling activities to be provided to couples should be enriched within this framework.

Keywords: Spousal support, fertility adjustment, infertility, women

Öz

Amaç: Araştırma, infertil olan kadınlarda fertilite uyumu ile algılanan eş desteği arasındaki ilişkiyi belirlemeyi amaçlamaktadır.

Materyal ve Metot: İlişkisel, tanımlayıcı tipte olan bu araştırma, Aralık 2019 ile Eylül 2020 tarihleri arasında Türkiye'nin doğusunda yürütülmüştür. Araştırmanın örneklemini, küme örnekleme yöntemiyle seçilen beş Aile Sağlığı Merkezine kayıtlı infertil kadınlar oluşturmuştur (n=139). Veriler, araştırmacı tarafından hazırlanan Katılımcı Bilgi Formu, Fertilite Uyum Ölçeği (FUÖ) ve Eş Desteği Ölçeği kullanılarak toplanmıştır. Verilerin analizinde tanımlayıcı istatistiklerin yanı sıra korelasyon ve regresyon analizleri kullanılmıştır.

Bulgular: Araştırmada kadınların FUÖ puan ortalaması 23.30±1.35, Eş Desteği Ölçeği puan ortalaması 65.41±10.41 bulunmuştur. Araştırmada fertilite uyumu ile eş desteği arasında yapılan korelasyon analizinde negatif, zayıf düzeyde anlamlı bir ilişki bulunmuş ve regresyon analizinde eş desteği toplam, maddi destek ve takdir boyutunun fertilite uyumunu sırasıyla %11, %13 ve %10 oranında açıkladığı görülmüştür ($p<0,001$). Çalışmada eş desteğinin alt boyutlarından biri olan duygusal destek ile fertilite uyumu arasında istatistiksel olarak çok zayıf anlamlı bir ilişki olduğu bulunmuş ve yapılan regresyon analizi sonucunda duygusal desteğin doğurganlık uyumunu %0,06 oranında açıkladığı görülmüştür. ($p<0.05$).

Sonuç: Çalışmada eş desteği arttıkça fertilite uyumunun arttığı ve yapılan ileri analizlerde eş desteğinin fertilite uyumunu %11 oranında açıkladığı görülmüştür.

Anahtar Kelimeler: Eş desteği, fertilite uyumu, infertilite, kadın

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INTRODUCTION

Infertility is defined as the absence of pregnancy, despite unprotected and regular sexual intercourse of couples of childbearing age for at least one year (1). The incidence of infertility varies among countries, and the incidence reported by the World Health Organization (WHO) is 15% (2). Similarly, in Turkey, 10-20% of couples is believed to be diagnosed with infertility (3,4). Infertility is a period of vital crisis that causes physical, mental, and social problems in couples, as well as affecting the cultural values, beliefs and class aspects of couples (3-6). However, methods and interventional procedures applied in the infertility treatment process can also cause the couple to be affected by the process (7). Treatment methods applied can cause women to experience different emotions, especially. These moods can negatively affect the couple's adherence to treatment and fertility. There are also studies that show that social support is effective in coping with the negative circumstances experienced (8). One of the variables that are believed to help cope with the infertility process is spousal support. Since the infertility process affects both women and men, spousal support becomes extremely important for couples. Spousal support is affected by numerous variables during marriage and is defined as the fact that spouses support each other as needed (9). Studies have shown that perceived spousal support is associated with marital satisfaction (9,10). Infertility can also affect couples' marital relationships. Health professionals who serve and communicate with couples at every stage of the infertility process are midwives and nurses. Therefore, one of the main goals of care is to evaluate couples with a holistic approach and provide care for the problems identified. Looking at the studies conducted, the psychosocial effects of infertility seems to be investigated more often (11,12). It is thought that it will be important for midwives and/or women's health nurses who care for women to evaluate their spouses together when evaluating the infertility problem. However, there was no study in a literature review that investigates the relation of fertility adjustment with spousal support. This study was conducted to investigate the relationship between fertility adjustment and perceived spousal support in women with infertility.

MATERIAL AND METHOD

This correlational, descriptive type research was conducted in FHCs located in a province in eastern Turkey between December 2019 and September 2020.

Study Population and Sampling

The study population consisted of infertile women registered in 5 FHCs located in the provincial center, selected by cluster sampling method. The whole study population was studied without performing any sample selection. However, 53 women were excluded from the study since 29 women did not meet the research inclusion criteria, 16 women refused to participate in the study, and 8 women were not available. Thus, the research was completed with 139 females.

The study inclusion criteria

- Living with her partner
- Diagnosed with primary infertility

The study exclusion criteria

- Women who did have any diagnosed psychiatric conditions

Data Collection Instruments: In the study, the data were collected using the Participant Information Form prepared by the researcher, The Fertility Adjustment Scale (FAS), and the Spousal Support Scale.

Participant Information Form: The form contains items to determine the age of women and their spouses, their level of education, family type, income status and the duration of marriage.

Spousal Support Scale: The spousal support scale used to measure the social support that married individuals receive from their spouses was developed by Yıldırım (2004) and its validity and reliability studies were conducted (9). The 27-item 3-point Likert type scale is scored over "Agree", "Somewhat agree", and "Disagree" options. A high score on the scale indicates a higher perceived spousal support from their partner, while a low score indicated lesser perceived spousal support. Analysis results show that the scale consists of four dimensions: emotional support, financial support and information support, appreciation support and social Interest support. Within the scope of the reliability of the scale, the scale's Cronbach's alpha reliability coefficient was found to be .95. The Cronbach's alpha coefficient was calculated as .94 in this study.

Fertility Adjustment Scale: The scale was developed by Glover et al. in 1999 to standardize the measurement of psychological adjustment in infertility (13). The scale was adapted into Turkish by Bilgiç et al. in 2016. The original scale consists of 12 items, and a 10-item structure was obtained as a result of Turkish validity and reliability study (14). The 4-point Likert type scale scored in the range of 10 to 40 points (1- Strongly disagree, 2- Disagree, 3- Agree, 4- Strongly agree). Items are balanced in terms of positive and negative expressions so as not to affect responses. Positive items 1, 4, 7, 8 and 10 are reverse coded. The total score is obtained by scoring on individual items. There is no cutoff point in this scale. The higher scores indicate an insufficient adjustment (7,14). The scale's Cronbach's alpha reliability coefficient was found to be .63 (14). This study Cronbach's alpha coefficient was calculated as .84.

Data Evaluation and Analysis: The data obtained as a result of the study were evaluated in a computer environment using the statistical package for social sciences (SPSS) 22.0 program. In addition to descriptive statistical methods (number, percentage, mean, standard deviation), advanced analysis methods such as pearson correlation

and linear regression analysis were also used to evaluate study data, p<0.05 and p<0.01 were accepted as the level of significance.

RESULTS

In the study, the mean age of women was 33.71±8.00 years, the mean age of their spouses was 37.94±8.32 years, and the mean duration of marriage was 11.24±8.58 years. Of the females, 38.1% was primary school graduate, and 30.2% of the spouses was high school graduate. Looking at the family type of the women, most of them was living in a nuclear family (Table 1).

Table 1. Distribution of descriptive characteristics of the participants (n=139)

Descriptive characteristics	n	%
Educational status		
Illiterate - Literate	19	13.7
Primary school	53	38.1
Secondary school	28	20.1
High school	24	17.3
University graduate	15	10.8
Educational Status of the Spouse		
Illiterate - Literate	19	13.7
Primary school	53	38.1
Secondary school	28	20.1
High school	24	17.3
University graduate	15	10.8
Income Status		
Income is higher than expenses	25	18.0
Balanced	80	57.5
Income is lower than expenses	34	24.5
Family type		
Nuclear Family	121	87.6
Extended Family	18	12.4
	X ± Sd / (min –max)	
Age	33.71 ± 8.00/ (20-59)	
Mean age of the spouse	37.94 ± 8.32/ (21-63)	
Duration of marriage	11.24 ± 8.58/ (1- 42)	

X: Mean, Sd: Standard deviation

It was found that the mean score of women in the Fertility Adjustment Scale was 23.30±1.35, and the mean score in the Spousal Support Scale was 65.41±10.41 (Table 2).

Table 2. Distribution of average scores that women receive from the fertility adjustment scale and spousal support scale and sub-scales (n=139)

Scale	n	%
Fertility Adjustment Questionnaire Total	19-29	23.30 ± 1.35
Spouse Support Scale sub-scales		
Emotional support	9 - 27	22.69 ± 4.25
Financial support	9 - 21	17.59 ± 2.65
Appreciation	10 - 24	19.97 ± 3.14
Social Support	3 - 9	7.58 ± 1.53
Spouse Support Scale Total	30 - 78	65.41 ± 10.41

X: Mean, Sd: Standard deviation

In the correlation analysis performed between fertility adjustment and spousal support in the study, a negative, weak, but significant relationship was found, and the regression analysis showed that spousal support explains fertility adjustment by 11% (p<0.001). In the study, it was found that there was a statistically very weak significant relationship between emotional support, which is one of the sub-dimensions of spousal support, and fertility adjustment, and the regression analysis showed that emotional support explains fertility adjustment by 0.06% (p<0.05). In the study, a statistically significant, but weak relationship was found between fertility adjustment and financial support, which is one of the sub-dimensions of spousal support, and the regression analysis showed that financial support explains fertility adjustment by 13% (p<0.001). In the study, it was found that there was a statistically significant, but weak relationship between fertility adjustment and appreciation, which is one of the sub-dimensions of spousal support, and the regression analysis showed that appreciation explains fertility adjustment by 10% (p<0.001). In the study, a statistically significant, but very weak relationship was found between fertility adjustment and social support, which is one of the sub-dimensions of spousal support, and the regression analysis showed that social support explains fertility adjustment by 0.06% (p<0.05, Table 3).

Table 3. Explanation of the effect of spousal support level and sub-dimensions on adaptation to fertility through correlation and regression analysis

	Fertility Adjustment Questionnaire Total Score								
	Regression					Correlation			
	R	R^2	β	t	p	df1, df2	F	r	p
Spouse Support Scale Total Score	0.337	0.114	-0.337	-4.196	0.000**	1, 137	17.608	-.337	0.000**
Emotional Support	0.249	0.062	-0.249	-3.015	0.003*	1, 137	9.090	-.249	0.003*
Financial Support	0.373	0.139	-0.373	-4.712	0.000**	1, 137	22.207	-.373	0.000**
Appreciation Support	0.324	0.105	-0.324	-4.007	0.000**	1, 137	16.055	-.324	0.000**
Social Support	0.255	0.065	-0.255	-3.088	0.002*	1, 137	9.538	-.255	0.002*

*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.001 level (2-tailed)

DISCUSSION

Infertility is a life crisis affecting couples with its physiological, psychological and socio-cultural dimensions (15). The findings of the study conducted to determine the relationship between fertility adjustment and perceived spousal support in women with infertility were discussed based on the relevant literature.

In the study, it was found that fertility adjustment increases as spousal support increases, and the regression analysis showed that spousal support explains fertility adjustment by 11%. In addition, it was found that the fertility adjustment of infertile women who were appreciated by their partners also increased, and that appreciation explained the fertility adaptation by 10%. As a matter of fact, studies have shown that women experience high levels of depression, despair symptoms, anxiety, loss of self-confidence, and lower quality of life during the infertility treatment, and that these psychiatric symptoms decrease in line with spousal support (16-18). Another study found that infertile women without spousal support experienced more anxiety and depression and were subjected to more stress (19). However, it has been noted that women experience more psychological problems such as anxiety, depression, despair, and decreased self-esteem than men during this difficult process (16, 20). Indeed, in a meta-analysis study conducted by Kiani et al., it was noted that infertile women experience more anxiety than men (12). This has shown that infertility affects women more negatively and therefore women need more support. Given these data, it is believed that women who receive support in the infertility process will experience less psychological disorders such as anxiety, depression, and their fertility adjustment will increase. Indeed, our research result also supports this finding, and it was found that women who received spousal support also had a high fertility adjustment. In addition, one of the main roles that gender perception imposes on women is the childbirth (16). Due to this perception and expectation, infertility has been reported to cause feelings such as decreased self-esteem, feelings of inadequacy and shame (21). For this reason, it is believed that women may experience more anxiety about breaking up with their partners if they cannot have children for a long time. It is therefore assumed that women may need more spousal support in the infertility process.

In the study, it was found that there was a significant relationship between emotional support, which is one of the sub-dimensions of spousal support, and adaptation to fertility. It is obvious that infertility affects both women and men physically, psychologically and socially. However, it has been noted that women are psychologically and emotionally challenged more than men (22). In addition, it was found that men experience fewer depressive symptoms in this process than women (16,18,20). However, a woman may experience more stress due to the inability to fulfill her social role in the form of motherhood/pregnancy, which our society imposes on a woman. In the study of Taşçı et al., (2008), it was found that half of infertile women needs psychological support (23). It is believed that this finding may be due to the negative impact that the traditional structure of Turkish society has on couples. In this case, it is assumed that the support that men will show to their partners will make it easier for them in the transition to a healthier fertility process by ensuring lesser psychological discomfort and increased fertility adjustment.

As a result of our research, it was found that the increase in financial support leads to increase in fertility adjustment, and financial support explains fertility adjustment by 13%. The infertility treatment is a long-lasting, expensive treatment, with unclear treatment outcome, worries infertile couples financially as much as it challenges them emotionally. It is believed that lack of financial means can

also affect the fertilization process (24). Failing treatment outcomes and prolongation of treatment, especially for low-income couples, may mean increased spending and more stress. Indeed, a meta-analysis study conducted by Kiani et al. found that the incidence of anxiety in middle- and low-income infertile women is almost twice as high in women living in high-income countries (12). Another study also found that infertile women with low income level had higher levels of despair (16). However, another study reported that marital adjustment increases in women with high income levels, and social stress associated with depression and infertility decreases (25). It is believed that the reduction of stress will contribute to the positive fertilization process.

In our research, a significant relationship was found between social support, which is one of the sub-dimensions of the spousal support scale, and adaptation to fertility. A study found that symptoms of depression and anxiety were also higher in infertile women who did not have social support (24). A study by Frederiksen et al. found that psychosocial support is effective both in reducing psychological stress and in increasing the chances of pregnancy in infertile couples (26). Another study found that social support in infertile women helps posttraumatic growth (27). Some studies have reported that infertile individuals often feel isolated and alienated and have difficulty accessing social support (28,29). A study has shown that social support is very important in reducing psychosocial problems caused by infertility (22, 30). Another study also reported that perceived social support may be useful in reducing infertility-related psychosocial problems (16). In addition, Karlıdere et al. reported that the frequency of depression and anxiety was higher in infertile women with insufficient social support (22). It is believed that this is due to the fact that social support has a buffer effect against stressors (31). This is thought to be due to the buffering effect of social support against stressors (31). It is thought that the social support that women will receive will play a protective role against all the negative situations they experience during the infertility process.

CONCLUSION

As a result, infertility is a condition that affects a woman very negatively from a biological, psychological and social point of view. In this difficult life event, it is seen that the support of a woman's partner contributes positively to the adaptation of fertility. It is recommended that midwives and/or women's health nurses who provide care to women should plan training to women and their spouses to increase spousal support regarding the fact that perceived spousal support will facilitate the fertility adjustment process during the infertility. Moreover, it is recommended that counseling activities to be provided to couples should be enriched within this framework.

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Research Article

Anatomy Courses Content of the Medical Faculty in Turkey

Türkiye'de Tıp Fakültelerinde Verilen Anatomi Derslerinin İçeriği

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Abstract

Aim: Our research in Turkey with the Higher Education Council (YÖK) depends on the content of the courses in Anatomy operating in the Faculty of Medicine, School of Medicine has identified and studied during class hours to reveal whether there is a standard in this regard.

Materials and Methods: Web pages of all Medical Faculties have been accessed by writing the names of Medical Faculties to search engines on the Internet. From these web pages, Anatomy course topics and course hours have been determined by referring to the Core Education Program (ÇEP) of the Turkish Anatomy and Clinical Anatomy Association (TAKAD) and the Medical School syllabus for the 2018-2019 period.

Results: Content of the curriculum could not be reached in most of the Foundation Universities websites (75%). Nearly half (48.8%) of the State University Medical Faculties have published their course programs regularly on their web pages.

Conclusion: This study makes us think that State Universities have a more serious education program in terms of accessibility to course content data, sharing knowledge experience infrastructure and archiving successes compared to Foundation University Medical Faculties. Period of anatomy class I / II is the awarding and course contents can be said to be the standard in Turkey.

Keywords: Anatomy, Medical faculty, Education, Turkey

Öz

Amaç: Yaptığımız araştırma ile Türkiye'de Yüksek Öğretim Kurumu'na (YÖK) bağlı faaliyet gösteren Tıp Fakültelerinde verilen Anatomi derslerinin içerikleri, ders saatleri tespit edilerek Tıp Fakültelerinde bu konuda bir standardın olup olmadığı ortaya çıkarılmaya çalışılmıştır.

Materyal ve Metot: Bütün Tıp Fakültelerinin web sayfalarına internette arama motorlarına Tıp Fakültelerinin isimleri yazılarak ulaşılmaya çalışılmıştır. Bu internet sayfalarından 2018-2019 dönemine ait Tıp Fakültesi ders programı Türk Anatomi ve Klinik Anatomi Derneği'nin (TAKAD) Çekirdek Eğitim Programı (ÇEP) referans alınarak Anatomi ders konu başlıkları ve ders saatleri tespit edilmiştir.

Bulgular: Vakıf Üniversitelerinin web sayfalarının çoğunda (%75) ders programı içeriğine ulaşılamamıştır. Devlete bağlı faaliyet gösteren Üniversite Tıp Fakültelerinin yarıya yakını (%48.8) ise ders programlarını muntazam bir şekilde internet sayfalarında yayımlamıştır.

Sonuç: Bu çalışmamız Devlet Üniversitelerinin, Vakıf Üniversite Tıp Fakültelerine göre internet ortamında ders içeriği verilerine ulaşılabilirlik, bilgi tecrübe alt yapılarını paylaşma ve arşiv tutma başarıları açısından daha ciddi bir eğitim programına sahip olduğunu bize düşündürmüştür. Anatomi derslerinin Dönem I/II'de verilmesi ve ders içerikleri konusunda ise Türkiye'de bir standartın olduğu söylenebilir.

Anahtar Kelimeler: Anatomi, Tıp Fakültesi, Eğitim, Türkiye

INTRODUCTION

Medical science is dynamic and medical education practices are changing rapidly. The purpose of the searches here is to find out how this education can best be applied. For this reason, different education models are applied in medical faculties around the world. Models such as problem-based learning, task-based learning, outcome-based learning and evidence-based learning are some of them. The purpose of institutions using different education models is to find the ideal model and prepare students for their professional life (1).

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There was a period in Turkey described as Medicine classical education system. Each department had its own curricula such as Anatomy, Physiology and Histology, and each course had separate exams. Although it was difficult to separately pass each course, the majority of that course will be dominated by the end of the year. So it was a difficult system but still taught (2). Classical education system is also known as Conventional ((lecture-based curricula) education system (3).

In the integrated system, courses are divided into systems. Some faculties refer to the committee, while others refer to the module. In this system, the exams of the courses are not separate but with a single question booklet. In the ratio of the number of courses you have seen, there are questions from each course. The integrated system is preferred by many medical faculties today (2).

While the rate of faculties applying only classical or integrated education in Turkey was 82% in 1997, this rate decreased to 57% in 2002. It is known that this rate decreased even more in 2004. In this period, some medical faculties switched to full active education, while others switched to the education system we call co-education (integrated + active or classical + active) (4).

Anatomy course is one of the first courses that come to mind among the basic medicine courses given in the preclinical period in Medical Faculties. It is the science that examines the shape and structure of the body. Examines the structural and functional relations between organs. It is one of the most difficult courses in the first years of the Faculty of Medicine (5,6). Anatomical knowledge supports a patient's examination, diagnosis formation and communication of these findings to the patient and other medical professionals. It provides a platform of knowledge suitable for all medical careers (7).

The National Core Education Program (UÇEP) criteria created by YÖK are used as a guide in creating curricula in medical faculties. The medical curriculum in Turkey is prepared using the UÇEP guidelines. The Core Education Program (ÇEP) published by the Turkish Society of Anatomy and Clinical Anatomy (TAKAD) in 2018 provides detailed information on the course content. Therefore, the ÇEP published by TAKAD has been taken as a reference in order to reach the content of anatomy lessons applied in Turkey. According to TAKAD, the main topics in systematic anatomy approach are; Introduction to anatomy (basic Latin knowledge, anatomical posture and importance, anatomy terminology) and systems part (respiration, circulation, digestion, reproduction, urinary, nerve, endocrine, movement, skin and attachments). Anatomy is one of the cornerstones of medical education. As far as possible, issues of anatomy should be associated with clinical practice (8). Cadaver, specimen, plastic model, computer simulation, anatomical photographs, and shapes should be preferred (8). In this direction, various methods and technologies such as independent learning, computer-assisted learning and problem-based learning should be used in anatomy education (9). The content and course hours of the Anatomy courses given in the Faculties of Medicine were determined and it was tried to find out whether there is a standard in the Faculties of Medicine by taking TAKAD's ÇEP as a reference.

MATERIAL AND METHOD

The names of the Medical Faculties in Turkey were taken from the official Higher Education Council (YÖK) website on 27/08/19. The web pages of all Medical Faculties have been tried to be accessed by writing the names of Medical Faculties to search engines on the Internet. A total of 95 universities in Turkey, 69 states with medical faculties, 23 foundations, 2 in the Turkish Republic of Northern Cyprus (TRNC) and 1 in Azerbaijan, affiliated to YÖK, were included in the study. Universities without medical faculties were not included in the study. Some universities have dual medical faculties that provide education in both Turkish and English. Therefore, in this study, a total of 115 medical faculties, 82 state, 28 foundations, 4 in the TRNC and 1 in Azerbaijan, were included in the study.

Anatomy course topics and course hours of the Faculty of Medicine curriculum for 2018-2019 period have been determined from these web pages. Based on the Core Education Program (ÇEP) data published by the Turkish Society of Anatomy and Clinical Anatomy (TAKAD) in 2018, the contents and hours of the Anatomy course education of all Medical Faculties were evaluated and compared in this study.

Introduction to Anatomy (basic Latin knowledge, anatomical posture and importance, anatomy terminology) and systems (respiratory, circulatory, digestive, reproductive, urinary, nerve, endocrine, movement, skin and attachments) in the ÇEP of TAKAD are searched on web pages. Anatomy course topics and course hours of Medical Faculties were evaluated in accordance with the internet contents that we could reach and statistical analysis was performed.

Statistical analysis

The qualitative data used in the study are summarized as number (percentage) and the quantitative ones as median (min.-max.). The conformity of the quantitative data to the normal distribution was examined with the Shapiro-Wilk test. The Mann-Whitney U test was used to determine whether there was a statistically significant difference between the groups in terms of quantitative variables. Pearson chi-square test was used to determine whether there was a statistically significant difference between the groups in terms of qualitative variables. $p \leq 0.05$ was accepted as statistical significance level. IBM SPSS Statistics 26.0 package program was used in the analysis.

RESULTS

115 medical faculties in 95 universities affiliated to YÖK were included in the study and examined.

The Faculties of Medicine operating under the Council of Higher Education in Turkey are given in Table 1 (10).

Table 1. Medical Schools in Turkey (the same university English / Turkish schools were counted separately)

	n	%
State Universities (eleven in both English and Turkish)	**82**	**71.3**
Foundation Universities (Five in both English and Turkish)	28	24.3
Turkish Republic of Northern Cyprus (One in both English and Turkish)	4	3.4
Azerbaijan	1	0.8
Total	115	100

The anatomy course topics in the ÇEP issued by TAKAD are given in table 2.

Table 2. Anatomy course topics in TAKAD's ÇEP

	Course Topics
Introduction to Anatomy	Basic knowledge of Latin
	Anatomical posture and its importance
	Anatomy terminology
Systems	Respiratory system
	The circulatory system
	Digestive system
	Reproductive System
	Urinary System
	Nervous system
	Endocrine System
	Locomotor System
	Skin and supplementary

Anatomy course topics applied by medical faculties are given in Table 3.

The web pages of the state and foundation medical faculties in Turkey and the medical faculties of universities affiliated to YÖK outside Turkey were accessed and examined.

Table 3. Faculty of Medicine Anatomy course topics

	Course Topics
Term I, II	Introduction to Anatomy
	Anatomy Terminology
	General Information About Bones
	Upper Extremity Bones, Lower Extremity Bones
	Columna Vertabralis, Costas and Sternum
	Head Bones
	General Information About Muscles
	Superficial Back Muscles, Shoulder Muscles, Arm Muscles
	Axilla Anatomy, Plexus Brachialis
	Forearm Anatomy, Fossa Cubiti, Rear area of Forearm
	Hand Anatomy
	Anatomy of Gluteal Region, Plexus Lumbosacralis
	Posterolateral regions of the thigh, Canalis Adductorius, Popliteal fossa
	Anteromedial regions of the thigh, Trigonum Femorale
	Foot Anatomy
	Anterolateral region of the leg and foot back
	Posteromedial region of the leg and soles
	Upper and Lower Limb Clinical Anatomy
	Facial Anatomy and Scalp
	Parotid and Temporal Regions, Fossa Infratemporalis and Fossa Pterygopalatina
	Neck, Front and Side Areas
	Deep Back Muscles, Suboccipital Region
	Heart Anatomy, Coronary Vessels and Nerves
	Pericardium and Great Vessels, Systemic, Pulmonary, and Fetal Circulations
	Neck Root (Veins and Plexus Cervicalis)
	Thorax Wall Anatomy, Diaphragma, Mediastinum
	Nasal Anatomy, Paranasal Sinuses, Larynx
	Nervous System Parts and General Information
	Morphology of Medulla Spinalis
	Brainstem Formations: Medulla Oblongata, Pons, Mesencephalon
	Cerebellum and Paths
	Cranial Nerves
	Endocrine System (Pituitary, Pineal, Suprarenal, Thyroid, Parathyroid, Thymus)
	Kidney and Ureter
	Vesica Urinaria and Urethra, Endocrine Organs
	Pelvis and Perineum
	Male Genital Organs
	Female Genital Organs
	Oral and Dental Anatomy
	Tongue and Chewing Muscles
	Pharynx, Oesophagus
	Abdominal Cavity Topography, Abdominal Front Wall, Abdominal Back Wall
	Canalis Inguinalis, Inguinal Hernias
	Stomach, Gros Anatomy of intestines, Small intestine, Large intestine
	Peritoneum, Omentum Majus, Minus and Bursa Omentalis
	Liver, Gallbladder, and Ways
	Pancreas and Spleen, Portal system and Portacaval anastomoses

State University Medical Faculties

The 2018-2019 academic year curriculum of Aksaray University, Amasya University, Canakkale Onsekiz Mart University, Dicle University, Dokuz Eylul University, Duzce University, Erzincan Binali Yildirim University, Eskisehir Osmangazi University, Giresun University, Hatay Mustafa Kemal University Tayfur Ata Sokmen, Hitit University, Kastamonu University, Kirikkale University, Kırsehir Ahi Evran University, Kocaeli University, Manisa Celâl Bayar University, Marmara University, Necmettin Erbakan University Meram, Nigde Omer Halisdemir University, Pamukkale University, Sivas Cumhuriyet University, Suleyman Demirel University, Trakya University, Usak University and Yozgat Bozok University Medical Faculties could not be accessed from the official web pages of the faculties.

Hacettepe University Faculty of Medicine, Istanbul University İstanbul Faculty of Medicine, Istanbul University-Cerrahpasa Cerrahpasa Faculty of Medicine, Mugla Sitki Kocman University Faculty of Medicine and Ondokuz Mayis University Faculty of Medicine have two faculties providing education in Turkish / English. The 2018-2019 academic year curriculum was not available on the official web page of these faculties.

In order to shed light on our study, the number of anatomy theoretical and practical courses of some state and foundation universities are given in our study.

Ankara University Faculty of Medicine has two faculties providing education in Turkish and English. The Anatomy course for term I students has 78 hours of theoretical and 78 hours of practical content. It has been observed that there are 23 hours of theoretical and 32 hours of practical courses for term II students (11).

Inonu University Faculty of Medicine has two faculties providing education in Turkish and English. Anatomy course for term I students has 67 hours of theoretical and 76 hours of practical content. It has been observed that 93 hours of theoretical and 96 hours of practical lessons are available for term II students (12).

Anatomy course for Akdeniz University Faculty of Medicine term I students have 88 hours of theoretical and 78 hours of practical content. It was observed that 94 hours of theoretical and 96 hours of practical lessons were applied to term II students (13).

Anatomy course for the students of Bursa Uludag University Faculty of Medicine term I students have 56 hours of theoretical and 46 hours of practical content. It was found that there are 67 hours of theoretical and 37 hours of practical lessons for term II students (14).

Anatomy course for Cukurova University Faculty of Medicine term I students have 56 hours of theoretical and 54 hours of practical content. It was observed that 91 hours of theoretical and 66 hours of practical lessons were provided for term II students (15).

Anatomy course for Ege University Medical Faculty term I students have 75 hours of theoretical and 17 hours of practical content. It was observed that 103 hours of theoretical and 29 hours of practical lessons were applied to term II students (16).

Anatomy course for Erciyes University Faculty of Medicine term I students have 57 hours of theoretical and 30 hours of practical content. It was found that 113 hours of theoretical and 62 hours of practical lessons were applied to term II students (17).

Anatomy course for Gaziantep University Medical Faculty term I students have 70 hours of theoretical and 56 hours of practical content. It was found that 110 hours of theoretical and 77 hours of practical lessons were applied to term II students (18).

Anatomy course for Harran University Medical Faculty term I students have 36 hours of theoretical and 26 hours of practical content. It was observed that 168 hours of theoretical and 118 hours of practical lessons were provided for term II students (19).

Anatomy course for Istanbul Medeniyet University Faculty of Medicine term I students have 71 hours of theoretical and 42 hours of practical content. It was observed that 98 hours of theoretical and 48 hours of practical lessons were provided for term II students (20).

Anatomy course for Karadeniz Teknik University Faculty of Medicine term I students have 98 hours of theoretical and 32 hours of practical content. It was observed that there were 134 hours of theoretical and 80 hours of practical lessons for term II students (21).

Anatomy course for Sakarya University Faculty of Medicine term I students have 78 hours of theoretical and 32 hours of practical content. It was found that 101 hours of theoretical and 39 hours of practical lessons were applied to term II students (22).

Anatomy course for Selcuk University Faculty of Medicine term I students have 62 hours of theoretical and 22 hours of practical content. It has been observed that 150 hours of theoretical and 112 hours of practical lessons are available for term II students (23).

Anatomy course for Zonguldak Bulent Ecevit University Faculty of Medicine term I students have 30 hours of theoretical and 12 hours of practical content. It has been observed that 160 hours of theoretical and 54 hours of practical lessons are available for term II students (24).

Foundation University Medical Faculties

The 2018-2019 academic year curriculum of Acibadem Mehmet Ali Aydinlar University, Bahcesehir University, Beykent University, Halic University, Istanbul Aydin University, İstanbul Bilim University, Izmir Ekonomi University, Koc University, KTO Karatay University, Sanko University, TOBB Ekonomi ve Teknoloji University, Ufuk University, Yeditepe University and Yuksek Ihtisas Faculty of Medicine were not available on the official web page of the faculties.

It has been observed that there are 102 hours of theoretical anatomy courses for term I students in the 2018-2019 academic year on the web page of Lokman Hekim University Faculty of Medicine. This faculty was evaluated among those who did not have a curriculum (25).

Baskent University, Istanbul Medipol University, Maltepe University Faculty of Medicine has two faculties providing Turkish / English education and the curriculum of the 2018-2019 academic year could not be accessed from the official web page of the faculties.

Istinye University Faculty of Medicine has two faculties providing education in Turkish and English. Anatomy course for the term I students have 32 hours of theoretical and 16 hours of practical content. It was found that 50 hours of theoretical and 17 hours of practical lessons were applied to term II students (26).

Anatomy course for Bezm-İ Âlem Vakıf University Faculty of Medicine term I students have 118 hours of theoretical and 58 hours of practical content. It was found that there are 57 hours of theoretical and 30 hours of practical courses for term II students (27).

Faculty of Medicine Affiliated YOK University Outside Turkey

Doğu Akdeniz University (UOLP-Marmara University), Girne University Medical Faculties 2018-2019 academic year curriculum could not be accessed from the official web page of the faculties.

Yakın Doğu University Faculty of Medicine has two faculties providing Turkish / English education and the curriculum of the 2018-2019 academic year could not be accessed from the official website of the faculty.

The 2018-2019 academic year curriculum of the Faculty of Medicine of Azerbaijan Medical University could not be accessed from the official web page of the faculty.

The numbers and proportions of state and foundation medical faculties, and medical faculties outside Turkey, whose anatomy curriculum have been accessed or not, are given in Table 4. A significant difference was found between the state, foundation and medical faculties outside Turkey in terms of accessing the anatomy curriculum. The rate of accessing the anatomy curriculum in state medical faculties was found to be significantly higher than the rates of other medical faculties (P<0.05) Table 4.

There was a significant difference in both theoretical and practical average course hours between state and foundation medical faculties in the second term. Both theoretical and practical average course hours in state medical faculties were found to be significantly higher than foundation medical faculties (P<0.05) (Table 5).

Table 4. Those with and without curriculum on the web page of the Faculties of Medicine

Curriculum on the web page	State	Foundation	Outside Turkey	Total	p*
Yes	40 (48.80%)[a]	7 (25.00%)[b]	0 (0.00%)[b]	47 (40.90%)	
No	42 (51.20%)[a]	21 (75.00%)[b]	5 (100.00%)[b]	68 (59.10%)	0.011
Total	82 (100.00%)	28 (100.00%)	5 (100.00%)	115 (100.00%)	

*: Pearson chi-square test
Note: Each subscript letter denotes a subset of university types whose column proportions do not differ significantly from each other at the 0.05 level

Table 5. The average of Anatomy course hours of Medical Faculties

	Term I*		Term II*	
	Theoretical (h)	Practical (h)	Theoretical (h)	Practical (h)
State	62 (26-98)	40 (12-120)	110 (23-168)	87 (50-115)
Foundation	42 (32-118)	17 (15-58)	87 (50-15)	41 (17-92)
p	0.22	0.086	0.004	0.01

*: Data are summarized as median (minimum-maximum) h:Hour

DISCUSSION

Anatomical knowledge plays a very important role in patient examination, diagnosis and treatment. Physicians need to have a good understanding of basic anatomy knowledge for safe medical practices. It has been reported that there is a 7-fold increase in medical errors due to anatomical reasons. The training of surgeons will also be affected in the future as the entire anatomy curriculum is reduced to ease the burden of students and teach other skills (28).

There has been a steady decline in the number of anatomy education hours in medical education worldwide in recent decades. Clinicians affirm that it remains a center of contemporary anatomy knowledge for medical examination and accurate diagnosis. Anatomy remains the cornerstone of medical education despite a significant reduction in lecture hours over the recent decades (29).

In order to provide medical education in the best way, different education models are applied in medical faculties around the world (1).

In the study of Craig et al., a total of 19 universities in Australia and New Zealand were surveyed. Significant differences have been identified in terms of time, content and presentation allocated for anatomy in medical faculties here. Average anatomy teaching hours were found to be 171 hours (SD 116.7, range 56/560) (30).

Leung et al. reported that the average teaching hours for gross anatomy in US medical schools decreased from a total of 549 hours in 1902 to a total of 167 hours in 1997 (31). In the United Kingdom and Ireland, the average time devoted to teaching gross anatomy was reported as 124.5 hrs in 1999–2000 (32).

With our research, the contents and course hours of the Anatomy courses given in Medical Faculties operating under the YÖK in Turkey have been determined, and it has been tried to reveal whether there is a standard in this subject in Medical Faculties, by taking TAKAD's ÇEP as a reference. It was seen that most of the Faculties of Medicine curriculum content, which we have access on the web pages are similar and overlap with the content of ÇEP Anatomy course education published by TAKAD in 2018.

The periods in which anatomy courses are given in all Medical Faculties in Turkey are determined as the first and second terms. In the curriculum of state universities affiliated to YÖK, there is an total average of 102 hours of anatomy courses, both theoretical and practical, in the first term, and 197 hours of anatomy courses in the second term. A total average of 299 hours of anatomy courses are given to medical students at the state university.

In foundation universities, a total average of 59 hours of anatomy courses, both theoretical and practical, are given in the first term, and 128 hours in the second term. The total average course hours given to medical students at foundation universities is 187. It has been observed that the total average course hours of both state and foundation universities in Turkey are higher than the course hours given in the literature.

In addition, the average course hours of both theoretical and practical anatomy in the 2nd term in the Faculties of Medicine of the State University were found to be significantly higher than in the Faculties of Medicine of the Foundation University.

It can be said that there is a standard in Turkey in terms of giving anatomy lessons in term I/II and course content. However, it can be said that there is an inconsistency between the average of Anatomy theoretical and practical course hours of State University Medical Faculties and Foundation University Medical Faculties.

The content of the curriculum could not be reached in most of the web sites of the universities (75%). Nearly half (48.8%) of the University Medical Faculties operating in the state have published their course curriculum on their web pages. This study makes us think that State Universities have a more serious education program in terms of accessibility to course content data, sharing knowledge experience infrastructure and archiving achievements compared to Foundation University Medical Faculties.

A study similar to our study did not appear in our literature review. In a study by Hegazy and Minhas, they mentioned the following: Criticism in recent decades regarding an overcrowded medical school curriculum delivered via didactic, passive techniques has resulted in revised medical courses throughout the world. These now cover a spectrum from problem-based to systems-based, delivered via lectures, clinical skills, and small-group classes. Within this, anatomy teaching in the United Kingdom utilizes a range of formats including dissection, prosection, information technology, living anatomy, and models. Yet there is scant published evidence on outcomes underlying many of these varied teaching styles and techniques. Much simply relies on perceptions of the learning experience and course feedback from students. Frequently these support the particular style of teaching employed by the author rather than attempting a critical appraisal. Recently, much attention has focused on the perceived lack of anatomical knowledge of Australian medical graduates, both in the popular press and academic literature. A sustained decline in the number of hours dedicated to teaching anatomy from the mid-1990s has been attributed to the introduction of integrated, problem-based curricula, the redesign of medical curricula to accommodate a vast expansion in basic science knowledge, as well as the rise of time-poor, four-year graduate programs (7).

CONCLUSION

Anatomy education holds a very important place in the practice of medicine. Various models are being tried today in order to provide better anatomy education. In Turkey, a standard was provided in terms of course content with the anatomy courses given in the medical faculties of the universities affiliated to YÖK in term I/II. It was concluded that most of the curriculum content of the faculties of medicine that we can access on the web pages are similar

and overlap with the contents of the ÇEP anatomy course published by the TAKAD in 2018.

Over the years, the hours of anatomy education in medical education in the world have shown a continuous decline. Reducing these anatomy education hours has been the subject of discussion in various studies. It has been observed that the anatomy course hours applied in medical faculties in Turkey are higher than the literature values.

It can be said that there is a mismatch between the average theoretical and practical hours of the state university medical faculties and the anatomy of foundation university medical faculties in Turkey. This study makes us think that state universities have a more serious education program in terms of accessibility to course content data, sharing knowledge experience infrastructure and archiving achievements compared to foundation university medical faculties. If the number of university medical faculties that open the curriculum to the web pages will increase, it will be possible to make clear conclusions in the researches.

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Research Article

Investigation of Clinical and Sociodemographic Characteristics of Critically Patients with COVID-19 Admitted to Intensive Care Unit

Yoğun Bakım Ünitesine Kabul Edilen COVID-19'lu Kritik Hastaların Klinik ve Sosyodemografik Özelliklerinin İncelenmesi

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Abstract

Aim: It is known that there is an increased risk of mortality due to COVID-19 in people with comorbid diseases. In this study, it was aimed to examine the comorbid diseases of patients treated in the intensive care unit due to COVID-19 and the effects of these diseases on mortality.

Material and Methods: In this study, the clinical and sociodemographic characteristics of 220 patients who were treated in the intensive care unit due to Covid-19 in a district state hospital between 01/06/2020-01/01/2021 were retrospectively analyzed.

Results: The mean age, urea, creatine, CRP, WBC, and neutrophil count were found to be significantly higher in the non-survivor group compared to the survivor group. Lymphocyte count, eosinophil count, HGB, and HCT were significantly higher in the survivor group. It was found that mortality was significantly increased in COVID-19 patients with DM, HT, CRF, COPD comorbid diseases.

Conclusion: According to the results we found, it is necessary to be more careful in the intensive care follow-up of COVID-19 patients with comorbid diseases such as DM, HT, COPD, CKD.

Keywords: COVID-19, intensive care, mortality, comorbidity

Öz

Amaç: Komorbid hastalıkları olan kişilerde COVID-19 nedeniyle mortalite riskinde artış olduğu bilinmektedir. Bu çalışmada COVID-19 nedeniyle yoğun bakım ünitesinde tedavi gören hastaların komorbid hastalıkları ve bu hastalıkların mortalite üzerindeki etkisinin incelenmesi amaçlanmıştır.

Materyal ve Metot: Bu çalışmada 01/06/2020-01/01/2021 tarihleri arasında bir ilçe devlet hastanesi'nde COVID-19 nedeniyle yoğun bakım ünitesinde tedavi gören 220 hastanın klinik ve sosyodemografik özellikleri retrospektif olarak incelenmiştir.

Bulgular: Yaş ortalaması, üre, kreatin, CRP, WBC ve nötrofil sayısı, yaşamını yitiren grupta, hayatta kalan gruba kıyasla anlamlı derecede yüksek bulundu. Hayatta kalan grupta lenfosit sayısı, eozinofil sayısı, HGB ve HCT anlamlı olarak daha yüksekti. DM, HT, KBY, KOAH komorbid hastalıkları olan COVID-19 hastalarında mortalitenin önemli ölçüde arttığı bulundu.

Sonuç: Bulduğumuz sonuçlara göre DM, HT, KOAH, KBY gibi komorbid hastalıkları olan COVID-19 hastalarının yoğun bakım takibinde daha dikkatli olunması gerekmektedir.

Anahtar Kelimeler: COVID-19, yoğun bakım, mortalite, komorbidite

INTRODUCTION

In December 2019, cases of pneumonia, whose clinical appearance resembled viral infections, emerged in Wuhan city of China for an unknown reason. Later, after examining the samples taken from the lower respiratory tract, a new type of coronavirus was identified and named 2019-nCoV. The disease resulted from this virus was named COVID-19 (1). COVID-19 often causes cough, fever, shortness of breath, muscle and joint pain, malaise, gastrointestinal complaints, and loss of smell and taste. COVID-19 has affected many countries worldwide due to severe pneumonia it causes, and the persistence of person-to-person transmission has made it a global concern and a major public health risk (2).

The need for intensive care treatment may arise between 2-10 days in hospitalizations due to COVID-19 pneumonia. COVID-19 may cause the need for intensive care in 5% of patients (3). For this reason, the evaluation of the clinical

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features of patients receiving intensive care treatment gains importance in the regulation of treatment (4). It has been shown in studies that the prognosis of COVID-19 is worse in people with diabetes mellitus (DM) of any age. It has been reported that morbidity, mortality, intensive care unit hospitalization rates and length of stay in the hospital are higher in COVID-19 patients with DM (5). Studies have shown that patients with chronic obstructive pulmonary disease (COPD) or those with any respiratory system disease have a more severe course of COVID-19, and death rates in COVID-19 patients with COPD increase four times compared to other patients (6).

In this study, it was aimed to examine the comorbid diseases of patients treated in the intensive care unit due to COVID-19 and the effects of these diseases on mortality.

MATERIAL AND METHOD

Study Sample

Two hundred twenty patients who admitted to intensive care unit due to COVID-19 in Kahta State Hospital between 01/06/2020-01/01/2021 were included in the study. In this study, COVID-19 patients were divided into two groups. The group that died due to COVID-19 was defined as non-survivor (NS), and the recovered COVID-19 patients were defined as survivor (S). Comorbid disease information of the patients was obtained from their medical history and from our hospital database.

This study was carried out following the ethical standards of the liable institution for human subjects and the Declaration of Helsinki. Research ethics approval was acquired from the Non-Invasive Ethics Committee of Adıyaman University Medical Faculty (Decision Date: 16/02/2021, Decision Number: 2021/02-38).

All patients admitted to an outpatient clinic or the emergency department with cough, dyspnea, headache, fever, myalgia, malaise, loss of appetite, weight loss, sore throat, diarrhea, nausea, vomiting, rhinitis, or loss of smell should undergo a complete medical assessment, physical examination, laboratory examination, and thorax CT done. Clinical, laboratory, radiological, and epidemiological findings were obtained from electronic medical archives and recorded documentation forms. While some patients in this study were treated in inpatient services due to COVID-19, they were taken to the intensive care unit due to worsening in their clinics.

SARS-CoV-2 pneumonia diagnosis was made according to the interim guidelines of the World Health Organization (7). COVID-19 patients, who had shortness of breath despite 5 L/min oxygen, respiratory rate >30/min, tachycardia >100/min, blood oxygen saturation level <90%, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen<300 mm Hg, on chest X-ray >% 50 infiltration, need for mechanical ventilation, development of acute organ dysfunction, sepsis, septic shock, immunosuppression, acute bleeding diathesis, arrhythmia or increased troponin level, were followed in the intensive care unit (ICU) (8).

Table 1. Comparison of demographic and laboratory values in non-survivor and survivor groups

	Survivor (n=142) Mean ± SD	Non-survivor (n=78) Mean ± SD	p value
Gender-Female *	(n=66) (%46.5)	(n=38) (%48.7)	0.750
Age	69.41±16.47	76±11.94	0.004
Peak Urea	66.54±49.36	127.99±73.93	<0.001
Peak Creatine	1.16±0.98	2.08±1.45	<0.001
Peak CRP	6.19±5.21	10.46±7.91	<0.001
WBC	11881.35±5868.23	15602.65±8015.37	<0.001
HGB	12.96 ±2.24	12.23±2.61	0.018
HCT	40.50±7.19	38.32±8.09	0.009
Neutrophil	9168.11±5588.81	12798.06±8072.73	<0.001
Lymphocyte	2107.40±2057.47	1754.43±2217.95	0.007
Monocyte	434.80±359.17	508.04±448.37	0.321
Eosinophil	100.65±195.25	67.41±178.02	0.004
Basophil	95.36±148.55	125.21±207.16	0.542
ICU Period	9.24±10.82	10.21±10.36	0.098
Number of Comorbid Diseases	2.92±1.71	1.06±1.42	<0.001

Mann Whitney U-test was applied. A p<0.05 statistical significance value was accepted.
* Chi-square test was applied.
CRP: C-reactive protein, WBC: White blood cell, HGB: Hemoglobin, HCT: Hematocrit

According to the treatment guidelines of the Ministry of Health, mechanical ventilation is planned for COVID-19 patients with signs of dyspnea, tachypnea (>30/min), use of additional respiratory muscles, paradoxical breathing, respiratory alkalosis (PaCO2 < 35 mmHg, pH >7.45) (9).

Reverse transcriptase polymerase chain reaction test (RT-PCR) negative patients and suspected COVID-19 patients were not included in the study. Patients whose comorbid disease information could not be reached were not included in the study.

Laboratory Analysis

Venous blood samples were examined during hospital admission, in the intensive care unit, and whenever necessary to assess the patient's clinical status. Total white blood cell count and neutrophil, lymphocyte, monocytes, eosinophil, and basophil counts were measured using a device (CELL-DYN Ruby; Abbott Diagnostics, Abbott Park, IL) and given as x 103 cells/mm3. Hemoglobin, hematocrit, and thrombocyte counts were also calculated. Creatinine, urea, and C-reactive protein (CRP) levels were analyzed using biochemistry kits (Abbott Diagnostics) and an Architect c8000 Chemistry System (Abbott Diagnostics) machine. Peak hemogram, biochemistry, and CRP values were recorded in the intensive care follow-up of the patients.

Nasopharyngeal swab samples were picked up by professional health personnel in a particular sampling room. Nasopharyngeal swab samples of the patients were analyzed by RT-PCR. Those with positive RT-PCR test were included in the study.

Radiological Evaluation

In COVID-19 patients, thoracic CT shows unilateral/bilateral patchy ground-glass density areas predominantly in the middle and lower lobes of the lungs. Areas of this ground glass density can also mimic consolidation or organized pneumonia. Interlobular septal thickening and honeycomb formation may also be seen (10).

Findings in the chest X-ray of COVID-19 patients may be normal in the early stages of the disease, or there may

Table 2. Comparison of the incidence of additional diseases in the non-survivor and survivor groups

	Survivor (n=142) (%64.5)	Non-survivor (n=78) (%35.5)	p value
DM	22 (%10)	33 (%15)	<0.001
HT	43 (%19.5)	67 (%30.5)	<0.001
COPD	26 (%11.8)	55 (%25)	<0.001
CAD	23 (%10.5)	27 (%12.3)	0.002
CKD	5 (%2.3)	23 (%10.5)	<0.001
CHF	20 (%9.1)	18 (%8.2)	0.091
AF	12 (%5.5)	5 (%2.3)	0.588

The chi-square test was used. A p<0.05 statistical significance value was accepted.
DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease, CKD: Chronic Kidney Disease, CHF: Congestive Heart Failure, AF: Atrial Fibrillation

Table 3. Evaluation of the effect of comorbid diseases on mortality due to COVID-19 according to regression analysis

	B	p value	Odds Ratio	95% CI	
				Lower	Upper
DM	1.074	0.045	2.928	1.024	8.373
HT	2.140	<0.001	8.499	3.548	20.361
COPD	1.942	<0.001	6.973	3.090	15.735
CAD	0.147	0.827	1.158	0.311	4.305
CKD	2.162	<0.001	8.688	2.319	32.552
CHF	-0.439	0.582	0.645	0.135	3.080
AF	-1.831	0.05	0.160	0.026	0.997
Constant	-3.134	0.000	0.044		

A Binary logistic regression test was used. A p<0.05 statistical significance value was accepted. DM: Diabetes Mellitus, HT: Hypertension, COPD: Chronic Obstructive Pulmonary Disease, CAD: Coronary Artery Disease, CKD: Chronic Kidney Disease, CHF: Congestive Heart Failure, AF: Atrial Fibrillation

be predominantly peripheral opacities in the unilateral/ bilateral subzones. In addition, the sensitivity of this imaging method is low since underlying diseases such as COPD and congestive heart failure (CHF) may also affect the chest X-ray (11).

Statistical analysis

All analyzes were performed in SPSS26.0 for Mac (SPSS Inc., Chicago, IL). Categorical data were expressed as numbers and percentages. The conformity of the data to the normal distribution was evaluated using the Kolmogorov-Smirnov test. The mean and standard deviation values of the continuous data were given. The Mann-Whitney U test was used to evaluate the difference between the two groups of non-normally distributed data. The chi-square test was used to compare the prevalence of comorbid diseases between the groups. Binary logistic regression analysis was used to assess the effect of comorbid diseases on the risk of death from COVID-19. P<0.05 was accepted as a statistical significance value.

RESULTS

The mean age of 220 COVID-19 patients hospitalized in the ICU was 71.69±15.37 years. 116 (52.7%) of the patients were male. 72 (32.7%) of the patients were intubated. COVID-19 was fatal in 78 (35.5%) of the patients. Hypertension (HT) in 110 (50%) patients, COPD in 81 (36.8%), DM in 55 (25%), coronary artery disease (CAD) in 50 (22.7%) patients, 38 (17.3%) patients had chronic kidney disease (CKD), 38 (%17,2) patients had CHF and 17 (7.7%) patients had atrial fibrillation (AF).

Demographic, laboratory, and radiological comparisons of NS and S groups are shown in Table-1.

The mean age in the NS was significantly higher than in the S. Urea, creatine, CRP, WBC, and neutrophil counts were significantly higher in the NS than in the S. HCT, lymphocyte count, and eosinophil count were significantly lower in the NS compared to the S. There was no significant difference between the groups in terms of gender distribution. The number of comorbid diseases was in the NS significantly higher than in S.

The comparison of the prevalence of comorbid diseases in the NS and S are shown in Table-2.

DM, HT, COPD, CAD, CKD were significantly common in the NS. However, there was no significant difference in prevalence between the two groups regarding CHF and AF.

According to logistic regression analysis, the evaluation of the effect of comorbid diseases on mortality due to COVID-19 is shown in Table-3.

According to the logistic regression model, DM, HT, COPD, CKD increased mortality risk due to COVID-19. (Nagelkerke R square=0.58, -2 Log likelihood= 165.401) This regression model explains the risk of mortality due to COVID-19 at the rate of 58%. Based on odds ratios, it is understood that CKD and HT increase mortality risk the most. However, CAD, CHF, and AF were not identified as risk factors for mortality due to COVID-19.

Figure 1 shows the incidence of comorbid diseases and the mortality rate from COVID-19. According to this, while the death rate is 3.9% in the group without comorbid disease, this rate rises to 65.1% in those with two comorbid diseases.

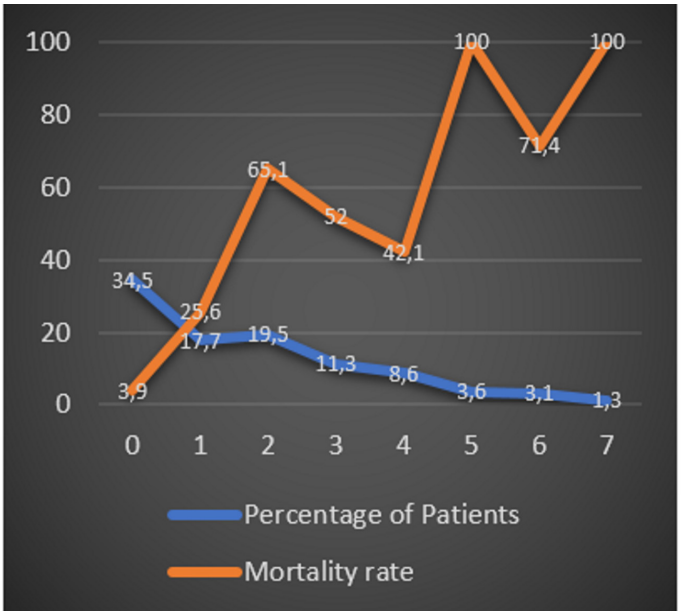

Figure 1. Number of comorbid diseases and mortality rate X-axis: Number of comorbid diseases, Y-axis: Percent (%)

DISCUSSION

Identification of predictive factors for severe infection is necessary to analyze patients' risk status due to the COVID-19 pandemic and to guide public health recommendations with the appropriate use of hospital resources (12).

This study defined the relationship between patients' comorbid conditions followed in the ICU due to COVID-19 and the mortality rate. In the present study the hospitalization rate in ICUs due to COVID-19 in males was higher than females. However, we did not find a significant difference between the genders regarding mortality.

Yang et al. examined the clinical and sociodemographic data of 52 patients receiving intensive care treatment for COVID-19. They found that the mean age of the patients was 59.7±13.3 years. While 35 (67%) of the patients were male, 17 (33%) were female, 21 (40%) had a chronic disease. Thirty-two (61.5%) of the patients died an average of 28 days after hospitalization. The average duration of the transition from hospitalization to the ICU was seven days. The mean age of the non-survivors was 64.6±11.2 (13). In our study, the mean age of the NS was higher. It can be said that Yang et al. did their research early stages of the COVID-19 pandemic. Progress in the treatment of COVID-19 during the pandemic process may be related to the increase in the average age of the patients in ICUs. In

this study, 144 (65%) patients with COVID-19 had at least one comorbid disease. Despite the higher rate of comorbid disease, the lower mortality rate in our study may be related to better recognition of COVID-19 and improved treatment opportunities. In addition, we think that the treatment of comorbid diseases in COVID-19 patients may have been disrupted in the first period of the pandemic.

Graselli et al., in their study in the Lombardy region of Italy, one of the regions first affected by the COVID-19 pandemic, examined 3988 patients treated in intensive care due to COVID-19 infection. In their research the mean age of the patients was 63 years. While 79.9% of the patients were male, 60.1% of them were found to have at least one comorbid disease. Mechanical ventilation was required in 87.3% of the patients (14). In our study, the rate of mechanical ventilation was found to be 32.7%. Similarly, the rate of those with at least one comorbid disease in our study was 65%.

Mitra et al. in their study on 117 patients receiving intensive care treatment due to COVID-19, found the mean age of the patients to be 69, while 79 (67.5%) of the patients were male. In their research while the number of patients with at least one comorbid disease was 86 (73.5%), the number of those who needed mechanical ventilation was 74 (63.2%). Eighteen of the patients (15.4%) died (15). In our study, a 35.5% mortality rate was found. This difference may be related to the time of admission to the hospital and the late initiation of treatment. It can also be said that the prognosis of COVID-19 is not as poor as before.

It has been reported that men with COVID-19 have a higher risk of severe illness and death than women. It was thought that respiratory tract diseases tend to be more severe in males and lead to more frequent deaths as the reason for this (16). The reason for this is that cardiovascular diseases are seen more frequently in men and the ratio of Angiotensin-converting enzyme/Angiotensin-converting enzyme 2 (ACE/ACE2) is low in women (17). Also, during the SARS epidemic in 2003, the mortality rate was higher in males (18). However, we did not find a significant difference in mortality rates in our study. Although, we found that men with COVID-19 were admitted to intensive care more frequently. The absence of a significant difference in mortality rates between the sexes in our study can be explained because women have more comorbidities than men in terms of comorbidity rates. This can be explained by the fact that HT was more common in women in our study (54.8%-45.8%). We found HT to be a risk factor for mortality in our study. We think that comorbid diseases may have a more predictive effect on mortality than gender.

Our study observed that the percentage of HT, COPD, DM, CKD was significantly higher in patients with severe COVID-19 and hospitalization in the ICU, use of mechanical ventilation, or death. Guan et al. found that the frequency of HT, DM, CAD, cerebrovascular disease, COPD, CKD, and cancer was significantly higher in patients with severe COVID-19 admitted to the ICU and required mechanical ventilation or died (16). Shi et al. reported that HT, DM, CAD, cerebrovascular disease, COPD, and cancer are more common in COVID-19 and myocardial damage (18). There was no statistically significant difference between the NS and S for CAD, CHF, and AF in our study.

It has been reported that ACE2 levels are high in cardiovascular diseases. It is thought that COVID-19 is more severe in cardiovascular diseases due to the use of ACE2 receptors by COVID-19. It has been reported that plasma ACE2 level is increased in AF and can be used to determine the severity of AF. Although AF was reported to be more common in severe COVID-19 (19), we could not conclude in our study that AF increased mortality. It is emphasized that well-controlled AF does not pose a risk for COVID-19 mortality (20). This result we found may be due to the regular use of antiarrhythmic treatments.

DM has been indicated as essential predictors of severity and mortality in patients infected with different viruses, comprising the 2009 influenza A pandemic (H1N1) (21), MERS-CoV (22), and SARS-CoV (23). Some studies from China (18,24) and Italy (25) showed that elderly patients with comorbid diseases, including DM, are at higher risk for severe COVID-19 and mortality. However, some studies have found no association between DM and severe COVID-19 (26,27). More recent data from Italy and the United States have associated COPD with a significantly more severe COVID-19 infection with a more than five-fold increased risk (28,29).

Emma et al. examined the comorbidities of COVID-19 and various diseases using meta-analysis from various early studies and found that just five articles had reported COPD. The prevalence of COVID-19 patients with COPD was only 0.95%, a relatively small number compared to other pre-existing conditions (20). The reason may be the difficulty in detecting COPD in China or that patients provide information about their comorbid conditions at hospitalization. We think that underreporting comorbidities due to lack of awareness or diagnostic tests may affect the relationships between comorbidities and clinical outcomes.

Chronic Kidney disease (CKD) is affiliated with a growing risk of pneumonia, both inpatient and outpatient (31). Pneumonia-related mortality rates in CKD patients are considerably higher than in the entire population (32). In this research, we obtained similar results to these studies. However, there was insufficient data on the subgroups and degree of CKD. The number of publications advocating that CKD is the most important risk factor for COVID-19 mortality is increasing (33). We also found that CKD increases the risk of mortality about 8.8 times.

Although our study included the cross-sectional data of a district state hospital, we found that comorbid diseases such as DM, HT, COPD, and CKD significantly increased the mortality risk due to COVID-19. Patients with these comorbid diseases should be followed carefully for COVID-19.

This study has some limitations. Since our study was retrospective, we did not have enough data about

socioeconomic status or ethnicity. Our study includes a small sample because it only covers the data of one district state hospital.

CONCLUSION

People with additional diseases that increase the mortality of COVID-19, which we mentioned in our study, need to be more careful about COVID-19, and in case these people have COVID-19, physicians should follow these patients more closely.

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Research Article

The Relationship between Nausea-Vomiting Severity and Activity Balance in Pregnancy

Gebelikte Bulantı-Kusma Şiddeti ile Aktivite Denge Arasındaki İlişki

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Abstract

Aim: Nausea and vomiting seen in early pregnancy are among the most common reasons for hospitalization of pregnant women in the first trimester. The aim of this study is to determine the relationship between the severity of nausea-vomiting during pregnancy and activity-specific balance-confidence.

Material and Method: The study was conducted cross-sectionally in a pregnant education class of a public university between June and September 2021. The sample size was calculated as 208 pregnant women according to the effect size calculation and the study was completed with 216 pregnant women. In the collection of data; "Personal Presentation Form", "PUQE Test (Pregnancy- Unique Quantification of Emesis and nausea) "Activity-Specific Balance Confidence Scale" was used. In statistical evaluation; Arithmetic mean, percentile distribution, standard deviation, pearson correlation, linear regression analysis, Cronbach Alpha (α) for reliability analysis, CR (Composite Reliability) and AVE (Average Variance Extracted) were used for validity analysis.

Results: It was determined that the mean PUQE test total score was 6.28±2.60, 62.04% of the pregnant women experienced mild nausea-vomiting, 37.96% of them had moderate nausea-vomiting, and none of the pregnant women had severe nausea-vomiting. The mean ASBCS score was found to be 53.56±26.37. It was determined that the mean ASBCS total score differed statistically according to the PUQE test classification, and the pregnants with moderate nausea and vomiting severity had more activity-specific balance confidence than mild pregnant women ($p<0.05$). It was determined that there was a highly significant negative correlation ($r=-0.760$; $p<0.05$) between the PUQE test mean score and activity-specific balance confidence, and the severity of nausea and vomiting affected activity-specific balance confidence as a result of linear regression analysis.

Conclusion: As a result, it can be said that the severity of nausea and vomiting affects activity-specific balance confidence and as the severity of nausea and vomiting increases, activity-specific balance confidence decreases. Health workers should create a care plan by considering the negative consequences of physical activity insufficiency.

Keywords: Nausea vomiting, pregnancy, activity-specific balance confidence

Öz

Amaç: Erken gebelik döneminde görülen bulantı kusma ilk trimesterdeki gebe kadınların hastanede yatmalarının en yaygın nedenleri arasındadır. Bu araştırmanın amacı, gebelikte bulantı-kusma şiddetinin aktiviteye özgü denge güven arasındaki ilişkiyi belirlemektir.

Materyal ve Metot: Araştırma kesitsel olarak bir kamu üniversitesine bağlı gebe eğitim sınıfında yürütülmüştür. Örneklem büyüklüğü etki büyüklüğü hesaplamasına göre 208 gebe olarak hesaplanmış olup 216 gebe ile çalışma tamamlanmıştır. Verilerin toplanmasında; "Kişisel Tanıtım Formu", "PUQE Testi (Pregnancy- Unique Quantification of Emesis and nausea) "Aktiviteye Özgü Denge Güven Ölçeği" kullanılmıştır. İstatistiksel değerlendirmede; aritmetik ortalama, yüzdelik dağılım, standart sapma, pearson korelasyon, linear regresyon analizi, güvenirlik analizi için Cronbach Alfa (α), Geçerlilik analizinde CR (Composite Reliability) ve AVE (Average Variance Extracted) kullanılmıştır.

Bulgular: APUQE testi toplam puan ortalamasının 6.28 ±2.60 olduğu, gebelerin %62.04'ünün hafif, %37.96'sının orta düzeyde bulantı-kusma yaşadığı, ağır düzeyde ise gebelerin hiçbirinin bulantı-kusma yaşamadığı belirlendi. ASBCS puan ortalamasının ise 53.56 ± 26.37 olduğu belirlendi. PUQE testi sınıflandırılmasına göre ASBCS toplam puan ortalamasının istatiksel açıdan farklılık gösterdiği ve bulantı kusma şiddeti orta düzeyde olan gebelerin hafif düzeyde olan gebelere göre daha fazla aktiviteye özgü denge güvenlerinin daha az olduğu belirlendi ($p<0.05$). PUQE testi puan ortalaması ile aktiviteye özgü denge güven arasında negatif yönde yüksek düzeyde önemli ilişki ($r=-0.760$; $p<0.05$) ve linear regresyon analizi sonucunda bulantı kusma şiddetinin aktiviteye özgü denge güveni etkilediği saptandı.

Sonuç: Sonuç olarak bulantı kusma şiddetinin aktiviteye özgü denge güveni etkilediği ve bulantı kusma şiddeti arttıkça aktiviteye özgü denge güvenin azaldığı söylenebilir. Sağlık çalışanları fiziksel aktivite yetersizliğinin olumsuz sonuçlarını göz önünde bulundurarak bakım planını oluşturmalıdır.

Anahtar Kelimeler: Bulantı kusma, gebelik, aktiviteye özgü denge güven

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INTRODUCTION

Pregnancy is a unique period of life for most women. Multiple hormonal, physiological, and biomechanical changes, such as increased blood volume and heart rate, weight gain and shift in the center of mass, proceed normally in almost all pregnant women (1). However, while physiological changes specific to pregnancy constitute the source of psychological changes, the complaints that occur with these changes can negatively affect the lifestyle of the pregnant woman (2). Nausea and vomiting in early pregnancy are among the most common reasons for hospitalization in the pregnant women in the first trimester (3,4). Although the exact cause of nausea and vomiting is not known yet, some studies have associated this condition with maternal age, sex of the baby, smoking status of the pregnant woman, hormones, the women's psychological state, and the vestibular system (3,5,6). Nausea and vomiting symptoms usually begin in gestational weeks 4-6, peak between gestational weeks 8 and 12, disappear after gestational week 20 (6), and rarely persist until childbirth (7). Symptoms may range from a mild dizziness to persistent vomiting (8). The onset and course of symptoms differ from person to person (9). Studies have shown that besides the effects of nausea and vomiting on general health, family life, work performance, quality of life, and psychosocial health are also affected, and it even increases the susceptibility to depression in the postpartum period (4,7,9). Psychosocial outcomes also affect women's perceptions of their conditions , and most women deny that this condition is psychological (10). It was reported that approximately 50% of pregnant women who experience nausea and vomiting have decreased work efficiency (11), approximately 35% lost work time (11), and 25% lost time from housework (11,12). At the same time, pregnant women with nausea and vomiting complain that their spousal relations are disrupted and they cannot perform their daily physical activities (13). As a matter of fact, maintaining physical activity and exercising during pregnancy have positive effects on the musculoskeletal system, especially the circulatory system and respiratory system, and weight gain. There are also studies suggesting that it increases psychological well-being and reduces the risk of gestational diabetes and preeclampsia (2,14-17). In a retrospective study, it is a remarkable finding that a sedentary life and low physical activity in the pre-pregnancy period increase nausea and vomiting during pregnancy (7). Women's daily physical activities include climbing stairs, walking around the house, getting in and out of the vehicle, walking, climbing a hill, walking on an icy pavement, and reaching for things at head/eye level in the house.

In the literature, there exist studies regarding severity of nausea and vomiting during pregnancy in relation with the psychosocial status (9), quality of life (4), and psychiatric and cognitive problems (18). However, there is no study investigating whether nausea and vomiting affect activity-specific balance and confidence in pregnant women. It is thought that our study result reveals that pregnant women with physical activity deficiency should also be evaluated in terms of nausea and vomiting. In addition, it has been determined that the activity-specific balance confidence scale is a valid and reliable tool that can also be used in pregnant women. For this reason, it is thought that this study will make an important contribution to the literature.

MATERIAL AND METHOD

Research Design and Sample

This cross-sectional study was conducted between June and September 2021 in order to determine the relationship of the severity of nausea and vomiting during pregnancy with the activity-specific balance. The universe of the study consists of pregnant women who attended a pregnant education class where the study was conducted. When the power analysis was performed, the sample size was calculated as 208 pregnant women with 95% confidence interval and 95% representative power. The study was completed with 216 pregnant women who accepted to participate in the study and met the inclusion criteria.

Inclusion criteria:

- Being over 18 years old,
- Being in gestational weeks 6-16,
- Not having a risky pregnancy,
- Not having any health problems preventing communication.

Data Collection Tools

Data were obtained using a Personal Information Form, the Pregnancy- Unique Quantification of Emesis and Nausea (PUQE) and Activity-Specific Balance Confidence (ABC) Scale.

Personal Information Form

The personal information form was prepared by the researcher in line with the relevant literature (9,19,20). In the form, there are questions about the socio-demographic characteristics of the pregnant woman (the women's age, education and employment status, income status and family type), obstetric characteristics (then-current gestational week and pregnancy history), and medical history (history of a chronic disease).

Pregnancy-Unique Quantification of Emesis and Nausea Test (PUQE)

Some assessment tools have been developed in order to objectively evaluate the clinical evaluation in patients with nausea and vomiting. The Rhodes test can be used in the evaluation of pregnancy-related nausea and vomiting (9,21). Although the Rhodes test is considered the gold standard in determining the complaint of nausea and vomiting, the high number of questions may be considered as an indication that it is not useful. On the other hand, the PUQE, which evaluates the severity of nausea-vomiting

during pregnancy and was prepared by adapting the Rhodes scoring system, was found to be as valuable and sensitive as the Rhodes test. (21). In the study conducted by Sucu et al. (2009) in Turkish pregnant women, the PUQE test was found to be an appropriate tool in the evaluation of the severity of nausea and vomiting during pregnancy (22). In the evaluation of the PUQE test, the total scores of 3-6 are considered as mild, 7-12 as moderate, and 13-15 as severe (21). In this study, the Cronbach Alpha (α) value for the PUQE was calculated as 0.841. In addition, the AVE value was calculated as 0.79, and the CR value as 0.92, and it was concluded that the questionnaire was valid and reliable.

Activity-Specific Balance Confidence Scale (ABC Scale)

It is a scale that evaluates how confidently people can perform 16 indoor/outdoor activities. Activities are scored between 0 (not-confident) and 100 (completely confident). A score is obtained by dividing the total score by 16. High scores indicate greater confidence. The Turkish validity study was conducted by Ayhan et al. in 2014 (23). The Cronbach Alpha (α) value was calculated as 0.96. In this study, the Cronbach Alpha (α) value was calculated as 0.957. In addition, the AVE value was calculated as 0.87 and the CR value as 0.93, and it was concluded that the questionnaire used was also valid and reliable for pregnant women.

Data Collection

The data were collected via face-to-face interviews in a pregnant education class offered in a public university between June and September 2021. The interviews lasted an average of 10-15 minutes per person.

Data Analysis

Data analysis was performed with the SPSS (Statistical Program in Social Sciences) 25 program. The Kolmogorov Smirnov Test was used to check whether the data included in the study fit the normal distribution. Since the skewness value of the model was between -2 and +2, it was seen that it yielded a normal distribution (24). Comparisons between the paired groups were made with the significance test (t-test) of the difference between the two means since the data were normally distributed. The homogeneity of variance was checked with Levene's test to decide which test result to use in comparisons ($p>0.05$). In addition, number, percentage, mean, and standard deviation were used for descriptive statistics. Pearson correlation, Cronbach Alpha (α) for reliability analysis, CR (Composite Reliability), and AVE (Average Variance Extracted) were used for validity analysis.

Ethical Considerations

Ethics Committee (Decision No: 2021/2027) approval was obtained to conduct the study. Participants were informed about the study and pregnant women who volunteered for participation were included in the study.

Limitation of the Research

Conducting the study in a single center and excluding women with risky pregnancies prevented the generalization of the study to all pregnant women. In addition, the fact that the majority of the pregnant women who participated in the study group were university graduates prevented commenting on the activity-specific balance scores of the pregnant women with low education levels.

RESULTS

It was determined that 54.6% of the participants included in the study were university graduates, 67.6% did not work, 75.9% lived in the city center, 71.3% had a medium income, and 88% had a nuclear family structure (Table 1).

Table 1. Sociodemographic of the Participating in the Study (n=216)

Variables	Group	n	%
Level of education	Primary school	16	7.4
	Middle School	26	12.0
	High school	56	25.9
	Undergraduate and Postgraduate	118	54.6
Employment Status	Yes	70	32.4
	No	146	67.6
Living Place	Province	164	75.9
	District	30	13.9
	Willage	22	10.2
Economical Situation	Low	58	26.9
	Middle	154	71.3
	High	4	1.9
Family structure	Nuclear Family	190	88.0
		26	12.0
		Mean± Sd	
Age (mean± sd)		28.91 ± 5.12	
Duration of Marriage		5.15 ± 4.69	
Size		159.96 ± 22.54	
Weight		66.37 ± 14.06	
Gestational Week		10.29 ± 2.93	

SD= Standard Deviation

It was found that 51.9% of the participants had their first pregnancy, 17.6% had at least one miscarriage, 83.3% had a planned pregnancy, 82.4% did not receive prenatal education, 14.8% experienced frequent dizziness, 25% had frequent sleep problems, 40.7% had frequent fatigue, 5.6% had frequent heart palpitations, and 14.8% had frequent fear and anxiety (Table 2).

Table 2. Distribution of obstetrical characteristics of pregnants participating in the study (n=216)

Variable	Group	n	%
Number of Pregnancy	One	112	51.9
	Two	40	18.5
	3 And Above	64	29.6
Living Child	No	2	0.9
	One	166	76.9
	2 And Above	48	22.2
Presence Of Abortion	No	178	82.4
	Yes	38	17.6
Planned Pregnancy	Yes	180	83.3
	No	36	16.7
Prenatal Education	Yes	38	17.6
	No	178	82.4
Dizziness	Never	38	17.6
	Rarely	70	32.4
	Sometime	76	35.2
	Often	32	14.8
Sleep Problem	Never	40	18.5
	Rarely	52	24.1
	Sometime	70	32.4
	Often	54	25.0
Weakness	Never	4	1.9
	Rarely	30	13.9
	Sometime	94	43.5
	Often	88	40.7
Heart Palpitations	Never	88	40.7
	Rarely	66	30.6
	Sometime	50	23.1
	Often	12	5.6
Fear Worry	Never	46	21.3
	Rarely	54	25.0
	Sometime	84	38.9
	Often	32	14.8
Total		216	100

The PUQE test classification and total score averages from the PUQE and the ABC scale are given in Table 3. It was determined that 62.04% of the pregnant women had mild nausea-vomiting complaints, 37.96% had moderate nausea-vomiting complaints, and none of the pregnant women had severe nausea and vomiting complaints. The mean PUQE test total score of the pregnant women with nausea and vomiting was 6.28±2.60, and the mean ABC total score was 53.56±26.37 (Table 3).

Table 3. PUQE Classification and Total Point Averages Received from PUQE and ASBCS (n=216)

PUQE Classification	n	%
Mild (3-6 point)	134	62.04
Moderate (7-12 point)	82	37.96
Severe (13-15 point)	0	0
Total	216	100
PUQE Total (mean±sd)	6.28 ±2.60	
ASBCS Total (mean± sd)	53.56 ± 26.37	

PUQE; The Pregnancy-Unique Quantification of Emesis and Nausea Test, ASBCS; Activities Specific Balance Confidence Scale

Comparisons of the ABC scale and the PUQE score averages are presented in Table 4. It was determined that the average ABC scale score of those with a mild PUQE score was 56.05±27.12, and the mean ABC score of those with a moderate score was 49.63±25.06. It was determined that the difference between the groups was statistically significant ($p<0.05$), and the activity-specific balance confidence score was lower in pregnant women with moderate nausea and vomiting (Table 4).

Table 4. ASBCS and PUQE comparison of scale score means

Variable	Group	Mean ± sd	p value
ASBCS	Mild	56.05± 27.12	0.004*
	Moderate	49.63 ± 25.06	

PUQE; The Pregnancy-Unique Quantification of Emesis and Nausea Test, ASBCS; Activities Specific Balance Confidence Scale, sd; Standard Deviation, p; statistical significance, *p<0.05; There is a statistically significant difference between the groups

The relationship between the ABC scale and the PUQE mean scores is presented in Table 5. A statistically significant correlation was found between the ABC scale score and the PUQE score at a high level (r=-0.760) in the negative direction ($p<0.05$, Table 5).

Table 5. ASBCS and PUQE relationship between scale score means

Variable 1	Variable 2	r value	p value
ASBCS	PUQE	-0.760	0.001*

PUQE; The Pregnancy-Unique Quantification of Emesis and Nausea Test, ASBCS; Activities Specific Balance Confidence Scale r; pearson correlation coefficient, p; statistical significance, *p<0.05; There is a statistically significant relationship between the scores

The results of univariate linear regression analysis of the PUQE's interpretation of the ABC scale score means are presented in Table 6. The univariate linear regression model established to test whether the dependent variable, the ABC scale score, was explained by the independent variable, the score from the PUQE scale, was found to be significant (F=21.194, p1<0.05, Table 6). In the established model, it was calculated that both the PUQE score and the constant term had a statistically significant effect on the

ABC scale score (p2<0.05, Table 6). It was determined that a 1-unit change in the PUQE scale score will cause a negative decrease of -4.768 units (β1) on the ABC scale score. It was calculated that 11.0% (R2=0.110) of the participants' ABC scale score is explained by the PUQE score.

Table 6. Univariate Linear Regression Analysis Results for PUQE's Prediction of ASBCS Score Mean

Dependent variable	Independent variable	R2	F Test	p1 value	β1	t Test	p2 Value
ASBCS	Sabit	0.110	21.194	0.001*	27.849	10.212	0.001*
	PUQE				-4.768	4.604	0.001*

Dependent variable; ACBSC score, İndependent variable; PUQE The Pregnancy-Unique Quantification of Emesis and Nausea Test, R2; Explanatory Coefficient, **p1<0.05; F test result for the significance of the model, β1; Non-standardized regression coefficients, *p2<0.05; t test result for the significance of the regression coefficients

DISCUSSION

Although the cause of nausea and vomiting in pregnant women cannot be fully elucidated, it is known that there are many effective factors. Among these factors is the vestibular system (3,5,6). The relationship between nausea and vomiting and the vestibular system in pregnant women draws attention to the difficulties experienced by pregnant women in their daily physical activities (13). It is also noteworthy that women generally reduce the duration of physical activity after conception (25,26). It was reported that only 15% of pregnant women reach the recommended physical activity level (27). Considering the studies examining the severity of nausea and vomiting during pregnancy, it is seen that the level of psychosocial health (9), blood pressure, the level of pain felt in the pelvic girdle, proteinuria (8), quality of life, and the desire to get pregnant again (4) is reported to be adversely affected by the severity of nausea and vomiting. The findings obtained as a result of this study, in which we aimed to determine the relationship between the severity of nausea-vomiting during pregnancy and the activity-specific balance-confidence, were discussed in line with the relevant literature.

It was reported that neurotransmitters released during pregnancy affect the biochemistry of the inner ear, and therefore hormonal abnormalities or changes may cause imbalance complaints in pregnant women (28). These physiological changes are accepted as a substrate for the development of audio-vestibular disorders in pregnant women (29). It was determined that the majority of the pregnant women participating in this study had various problems such as sleep problems, fatigue, heart palpitations, fear, and anxiety. In addition, vertigo symptoms were seen at different levels in the vast majority of the pregnant women. Guannan Bai et al. (2016) stated that 44.4% of the pregnant women had symptoms of fatigue, causing both physical and mental impacts in pregnant women (30). It has been stated that there are patient groups experiencing significant balance problems during pregnancy (28,31). In a study, it was determined that the severity of nausea and vomiting was higher especially in those with a history of motion sickness, migraine, and headache (32). The present finding in this regard agrees with the literature.

It was observed that the mean PUQE total score of the pregnant women participating in the study was 6.28 ± 2.60, and it was observed that 62.04% had mild and 37.96% had moderate levels of complaints, and there was no pregnant woman with severe nausea-vomiting complaints. When the studies in the literature evaluating the severity of nausea and vomiting in pregnant women were examined, it was seen that the PUQE total score averages were 9.05±2.30 (9), 8.44±1.87 and 9.55±2.05 (33), and 5.94±2.67 (34). The difference in the mean scores may be due to the fact that nausea and vomiting are due to many reasons, such as maternal age, gender of the baby, smoking status of the pregnant woman, hormones, psychological and vestibular system, insomnia, and bad mood (3,5,6,34). For this reason, it is thought that studies with large samples are needed to examine the factors affecting nausea and vomiting. In addition, it was found that the majority of the pregnant women experienced mild nausea and vomiting, and this finding was in parallel with the literature (6,34).

It was determined that the total average score of the activity-specific balance confidence scale of the pregnant women participating in the study was 53.56 ± 26.37. It was reported as 63.08±29.58 (35) in the elderly groups with a history of falling and 73.5±20.1 (İşler, 2017) in a study conducted with patients with lower extremity amputation. Since no instance of ABC scale used in pregnancy was found in the literature, it is a remarkable finding that pregnant women with nausea and vomiting during pregnancy have lower activity-specific balance confidence compared to the elderly and patients with lower extremity amputation. In this case, it is thought that pregnant women are at risk in terms of balance and confidence, and family and health professionals who support the pregnant should be more careful in this regard.

It is stated that nausea and vomiting in pregnant women seriously affect the quality of life and the functioning of social, occupational, and domestic daily life (4,36). It is also noteworthy that the effects of nausea and vomiting

increase as the severity of the symptoms increases (4, 36,37). This study is also compatible with the literature that nausea and vomiting symptoms of the pregnant women affect their daily living activities, and their daily life activities are affected more by the increase in the severity of these symptoms. Lacasse et al. and Bai et al. compared pregnant women with and without nausea and vomiting symptoms, and they stated that symptoms of nausea and vomiting significantly affected physical activities (30,38). In addition, Chan et al. stated that nausea and vomiting symptoms had negative effects on physical activities (3). Also, Guannan Bai et al. reported that 33.6% of the pregnant women stated that they experienced daily nausea, 9.6% vomiting, and 44.4% fatigue. In this study, lower scores were obtained in both physical and mental fields in the subjective evaluations of the pregnant women with complaints of nausea, vomiting, and fatigue (30). The research finding is similar to the literature.

In addition, it was determined that a 1-unit change in the PUQE score would cause a negative decrease of -4.768 units (β1) on the ABC scale score. It was calculated that 11.0% (R2= 0.110) of the ABC Score of the participants was explained by the PUQE scale score. These findings show that the severity of nausea and vomiting is an effective variable in decreasing activity-specific balance confidence in pregnant women. It is thought that our study result will contribute to the literature.

CONCLUSION

The results of the research show that the severity of nausea and vomiting during pregnancy is highly correlated with activity balance. This finding can be a guide for health professionals working with pregnant women. Health workers should create a care plan by considering the negative consequences of physical activity insufficiency. In addition, pregnant women with physical activity deficiency should be evaluated in terms of nausea and vomiting. It is thought that as a result of the elimination of these symptoms, some of the pregnant women will reach the desired physical activity levels.

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MEDICAL RECORDS-International Medical Journal

Research Article

Counterfeit Probiotic Drugs

Probiota İlaçlarinda Sahtecilik

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Abstract

Aim: Counterfeit drugs are a threat to human health worldwide. It can be seen that insufficient research has been conducted on the subject of counterfeit drugs related to potentially addictive drugs seized by the authorities. The aim of this study was to investigate whether or not there are drugs for sale in the Turkish market, which are counterfeit drugs under the heading of probiotics which are defined as micro-organisms with a positive effect on health when taken in certain quantities.

Material and Method: : A total of 17 different probiotic products in capsule, drops or sachet form, which were permitted for sale, were obtained from randomly selected chemist's shops in the province of Malatya.

Results: There was nothing missing or counterfeit on the packaging of the 17 products examined. When the contents were investigated, no deficiencies or excess micro-organism production was determined in the first 12 products. In product #13, there was no production of one of the mentioned micro-organisms. In products # 14,15, 16, and 17, more than one micro-organism stated in the prospectus could not be obtained.

Conclusion: As the checking of products sold in chemist's but controlled by the Ministry of Food, Agriculture and Livestock is not easy, there is a need for tighter supervision. This can be provided by sending the samples taken during audits to the correct laboratories, making detailed examinations, and evaluation the amount of active substance.

Keywords: Probiotic, counterfeit drugs, drug evaluation

Öz

Amaç: Dünya genelinde sahte ilaçlar insan sağlığını tehdit etmektedir. Yapılan çalışmalar göz önüne alındığında; sahte ilaç konusunda adli olarak ele geçirilmiş, bağımlılık potansiyeli bulunan ilaçlar ile ilgili çalışmalar yapıldığı ancak diğer ilaç grupları ile ilişkili yeterli çalışma yapılmadığı görülmektedir. Biz bu çalışmamızda Türkiye piyasasında; belirli miktarlarda alındıklarında sağlığı olumlu yönde etkileyen mikroorganizmalar şeklinde tanımlanan; probiyotikler başlığı adı altında satılan ilaçların sahte olup olmadıklarını araştırmayı amaçladık.

Materyal ve Metot: Malatya ilinde randominize bir eczaneden kapsül, damla ve şase formu bulunan ve satışı için izinleri bulunan 17 adet farklı marka probiyotik ürün alındı.

Bulgular: İncelenen 17 ürüne ait kutular ve kutu üzerinde olması gereken bilgiler açısından herhangi bir eksiklik ve sahtecilik göze çarpmadı. İçerikleri açısından yapılan araştırmada ilk 12 üründe herhangi bir eksik ya da fazla organizma üremesine rastlanmadı. On üç numaralı üründe içerikte bahsedilen mikroorganizmalardan 1 tanesi üremedi. On dört on beş, on altı ile on yedi numaralı ürünlerde prospektüste belirtilen birden fazla mikroorganizma ise elde edilemedi.

Sonuç: Eczanelerde satılan ancak Gıda Tarım ve Hayvancılık Bakanlığı tarafından kontrolü yapılan ürünlerin kontrolleri kolay olmayıp sıkı denetimlerin yapılması gereklidir. Bu ürünlerin denetimleri esnasında alınan numunelerin doğru laboratuvarlara gönderilerek detaylı incelemeleri yapılmalı aynı zamanda ilaç etken maddelerinin de miktar yönünden değerlendirilmesi sağlanmalıdır.

Anahtar Kelimeler: Probiyotik, sahte ilaçlar, ilaç değerlendirmesi

INTRODUCTION

In recent years, counterfeit drugs have become a serious problem in both developed and developing countries. Although there is no clear definition of exactly what counterfeiting is, each country has a definition according to their own laws. Drugs accepted as counterfeit in one country may not be accepted as such in other countries (1).

The World Health Organization (WHO) has defined counterfeit drugs as fake brands that have been deliberately mis-labelled in respect of identity or source, and drugs on the market with the correct content but without the active substance or which do not contain sufficient active substances (2).

The Turkish Ministry of Health defines counterfeit drugs as a product produced or imported with a different

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composition from the formulation of the product licensed and permitted by the Ministry of Health (eg, deficient amount of active substance, containing too much or none of the active substance, or containing a different auxiliary substance) (3). The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) accepts that 7% of all the medications sold throughout the world are counterfeit (4).

According to the WHO definition, the active substances and doses contained in these types of products may be different from the information on the label, or products may not even contain any active substance (5). The concept of counterfeit and smuggled drugs changes from country to country, and as there is no full explanation and consensus has not yet been reached on this subject, studies related to the frequency of these drugs have determined frequency rates in a wide range of 1%-50% (6).

However, there are drug groups that are used by many patients and are not thought to be counterfeited. Probiotics, which are classified as containing foodstuff, are licensed for manufacture and sale by the Turkish Ministry for Food, Agriculture and Livestock, and are sold in chemist's, and are evaluated as in this group (7). Probiotics are defined as micro-organisms that have a positive effect on health when taken in certain quantities (8). The nutritional sources of probiotics are fermented yoghourts, cheese, koumiss, kefir, bread, beer and wine, which use Lactobacilli, Bifidobacteria, Enterococci, and Streptococci (9). Probiotics are used on a broad scale and may be purchased either on prescription or over the counter in chemists'.

In a screening of literature on the subject of counterfeit drugs, studies have been conducted related to drugs with the potential for dependence, but there can be seen to have been insufficient studies on other drug groups. The aim of this study was to investigate whether or not counterfeit drugs under the heading of probiotics are being sold on the Turkish market.

MATERIAL AND METHOD

The necessary permissions for this study were obtained from the Clinical Research Ethics Committee of Inonu University. A total of 17 different brands of probiotic products in capsule, drops, or sachet form, which were permitted for sale, were obtained from randomly selected chemists in Malatya province.

The products were numbered from 1 to 17, and were evaluated in respect of points which could be counterfeited; the packaging, labelling, barcode, and contents. The examinations in respect of the active substances contained in these products were made in the Microbiology Department Laboratory of Inonu University Medical Faculty.

The form in which the products were presented for sale was evaluated in respect of whether there were any erasures or signs of damage on the barcodes and packaging. The presence or absence of any hologram on the packaging was noted, together with date of production and use-by date.

Content Analysis

The smear method described by HALKMAN was used to determine the number of micro-organisms. In this method, a 0.1ml sample was quantitatively inoculated into sheep's blood, EMB, Saboura Dextrose and chocolate (Oxoid, USA) media. After incubation for 18-24 hours, the colonies formed in the media were counted. Insufficient productions were extended for up to 48 hours. In the calculation of the colony numbers, the formula below, which was described by HALKMAN, was used. The micro-organisms were identified using Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (Maldi-Tof MS) (Bio Mérieux, France).

$$N = C / (V(n1+0,1 \times n2) Xd)$$

N = the number of micro-organisms in 1 gr or 1 ml of the sample

C = the total number of colonies in all the petri dishes where counting was applied

V = the volume (ml) transferred to the petri dishes where counting was applied

n1= the number of petri dishes counted in the count made from the first dilution

n2= the number of petri dishes counted in the count made from the second dilution

d = the greater dilution concentration from 2 consecutive dilutions applied with counting

The number obtained as a result of the count was stated as Colony Forming Unit/gr (CFU/gr). The method described by Kadir HALKMAN was used in the calculation of the colony numbers (10).

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Inonu Unıversıty Scıentıfic Research And Publıshıng Ethıcs Board Health Sciences Non-Interventional Clinical Research Ethics Committee (26.01.2021-2021/1497).

RESULTS

The results of the examinations of the packaging of the 17 products examined are shown in Table 1. The vast majority of these products were seen to be sold in the form of sachets. No missing information or signs of counterfeiting were observed in any of the information on the packaging examined.

It was found that the mean score of women in the Fertility Adjustment Scale was 23.30±1.35, and the mean score in the Spousal Support Scale was 65.41±10.41 (Table 2).

In the first 12 products investigated in respect of content, there were no deficiencies or production of extra organisms. In product no 13, only 1 micro-organşism was produced of those stated in the contents. In product nos 14, 15, 16 and 17, there was determined to be no production of at least one of the micro-organisms listed in the prospectus (Table 2).

Table 1. Findings of the evaluations of the information on the packaging of the drugs

Drug no	Damage to the packaging	Hologram	Date of production	Use-by date	Scraping or erasure on the price label	Form of sale
1	-	+	+	+	-	ampoule
2	-	+	+	+	-	sachet
3	-	+	+	+	-	sachet
4	-	+	+	+	-	drops
5	-	+	+	+	-	sachet
6	-	+	+	+	-	sachet
7	-	+	+	+	-	sachet
8	-	+	+	+	-	drops
9	-	+	+	+	-	sachet
10	-	+	+	+	-	sachet
11	-	+	+	+	-	sachet
12	-	+	+	+	-	sachet
13	-	+	+	+	-	sachet
14	-	+	+	+	-	capsule
15	-	+	+	+	-	sachet
16	-	+	+	+	-	sachet
17	-	+	+	+	-	sachet

Table 2. Results obtained from the microbiological examinations of the drugs

Drug no	Organism content stated in the prospectus	Organism obtained
1	10^9 cfu/ml Bacillus clausii	10^9 cfu/ml Bacillus clausii
2	10^9 cfu/ml Entercoccus faecium+ Lactobacillus acidophilus+ Lactobacillus rhamnosus+ Bifidobacterium longum+ Bifidobacterium bifidum	109 cfu/ml Entercoccus faecium+ Lactobacillus acidophilus+ Lactobacillus rhamnosus+ Bifidobacterium longum+ Bifidobacterium bifidum
3	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
4	10^9 cfu/ml Laclobacillıs yetileri	10^9 cfu/ml Laclobacillıs yetileri
5	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
6	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
7	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
8	10^9 cfu/ml Bifidobacterium animalis	10^9 cfu/ml Bifidobacterium animalis
9	10^9 cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
10	10^9 cfu/ml Streptococcus thermophillus, Lactobacillus plantarum, Bifidobacterium breve, Bifidobacterium longum	10^9 cfu/ml Streptococcus thermophillus, Lactobacillus plantarum, Bifidobacterium breve, Bifidobacterium longum
11	10^9 cfu/ml Laclobacillıs rhamnosus	10^9 cfu/ml Laclobacillıs rhamnosus
12	1^{09} cfu/ml Saccharomyces boulardii	10^9 cfu/ml Saccharomyces boulardii
13	10^9 cfu/ml, Lactobacillus bulgaricus, Lactobacillus acidophilu, Bifidobacteria Streptococcus thermophillus	10^9 cfu/ml, Lactobacillus bulgaricus, Lactobacillus acidophilus, Bifidobacteria. No production of Streptococcus thermophillus
14	10^9 cfu/ml Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus rhamnosus ve Saccharomyces boulardii	10^9 cfu/ml Bifidobacterium longum. No production of Lactobacillus acidophilus, Lactobacillus rhamnosus and Saccharomyces boulardii
15	10^9 cfu/ml Streptococcus thermophillus Saccharomyces boulardii	10^9 cfu/ml Streptococcus thermophillus. No production of Saccharomyces boulardii
16	10^9 cfu/ml Bifidobacterium animalis	$5x10^4$ cfu/ml Bifidobacterium animalis
17	Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacilluscasei, Bifidobacterium bifidum	No production

DISCUSSION

Probiotics, which have many equivalents and rapid circulation, are currently used in the treatment of many diseases. These products can be purchased from chemists on patient request both with and without a prescription. However, there has been insufficient research in respect of counterfeit probiotics obtained in this way from chemists. It is noticeable that studies have been more focused on the abused illegal drug group of phosphodiesterase inhibitors, which are sexual performance enhancing drugs (11,12). As this group of drugs are sold at a lower price than the originals and because of the indications for use, they are thought to be more vulnerable to exploitation (12). This group of phosphodiesterase type 5 enzyme inhibitors, which is known to be the most common sexual performance stimulant on the black market, is the most commonly abused drug group in the black market for drugs in Europe (13). It has been reported that this group has entered the system through manufacture and distribution by large, well-organized, criminal networks, then placement in the counterfeit drug market by drug wholesalers (14). These types of drugs with a large market share and high consumption are often encountered in judicial processes. There are several studies in literature related to these drugs obtained especially during smuggling and other control operations. In addition, this group of drugs together with other drugs open to abuse are frequently audited.

Studies, announcements and reports published about drugs obtained, particularly in judicial processes, have attempted to raise awareness on the subject of counterfeit drugs. However, there have been insufficient checks and studies on the subject of drugs not in this group which are sold in chemists.

On the internet website of the Turkish Drugs and Medical Device Institute, it is emphasized that "it is important to check drugs sold at a lower price than that defined by the Ministry of Health in respect of the information on outer packaging by comparing if possible with a previously purchased drug, and attention must be paid to any change to the use-by date and whether or not there has been any erasure or scratching away of the label or on the box" (15).

In this study, 17 products were obtained from chemists and were checked in respect of date of manufacture and use-by date, holograms and packaging. All the drugs examined were seen to be in the original packaging, original holograms were on the packaging, date of manufacture and use-by date were written, and the serial number. No physical findings were determined which suggested that there would be any problems in using the product.

In counterfeit products, as the active substance content and dose are unknown by the user, this constitutes a danger. Potential side-effects which could develop to the active substances may even lead to death, and different active substances in the content can cause drug-drug interactions. Moreover, diagnosis of patients using drugs with unspecified content is made more difficult and may not always be possible (17). In the current study, the drugs were numbered from 1 to 17, and while the active substances of drug nos 1-12 were determined to be as written on the prospectus, active substances in nos 13-17 were insufficient or absent. Furthermore, in the drug labelled no 17, no micro-organism written in the prospectus was determined in the laboratory tests.

Probiotics are contribute to the flora by improving the bacterial balance in the intestine, and by binding to the receptors through competition, they do not leave room for pathogenic agents and allow them to be excreted with feces. Bacteria used as probiotics must be obtained from the intestinal flora, be viable, resistant to stomach and bile acids, and have the ability to adapt and colonize intestinal cells. They should also be able to maintain their effects when taken with antibiotics. Nutritional sources of probiotics are fermented yogurts using Lactobacilli, Bifidobacteria, Enterococci and Streptococci, cheese, pickles, bread, beer, wine, kumiss and kefir (9,16). In the current study, active ingredients 13-17 were insufficient or absent. In addition, no microorganism written in the package insert was detected in the laboratory tests of the drug labeled 17. These, in turn, may prolong the treatment process or cause worse outcomes.

The Turkish Drugs and Medical Device Institute has also stated that patients must obtain drugs frrom chemists, and as the sale of drugs over the internet is illegal, when drug sales are encountered on internet sites or from different sources, this must be communicated to the Ministry of Health, and drugs must not be purchased from those sites (15). However, this group of drugs can be easily obtained from internet sites. The sale of drugs from these sites must be regulated and even restricted by the relevant authorities.

When drugs prescribed for a patient at what is thought to be a sufficient dose of active substance in the content are perceived by the patient not to be of benefit, the patient may try other treatment methods. In this way, the treatment process will be prolonged and the healthcare costs will increase.

Although not easy, frequent checks should be made of products which are sold by chemists but controlled by the Ministry of Food, Agriculture and Livestock. During these checks, samples of the products should be taken and examinations made by sending them to the correct laboratories.

CONCLUSION

It is also necessary to make more detailed checks of the products sold by chemists by collecting them under one body. Checks should be made not only of products which can be abused, but of all drugs, both those obtained with prescription or without. In these checks, detailed examinations must be made and the active substances of the drugs must be examined.

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Research Article

Relationship Between Interleukin-28B Gene Polymorphism and Chronic Hepatitis B Infection

Kronik Hepatit B Enfeksiyonu ile İnterlökin-28B Gen Polimorfizminin İlişkisi

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Abstract

Aim: Interleukin 28B (IL28B) gene polymorphism may play a role in hepatitis B virus (HBV) infection prognosis. We investigated the effects of IL28B gene polymorphism on viral clearance and viral load in chronic hepatitis B (CHB) patients.

Material and Methods: We included 146 individuals who applied to our center between October 2011 and October 2012. CHB (N=117) and control (N=29) groups were compared in terms of IL28B gene rs12979860, rs12980275 gene region polymorphisms, and IL28B gene expression (mRNA) levels.

Results: There was no statistically significant difference between groups in terms of rs12979860 gene region polymorphism rates ($\chi2=0.36$, $p=0.835$). But there was a significant association between groups in terms of rs12980275. In the CHB group, the A/A genotype was much more, ($\chi2=55.2$, $p<0.001$), G/A and G/G genotypes were less frequent. There was no statistically significant difference between the groups in terms of IL28B expression levels.

Conclusion: This study revealed the genotype profile of the IL28B gene of our region. It is the first study on this subject in our region. The association between CHB and rs12980275 polymorphism may be important. Our results will contribute to future studies.

Keywords: Chronic hepatitis B, IL 28B polymorphism, IL 28B expression, Turkey

Öz

Amaç: İnterlökin-28B (IL28B) geni polimorfizmi hepatit B virus (HBV) enfeksiyonunun prognozunda önemli olabileceğine dair yayınlar bulunmaktadır. Bu çalışmada IL28B geni ile HBV enfeksiyonunun viral klirens ve kronik HBV enfeksiyonunda viral yük arasındaki ilişkiyi araştırmayı planladık.

Materyal ve Metot: Ekim 2011 ile Ekim 2012 tarihleri arasında merkezimize başvuran 146 kişi çalışmaya dahil edildi. Kronik hepatit B (KHB) grubunda 117, kontrol grubunda 29 kişi vardı. Tüm gruplarda IL28B geni rs12979860, rs12980275 polimorfizmlerine ve IL28B geni ekspresyon düzeylerine (mRNA) bakıldı ve gruplar karşılaştırıldı.

Bulgular: Rs12979860 gen polymorfizmi oranları açısından gruplar arasında fark yoktu ($\chi2=0.36$, $p=0.835$). Ama rs12980275 bölgesi açısından KHB grubunda A/A genotipi daha fazla iken ($\chi2=55.2$, $p<0.001$), G/A ve G/G genotipleri istatiksel anlamlı olarak daha az bulundu. Gruplar arasında MRNA düzeyleri açısından fark yoktu

Sonuç: Öncelikle bu çalışma bölgemizdeki IL28 gen polimorfizm oranlarını ortaya koyan ilk çalışma olmasından dolayı önemlidir. KHB ile rs12980275 polimorfizmi arasındaki ilişkinin klinik önemi bulunduğu düşünülmektedir. İleride bu konuda yapılacak çalışmalara ışık tutmaktadır.

Anahtar Kelimeler: İL28 B polimorfizmi, İL28B ekspresyonu, kronik hepatit B, Türkiye

INTRODUCTION

More than 350 million people are diagnosed with chronic hepatitis B (CHB) in the world, annually. Around 600 thousand people die from CHB related complications worldwide per year (1). The most common complications of CHB are liver cirrhosis and hepatocellular carcinoma (HCC). Age, gender, blood TNF, IFN, vitamin D, estrogen receptor alpha level, and genetic variations in many HLA loci have been shown to correlate with the prognosis of CHB infection (2). There are many reports that IL28B gene polymorphisms are closely related to viral load and spontaneous clearance of hepatitis C infection. The IL28B gene encodes the cytokine IFN-lambda3 (INF-λ3), which belongs to the type III INF family (INF-λ) (3). The pathogenesis and the transmission characteristics of

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HBV and hepatitis C virus (HCV) are similar. Recently, an increasing number of studies have been published about the effects of the IL28B gene on HBV infection (4). In a study, the relationship between viral replication, spontaneous clearance rates of HBV, and IL28B polymorphism variants (rs12979860, rs12980275, rs8099917) were investigated. In that study, 203 patients with chronic hepatitis B, 203 hepatitis B carriers, and 203 healthy individuals had included. It was reported that there was no statistical difference between the three groups in terms of IL28B gene polymorphism and viral replication, and viral clearance (5). In another study, it was reported that HBV-related HCC has a statistically significant relationship with IL28B gene polymorphism (6).

In our study, we aimed to reveal the frequency of IL28B polymorphism and to investigate the relationship between IL28B polymorphism, and CHB infection, HBV viral load, viral clearance, and other factors.

MATERIAL AND METHOD

We included 146 volunteers in our study who applied to our center's outpatient clinic between October 2011 and October 2012. There were 117 CHB patients in the study group and 29 resolved hepatitis B patients in the control group. IL 28B gene rs12979860, rs12980275 polymorphism, and IL 28B gene expression level (mRNA level) were measured in all patients included in the study. Rs12979860 gene region has homozygous (CC), heterozygous (CT), and mutant (TT) genotypes. The Rs12980275 gene region has homozygous (AA), heterozygous (GA), and mutant (GG) genotypes. The study and control groups were compared for frequency of both gene region polymorphisms, IL28B gene expression levels, gender, HBsAg level, hepatosteatosis level (mild if <5% fat, moderate if <5%, severe if >30%), HBeAg positivity presence of liver cirrhosis, HBV DNA level (those with <104 copies/ml, those between 104-107 copies/ml and those >107 copies/ml), response to IFN treatment (those who became HBV DNA negative with IFN treatment before 1 year, after 1 year and those who were unresponsive to IFN therapy).

Eligibility criteria

1) Chronic Hepatitis B group was defined as, HBs-Ag positive for more than 6 months, anti-HBc IgG positive, and anti-HBs Ag negative. A liver biopsy must be done before. Anti-HCV, Anti-HIV, HBV-DNA, HBeAg, Anti-HBeAg, AST, ALT, liver ultrasound tests must be checked regularly.

2) For the control group; it must be HBsAg negative, Anti-HBs, and Anti-HBc IgG positive.

Exclusion criteria

1) HCV or HIV positive

2) Malignancy (except HCC)

3) Severe systemic disease

Genomic Isolation and Measurement Method

Approximately 3cc of blood was obtained from peripheral venous blood from the patients and control group included in the study. DNA isolation was performed with a DNA isolation kit (purelink™ genomic DNA kits) in the Medical Genetics laboratory. Patient DNA was stored at -20 degrees until the study was conducted. RNA isolation was performed with a Roche Magna compact magic isolation device in the medical genetics laboratory, and the samples were stored at minus 80 degrees. Genomic DNAs obtained from blood samples rs12979860 showing TNP in the IL28B gene, rs12980275 amplification mix, and "Light Cycler Fast Start DNA Master Hybridization" probes (Roche, Germany) using the LightCycler 2.0 (Roche Applied Science, Germany) instrument. The prepared mixtures and DNAs were mixed, and the results were uploaded to the Real-Time device, and the results were added to the data. The obtained RNAs were measured by nanodrop and brought to an equal position for obtaining cDNA. Obtained RNAs were mixed with 1 µl H2O, 1 µl Random hexamer primer, anchored-oligo (Dt) 18 primer on 10 µl and put into 0.2 Eppendorf tubes and waited for 10 minutes at 65 decimal points in the PCR protocol using the "transcriptor first-strand cDNA synthesis" kit. A mixture was prepared for overlaying the RNAs. The appropriate protocol was loaded into the Real-Time PCR device by adding cDNA to the prepared mixture following the protocol in the kit. Forward and Reverse Primers specific to the IL28B gene in Gene Expression Assay (GENEX-250, Suarge Biotechnology, Turkey) were prepared according to the AMPLIFYME SYBR Universal Mix (AM02, BLIRT, Poland) protocol by preparing qPCR experiments with the StepOnePlus™ Real-Time PCR System (ThermoFisher Scientific, USA) device, RNA expression levels were measured. RNA expression levels were determined by the ΔΔCт method according to normalization with G6PDH endogenous control. In this study, the "G6PDH detection mix" was used as a control. For each sample, one control was used and the study was repeated for control purposes. The obtained results were arranged and entered by the light cycler relative quantitation software program.

Statistical analysis

The statistical package program SPSS 16 (Statistical Package for the Social Sciences, version 16 (SSPS Inc, Chicago, IL, USA) was used for the analysis of the data set. Independent t-test and one-way ANOVA test were used in the evaluation of the data, while Pearson $\chi 2$ test was used for the evaluation of categorical data, and $p < 0.05$ was considered statistically significant.

Ethical issue

Approval was obtained from the ethics committee of our center. Detailed information was given to all participants and an informed consent form was signed.

RESULTS

The IL28B gene rs12979860 polymorphism was examined in 111 individuals (89 patients in the CHB group and 22 people in the control group) (Table 1). In CHB group there were 46 (51.7%) C/C, 38 (42.7%) C/T, 5 (5.6%) T/T genotype. In the control group, there were 11 (50%) C/C, 9 (40.9%) C/T, 2 (9.1%) T/T. There was no association between rs12979860 polymorphism and CHB ($\chi 2(2, N=111)=0.36$, p=0.835). Rs12979860 genotypes (C/C, C/T, and T/T) were compared in terms of gender, hepatosteatosis level, presence of HBe antigen, presence of liver cirrhosis in the CHB group, and no statistically meaningful difference was found between genotype groups.

Patients in the CHB group were divided into three subgroups in terms of HBV-DNA levels (<104, 104-107,> 107), and it was found that they had statistically similar genotypes in the subgroups. We didn't find a statistically meaningful difference between the genotype distributions of those who responded to interferon treatment before one year, after one year, and those who did not respond at all. Interleukin 28B gene rs12980275 region has 3 polymorphisms namely A/A, G/A, and G/G. In the CHB group, 52 patients (59.8%) were A/A, 34 patients (34.1%) were G/A, 1 patient (1.1%) was the G/G genotypes. In the control group, 1 patient (3.8%) was A/A, 11 patients (42.3%) were G/A, and 14 patients (53.8%) were G/G genotype. A/A genotype was much more in the CHB group than the control group, and the difference was statistically meaningful ($\chi 2(2, N=113)=55.2$, p<0.001). In addition, IL28B rs12980275 gene region A/A, G/A, and G/G genotypes were compared in terms of gender, hepatosteatosis, HBe antigen positivity, liver cirrhosis, HBV DNA level and, response to INF treatment There was no statistical difference between genotypes (Table 2).

Interleukin 28B gene expression level was measured in 117 patients (95 in the CHB group and 22 in the control group). The mean values in the groups were compared using the T-test and no statistically meaningful difference was found between the groups (Table 3). In addition, the rs12979860 gene polymorphisms, those with C/C genotype and those with C/T and T/T genotypes were compared separately and the total (C/T + T/T) IL28B gene expressions of the two, and there was no statistical difference between the groups (p=0.35).

Table 1. Comparison of Groups in Terms of IL 28B Rs12979860 Gene Polymorphism (Chi-Square Test)

rs12979860	C/C		C/T		T/T		P-value
	N		N		N		
Polymorphism Distribution							
Chronic Hepatitis B	46	51.7%	38	42.7%	5	5.6%	0.835
Control group	11	50.0%	9	40.9%	2	9.1%	
Sex							
Men	22	44%	24	48%	4	8%	0.295
Women	23	64%	12	33%	1	3%	
Hepatosteatosis							
<%5	33	76%	26	72%	4	100%	
%5-30	10	24%	9	25%	0	0%	0.615
>%30	0	0%	1	3%	0	0%	
HBeAg							
Negative	36	54%	26	39%	4	7%	0.701
Positive	9	45%	10	50%	1	5%	
Cirrhosis							
Yes	7	85%	33	92%	3	60%	0.145
No	38	15%	3	8%	2	40%	
HBV DNA levels							
$<10^4$	6	13%	6	17%	1	20%	
10^4-10^7	22	48%	17	48%	2	40%	0.891
$>10^7$	17	37%	12	35%	2	40%	
Response to IFN treatment							
<1 year	2	15%	1	11%	1	33%	
>1 year	1	7.5%	1	11%	1	33%	0.913
Unresponsive	10	77.5%	7	78%	1	33%	

Abbreviations; IFN: Interferon. HBeAg: Hepatitis B e antigen. HBV-DNA: Hepatitis B virus deoxyribonucleic acid

Table 2. Comparison of Groups in Terms of IL 28B Rs12980275 Gene Polymorphism (Chi-Square Test)

rs12980275	A/A		G/A		G/G		P-value
	N		N		N		
Polymorphism Distribution							
Chronic Hepatitis B	52	59.8%	34	39.1%	1	1.1%	<0.001
Control group	1	3.8%	11	42.3%	14	53.8%	
Sex							
Men	26	54.2%	21	43.8%	1	2%	0.295
Women	25	70%	11	30%	0	0%	
Hepatosteatosis							
<%5	37	77%	24	75%	1	100%	
%5-30	11	23%	7	21%	0	0%	0.763
>%30	0	0%	1	4%	0	0%	
HBeAg							
Negative	38	74%	23	71%	1	50%	0.807
Positive	13	26%	9	29%	1	50%	
Cirrhosis							
Yes	47	77%	28	78%	1	50%	0.915
No	7	23%	4	22%	1	50%	
HBV DNA levels							
$<10^4$	6	11%	6	19%	1	44%	
10^4-10^7	23	45%	15	48%	1	33%	0.147
$>10^7$	22	44%	10	33%	1	33%	
Response to IFN treatment							
<1 year	1	7%	1	11%	1	33%	
>1 year	1	7%	1	11%	1	33%	0.913
Unresponsive	12	86%	7	78%	1	33%	

Abbreviations; IFN: Interferon, HBeAg: Hepatitis B e antigen, HBV-DNA: Hepatitis B virus deoxyribonucleic acid

Similarly, no significant meaningful difference was found between those with the rs12980275 gene region A/A genotype and those with the G/A and G/G genotype in terms of IL28B gene expressions (p=0.31).

Table 3. Comparison of patient and control groups in terms of IL28B gene expression levels (T-test)

Groups	N	Mean	S.D	S.E
CHB	95	2.6823	8.39663	.86148
Control	22	1.8150	3.02216	.64433

Abbreviations; CHB: Chronic hepatitis B, SD: Standart deviation, SE: Standart error

DISCUSSION

Chronic hepatitis B is an important health problem. Several factors predict the prognosis of CHB infection and response to treatment. In several studies, the relationship between the IL28B gene and CHB showed, before. In our study, CHB (n=117) and control (n=29) groups were compared in terms of IL28B gene rs12979860 and rs12980275 gene region polymorphisms. There was a significant difference between these two groups in terms of rs12980275 but not in terms of rs12979860 gene region polymorphism rates (p=0.835). We found that the CHB group have more A/A genotype than the control group at the rs12980275 gene region (p<0.01). Also, the control group has more G/A and G/G genotype rates. We can say that if individuals do have not the G allele in the rs12980275 region they tend to be CHB infection. However, in a meta-analysis, in which 18 studies were conducted, it was reported that there is no relationship between rs12979860, rs12980275, rs8099997 polymorphism, and HBsAg clearance. The difference between this meta-analysis and our study may be attributed to the different genotype rates of the virus or the ethnic origin of the patients. Because, in the meta-analysis mentioned above, the patient population consists of Asians. In Asian CHB patients mostly infected genotypes other than D (genotypes A, B, C). But in Turkey, genotype D is by a percentage of 78% (7). Martin MP et al. (8) reported that the C/C genotype of rs12979860 was not associated with HBV recovery, but in that

study, 20% of the patients were HCV and 69% were HIV positive patients. In our study, HCV or HIV positivity was an exclusion criterion. In our study, the co-mutation of rs12980275 and rs12979860 gene regions was found to be very high (p<0.01). However, the clinical significance of this situation isn't known. In our study, it was planned to investigate the relationship between HCC and IL28B gene polymorphism, but it could not be evaluated due to only 7 patients had HCC. In our study, no significant relationship was found between IL28B rs12979860 and rs12980275 polymorphisms and HBV recovery. In the study of Sonneveld et al. (9), It was emphasized that especially patients with the rs12979860 C/C allele had 3 times more HBV recovery than those with C/T and T/T alleles. It has been reported that the C/C allele is high in genotypes A, B, C, while the C/C allele is less in the D genotype. In our study, IL28B rs12979860 CC allele frequency was found 56%. Since HBV genotype D is higher in the Turkish population, HBsAg seroconversion may not be affected by IL28B polymorphism. In a study, it has been reported that the prevalence of the C/C allele is 95% in Asians, 75% in Europeans, and 42% in Africans (9). In our study, neither rs12979860 nor rs12980275 was found the predictive factor of IFN treatment outcomes. It is well-known that hepatitis C patients who have rs12979860 CC genotype, respond to IFN therapy better and have a higher sustained virological response. However, there is no consensus for CHB on this issue. Lampertico et al. (10) reported that in a study conducted 101 HBeAg negatives (all patients HBV genotype D) CHB patients, the IL28B rs12979860 CC genotype has a significant positive effect on response to IFN treatment, persistent virological response, and HBsAg clearance compared to the CT + TT genotype. Sonneveld et al. (9) showed the CC genotype as a positive predictor of response to IFN treatment in 203 HBeAg positives (HBV genotype not specified) CHB patients. On the contrary, in three separate studies conducted with 512 CHB (HBV genotype B and C) patients in China, 115 HBeAg positives (HBV genotype B and C) patients in Taiwan and, 95 HBeAg positive or negative patients in Germany, a significant relationship between response to PegIFN treatment and IL28B polymorphism has not been found (11,12). The reason for these contradictions may be due to the inhomogeneity of the patient population, the effects of other genetic factors of the host, the genotype difference of HBV in the studies, and the fact that some studies were conducted with HBeAg positive patients and some with HBeAg negative and some without considering HBeAg. In future studies, we can have more clear information on this issue with homogeneous patient groups.

There were some limitations of our study. Because our study was single-center, the results cannot be generalized to the entire country population. The two most frequently studied gene regions in CHB were evaluated, but the effects of polymorphisms in other gene regions could not be compared. The false-positive and false-negative rates of the PCR method can be high. Next-generation sequencing might be more accurate for reliable results.

CONCLUSION

In conclusion, our study is the first study on this subject in our region. Our findings will be useful for future studies in terms of revealing the genotype profiles of the IL 28B gene. The high co-mutation rates of rs12979860 and rs12980275 may be important but we do not know clinical significance at the moment. Individuals with A/A or G/A genotype at rs12980275 were found significantly more in CHB patients. This polymorphism will be important in the prediction of the prognosis of HBV infection. In this study, no relationship was found in terms of sex, HBsAg level, percentage of hepatosteatosis, HBeAg, liver cirrhosis rates, and HBV DNA levels, for both gene regions, in CHB patients. In the future, IL28B may be useful in clinical practice for predicting the response to treatment and prognosis as in CHB infection. However, available data are not sufficient for this, yet.

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MEDICAL RECORDS-International Medical Journal

Research Article

Relaxing Effects of Paracetamol on Uterine Spontaneous Contraction in Rats in Vitro

Parasetamolün Sıçanlarda In Vitro Uterus Spontan Kasılmaları Üzerindeki Gevşetici Etkileri

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Abstract

Aim: Paracetamol is a commonly used drug in acute and chronic pain. It is known that paracetamol, which is a pain reliever and antipyretic drug, is safe to use during pregnancy. The aim of this study was to investigate the effects of paracetamol on the uterine smooth muscle contraction- relaxation mechanism in female rats in diestrus.

Material and Methods: Wistar-albino intact female rats were used in the study. Longitudinal strips of myometrium obtained from animals at the diestroeus stage. Stripes were suspended in an isolated organ bath containing crebs solution under 1 g passive tension. After the regulation period, paracetamol were added non-cumulatively at 1000μM and 2000μM concentrations. Before and after the application, the area under the curve (AUC) and peak to peak (p-p) values were normalized as % change.

Results: Paracetamol caused a statistically significant decrease in p-p and area under the curve parameters of spontaneous uterine contractions at 1000 and 2000 μM doses ($p < 0.001$).

Conclusion: Paracetamol causes uterine relaxation by inhibiting uterine contraction. This effect should be taken into account in clinical use.

Keywords: Paracetamol, uterus, isometric contraction, rat

Öz

Amaç: Parasetamol akut ve kronik ağrıda yaygın olarak kullanılan bir ilaçtır. Ağrı kesici ve ateş düşürücü bir ilaç olan parasetamolün gebelikte kullanımının güvenli olduğu bilinmektedir. Bu çalışmanın amacı, diöstrustaki dişi sıçanlarda parasetamolün uterus düz kas kasılma gevşeme mekanizması üzerindeki etkilerini araştırmaktır.

Materyal ve Metot: Çalışmada Wistar-albino intak dişi sıçanlar kullanıldı. Longitudinal miyometriyum şeritleri diöstrustaki hayvanlardan elde edildi. Şeritler, 1 g pasif gerilim altında krebs solüsyonu içeren izole organ banyosuna asıldı. Regülasyon periyodundan sonra, parasetamol 1000μM ve 2000μM konsantrasyonlarda kümülatif olmayan şekilde eklendi. Uygulama öncesi ve sonrası eğri altında kalan alan (AUC) ve zirveden zirveye (p-p) değerleri % değişim olarak normalize edilmiştir.

Bulgular: Parasetamol spontan uterus kontraksiyonlarının p-p ve eğri altında kalan alan parametrelerinde 1000 ve 2000 μM dozlarda istatistiksel olarak anlamlı azalmaya neden oldu ($p < 0.001$).

Sonuçlar: Parasetamol uterus kasılmasını inhibe ederek uterus gevşemesine neden olur. Klinik kullanımında bu etki göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Parasetamol, uterus, izometrik kontraksiyon, sıçan

INTRODUCTION

Smooth muscles line the walls of hollow organs, including vessels, gastrointestinal tract, uterus, and bladder, and respond to signals and maintain the homeostasis (1). Smooth muscle contraction is initiated by the cross-bridge action of myosin II-based thick and F-actin-based thin filaments. Myosin activity is significantly stimulated by regulatory light chain (RLC) phosphorylation in contact with actin (2). Therefore, smooth muscle RLC phosphorylation by calcium/calmodulin-dependent myosin light chain kinase is required mainly for smooth

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muscle contraction and physiological activities of organs lined with smooth muscle (3,4). It is known that the uterus, which is a smooth muscle, shows spontaneous contraction and many hormones and drugs affects their activity.

Paracetamol (acetaminophen) is a commonly used drug in acute and chronic pain in the world (5). The mechanism of action of paracetamol is related to the inhibition of cyclooxygenases and the endocannabinoid system and serotonergic pathways (6). Paracetamol is widely used for the relief of a number of acute pain conditions such as dysmenorrhea, muscle and joint pain, headache and toothache. Unlike non-steroidal anti-inflammatory drugs, paracetamol has no anti-inflammatory activity and is thought to exert antipyretic and analgesic effects through various mechanisms, including activation of selective and variable inhibition of prostaglandin synthesis and serotonergic pathways and cannabinoid receptors (7-9). Due to World of Health Organization's inclusion of this drug in the analgesic drug step (10) and also due to its decades of clinical experience, it is frequently prescribed in chronic pain conditions such as low back pain and osteoarthritis. Recently, meta-analyzes of randomized controlled trials covering these conditions have shown that effect sizes are moderate but still statistically significant compared to placebo (11-14).

Paracetamol is preferred over other analgesics, such as non steroid anti inflamatory drugs, which have a less favorable risk profile and aspirin, concerning about its effect on the fetus with limited use in pregnant women (15,16). Paracetamol is considered to be safe to use at all stages of pregnancy, making it the first-choice pain reliever and antipyretic drug for pregnant women (17). In addition, the United States Food and Drug Administration has classified paracetamol as Pregnancy Category B, and supports that these drugs can be used without maternal health and fetal development concerns (18). Paracetamol crosses the placenta freely and creates a direct effect on the fetus (19). It decreases the production of prostacyclin both in the culture of endothelial cells isolated from umbilical vessels and in the third trimester of pregnancy (20). It has been used by pregnant women for years without any obvious harmful effects on the developing baby. Therefore, paracetamol is generally recommended as the first choice among pain relievers and antipyretic drugs for pregnant women (21).

In recent years, there has been an increasing review regarding the safety of paracetamol in pregnancy. Various embryo-fetal and neonatal effects of paracetamol have been demonstrated depending on the duration of treatment, dose, and trimester of exposure. Large cohort studies have not found a relationship between maternal paracetamol use in the first trimester and congenital malformations or adverse pregnancy outcomes (22,23). A recent study has shown that when paracetamol was administered to a pregnant rat at doses in the clinical range used in patients, approximately 40% of the drug levels in the maternal circulation reached the fetus by crossing the placenta (24). Thus, the placenta provides of protection for the developing fetus, but the mechanisms involved or the effects of paracetamol on placental functions are not yet understood (24). Besides these known effects of paracetamol, its effects on the uterine smooth muscle contraction-relaxation mechanism are unknown. For this purpose, this study aimed to investigate the effects of paracetamol on the contraction-relaxation activity of rat uterine strips in diestrus.

MATERIAL AND METHOD

Animals and Tissue Preparation

In the study, intact female wistar rats (200-220 g) in diestrus were used. All procedures were approved by the Local Ethics Committee of Firat University Experimental Animals (14.04.2021, Issue:07). Rats were housed in the Firat University Experimental Animal Unit at 12: 12-h light-dark cycle, in rooms that were regularly ventilated at 21^{0}C room temperature. Animals were given free access to standard rat feed and tap water. All experiments on rats were carried out during the diestrus phase to control the reproductive cycle and endocrine hormones. Oestrus cycle was determined by taking a vaginal smear with a pasteur pipette in the every morning. On the day of the experiment, rats were euthanized without anesthesia. The abdominal cavities of the animals were quickly opened and their uterus rapidly excised. The excised uterine tissues were taken into Krebs solution and the connective tissue was carefully cut and cleaned. The uterine tissues were removed and divided into strips of 1.2x2x1 mm along its longitudinal axis. Cumulative data from 8 strips were collected.

Isometric Contraction

The myometrial sections were immediately suspended from each end in the isolated organ bath using surgical thread. Each strip of myometrium was suspended in a double wall tissue bath (MAY IOBS 99) filled with Krebs solution. System was continuously ventilated with a mixture of 95% O_2 and 5% CO_2 at 37°C. The upper side of the uterine strip was connected to an isometric power transducer and the other end was attached to a fixed hook under the tissue bath. To establish the basal tension-contraction relationship, the uterine strips were suspended under 1 g tension. The isometric power transducer senses the physical forces caused by isometric contractions in the smooth muscle strands in the chambers and converts them into electrical signals. These signals are delivered to the amplifier simultaneously. Amplified electrical signals are transmitted to the recording unit as frequency and amplitude parameters compatible with those in the original trace. Then the data were analyzed on the computer.

The myometrium strips exhibited spontaneous contractile activity of uneven frequency and intensity while washing every 10 minutes until equilibrated in crebs solution for 90 minutes. After the regulation period, paracetamol was

applied non-cumulatively in two separate doses of 1000μM and 2000μM. The effects of paracetamol on spontaneous uterine contractions were measured by mean peak to peak changes (p-p) and area under the contraction curve (AUC). During the control period, contraction activity (mean p-p and AUC) was taken as 100%. Before and after the application, the AUC and p-p values were normalized as% change.

Statistical Analysis

Statistical analysis of the data was evaluated using the paired sample T test in the SPSS 22.0 program. All values were determined as mean ± standard deviation (mean ± SD). For all analysis, p <0.05 was considered statistically significant.

RESULTS

Paracetamol exerted a relaxing effect on spontaneous contraction of uterine smooth muscle at 1000 μM and 2000 μM doses. Relaxing effects were statistically significant at 1000 μM and 2000 μM doses (p<0.001, Figure 1 and Figure 2). AUC and p-p values of spontaneous myometrial contractions were measured as 100±0. The mean values of p-p and AUC were 40.2±22.5 and 23.2±19.5, respectively, after the application of 1000 μM dose in uterine contraction. The mean values of p-p and AUC were 12.6±23.8 and 8.9±16.5, respectively, after uterine contraction at a dose of 2000 μM. Measurements were given as percent inhibition of the control period. The original traces obtained in the isolated organ bath at 1000 μM and 2000 μM doses were shown in Figure 3 and Figure 4, respectively.

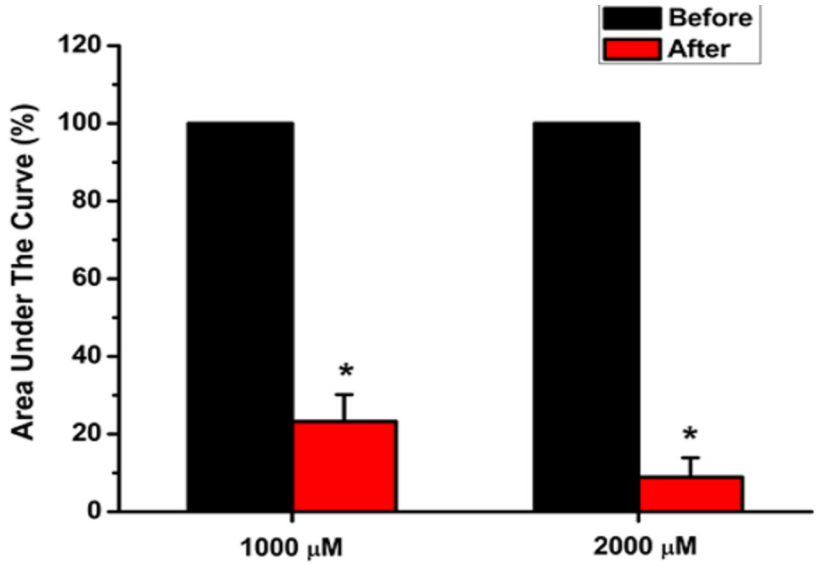

Figure 1. Effects of paracetamol on the area under the contraction curve (AUC) measurements in myometrial contractions. *p <0.001

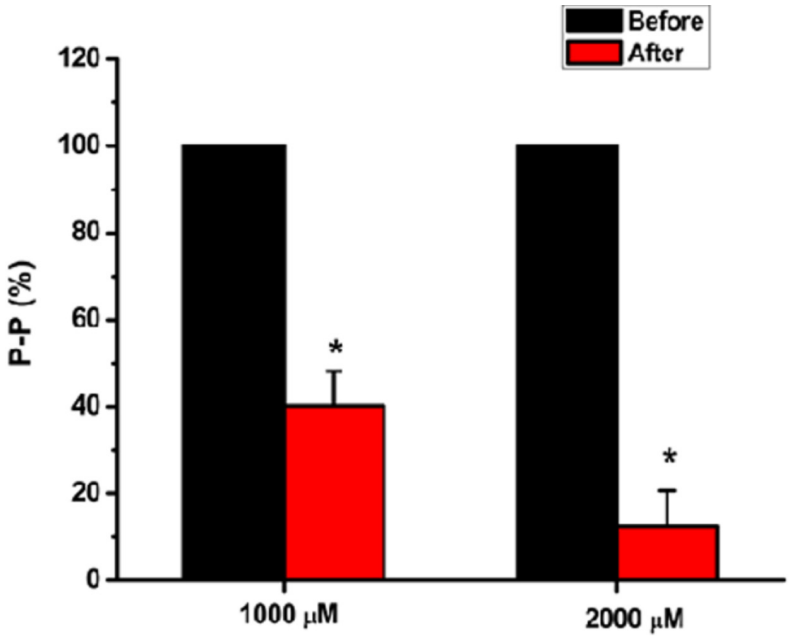

Figure 2. Effects of paracetamol on the peak to peak (p-p) measurements in myometrial contractions. *p<0.001

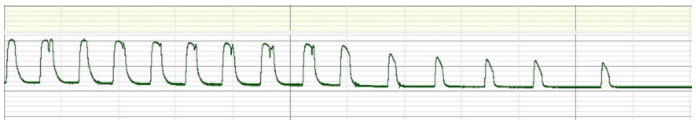

Figure 3. Original trace obtained when a 1000 μM dose of paracetamol was administered in an isolated organ bath

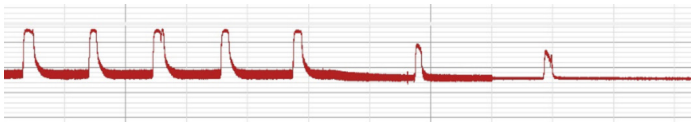

Figure 4. Original trace obtained when a 2000 μM dose of paracetamol was administered in an isolated organ bath

DISCUSSION

The study showed that paracetamol has an inhibitory effect on uterine spontaneous contractions. It was observed that the inhibitory effect was greater as the dose increased. In a study, it was shown that paracetamol exposure in female rats was associated with a significantly longer gestational period (mean 2.8 days) and a trend towards a lower incidence of preterm labor (4.7% versus 0.7%) (25). Notably, in a retrospective study, a similar increase in mean gestational age and a significant decrease in preterm births were reported in babies exposed to paracetamol during pregnancy, but no difference was observed between female and male babies (26). The authors predicted that paracetamol could prolong pregnancy through a decrease in prostacyclin synthesis, consistent with the findings of a randomized controlled trial that showed that low-dose aspirin (another cyclooxygenase inhibitor) also reduced preterm labor (27). However, another observational study did not find a significant association between paracetamol and preterm labor (28). One large prospective study reported that women taking paracetamol in their third trimester had a significantly increased risk of preterm labor, and analysis showed that this only applies to mothers with preeclampsia who took paracetamol for hypertension-related headache (22). Today, preterm birth is an important problem in obstetrics and accounts for 70% of perinatal deaths and almost half of long-term neurological morbidity (29,30). Therefore, prevention of spontaneous onset of preterm labor or rupture of membranes (31) will be of great public health importance. In the literature, it has been reported that the risk of preterm birth (26) and stillbirth (32) decreases after the use of paracetamol, and no association with miscarriage has been reported (33).The imbalance between Prostaglandin I2 (PGI2), or prostacyclin and Thromboxane A2 (TXA2, a vasoconstrictor) and inhibition of PGI2 synthesis has been proposed as an explanation for this situation (26,33).

It has been shown that paracetamol can be used after gynecological surgical procedures (34). Preoperative or intraoperative intravenous paracetamol was administered to hysterectomy patients and postoperative analgesic effects were evaluated. Paracetamol has been shown to provide significant postoperative analgesia with a reduction in morphine consumption and minimal side effects (35). Similarly, the pain score was significantly decreased by using paracetamol in the postoperative period of suction curettage (36). In our study, the inhibition of rat uterine contractions with paracetamol may shed light on the molecular causes underlying the results obtained in these studies. It can be said that paracetamol, which can also be used during pregnancy, can be reliable in pregnancies with clinical miscarriage risk and preterm birth risk.

CONCLUSION

In conclusion, it can be said that the use of paracetamol may have a potential preventive effect on preterm labor and prevent the risk of miscarriage. This effect may be associated with a decrease in the production of paracetamol-induced prostacyclin in women during pregnancy. However, the clinical effects of paracetamol using can be supported by studies using larger animal numbers of our findings. Although the findings of this study are based solely on experiments conducted in the rat uterus, must be careful when advising pregnant patients on the use of paracetamol in pregnancy.

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Research Article

Estimation of Risk Factors Related to Heart Diseases With Multilayer Perceptron Model

Kalp Hastalıklarına İlişkin Risk Faktörlerinin Multilayer Perceptron Modeli ile Tahmini

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Abstract

Aim: Heart diseases (HD) refer to many diseases such as coronary heart disease, heart failure, and heart attack. Every year, approximately 647.000 people die in the United States (U.S.) from HD. Genetic and environmental risk factors have been identified due to numerous studies to determine HD risk factors.

Material and Method: In this study, the Multilayer Perceptron (MLP) model was constructed to predict the risk factors related to HD in both genders. The relevant dataset consisted of 270 individuals, 13 predictors, and one response/target variable. Model performance was evaluated using overall accuracy, the area under the ROC (Receiver Operating Characteristics) curve (AUC), sensitivity, and specificity metrics.

Results: The performance metric values for accuracy, AUC, sensitivity and specificity were obtained with 95% CI, 0.876 (0.79-0.937), 0.935 (0.877-0.992), 0.921 (0.786-0.983) and 0.843 (0.714-0.93), respectively. According to the relevant model findings, blood pressure, the number of significant vessels coloured by fluoroscopy, and cholesterol variables were the three most crucial HD classification factors.

Discussion: It can be said that the model used in the present study offers an acceptable estimation performance when all performance metrics are considered. In addition, when compared with the studies in the literature from both data science and statistical point of view, it can be stated that the findings in the current study are more satisfactory.

Conclusion: Due to the predictive performance in this study, the MLP model can be recommended to clinicians as a clinical decision support system. Finally, we propose solutions and future research pathways for the various computational materials science challenges for early HD diagnosis.

Keywords: Heart disease, multilayer perceptron, risk factors, prediction, clinical decision support system

Öz

Amaç: Kalp hastalıkları (HD); koroner kalp hastalığı, kalp yetmezliği ve kalp krizi gibi birçok hastalığı ifade eder. Amerika Birleşik Devletleri'nde (U.S.) her yıl yaklaşık 647.000 kişi HD'den ölmektedir. HD risk faktörlerini belirlemeye yönelik çok sayıda çalışma neticesinde genetik ve çevresel risk faktörleri tanımlanmıştır.

Materyal ve Metot: Bu çalışmada, her iki cinsiyette de kalp hastalığına bağlı risk faktörlerini tahmin etmek için Multilayer Perceptron (MLP) modeli oluşturulmuştur. İlgili veri seti 270 kişiden, 13 tahmin ediciden ve bir yanıt/hedef değişkeninden oluşmaktadır. Model performansı, genel doğruluk, ROC (Alıcı Çalışma Karakteristikleri) eğrisi (AUC) altındaki alan, duyarlılık ve özgüllük metrikleri kullanılarak değerlendirildi.

Bulgular: Doğruluk, AUC, duyarlılık ve özgüllük için performans metrik değerleri sırasıyla 95% CI, 0.876 (0.79-0.937), 0.935 (0.877-0.992), 0.921 (0.786-0.983) ve 0.843 (0.714-0.93) şeklinde elde edildi. İlgili model bulgularına göre, kan basıncı, floroskopi ile renklendirilen önemli damar sayısı ve kolesterol değişkenleri en önemli üç HD sınıflandırma faktörü olarak görüldü.

Tartışma: Bu çalışmada kullanılan modelin tüm performans ölçütleri dikkate alındığında kabul edilebilir bir tahmin performansı sunduğu söylenebilir. Ayrıca hem veri bilimi hem de istatistiksel açıdan literatürdeki çalışmalarla karşılaştırıldığında, mevcut çalışmadaki bulguların daha tatmin edici olduğu ifade edilebilir.

Sonuç: Bu çalışmadaki öngörücü performans nedeniyle, MLP modeli klinik karar destek sistemi olarak klinisyenlere önerilebilir. Son olarak, erken HD teşhisi için çeşitli hesaba dayalı bilim alanında çözümler ve yeni araştırmalar öneriyoruz.

Anahtar Kelimeler: Kalp hastalığı, çok katmanlı algılayıcı, risk faktörleri, tahmin, klinik karar destek sistemi

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INTRODUCTION

In the world full of advanced computer technologies, artificial intelligence (machine learning and deep learning), one of the essential computer science fields, is used in many areas, especially in medicine. It is used to predict the presence of diseases such as heart diseases (HD) (1). These estimates can be made by obtaining important data obtained from patients' medical databases using various algorithms (2).

Medical organizations around the world collect a lot of essential health data. Increasing data in today's world can be useful in early diagnosis or triage in medicine using machine learning techniques (3). However, the data collected is extensive, complex, difficult to analyze, and takes much time. These datasets, which are too overwhelming for the human mind to understand, can be easily analyzed using various machine learning techniques. Therefore, these algorithms have recently become very useful for accurately predicting heart-related diseases' presence or absence (4).

Heart Diseases (HD)

Cardiovascular disease (CVD) is a term used for conditions that affect the heart or blood vessels (5). Although there are different variations, CVD is divided into four main headings:

1. Coronary heart disease: Myocardial infarction (MI), angina pectoris, and heart failure (HF)
2. Cerebrovascular disease: Stroke and transient ischemic attack
3. Peripheral artery disease
4. Aortic atherosclerosis and thoracic or abdominal aortic aneurysm

In coronary heart disease, the heart tissue cannot be fed sufficiently due to the cholesterol accumulated in the coronary vessels. The heart cannot receive enough blood due to the cholesterol and fat accumulated in the arteries' wall that supplies the blood to the heart. In MI, also known as a heart attack, it is a fatal condition caused by blockage of blood in the coronary artery wall. HF is a progressive clinical picture that does not fill/discharge due to a problem due to the heart tissue's function or structure, resulting in the peripheral tissues' inability to send enough blood to meet their metabolic needs (5). Angina is a chest pain caused by insufficient blood flow to the heart. Due to the low return, the heart cannot work physiologically. Cerebrovascular disease refers to diseases that affect blood flow to the brain due to congestion or malformation that affect blood vessels. Peripheral artery disease is a condition where the peripheral tissues are not fed enough blood due to narrowing the legs' arteries. Other forms of HD include valvular heart disease, stroke, hypertension, etc.

Epidemiology

CVD is a group of diseases that affect most adults older than 60 years of age and have severe morbidity and mortality. It is common in the general population worldwide, and estimated that 17.3 million deaths from CVD occurred annually in the early 2010s. CVD caused more than 12 million (25.8%) deaths in 1990 and approximately 18 million (32.1%) deaths in 2015 (6). Also, HD and stroke constitute 80% of deaths due to CVD in men and 75% in women (7).

HD more common in older ages, and age is a significant risk factor for CVD. Recently, it was reported that CVD occurs in only 11% of people aged 20-40, while 37% of people aged 40-60, 71% of people aged 60-80, and 85% of people over 80 in the U.S. Approximately 50% of people over the age of 20 have CVD in the U.S., according to the 2019 Heart Disease and Stroke Statistics update of the American Heart Association (8).

HD are the leading cause of death for men, women, and people in most racial and ethnic groups in the U.S. One person with CVD dies every 37 seconds in the U.S. About 647.000 Americans die each year from HD (8). Also, HD cost is about $219 billion annually from 2014 to 2015 in the U.S. (9), including healthcare, medicines expenditure, and loss of productivity from death.

The average age of death from coronary artery disease is around 80 in developed countries; however, it is about 68 in developing countries. The disease's symptoms and diagnosis typically occur in men 7-10 years earlier than in women (7).

HD accounts for approximately one-third and half of total CVD patients. Also, ischemic HD are the most common cause of death in adults in all low, middle, and high-income countries (10). About 9 million people died in 2016 due to ischemic heart disease (5). The lifetime risk of HD has been demonstrated in the Framingham Heart Study in 7.733 individuals aged 40-94 years. The lifetime risk of 40 years old is 49% for men, while women have a lower risk and 32%. Similar results were achieved in a meta-analysis study in which more than 250.000 women and men were included, and data on 18 studies were analyzed (11).

Although it is more common in older ages, it has been shown that the early stages of atherosclerosis begin to occur starting from the second and third years of life according to autopsy data (12). The life span has been long since 1975, CVD's prevalence and related complications are still very high, and treatment costs are relatively high (13).

In a cohort study of over 1.9 million people older than 30 years old who did not have CVD before, patients were followed up for six years. According to this; angina, HF, peripheral artery disease, transient ischemic attack, and abdominal aortic aneurysm constitute 66% of CVD (14).

More than 4 million people die from HD annually among 49 countries in Europe and North Asia. About 1,5 million people experience a heart attack or stroke annually, resulting in over 250.000 deaths in the U.S. (15). Despite advances in medicine and science, CVD's prevalence is increasing rapidly in developing countries. It is estimated that the global HD burden increased by 29% between 1990 and 2010 (16).

Risk factors

There are many known risk factors for HD including genetic predisposition, family history, age, gender, tobacco use, physical inactivity, excessive alcohol consumption,

unhealthy diet, obesity, hypertension, diabetes mellitus, hyperlipidemia, psychosocial factors, poverty, low educational status, and air pollution, etc. (5).

Nine potentially changeable risk factors were placed in the INTERHEART study, which included 52 countries. These are smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, daily fruit and vegetable consumption, alcohol consumption, and regular physical activity. It has been shown that improving these risk factors can reduce CVD by approximately 90% (17).

Genetic and family history

Genetic factors affect the development of CVD, especially in men under 55 and women under 65. Having a CVD in one of the parents increases CVD's risk in the person three times. The risk of developing HD varies between 15-100% in the presence of positive family history (18).

According to information obtained from several extensive cohort studies following more than 163.000 patients, it has been observed that a positive family member for CVD is associated with the risk of developing HD (19). Also, 3.9 million people who were born between 1950-2008 were followed in another study. It has been found that children who have had two or more early cardiovascular deaths among their first-degree relatives had three times the risk of developing CVD before age 50 (20). More than one single nucleotide polymorphism is associated with CVD in genetic association studies; however, it generally has little individual effects, and genetic contributions to CVD are not fully understood (21). Some mutations associated with leukemia in blood cells are also thought to cause an increased risk of CVD. According to the data obtained from many studies examining CVD's genetic background, it has been observed that the presence of these mutations can cause events and mortality associated with CVD (22).

Age

Age is the most critical risk factor in CVD development and carries about three times more risk every ten years of life (23). Coronary fat lines may begin to form during adolescence (24). Nearly 82% of people aged 65 and over are thought to have died due to HD (25).

Although multiple reasons increase CVD incidence with aging; the most common are pathological changes in blood vessels and increased serum cholesterol levels. The serum total cholesterol level rises with aging in most populations. This increase is around 45-50 years old in males, while in females, it is evident in 60-65 years old (26). Depending on aging, arterial elasticity loss occurs, which can reduce the artery's ability to adapt and lead to coronary artery disease (26).

Gender

Men are more likely to suffer from HD than premenstrual women (23). It is known that coronary HD is seen 2-5 times more in middle-aged men than in women (26). A study conducted by the World Health Organization (WHO) showed that gender had a 40% impact on HD mortality (27). Similar results have been reported showing that gender differences explain approximately half of CVD's risk in another study (26). Also, the predominant hormone in women is an estrogenic effect. Estrogen is known to have significant impacts not only on carbohydrate metabolism but also on the cardiovascular system. It is also known to have significant protective effects on hemodynamics and directly affect improving endothelial cell function. Estrogen production decreases, which negatively affects lipid levels in women after menopause (26).

There are also differences between men and women regarding body weight, height, body fat distribution, and hemodynamic parameters. This situation may cause CVD to be more common in men due to these changes. It is known that male sex is a significant and independent risk for HD. The reason for this is not fully known (28).

According to the data obtained from ONTARGET and TRANSCEND studies (9.378 women, 22.168 men) performed on 31.000 patients followed for an average of 56 months, women were at a 20% lower risk of all major cardiovascular events, including cardiovascular death, than men (29).

Hypertension

It is known that hypertension is the most investigated and important risk factor for many cardiovascular system diseases including HD. In a cohort study of over 1.25 million patients aged 30 years and older without CVD, including 20% with initially treated hypertension, the risk of developing lifetime CVD in patients with hypertension was 63.3% (30).

Smoking

Health risks arising from smoking arise from direct tobacco consumption and passive exposure. Approximately 10% of CVD occurs due to smoking (7). The incidence of MI increases six times in women and three times in men who smoke at least 20 cigarettes daily than non-smokers (31).

Physical inactivity

Insufficient physical activity (less than 5x30 minutes per week) is now ranked 4th among the causes of mortality worldwide (7). According to the 2008 study, 31.3% (28.2% men and 34.4% women) of adults aged 15 and over are not physically active (7). The risk of HD and diabetes mellitus decreases by approximately one-third in those who regularly participate in a moderate sports activity for about 2.5 hours each week. Also, weight control is provided depending on physical activity, and blood glucose and lipid parameters also improve. Physical activity also improves blood pressure and insulin sensitivity, leading to reduced CVD (7).

Diet

It is known that high amounts of saturated fat, trans-fatty acids, salt, low consumption of fruits, vegetables, and fish increase the risk of CVD. WHO reported that 1.7 million people died worldwide due to not consuming enough fruits and vegetables (7). It is known that consuming

foods with high fat and sugar content increases important risk factors for CVD, such as obesity (7). It has also been shown that the amount of salt consumed daily affects blood pressure and is an important risk factor for CVD (7). Also, it has been shown that reducing the consumption of saturated fat for about two years reduces the risk of CVD. Also, consuming high sugar foods negatively affects blood lipid and glucose parameters and increases diabetes mellitus and HD incidence. Also, excessive consumption of processed meats increases the risk of CVD (32).

Socioeconomic level

Although CVD affects all countries, it affects low and middle-income countries more than other countries. Although there is not much information, low income and low education levels have a higher risk of CVD (32).

Air pollution

According to the related-studies, long-term exposure to particles in the air under 2.5 micrometers diameter increases the rate of atherosclerosis and inflammation. Short-term (2 hours) exposure to air pollution causes an approximately 50% increase in CVD's mortality rate. It has also been shown that, after just five days of exposure to air pollution, both systolic and diastolic blood pressure increases by 2.8 mmHg and 2.7 mmHg, respectively (33). According to other studies, air pollution causes both arrhythmia and HF. Also, it is associated with carotid artery thickening and acute MI (34).

Machine Learning Algorithms

Today, machine learning algorithms assist clinicians in decision support systems in various tasks in medicine (35). Thanks to data science developments, computer technologies, and neural network-based systems, machine learning technologies are strengthening their position every day in the medical world where large and different data types (image, video, and soon) are abundant (36). As a result of these developments, health services in some areas are aimed to be faster, less costly, and reliable (37).

It is a complicated process that is decided by using clinical data and clinical experience in diagnosing a disease. Making this decision-making process less costly, more accessible, faster, more accurate, and efficient will improve patients' quality of life. As mentioned above, too many people suffer from HD in today's world and die or fight their complications due to these diseases. Also, patients cannot benefit from health services sufficiently because of time limitations and the excessive number of patients. For all these reasons, early and accurate detection of HD will save many patients' lives. Unfortunately, the cardiovascular system's complicated process, late onset of many symptoms, and genetic differences delay inappropriate treatment.

Therefore, there is a need to develop HD estimation systems to assist medical professionals in the early and accurate HD diagnosis. In this study, Multilayer Perceptron (MLP), one of the well-known neural network-based machine learning models, was utilized to diagnose of HD and determine the essential variables/factors as a risk factor related to HD (38).

MATERIAL AND METHOD

The dataset used in this study consisted of 270 individuals, 13 predictors, and one response/output variable. The dataset used in this study was taken from the www.kaggle.com/ronitf/heart-disease-uci. A detailed information table regarding the variables is shown in Table 1, and descriptive statistics of all variables in the dataset are shown in Table 2-3.

The MLP is a type of artificial neural network that is performed in many disciplines. The MLP architecture has one input layer, one or more hidden layers, and one output layer. Each layer comprises of several nodes. The inputs in the first layer nodes are weighted and sent simultaneously to a second or hidden layer. Each of the nodes takes the weighted sum of the outputs of the previous layer as input and implements an activation function to determine its output. The activation function is usually a sigmoid function that converts the output to a number between 0 and 1 (39).

The MLP model was applied to predict HD using these 13 risk factors. The dataset is randomly divided into training and testing at 70% and 30% ratios in order to obtain unbiased model performance metrics at 70% and 30% ratios, respectively. While model training was done in 70% of the dataset, the model's learning performance was tested in the remaining 30%. The tuning hyperparameters for the MLP model are shown in Table 2.

Table 1. Types and roles of the variables

Variable	Type	Role
Age	Numerical	Predictor
Sex	Categorical	Predictor
Chest pain type	Categorical	Predictor
Blood pressure	Numerical	Predictor
Cholesterol	Numerical	Predictor
FBS over 120	Categorical	Predictor
ECG results	Categorical	Predictor
Max heart rate	Numerical	Predictor
Exercise angina	Categorical	Predictor
ST depression	Numerical	Predictor
Slope of ST	Categorical	Predictor
Number of vessels fluro	Categorical	Predictor
Thallium	Categorical	Predictor
Heart disease	Categorical	Response/output

FBS, fasting blood sugar; ECG, electrocardiogram

Table 2. Tuning hyperparameters of the MLP model	
Parameter	Value
Number of the hidden layer(s)	1
Number of node(s)	2
Activation function	Softmax
Error function	Cross-entropy
Optimization function	Gradient descent
Learning rate	0.4
Momentum	0.9

Model performance was evaluated using overall accuracy ratio, area under the ROC (Receiver Operating Characteristics) curve (AUC), sensitivity, and specificity metrics. IBM SPSS Statistics 25 package program was used for the analyses.

RESULTS

The descriptive statistics of the categorical and numerical variables are summarized in Tables 3 and 4. Also, the ROC curve graph for the performance metrics of the MLP model by the classification matrix is presented in Table 5 and shown in Figure 1. The contributions of the predictive variables to the classification performance of the MLP model are shown in Table 6.

The performance metric values for accuracy, AUC, sensitivity and specificity were obtained with 95% CI, 0.876 (0.79-0.937), 0.935 (0.877-0.992), 0.921 (0.786-0.983) and 0.843 (0.714-0.93), respectively. The general structure and performance metric values of MLP for HD is shown in Figure 2.

Table 3. The descriptive statistics of the categorical variables			
Variable	**Category**	**n**	**%**
Heart disease	Negative	150	55.56
	Positive	120	44.44
	Total	270	100.00
Sex	0	87	32.22
	1	183	67.78
	Total	270	100.00
Chest pain type	1	20	7.41
	2	42	15.56
	3	79	29.26
	4	129	47.78
	Total	270	100.00
FBS over 120	0	230	85.19
	1	40	14.81
	Total	270	100.00
ECG results	0	131	48.52
	1	2	0.74
	2	137	50.74
	Total	270	100.00
Exercise angina	0	181	67.04
	1	89	32.96
	Total	270	100.00
Slope of ST	1	130	48.15
	2	122	45.19
	3	18	6.67
	Total	270	100.00
Number of vessels fluro	0	160	59.26
	1	58	21.48
	2	33	12.22
	3	19	7.04
	Total	270	100.00
Thallium	3	152	56.30
	6	14	5.19
	7	104	38.52
	Total	270	100.00

FBS, fasting blood sugar; ECG, electrocardiogram

Table 4. The descriptive statistics of numerical variables

Statistics	Variables				
	Age	Blood Pressure	Cholesterol	Max Heart Rate	ST depression
N	270	270	270	270	270
Mean	54.43	131.34	249.66	149.678	1.05
Median	55	130	245	153.5	0.8
Std. Deviation	9.109	17.86	51.686	23.166	1.145
Minimum	29	94	126	71	0
Maximum	77	200	564	202	6.2

Table 5. The confusion matrix

Heart Disease (Model prediction)	Heart Disease (Real)		
	Positive	Negative	Total
Positive	35	8	43
Negative	3	43	46
Total	38	51	89

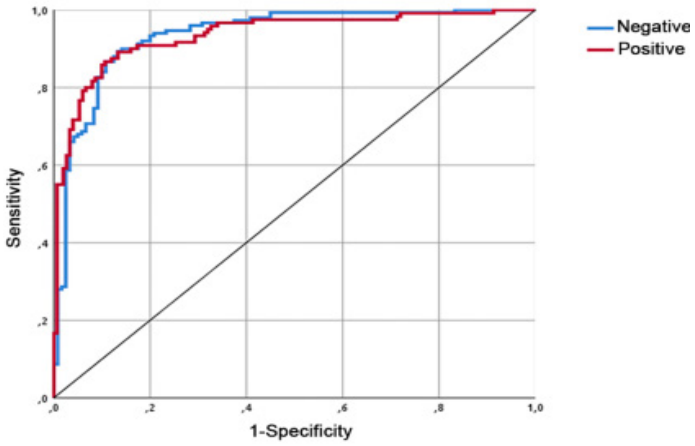

Figure 1. The ROC curve

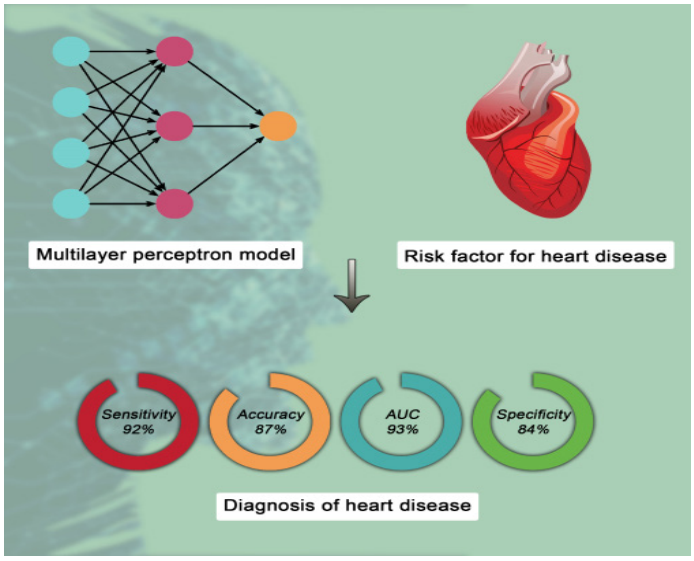

Figure 2. The general structure and performance metric values of MLP for HD

Table 6. The variable importance statistics (In descending order)

Variables	Importance	Importance (%)
Blood pressure	0.155	100.00
Number of vessels fluro	0.141	90.95
Cholesterol	0.109	70.22
Thallium	0.108	69.79
Max heart rate	0.101	65.27
Chest pain type	0.094	60.77
Sex	0.076	48.76
Age	0.052	33.40
ST depression	0.042	27.16
Slope of ST	0.040	25.65
ECG results	0.030	19.03
FBS over 120	0.027	17.49
Exercise angina	0.025	16.37

FBS, fasting blood sugar; ECG, electrocardiogram

DISCUSSION

In this study, HD prediction was made by modeling various risk factors with an artificial neural network model, MLP. Considering similar studies in the literature, HD classification was made using various machine learning models in a study conducted in 2021 (40). Considering the overall accuracy ratios, it was seen that the highest value was obtained with the Random Forest model (84%). This value is considerably lower than the classification performance obtained in the current study.

In another study (41), the individual and ensemble performances of various data mining models were discussed. In related study, in which extensive data preprocessing was performed, the ensemble model (majority vote) formed by combining the support vector machine and logistic regression model gave the highest classification accuracy (91.23%). This ensemble learning approach does not appear to have significantly higher classification performance than the model in the current study. In addition, this ensemble learning model created lacks the knowledge of how predictive variables contribute to the classification performance of the model.

In another study on the prediction of HD (42), the classification performances of Logistic Regression, Decision Forest, Random Forest, Artificial Neural Networks, K-Nearest Neighbors and Support Vector Machines models were compared. According to the results of this study, the Random Forest model correctly classified all cases with 100% accuracy. However, in this study, the classification performance of the model was evaluated only with its overall accuracy. Considering that the Random Forest model is highly prone to overfitting, it is inconvenient to evaluate the classification performance over only one metric. In our study, the performance of the model was evaluated by giving 4 different metrics and their 95% confidence intervals. Thus, the findings were evaluated from both data science and statistics perspectives.

Performance measurement is a significant issue in machine learning. One of the most critical evaluation criteria for checking any classification model's performance is the area under the curve and explains how well the model is at its prediction. The larger the area covered, the better the machine learning models at differentiating the classes given. In addition to the high accuracy of the MLP test used in our study, the AUC value is more excellent than 90%, indicating that the model's predictive value is high. Also, the sensitivity value appears to be greater than the specificity value. This is valuable in the classification of HD in patients, and its high level is of great clinical importance.

In brief, it was found that the three most essential variables in the classification of HDs in the MLP model are blood pressure, the number of major vessels colored by fluoroscopy, and cholesterol. It was also shown to have high accuracy, AUC, sensitivity, and specificity values.

CONCLUSION

The MLP model, which was trained using 13 predictive variables, was found to be successful in the classification of HD. According to the relevant model findings; blood pressure, the number of major vessels colored by fluoroscopy, and cholesterol variables were the three most important HD classification variables. The performance metric values for accuracy, AUC, sensitivity, and specificity were obtained with 87%, 93%, 92%, and 84%, respectively.

Due to the predictive performance in this study, the MLP model can be recommended to clinicians as a clinical decision support system. As future research, for boosting classification performance and obtaining more reliable results, implementing ensemble learning-based models to real dataset(s) having more observations and risk factors should be planned.

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Research Article

An Investigation of the Nutrient Foramen in the Long Bones of the Upper and Lower Limbs in Turkish Population

Türk Populasyonunda Üst Ve Alt Ekstremite Uzun Kemiklerinde Foramen Nutricium'larin İncelenmesi

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Abstract

Aim: We aimed to examine the presence, number, anatomic location of the nutrient foramen in the long bones of the upper and lower limbs and calculate the foramen index.

Materials and Methods: Our study was conducted on a total of 295 bones, including 25 clavicle, 59 humerus, 49 radius, 32 ulna, 59 femur, 49 tibia, and 22 fibula. The number of the nutrient foramen in each bone, the anatomic location of the nutrient foramen on the bone, and the direction of its opening were determined and recorded. All bones were photographed with a millimeter ruler. The bone length and the distance of the nutrient foramen to the proximal of the bone were measured using the ImageJ program. The foramen index was calculated for each foramen.

Results: At least one nutrient foramen was observed in all bones, except for one humerus and three fibula. The highest mean foramen index belonged to the humerus and clavicle, while the lowest mean foramen index belonged to the tibia. The direction of the nutrient foramen is mostly toward the acromial end (87.5%) in the clavicle, toward the distal in the humerus (97.6%), tibia (96.15%) and fibula (75%), and toward the proximal in the radius (96.36%), ulna (100%), and femur (98.97%).

Conclusion: There are few studies on the nutrient foramen in which bones of the upper and lower limbs are examined together and comparisons between populations are made. Therefore, we think that our study will enrich the limited literature on this subject and contribute to clinicians.

Keywords: Foramen index, fracture, localization, nutrient artery

Öz

Amaç: Üst ve alt ekstremite uzun kemiklerinde foramen nutricium'ların varlığını, sayısını, anatomik konumunu incelemeyi ve foramen indeksini hesaplamayı amaçladık.

Materyal ve Metot: Çalışmamız 25 clavicula, 59 humerus, 49 radius, 32 ulna, 59 femur, 49 tibia ve 22 fibula olmak üzere toplam 295 kemik üzerinde gerçekleştirildi. Bütün kemiklerdeki foramen nutricium'ların sayısı, foramen nutricium'ların kemik üzerindeki anatomik konumu ve açıklığının yönü belirlenerek kaydedildi. Tüm kemikler bir milimetrik cetvel ile fotoğraflandı. Kemik uzunluğu ve foramen nutricium'ların kemiğin proksimaline olan mesafesi ImageJ programı kullanılarak ölçüldü. Bütün foramenler için foramen indeksi hesaplandı.

Bulgular: Bir humerus ve üç fibula dışında tüm kemiklerde en az bir foramen nutricium gözlendi. En yüksek foramen indeksi ortalaması humerus ve clavicula'ya aitken, en düşük foramen indeksi ortalaması tibiaya aitti. Foramen nutricium'ların açıklığının yönü clavicula'da çoğunlukla extremitas acromialis'e (%87,5), humerus'ta (%97,6), tibia (%96,15) ve fibula'da (%75) distale ve radius (%96,36), ulna (%100) ve femur'da (%98,97) proksimale doğruydu.

Sonuç: Üst ve alt ekstremite kemiklerinin birlikte incelendiği ve popülasyonlar arası karşılaştırmaların yapıldığı foramen nutricium'larla ilgili az sayıda çalışma bulunmaktadır. Bu nedenle çalışmamızın bu konudaki sınırlı literatürü zenginleştireceğini ve klinisyenlere katkı sağlayacağını düşünüyoruz.

Anahtar Kelimeler: Foramen indeksi, kırık, lokalizasyon, arteria nutricia

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INTRODUCTION

The nutrient foramen (NF) is an opening in the shaft of the bone that provides nutrition and growth of the bone thanks to the artery passing through it. The nutrient artery enters the bone obliquely from the NF (1). The nutrient artery is the main source of nutrition for the long bones. The restriction of the blood flow from this nutritional source can cause ischemia in the bones (2). This artery is especially important in the active growth period of the embryo and fetus and the early stage of ossification (1).

The fracture of the long bones is a common situation. Delayed union is one of the most common complications after a fracture. This complication may have many causes. Poor bone nutrition is one of the conditions that cause this complication to occur. Therefore, the nutrient artery plays an important role in fracture healing (3). It has been reported that places where union problems are common in the forearm are correlated with the localization of the NF (4). Longitudinal stress fractures may cause the rupture of the nutrient artery. Moreover, conditions such as developmental abnormalities and hematogenic osteomyelitis, apart from fracture healing, are also related to the nutrition of the bone (2). It has been emphasized that union problems may occur due to the injury of the nutrient artery during open reduction (4). Therefore, the topography of the NF is important in surgery for the protection and maintenance of circulation (1). Furthermore, the details about the nourishment of the long bones are very important in the development of new transplantation and resection techniques in orthopedics. Therefore, the variety of studies on the NF gains importance (5).

Thus, in the present study, we aimed to examine the presence, number, and anatomic location of the NF in bones of the upper and lower limbs and determine in which of the proximal, middle, and distal 1/3 parts of the bone it is localized through the foramen index.

MATERIAL AND METHOD

Our study was conducted on a total of 295 bones, including 25 clavicle, 59 humerus, 49 radius, 32 ulna, 59 femur, 49 tibia, and 22 fibula of unknown age and sex in the Anatomy Department Laboratory of the Faculty of Medicine. Broken or deformed bones were not included in the present study since they could be misleading with regard to the findings. This study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine (Date: 11.17.2020, Decision No: 362).

The number of the NF in each bone was determined. The anatomic location and direction of the NF on the bone were determined and recorded. All bones were photographed with a millimeter ruler. Anatomically, two parallel lines passing through the most distal and proximal parts of the bone were drawn on the photographs. These lines were taken as a reference, and the bone length and the distance of the NF to the proximal of the bone (Figure 1) were measured using the ImageJ program. Data analysis was done using SPSS 20.0 for Windows. Means and standard deviations of the bone length, the distance of the NF to the proximal of the bone and foramen index were determined. In addition results regarding the number, location and direction of the nutrient foramen obtained by frequency analysis. Since the gender of the bones was not known, the differences between male and female could not be compared.

Figure 1. The distance of the nutrient foramen in the upper and lower limb bones to the proximal. a. Clavicle b. Humerus c. Radius d. Ulna e. Femur f. Tibia g. Fibula (Arrows show the nutrient foramen)

Hughes (6) described the foramen index (FI) formula to determine the localization of the NF. The present study, the following formula described by Hughes (6) was used when calculating the FI.

$$\text{Foramen Index (FI)} = \frac{\text{Distance of the foramen to the proximal end of the bone}}{\text{Total length of the bone}} \times 100$$

Upon examining the FI value, as in the literature, the foramen with an FI value of 0-33.33% was accepted to be localized in the proximal 1/3 of the bone (in the medial 1/3 in the clavicle), the foramen with an FI value of 33.33-66.66% was accepted to be localized in the middle 1/3 of the bone, the foramen with an FI value of 66.66-100% was accepted to be localized in the distal 1/3 of the bone (in the lateral 1/3 in the clavicle) (1,7,8).

RESULTS

1. The number of the nutrient foramen

Of the 295 bones examined in our study, 217 (73.56%) had a single NF, 59 (20%) had two, 9 (3.06%) had three, 2 (0.68%) had four, 4 (1.35%) had five NF, while 4 (1.35%) had no NF. One of the bones without the nutrient foramen was the humerus, and three were the fibula (Table 1).

2. The foramen index

In all bones, except for the tibia, the NF was mostly localized in the middle 1/3 of the bone (Table 1). In the tibia, the NF was mostly found in the proximal 1/3 of the bone. The highest mean FI belonged to the humerus and clavicle, while the lowest mean FI belonged to the tibia (Table 2).

Table 1. The number of bones, the number and the localization of nutrient foramen

		Clavicle*	Humerus	Radius	Ulna	Femur	Tibia	Fibula
Number of Bones	Right (N)	12	24	25	16	31	30	9
	Left (N)	13	35	24	16	28	19	13
	Total	**25**	**59**	**49**	**32**	**59**	**49**	**22**
Number of NF	0	-	1	-	-	-	-	3
	1	15	39	43	29	27	46	18
	2	3	16	6	3	27	3	1
	3	4	1	-	-	4	-	-
	4	-	1	-	-	1	-	-
	5	3	1	-	-	-	-	-
	Total	**48**	**83**	**55**	**35**	**97**	**52**	**20**
Localization of NF	Proximal 1/3	12	9	25	9	15	37	-
	Middle 1/3	30	64	30	26	80	15	19
	Distal 1/3	6	10	-	-	2	-	1

NF: Nutrient foramen, * Instead of the medial 1/3 in the clavicle, the expression "proximal 1/3" was used, and the expression "distal 1/3" was used instead of the lateral 1/3

Table 2. Foramen indices of the upper and lower limbs

Bone	Total length of the bone (mm)	Distance of the NF to the proximal end of the bone (mm)	Foramen Index
Clavicle	137.93±13.6	66.96±27.78	52.27±19.12
Humerus	311.33±30.9	160.92±45.67	52.39±14.84
Radius	228.39±15.87	77.88±16.95	34.11±7.08
Ulna	254.71±21	96.34±18.9	37.75±6.46
Femur	432.28±36.89	196.61±52.32	45.64±11.34
Tibia	373.55±26.74	123.92±24.45	33.23±6.31
Fibula	339.11±23.02	166.86±36.19	47.14±14.37

NF: Nutrient foramen

3. The anatomic location of the nutrient foramen

Of the NF present in the clavicle, 52.08% were in the inferior surface, 35.42% were in the posterior of the bone, 10.42% were in the superior surface, and 2.08% were present in the anterior of the bone. Of the NF present in the humerus, 45.79% were determined in the anteromedial surface, 25.30% in the posterior surface, 19.28% in the medial border, 8.43% in the intertubercular sulcus, and 1.20% were determined in the anterior border. Of the NF present in the radius, 85.45% were in the anterior surface, 9.1% in the interosseous border, and 5.45% in the posterior surface. Of the NF present in the ulna, 80% were in the anterior surface, 17.14% were in the interosseous border, and 2.86% were in the posterior surface. While 98.97% of the NF detected in the femur were located in the posterior surface, 1.03% were in the anterior surface. Of the NF determined in the femur, 49.48% were found in the medial of the linea aspera, 42.27% were above the linea aspera, and 7.22% were in the lateral of the linea aspera. The location of 1.03% of the NF with respect to the linea aspera could not be evaluated since the NF was not on the surface where the linea aspera was present. Of the NF present in the tibia, 96,16% were found in the posterior surface, 1.92% were in the anterior of the bone, and 1.92% were in the medial border. Of the NF present in the tibia, 86.54% were in the lateral of the soleal line, and 7.7% were above the soleal line. The location of 3.84% of the NF in the tibia with respect to the soleal line could not be evaluated since the NF was not on the surface where the soleal line was present, and the location of 1.92% with respect to the soleal line could not be evaluated since the NF was in the body. Of the NF present in the fibula, 40% were in the medial surface, 20% were in the interosseous border, 15% were in the lateral surface, 15% were in the posterior surface, and 10% were in the anterior border.

4. Direction of the nutrient foramen

Of the NF in the clavicle, 87.5% were directed to the acromial end, 12.5% were directed to the sternal end; of the NF in the humerus, 97.6% were directed distally, and 2.4% were directed proximally; of the NF in the radius, 96.36% were directed proximally, and 3.64% were directed distally. All the NF present in the ulna were directed proximally. This suggests that the NF is generally directed to the elbow joint.

Of the NF in the femur, 98.97% were directed proximally, 1.03% were directed distally; of the NF in the tibia, 96.15% were directed distally, and 3.85% were directed proximally; of the NF in the fibula, 75% were directed distally, and 25% were directed proximally. It is note worthy that the NF is directed in the opposite direction to what is frequently observed in some clavicle, humerus, radius, and femur, and this NF is the other NF from the main NF feeding the bone.

DISCUSSION

The presence, number, anatomic location, and localization of the NF are important in the nutrition of the bone, fracture healing, in the surgical interventions to be performed after the fracture, and in the nutrition and recovery of the bone after surgical interventions. Due to this clinical significance, there are many studies in the literature (2,4,9,10).

Injury of the nutrient artery associated with femoral shaft fractures is considered a cause of delayed union (11). However, even in the long bones of the upper and lower extremities, a few is known about the origin and bone course of the nutrient arteries, but this information is crucial for preserving the feeding arteries during operative procedures (10).

We examined the previous studies in the literature investigating the NF and compared the results of these studies with our study. When the studies examining the NF in upper limb bones were compared, it was observed that there was mostly one NF in the humerus, radius, and ulna in our study in line with the literature (Table 3).

While there are studies reporting a single NF in most of the clavicles examined, as in our study (12,13), there are also studies reporting double NF (Table 3) (14-16). Furthermore, 5 NF were detected in 3 clavicles and one humerus in our study (Figure 2).

Figure 2. Views of the humerus and clavicle with five nutrient foramina, a. Humerus (posterior) b. Humerus (anterior) c. Clavicle (anterior) d. Clavicle (superior) e. Clavicle (posterior) f. Clavicle (inferior) (Acupuncture needles are inserted into the nutrient foramina for a clearer understanding)

In the literature review we performed, we did not encounter any other study in which five NF were observed in the clavicle and humerus (Table 3). Similar to the results of previous studies examining the NF in lower limb bones, mostly single NF was observed in the tibia and fibula in our study (Table 4).

Table 3. Comparison of studies examining nutrient foramen in upper limb bones

Study	Bone	Year	Population	Number of Bones	Foramen Index	Number of NF						Total number of NF	Proximal 1/3	Middle 1/3	Distal 1/3
						0	1	2	3	4	5				
Rai et al. (14)	Clavicle	2014	India	40	48.01	-	17	21	2	-	-	65	10	48	7
Tanna et al. (15)		2015	India	50	49.01	-	21	26	3	-	-	82	15	59	8
Saha et al. (13)		2017	India	54	47.65	-	29	22	3	-	-	82	14	61	7
Hussain at al. (16)		2018	Pakistan	60	51.41	-	22	30	6	2	-	108	-	54	6
Leschinger et al. (33)		2019	Germany	317	53.2	17		300				317	1	287	12
Kumar et al. (12)		2019	India	102	-	10	75	15	2	-	-	92	-	92	-
Our Study		2021	Turkey	25	52.27±19.12	-	15	3	4	-	3	48	12	30	6
Xue et al. (24)	Humerus	2016	China	38	43.76	1	32	5	1	-	-	42	-	-	-
Pankaj et al. (23)		2017	India	350	-	19	283	47	4	-	-	380	2	371	7
Ghule et al. (25)		2018	India	100	R:56.31 L: 56.88	-	100	-	-	-	-	100	1	92	7
Khandve et al. (26)		2018	India	80	-	3	70	29	-	-	-	128	-	94	2
Rathwa et al. (7)		2019	India	68	55.20	-	64	4	-	-	-	72	6	62	4
Kumari et al. (22)		2019	India	64	-	-	58	5	-	-	-	63	-	52	1
Our Study		2021	Turkey	59	52.39±14.84	1	39	16	1	1	1	83	9	64	10
Rangasubhe et al. (19)	Radius	2014	India	100	-	-	97	3	-	-	-	103	68	35	-
Solanke et al. (27)		2014	India	80	34.36	4	74	2	-	-	-	78	18	58	-
Kumar et al. (34)		2017	India	110	R: 35.64 L: 34.96	-	108	2	-	-	-	112	-	-	-
Our Study		2021	Turkey	49	34.11±7.08	-	43	6	-	-	-	55	25	30	-
Solanke et al. (27)	Ulna	2014	India	80	36.52	3	77	-	-	-	-	77	18	59	-
Chavda et al. (28)		2018	India	150	35.34	3	145	2	-	-	-	149	33	95	21
Rangasubhe et al. (20)		2019	India	100	-	-	86	13	1	-	-	115	98	14	3
Priya et al. (29)		2019	India	200	35.83±6.12	-	188	12	-	-	-	212	80	120	-
Our Study		2021	Turkey	32	37.75±6.46	-	29	3	-	-	-	35	9	26	-

NF: Nutrient foramen

Table 4. Comparison of studies examining nutrient foramen in upper limb bones

Study	Bone	Year	Population	Number of Bones	Foramen Index	Number of NF						Total number of NF	Proximal 1/3	Middle1/3	Distal 1/3
						0	1	2	3	4	5				
Gupta et al. (17)	Femur	2016	Nepal	100	-	3	71	25	1	-	-	124	26	97	1
Zahra et al. (2)		2018	Turkey	107	R:44.58±10.25 L:45.29±11.46	17	69	20	1	-	-	112	15	97	-
Uzuner et al. (18)		2018	Turkey	131	-	-	58	120	-	-	-	298	95	83	10
Our Study		2021	Turkey	59	45.64±11.34	-	27	27	4	1	-	97	15	80	2
Singh et al. (30)	Tibia	2015	India	70	-	-	70	-	-	-	-	70	70	-	-
Sinha et al. (35)		2017	India	50	-	-	-	-	-	-	-	70	59	11	-
Udaya Kumar et al. (36)		2017	India	151	R: 32.09±3.76 L: 32.12±3.13	-	131	18	2	-	-	173	-	-	-
Zahra et al. (2)		2018	Turkey	91	L: 32.5±4.6 R:32.39±2.21	1	88	2	-	-	-	92	66	26	-
Chavda et al. (8)		2019	India	70	R: 33.8±5.43 L: 33.5±5.56	-	70	-	-	-	-	70	45	25	-
Ghosh et al. (37)		2020	India	172	-	-	172	-	-	-	-	172	161	2	-
Our Study		2021	Turkey	49	33.23±6.31	-	46	3	-	-	-	52	37	15	-
Zahid et al. (38)	Fibula	2015	Pakistan	168	49.03±9.88	-	164	4	-	-	-	172	1	156	10
Jayaprakash et al. (32)		2016	India	50	43.73±9.69	4	45	1	-	-	-	47	5	39	3
Zahra et al. (2)		2018	Turkey	67	L: 49.51±8.36 R: 46.02±7.46	14	52	1	-	-	-	54	1	53	-
Gaharwar ve Sinha (21)		2020	India	100	-	-	78	22	-	-	-	122	122	-	-
Our Study		2021	Turkey	22	47.14±14.37	3	18	1	-	-	-	20	-	19	1

NF: Nutrient foramen

While there are studies stating that mostly single NF is observed in the femur, it has also been reported that double NF can be found (Table 4) (2,17,18). Result of study, the number of femur with single and double NF was equal (Table 4).

When the localization of the NF in the clavicle and humerus was examined, our results were similar to the results of previous studies (Table 3). Result of this study, most of the NF in the radius and ulna are localized in the middle 1/3 of the bone, while there are studies in the literature in which the NF is mostly localized in the proximal 1/3 of the bone (Table 3) (19,20). This strengthens the likelihood of differences between populations.

The present study, it was observed that the NF in the tibia was mostly localized in the proximal 1/3 of the bone, and the NF in the femur and fibula were localized in the middle 1/3 of the bone, similar to the results of other studies, except for two studies we encountered (Table 4) (18,21).

There are studies reporting that NF in the clavicle is mostly located on the posterior and lower surface of the bone (12-16). Result of this study, the NF in the clavicle was most frequently observed in the inferior surface, and the NF was also found in the superior surface and anterior of the bone. As in our study, there is a study reporting the NF located in the superior surface and anterior of the bone (13).

In previous studies, the most common anatomical location of NF in the humerus was the anteromedial surface, as in our study, while a study we encountered reported the most common anatomical location of NF as the medial border (22-26).

In the radius we examined, the most common anatomical location of NF was on the anterior surface, similar to the results of other studies. We encountered the NF also in the interosseous border in the current study, differently from the literature (7,27). In the ulna we examined, the most common anatomic location of the NF was the anterior surface, as in previous studies (20,24-26). While there are studies indicating the NF in the anterior border and medial surface of the ulna, we did not encounter the NF in the anterior border and medial surface in our study (27-29).

Studies in the literature have indicated that NF in the femur is mostly located on the posterior surface, although there are differences in localization compared to the linea aspera (2). The current study, we also found 1 NF in the anterior surface, although the NF in the femur was mostly found in the posterior surface. The present study, similar to the results in the literature, while the NF in the tibia was mostly found in the posterior surface, differently, the NF was found in the anterior of the bone (2,8,30,31). It has been reported that the NF in the fibula is most frequently observed in the posterior surface (2,21,32). Result of this study, the most common anatomic location of the NF in the fibula was the medial surface. We think that this is due to differences between and within populations.

Similar to the results in the literature, in the present study, the NF in the clavicle was mostly directed toward the acromial end (12). It has been reported that NF in the humerus is mostly directed distally (7,22-25). The current study, it was observed that the NF in the humerus was mostly directed distally, while there was also NF directed proximally. Previous studies have reported that all of the NF in the radii examined are directed proximally. On the other hand, in our study, although most of the NF were proximally directed, there were also NF directed distally (19,27). Similar to the results in the literature, all of the NF in the ulna we examined in the present study were proximally directed. Furthermore, another study reported that it was directed distally and horizontally (20,27-29).

The present study, as in other studies, the NF in the femur was mostly directed proximally. Although it has been reported that there is horizontally directed NF in the femur, we did not find any NF directed horizontally in our study (2). However, we encountered one distally directed NF. The distally directed NF was the third NF in the same bone. As in previous studies, although the NF in the tibia and fibula were mostly directed distally, there were also NF directed proximally (2,8).

Our study had some limitations. These are the low number of bones we examined and not knowing the age and sex of bones and the existence of metabolic pathologies (such as osteoporosis) that would affect the bone structure.

CONCLUSION

In addition to the fact that most of the data in the literature are similar to our study, it also draws attention that there are differences. Due to the results we obtained in the present study, we think that the data on the NF may differ between populations. This reveals that the NF should be examined in more studies, and the literature should be expanded in this field. There are few studies on the NF that examine the bones of the upper and lower limbs together and make comparisons between populations. Therefore, we think that our study will enrich the limited literature on this subject and contribute to clinicians.

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MEDICAL RECORDS-International Medical Journal

Research Article

Diffusion MRI Evaluation of Vitreous Humor Changes in Diabetic Retinopathy Patients

Diyabetik Retinopatili Hastalarda Humor Mizah Değişikliklerinin Difüzyon MRG ile Değerlendirilmesi

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Abstract

Aim: The objective of this study was to use diffusion-weighted imaging (DWI) to determine changes in the vitreous humor in diabetic retinopathy patients.

Materials and Methods: All diabetic retinopathy patients over the age of 18 who had brain diffusion magnetic resonance imaging between May 1, 2019, and May 1, 2021, and whose images were available in the radiological information system were retrospectively scanned on our database. The study included 51 diabetic retinopathy patients and 51 non-diabetic control group patients. The t-test was used to compare the values of the vitreous humor apparent diffusion coefficient (ADC) in diabetic retinopathy patients with control group patients.

Results: Patients with diabetic retinopathy had significantly higher minimum, median, and maximum ADC mean values in the right eye than the control group (p=0.011, p=0.007, p=0.026). Patients with diabetic retinopathy had significantly higher median and maximum ADC averages in the left eye than those in the control group (p=0.020, p=0.012). Although the mean minimum ADC of the left eye was higher in diabetic retinopathy patients than in the control group, the difference was not statistically significant (p=0.387).

Conclusion: Because of the rise in ADC values in diabetic retinopathy patients compared to the normal control group, we detected that DWI could be used to assess if the vitreous humor is affected in this disease.

Keywords: Diabetic Retinopathy, diffusion MRI, vitreous humor, eye

Öz

Amaç: Bu çalışmada, diyabetik retinopatili hastalarda vitreus humor 'de oluşan değişiklikleri difüzyon ağırlıklı görüntüleme (DAG) ile belirlemeyi amaçladık.

Materyal ve Metot: 01 Mayıs 2019 ile 01 Mayıs 2021 tarihleri arasında beyin difüzyon manyetik rezonans görüntüleme yapılmış ve görüntüleri radyoloji bilgi sisteminde bulunan, 18 yaşından büyük olan tüm diyabetik retinopati hastaları veri tabanımızda retrospektif olarak tarandı. Görüntüsü artefaktlı olanlar, vitreus kanaması, glokom, kontrolsüz hipertansiyon olan hastalar çalışma dışında bırakıldı. Sonuçta, 51 diyabetik retinopati hastası ve diyabet hastası olmayan 51 kontrol grubu hastası çalışmaya dahil edildi. Diyabetik retinopatili hastalar ile kontrol grubu hastalarının vitreus humor görünür difüzyon katsayısı (ADC) değerleri t testi ile karşılaştırıldı.

Bulgular: Diyabetik retinopatili hastaların sağ gözde minimum, ortanca ve maksimum ADC ortalamaları kontrol grubu hastalarına göre anlamlı yüksekti (p=0,011, p=0,007, p=0,026). Diabetik retinopatili hastaların sol gözde ortanca ve maksimum ADC ortalamaları kontrol grubu hastalarına göre anlamlı yüksekti (p=0,020, p=0,012). Sol göz minimum ADC ortalaması diyabetik hastalarda kontrol grubuna göre yüksek olmakla birlikte istatistiksel olarak anlamlı değildi (p=0,387).

Sonuç: DAG ile diyabetik retinopatili hastalarda ADC değerlerinde normal kontrol gurubuna göre artış olması nedeniyle vitreus humor 'un bu hastalıkta etkilenip etkilenmediğinin değerlendirilmesinde kullanılabileceğini saptadık.

Anahtar Kelimeler: Diyabetik Retinopati, difüzyon MRG, vitreus humor, göz

INTRODUCTION

The vitreous makes up about 80% of the volume of the eye and is the transparent part between the lens and the retina. Its structure includes hyaluronic acid, type 2 collagen, and water molecules (1).

Diabetes results in capillary basement membrane thickening, loss of intramural pericytes, and endothelial cell damage. The increase in erythrocyte and thrombocyte aggregation and high fibrinogen levels also contribute to vascular occlusion. Thus, developing capillary and

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arteriolar occlusion creates retinal hypoxia, which drives the retina to release angiogenic factors, which cause the formation of new vessels in various areas of the eye (retina, optic disk, iris, anterior chamber angle). These veins are abnormal veins that bleed easily. Moreover, microaneurysms and increased permeability result from cell loss in the retinal vessel wall, and retinal macular edema develops due to microaneurysms and deterioration of the internal blood-retinal barrier (2).

Diffusion-weighted imaging (DWI) is a method of magnetic resonance imaging (MRI) based on the random motion of water molecules. The amount of diffusion is influenced by the adjacent environment and the anatomical and physiological structures. Furthermore, the amount of diffusion and the tissue's cellular density have an inverse relationship. When cell density rises, diffusion is limited, and a low signal is acquired in DWI, whereas when cell density lowers, diffusion increases and a high signal is obtained in DWI. The apparent diffusion coefficient (ADC) values and region of interest (ROI) from ADC maps in diffusion MRI are used to obtain quantitative values (3,4). Tight junctions connect the endothelium on the inner surface of retinal vessels to each other. Large and non-carrier molecules are prevented from leaking into the retina and vitreous by these tight junctions, which operate as barriers. In diabetic retinopathy, this barrier, known as the blood-retina barrier, is disrupted, resulting in leakage into the retina and vitreous (5).

The structural content of the vitreous humor changes in patients with diabetic retinopathy (DR); these changes can be assessed with DWI. This study aimed to determine the changes in ADC values due to retinopathy in the vitreous humor.

MATERIAL AND METHOD

51 (29 female, 22 male) patients diagnosed with diabetic retinopathy who underwent diffusion MRI for any reason between May 01, 2019, and May 01, 2021, at Malatya Training and Research Hospital were included in the study. Moreover, 51 (29 female, 22 male) patients from the control group were included in the study, randomly selected at the same dates and matched for age and gender and underwent diffusion MRI for any reason. All patients were evaluated with a standard head-neck coil with a 1.5 T MRI unit. The system generated ADC maps automatically from images with b values of 50 and 1,000. Two radiologists were blinded to the patients' clinical information when evaluating MR images. The minimum, median, and maximum ADC values were measured by placing ROI on the vitreous humor (average 20 mm^2 in all patients) in the right and left orbit (Figure 1).

Statistical analysis

For statistical analysis, the SPSS version 22.0 program was used. For comparisons, the t-test was used. Statistical significance value was accepted as $p<0.05$.

Ethical approval, This retrospective study received ethical approval from the Malatya Turgut Özal University Clinical Research Ethics Committee. Decision no: 2021/90.

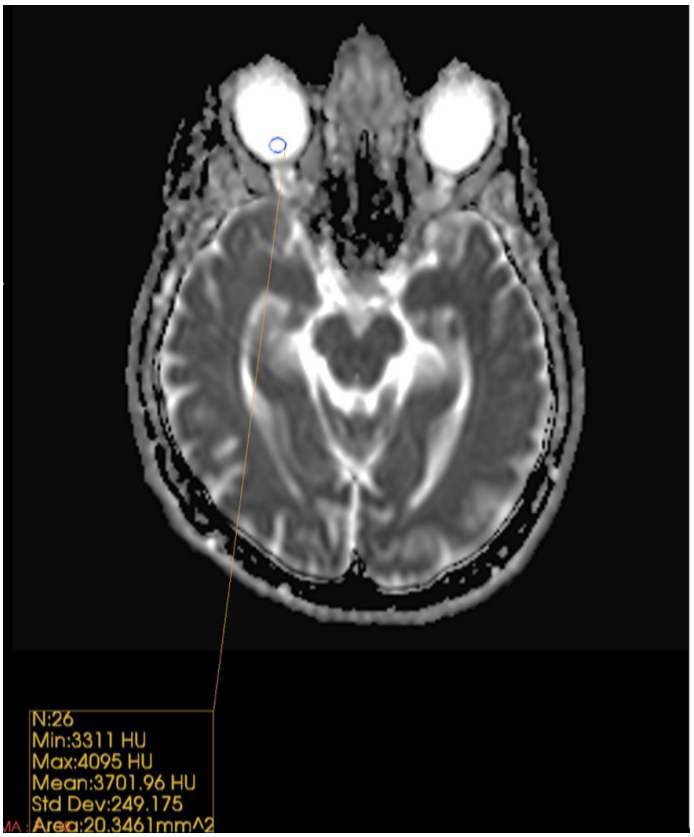

Figure 1. The minimum, median, and maximum ADC values were measured by placing the ROI on the vitreous humor in orbit

RESULTS

58 (56.9%) of the patients were women. The patients' ages ranged from 41 to 88 years old, with a mean of 63.06±9.90. Patients with diabetic retinopathy had significantly higher minimum, median, and maximum ADC mean values in the right eye than the control group ($p=0.011$, $p=0.007$, $p=0.026$).

Table 1. Average ADC values of patients with Diabetic Retinopathy and the control group

VITREOUS HUMOR (VH) ADC	Patients with retinopathy (n=51) Average ADC±SD	Control group (n=51) Average ADC±SD	p
Right VH Min. ADC	2957.6±268.1	2813.9±180.6	0.011
Right VH Avg. ADC	3229.3±281.7	3013.0±193.8	0.007
Right VH Max. ADC	3550.3±319.7	3219.4±234.1	0.026
Left VH Min. ADC	2875.6±214.6	2810.3±189.0	0.387
Left VH Avg. ADC	3167.0±245.5	3006.6±181.9	0.020
Left VH Max. ADC	3477.0±310.4	3199.9±224.5	0.012

SD: Standard deviation; p values were calculated by t-test.
Max.: Maximum, Min.: minimum, Avg.: average

Patients with diabetic retinopathy had significantly higher median and maximum ADC averages in the left eye than those in the control group (p=0.020, p =0.012). Although people with diabetes had a higher mean minimum ADC of the left eye than the control group, this was not statistically significant (p=0.387). Table 1 shows the ADC averages and p-values.

DISCUSSION

Diabetic retinopathy is the leading preventable and/or treatable cause of blindness worldwide in the 20-65 age group. It is one of the most severe complications of diabetes mellitus. The risk of blindness is increased 25 times more compared with the general population (6). Blindness in DR patients is frequently caused by vitreous hemorrhage, tractional retinal detachment, or diabetic macular edema (7).

At DR, pathological changes are observed with increased leukocyte adhesion to vessel walls, death of pericytes, and thickening of the vascular basement membrane. The weakening of endothelial cell connections causes increased vascular permeability. If the fluid leakage is large enough, lipid accumulation in the retina may occur (8). DWI can be used to assess changes in the permeability of cell membranes, changes in water content, such as cell lysis, and morphological and physiological changes in tissues (9). DWI can also be used to assess the microstructural structure of tissues (10). In our study, we assume that DR -related changes in vitreous humor can be detected by DWI.

Our research discovered that patients with DR have high ADC values in vitreous humor in all measurements in the right eye and high maximum and median values in the left eye. Although the minimum ADC value was higher in the left eye than in the normal group, it was not statistically significant. This, we think, is due to the limited number of patients that we have. We think that the increased vascular permeability at DR causes more fluid to enter the vitreous and, accordingly, ADC levels increase.

A low ADC value indicates limited or restricted diffusion and is observed in highly cellular tissues. On the other hand, a high ADC value is observed in structures with relatively free diffusion of tissue fluid, with low cellularity, or in cystic structures (11).

Aldose reductase converts glucose to sorbitol in hyperglycemia. Therefore, sorbitol concentration in the cell may increase to a high level. Sorbitol can lead to an increase in osmolarity (12). We believe that the high ADC values we measured in our study are due to impaired vascular permeability, as more fluid leaks into the extracellular space in DR patients.

DWI is known to be used to diagnose endophthalmitis, optic nerve infarction, orbital cellulitis, pseudotumor, differentiation of lymphoid lesions, diagnosis of orbital abscesses, and characterization of retinoblastoma in pediatric patients, and differentiation of benign and malignant ocular tumors (13). DWI can also be used to assess the microstructural structure of the tissue, so changes due to DR can be detected with DWI. Our research discovered that DWI could be used to evaluate changes in the vitreous humor caused by an increase in ADC values in patients with DR compared to the control group.

Our study's main limitations are the insufficient number of patients and the retrospective character of the study.

CONCLUSION

Using the values from ADC may be essential to understand the structural changes in the vitreous humor due to DR, provide better treatment, and follow up on treatment. More comprehensive studies are still needed on this topic.

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

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MEDICAL RECORDS-International Medical Journal

Research Article

Early Diagnosis of Diabetes Mellitus by Machine Learning Methods According to Plasma Glucose Concentration, Serum Insulin Resistance and Diastolic Blood Pressure Indicators

Plazma Glukoz Konsantrasyonu, Serum İnsülin Direnci ve Diastolik Kan Basıncı Göstergeleri ile Makine Öğrenme Yöntemleri Kullanılarak Diyabet Hastalığının Erken Tanısı

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Abstract

Aim: It is a known fact that diabetes mellitus is increasing frequently and triggering many different diseases. Therefore, early diagnosis of the disease is important. This study was trying to predict the early diagnosis of the disease, according to machine learning methods by measuring plasma glucose concentration, serum insulin resistance, and diastolic blood pressure.

Material and Methods: In the study, the public dataset from a website consists of 768 samples and nine variables. Three different machine learning strategies were used in the early diagnosis of diabetes mellitus (Support Vector Machine, Multilayer Perceptron, and Stochastic Gradient Boosting). 3 repeats and 10 fold cross-validation method was used to optimize the hyperparameters. The model's performance parameters were evaluated based on accuracy, specificity, sensitivity, confusion matrix, positive predictive value (precision), negative predictive value, and AUC (area under the ROC curve).

Results: According to the experimental results (the criteria of accuracy (0.79), sensitivity (0.57), specificity (0.91), positive predictive value (0.79), negative predictive value (0.80), and AUC (0.74)) the Support Vector Machine was more successful than other methods.

Conclusion: Plasma glucose concentration, serum insulin resistance, and diastolic blood pressure markers are important indicators in the early diagnosis of diabetes mellitus. In this study, it was seen that these markers make a significant contribution to the early diagnosis of diabetes mellitus. However, it has been observed that these indicators alone will not be sufficient in the early diagnosis of the disease, especially since age, body mass index and pregnancy contribute significantly.

Keywords: Diabetes mellitus, plasma glucose concentration, serum insulin resistance, diastolic blood pressure, machine learning

Öz

Amaç: Diyabetin sıklıkla arttığı ve bir çok farklı hastalığı tetiklediği bilinen bir gerçektir. Bu nedenle hastalığın erken teşhisi önemlidir. Bu çalışmada plazma glukoz konsantrasyonu, serum insülin direnci ve diyastolik kan basıncı göstergelerinden, makine öğrenmesi yöntemlerine göre hastalığın erken teşhisi öngörülmeye çalışılmıştır.

Materyal ve Metot: Çalışmada, bir web sitesinden alınan halka açık veri seti 768 örnek ve dokuz değişkenden oluşmaktadır. Diyabetin erken teşhisinde üç farklı makine öğrenme stratejisi kullanıldı (Destek Vektör Makineleri, Çok Katmanlı Algılayıcılar ve Stokastik Gradyan Artırma). Hiper parametre optimizasyonu için 3 tekrarlı 10 kat tekrarlı çapraz doğrulama yöntemi kullanıldı. Modellerin performansı doğruluk, seçicilik, duyarlılık, karışıklık matrisi, pozitif tahmin değeri (kesinlik), negatif tahmin değeri ve AUC (ROC eğrisi altında kalan alan) temel alınarak değerlendirilmiştir.

Bulgular: Deneysel sonuçlara göre (doğruluk (0.79), duyarlılık (0.57), özgüllük (0.91), pozitif tahmin değeri (0.79), negatif tahmin değeri (0.80) ve AUC (0.74) kriterleri), Destek Vektör Makineleri diğer yöntemlere göre daha başarılı çıkmıştır.

Sonuç: Diyabet hastalığının erken tanısında plazma glukoz konsantrasyonu, serum insülin direnci ve diastolik kan basinci belirteçleri önemli göstergelerdir. Bu çalışmada da bu belirteçlerin diyabetin erken tanısında önemli katkı sağladığı görülmüştür. Ancak tek başlarına bu göstergelerin hastalığın erken tanısında yeterli olmayacağı özellikle yaş, beden kitle indeksi ve gebeliğin de önemli derecede katkı sağladığı görülmüştür.

Anahtar Kelimeler: Diyabet hastalığı, plazma glukoz konsantrasyonu, serum insülin direnci, diyastolik kan basıncı, makine öğrenme

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INTRODUCTION

Diabetes mellitus is still a very common disease in the world, negatively affecting the daily lives of patients, and continues to be a serious economic burden, especially in countries where obesity is common. It is estimated that diabetes affects 246 million people in the world and about 20-30 million of these patients are affected by symptomatic diabetic polyneuropathy. Considering the increase in obesity rates and the associated increase in type 2 diabetes prevalence, this number will double by 2030 is expected. In young patients with type 1 diabetes, polyneuropathy may occur within a few months of the onset of the disease as a result of poor control of diabetes. Studies show that intense diabetes control reduces the prevalence of clinical neuropathy by 60-69%. Therefore, early diagnosis is very important (1-3).

Machine learning is a system that studies the creation and operation of algorithms that can learn and predict data. Such algorithms work by constructing a model to make and predict decisions based on sample input (1).

The findings of Support Vector Machine (SVM), Multilayer Perceptron (MLP) and, Stochastic Gradient Boosting (SGB) approaches from data mining algorithms for the early diagnosis of diabetes mellitus are presented in this paper.

MATERIAL AND METHOD

Dataset

The dataset used in the study was carried out on the Pima Indians Diabetes Database (PIDD) dataset (4) in the Kaggle database. The data set contains 768 samples and nine variables. These variables are age, pregnancies (PR), plasma glucose (PG) concentration, diastolic blood pressure (BP), tri-fold thick, resting electrocardiography results, serum insulin, body mass index (BMI), Diabetes pedigree (DP) function, and diabetes. A detailed description of the variables is given in Table 1. Ethics committee approval is not required for this study. In this study, the R programming language, and SPSS used.

Table 1. The Detailed Explanation of the Variable

Variables	Abbreviation	VariableType	Role
Age (year)	-	Numerical	Input
Pregnancies	PR	Numerical	Input
Diastolic BP(Blood Pressure (mm/Hg)	BP	Numerical	Input
PG (Plazma Glukoz) Concentration	PG	Numerical	Input
Skin-Fold Thick (mm)	SFT	Numerical	Input
Serum Insilun (mu U / m)	SI	Numerical	Input
Body Mass Index	BMI	Numerical	Input
DP (Diabetes Pedigree) Function	DP	Numerical	Input
Diabet	-	Categorical	Output

Preprocessing of the Data Set

The data set was included in the analysis without splitting. SVM, MLP, and SGB algorithms were used for the classification task. 65 rows with extreme/outlier values were detected in our data set and deleted (figure 1). The optimal hyper-parameters of each model were determined by grid search with 3 repeats and 10-fold repeated k-fold cross-validation. The created models were evaluated with accuracy, specificity, sensitivity, confusion matrix, negative predictive value, positive predictive value, and AUC.

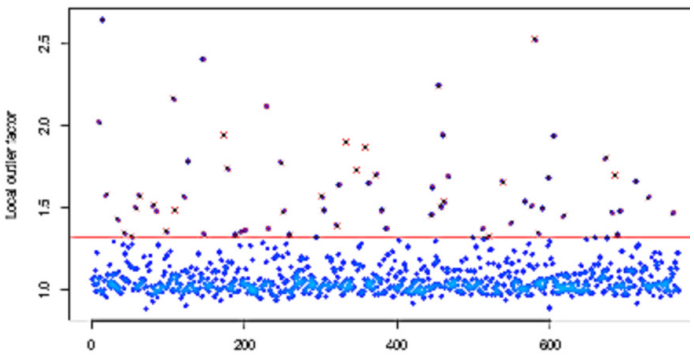

Figure 1. Extreme/Outlier Values Analysis

Support Vector Machine (SVM)

Support Vector Machine is a set of supervised learning algorithms that detect patterns. Makes model estimation by running the support vector machine at each stage of the smallest optimization problem involving two lagrangian multipliers (5). SVM generates linear and nonlinear estimates of the target variable in classification and estimation problems with different kernel functions to determine the best planes. Determining the optimal kernel function is an important criterion for the accuracy performance of the model (6,7). Kernel functions such as radial, linear, Laplace are used in the SVM algorithm. Thanks to its optimized technique, SVM offers optimal solutions in large and complex data sets (8,9). The hyperparameters of the SVM classifier are C, sigma, and interaction depth. The hyperparameters of models are presented in Table 2.

Stochastic Gradient Boosting (SGB)

Boosting is an ensemble-based data mining meta-algorithm that improves the performance of prediction and classification of any learning approach (10). Stochastic gradient boosting (SGB) is a data processing approach introduced by (11). SGB is a crucial technique accustomed to creating forecasts and classification tasks and adjusting forecast performance through the appliance of preprocessing procedures. SGB was implemented in R by the Generalized Boosted Regression Models (GMB) Package (12). The hyperparameters of the SGB classifier are n.trees, shrinkage, and n.minobsinnode. The hyperparameters of the model are illustrated in table 2.

Multilayer Perceptron (MLP)

The most commonly used artificial neural network model

is the MLP network, which has also been comprehensively analyzed and lots of learning algorithms are developed from it (13). MLP is a feed-forward, fully neural network model that maps input data set to a convenient output set by adjusting the weight between internal data nodes. The hyperparameters of the MLP classifier are hiding the layer size, activation, alpha, and learning rate. The hyperparameters of the model are illustrated in Table 2.

Table 2. The Hyper Parameters of Models

Model	Hyper Parameters	Range	Number of Combination
SVM	C	(2-5–215)	300
	Sigma	(2-15–23)	
	Interaction Depth	(1–100)	
SGB	n.treesa	(50–1500)	3000
	Shrinkage	0.1	
	n.minobsinnodeb	20	
MLP	Hidden layer size	(50–100)	100
	Alpha	(0.0001, 0.05)	
	Learning rate	(constant-adaptive)	

[a] A total number of trees.
[b] A minimum number of observations in the trees terminal nodes.

RESULTS

Statistical Analysis

Quantitative data were summarized as the arithmetic means with standard deviation, qualitative data as numbers by percentage, and median with min and max values. After suitability of the data to multiple normal distributions, the difference between the groups in normally distributed groups was examined by t-test in independent samples and the Mann-Whitney U test for variables that didn't normally distribute. For statistical analysis, IBM SPSS version 22 (14) and R Studio version 1.1.463 (15) were used. In the diabetes data set, the health status of individuals is shown as '0' or '1'.'0' indicates that the individual does not have diabetes, and '1' indicates that the individual has diabetes. In the data set, 500 individuals are diabetic and 268 individuals are not diabetic. The distributions of the features in the data set are presented in Figure 2 and the correlation matrix in Figure 3. In Figure 3, when the relationship of the features with the class label (cl) is examined, it is observed that diabetes mellitus is associated with the highest (0.47) PG concentration, followed by BMI, age, and PR.

The performance metrics of each model are shown table 3. The accuracy values were 0.79 for SVM, 0.78 for SGB and 0.65 for MLP. The sensitivity values were 0.57 for SVM, 0.55 for SGB and 0.00 for MLP. The specificity values were 0.91 for SVM, 0.91 for SGB and 1.00 for MLP. The positive predictive values were 0.79 for SVM, 0.76 for SGB and non-computed for MLP. The negative predictive values were 0.80 for SVM, 0.80 for SGB and 0.65 for MLP. The AUC values were 0.74 for SVM, 0.73 for SGB and 0.50 for MLP.

Table 4 and figure 4 presents the relative importance values of the best classifier model (SVM) which was chosen by the majority of measurements metrics. The furthest interrelated variables with diabetes mellitus were sorted from highest to smaller by the significance values. Figure 5 presents the model's comparison of ROC curves. Figure 6 illustrates the confusion matrix for the best model (SVM).

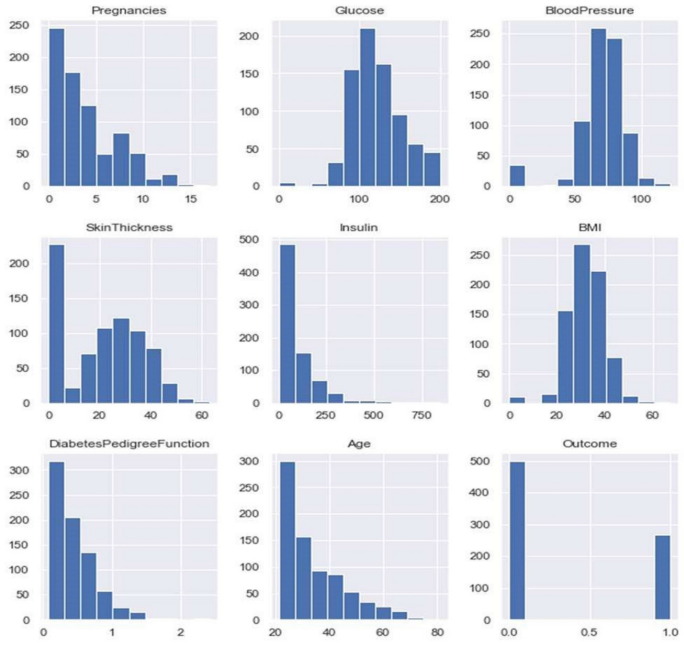

Figure 2. Distributions of Variables

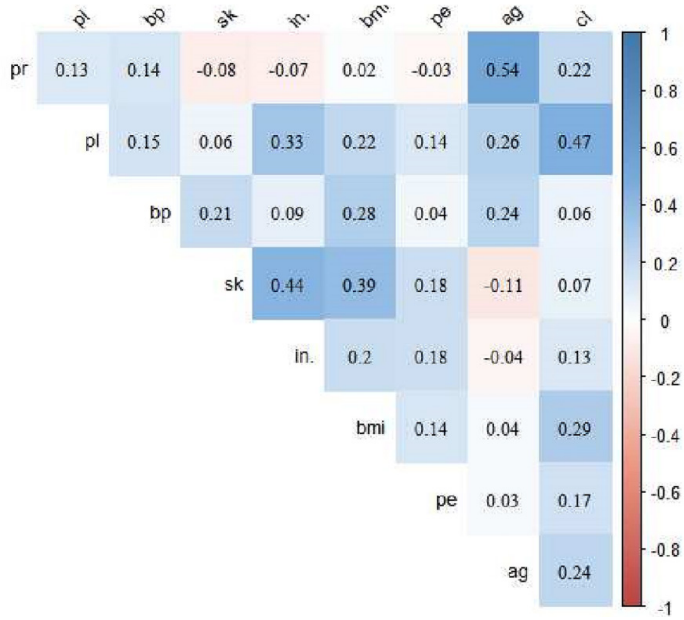

Figure 3. Correlation Matrix

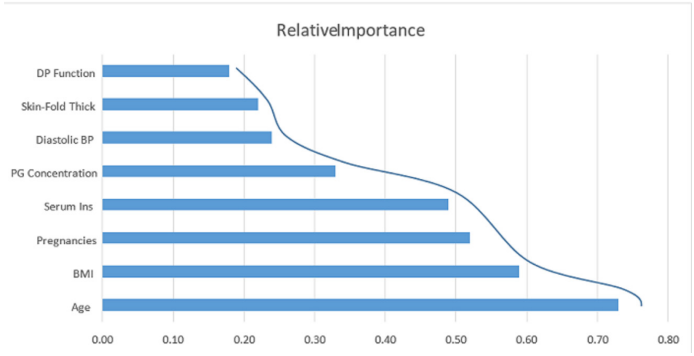

Figure 4. The Variables Importance Values of the Best Classifier

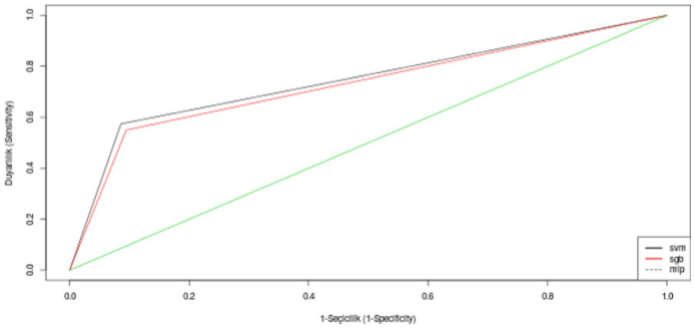

Figure 5. Comparison of ROC Curves

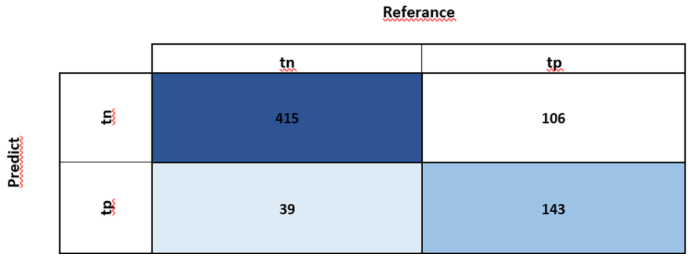

Figure 6. Confusion Matrix for Best Model

Table 3. Performance Metrics of Models

Performance Metrics	Models		
	SVM	SGB	MLP
Accuracy	0.79	0.78	0.65
Sensitivity	0.57	0.55	NaN
Specificity	0.91	0.91	1.00
Positive predictive value (Precision)	0.79	0.76	NaN
Negative predictive value	0.80	0.80	0.65
AUC	0.74	0.73	0.50

Table 4. The Variables Importance values of the Best Classifier

Variable	Relative Importance
Age	0.73
BMI	0.59
Pregnancies (PR)	0.52
Serum Insilun (SI)	0.49
PG (Plazma Glukoz) Concentration	0.33
Diastolic BP (Blood Pressure)	0.24
Skin-Fold Thick (SFT)	0.22
DP (Diabetes Pedigree) Function	0.18

DISCUSSION

Early detection of diabetes mellitus is an important medical problem. Machine learning methods have made a place for themselves in early diagnosis and planning in the field of health. Especially in chronic diseases with high costs, machine learning methods become very useful. In this study, the performances of different machine learning classification methods in predicting diabetes were compared.

According to the experimental results, the SVM was more successful than other methods according to the criteria of accuracy (0.79), specificity (0.91), sensitivity (0.57), positive predictive value (0.79), negative predictive value (0.80), and AUC (0.74).

Plasma glucose concentration, serum insulin resistance, and diastolic blood pressure markers are important indicators in the early diagnosis of diabetes mellitus. In this study, it was seen that these markers make a significant contribution to the early diagnosis of diabetes mellitus. However, it has been observed that these indicators alone will not be sufficient in the early diagnosis of the disease, especially age, BMI and pregnancy contribute significantly.

In similar studies in the literature, Bahat et al., with five different machine learning algorithms (decision tree, support vector machine, random forest, logistic regression, and k nearest neighbor) only examined the classification performances in the early diagnosis of diabetes in terms of accuracy metric. In terms of accuracy values, the decision tree was 0.79, the support vector machine was 0.72, the random forest was 0.75, logistic regression was 0.76, and the k nearest neighbor was 0.80 (16).

In his work on the impact of machine learning and feature selection on type 2 diabetes risk prediction, Riihimaa looked at the area under the ROC curve as a model performance measure. In the study, AUC values according to logistic regression and machine learning methods were found to be 0.64 and 0.85, respectively (17).

Islam et al., in their research on prediction of onset diabetes using machine learning techniques, using different machine learning methods (naiveBayess, logistic regression, multilayer perceptron, support vector machines, lazy and meta classifiers, rules, and trees). They compared classification performances in terms of accuracy, sensitivity, selectivity, positive predictive value, negative predictive value, and AUC metrics. The logistic regression model provided the highest performance with an accuracy value of 0.78 (18,19).

CONCLUSION

The use of machine learning methods in the early diagnosis of diabetes is increasing day by day. With the development of independent classifiers or ensemble learning algorithms, the number of current algorithms used in medicine is increasing. Studies to be carried out based on more than one performance measure, without being dependent on a single performance criterion will enable more meaningful comparisons to be made. In this study, an evaluation was made according to more than one performance criteria in machine learning methods and the best model was determined. In general, the model gave more successful results in separating the healthy than in separating the patients. The model is at a reasonably acceptable level according to the general criteria, but it is thought that there will be improvements in the model performance criteria to be used by increasing the number of variables. In addition, classification success can be increased by using methods that can provide more success with ensemble learning and hybrid methods.

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

Ethical approval: Ethics committee approval is not required for this study. In this study, the R programming language, and SPSS used.

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MEDICAL RECORDS-International Medical Journal

Research Article

Artificial Intelligence-based Colon Cancer Prediction by Identifying Genomic Biomarkers

Genomik Biyobelirteçleri Belirleyerek Yapay Zeka Tabanlı Kolon Kanseri Tahmini

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Abstract

Aim: Colon cancer is the third most common type of cancer worldwide. Because of the poor prognosis and unclear preoperative staging, genetic biomarkers have become more important in the diagnosis and treatment of the disease. In this study, we aimed to determine the biomarker candidate genes for colon cancer and to develop a model that can predict colon cancer based on these genes.

Material and Methods: In the study, a dataset containing the expression levels of 2000 genes from 62 different samples (22 healthy and 40 tumor tissues) obtained by the Princeton University Gene Expression Project and shared in the figshare database was used. Data were summarized as mean ± standard deviation. Independent Samples T-Test was used for statistical analysis. The SMOTE method was applied before the feature selection to eliminate the class imbalance problem in the dataset. The 13 most important genes that may be associated with colon cancer were selected with the LASSO feature selection method. Random Forest (RF), Decision Tree (DT), and Gaussian Naive Bayes methods were used in the modeling phase.

Results: All 13 genes selected by LASSO had a statistically significant difference between normal and tumor samples. In the model created with RF, all the accuracy, specificity, f1-score, sensitivity, negative and positive predictive values were calculated as 1. The RF method offered the highest performance when compared to DT and Gaussian Naive Bayes.

Conclusion: In the study, we identified the genomic biomarkers of colon cancer and classified the disease with a high-performance model. According to our results, it can be recommended to use the LASSO+RF approach when modeling high-dimensional microarray data.

Keywords: Colon cancer, microarray, genomics, LASSO, random forest, decision tree, gaussian naive bayes

Öz

Amaç: Kolon kanseri dünya genelinde en sık görülen üçüncü kanser türüdür. Kötü prognoz ve net olmayan preoperatif evreleme nedeniyle, hastalığın tanı ve tedavisinde genetik biyobelirteçler daha önemli hale gelmiştir. Bu çalışmada kolon kanseri için biyobelirteç adayı genlerin belirlenmesi ve bu genlere dayalı olarak kolon kanserini başarılı bir şekilde tahmin eden bir modelin geliştirilmesi amaçlanmıştır.

Materyal ve Metot: Çalışmada, Princeton Üniversitesi Gen Ekspresyon Projesi ile elde edilen ve figshare veri tabanında paylaşılan 62 farklı örnekten (22 sağlıklı ve 40 tümör dokusu) 2000 genin ekspresyon düzeylerini içeren bir veri seti kullanıldı. Veriler ortalama ± standart sapma olarak özetlendi. İstatistiksel analizler için bağımsız örneklerde T-testi kullanıldı. Veri setindeki sınıf dengesizliği sorununu ortadan kaldırmak için öznitelik seçiminden önce SMOTE yöntemi uygulandı. Kolon kanseri ile ilişkili olabilecek en önemli 13 gen, LASSO öznitelik seçim yöntemi ile seçildi. Modelleme aşamasında Rastgele Orman (RF), Karar Ağacı (DT) ve Gauss naive Bayes yöntemleri kullanıldı.

Bulgular: LASSO tarafından seçilen 13 genin tümü, normal ve tümör numuneleri arasında istatistiksel olarak anlamlı bir farka sahipti. RF ile oluşturulan modelde doğruluk, seçicilik, f1-skor, duyarlılık, negatif ve pozitif prediktif değerlerinin tümü 1 olarak hesaplanmıştır. DT ve Gaussian Naive Bayes ile karşılaştırıldığında RF yöntemi en yüksek performansı vermiştir.

Sonuç: Çalışmada kolon kanserinin genomik biyobelirteçlerini belirledik ve hastalığı yüksek performanslı bir model ile sınıflandırdık. Elde ettiğimiz sonuçlara göre, yüksek boyutlu mikrodizi verilerinin modellenmesinde LASSO+RF yaklaşımının kullanılması önerilebilir.

Anahtar Kelimeler: Kolon kanseri, mikrodizi, genomik, LASSO, rastgele orman, karar ağacı, gaussian naive bayes

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INTRODUCTION

According to the World Health Organization, cancer is the second leading cause of death after cardiovascular disease. Colon cancer ranks 3rd in the world in terms of incidence and is the 4th most common cancer. With the introduction of screening programs in the USA in the last 30 years, an improvement in cancer prognosis has been detected thanks to early diagnosis, and this screening program has been implemented in our country since 2009 (1,2).

Being able to perform postoperative staging and determining prognosis by staging alone emphasizes biomarkers and genetic evaluation in colon cancer. For this reason, examination of colon cancer based on genetic biomarkers is very important in the diagnosis and treatment of the disease (3).

Microarray technology has allowed the simultaneous measurement of thousands of gene expressions. Identifying disease-related biomarker candidate genes using microarray gene expression datasets and distinguishing (classifying) disease samples from non-disease samples has been an important research topic in biomedicine and medicine. However, the resulting large-scale datasets created many barriers to computational techniques. The high dimensionality problem affects most microarray gene expression datasets where dimensionality is high (up to tens of thousands of genes) and sample size is small (normally up to hundreds). Also, the high noise-to-variability ratio of microarray trials adds to the difficulties (4).

Machine learning methods are frequently used to overcome current challenges. Machine learning; it can be defined as obtaining previously unknown, valid and applicable information from data stacks through a dynamic process. In this process, many techniques such as clustering, data summarization, learning classification rules, finding dependency networks, developing predictive models, variability analysis and anomaly detection are used. With machine learning, confidential information is retrieved in database systems comprising large data stacks. This process is done using statistics, mathematical disciplines, modeling techniques, database technology and various computer programs (5,6).

Before constructing classification models in machine learning with high-dimensional microarray datasets, it is an important step to remove disease-related genes from the dataset using trait (gene) selection methods. In this way, both biomarker candidate genes can be selected and the performance of the classification models to be created will be improved (7).

In this study, we aimed to determine biomarker candidate genes for colon cancer by using gene expression dataset and to develop a classification model that can provide clinical decision support to healthcare professionals.

MATERIAL AND METHOD

Dataset

In this study, an open source colon cancer gene expression dataset obtained by Princeton University Gene Expression Project and shared in figshare database (https://figshare.com/articles/dataset/The_microarray_dataset_of_colon_cancer_in_csv_format_/13658790/1) was used (8). The dataset includes expression levels of 2000 genes from 62 different samples (22 healthy and 40 tumor tissues).

Statistical Evaluation

Data were summarized as mean ± standard deviation. Compliance with the normal distribution was done with the Kolmogorov-Smirnov test. Independent Samples T Test was used for statistical analysis. Statistical tests with a p value of less than 5% were considered significant. All statistical analyzes were performed using IBM SPSS Statistics for Windows version 26.0 (New York, USA).

Data Preprocessing and Modeling

In datasets with class imbalance problem, most machine learning techniques ignore minority class performance and therefore underperform in minority class. One approach to these datasets is to oversample the minority class and is called the Synthetic Minority Oversampling Technique, or SMOTE for short (9). In order to eliminate the class imbalance problem in the colon cancer gene expression dataset (22 normal and 40 tumor tissues), the SMOTE method was applied before feature selection. In this way, the number of samples in the groups, 40 normal and 40 tumor tissues, was equalized.

Afterwards, the 13 most important genes that may be associated with colon cancer were selected with the LASSO feature selection method. For the generalizability of the model, 80% of the data set is divided as the training set and 20% as the test set. Random Forest, Decision Trees and Gaussian Naive Bayes classification methods were used to predict colon cancer based on selected genes. The performance of the models was evaluated with accuracy, specificity, sensitivity, f1-score, negative predictive value and positive predictive value.

LASSO Feature Selection

In 1996 the LASSO method was first used by Robert Tibshirani. Regularization and property selection are the two main tasks of the method. The LASSO method puts a constraint on the sum of the absolute values of model parameters; the sum must be less than a fixed value (upper bound). To do this, the method implements a narrowing (regularization) process in which regression variables punish their coefficients, some of which reduce them to zero. During the property selection process, variables that still have a coefficient of zero after collapse are selected for the model. This operation minimizes the prediction error. In practice, the parameter that controls the power of

punishment, is of great importance. When large enough, the dimensionality is can be reduced in this manner. The larger the parameter, the more coefficients are reduced to zero. There are many advantages to using the LASSO method. First, it can provide very good forecast accuracy, since the reduction and removal of coefficients can reduce variance without a significant increase in deviation. It is especially useful when there are few observations and many variables in the data set. LASSO also helps to improve the interpretability of the model by eliminating irrelevant variables that are not associated with the response variable, so that the problem of overlearning can also be addressed (10,11).

Random Forest

The Random Forests algorithm, a community learning method, aims to increase the classification value by generating multiple decision trees during the classification process. Because it includes random sampling and improved properties of techniques in community methods, the RF method offers better generalizations and makes more valid predictions than conventional machine learning methods. The reasons for the precise estimates of the RF method are that it gives low deviation and low correlation between trees. The low amount of deviation is obtained as a result of the creation of rather large trees. By creating as many different trees as possible, a low correlation structure is achieved. Individually created classification and regression decision trees come together to form the decision forest community. The decision trees here are randomly selected subsets from the data set to which they are connected. The results obtained during the formation of the decision forest are combined to make the latest prediction. For classification, trees each leaf node is created to contain only members of one class. For regression, trees continue to divide until a small number of units remain in the leaf node (12).

Decision Trees

Decision trees (DT) consist of root nodes, branches and leaves. The leaves in the decision trees are the places where the classification occurs and the branches refer to the result. The tree is created by the division variation method from the root node to the leaf nodes. A decision node can contain one or more branches. A decision tree can consist of both categorical and numerical data. The decision tree contains two basic process steps. These operations are splitting and pruning operations (13). The most important step when creating a DT is to decide which attribute values to base it on and which branching to create. In the knowledge gain and gain ratio approach that includes entropy rules, all attributes at hand are tested subjectically and the attribute with the highest knowledge gain is selected for branching. DT are a classification method that creates a model in the form of a tree structure consisting of decision nodes and leaf nodes by classification, property, and target. The decision tree algorithm is developed by dividing the data set into smaller pieces (14,15).

Gaussian Naive Bayes

A simple structured classification based on conditional probability, which is assumed to be equal and independent of each other in the classification of all attributes based on conditional probability. The classification process is done by combining the effects of different attributes on the result. Naive Bayes classifies using statistical methods and is an important algorithm in terms of performance. The importance of qualifications is considered equal in all. The Gaussian Naive Bayes (GNB) classifier is the Naive Bayes method, which is created by assuming that the class label is a Gaussian distribution on the given property values. GNB assigns all data to the closest location. However, instead of using Euclidean distance to calculate the distance between them, it calculates by taking into account the distance from the average and the class variance (16).

RESULTS

Table I contains descriptive statistics for 13 genes selected by LASSO trait selection. When Table I is examined; all 13 genes selected by LASSO had a statistically significant difference between normal and tumor samples. Hsa.8125, Hsa.2710, Hsa.8147, Hsa.36689, Hsa.31933, Hsa.1387 and Hsa.865 were expressed lower in tumor samples, while Hsa.3306, Hsa.22762, Hsa.3016, Hsa.5392, Hsa.1410 and Hsa.2928 were expressed higher in tumor samples.

Table 1. Descriptive statistics for selected genes

Gene Name	Normal (Mean ± SD)	Tumor (Mean ± SD)	t value	p-value
Hsa.8125	2.144 ± 0.496	1.444 ± 0.442	6.87	<0.001
Hsa.2710	1.289 ± 0.392	0.89 ± 0.359	5.3	<0.001
Hsa.8147	2.092 ± 0.799	0.725 ± 0.637	9.97	<0.001
Hsa.36689	0.741 ± 0.42	-0.01 ± 0.318	9.83	<0.001
Hsa.3306	0.289 ± 0.504	1.138 ± 0.482	-8.07	<0.001
Hsa.22762	-0.242 ± 0.564	0.337 ± 0.759	-4.05	0.003
Hsa.31933	-0.107 ± 0.263	-0.475 ± 0.377	5.24	<0.001
Hsa.3016	-0.222 ± 1.074	0.962 ± 1.049	-5.16	<0.001
Hsa.5392	-1.064 ± 0.655	-0.486 ± 0.486	-4.82	<0.001
Hsa.1410	-0.794 ± 0.73	0.002 ± 0.694	-5.53	<0.001
Hsa.2928	-1.312 ± 0.563	-0.526 ± 0.518	-6.98	<0.001
Hsa.1387	0.827 ± 0.648	0.017 ± 0.779	5.4	<0.001
Hsa.865	0.45 ± 0.393	0.06 ± 0.568	3.78	0.006

SD: Standard deviation

Table II presents the results of the performance measures of the RF, DT, and GNB classification models. Specificity, accuracy, f1-score, sensitivity, negative and positive predictive value criteria obtained from the RF model were all calculated as 1. That is, the RF model correctly predicted all samples in the test set. From the DT model, all performance measures were obtained as 0.9. Finally, in the model created with the GNB method, the performance measures were found to be accuracy 0.95, specificity 1, f1-score 0.95, sensitivity 0.9, negative predictive value 0.9091, and positive predictive value 1. The RF method offered the highest performance compared to DT and GNB.

Table 2. Performance measures results for classification models

Metric	Random Forest	Gaussian Naive Bayes	Decision Trees
Accuracy	1	0.95	0.9
Sensitivity	1	0.9	0.9
Specificity	1	1	0.9
PPV	1	1	0.9
NPV	1	0.9091	0.9
F1 score	1	0.95	0.9

PPV: Positive predictive value, NPV: Negative predictive value

DISCUSSION

Since knowing the biological functions of genes is useful for knowing the origin, causes and treatment of many diseases, studies in the field of genomics have been on the agenda of the scientific world for years. In addition to their biological functions, the detection and relationships of genes in the same biological pathway bring microarray studies to the fore. Thanks to the detection of possibly related genes, the detection and treatment of diseases has become easier with the identification of gene clusters (17). Based on this information, in the current study, we developed a model that can predict the disease by identifying the genes associated with colon cancer to provide clinical decision support to physicians.

In this study, we used the LASSO feature selection method to identify colon cancer-related genes. With the LASSO method, Hsa.8125, Hsa.36689, Hsa.3306, Hsa.3016, Hsa.8147, Hsa.2710, Hsa.22762, Hsa.31933, Hsa.5392, Hsa.1410, Hsa.2928, Hsa.1387 and Hsa.865 genes may be associated with colon cancer. Some of the biomarker candidate genes we identified were in agreement with the literature. Shaik et al. showed differential expression of Hsa.8125, Hsa.36689 and Hsa.3306 genes in colon cancer (genes1). In another study, Hsa.8125 and Hsa.3306 were among 100 genes associated with colon cancer (18). Hsa.8125; it is a gene that activates RNA binding activity, is involved in nucleocytoplasmic transport, is located in the endoplasmic reticulum, nucleus and perinuclear region of the cytoplasm. Yan et al. showed that this gene, also known as ANP32A, is overexpressed in colorectal cancer patients and ANP32A levels are higher in poorly differentiated tumors (19). Velmurugan et al. reported that this gene is associated with lymph node metastasis (20).

When the relationship between the Hsa.36689 gene, whose main task is guanylate cyclase activation in the colon, and colon cancer was examined, Yang et al. identified this gene among the top 5 most related genes (21). The Hsa.3016 and Hsa.8147 genes that we detected were also detected as the other genes with the highest frequency in this study.

The Hsa.3306 gene is a gene that plays a role in cell proliferation and is increased in cancer. In another study examining the colon gene data set in the literature, it was identified as one of the ten most closely related genes among 2000 genes due to its association with colon cancer. Among the genes detected in this study, Hsa.8125, one of the genes we detected, is also included. It has been shown that this gene, whose functions are important in the construction of intestinal villi, increases in normal cells and decreases in colon cancer cells (22).

Hsa.8147, also known as the desmin gene, is the gene responsible for the production of desmin, a smooth muscle-type intermediate filament protein expressed by smooth muscle cells, but also in fibrotic tissue in wound healing and tumor 'desmoplastic' stroma. Desmin also surrounds the vasculature by being produced by pericytes during angiogenesis in capillaries. It also plays a role in angiogenesis in cancer tissue. Studies have shown an increase in desmin expression in advanced cancer patients (23). In a study conducted in patients with gallbladder cancer, down-regulation of the desmin gene was detected (24).

The Hsa.3016 gene, which we have observed to be strongly associated with colon cancer, is one of the genes responsible for coding the S-100P protein. S100 proteins are involved in many events such as regulation of calcium homeostasis, cell proliferation, apoptosis, and cell migration. The S100 protein family plays a role in many stages of cancer formation and progression. S-100P acts as an inducer of metastasis, overexpression of S-100P increases the expression of S-100A6 and Cathepsin D, which are involved in cellular invasion. Furthermore, S100P promotes transendothelial migration of tumor cells (25).

The Hsa.2710 gene is one of the genes responsible for making Fibulin-1, a secreted glycoprotein that is included in the fibrillar extracellular matrix. It is involved in cell adhesion and migration along protein fibers within the extracellular matrix (ECM). Considered to have a role in cellular transformation and tumor invasion, it acts as a tumor suppressor (26). In the study of Xu et al. , it was shown that fibulin downregulation is associated with colorectal cancer (27).

Nucleolin; it is a multifunctional protein that is also found in the nucleolus, nucleoplasm, and cytoplasm. Hsa.22762 is one of the genes involved in the synthesis of nucleolin.

It is involved in the regulation of translation and stability of oncogenic mRNAs in the nucleoplasm. In our study, the presence of this gene was found to be significantly related in colon cancer patients. It has also been shown in other studies that nucleolin is overexpressed in many cancer types such as stomach, pancreatic, breast, cervix, prostate cancers, leukemias, melanomas and colorectal cancers (28).

The Hsa.31933 gene, which we detected in our study, is one of the genes that helps Autographa californica multiple nuclear polyhedrosis virus (AcMNPV), which is from the Baculovirus family, to successfully initiate the expression of viral genes by preparing the host environment and controlling the subsequent viral gene expression like other DNA viruses to infect their hosts. Viral genes, which are expressed immediately after infection, play a critical role in the early infection process; Hsa.31933 (Immediate-Early Regulatory Protein IE-N gene) is one of these genes. AcMNPV has been studied as a gene therapy vector. In a study by Ono et al., they determined AcMNPV induces antitumor acquired immunity; they showed AcMNPV can act as an effective immune-inducing virus and eukaryotic expression vector for gene carrier and has the potential to be a tumor therapy agent (29).

In another study, recombinant DNA obtained with this virus enabled the production of a natural antigen associated with carcinoma in mice (30). Although there are no studies related to this virus DNA in colon cancer yet, the data in our study showed that there is a strong relationship between colon cancer and this gene. We think that meaningful results can be obtained as a result of the use of AcMNPV as a vector with more comprehensive studies on the treatment of colon cancer.

The Hsa. 5392 gene is also known as ribosomal protein L24 (RPL24). It is one of the genes responsible for the expression of ribosomal proteins. It encodes the ribosomal protein L24, a homolog of the cytosolic RPL24 found in higher eukaryotes. Studies have been conducted on the overexpression of a number of ribosomal protein genes in human tumors and their contribution to tumorigenesis (31).

Hsa.1410 is the gene responsible for the synthesis of the eukaryotic translation initiation factor eIF-2. The role of protein synthesis changes is important in cancer development and progression. Studies show that ribosomal protein synthesis plays a direct role during tumor initiation. The translation initiation process is the rate-limiting step of protein synthesis in eukaryotes, and a group of eukaryotic translation initiation factors (eIFs) are involved. In previous studies, it has been shown that a significant increase in eIF3 subunits, eIF3A, eIF3B and eIF3M overexpression, which is one of the translation initiation factors, in colorectal cancer patients, and eIF4 subunits, of which eIF3C is an oncogene, are also increased in cancer cells (32).

In studies, eIF2a expression was described as transiently increased in normal cells, whereas constitutive overexpression indicated tumor initiation and progression. Golob-Schwarzl et al., they also showed that eIF2 is overexpressed in colorectal cancers (32).

Among the genes we determined, Hsa.2928 is the mRNA gene responsible for the expression of P-cadherin. Cadherins are calcium-dependent cell adhesion proteins that provide cell architecture and integrity, and their degradation is often associated with human cancer (33). Neo-expression or up-regulation of placental cadherin (P-cadherin) has been reported in a variety of carcinomas, including colorectal and bladder carcinomas (34).

The Hsa.1387 Human 11 beta-hydroxysteroid dehydrogenase type II mRNA gene is a gene that has a strong association with colon cancer and has been found to be associated with colon carcinomas. 11 beta-Hydroxysteroid dehydrogenase type II enzyme (11 beta HSD2), which is also located in the colon, which has an important role in water and electrolyte homeostasis, gives specificity to the mineralocorticoid receptor (35).

MAP kinases, also known as (ERKs) encoded by the Hsa.865 (ERK-1, M84490) gene, are regulated by extracellular signaling and act in a signal cascade that regulates various cellular processes such as proliferation, differentiation and cell cycle through the action of extracellular signals. The tumor suppressor pathway is stimulated by ERK-1 phosphorylation (36). The relationship between colon cancer and ERK-1 has been shown in many studies (37-39). In our study, we showed its relationship with colon cancer.

In a similar study using the same data set in the literature, PCA and PLS feature extraction methods were applied and then they classified colon cancer with the support vector machine method with an accuracy of 0.9516 (40). In another study, they found that the combined use of PSO and SVM outperformed the model created with only the SVM algorithm in terms of accuracy (0.94) and performance, and was faster in terms of time analysis (41). In the current study, three models were created using RF, DT and GNB classifiers based on biomarker candidate genes determined by LASSO feature selection method. According to the performance criteria obtained, the LASSO + RF model showed the best performance by correctly classifying all samples.

CONCLUSION

In conclusion, this study identified genomic biomarkers of colon cancer and classified the disease with a high-performance model. According to the results obtained, the LASSO method gave results compatible with the literature while determining the genomic biomarkers. For this reason, genes selected with LASSO can provide clinical decision support to physicians in the diagnosis and treatment of colon cancer. In addition, it can be suggested that the LASSO+RF approach be used in modeling high-dimensional data in medicine.

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Research Article

How are Lung Volume and Respiratory Muscles Affected in Non-Severe Patients With Covid-19?

Akciğer Hacmi ve Solunum Kasları Ağır Seyretmeyen Covid-19 Hastalarında Nasıl Etkilenir?

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Abstract

Aim: Coronavirus-2019 (Covid-19) primarily affects the respiratory system, and how it affects respiratory muscles and lung volume is still not fully understood. Our study aimed to assess the time-dependent changes that may occur in lungs and respiratory muscle sizes on chest computed tomography (CT) in adult coronavirus disease 2019 (COVID-19) patients.

Material and Methods: The clinical and radiological records of 101 adult patients who had at least two non-contrast chest CT images in stage 1 (0-4 days) and stage 6 (>28 days) were collected retrospectively. ImFusion Suite program were used to calculate lung volumes, and the cross-sectional areas of the pectoral and intercostal muscles were also calculated using with "ImageJ" program.

Results: One-hundred one patients (51 females, 50.49%) were included in the study. ANCOVA revealed a significant stage*side interaction effect regarding cross-sectional area (CSA) of intercostal muscles [(p=.010; η^2p=.064)]. There was no significant difference between the two stages in terms of CSA of pectoralis major and minor muscles [(p=.314; η2p=.010), (p=.644; η^2p=.002)] respectively and lung volume [(p=.340; η^2p=.009)].

Conclusion: Covid-19 pneumonia causes an atrophy in respiratory muscles. However, it seems to have a nonsignificant effect on auxiliary respiratory muscles and lung volume. Further investigation of respiratory muscles and respiratory muscle training to reduce the risk of serious complications during viral infections are required.

Keywords: Covid-19, computed tomography, imaging, lung volume, respiratory muscles

Öz

Amaç: Coronavirus-2019 (Covid-19) öncelikle solunum sistemini etkiler ve solunum kaslarını ve akciğer hacmini nasıl etkilediği hala tam olarak anlaşılamamıştır. Çalışmamız erişkin koronavirüs hastalığı 2019 (COVID-19) hastalarında akciğer bilgisayarlı tomografisinde (BT) akciğerlerde ve solunum kası boyutlarında zamana bağlı olarak oluşabilecek değişiklikleri değerlendirmeyi amaçladı.

Materyal ve Metot: Evre 1 (0-4 gün) ve evre 6'da (>28 gün) en az iki kontrastsız göğüs BT görüntüsü olan 101 erişkin hastanın klinik ve radyolojik kayıtları geriye dönük olarak toplandı. Akciğer hacimlerini hesaplamak için ImFusion Suite programı kullanıldı ve pektoral ve interkostal kasların kesit alanları da "ImageJ" programı kullanılarak hesaplandı.

Bulgular: Yüz bir hasta (51 kadın, %50,49) çalışmaya dahil edildi. ANCOVA, interkostal kasların kesit alanına (KA) ilişkin önemli bir evre*yan etkileşim etkisi ortaya çıkardı [(p=.010; η^2p=.064)]. Sırasıyla pektoralis major ve minor kaslarının KA'sında [(p=.314; η^2p=.010), (p=.644; η^2p=.002)] ve akciğer hacminde [(p=.340; η^2p=.009)] iki evre arasında anlamlı bir fark bulunmadı.

Sonuç: Covid-19 pnömonisi solunum kaslarında atrofiye neden olur. Ancak yardımcı solunum kasları ve akciğer hacmi üzerinde önemsiz bir etkiye sahip olduğu görülmektedir. Viral enfeksiyonlar sırasında ciddi komplikasyon riskini azaltmak için solunum kaslarının daha fazla araştırılması ve solunum kas eğitimi gereklidir.

Anahtar Kelimeler: Covid-19, bilgisayarlı tomografi, görüntüleme, akciğer hacmi, solunum kasları

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INTRODUCTION

The world has been struggling with coronavirus 2019 (Covid-19), which appeared in Wuhan, and spread rapidly causing a pandemic (1). Due to the risk of rapid contagion, early diagnosis, isolation, and early treatment interventions are of great importance in these patients. The Real-Time Polymerase Chain Reaction (RT-PCR) test is used to considered the gold standard for diagnosis; however, the drawbacks of the test include false-negative results especially in the early period of the disease, the time-consuming nature of the test, and the unavailability of the test facilities in some places (2). Thus, radiological methods in identifying the characteristic findings of Covid-19-induced pneumonia are important for early diagnosis and follow-up of the patient's prognosis (3,4). Considering the adverse impact of the Covid-19 infection on the lungs, chest radiology and computer tomography (CT) are extensively used to verify lung involvement (5).

Thin-section CT is an important tool in the early detection, monitoring, and evaluating the efficiency of the treatments. At the onset of the disease, the sensitivity of the RT-PCR test and chest CT are 71% and 98%, respectively; indicating the reliability of using CT primarily in symptomatic cases with suspicious chest X-ray who are prone to develop complications (3). Some studies in the relevant literature have reported that the normal lung volume may decrease due to alveolar collapse in patients with Covid-19 pneumonia (6). Additionally, the proinflammatory effects of Covid-19 and the deconditioning during the convalescent period may lead to losses in both muscle strength and endurance (7). However, long-term follow-up studies and objective data on the subject are scarce (8).

Previously published studies have evaluated the typical and atypical CT degree of Covid-19 pneumonia (9), the time-dependent variation of CT findings (10), and the correlation between CT features and clinical characteristics (11). However, to the best of our knowledge, there are no studies investigating the time-dependent changes in lung volume and respiratory muscle sizes in Covid-19 patients, and respiratory muscle performance and lung volume are important in developing early rehabilitation strategies. For these reasons, our study aimed to determine the possible time-dependent changes that may occur in lungs and respiratory muscle sizes on the CT images of patients which diagnosed with Covid-19.

MATERIAL AND METHOD

Study plan and study population

Ethical approval for this study was obtained from the Ankara Medipol University Medical Faculty Clinical Research Ethics Committee (Registration date/no: Registration date/no: 23.09.2021/35). This retrospective study imposed no risk for the participants and informed consent was waived. Our cohort composed of 101 patients subjected to the RT-PCR test for suspicious Covid-19 infection between March 30, 2020, and June 30, 2021. To collect data, the clinical and radiological records of 101 adult non-severe Covid-19 patients retrospectively reviewed who: 1. had at least two non-contrast chest CT images in stage 1 (0-4 days) and stage 6 (28 days) (12), 2. had a positive RT-PCR test result at stage 1, and 3. had confirmed CT findings typical to Covid-19 pneumonia detected by a 20 years of experience radiologist. The severe of the COVID-19 score was determined as; development of respiratory rate more than 30 per minute, arterial partial pressure of oxygen (PaO2) / oxygen concentration (FiO2) of 300 mmHg or less, the rate of resting oxygen saturation was 93% or less, or needed mechanical ventilation (13).

Exclusion criteria were as following: 1. being younger than 18 years of age, 2. being presenting with severe COVID-19 or having a history of intubating (atrophy of the respiratory muscles is the expected finding in mechanically ventilated patients). 3. having a myasthenia gravis or similar muscle disease, 4. having distorted CT images due to major motion artifact, and 5. absence of pectoral and intercostal muscles on CT images. Lung volume (LV in cm^3) and respiratory muscles' cross-sectional areas (CSA in cm^2) were calculated on the CT images in stage 1 and stage 6.

CT protocol

CT imaging carried out using with a single inspiratory phase in a multi-detector CT scanner (Philips Ingenuity Core 128, Philips, Netherlands). Participants were instructed on breath-holding to minimize of the motion artifacts, and CT images were obtained during a single breath-hold. The mean CTDI vol was 8.4±2.0 mGy (range: 5.2-12.6 mGy). The tube voltage was 120kVp with automatic tube and from the raw data. CT images which thickness of 1.5 mm were reconstructed with a matrix size of 512×512 as axial images. No intravenous contrast medium was administered to any patient.

Measuring lung volume

We used the ImFusion Suite program to calculate lung volumes. First, the original CT images that in Digital Imaging and Communications in Medicine (DICOM) format were converted to SPM8 (3D Niftii) format using the "dcm2niigui" software. These images were then used to calculate lung volume in the ImFusion Suite program.

The steps can be summarized as following

1. "Interactive Segmentation" section was activated by selecting "Segmentation" under "Algorithms" tab in ImFusion Suite program.
2. For each image, the borders of the lungs were adjusted in the axial, coronal, and sagittal planes. These borders were painted in all 3 planes by selecting the "Paint Object" tab, to obtain a 3D representation of each lung.
3. By choosing the "Paint Background" tab, the background noise was eliminated.
4. Using the "Accept Segmentation", "Run Segmentation",

"Export as Label Map" and "Export as Annotation" tabs respectively, we completed the 3D model process.

5. Using the 3D models, the lung volumes were obtained via clicking on the "Show Segmentation Statistics" tab, then "Background" and then the "Object" tab. The whole process was repeated for the CT images of both stage 1 and 6 of each participant. The collected lung volumes (in mm^3) were converted to cm^3 and recorded.

Measuring cross-sectional areas of respiratory muscles

The measurement of the cross-sectional areas of the pectoral and intercostal muscles at the determined reference points was performed by two anatomists and a radiologist without access to clinical or laboratory findings. The mean of these three values was recorded in cm^2 for each muscle.

Cross-sectional area of the pectoral muscles

Pectoral muscles were chosen as auxiliary respiratory muscles. To calculate the cross-sectional surface area, all images saved in JPEG format were imported to the "ImageJ" program, that can be obtained free of charge from the https://imagej.nih.gov/ij/download.html. The images were created by selecting "stack image to stack" tab under the "image" tab. In the RadiAnt program, using with the "measurement and tools" tab, one of the lengths of any structure selected location on the image and measured. Then, the measured location was selected in the same section and the image was calibrated using "Set Calibrate" located under the "Analyze" tab. Then, the pectoralis major (PMa) and pectoralis minor (PMi) muscles were determined manually with the reference point of the supraaortic arteries level using the "Free Hand" button of the ImageJ program (Figure 1). The cross-sectional surface areas of the muscles were calculated on an ImageJ tab using the "M" button. The entire process was repeated on both stage 1 and stage 6 of the CT image of each participant and the results were recorded in cm^2.

Cross-sectional area of the intercostal muscles

The intercostal muscles (ICM) were chosen as the main respiratory muscles. To calculate the cross-sectional surface areas, CT images -in DICOM format- were imported to the Imfusion Suite (demo version 2.15.1) program to get a 3D view on axial, sagittal, and coronal planes. These 3D images were used to create screenshots of the sections corresponding to the right and left midclavicular line on the sagittal axis. These screenshots -saved in the Joint Photographic Experts Group (JPEG) format- were imported to the ImageJ program. Using the "straight" button in the ImageJ program, the scale bar on the image was marked and the image was calibrated using with "Set Calibrate" under the "Analyze" tab. Then, in the ImageJ program, the borders of 1, -5 ICMs were identified with manually using the "Free Hand" button. Finally, the cross-sectional surface areas of the muscles were calculated on an ImageJ tab using the "M" key (Figure 2). This process was repeated on both stage 1 and stage 6 of the CT image of each participant and the results were recorded in cm^2.

Statistical analysis

We used Statistical Package for the Social Sciences 22.0 program to evaluation. To check normality, we used visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test). For categorical data we used descriptive statistics, reported counts, and proportions and we used data measures of distribution for continuous. To compare the baseline characteristics, we used an independent t test or $\chi 2$ test was performed. To assess the changes in the cross-sectional areas (CSA) of pectoralis major, pectoralis minor, and intercostal muscles and changes in the lung volumes, a 2*2 [stage (image changes in stage 1 and stage 6) * side (right or left)] repeated measures ANCOVA was performed with stage as a between-groups factor and side as a within-subjects factor, and with demographical measures set as the covariates. When the F-ratio was significant, Bonferroni's post hoc test was used to identify the mean differences. Effect sizes were determined as partial eta squared ($\eta^2 p$). The significance level was set at $p<.05$.

RESULTS

One hundred and one participants (51 female, 50 male) with the diagnosis of Covid-19 were included in our study. Clinical and demographic characteristics of the participants are presented in Table 1. The examined stages were similar with respect to most assessed basic parameters ($p>.05$). There were significant differences in body mass index scores ($p<.001$) and the obesity rate ($p<.001$), both of which were higher in stage 1.

Table 1. Demographic and clinical characteristics of participants

Variable	Stage 1	Stage 6	p
Age	51.14±14.92	-	-
Body mass index (kg/m^2)	28.48±5.98	25.72±4.74	<.001
Female (n, %)	51 (50.49%)	-	-
Days from symptom onset to study protocol	-	30.12±2.41	-
Smoking rates (n, %)	17 (16.83%)	17 (16.83%)	1.00
Coexisting conditions			
Diabetes mellitus (n, %)	15 (14.85%)	15 (14.85%)	1.00
Obesity (BMI ≥ 30) (n, %)	29 (28.71%)	25 (24.75%)	<.001
Hypertension (n, %)	29 (100%)	29 (100%)	1.00
COPD (n, %)	23 (100%)	23 (100%)	1.00

Independent samples t test or χ^2 test; COPD: Chronic obstructive pulmonary disease

Table 2. Comparison of cross-sectional areas of muscles and changes in lung volume between the two stages

	Stage 1			Stage 6			2 x 2 ANCOVA	
	Right	Left	p^1	Right	Left	p^1	Side p^2 (η^2p)	Stage*Side p^2(η^2p)
PMa (cm^2)	12.40±2.49	12.13±2.70	.73	11.23±2.43	11.07±2.73	.79	.677 (.002)	.314 (.010)
PMi (cm^2)	4.28±0.97	4.19±1.03	.88	3.91±0.90	3.83±1.04	.85	.807 (.001)	.644 (.002)
ICM (cm^2)	4.07±0.89	3.71±0.81	.12	3.84±0.86	3.50±0.81	.06	.059 (.035)	.010 (.064)*
Lung volume (cm^3)	2334.30±600.16	2092.30±576.33	<.001	2238.42±632.62	2035.06±592.88	<.001	<.001 (.297)	.340 (.009)

PMa: Pectoralis major muscle; PMi: Pectoralis minor muscle; ICM: Intercostal muscle; p^1: Independent samples t test results for within-stage side comparisons; p^2: two-way repeated measures analysis of covariance with a mixed model. Figures in parentheses are effect sizes partial eta squared (η^2p).

ANCOVA revealed a significant stage*side interaction effect regarding CSA of intercostal muscle [(p=.010; η^2p=.064)]. This value was smaller in stage 6 compared to stage 1 (Table 2). There was no significant difference between the two stages in terms of CSA of pectoralis major muscle [(p=.314; η^2p=.010)], CSA of pectoralis minor muscle [(p=.644; η^2p=.002)] and changes in the lung volume [(p=.340; η^2p=.009)]. In addition, within-group analysis showed that the lung volume scores were higher for the right side both in stage 1 and 6 (p=<.001).

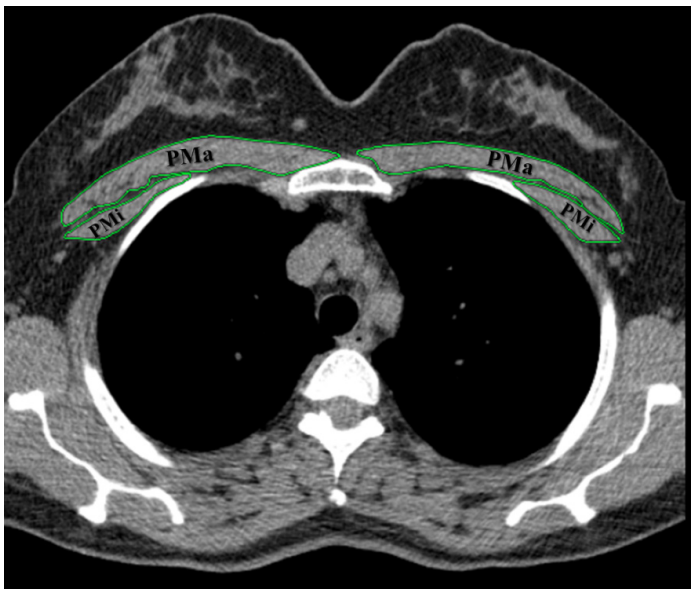

Figure 1. Measurement of the pectoral muscles. Cross-sectional area measurement of the pectoral muscles at the supra-aortic arteries level. PMa: Pectoralis major muscle; PMi: Pectoralis minor muscle

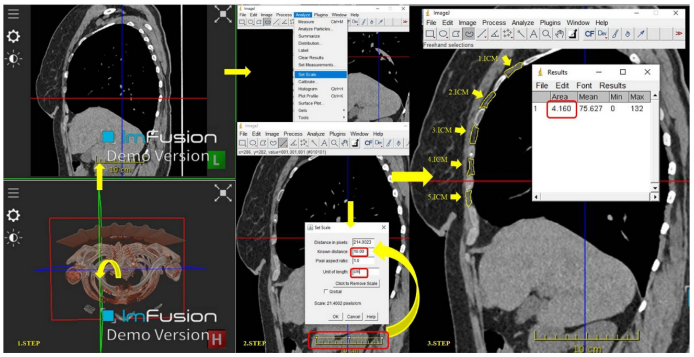

Figure 2. Measurement of the intercostal muscles. Cross-sectional area measurement of the intercostal muscles at the midclavicular line. ICM: Intercostal muscle

DISCUSSION

The primary aim of our study was to determined the potential effects of Covid-19 infection on respiratory muscles and lung volume. As a secondary objective, by scanning impaired respiratory muscle performance and lung volume we tried to provide theoretical information and propose early rehabilitation strategies to alleviate the burden on the health system during the pandemic period. Evaluating the CT images of the same patients at stage 1 and stage 6 revealed that Covid-19 pneumonia led to a decrease in the cross-sectional area of the intercostal muscles, whereas it caused no significant decrease in the cross-sectional area of the pectoral muscles nor in the lung volumes. In addition, 15% to 29% of the patients had an accompanying diagnosis of diabetes mellitus, obesity, and hypertension, indicating that people with underlying chronic diseases are more affected by Covid-19 pneumonia, as previously reported in similar studies.

Such as yawning and effective coughing behaviors are necessary to providing and maintaining pulmonary hygiene (14). This requires an optimal level of breathing together with optimal performance of the respiratory muscles. It is known that factors such as aging, smoking, obesity, chronic diseases, and physical inactivity increase respiratory workload and decrease respiratory muscle performance (15, 16). Previous studies have reported that the respiratory muscle weakness may increase the age-related decline in respiratory muscle performance in patients with multiple morbidity (16). Given the fact that the Covid-19 virus primarily affects the respiratory system and causes pneumonia, it is important to determine the impact of the infection on respiratory muscle performance. Currently, there are no studies directly investigating the effect of Covid-19 viral infection on respiratory muscles. In the present study, we obtained absolute values of the cross-sectional areas of the ICMs (as the main respiratory muscles) and the pectoral muscles (as the auxiliary respiratory muscles). The obtained data showed that Covid-19 pneumonia can cause atrophy in the respiratory muscles in a period as short as four weeks. The relationship between respiratory muscle weakness and shortness of breath is clearly demonstrated (17). Thus, we think that Covid-19-induced atrophy in the respiratory muscles may increase the risk of acute respiratory distress syndrome and respiratory failure, increasing the need for mechanical ventilation support and increasing the length of stay in the intensive care unit.

Lung volume measured on CT images, is closely related to pulmonary function test results such as forced vital and total lung capacities (18). Reduced lung volume may be an important sign of disease severity and prognosis of Covid-19 infection. Studies have reported that in severe cases of Covid-19, smaller CT lung volume is associated with alveolar collapse (6, 19). In the presented study, however, we found no significant decrease in the lung volumes between stage 1 (0-4 days) and stage 6 (>28 days). One reason could be that the lung involvement does not reach the highest level at stage 1 of the disease. Previous studies have shown that in patients with Covid-19 pneumonia, lung abnormalities on CT peak at about 10 days after the first symptoms (12). Second reason for the absence of significant lung volume difference could be the improvement of lung involvement up until the 6th stage of the disease.

The limitations of our study can be listed as following: First, lesion areas in the lungs were not evaluated. Second, prognostic data of the patients was not included due to unavailability of such data for some of the participants. Third, since physical or pulmonary performance levels of the participants were not recorded, they could not be compared with the tomographic parameters. Fourth, it was not specified from which mutations the participants were infected.

CONCLUSION

In conclusion, it can be concluded that Covid-19 pneumonia causes an atrophy in respiratory muscles. However, it seems to have a nonsignificant effect on lung volume. This indicates that despite the relation between lung volume and respiratory muscles, changes in respiratory muscle areas could occur independently of changes in lung volume. Current evidence suggests the need for further investigation of respiratory muscles and respiratory muscle training to reduce the risk of serious complications during viral infections. Moreover, the development of treatment strategies for weakened respiratory muscles may contribute to alleviating the burden on the health system during the current pandemic period.

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

Ethical approval: *This study was approved by Ankara Medipol University Medical Faculty Clinical Research Ethics Committee (Registration date/no: 23.09.2021/35).*

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MEDICAL RECORDS-International Medical Journal

Research Article

Evaluation of Coronary Atherosclerosis in Patients with Coronary Artery Aneurysm With CAD-RADS Scoring System Using MDCT Angiography

Koroner Arter Anevrizmalı Hastalarda Koroner Aterosklerozun MDBT Anjiyografi Kullanılarak CAD-RADS Skorlama Sistemi ile Değerlendirilmesi

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Abstract

Aim: This article aims to investigate the degree and frequency of atherosclerosis using the "Coronary Artery Disease Reporting and Data System" (CAD-RADS) classification in patients who underwent coronary Multidetector Computed Tomography (MDCT) Angiography with a preliminary diagnosis of coronary artery disease and were found to have coronary artery aneurysm (CAA) and also to discuss the predisposing factors, prevalence, diagnostic criteria and complications in CAA with CT images.

Material and Methods: We retrospectively evaluated the examinations of 3694 patients who underwent coronary MDCT angiography. We evaluated a total of 69 patients including 23 patients with CAA and 46 patients without CAA, in terms of atherosclerotic involvement using the CAD-RADS classification system and compared the findings.

Results: CAA was most frequently found in the right coronary artery (RCA), followed by the left anterior descending artery (LAD), left circumflex (LCX), left main coronary artery (LMCA), and posterolateral branch (PLB). In patients with CAA, the most frequently atherosclerosis observed vessels were LAD, LCX, RCA, and LMCA, respectively, while LAD, RCA, LCX, LMCA, PLD, and PDA were detected in patients without an aneurysm. No atherosclerosis was detected in 5 patients (21.7 %) with CAA and 15 patients (32.6 %) without CAA (p>0.05).

Conclusion: The number of atherosclerotic vessels and the degree of stenosis calculated using the CAD-RADS scoring in patients with CAA are similar to patients without an aneurysm. The fact that atherosclerosis is an important factor in the etiology of aneurysms may explain this situation.

Keywords: Coronary artery aneurysm, coronary atherosclerosis, MDCT angiography

Öz

Amaç: Bu makale koroner arter hastalığı ön tanısı ile koroner Multidedektör Bilgisayarlı Tomografi (MDBT) Anjiyografi yapılan ve koroner arter anevrizması (KAA) saptanan hastalarda, "Coronary Artery Disease Raporting And Data System" (CAD-RADS) sınıflaması ile aterosklerozun derecesini ve sıklığını araştırmak ve ayrıca KAA'da predispozan faktörleri, yaygınlığını, tanı kriterlerini ve komplikasyonlarını BT görünümleri eşliğinde ele almaktır.

Materyal ve Metot: Koroner MDBT Anjiyografi çekilen 3694 hastanın tetkiklerini retrospektif olarak inceledik. KAA tespit edilen 23 hasta ile birlikte KAA bulunmayan 46 hasta dahil toplam 69 hastayı aterosklerotik tutulum açısından CAD-RADS sınıflama sistemini kullanarak değerlendirdik ve bulguları karşılaştırdık.

Bulgular: KAA en sık sağ koroner arterde (RCA) bulunurken, bunu sol anterior desendan arter (LAD), sol sirkümfleks (LCX), sol ana koroner arter (LMCA) ve posterolateral dal (PLD) izledi. KAA olan hastalarda en sık ateroskleroz görülen damarlar sırasıyla LAD, LCX, RCA ve LMCA iken anevrizması olmayan hastalarda LAD, RCA, LCX, LMCA, PLD ve PDA olarak tespit edildi. KAA olan 5 hastada (21.7 %) ve olmayan 15 hastada (32.6 %) ateroskleroz saptanmadı (p>0.05).

Sonuç: KAA'lı hastalarda CAD-RADS skorlaması kullanılarak hesaplanan aterosklerotik damar sayısı ve darlık derecesi, anevrizması olmayan hastalar ile benzerdir.

Anahtar Kelimeler: Koroner arter anevrizması, koroner ateroskleroz, MDBT anjiyografi

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INTRODUCTION

There are many publications in the literature about coronary artery aneurysm (CAA) which was first described by Bougon in 1812 (1). Coronary artery aneurysmal dilatation has been defined in two ways, coronary artery ectasia and CAA, and a male-female ratio of 3:1 has been reported with a prevalence rate of 1.2 - 4.9% in their CAA, however, there are also studies reporting this ratio between 0.3% and 5.3% (2-4). CAA is defined as abnormal focal dilatation of the coronary artery exceeding 1.5 times the adjacent normal segment. On the other hand, coronary artery ectasia is used to describe lesions of similar but widespread length involving ≥50% of the coronary artery (5).

The most frequently observed vessels are right coronary artery (RCA), left anterior descending artery (LAD), left circumflex (LCX), and left main coronary artery (LMCA), respectively (6). CAA involves more in proximal segments of coronary arteries (7). CAA can be of the saccular or fusiform type, and fusiform types are usually found in LAD (8). When the aneurysm is more than four times the diameter of the adjacent normal segment, it is called a giant coronary aneurysm (9). Both RCA involvement and 3-vessel involvement are more common in men than women in CAAs. The development of CAA is closely related to gender, genetic syndromes (Loeys-Diet and Ehlers-Danlos syndrome) and connective tissue diseases such as scleroderma, and systemic vascular diseases such as Kawasaki disease, Takayasu arteritis, and it is known that the most common etiology of CAA is atherosclerosis (50%), but Kawasaki disease is the most common cause worldwide. Additionally, pseudoaneurysms may be seen due to iatrogenic or traumatic causes (cardiac catheterization, surgery) or infectious processes (10,11).

CAA is detected incidentally by catheter coronary angiography (CCA) or MDCT angiography. Chest pain, acute myocardial infarction, congestive heart failure, and sudden cardiac death can be seen in patients due to complications such as rupture, compression on cardiopulmonary structures, thrombus formation, distal embolization, and arteriovenous fistula development. Acute presentations can be seen especially in cases of infectious causes and Kawasaki disease. It is known that atherosclerosis, proteolytic imbalance, and inflammatory reactions play a role in aneurysm development. The ideal treatment for CAA has not been defined yet, but computed tomography angiography, a non-invasive method, is recommended for long-term follow-up (12,13). Coronary magnetic resonance angiography (MRA) can also be used for diagnosis and long-term follow-up, but MDCT angiography is considered to be superior (14).

Coronary MDCT angiography is an important diagnostic method used to evaluate coronary atherosclerosis in patients with known low or moderate risk of coronary artery disease. The diagnostic performance of MDCT angiography is high, especially in acute or stable chest pain. Guidelines have been established by the Society for Cardiovascular Computed Tomography (SCCT) to exclude coronary atherosclerotic disease and categorize luminal stenosis in the interpretation and reporting of MDCT angiography. However, it was observed that there were major differences in reporting among practitioners due to the lack of standardization (15). In 2016, radiology and cardiology associations introduced the CAD-RADS system to ensure standardization in reporting, improve quality, and produce consistent data for research and education. CAD-RADS provides a consistent assessment of stenosis as well as effective communication, management recommendations, and risk estimation. Comprehensive data collection and better training and research have been made possible thanks to a standardized reporting system. The inclusion of CAD-RADS in MDCT angiography reports may reduce the cost and length of hospital stay by reducing the number of unnecessary invasive CCAs (15). CAD-RADS has been shown to accurately predict major cardiovascular events, particularly angina, myocardial infarction, or death. CAD-RADS has also been shown to correlate with the degree of stenosis measured by invasive CCA with high sensitivity (100%), specificity (96.8%-98.7%), and accuracy (98.3%-99.3%) (17). Besides, CAD-RADS has limitations such as misclassification of observed findings and misinterpretation of the last category (15).

This article aims to review coronary artery aneurysms with predisposing factors and categorize accompanying atherosclerotic changes using the CAD-RADS classification.

MATERIAL AND METHOD

This retrospective study protocol was approved by our institutional review board. This single-center study is based on coronary MDCT angiography data from the Department of Radiology database. The imaging data of all patients (3694 patients) who underwent coronary MDCT angiography between December 2018 and January 2022 for the investigation of coronary artery disease in our institution were evaluated by a radiology specialist. After excluding patients with poor diagnostic image quality due to high pulse rate or arrhythmia and studies performed for reasons other than coronary artery evaluation (calcium scoring, valve evaluation, surgical planning, investigation, cardiac masses, evaluation of pulmonary/cardiac veins, and non-coronary congenital heart disease), 23 patients with CAA (abnormal focal dilatation of the coronary artery exceeding 1.5 times the adjacent normal segment) were included in the study. A control group was formed with 46 randomly selected patients without CAA but with similar demographic characteristics. Aneurysm types were analyzed with coronary arteries with aneurysm and involved segments. In CAD-RADS, every segment with a diameter greater than 1.5 mm is evaluated, but the segment with the highest degree of stenosis is considered for classification. The CAD-RADS system has two sections, categories, and modifiers (16). With the CAD-RADS classification, each coronary segment is evaluated in detail and the CAD-RADS category is decided by analyzing the severity of the stenosis, plaque morphology, stents, and coronary artery

bypass grafts. In the CAD-RADS classification, there are 6 categories ranging from 0 (no atherosclerotic disease in any coronary artery) to 5 (total occlusion of at least one vessel), and the highest stenotic lesion is taken into account. There are four modifiers in the CAD-RADS classification. These; non-diagnostic image quality (N), stents (S), bypass grafts (G), and high-risk and sensitive plaques (V) (Table 1). All patients categorized with the CAD-RADS classification were reassessed for atherosclerotic involvement and degree of coronary obstruction, plaque morphology, type, presence, and patency of bypass grafts and stents. Both groups were compared in terms of the severity and prevalence of coronary atherosclerotic involvement using the CAD-RADS classification.

MDCT scanning protocol

All coronary MDCT angiography examinations were performed using a 128-detector, 160-slice computed tomography (Prime Aquilion, Toshiba Medical Systems, Otawara, Japan). 70-100 ml iohexol, 350 mg/ml of iodinated contrast material was injected into the left antecubital vein at a rate of 4 ml/s with an automatic injector system. MDCT scan was performed with bolus tracking technique from heart apex to baseline after the start of contrast agent injection. All coronary MDCT angiography studies were performed in the craniocaudal supine position within a single inhalation period. Examinations were performed using prospective or retrospective modulation accompanied by Electrocardiography (ECG). In retrospective modulation, all phases from 0% to 90% were evaluated by reconstructing the R-R interval at 10% intervals.

Coronary MDCT angiography imaging protocol for coronary artery disease: Section thickness: 0.5 mm, section spacing: 0.25 mm, rotation time: 400 ms,100 kVp, and 300-400 mAs. Axial MDCT sections were transferred to the workstation and examined using 3D volume rendering and maximum intensity projection (MIP) as well as 2D multi-plane reconstructions (MPR). A special cardiac analysis program (Terarecon-Aquarius Workstation Intuition Edition ver.4.4.7.1021.7056) was used for vessel segmentation.

Ethics committee approval was obtained with the number 2022/36 and the study was done in accordance with the Helsinki Declaration.

Statistical Analyses

Conformity of continuous variables to normal distribution was examined by the Kolmogorov-Smirnov test. Since all continuous variables demonstrated normal distribution, descriptive statistics were shown as mean±standard deviation, and independent samples were analyzed by t-test for comparisons according to groups. Descriptive statistics of categorical variables were shown as numbers (%), and chi-square tests were used in the analysis of crosstabs. P<0.05 values were considered statistically significant.

RESULTS

Among all patients participating in the study

There were 69 patients, 51 male (73.9%) and 18 female (26.1%). The mean age of female patients was 63.39±9.69 years, and the mean age of male patients was 59.41±10.02. There was right dominance in 61 patients, left dominance in 5 patients, and codominance in 3 patients. There was a family history in 31 patients (44.9%), a history of smoking in 31 patients (44.9%), a history of diabetes in 18 patients (26.1%), and a history of hypertension in 40 patients (58%). None of the patients had genetic syndromes, connective tissue diseases, and systemic vascular diseases such as Kawasaki disease seen in the etiology of CAA.

Among patients with CAA

There were 17 male (73.9%) and 6 female (26.1%) patients. The mean age of male patients was 58.24±9.76 years, and the mean age of female patients was 68.67±10.23. 22 patients had right dominance and one patient had codominance. No left dominance was observed. Fusiform aneurysm was observed in 22 patients while saccular aneurysm was observed in LMCA in only one patient (Figure 1). Single vessel aneurysms in 12 patients, two vessel aneurysms in 5 patients, three vessel aneurysms in 4 patients, and four vessel aneurysms including LMCA in one patient were observed. Two aneurysms were thrombosed (Figure 2). RCA aneurysm in 14 patients (60.9%), LAD aneurysm in 12 patients (52.2%), LCX aneurysm in 8 patients (34.8%), LMCA aneurysm in 3 patients (13%), PLD aneurysm in one patient (4.3%), and PDA aneurysm in one patient (4.3%) were observed (p<0.001) (Table 2).

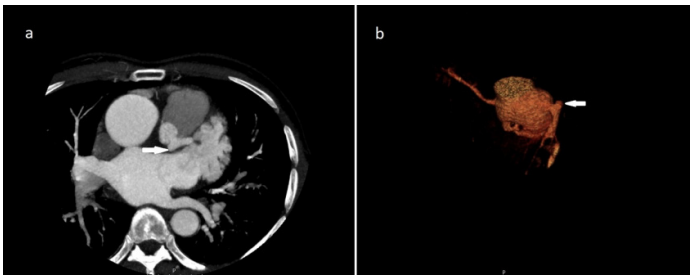

Figure 1. Axial maximum intensity projection (MIP) (a) and volüme rendering (VR) (b) images on MDCT showing LMCA aneurysm (Arrows)

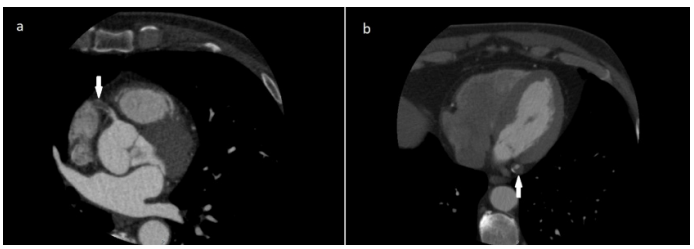

Figure 2. Axial MDCT images show thrombosed aneurysm in RCA (a) and LCX (b) (Arrows)

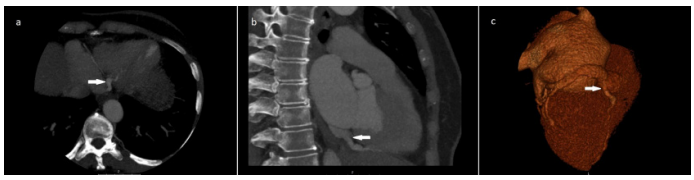

Figure 3. Axial (a) PDA aneurysm on MDCT images. Sagittal MIP (b) and MPR (c) images show PDA fistulized into the left atrium

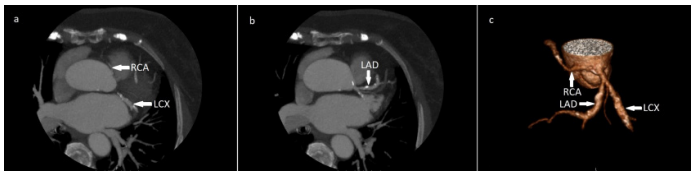

Figure 4. Axial MIP images on MDCT (a-b) and VR images (c) show RCA originating from the left coronary sinus, and fusiform aneurysm in LCX and LAD

The patient with a PDA aneurysm had a left atrial fistula (Figure 3). In addition, one patient had RCA originating from the left coronary sinus and a fusiform aneurysm were present in the LAD and LCX proximal segment (Figure 4). In one patient, both LAD and LCX were completely occluded and there was LIMA-LAD and aorta-LCX saphenous vein graft in patent appearance. Atherosclerotic involvement was in single-vessel in 8 patients (44.4%), in two-vessel in 6 patients (33.3%), and in three vessel in 4 patients (22.2%). No plaque was observed in 5 patients. Five patients (21.7%) were categorized as CAD-RADS 0, nine patients (39.1%) as CAD-RADS 1, three patients (13%) as CAD-RADS 2, two patients (8.6%) as CAD-RADS 3, one patient (4.3%) as CAD-RADS 4 and three patients (13%) as CAD-RADS 5. Calcific plaques were observed in 15 patients (65.2%), fibrous plaques in one patient (4.3%), and mixed plaques in two patients (8.6%). There was a vulnerable plaque in 13 patients (56.5%). Three patients (13.04%) had patent appearance stent, two patients (8.7%) had bypass graft and one had thrombosis. There was a family history in 9 patients (39.1%), smoking in 10 patients (43.5%), diabetes in 6 patients (26.1%), and hypertension in 13 patients (56.5%). Two patients had at least two of these risk factors, and 8 patients had at least three of them. In three patients, none of these risk factors were present. The mean cholesterol value was 214.70±38.03.

Table 1. CAD-RADS scoring system

CAD-ADS Category	Interpretation	Degree of Maximal Coronary Stenosis	Further Cardiac Workup	Management
0	Absence of CAD	0%, no plaque or stenosis	None	Consider nonatherosclerotic causes of chest pain
1	Minimal CAD	1%-24%, minimal stenosis or plaque without stenosis	None	Consider nonatherosclerotic causes of chest pain Preventive therapy and risk modification
2	Mild CAD	25%-49%	None	Consider nonatherosclerotic causes of chest pain Preventive therapy and risk modification, especially for plaque in multiple segments
3	Moderate stenosis	50%-69%	Functional assessment	Consider symptoms-guided anti-ischemic and preventive pharmacotheraphy and risk factor modification per-guideline-directed care
4A	Severe stenosis	One or two vessels, 70%-99%	ICA or functional assessment	Consider symptoms-guided anti-ischemic and preventive pharmacotheraphy and risk factor modification per-guideline-directed care
4B	Severe stenosis	Left main artery >50% or three vessels ≥70%	ICA is recommended	Other treatments including revascularization should be considered per quideline-directed care
5	Total occlusion	100%	ICA and/ or viability assessment	Same as for CAD-RADS 4A and 4B
N	Obstructive CAD cannot be excluded	Nondiagnostic	Additional or alternate evaluation	Additional or alternate evaluation

Note. -Modifiers include N (nonevaluable segment), S (coronary stent), G (coronary bypass graft) and V (vulnerable plaque).
ICA = invasive coronary angiography

Among the patients in the control group

There were 34 male (73.9%) and 12 female (26.1%) patients. The mean age of male patients was 60±10.25, and the mean age of female patients was 60.75±8.65. There was right dominance in 44 patients, left dominance in 5 patients, and codominance in 2 patients. In one patient, the LAD was occluded and there was a patent appearance LIMA-LAD saphenous vein graft. In one patient, both LAD and RCA were in total occluded appearance, and there was a patent appearance LIMA-LAD saphenous vein graft and an occluded aortic-RCA saphenous vein graft. Atherosclerotic involvement was in single-vessel in 12 patients (26.1%), two-vessels in 7 patients (15.2%), three vessel in 8 patients (17.4%), four vessel in 3 patients (6.5%), and five vessel in one patient (2.2%). No plaque was observed in 15 patients. 15 patients (32.6%) were categorized as CAD-RADS 0, 10 patients (21.7%) as CAD-RADS 1, 5 patients (10.9%) as CAD-RADS 2, 9 patients (19.6%) as CAD-RADS 3, 5 patients (10.9%) as CAD-RADS 4, and 2 patients (4.3%) as CAD-RADS 5. Calcific plaques were observed in 29 patients (63%) and fibrous plaques in 2 patients (4.3%). The vulnerable plaque was present in 28 patients (60.9%). 4 patients (8.7%) had patent appearance stent, 2 patients (4.3%) had bypass graft and one had thrombosis. There was a family history in 22 patients (47.8%), smoking in 21 patients (45.7%), diabetes in 12 patients (26.1%), and hypertension in 27 patients (58.7%). At least two of these risk factors were present in 10 patients, at least three in 10 patients, and at least four in 6 patients. 13 patients had none of these risk factors. The mean cholesterol value was 208.63+43.61.

When the groups with and without aneurysms were compared in terms of the specified risk factors, no significant difference was observed (p>0.05).

In order of frequency, the vessels in which coronary atherosclerosis is most frequently seen are; In the group with CAA, 15 vessels (65.2%) were observed in the LAD, 9 vessels (39.1%) in the LCX, 6 vessels (26.1%) in the RCA, 2 vessels (8.7%) in the LMCA, while in the control group, 27 vessels (58.7%) in LAD, 15 vessels (32.6%) in RCA, 14 vessels (30.4%) in LCX, 8 vessels (17.4%) in LMCA, 3 vessels (6.5%) in PLD and 1 vessel (2.2%) in PDA (p<0.001) (Table 3). No plaque was observed in PLD and PDA in the group with CAA.

Table 2. Vessels with the most frequent coronary artery aneurysm

Aneurism type	n (%)
RCA	14 (60.9)
LAD	12 (52.2)
LCX	8 (34.8)
LMCA	3 (13)
PLD	1 (4.3)
PDA	1 (4.3)

Table 3. Vessels where coronary atherosclerosis is most frequent in patients with and without CAA

	CAA patients n (%)	Control group n (%)
LAD	15 (65.2)	27 (58.7)
RCA	6 (26.1)	15 (32.6)
LCX	9 (39.1)	14 (30.4)
LMCA	2 (8.7)	8 (17.4)
PLD	0 (0)	3 (6.5)
PDA	0 (0)	1 (2.2)

The incidence of coronary atherosclerosis in at least one vessel was 78.3% in patients with CAA and 67.4% in the control group, and no significant difference was observed between the two (p>0.05).

DISCUSSION

The pathophysiological mechanisms of CAA are not well understood, but atherosclerosis in adults and Kawasaki disease in children are the main etiologies (12). Other common causes of CAA include mycotic and infectious septic embolism, Marfan syndrome, and connective tissue diseases. Other vasculitic disorders such as Takayasu's arthritis, polyarteritis nodosa, systemic lupus erythematosus, and rheumatoid arthritis may lead to CAA (12). Kawasaki disease is a vasculitis that causes symmetric wall thickening, stenosis, and aneurysmal dilatation by affecting medium and large vessels such as the aorta and its branches. In Takayasu's disease which classically affects the aorta and pulmonary arteries, 10-30% of patients have coronary artery involvement. Patients may have osteal stenosis, arthritis, or aneurysm. Pulmonary artery involvement and pulmonary hypertension can be seen at a rate of 15-17%. Angina, myocardial infarction, heart failure, and sudden death may develop in patients due to ischemic cardiac involvement (13).

Atherosclerosis is a chronic progressive transmural inflammatory disease affecting different vascular layers. Stenotic coronary atherosclerosis and CAA commonly coexist which have several histological patterns in common, such as hyalinization, lipid deposition, focal calcification, and fibrosis (12). CAA is thought to be a result of atherosclerosis since patients with and without CAAs are similar in terms of both risk factors and clinical manifestations of atherosclerosis (13). CAA may also result from apical hypertrophic cardiomyopathy secondary to the high-tensile wall. Aneurysm development may occur as a result of iatrogenic injury of the blood vessel in post-percutaneous coronary interventions such as stent placement, atherectomy, and balloon angioplasty (14). A low incidence of CAA has been detected in diabetic patients. Besides, it has been reported in the literature that the biggest risk factor for CAA is hypertension, and smoking habit is more common in patients with CAA compared to patients with coronary artery disease (19). However, in our study, we did not observe a statistically

significant difference between the group with CAA and the control group in terms of risk factors such as family history, diabetes history, hypertension, and smoking (p>0.05).

Most patients with CAA are asymptomatic, but clinical signs may occur due to the development of atherosclerotic coronary artery disease or complications (12). Complications include the clinical sequelae of myocardial infarction and thrombosis or rupture of an aneurysm potentially resulting in sudden death. Larger aneurysms (>8 mm) have a higher risk of complications, including myocardial infarction, stenosis, and thrombosis. A study on CCA showed that 3-vessel coronary artery disease and a history of myocardial infarction were more common in male patients (13). Distal embolization, coronary spasm, massive expansion of the CAA, and compression of the adjacent structure are the other most frequent complications. CAA rupture is rare but may result in cardiac tamponade and sudden death. The CAA may expand excessively, compressing adjacent cardiopulmonary structures such as the right atrium, right ventricular wall, pulmonary artery, and tricuspid valve (12). Other common clinical manifestations in patients with CAA include heart failure and syncope (20). If associated cardiovascular risk factors such as hypertension and diabetes are controlled, the progression of the disease can be reduced (14).

It has been stated that conventional coronary angiography (CCA) is an invasive gold standard tool to evaluate the anatomical features of CAA, and coronary MDCT angiography is the preferred alternative noninvasive technique for follow-up (21). However, although CCA can show the location, size, and shape of the CAA, it can be misleading about the size of the CAA when a thrombus forms in the lumen of the aneurysm (9). MDCT angiography or cardiac magnetic resonance angiography (MRA) can play an important role in the diagnosis of CAAs as they are fast, non-invasive, and reliable (22). MDCT angiography is capable of detecting coronary plaque location, severity, and plaque characterization. The prognostic power of MDCT angiography has been demonstrated in high-risk patients (23). MDCT angiography has been shown to be highly sensitive and specific for CAAs in Kawasaki patients. For significant coronary artery stenosis, the sensitivity was 87.5% and the specificity was 92.5% (24). In another study, MDCT was found to be more sensitive than 2D echocardiography in detecting fusiform and distally located aneurysms (25). The sensitivity of MDCT angiography for the detection of CAA and related complications is considerably high and has proven its value in the evaluation of coronary artery diameter in adults and patients with Kawasaki disease compared to CCA (12). Since radiation exposure causes an increase in the lifetime cancer risk, especially in children, the absence of radiation is the main advantage of cardiac MRA over CCA and MDCT angiography in the diagnosis of CAA (26). Finally, MDCT angiography is the imaging method of choice for long-term monitoring of CAA due to providing accurate data on coronary anatomy, calcification, lumen diameter, thrombus, and aneurysmal features (12).

The use of CAD-RADS provides standardization by classifying the severity of coronary artery disease and makes MDCT angiography more valuable by including management recommendations. It has been reported that the predictive value of CAD-RADS is similar to both Duke's index and traditional methods and can be used as a prognostic determinant in high-risk asymptomatic coronary artery disease (27). Nam et al. showed that CAD-RADS provides prognostic value for major cardiovascular events and provides better risk differentiation compared to coronary artery calcium score alone (28). The additive prognostic value of the CAD-RADS scoring system has been shown to be above and beyond traditional methods (29). Assigning appropriate CAD-RADS category is dependent on accurate measurement of luminal stenosis on coronary MDCT angiography. Although coronary MDCT angiography is a robust modality for the evaluation of coronary arteries, artifacts due to densely calcified plaques often lead to an overestimation of luminal stenosis, thus assigning a higher category. Similarly, the spatial resolution of coronary MDCT angiography does not allow to distinguish between near-total (close to 99%) and total (100%) occlusion of coronary arteries (15). In addition, coronary artery anomalies, coronary artery dissection, coronary aneurysms or pseudoaneurysm are not categorized in the CAD-RADS system (18).

It has been reported that CAA is seen in LAD, RCA, LCX in order of frequency, but there are also studies showing that the most common localization is in RCA (31,32). It has been reported that CAA is found frequently in proximal-mid-RCA (68%), proximal LAD (60%), and LCX (50%). According to the same study, LMCA aneurysm (0.1%) is extremely rare (20). In our study, we detected CAA in RCA, LAD, LCX, LMCA, PLD, and PDA, in order of frequency. Studies have demonstrated that the order of frequency of vessels with CAA varies. This may be due to the definition of CAA (<50% involvement of a coronary artery aneurysm, >50% involvement ectasia) and genetic differences in the patient population used. In addition, the difference in CAA frequencies in different regions may also lead to this result when the effect of atherosclerosis on the development of CAA is considered. Although the number of patients with an aneurysm was limited in our study, the current results regarding the localization of CAA in the coronary arteries were consistent with the literature, but we think that it is important to conduct new studies with larger patient series.

Studies in the general population have shown that in asymptomatic individuals without aneurysm, vessels with coronary artery disease are LAD, RCA, LCX, and LMCA, in order of frequency (33). Similarly, we determined coronary atherosclerotic involvement in patients without CAA as LAD, RCA, LCX, LMCA, PLD, and PDA, in order of frequency.

Farrag et al. stated that only 16% of CAA patients do not have atherosclerotic lesions, MDCT angiography is an appropriate technique to determine and evaluate CAA morphology, and they think that CAA is an advanced form of atherosclerosis (34). There are other publications in the

literature investigating atherosclerotic involvement with MDCT angiography in patients with CAA (12-14). Besides, we also investigated the vessels in which atherosclerosis is most common in these patients and determined the coronary atherosclerotic involvement as LAD, LCX, RCA, and LMCA, in order of frequency. Additionally, we conducted our study using the CAD-RADS scoring system which provides standardization in the identification and reporting of coronary atherosclerotic diseases and is known to be reliable. We think that our study is remarkable in this respect and will contribute to the literature.

Finally, in our study, we found that the incidence of coronary atherosclerosis in at least one vessel was similar in patients with and without an aneurysm. We think that this may be due to the relatively small number of patients with CAA included in the study.

Limitations

The limitations of our study are the low number of cases.

CONCLUSION

Although patients with and without CAA have similar findings in terms of atherosclerotic involvement, the use of MDCT angiography and CAD-RADS scoring system, which has high diagnostic features, is extremely effective in preventing the development of serious and fatal complications, especially in patients with CAA who have obstructive coronary artery disease.

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Research Article

The Relationship Between Malnutrition, Depressive Symptoms, and Cognitive Impairment in Geriatric Patients

Geriatrik Hastalarda Malnütrisyon, Depresif Belirtiler Ve Bilişsel Bozulma Arasındaki İlişki

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Abstract

Aim: Malnutrition is an important health problem that is frequently seen in elderly individuals and has cognitive and psychological effects. In this study, it was aimed to evaluate the frequencies of malnutrition, cognitive impairment and depression in the elderly population and the relationship between these three variables.

Material and Methods: In this retrospective study, data of 433 patients aged 65 and over who applied to a university hospital geriatrics outpatient clinic in Turkey were included. Nutritional status was evaluated with the Mini Nutritional Assessment Short Form (MNA-SF), depressive symptoms with the Geriatric Depression Scale-Short Form (GDS-15) and cognitive functions with the Mini Mental State Examination results (MMSE).

Results: According to the MNA-SF results, 13.6% of the elderly were malnourished, 30% were at risk of malnutrition. Of all patients, 45.0% had a GDS-15 score of ≥5, 12.5% had severe dementia, and 24.7% had mild dementia. The frequency of depressive symptoms was 62.7% in malnourished patients, and 42.3% in those with malnutrition risk. Malnutrition and malnutrition risk were observed in 70.4% of patients diagnosed with severe dementia. There was a correlation between the severity of malnutrition and depressive symptoms and cognitive dysfunction.

Conclusion: Malnutrition was common in the older population sample and was associated with cognitive impairment and depressive symptoms. These findings emphasize that counseling and psychiatry services should be provided to risky groups and they should be evaluated regularly for early diagnosis.

Keywords: Elderly, nutritional status, cognitive impairment, depression

Öz

Amaç: Beslenme bozukluğu, yaşlı bireylerde sık görülen, bilişsel ve psikolojik etkileri olan önemli bir sağlık sorunudur. Bu çalışma yaşlı popülasyonda yeme bozukluğu, bilişsel bozukluk ve depresyon yaygınlığı ile bu üç değişken arasındaki ilişkiyi değerlendirmeyi amaçlamıştır.

Materyal ve Metod: Retrospektif nitelikteki bu çalışmaya Türkiye'de bir üniversite hastanesi geriatri polikliniğine başvuran 65 yaş ve üstü 433 hastaya ait veriler dahil edildi. Beslenme düzeyleri Mini Nutrisyon Testi Kısa Formu (MNA-SF), depresif semptomlar Geriatrik Depresyon Skalası-Kısa Form (GDS-15) ve bilişsel fonksiyonlar Mini Mental Durum Değerlendirme Test (MMSE) sonuçlarıyla değerlendirildi.

Bulgular: MNA-SF sonuçlarına göre yaşlıların %13.6'sı malnutre, %30'u malnutrisyon riski altındaydı. Hastaların %45'inin GDS-15 puanı ≥5 iken, %12.5'inde ciddi demans, %24.7'sinde hafif demans vardı. Malnütrisyonlu hastalarda depresif belirtilerin sıklığı %62.7, malnütrisyon riski olanlarda %42.3 idi. Demans teşhisi alan hastaların %70.4'ünde malnütrisyon ve malnutrisyon riski görüldü. MNA-SF puanı ile depresif belirtiler ve bilişsel fonksiyonlar arasında ilişki vardı.

Sonuç: Yaşlı popülasyon örneğinde malnütrisyon yaygındı ve bilişsel bozulma ve depresyon ile ilişkiliydi. Bu bulgular, riskli gruplara danışmanlık ve psikiyatri hizmetlerinin verilmesi, erken teşhis için düzenli olarak değerlendirilmesi gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Yaşlı, beslenme durumu, bilişsel bozulma, depresyon

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INTRODUCTION

Starting from the early stages of life, a balanced diet, maintaining a healthy body weight and a physically active lifestyle are the main effective factors that help individuals avoid physical and mental deterioration associated with aging (1,2).

On the other hand, aging brings with it many physiological and psychological changes that may make it difficult to meet nutritional needs (3,4). The prevalence of malnutrition is generally high in older adults. A meta-analysis study examining 4507 elderly individuals reported that approximately two-thirds of its participants were undernourished and at risk of malnutrition (5). Another study in Canada in a population of older adults concluded that one-third of the participants were at nutritional risk. Moreover, it has been reported that these individuals at risk have a 20% higher probability of requiring acute hospital care and a 60% higher mortality rate (6). Therefore, adequate nutrition is one of the requirements of independent living and malnutrition is an important factor affecting mortality and morbidity (7-9).

Depression and cognitive disorders are important public health problems in the elderly and are closely related to malnutrition (10,11). Although studies cannot provide a definite causality regarding this relationship, it is thought that malnutrition disrupts the functions of a series of immune, neurohumoral and neurotransmitter systems by causing a deficiency of essential molecules that play a role in the execution of brain functions. Depression creates reluctance, physical weakness, and loss of appetite; dementia on the other hand may lead to malnutrition due to reasons such as not feeling hungry as a result of brain atrophy, eating behavior disorder, and difficulty in swallowing (12-15). As a result, all these changes affect each other negatively and bring along many problems such as a decrease in life expectancy, the need for care from others, and an increase in the burden on health services (8).

Although malnutrition is common especially in the geriatric population and its proven impact on morbidity and mortality rates is known, it is still a neglected issue by many clinicians. However, considering that the number of individuals over the age of 60 will double in the next 20 years (16), it is necessary to examine this issue and to determine the necessary precautions for public health. In the light of this information, we aimed to determine the nutritional status, depression and cognitive impairment levels of a group of elderly population and to evaluate the possible relationship between these three variables in this study.

MATERIAL AND METHOD

Participants and Study Protocol

The study was carried out by retrospectively examining the medical files of the patients who applied to the geriatric's outpatient clinic of Inonu University. The files were reviewed by the researchers; the Geriatric Depression Scale-Short Form (GDS-15), Mini Nutritional Assessment Short Form (MNA-SF) and Mini Mental State Examination (MMSE) results and gender, education (uneducated, primary-high school-university), marital status, living environment (alone, with spouse, relatives, caregiver, nursing home), smoking and alcohol use, number of drugs used, comorbid diseases, body mass index (BMI), waist circumference, calf circumference, upper middle arm circumference, albumin and C-reactive protein (CRP) values were recorded. Data of patients who lacked comprehensive geriatric tests were excluded from the study.

It was evaluated and approved by the Inonu University Faculty of Medicine Non-Invasive Ethics Committee beforehand. (2022/2989).

Sample size

For the Geriatric Depression Scale-Short Form total score value, which is one of the important output variables to be examined within the scope of the study, Type I error amount (alpha) is 0.05, test power (1-beta) is 0.9, effect size is 0.5, and alternative hypothesis (H1) is two-sided and the required minimum sample size was calculated as 40 patients, according to the theoretical power analysis procedure applied using the single sample t-test (17).

Data Collection Tools

Mini Nutritional Assessment Short Form (MNA-SF): It is a screening test used to identify older adults (> 65 years) who are malnourished or at risk of malnutrition. The MNA-SF is based on the original 18-item questionnaire published in 1994 by Guigoz et al. The MNA-SF was last updated in 2009 (18). Its validity and reliability in Turkey were done by Sarikaya et al in 2013 (19). MNA-SF starts with six screening questions and the total score to be obtained from the scale is 14. A total score of 12-14 indicates normal nutritional status, 8-11 indicates malnutrition risk, and 0-7 indicates malnutrition.

Geriatric Depression Scale-Short Form (GDS-15): The scale was developed by Sheikh and Yesavage in 1986 to screen depression in elderly patients (20). The validity and reliability of the 15-item test in Turkey was determined by Durmaz et al. by in 2018 (21). The total score to be taken from the scale is 15. A score of five or more is considered compatible with depression.

Mini Mental State Examination (MMSE)

The MMSE is a simple screening test that is used to evaluate cognitive functions and it takes approximately 3 minutes to administer (22). Its validity and reliability in Turkey were tested in 2002, and a threshold value of 24 was found to be sensitive and specific (23). A score of

24-30 is normal, a score of 18-23 is compatible with mild dementia, and a score of 17 and below is compatible with severe dementia (24).

Statistical analysis

The data were analyzed after transferring the SPSS 22.0 package program. Whether the data were normally distributed or not was evaluated with the Shapiro-Wilk test. Non-parametric Kruskal-Wallis test, and ANOVA, which is the parametric test, was applied to the others. Spearman and Pearson correlation tests were used according to distributions for number of medications, age, MNA-SF, GDS-15 and MMSE scores. The results were evaluated at 95% confidence interval and $p<0.05$ significance level.

RESULTS

A total of 433 patients, 161 (mean age 72.3±6.9) male and 272 (mean age 71.8±7.0) female were included in the study. Of the participants, 31.4% were illiterate and most of them lived with their spouses (51%). Demographic and clinical data of the participants are given in Table1.

In the nutritional evaluation made according to MNA-SF scores, it was determined that 59 (13.6%) of the patients had malnutrition and 130 (30%) had a risk of malnutrition. In the comparison between nutritional status and demographic characteristics, there was a statistically significant difference between the groups in terms of living environment and marital status ($p=0.024$, $p=0.038$, respectively) (Table 2).

In the comparison between nutritional status and anthropometric measurements; While the GDS-15 score of the malnourished group was significantly higher than the other two groups ($p<0.001$), BMI, hip and upper middle arm circumference measurements and the MMSE score of them were significantly lower in the malnourished group compared to the other groups ($p<0.001$, $p=0.002$, $p<0.010$; $p<0.001$; respectively) (Table 3).

When all patients were evaluated, depression was detected in 195 (45.0%) patients, 146 of whom were women, severe dementia in 54 (12.5%) patients and mild dementia was detected in 107 (24.7%) patients. While there was depression in 62.7% (n=37) of 59 patients with malnutrition according to nutritional status, this rate was 42.3% (n=55) in those with malnutrition risk. Malnutrition and malnutrition risk were detected in 38 (70.4%) of 54 patients with severe dementia and 40 (37.4%) of 107 patients with mild dementia. In the correlation analysis between nutritional status and the number of drugs used, age, anthropometric measurements, MMSE and GDS-15: There was a negative correlation between MNA-SF score and age and GDS-15 scores, while a positive correlation was found between MMSE scores. There was a negative correlation between GDS-15 scores and MMSE scores, and a positive correlation with the number of medications used (Table 4).

Table 1. Demographic and clinical data of the patients (n=433)

		n	%
Age (year) mean±SD		72.02±6.97	
Gender	Male	161	37.2
	Female	272	62.8
Education status	Illiterate	135	31.3
	Primary school	194	44.8
	Middle School	53	12.2
	High School	20	4.4
	University	31	7.3
Marital status	Married	300	69.3
	Single	55	12.7
	Widowed	70	16.2
	Divorced	8	1.8
Domestic status	Alone	35	8.1
	Living with spouse	221	51.0
	With relatives	133	30.7
	With a caregiver	42	9.7
	Nursing home	2	0.5
Number of medications	1-4	294	67.9
	5-9	125	28.9
	≥10	14	3.2
Smoking history	Yes	67	15.5
	No	366	84.5
History of alcohol use	Yes	15	3.5
	No	418	96.5

Table 2. Nutritional status and demographic characteristics

		Nutritional Status			
		Malnutrition n (%)	Malnutrition Risk n (%)	Normal n (%)	p
		59 (13.6)	130 (30.0)	244 (56.4)	
Gender	Female	18 (4.2)	52 (12.0)	91 (21.0)	0.457
	Male	41 (9.5)	78 (18.0)	153 (35.3)	
Education status	Illiterate	12 (8.9)	37 (27.4))	86 (63.7)	0.070
	Primary school	32 (16.5)	61 (31.4)	101 (52.1)	
	Middle school	12 (22.6)	11 (20.8)	30 (56.6)	
	High School	1 (5.3)	7 (36.8)	11 (57.9)	
	University	2 (6.5)	13(41.9)	16 (51.6)	
Marital status	Married	35 (11.7)	90 (30.0)	175 (58.3)	0.038#
	Single	16 (29.1)	14 (25.5)	25 (45.5)	
	Widowed	7 (10.0)	23 (32.9)	40 (57.1)	
	Divorced	1 (12.5)	3 (37.5)	4 (50.0)	
Domestic status	Alone	3 (8.6)	11 (31.4)	21 (60.0)	0.024†
	Living with spouse	19 (8.69)	64 (29.0)	138 (62.4)	
	With relatives	26 (19.5)	42 (31.6)	65 (48.9)	
	With a caregiver	11 (26.2)	12 (28.6)	19 (45.2)	
	Nursing home	0 (0.0)	1 (50.0)	1 (50.0)	
Smoking	Yes	10 (14.9)	18 (26.9)	39 (58.2)	0.815
	No	49 (13.4)	112 (30.6)	205 (56.0)	
Alcohol	Yes	1 (6.7)	4 (26.7)	10 (66.7)	0.636
	No	58 (13.9)	126 (30.1)	234 56.0)	
Depression	Yes	37 (19.5)	55 (28.9)	103 (51.6)	<0.001†
	No	22 (9.0)	75 (30.9)	141 (60.1)	
Dementia	Mild	13 (3)	27 (6.2)	67(15.5)	0.002§
	Serious	20 (4.6)	18 (4.2)	16 (3.7)	

Statistically significant difference between Malnutrition vs. Normal
§ Statistically significant difference between Malnutrition Risk vs. Normal
† Statistically significant difference between Malnutrition vs. Malnutrition Risk; Malnutrition vs. Normal

Table 3. Comparison of nutritional status and anthropometric values, GDS-15 and MMSE scores

	Nutritional Status			
	Malnutrition (n=59)	Malnutrition Risk (n=130)	Normal (n=244)	p
Calf circumference (cm) [a]	40.54±10.62	41.38±11.57	40.25± 11.17	0.660
BMI (kg/m^2) [a]	26.50±5.93	29.36±8.94	30.71± 5.68	<0.001†
Hip circumference (cm) [a]	103.16±14.82	105.37±20.21	111.06± 18.04	0.002‡
Upper middle arm circumference_(cm) [a]	28.88±4.10	29.70±4.83	30.69± 4.18	0.010#
Number of medications	2 (0-8)	4 (0-13)	3 (0-13)	0.068
CRP [b]	2.1 (0.2-7.6)	3.6 (0.4-10.3)	3.6 (0.2-10.8)	0.185
Albumin [b]	3.82±0.31	3.88± 0.42	3.98± 0.61	0.771
GDS-15 [b]	6 (1-15)	6 (0-15)	7 (0-15)	<0.001§
MMSE [b]	24 (10-30)	25 (10-30)	26 (12-30)	<0.001†

Data are presented as mean ± SD.
BMI: Body mass index, CRP : C-reactive protein, MMSE: Mini Mental State Examination, GDS-15: Geriatric Depression Scale
[a]Data are presented as Mean±SD. b Data are presented as median (min-max)
Statistically significant difference between Malnutrition vs. Normal
§ Statistically significant difference between Malnutrition Risk vs. Normal
† Statistically significant difference between Malnutrition vs. Malnutrition Risk; Malnutrition vs. Normal;
‡ Statistically significant difference between Malnutrition vs. Malnutrition Risk; Malnutrition vs. Normal; Malnutrition Risk vs. Normal

Table 4. Correlation analysis results between age, MMSE, GDS-15, and MNA-SF scores

Correlations					
		Age	MMSE	GDS-15	MNA-SF
Age	r	1	-0.256**	0.008	-0.182**
	p		0.000	0.871	0.000
Number of medications	r		0.004	0.097*	0.015
	p		0.927	0.044*	0.762
MMSE	r		1	-0.165**	0.156**
	p			0.001	0.002
GDS-15	r			1	-0.211**
	p				0.000
MNA-SF	r				1
	p				

Only significant values are shown in the table. *p<0.05, ** p< 0.01. MMSE; Mini Mental State Examination, GDS-15; Geriatric Depression Scale, MNA-SF; Mini Nutritional Assessment-Short Form

DISCUSSION

Although dietary changes are not a natural component of aging, older adults are at risk for malnutrition due to physiological, psychological, social and environmental factors. This study investigated the relationship between the malnutrition and depressive symptoms and cognitive functions in geriatric patients.

A meta-analysis study evaluating the data of 12 countries showed that 22.8% of the entire geriatric population is severely malnourished, and 46.2% is within the risk limits, although it differs from country to country (5). The study by Mantzorou et al. on elderly individuals in Greece showed that 11.3% of 2092 individuals were malnourished and 35% were at risk (9). Gunduz et al. also found that 196 (19%) of 1030 geriatric patients had malnutrition and 300 (29.1%) had a risk of malnutrition (25). Our study was also compatible with previous studies, the frequency of individuals with malnutrition was found to be 13.6%, and the frequency of those with malnutrition risk was found to be 30%.

Previous studies (9,26) have shown that nutritional status declines with increasing age. Our study also confirmed this relationship and showed a positive relationship between age and malnutrition. In addition, it was determined that marital status and living environment pose a risk for malnutrition, and this rate is higher especially in singles and those who have to live with their caregivers for certain reasons.

Considering that appetite is strongly affected by the environment and mood, and the psychological and social changes that may occur with aging (27), this result was remarkable in that it showed that being dependent on others as well as being alone can pose a risk in terms of malnutrition.

Depression is a common condition in the elderly population and is associated with morbidity. A meta-analysis study reported that depressive complaints are common in elderly individuals (28). Our study supported these studies, which showed that depression was common in elderly patients (45%) and that women were especially at higher risk.

It has been reported that there is a positive correlation between depression and malnutrition in elderly individuals (30). Similarly, in this study, the malnutrition and malnutrition risk group had higher depressive symptom scores than the adequate nutritional status group, and a positive correlation was found between malnutrition severity and depressive symptoms. Although the causal relationship between depression and nutrition is not certain, malnutrition is accepted as one of the predictors of depression in elderly patients (31). A cohort study conducted in the USA found that depression was associated with weight gain in individuals younger than 50 years of age, while it led to weight loss at later ages (32). Therefore, this result may be related to the decrease in appetite accompanying depression (33), and it can be interpreted that the lack of essential nutrients in the body of malnourished patients activates some mechanisms that will lead to the development of depression (34). In this case, cognitive functions are also expected to be affected, and the positive relationship we found between depressive symptoms and cognitive impairment supported our judgment. Indeed, studies have argued that depression may be a risk factor for dementia and depressive symptoms may be observed during the development of cognitive impairment (35). In addition, existing depression is defined as a prognostic factor for the rapid progression of mild cognitive impairment (36). Therefore, early detection and treatment of malnutrition is vital for independent living.

In this study, according to the MMSE score, 12.5% of the elderly participants had severe cognitive impairment and 24.7% had mild cognitive impairment. The ratios obtained were higher than Mantzorou et al.'s study which reported that 18.2% of the population had mild, 13.6% moderate, and 2.7% severe cognitive impairment (9), and Plasman et al's sample study which reported the mild cognitive impairment rate as 22.2% (37). From this perspective, this study showed a relatively high prevalence of cognitive impairment in Turkish elderly people and pointed to a serious public health problem. In addition, our study showed a positive relationship between increased severity of malnutrition and cognitive impairment, and this result was consistent with studies showing that malnutrition is a prognostic factor for cognitive decline (38-40).

In our anthropometric analyzes, it was seen that BMI and upper middle arm and hip circumference measurements could be used in the evaluation of malnutrition. In the study of Gündüz et al., BMI was also found to be independently

associated with malnutrition (25). In fact, although it is known that BMI, arm and calf circumference measurements will be used in the evaluation of malnutrition (41), there was no difference in calf circumference results between the groups in this study. If this result is attributed to the physical differences between the populations and the disruptions in the standardization of the measurements, it was important in terms of revealing the necessity of considering all of the anthropometric measurements in the general evaluation.

Another correlation obtained in the study was that depressive symptom scores increased as the number of medications increased. Although the types of medicine used in our study were not evaluated, it is possible that some of the medicine used produced depressive effects. On the other hand, the use of multiple drugs may reflect more comorbidity, and increased comorbidity may impair mental health by creating biological, sociological and psychological problems.

There are some limitations of our study. First and perhaps most important of these, the rate of diagnosis of dementia and depression may have been found to be high, since the study was conducted in the geriatrics outpatient clinic in a tertiary health institution. Therefore, the results obtained may not reflect the entire population. The retrospective design of the study prevented the investigation of some social factors (economic status, family relationships, bereavement/grief status, and social stressors) that may affect the results. Prospective and multicenter studies in the future may correct these limitations. On the other hand, it had sufficient sample size and validated scales were used to measure cognitive functions and depressive symptoms. These data could add to the small but growing literature on nutrition, aging and health in Turkey.

CONCLUSION

In conclusion, malnutrition is common in older adults, and increasing age and living with a caregiver pose a risk for malnutrition. In addition, there is a relationship between cognitive dysfunction and depressive symptoms and malnutrition. Therefore, simple questionnaires and measurements used during routine outpatient controls of geriatric patients can detect the risk of malnutrition and provide guidance to clinicians in taking measures that will contribute to the improvement of mortality and morbidity of elderly patients by evaluating their cognitive and psychological status.

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Research Article

Is There an Association Between Benign Paroxysmal Positional Vertigo and the COVID-19 Pandemic?

Pandemi Sürecinde Bulunmanin Benign Paroksismal Pozisyonel Vertigo İle İlişkisi Var Mı?

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Abstract

Aim: To determine whether or not there is any relationship between benign paroxysmal positional vertigo (BPPV) and the COVID-19 pandemic.

Material and Methods: The study included 67 patients who presented at Karaman Training and Research Hospital between November 2020 and February 2021, were diagnosed with BPPV with provocative tests, and were applied with canal-specific repositioning manoeuvre. The patients were questioned in respect of how many days after the onset of dizziness complaints they presented at the polyclinic, whether or not they had previously experienced such an attack, how many times the manoeuvre was applied in treatment, and when the dizziness recovered after the manoeuvre. The patients were followed up for 12 months in respect of recurrence.

Results: The 67 patients comprised 64.2% females and 35.8% males with a mean age of 55.34±16.58 years. A previous attack was reported by 80.6% of the patients. During the mean 12-month follow-up period, 94% of the patients experienced no new attack. The mean number of therapeutic manoeuvres applied to each patient was 1.5. There was determined to be a history of COVID-19 infection in 14 patients.

Conclusion: The results of the study showed that there seemed to be a relationship between BPPV and the pandemic by COVID-19 infection affecting the peripheral vestibular system. The association with COVID-19 infection did not cause any increase in the number of therapeutic manoeuvres or BPPV recurrence. Further studies will contribute to clarifying this condition.

Keywords: Benign paroxysmal positional vertigo, Recurrence, COVID-19, Dizziness

Öz

Amaç: Bu çalışmamızda COVID-19 enfeksiyonuna bağlı pandemi sürecinde bulunmanın BPPV ile ilişkisi araştırılmaktadır.

Materyal ve Metot: Bu çalışmaya 2020 Kasım-2021 Şubat arasında Karaman Eğitim ve Araştıma Hastanesi'ne başvuran ve kendisine provakatif testlerle BPPV tanısı konulup kanala spesifik repozisyon manevrası uygulanan 67 hasta çalışmaya dahil edildi. Hastalara baş dönmesi şikayeti başladıktan kaç gün sonra polikliniğe başvurdukları, daha önce atak geçirip geçirmedikleri, tedavi için kaç defa manevra uygulandığı ve manevra sonrası baş dönmelerinin ne zaman düzeldiği soruldu. Rekürrens açısından hastalara 12 ay takip süreci uygulandı.

Bulgular: Çalışmaya katılanların %64.2'si kadın, %35.8'i erkeklerden oluşmaktaydı. Hastaların ortalama yaşları 55.34±16.58 idi. Hastaların %80.6'sinin daha önce atak geçirmedikleri tespit edildi. Ortalama 12 aylık takip sürecinde hastaların %94'ünde yeni bir atak tespit edilmedi. Hastalara uygulanan tedavi edici manevra sayısının ortalama 1.5 olduğu gözlendi. Hastaların 14'ünde COVID-19 enfeksiyonu öyküsü mevcuttu.

Sonuç: Çalışmamızda, COVID-19 enfeksiyonuna bağlı pandemi süreci periferik vestibüler sistemi etkileyerek BPPV ile ilişkili gibi görülmektedir. COVID-19 enfeksiyonuna bağlı pandemi süreci tedavi manevra sayısında ve BPPV rekürrensinde de bir artışa neden olmamaktadır. Bu konuda yapılacak çalışmalar bu durumun aydınlatılmasında bize ayrıca katkı sağlayacaktır.

Anahtar Kelimeler: Benign paroksismal pozisyonel vertigo, Rekürrens, COVID-19, Dizziness

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INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is a disease characterised by temporary nystagmus and vertigo triggered by changes in head position, and is the most common cause of peripheral type vertigo. Movement within the semicircular canal of separated fragments of otoconia is thought to be in the pathogenesis. The diagnosis of BPPV is made from patient history and the observation of typical positional nystagmus following the application of a provocative manoeuvre (1).

A previous study has shown a relationship between BPPV and positive viral serology in certain months of the year, especially in spring and autumn. It was reported in that study that the viral infection could cause the formation of BPPV attacks by causing the development of vestibulopathy or through the infection-related neurolabyrinth pathway (2).

There are few studies in literature which have examined the relationship between BPPV and COVID-19 infection. The aim of this study was to examine the relationship between BPPV determined during the pandemic associated with COVID-19 infection.

MATERIAL AND METHOD

The study included patients who presented at Karaman Training and Research Hospital, who were diagnosed with BPPV with provocative tests, and were applied with canal-specific repositioning manoeuvre. The patients were re-evaluated after 1 week, and recovery of nystagmus and symptoms was accepted as sufficient treatment. Patients were excluded from the study if the manoeuvre could not be applied, if they were mentally unbalanced, were determined with central vertigo, or were in the paediatric age group.

The files of 80 patients who met these conditions between November 2020 and February 2021 were examined. After implementation of the exclusion criteria and patients who withdrew during follow-up, the results of 67 patients were analyzed. The patients were followed up for 12 months in respect of recurrence.

A record was made for each patient of how many days after the onset of dizziness complaints they presented at the polyclinic, whether or not they had previously experienced such an attack, how many times the manoeuvre was applied in treatment, and when the dizziness recovered after the manoeuvre. Conditions such as osteoporosis, ear surgery, and head trauma were recorded in respect of the risk of recurrence.

Approval for this retrospective clinical study was granted by the Clinical Research Ethics Committee of Karamanoglu Mehmetbey University Medical Faculty (decision no:07-2021-12; dated:11.10.2021). Permission for the study was also obtained from the Ministry of Health. All procedures were applied in accordance with the 2008 Helsinki Declaration. All patients provided written informed consent.

Data obtained in the study were analyzed statistically using IBM SPSS vn.22.0 software. The Chi-square test and the Independent Samples t-test were used in the data comparisons. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The patients included in the study comprised 64.2% females and 35.8% males, giving a female /male ratio of 1.79/1, with a mean age of 55.34±16.58 years. No statistically significant difference was determined between the genders in respect of age. No significant difference was determined in respect of the time of presentation at the polyclinic, the number of manoeuvres applied, the time to recovery of dizziness, and recurrence of attacks according to age and gender ($p>0.05$).

A history of BPPV attack was determined in 80.6% of the patients. During the follow-up period of mean 12 months, 94% of the patients experienced no new attack. The number of therapeutic manoeuvres applied to the patients was observed to be mean 1.5 (Table 1). The time of presentation at the polyclinic was mean 6 days after the onset of complaints and the mean time to recovery of dizziness was 10 days.

A risk factor for BPPV, mostly osteoporosis, was determined in 8 patients. There was a history of COVID-19 infection in 14 of the 67 patients. Of these, 11 had not previously experienced an attack of BPPV, and 13 patients were determined to have experienced the BPPV attack following COVID-19 infection.

Table 1. The number of manoeuvres applied to patients and percentage values

No. of manoeuvres	No.of patients	Percentage (%)	Total % value
1	45	67.2	67.2
2	15	22.4	89.6
3	4	6	95.5
4	2	3	98.5
5	1	1.5	100
Total	67	100	100

DISCUSSION

The most frequently seen general symptoms during the COVID-19 pandemic are listlessness, fatigue, headache, fever, and myalgia (3). In a study by Elibol, it was reported that other symptoms such as vertigo, tinnitus, and sudden hearing loss, which are otorhinolaryngological symptoms, were less frequently seen than the most commonly seen symptoms such as cough, anosmia, changes in sense of taste, and sore throat in patients determined with

COVID-19 infection. It was also shown in that study that otorhinolaryngological symptoms were seen more often in females than in males (4).

Picciotti et al reported that BPPV was determined in 8 patients following COVID-19 infection, and these were all successfully treated with therapeutic manoeuvres. In that study, the occurrence of BPPV after COVID-19 infection was considered to be linked to the prolonged bedrest and drugs used, and especially to the secondary inflammatory response and the direct damage to the peripheral vestibular system by the viral infection associated with the interaction of the otolithic membrane related to the cytopathic effect of the virus (5). In another study, the number of BPPV patients were compared in the months of July and August in 2019 before the pandemic, and in 2020, during the pandemic. There was observed to be an increase in the prevalence of BPPV during the preventative quarantine for COVID-19 and at a higher rate in females (6). BPPV was determined more often in the current study females, consistent with that study. In another study that showed that BPPV developed after COVID-19 infection, it was reported that the effect on the inner ear blood supply associated with microthrombus and hypercoagulation could be responsible in the pathophysiology (7).

Although the cause of BPPV is not known in the majority of cases, previous studies have shown an association with age over 65 years, female gender, the presence of osteoporosis, various diseases affecting the inner ear, prolonged bedrest, and head trauma (8-12). The predominance of female gender (1.79/1) in the current study was seen to be consistent with the literature .

In the current study, the predominance of female gender, the prolonged bedrest of patients associated with the pandemic, the greater number of patients who had not had a previous attack, and that the majority of the patients were determined with BPPV following COVID-19 infection, suggest that there could be a relationship between BPPV and the COVID-19 pandemic. Probable reasons for this could be the restricted physical activity of elderly patients because of the pandemic precautions, a more sedentary lifestyle because of various restrictions related to the pandemic, prolonged bedrest of patients who had contracted COVID-19 infection, the viral load associated with the pandemic (13), direct damage to the peripheral vestibular system caused by the viral infection (5), and inner ear blood supply affected by the virus (7).

The success of the therapeutic manoeuvres in the current study was observed to be consistent with the findings of previous studies (14). When the number of therapeutic manoeuvres applied to the patients and the fact that no new attack was determined in 94% of the patients during the follow-up period of mean 12 months are taken into consideration, these suggest that the pandemic had no short-term effect in respect of the recurrence of BPPV and did not cause an increase in the number of therapeutic manoeuvres required.

A previous study in Turkey showed a relationship between BPPV and positive viral serology especially in the spring and autumn months, and reported that viral infection led to BPPV attacks (2). Another study from the USA reported that a fall in Vitamin D level associated with seasonal changes in early spring led to BPPV attacks (14). When the previous study from Turkey is taken into consideration together with the inclusion of the autumn months in the current study, an increase in viral infection at the same time as seasonal changes could be thought to conribute to the formation of BPPV.

The time of presentation of patients at the polyclinic was determined to be mean 6 days, suggesting that being in a period of pandemic and the presence of some restrictions did not cause an interruption or lengthening of time to presentation at the polyclinic. Previous studies have shown that the period of residual dizziness after BPPV can last from a few days to a few weeks (15,16). Consistent with those studies, the time to recovery of dizziness in the current study was determined to be mean 10 days. According to this finding, the pandemic did not seem to cause any prolonged duration of residual dizziness.

CONCLUSION

The results of this study show that by affecting the peripheral vesttibular system, the pandemic related to COVID-19 infection seems to be associated with BPPV. However, the COVID-19 pandemic conditions did not cause an increase in the number of therapeutic manoeuvres or in recurrence of BPPV. Further studies on this subject will contribute to clarifying this condition.

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Research Article

Comparison of Emotion Regulation Strategies in University Students with and without Food Addiction

Yeme Bağımlılığı Olan ve Olmayan Üniversite Öğrencilerinde Duygu Düzenleme Stratejilerinin Karşılaştırılması

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Abstract

Aim: The purpose of the present study is to compare the emotion regulation strategies in university students with and without food addiction.

Material and Methods: 214 university students were included in the study. Each participant completed Yale Food Addiction Scale (YFAS), Difficulties of Emotion Regulation Scale (DERS) and a sociodemographic form. The body mass index (BMI) of each participant was calculated by dividing the body weight by the square of the height in meters.

Results: %18.7 of the participants (n=40) met the diagnostic criteria of food addiction according to the YFAS. The frequency of food addiction in male participants was statistically higher than female participants (p=0.006). Non-acceptance, strategies and impulses subscales scores of DERS were statistically higher in participants with food addiction than those without food addiction (p=0.005; p<0.001 and p=0.048 respectively). There were correlations between number of food addiction criteria and strategies subscale score and DERS total score (r=.41 and r=.36 respectively).

Conclusion: It can be said that individuals with food addiction experience more difficulty in emotion regulation

Keywords: Addiction, food addiction, emotion regulation, university students

Öz

Amaç: Bu çalışmanın amacı, yeme bağımlılığı olan ve olmayan üniversite öğrencilerinin duygu düzenleme stratejilerini karşılaştırmaktır.

Materyal ve Metot: Araştırmanın örneklemini 214 üniversite öğrencisi oluşturdu. Her katılımcı Yale Yeme Bağımlılığı Ölçeği (YYBÖ), Duygu Düzenleme Güçlüğü Ölçeği (DDGÖ) ve sosyodemografik formu doldurdu. Her katılımcının vücut kitle indeksi (VKİ) vücut ağırlığının, boyunun metre cinsinden karesine bölünmesiyle hesaplandı.

Bulgular: Katılımcıların %18.7'si (n=40) YYBÖ'ye göre yeme bağımlılığı tanı kriterlerini karşıladı. Erkek katılımcılarda yeme bağımlılığı yaygınlığı kadın katılımcılara göre daha yüksekti (p=0,006). DDGÖ kabul etmeme, stratejiler ve dürtüler alt ölçek puanları, yeme bağımlılığı olanlarda yeme bağımlılığı olmayanlara göre istatistiksel olarak daha yüksekti (sırasıyla p=0,005; p<0,001 ve p=0,048). Yeme bağımlılığı ölçüt sayısı ve stratejiler alt ölçek puanı ile DDGÖ toplam puanı (sırasıyla r=.41 ve r=.36) arasında pozitif yönde ilişki saptandı.

Sonuç: Bu çalışmanın bulgularına göre, yeme bağımlılığı olan bireylerin duygu düzenlemede daha fazla zorluk yaşadıkları söylenebilir.

Anahtar Kelimeler: Bağımlılık, yeme bağımlılığı, duygu düzenleme, üniversite öğrencileri

INTRODUCTION

In recent years, there has been evidence that some foods cause addictive consumption behaviors. Although the term food addiction has been used frequently in the last few decades, food addiction is still a controversial concept. It is still debated whether food addiction is a type of addiction that occurs with the direct biological effects of some foods, or whether it is behavioral addiction (1,2). Food addiction (FA) has been defined as craving for certain foods with increased stress, loss of control over eating behavior, and excessive consumption of particularly tasty and high-carbohydrate foods (3). Although clinical studies have reported that it is more common in individuals followed up with a diagnosis of obesity, it has been emphasized that the frequency of FA in non-obese individuals also draws

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attention (3,4).

Some neuroimaging researches have shown that individuals who are thought to be food addicts have changes in the central nervous system similar to those in substance abusers. It has been reported that the changes observed in the amygdala, orbitofrontal cortex, insula and striatal areas in individuals with FA are similar to those of drug/substance addicted individuals (5,6). Gunnars structured the definition of FA based on the substance addiction diagnostic criteria, along with the similarities of clinical features and neurobiological changes (7). According to the definition of Gunnars, symptoms such as craving for some foods despite the feeling of satiety, not being able to control the eating behavior when starting to eat, failure in attempts to prevent eating, continuing to eat these foods continuously despite the negative physical effects are important diagnostic criteria for FA (7).

The concept of emotion regulation has been defined as recognizing emotions, recognizing what emotions they experience in which situations, having the ability to express emotions effectively and using emotions in a healthy way (8). Gratz and Roemer defined emotion regulation difficulties as difficulties in controlling impulses and acting in accordance with a purpose in the presence of negative emotions, inability to understand emotions and not accepting experienced emotions, and lack of awareness of emotions (9). Some studies have shown that individuals who have difficulty in coping with negative emotions consume foods with high caloric value and have more difficulty in controlling their eating behavior (10-12). The fact that the relationship between negative emotions accompanying the stress response and eating behavior has been shown in many studies has led to the use of the concept of "emotional eating" in the literature (13,14).

Although results suggesting that there may be a relationship between difficulty in emotion regulation and eating behavior have been reported in the literature, it has not been sufficiently investigated whether emotion regulation strategies differ in individuals with FA compared to individuals without FA. The purpose of the present study is to compare the emotion regulation strategies of individuals with and without FA in university students.

MATERIAL AND METHOD

214 university students who are continuing their education at a foundation university in Istanbul were included in the study. Inclusion criteria for the study; not having a known severe mental illness (schizophrenia, bipolar disorder, alcohol/substance use disorder), no history of psychotropic drug use in the last 6 months, and body/mass index below 30 kg/m². Non-Interventional Ethics Committee of Halic University was approved the study protocol (2018/60).

Sociodemographic form: It was a questionnaire that includes the participant's characteristics such as age, gender, marital status.

Yale Food Addiction Scale (YFAS): Gearhardt, Corbin, and Brownell developed the scale by considering The Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision DSM-IV-TR substance addiction diagnostic criteria (15). The Turkish validity and reliability study of the scale was carried out by Bayraktar et al (16). The internal consistency coefficient (Cronbach alpha) for the Turkish version of the scale was .93. The scale consists of 27 items in total. For the diagnosis of FA, in addition to meeting at least 3 of the 7 diagnostic criteria, clinical significance is required. These sub-criteria include excessive and long-term consumption of food, desire to quit and unsuccessful attempts to quit, the level of time and activity spent in accessing and using food, the effect of social-occupational functioning, continued use despite knowing that it has adverse effects and consequences, tolerance, withdrawal symptoms.

Difficulties of Emotion Regulation Scale (DERS): It is a five-point Likert-type scale consisting of 36 items developed by Gratz and Roemer (9). DERS includes six-subscale as awareness, clarity, non-acceptance, strategies, impulse, and goals. These subscales assess awareness of emotional reactions, lack of understanding of emotional reactions, rejection of emotional reactions, narrow availability of emotion regulation strategies that are thought to be effective, difficulty in impulse control when experiencing negative emotions, and engaging in goal-oriented behaviors when negative emotions are felt. The Turkish validity and reliability study was carried out by Rugancı and Gençöz (17). The Cronbach's alpha coefficient for the Turkish version of the scale was .93, and the test-retest consistency was 83. The Cronbach's alpha coefficients of the sub-dimensions of the scale are .82 for clarity, .90 for goals, .90 for impulses, .83 for non-acceptance, .89 for strategies, and .75 for awareness. High scale scores indicate difficulty in emotion regulation.

Body/Mass Index (BMI): It was obtained by dividing the participants' body weight by the square of their height in meters (kg/m²) (18).

Statistical Analysis

All statistical analyzes of the study were performed using SPSS 23.0 package program. The normality distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. Parametric tests were used in the analysis of the data due to the normal distribution of the data. DERS subscale scores were compared by using independent samples t-test among students with and without FA. Categorical variables of the groups were compared using the chi-square test. The relationship between the number of FA symptoms and the DERS subscale scores of the participants with FA was analyzed using the Pearson correlation analysis. The level of significance was accepted as $p<0.05$ in all statistical analyzes.

RESULTS

Of the 214 participants, 72.9% (n=156) were male and 27.1% (n=58) was female. The mean age of the participants was 21.67±3.12. All sociodemographic features of the participants were shown in Table-1.

Table 1. Sociodemographic features of the participants

	n(X)	%(ss)
Gender		
Male	156	72.9
Female	58	27.1
Age		
20 ≤	112	52.3
21-23	66	30.8
≥ 24	**36**	**16.8**
Class		
First	44	20.6
Second	38	17.8
Third	66	30.8
Fourth	66	30.8
Mother's Education Level		
Primary	94	43.9
High	74	34.6
University	46	21.5
Father's Education Level		
Primary	**68**	**31.8**
High	**84**	**39.3**
University	**62**	**29.0**
Number of Siblings		
Single	**51**	**23.8**
1	**74**	**34.6**
2	**54**	**25.2**
≥ 3	**35**	**16.4**
Monthly spending amount		
≤750 Turkish Lira	**72**	**33.6**
751-1000 Turkish Lira	**86**	**40.2**
≥ 1001 Turkish Lira	**56**	**26.2**

18.7% of the participants (n=40) met the diagnostic criteria for FA according to the YFAS. 23.1% (n=36) of male participants and 6.9% (n=4) of female participants met the criteria for FA, and the frequency of FA in male participants was found to be statistically significantly higher than in females (x2=7.283; p=0.006).

DERS non-acceptance, strategies, and impulse subscales scores were higher in the participants with FA than those without FA (p=0.005, p<0.001 and p=0.048, respectively). There was no difference between the DERS awareness, clarity and goals subscale scores of the participants with and without FA (p=0.072, p=0.099 and p=0.965, respectively) (Table-2).

Table 2. Comparison of emotion regulation scale subscale and total scores of participants with and without food addiction

	n	X	ss	t	p
Awareness					
Yes	40	22.20	3.70	1.81	0.072
None	174	20.98	3.89		
Clarity					
Yes	40	12.60	1.88	-1.66	0.099
None	174	13.18	2.04		
Non-acceptance					
Yes	40	14.40	5.68	2.93	0.005
None	174	11.61	4.16		
Strategies					
Yes	40	23.70	7.36	4.44	0.000
None	174	18.29	4.83		
Impulse					
Yes	40	15.00	5.20	2.03	0.048
None	174	13.24	3.56		
Goals					
Yes	40	14.30	4.44	-0.04	0.965
None	174	14.33	3.62		
Total					
Yes	40	102.20	19.73	3.23	0.002
None	174	91.63	13.14		

There was positive correlation between the number of FA diagnostic criteria and the DERS strategies subscale score and DERS total score of the participants with FA (r=.41 and r=.36, respectively) (Table-3).

Table 3. Correlations between the number of food addiction symptoms and emotion regulation strategies in participants with food addiction

	Number of FA symtomps
DERS-Awareness	.14
DERS-Clarity	.09
DERS-Non-acceptance	.27
DERS-Strategies	.41*
DERS-Impulse	.22
DERS-Goals	.09
DERS-Total	.36*

* p<0.05

DISCUSSION

The purpose of the present study was to compare emotion regulation strategies in university students with and without FA. Our findings showed a significant portion of university students (18.7%) met the diagnostic criteria for FA according to the YFAS, and university students who were thought to be food addicts had more difficulties in emotion regulation.

There has been a notable increase in the number of national and international studies investigating the prevalence of FA. Studies with different sample groups have shown that the frequency of FA varies in a wide range (4,19,20). According to the results of the study conducted by Brunault et al. in a non-clinical sample, the frequency of FA is found to be 16.9% (21). In a study conducted in Turkish population, the frequency of FA among university students is reported as 11.4% (22). The rate of FA obtained in the sample of this study differs from the rates reported in previous studies. This difference between the results obtained can be explained by the cross-sectional characteristics of the studies and the different sociodemographic features of the selected samples. However, the use of self-report scales for the diagnosis of FA may be effective in the emergence of different findings. Future studies that will help define food addiction clinically may help to interpret self-reported findings more objectively.

The findings of this study have shown that the prevalence of FA is higher in males than in females. Dinçyürek et al. (2018) have reported that FA is higher in male university students than those in females (23). In a study conducted by Özgür and Uçar (2018), it has been found that FA differed between genders (24). Different reports on the prevalence of FA among the gender may be related to the cross-sectional nature of the studies and, accordingly, the different distribution of FA among university students. On the other hand, the presence of evidence showing lower impulse inhibition in young adult males may explain the higher addiction rate in males (25,26). Indeed, according to the findings of a recently published study, impulsivity may be a predictor for food addiction (27). Future studies may better explain whether food addiction differs between genders, and the relationship between impulse inhibition and addiction severity in individuals with FA.

The findings of this study have shown that individuals with FA have more difficulty in using functional strategies in emotion regulation. Some studies reveal that individuals with FA generally have insufficient skills to cope with undesirable emotions and experience more emotion regulation difficulties. Individuals who cannot use functional emotion regulation strategies resort to non-adaptive cognitive emotion regulation strategies. Some studies have shown that the inability to cope with emotions causes eating disorders (28,29). However, the fact that mood disorders often accompany eating disorders reveals that these individuals experience more negative emotions (30,31). It is stated in many studies that emotion regulation difficulties, which are frequently related to anorexia nervosa and bulimia nervosa, appear as purging and binge eating disorders in bulimia nervosa and excessive exercise behaviors in anorexia nervosa (32,33). Svaldi et al. have compared difficulty in emotion regulation between eating disorders patients and healthy controls (34). Accordingly, while the group with eating disorder had higher emotional intensity and difficulty in emotion regulation than the control group, it was determined that emotion acceptance, emotional openness and awareness were higher in the healthy control group. In another study by Sternheim et al., it is revealed that patients with eating disorders experienced more anxiety and designed more catastrophizing anxiety than the healthy controls (35). Brockmeyer et al. have reported that individuals diagnosed with anorexia nervosa and blumia nervosa have more emotion regulation difficulties than healthy controls (36). In another study, emotion regulation difficulties are found to be higher in patients with anorexia nervosa than in the healthy volunteers (37). In another study conducted with male students by Lavender and Anderson, it is reported that difficulty in emotion regulation is a predictor of FA (38). It can be said that the results of the presents study are generally similar to the results in the literature. As a matter of fact, according to the results of the study, it is thought that participants with FA have more difficulty in accepting negative emotions, developing functional strategies to cope with negative emotions, and providing impulse control when they encounter negative emotions. Observing more difficulty in emotion regulation in food addiction is interpreted as a maladaptive copying strategy that mediates the reduction of negative emotional pressure of inappropriate eating behavior. In other words, it can be said that individuals who have difficulty in accepting negative emotions and maintaining impulse control have more difficulty in controlling their eating behavior (27). In this study, the determination of a relationship between the number of symptoms of the participants with FA and the difficulty in developing functional strategies to cope with negative emotions can be interpreted as the severity of addiction may be related to experiencing more problems

in some areas of emotion regulation. As a matter of fact, according to the results of some studies, it has been reported that individuals with FA may encounter more difficulties in the severity of addiction and emotion regulation (39).

This study has some limitations. First of all, there is no clear clinical consensus on the diagnosis of FA yet. In this case, the interpretation of the diagnosis of FA with the self-assessment scale can be interpreted as a limitation. Although YFAS evaluates food addiction according to substance addiction diagnostic criteria, the fact that this scale was prepared according to DSM-IV diagnostic criteria can also be considered as a limitation. As a matter of fact, some changes were made in the diagnostic criteria of substance abuse with the DSM-5. The fact that other findings obtained from the study were obtained with self-evaluation scales is limited to the subjective definitions of the findings. In addition, it can be stated as a limitation that the study sample is limited to only university students in an educational institution.

CONCLUSION

It has been concluded that individuals with FA have more difficulty in accepting negative emotions, reaching functional coping strategies that can be used to manage negative emotions, and maintaining impulse control while experiencing negative emotions. Therefore, psychosocial intervention strategies focused on emotion regulation may help to obtain positive results in treatment in individuals with FA.

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Research Article

Postnatal Outcomes of the Traumatic Childbirth Perception: An Analysis of the Traumatic Childbirth Perception with Pregnancy Avoidance and Mental Health Outcomes

Travmatik Doğum Algısının Doğum Sonu Sonuçları: Travmatik Doğum Algısının Gebelikten Kaçınma ve Mental Sağlık Sonuçlarının Analizi

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Abstract

Aim: Several postpartum outcomes of traumatic birth perception have been identified. However, the postpartum results could not be clarified. The study aims were to describe and compare the pregnancy avoidance and mental health outcomes in the women with and without traumatic childbirth perception and to infer which factors may influence the traumatic childbirth perception.
Material and Methods: This cross-sectional and comparative study was conducted with 1109 women who were in the 6-12 months of the postnatal period. The Scale of Traumatic Childbirth Perception (STCP), the Desire to Avoid Pregnancy (DAP) Scale, and the Depression Anxiety Stress Scale-21 were used in the collection of research data. In the study, the women with a moderate or higher level of traumatic childbirth perception (53 points or above) were categorized as 'childbirth perception traumatic'.
Results: In the study, 74.8% of the women obtained 53 points or above from the STCP. It was found that, of the women with traumatic childbirth perception, 46.4% exhibited depressive symptoms, 54.5% experienced anxiety, 41.1% had stress, and the mean of their DAP scores was 2.13±0.96. Women with traumatic birth perception were higher in avoiding depression, anxiety, stress and pregnancy ($p<0.05$). The logistic regression analysis showed that that the variables of being below the age of 30 years (OR=0.543), primiparity (OR=0.459), having depressive symptoms (OR=2.627), having anxiety (OR=1.752), and pregnancy avoidance (OR=1.701) were significant risk factors for traumatic childbirth perception.
Conclusion: It has been found that the perception of traumatic birth can lead to psychological problems and pregnancy avoidance in women.

Keywords: Anxiety, childbirth perception, depression, pregnancy avoidance, stress, trauma

Öz

Amaç: Travmatik doğum algısının çeşitli postnatal sonuçları tanımlanmıştır. Ancak net değildir. Çalışmanın amacı doğum sonu dönemde travmatik doğum algısı olan ve olmayan kadınlarda gebelikten kaçınma ve mental sağlık sonuçlarını tanımlamak ve karşılaştırmak ve travmatik doğum algısını hangi faktörlerin etkileyebileceğini anlamaktır.
Materyal ve Metot: Kesitsel ve karşılaştırmalı tipte tasarlanan araştırma Türkiye'de, 15 Şubat- 15 Mart 2021 tarihleri arasında yürütüldü. Çalışmaya doğum sonu 6-12 ayda olan gönüllü 1109 kadın katıldı. Veriler sosyal medyada (Facebook, Instagram gibi) lohusa kadın grupları aracılığıyla web tabanlı bir çevrimiçi anket kullanılarak toplandı. Veriler toplanırken Kişisel Bilgi Formu, Travmatik Doğum Algısı Ölçeği (TDAÖ), Gebelikten Kaçınma Ölçeği (GKÖ) ve Depresyon Anksiyete Stres Ölçeği (DASÖ-21) kullanıldı. Çalışmada orta düzey ve üzeri travmatik doğum algısı olanlar (53 ve üzeri puan) "travmatik doğum algısı olanlar" olarak sınıflandırıldı.
Bulgular: Kadınların %74.8'i (n=830, travmatik doğum algısı olanlar) TDAÖ'den 53 ve üzeri puan aldı. Travmatik doğum algısı olanların %46.4'ünün depresif semptom, %54.5'inin, anksiyete ve %41.1'inin stres yaşadığı; GKÖ skorunun 2.13±0.96 olduğu belirlendi. Travmatik doğum algısı olan kadınların depresif semptom, anksiyete, stres ve gebelikten kaçınma olasılığının daha fazla olduğu belirlendi ($p<0.05$). Lojistik Regresyon analizine göre kadınlarda 30 yaş altı olma (OR=0.543), primiparite (OR=0.459), depresif semptom varlığı (OR=2.627), anksiyete varlığı (OR=1.752) ve gebelikten kaçınma (OR=1.701) değişkenlerinin travmatik doğum algısı için önemli risk faktörleri olduğu saptandı.
Sonuç: Araştırma bulguları travmatik doğum algısının kadınlarda psikolojik sorunlara ve gebelikten kaçınmaya neden olabileceğini ortaya koymuştur.

Anahtar Kelimeler: Anksiyete, doğum algısı, depresyon, gebelikten kaçınma, stres, travma

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INTRODUCTION

Childbirth serves as a critical role transition in the women's lives and is generally viewed as a positive occasion that changes the women's lives (1). Traumatic childbirth is, on the other hand, the case that the woman perceives the act of childbirth as a threat likely to lead to the injury or death of the infant to be born and herself (2). The women with traumatic childbirth experience define the moment of giving birth as a moment of helplessness, strong fear, and horror (1, 3). In relation to the prevalence of traumatic childbirth perception, various percentages are presented. Around 20-45% of the women state that they had a traumatic childbirth experience (4-6). The traumatic childbirth perception that is described as negative is the entire set of perceptions that come into play as a consequence of blending the childbirth theme created by the woman in her mind and all information acquired by her about childbirth with each circumstance that she is likely to experience during the act of giving birth (7). The traumatic childbirth perception is made up of thoughts, behaviors, information, and attitudes related to that the childbirth is quite bloody, painful, and terrifying incident (8).

The childbirth perception is affected by the woman's viewpoint about childbirth, personal characteristics, previous childbirth experience, and the cultural structure of the society (3). Also, tokophobia plays a quite crucial role in the formation of traumatic childbirth perception (2, 9). Having excessive anxiety and fear can have a negative effect on the woman both physically and emotionally, and thus, even if the woman wants to have a baby, she can avoid becoming pregnant and, accordingly, giving birth (10,11). To avoid pregnancy, particularly the women with tokophobia can prefer to use the birth-control family planning methods that have high rates of effectiveness (12,13).

If childbirth takes place as a negative experience for the women, the women can develop conflicting feelings (14). It was ascertained that, in the postnatal period, the traumatic experience was associated with anger, guilt, depression, and suicide (6, 15). In a qualitative study conducted with the participation of women experiencing childbirth trauma, it was put forward that the women had negative feelings such as fear, horror, and sadness during the process of childbirth (16).

The perception that childbirth which is a natural component of the female sexuality is a traumatic experience besides the psychological problems likely to be produced by this perception can lead to negative outcomes for the woman herself, her family, and the future generations (7). Having awareness about the variables that are associated with the traumatic childbirth perception in the woman can make it possible to take psychological initiatives at the early stage. Therefore, this study aimed to define and compare the pregnancy avoidance and mental health outcomes of the women with traumatic childbirth perception and the women with no traumatic childbirth perception in the postnatal period and to understand which factors were likely to affect the traumatic childbirth perception.

MATERIAL AND METHOD

Study design and setting

Designed as a cross-sectional and comparative study, the research was carried out in Turkey on 15 February - 15 March in 2021. The research data were collected with a web-based online survey form shared via puerperal women groups in social media (Facebook, Instagram, and so on). The survey form was created by using the application, Google Forms (Google LLC, Mountain View, CA, the USA), and the survey link was shared with the women through social media. The first page of the online survey form presented information on the aim and content of the research besides a form for the women to express consent to participate in the study. The women who consented to participate in the research and satisfied the required inclusion criteria were included in the study. The criteria prescribed for being included in the research were for the woman to be in the 6-12 months of the postnatal period, to be aged 18 years or above, and to have no complications developing in her or her newborn in the postnatal period. A total of 1132 women responded to the online survey. The survey forms with missing data, incomplete parts, or inaccurate coding were identified, and accordingly, 23 respondents were left out of the evaluations as their survey forms were deemed ineligible for evaluations. Thus, the research sample was comprised of 1109 women in total. In the research, upon the collection of research data, the women were categorized into two groups as per having traumatic childbirth perception. In this respect, the women who obtained 52 points or below from the Scale of Traumatic Childbirth Perception were categorized as 'childbirth perception non-traumatic' whereas the women who had 53 points or above were grouped as 'childbirth perception traumatic'. There were 279 women in the group categorized as 'childbirth perception non-traumatic' whilst 830 women were present in the group categorized as 'childbirth perception traumatic', and the data obtained from the two groups were compared.

Measures

The research data were collected by using the Personal Information Form, the Scale of Traumatic Childbirth Perception (STCP), the Desire to Avoid Pregnancy (DAP) Scale, and the Depression Anxiety Stress Scale-21 (DASS-21).

Personal Information Form

This form had questions designed to find out the women's socio-demographic and obstetric characteristics (age, education level, income level, employment status, marriage duration in years, method of childbirth, parity, pregnancy planning, and using contraceptive methods).

STCP

Yalnız H, et al. (2016) developed the scale was to evaluate the traumatic childbirth perception levels of the women in the reproductive age and performed the study to

test its validity and reliability in Turkish (2). The scale is comprised of 13 questions aspiring to uncover the thoughts and feelings such as anxiety, fear, and worry that the woman has when she thinks of the childbirth concept. Each problem is scored from 0 (I am not afraid at all) to 10 points (I am extremely afraid). The minimum and maximum scores to be obtained by a respondent from the scale are respectively 0 and 130 points. The scores ranging from 0 to 26 points, from 27 to 52 points, from 53 to 78 points, from 79 to 104 points, and from 105 to 130 points successively refer to 'very low-level', 'low-level', 'moderate-level', 'high-level', and 'very high-level' traumatic childbirth perception. The Cronbach's alpha coefficient was found as 0.89 for the scale (2). The women with a medium or higher level of traumatic childbirth experience (53 points or above) were categorized as 'childbirth perception traumatic' in this current study. The Cronbach's alpha coefficient was calculated as 0.90 for the scale under the current study.

DAP Scale

The scale was developed by Rocca, Ralph, Wilson, Gould, and Foster (2019) and the study to test its validity and reliability in Turkish was conducted by Karataş Okyay, Güney, and Uçar (2021) (17,18). The scale addresses a woman's future preferences about pregnancy and childbirth. Comprised of 14 items, the scale pertains to the woman's emotions and thoughts about becoming pregnant and childbirth. The items of the five-point Likert-type scale are scored as 0 (I strongly agree), 4 (I strongly disagree). Seven items of the scale are reverse-scored. After the scores calculated from the reverse-scored items are also converted into straight scores, they are added to the scores obtained from the straight-scored items. Subsequently, this sum is divided by 14 and hence, the final score is obtained. The minimum and maximum scores to be obtained from the scale are consecutively 0 and 4 points. A high score obtained from the scale shows that the woman has a high-level desire to avoid pregnancy. As per the analysis of internal consistency conducted to find out the reliability of the scale, the Cronbach's alpha coefficient was found as 0.94 for the scale (18).18 In this current study, the Cronbach's alpha coefficient was calculated as 0.94 for the scale.

DASS-21

The DASS-21 is the measurement tool abridged from the 42-item scale that was developed by Lovibond and Lovibond to evaluate the individual's depression, anxiety, and stress levels (19). The study to test the validity and reliability of the scale in Turkish was performed by Sarıçam (2018). The scale has three sub-scales, that is, depression, anxiety, and stress. Each sub-scale has seven items and thus, the overall scale has 21 items. The items of the four-point Likert-type scale are scored from 0 (Never) to 3 (Always). The scores obtained by a respondent from items under each sub-scale are summed and the sum is evaluated as per a score range specific to each sub-scale. In this regard, the score ranges that are taken into consideration in the evaluations are exhibited in Table 1 (20).

Table 1. DASS-21 Scoring Ranges

Level	Depression	Anxiety	Stress
Normal	0-4	0-3	0-7
Mild	5-6	4-5	8-9
Moderate	7-10	6-7	10-12
Severe	11-13	8-9	13-16
Extremely severe	14+	10+	17+

DASS-21: Depression Anxiety Stress Scale

As the measure of internal consistency, the Cronbach's alpha coefficient was found successively as 0.87, 0.85, and 0.81 for the depression, anxiety, and stress sub-scales (20). Under this current study, the Cronbach's alpha coefficient was calculated consecutively as 0.79, 0.87, and 0.85 for the above DASS-21 sub-scales.

In this current study, the women were divided into two groups as per their depression, anxiety, and stress levels. The women who were deemed to have normal levels of depression, anxiety, and stress as per Table 1 were evaluated as 'having no depression', 'having no anxiety', and 'having no stress'. In this context, firstly, the women who obtained 0-4 points from the depression sub-scale were categorized as 'having no depression' while the women who obtained 5-21 points were categorized as 'having depression', secondly, the women who obtained 0-3 points from the anxiety sub-scale were categorized as 'having no anxiety' whilst the women who obtained 4-21 points were categorized as 'having anxiety', and thirdly, the women who obtained 0-7 points from the stress sub-scale were categorized as 'having no stress' whereas the women who obtained 8-21 points were categorized as 'having stress'.

Statistical analysis

The research data were evaluated with SPSS 25.0 for Windows (SPSS, Chicago, IL, USA). The descriptive statistics were expressed as number, percentage, mean, and standard deviation. While analyzing the research results, the women who obtained 0-52 points from the STCP were categorized as 'childbirth perception non-traumatic' whereas the women who obtained 53-130 points from the STCP were characterized as 'childbirth perception traumatic'. The chi-squared test was used in the comparison of the categorical independent variables. In the evaluation of the continuous data, firstly, whether the variables were normally distributed was checked via the Kolmogorov-Smirnov test. As the data were normally distributed, independent samples t-test was utilized in the comparison of the two groups whilst one-way analysis of variance was employed in the comparison of multiple groups. The variables affecting the traumatic childbirth

perception in the women were evaluated with logistic regression analysis. In the context of identifying the variables to be considered under the regression model, the variables that had a statistically significant relationship ($p<0.05$) with the traumatic childbirth perception were included in the model. In this regard, the regression model covered the age, income level, parity, and the use of contraceptive methods together with the scales that identified the levels of depression, anxiety, stress, and pregnancy avoidance. The statistical significance was identified if the P-value was lower than 0.05.

Ethical aspect of the research

Before collecting the research data, the ethical endorsement was obtained from the Health Sciences Non-Invasive Clinical Trials and Publications Ethics Committee (Endorsement no. 2021/1694). Upon getting information about the research on the first page of the survey form, the respondents were informed that the confidentiality of their personal data would be protected.

RESULTS

In the context of this study, it was found that, of the women, 7.4% had very low-level traumatic childbirth perception (n=82), 17.8% had low-level traumatic childbirth perception (n=197), 30.4% had moderate-level traumatic childbirth perception (n=337), 29.8% had high-level traumatic childbirth perception (n=331), and 14.6% had very high-level traumatic childbirth perception (n=162). In the study, 74.8% of the women obtained 53 points or above from the STCP (n=830, childbirth perception traumatic) whereas 25.2% of them had 52 points or below (Figure 1). On the basis of the STCP scores, Table 2 displayed the comparison of traumatic childbirth perception according to the characteristics of the women. It was discerned that the women who were aged 30 years or below, who had moderate/high-level income, who were primiparous, and who currently used contraceptive methods had higher frequencies of having 'childbirth perception traumatic' and the differences between the groups were statistically significant ($p<0.05$, Table 2).

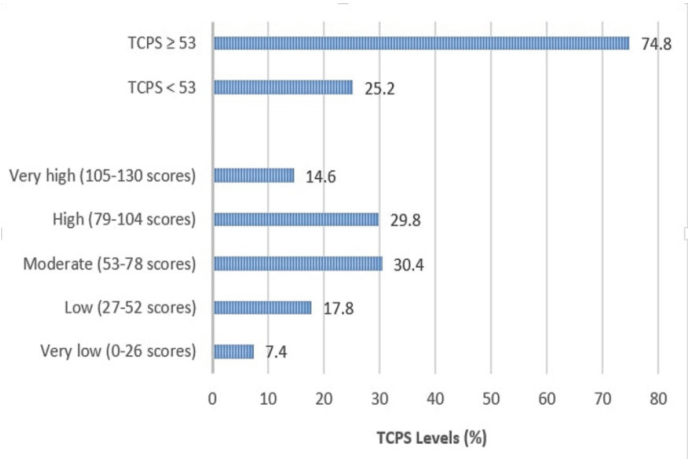


Figure 1. Women's Perception of Traumatic Childbirth Levels

Table 2. Comparison of traumatic childbirth perception (according level of STCP) according to the characteristics of the women (n=1109)

Characteristics	STCP < 53 score (n=279)		STCP ≥ 53 score (n=830)		Total (n=1109)		Test* and p value
	n	%	n	%	n	%	
Age, y							
≤30	112	40.1	422	50.8	534	48.2	χ^2=9.576
>30	167	59.9	408	49.2	575	51.8	p=0.002
Educational level, y							
≤12	170	60.9	535	64.5	705	63.6	χ^2=1.121
>13	109	39.1	295	35.5	404	36.4	p=0.290
Income status							
Low	6	2.2	45	5.4	51	4.6	χ^2=5.093
Moderate/ High	273	97.8	785	94.6	1058	95.4	p=0.024
Employment status							
Employed	79	28.3	204	24.6	283	25.5	χ^2=1.534
Unemployed	200	71.7	626	75.4	826	74.5	p=0.215
Marriage, y							
≤5	100	35.8	330	39.8	430	38.8	χ^2=1.349
≥ 6	179	64.2	500	60.2	679	61.2	p=0.245
Mode of birth							
Vaginal	165	59.1	489	58.9	654	59.0	χ^2=0.004
Caesarean section	114	40.9	341	41.1	455	41.0	p=0.948
Parity							
Primipara	35	12.5	159	19.2	194	17.5	χ^2=6.325
Multipara	244	87.5	671	80.8	915	82.5	p=0.012
Planning to pregnancy							
Yes	95	34.1	242	29.2	337	30.4	χ^2=2.364
No	184	65.9	588	70.8	772	69.6	p=0.124
Current contraceptive use							
Yes	172	61.6	569	68.6	741	66.8	χ^2=4.491
No	107	38.4	261	31.4	368	33.2	p=0.034

TCP: Traumatic Childbirth Perception, STCP: The Scale of Traumatic Childbirth Perception, *chi-square test

On the basis of the STCP scores, Table 3 displayed the pregnancy avoidance and mental health outcomes of the traumatic childbirth perception. It was ascertained that 46.6% of the women with traumatic childbirth perception and 21.1% of the women with no traumatic childbirth perception exhibited depressive symptoms, 54.5% of the women with traumatic childbirth perception and 30.5% of the women with no traumatic childbirth perception had anxiety, 41.1% of the women with traumatic childbirth perception and 25.4% of the women with no traumatic childbirth perception had stress, and the differences between the groups were statistically significant. Besides, it was identified that the women with traumatic childbirth perception had a higher mean of DAP Scale scores than the women with no traumatic childbirth perception (2.13±0.96 points vs. 1.73±0.99 points, p<0.001, Table 3).

Table 3. Comparison of traumatic childbirth perception (according level of STCP) of women according to the DASS-21 and DAP (n=1109)

		STCP<53 score (n=279)		STCP≥53 score (n=830)		Total (n=1109)		Test* and p value
	Scales	n	%	n	%	n	%	
DASS-21	**Depression**							
	Yes (5-21 score)	59	21.1	385	46.4	444	40.0	χ^2=55.404
	No (0-4 score)	220	78.9	445	53.6	665	60.0	p<0.001
	Anxiety							
	Yes (4-21 score)	85	30.5	452	54.5	537	48.4	χ^2=48.125
	No (0-3 score)	194	69.5	378	45.5	572	51.6	p <0.001
	Stress							
	Yes (8-21 score)	71	25.4	341	41.1	412	37.2	χ^2=21.865
	No (0-7 score)	208	74.6	489	58.9	697	62.8	p <0.001
		Mean ± SD		**Mean ± SD**		**Mean ± SD**		**Test** and p value**
	DAP score	1.73±0.99		2.13±0.96		2.03±0.99		t=-5.974 p<0.001

* chi-square test, **Independent Samples t Test, SD: Standard Deviation, STCP: The Scale of Traumatic Childbirth Perception, DASS-21: Depression Anxiety Stress Scale, DAP: Desire to Avoid Pregnancy Scale

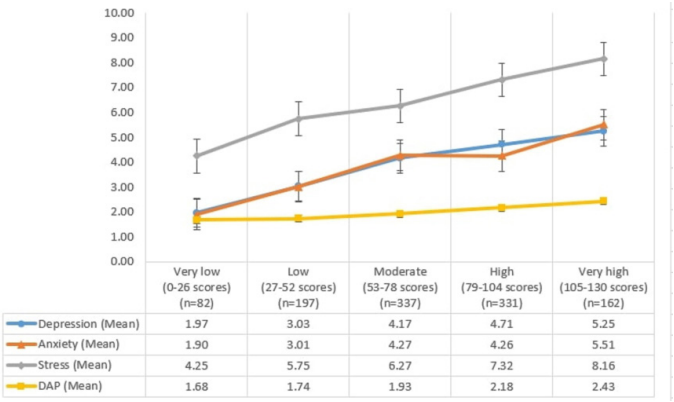
In the context of the model created with the variables that had a statistically significant relationship with traumatic childbirth perception as per the above bivariate analyses, the results of the logistic regression analysis were shown in Table 4. According to the results of the logistic regression analysis, it was identified that the variables of being below the age of 30 years (OR=0.543), primiparity (OR=0.459), exhibiting depressive symptoms (OR=2.627), having anxiety (OR=1.752), and pregnancy avoidance (OR=1.701) were significant risk factors for traumatic childbirth perception.

Table 4. Logistic Regression Analysis of significant variables related to STCP

	B	SE	df	P	OR	95% CI Lower	95% CI Upper
Age, y							
≤30	(Reference)						
>30	-0.610	.165	1	<0.001	.543	.543	.750
Income status							
Moderate/ High	(Reference)						
Low	0.614	.467	1	0.188	1.848	.740	4.614
Parity							
Primipara	(Reference)						
Multipara	-0.780	.235	1	0.001	.459	.289	.727
Current contraceptive use							
Yes	(Reference)						
No	-0.201	.162	1	0.215	.818	.595	1.124
Depression							
Yes(5-21 score)	(Reference)						
No (0-4 score)	0.966	.180	1	<0.001	2.627	1.846	3.738
Anxiety							
Yes(4-21 score)	(Reference)						
No (0-3 score)	0.561	.173	1	<0.001	1.752	1.249	2.457
Stress							
Yes(8-21 score)	(Reference)						
No (0-7 score)	0.026	.184	1	0.886	1.027	.716	1.472
DAP score [a]	0.531	.089	1	<0.001	1.701	1.430	2.023

a Numerical data were used, B: Regression Coefficient; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval. DAP: Desire to Avoid Pregnancy Scale

Figure 2 indicated the means of the women's depression, anxiety, stress, and DAP Scale scores as per their traumatic childbirth perception levels. The means of depression scores of the women with very low-level, low-level, moderate-level, high-level, and very high-level traumatic childbirth perception were successively 1.97±2.11, 3.03±2.28, 4.17±3.15, 4.71±3.21, and 5.25±3.40 points, the means of anxiety scores of the women with very low-level, low-level, moderate-level, high-level, and very high-level traumatic childbirth perception were respectively 1.90±2.78, 3.01±3.12, 4.27±3.76, 4.26±3.77, and 5.51±3.98 points, the means of stress scores of the women with very low-level,low-level,moderate-level,high-level,andveryhigh-level traumatic childbirth perception were consecutively 4.25±3.74, 5.75±4.19, 6.27±3.78, 7.32±4.16, and 8.16±4.40 points, and the means of the DAP Scale scores of the women with very low-level, low-level, moderate-level, high-level, and very high-level traumatic childbirth perception were successively 1.68±0.97, 1.74±1.00, 1.93±0.91, 2.18±0.99, and 2.43±0.92 points. It was discerned that there were statistically significant differences in the means of the women's depression, anxiety, stress, and DAP Scale scores as per their STCP levels (respectively, F=25.886, F=18.355, F=18.124, F=17.048; p< 0.001, Figure 2).



	Very low (0-26 scores) (n=82)	Low (27-52 scores) (n=197)	Moderate (53-78 scores) (n=337)	High (79-104 scores) (n=331)	Very high (105-130 scores) (n=162)
Depression (Mean)	1.97	3.03	4.17	4.71	5.25
Anxiety (Mean)	1.90	3.01	4.27	4.26	5.51
Stress (Mean)	4.25	5.75	6.27	7.32	8.16
DAP (Mean)	1.68	1.74	1.93	2.18	2.43

Figure 2. Means of the participant women's depression, anxiety, stress, and DAP Scale scores as per their STCP levels

DISCUSSION

In this study in which the women's traumatic childbirth perceptions were analyzed, it was found that approximately three fourth of the women (74.8%) had traumatic childbirth perceptions. In relation to the traumatic childbirth perception prevalence, various percentages are present. Just as the changes in these percentages are affected by a variety of factors, they can also be affected by the use of a different measurement tool. In the study by Alcorn et al. (2010), it was ascertained that 45.5% of the women characterized their childbirth experiences as traumatic according to the criteria outlined in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Version) (6). The study by Boorman et al. (2014) found that 29.4% of the women satisfied the criteria for traumatic childbirth (11). In these two studies, the Posttraumatic Diagnostic Scale was utilized. In Turkey, until 2016, no scale measured the traumatic childbirth perception. The finding of this current study is closer to the prevalence rate, 69.5%, that was obtained in the study performed by Aktaş (2018) on multigravidas with the STCP (21). The STCP that was used in this current study is a relatively new scale that helps to measure any form of childbirth trauma.

In this current study, it was identified that the women with traumatic childhood perception were more likely to have emotional distress (depression, anxiety, stress) and pregnancy avoidance. Also in the previous studies, it was asserted that the traumatic childbirth experience could be associated with a minimum of one post-natal emotional health problem and the childbirth-related negative emotions could give rise to outcomes such as preferring not to get pregnant again (6,22,23). Grenfield et al. (2019) found that the women with traumatic childbirth perception made research and analysis about pregnancy and childbirth to prevent their previous childbirth experiences from occurring once again (24). James (2015) ascertained that the women exhibited avoidance behaviors to control threats and symptoms emerging in the wake of the traumatic childbirth experience (25). In the study by Boorman et al. (2014), it was put forth that stress, anxiety, and depression were predictors of the traumatic childbirth criteria (11). In the study by Simpson and Catling (2016), it was reported that there was a relationship between traumatic childbirth and mental diseases in women (26). Of course, this study and other similar studies do not indicate that there is causation between a traumatic childbirth experience and emotional problems. The postnatal period is not the sole factor for the traumatic childbirth perception as the perinatal period is characterized by the physical, social, and psychological transitions that are likely to influence a woman's emotional well-being (25).

Under this current study, it was found that being young and being primiparous were significant risk factors for the women to have traumatic childbirth perception. Considering this finding, it is inevitable that the primiparous women at a relatively early age view childbirth as an unknown phenomenon and, as it is an unknown phenomenon for them, they cannot avoid having fears and hence, their childbirth perceptions become negative (11,27). Likewise, Boorman et al. (2014) set forward that the primipara, the women who gave birth for the first time, were more likely to find childbirth as a traumatic experience (11). In this current study, it was identified that the women that used contraceptive methods were more likely to have traumatic childbirth perception. It can be considered that the women with traumatic childbirth experience might have escaped from becoming pregnant to avoid having this experience again and used contraceptives for this purpose. As a matter of fact, in the study by Gipson, Bornstein, Berger and Rocca (2021), it was stated that the women with a high percentage of using contraceptives exhibited pregnancy avoidance attitudes (28). Thus, it is discerned that the result of the study by Gipson et al. supported the finding of this current study.

As per this current study, the women with medium/high-level income were more likely to have traumatic childbirth perception. Güleç et al. (2014) asserted that there was a relationship between childbirth fear and income level (29). On the other hand, Üst and Pasinlioğlu (2015) put forward that the income level had no effect on childbirth and post-natal worries (30). In this sense, it can be considered that the income level is not the sole factor affecting childbirth perception, nevertheless, as it is accompanied by other negative circumstances such as the place of childbirth, setbacks in accessing the necessary information, and the lack of social support, it can have an effect on the traumatic childbirth perception held by the women.

CONCLUSION

This study indicated that pregnancy avoidance and psychological factors (depression, anxiety, and stress) affected the traumatic childbirth perception and were significant risk factors for the traumatic childbirth perception. To ensure that childbirth which is considered as a physiological process does not turn to be a traumatic experience by being estranged from its normal course, the identification of risk factors in the prenatal period and the application of necessary midwifery approaches at an early stage are quite essential. Raising the individuals' awareness about these risk factors, restructuring negative memories if any, and reducing risk factors by referring the women who have depression, anxiety, and stress to the specialists when necessary will also lower the risk of having traumatic childbirth perception. Moreover, it is considered that the psychoeducational interventions will be effective in alleviating the tokophobia and, accordingly, changing the traumatic childbirth perception.

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Research Article

Investigation of the Relationship Between HMGB1 and Obesity in the Adrenal Gland

Böbreküstü Bezinde HMGB1 ile Obezite İlişkisinin Araştırılması

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Abstract

Aim: The interaction between obesity and increased production of pro-inflammatory cytokines results the existence of inflammation HMGB1 secreted from the adrenal gland can play a role in inflammation pathways. The aim of this study is to explain the link between HMGB1 and obesity in the adrenal gland.

Material and Methods: In this study; eighteen female Wistar Albino rats were divided into two groups: untreated control group (n=8) and obese group (n=10). The rats in obese group were fed with high fat diet for ten weeks. Morphometric parameters of adrenal gland were assessed by using stereological techniques. The expression of high mobility group box protein 1 (HMGB1) in adrenal gland was evaluated.

Results: At the end of the analyses; mean volumes of zona fasciculate, zona reticularis, and medulla were significantly increased in obese group. Also, the number of HMGB1 stained cells was significantly increased in the obese group in comparison to control group.

Conclusion: The results suggest that obesity may be one of the reasons of inflammation and hypertrophy in the adrenal gland. HMGB1 may provide a novel perspective into the anti-inflammatory therapeutic strategies in obese patients.

Keywords: Adrenal gland, HMGB1, inflammation, obesity, stereology

Öz

Amaç: Obezite ile artan proinflamatuar sitokin üretimi arasındaki etkileşim sonucu inflamasyonun varlığı adrenal bezden salgılanan HMGB1 inflamasyon yolaklarında rol oynayabilir. Bu çalışmanın amacı, adrenal bezde HMGB1 ile obezite arasındaki bağlantıyı açıklamaktır.

Materyal ve Metot: Bu çalışmada; on sekiz dişi Wistar Albino sıçanı tedavi edilmeyen kontrol grubu (n=8) ve obez grup (n=10) olmak üzere iki gruba ayrıldı. Obez gruptaki ratlar on hafta süreyle yüksek yağlı diyetle beslenirken, control grubu standart diyet ile beslendi. Adrenal bezin morfometrik parametreleri ve mobilite grubu kutu protein 1 (HMGB1) ekspresyonu stereolojik teknikler kullanılarak değerlendirildi.

Bulgular: Analizler sonunda; zona fasikülata, zona retikülaris ve medulla ortalama hacimlerinim obez grupta anlamlı olarak arttığı görüldü. Ayrıca obez grupta HMGB1 ile boyanmış hücre sayısı kontrol grubuna göre önemli ölçüde artmıştı.

Sonuç: Sonuçlar obezitenin adrenal bezdeki inflamasyon ve hipertrofi nedenlerinden biri olabileceğini düşündürmektedir. HMGB1, obez hastalarda anti-inflamatuar terapötik stratejilere yeni bir bakış açısı sağlayabilir.

Anahtar Kelimeler: Adrenal bez, HMGB1, inflamasyon, obezite, stereoloji.

INTRODUCTION

Obesity is a rising prevalent health concern in both developed and developing countries. The excessive accumulation of adipose tissue in the body is defined as obesity by the World Health Organization (1). In particular, increased consumption of saturated fatty acids results in excess visceral adiposity. Obesity is associated with many metabolic and non-metabolic diseases including hyperglycemia (2), type 2 diabetes mellitus (T2DM) (5), cancer (3), hypertension (6), and atherosclerosis (7). These diseases are associated with chronic inflammation therefore, several mechanisms have been proposed to highlight the relationship with adipose tissue (8-10). The

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increased infiltration of immune cells into and around the adipose tissue and elevated production of multiple plasma pro-inflammatory cytokines in the circulation are the most comprehensive approach that shows the relation between obesity and the development of local and systemic chronic low-grade inflammation (4-11).

High mobility group box protein 1 (HMGB1) is defined as a DNA-binding non-histone protein that plays an important role in transcription, repair and replication of DNA (12). The nuclear HMGB1 acts in response to oxidative stress in the cytoplasm (13,14). HMGB1 is released extracellularly from active immune cells and necrotic cells (15). Also, plays an important role to attract immune cells acting as a pro-inflammatory mediator or alarmin (16,17). The increase of H-MGB1 gene expression may be a direct link between inflammation, obesity, and subclinical cardiovascular risk (18,19).

The adrenal steroid level plays a role in obesity and cardiovascular diseases. Elevated adrenal steroid level is associated with obesity (20,21). Interestingly, an increased level of adrenal hormones causes cardiovascular diseases and triggers insulin resistance (22). All this information reveals the necessity of showing the relationship between adrenal glands responsible for adrenal steroid secretion and obesity and investigating the effect of HMGB1 in this relationship. For that reason, the study aimed to investigate the role of HMGB1 in adrenal glands of obese rats.

MATERIAL AND METHOD

Animals

All procedures were conducted according to the experimental protocol approved by the Faculty of Gulhane Military Medicine and authorization of the ethics committee of Gulhane Military Hospital, Turkey (16/37). The study included 18 adults (8 weeks old) female Wistar albino rats (180-200 gr). All animals were kept at constant temperature 22±1°C with a regular 12 hours of light/dark cycle and with free access to food and water. Animals were randomly divided into two groups. (I) control group (n=9): animals were healthy and fed with normal commercial diet for 10 weeks. (II) obese group (n=9): animals were fed with a special diet (42% carbohydrate, 40% lipid and 18% protein) for 10 weeks. The body mass index (BMI) was used to determine obesity. The rats were regularly weighed during the experiment. Weight and height parameters were used to calculate BMI. BMI values greater than 5 kg/m2 were considered as obese. Therefore, two rats were excluded from experiment because of BMI parameters. Animals were anesthetized with a mixture of ketamine (80mg/kg Ketalar i.p.; Eczacıbaşı, Istanbul, Turkey) and xylazine (10mg/kg Rompun i.p.; Bayer, Istanbul, Turkey). Blood samples were taken and rats were perfused with intracardiac 4% formaldehyde. Then, adrenal glands were quickly removed and animals were sacrificed.

Tissue preparation and immunohistochemical procedures

The adrenal glands were fixed in 10% formaldehyde solution (Sigma-Aldrich, St. Louis, MO) for 24 hours. Then, adrenal glands were processed through alcohol (Sigma-Aldrich, St. Louis, MO) and xylene (Merck, Darmstadt, Germany) series and embedded in paraffin blocks. Using a microtome, 5 µm thick sections were taken in the sagittal plane with a sampling rate of 1/6 (RM2125RT; Leica Nussloch, Germany) and stained with Hemotoxylin and Eosin (H&E). For immunohistochemical evaluation, 5 µm sections were stained with anti-HMGB1 rabbit polyclonal antibody (Abcam, Cambridge, United Kingdom) diluted 1/50 (Zymed Laboratory, Cambridge, UK) using the avidin-biotin complex (ABC) method. The process was performed as previously described (23).

Stereological analyses

Cavalieri Principle was used to estimate the total volume (Vt), zona glomerulosa (ZG), zona fasciculate (ZF), zona reticularis (ZR), and medulla of the adrenal gland (23). The sampling interval was 1/6. Choosing the first section was carried out randomly. At least 20 sections were sampled from each adrenal gland. Olympus BX43 microscope was used to analyze sections.

The point counting grid was randomly placed on the screen (d=1 mm) and hitting points on the grid of the interested area were counted (Figure 1). The area among each of four points was called as a unit area and shown with area/point (a/p). The total counted number of points (P) and thickness (t) of the section were multiplied by the unit area to estimate the volume of the adrenal gland (24). The following formula was used for the volume estimations;

$$Vt = t \times \left(\frac{a}{p}\right) \times P$$

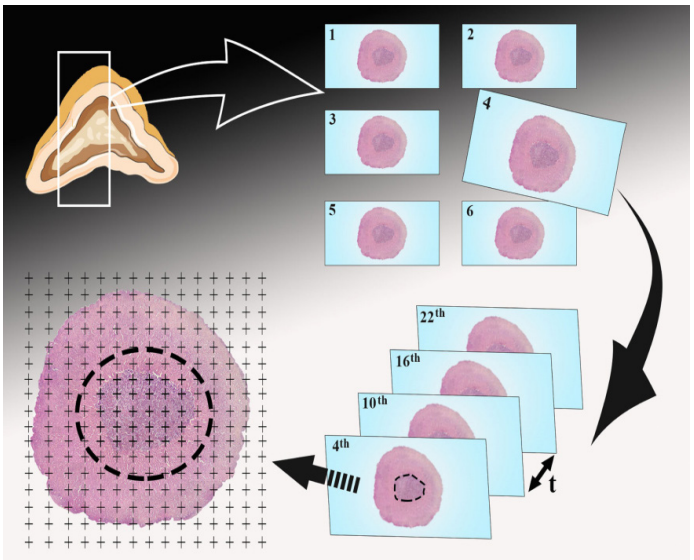

Figure 1. The application of the Cavalieri principle is illustrated on the medulla of adrenal gland

HMGB1 positive cells were counted with physical disector method

Sections were stained with HMGB1 antibody and two consecutive sections were placed upon each glass slide. The first section was called reference and second was called look-up. Sections were photographed at x400 magnification and an unbiased counting frame (2.500 µm2) was placed on the images of reference and the look-up sections on the screen (25). To perform the counting according to the physical disector counting method, the bottom and the left-hand edges of the counting frame were considered as an exclusion line. For that, if the nucleus of the cell touched the left and bottom edges of the frame, it was not counted (red line). All counted nuclei (disector particles) were in the frame or touched the right or upper edges (inclusion lines) of frame (green line). Also, only the nuclei seen in the reference section but not seen in the look-up section were counted. In order to increase the efficiency of the work, the reference and look-up areas of the disector section pairs were also used reversely, as suggested in the literature. Look-up section was used as a reference section while reference section was used as a look-up.

Biochemical analyses

Blood samples (2mL) were collected in the Tubes with EDTA and centrifuged at 10 000g for 3mm at room temperature. After that 1mL plasma was processed according to protocol of the calorimetric glucose, cholesterol, superoxide dismutase and catalase assay kits (Item no: 10009582, 10007640, 707002, 706002 Cayman Chemical Company, Michigan; USA).

Statistical analyses

Leavene test was used to determine whether the data in the groups were parametric. The Independent Samples T-Test was used to compare parametric data of the groups. Mann Whitney U test was used for comparison of nonparametric data. A value of $p<0.01$ and $p<0.001$ were considered statistically highly significant and $p<0.05$ was considered statistically significant. All statistical analyzes were performed with SPSS (Version 15.0 for Windows®, IBM Corp, NY, USA).

RESULTS

Assessment of obesity

Weekly weight gain of subjects was followed. At the end of 10th week, BMI calculations were done to evaluate whether the subjects were obese. The weight increased in obese group than control group. Also, highly significant difference was found between groups in terms of the BMI values (Figure 2.)

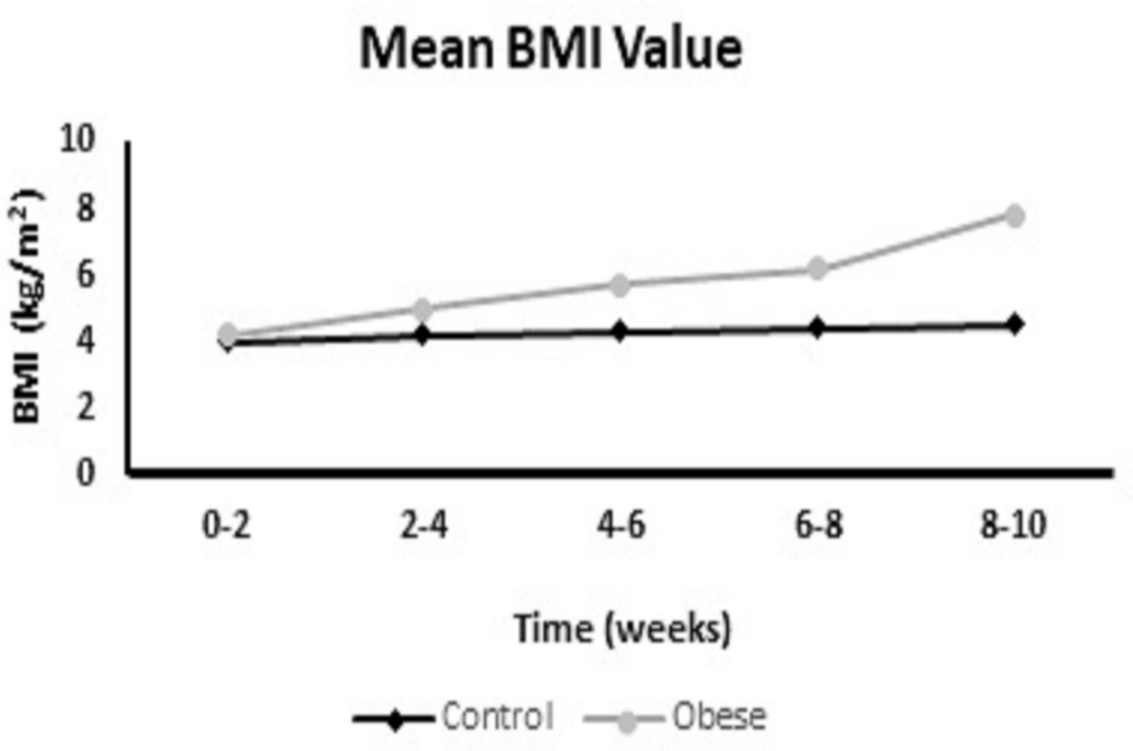

Figure 2. Mean BMI values in control and obese groups. The mean BMI values are increased significantly ($p<0.01$) in the obese group compared to the control group

Stereological evaluation

Stereological results and the mean error coefficient and the coefficient of variation values of the groups showed in Table 1. Stereological results showed that the estimated mean volume of adrenal gland significantly increased in Obese group compared to Control group. In the Obese group, the estimated volume of ZF, ZR and medulla showed highly significant increase ($p<0.001$) whereas the estimated volume of ZG significantly increased in Control group ($p<0.01$) (Figure 3). Both Control and Obese group sections were stained with anti-HMGB1 antibody and sections were evaluated. The number of HMGB1 antibody stained cells was significantly higher in both cortex and medulla of the Obese group compared to Control group ($p<0.001$).

Table 1. The mean error coefficient and coefficient of variation values of the groups

ESTIMATION	Mean CE	Mean CV
Volume of the zona glomerulosa	0.033	0.84
Volume of the zona fasciculata	0.041	1.12
Volume of the zona reticularis	0.037	0.89
Mean number of HMG1 positive cells	0.056	1.4

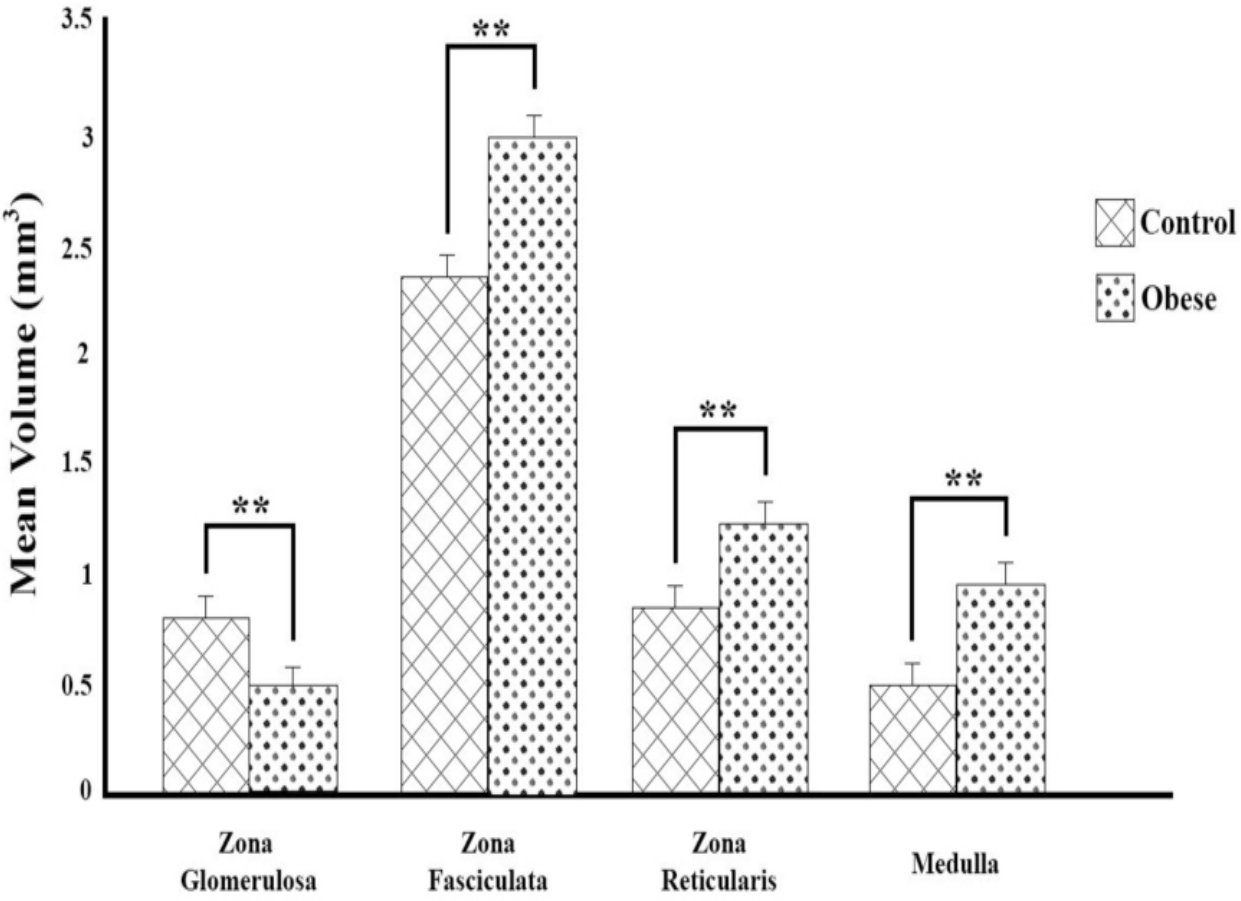

Figure 3. Stereological volume estimations between Control and Obese groups are seen (**; $p<0.01$) (Mann Whitney U test)

Histopathological evaluation

Histological changes were assessed by light microscopic evaluation of tissue sections. In the Control group, the cortex was encircled by a capsule composed of dense irregular connective tissue. Medulla was rich in blood vessels and chromaffin cells. Rarely, healthy appearance of ganglion cells attracted attention. In contrast, the capsule was found thicker in Obese group. Also, there were more and larger fat tissue cells around the capsule of Obese group samples. In Obese group, it was also observed that the ZG layer was thinner than the Control group whereas the ZF layer was thicker than the Control group (Figure 4A, 4B). In the Control group, the ZG layer was found in a normal structure just below the capsule. This layer consisted of parenchymal cells forming concentric or glomerular rings. These small ZG cells were healthy with small dark nuclei containing one or two nucleolus and acidophilic cytoplasm. In contrast to Control group, the selection of cells was difficult and capillaries were dilated in the Obese group.

In the Control group, the ZF was the thickest layer of the cortex. In this layer, sinusoidal capillary vessels that longitudinally located between parallel cell columns were observed. The polygonal cells in this layer had pale acidophilic staining and appeared with vacuoles in some areas. In the ZF of the Obese group, among the steroid content increased cells, new generated cells that had eosinophil cytoplasm and thought to had recently participated on this layer were found. Also, fatty degeneration and necrosis were detected in the ZF of the Obese group (Figure 4C, 4D).

The cells of the ZR in the innermost layer of the cortex were arranged in cords that painted dark acidophiles and anastomosed to each other in the Control group. These cells were contained fewer lipid droplets than ZF cells. Importantly, inflammatory cell infiltration was noted in the ZR layer of the Obese group (Figure 4E, 4F).

The chromaffin cells were arranged as a bundle or cord shaped and sympathetic ganglion cells were dispersed in the connective tissue of the medulla in the Control group. The first notable finding in the medulla of the Obese group was dilated vessel branches compared to the Control group. In the medulla, fibrin depositions were also seen in Obese group. In addition; some of the ganglion cells were healthy, while others were damaged with eosinophilic cytoplasm and shrunken cell borders (Figure 4G, 4H).

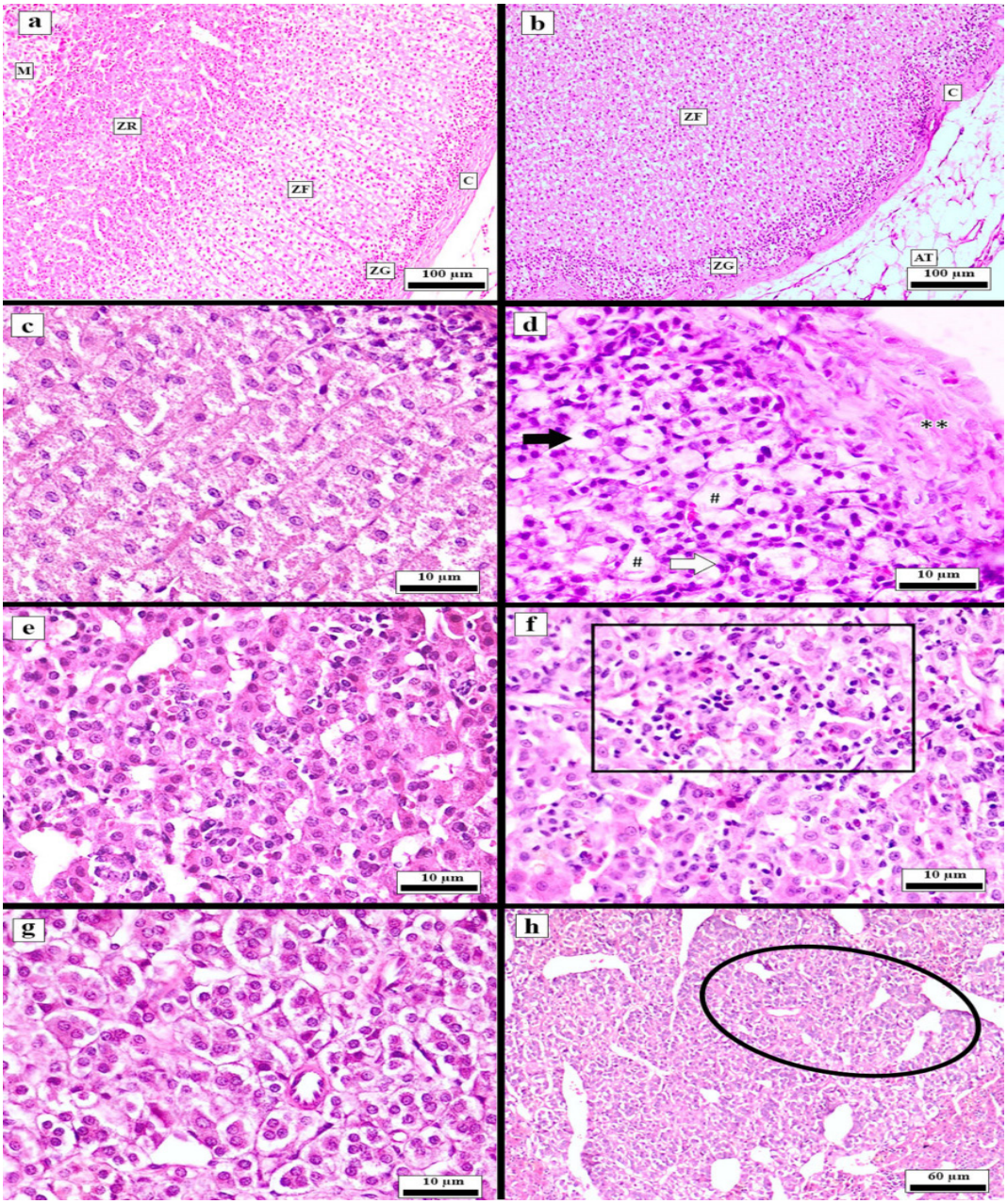

Figure 4. Histopathological evaluation of adrenal glands in both Control and Obese groups are seen. Control group is represented with a, b, c, d. Obese group is represented with e, f, g, h. C; Capsule, ZG; Zona Glomerulosa, ZF; Zona Fasciculata, ZR; Zona Reticularis, M; Medulla, (**); thick capsule, (#); diliated capillaries, black arrow; increased cell volume, white arrow; newborn cells

Immunohistochemical evaluation

The positive stained cells were stereologically evaluated in both groups and a significant difference was found between the groups (p <0.01, Figure 5). According to these results, there was HMGB1 positivity found neither in the cortex layer nor in medullary of the control group.

In the Obese group, strong positive HMGB1 staining was observed in both medullary connective tissue cells and chromaffin cells. Furthermore, a strong HMGB1 positivity was detected in nerve fibers and possible macrophage cells in the medullary of the adrenal gland (Figure 6).

Biochemical results

In this study; glucose and cholesterol levels were calculated. Glucose and cholesterol levels were increased in the obese group compared to the control group (p<0.01, Figure 7).

Catalase and sod levels were calculated for the estimation of oxidative stress levels. These parameters significantly increased in the obese group compared to the control group (p<0.01, Figure 8).

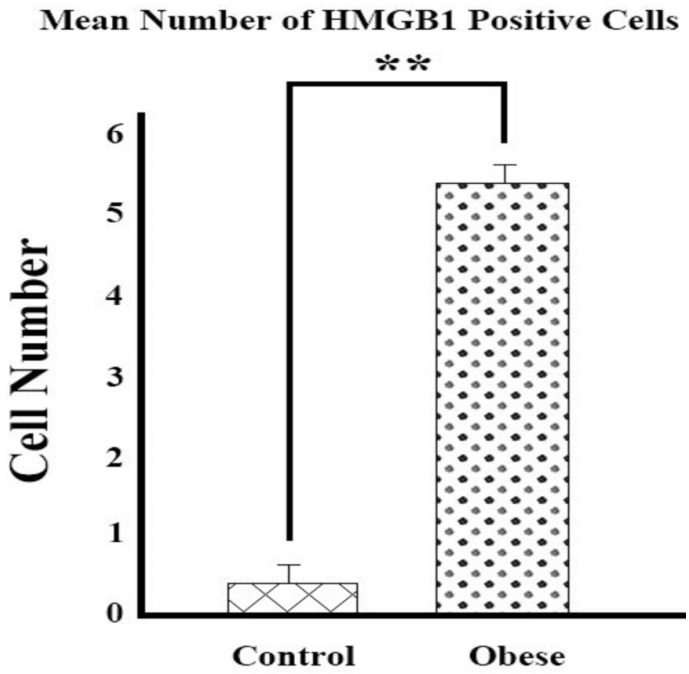

Figure 5. Mean HMGB1 positive cell numbers are seen in both Control and Obese groups. **; p <0.01 (Mann Whitney U test)

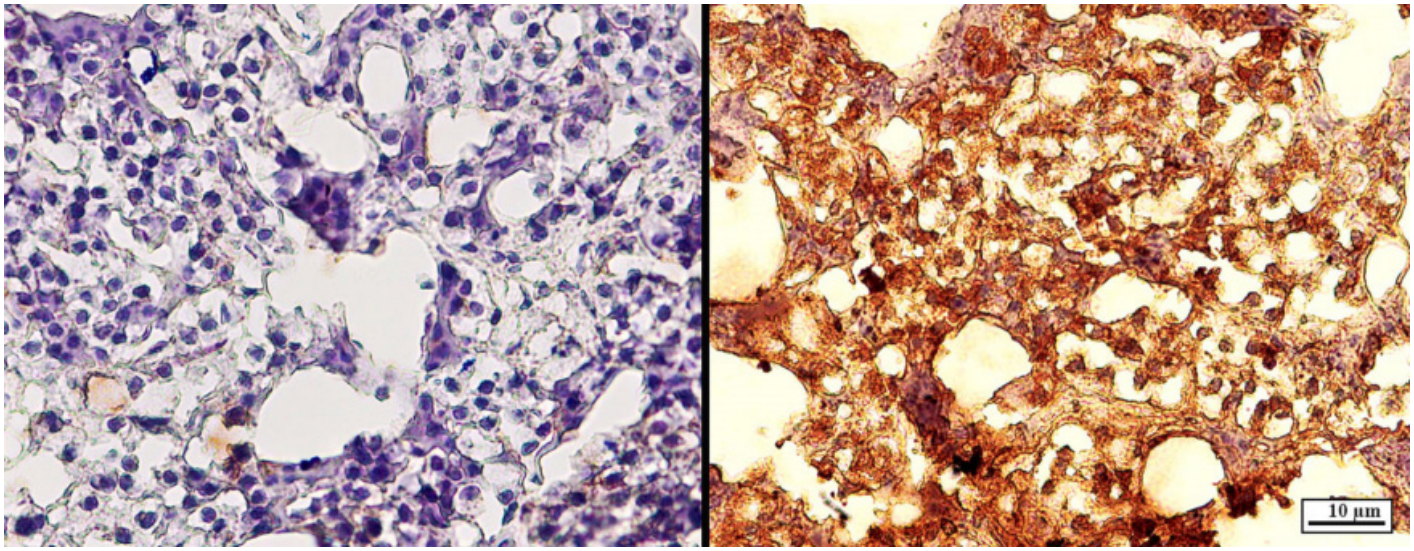

Figure 6. The strong positive HMGB1 staining is observed in the adrenal gland of the Obese group

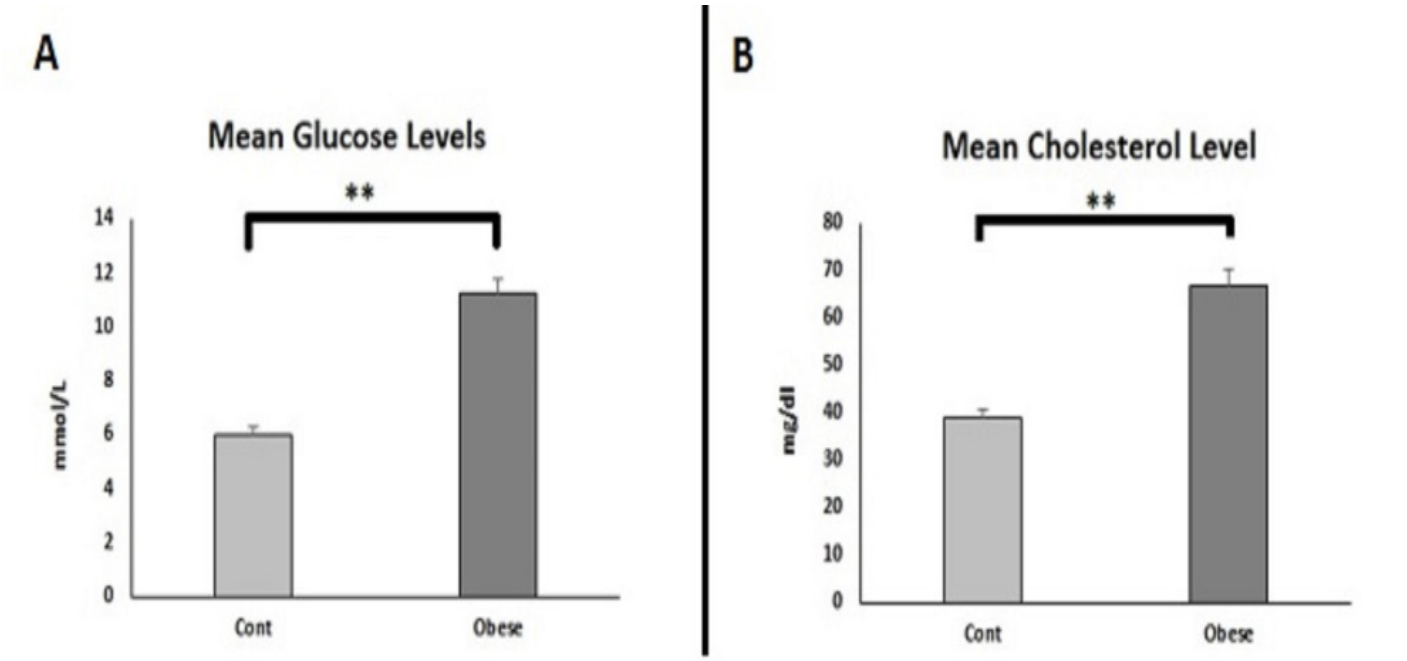

Figure 7. Mean levels of glucose and cholestrerol in all groups are observed (±SD). **Significant differences $p < 0.01$

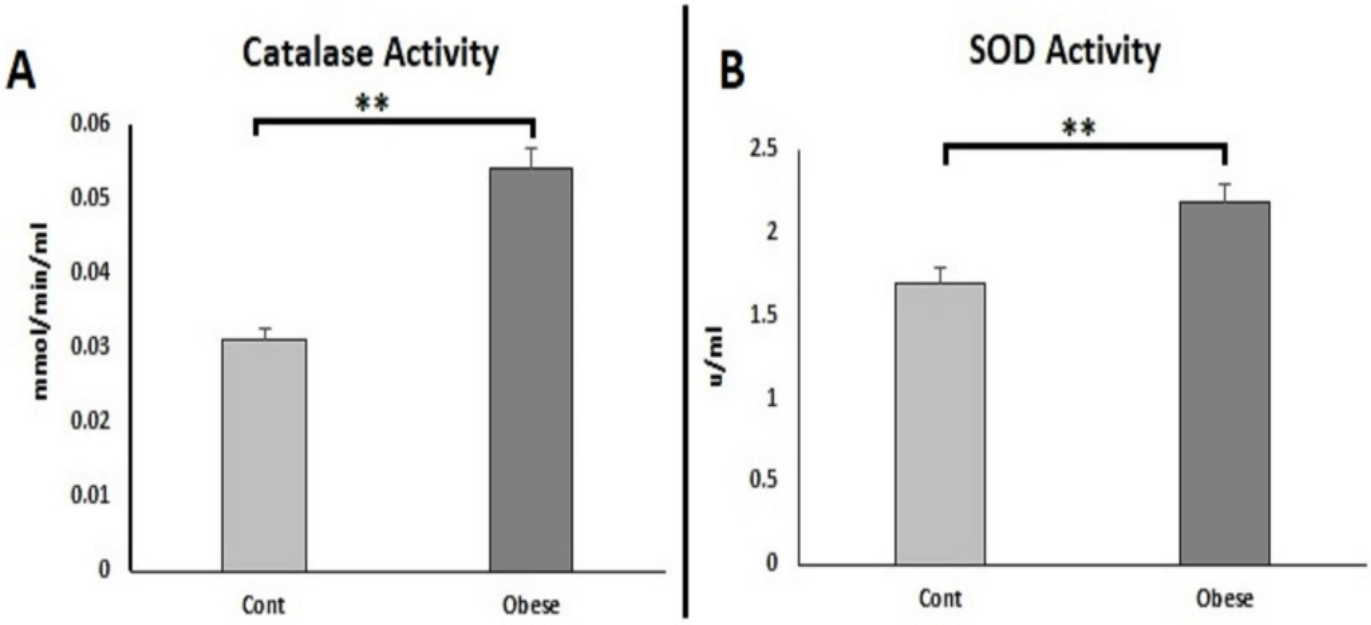

Figure 7. Mean levels of catalase, superoxide dismutase activities in all groups are observed (±SD). **Significant differences $p<0.01$

DISCUSSION

Obesity and overweight are major public health problem worldwide, especially in developing and developed countries (26). The obesity associated adipose inflammation elevates the secretion of pro-inflammatory factors, induces production of reactive oxygen species (ROS) and weakens the antioxidant defence system (27). For that reason, HMGB1 plays a critical role during the inflammation to induce the immune system for the defense (28). In addition, direct relation between development of obesity and BMI and adrenal gland changes has been shown (22).

BMI is used as a standard for classifying weight and is a very useful method to determine the obesity (29). We observed faster weight gain in the diet induced group and that BMI correlates significantly with the body weight only in rats fed with a high fat diet, but not in animals fed a normal diet. For that reason, diet induced group subjects were evaluated as an obese. There were significantly volume differences found in the cortex and medulla of Obese group. Previously, the effects of feeding with high fat diet has been shown as a reason of hyperplasia of the adrenal cortex in response to various environmental stimuli (21,22). Similarly, in the current study, statistically highly

significant increase of estimated mean volumes of ZF, ZR and medulla were found in Obese group. In our results; a significant volume decrease in the ZG of Obese group. In literature, some studies on the relationship between obesity and the adrenal cortex showed that obesity plays a role in changing the ZF and ZR histological structure (22,30). The increase of the ZF cell number caused the change in the ZG cell structure and form the ZF pattern (30). All these result supported by histopathological results. In the obese group there was a thin ZG layer and a thicker ZF layer.

The biochemical study in this research; plasma cholesterol concentration was markedly increased in Obese group. Similar to our results, a positive relationship between plasma cholesterol concentration and lipid peroxidation level was previously shown (31). This study supports the view that the increased oxidative stress may related with elevated cholesterol levels in the adrenal glands of Obese group. In ZF and ZR, cortisol is derived biosynthetically from cholesterol (32). The amount of cholesterol strongly affects the rate of steroidogenesis. In addition, increased cholesterol production and lipoprotein uptake were shown in the adrenal glands of obese animals (22). The stereological analyses of this study support these results because the volumes of the ZF and ZR were increased in the obese group. Also we observed some lipid drop in the cell of the ZF in the histopathological analysis.

Although the relationship between obesity and oxidative stress is clear, it is not clear which is the cause and which is the result (33). It is well known that increased fat tissue is one of the main reasons of the association of elevated oxidative stress with obesity (9). Adipocytes have been described as the source of pro-inflammatory cytokines, and therefore obesity is considered as a chronic inflammatory condition (34). Biochemical markers indicating oxidative stress damage were found very high levels in obese individuals and were directly related to BMI (35). On the other hand some studies shown that oxidative stress, per se, leads to weight gain (33,36). In our study, increased SOD and Catalase enzyme activities were found in obese subject's blood that could be evaluated as a reason of increase in the production of hydrogen peroxide and elevated formation of superoxide radicals.

In particular, HMGB1 from adipocytes plays a dominant role in necrosis. Extracellular HMGB1 activates adipose tissue-resident immune cells, causing active additional HMGB1 secretion from immune cells, and this activation induces adipocyte death (37). Also, the HMGB1 that play a role in inflammation cause to upregulation of cytokines, chemokines, and adhesion molecules, and this regulation is associated with cellular oxidative stress (38,40). In this study, there was a significant increase of the HMGB positive cell in obese groups. Considering that oxidative stress increases in obesity, it is quite possible that HMGB1, which is related to oxidative stress, is increased in the obese group. The HMGB1 positive cells were localized in the all fields of adrenal glands in Obese group while there was a significant density in the ZF. The increased expression of HMGB1 protein might be explained by cholesterol accumulation in immune cells that promotes inflammatory responses (39).

CONCLUSION

Although there are studies in the literature regarding the relationships between each of the parameters in our study separately, no study has been found in which these parameters were studied in chorea in the adrenal gland. It is quite possible that the oxidative stress that develops in the adrenal cortex, especially in the ZF, due to the increased cholesterol and glucose levels in obesity seen in this study, increases the HMGB1 level. However, the relationship between obesity-oxidative stress-HMGB1 in the adrenal gland needs to be examined in detail with pathway analyzes.

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Erratum

Assessment of Thyroid Function Tests in Patients with COVID-19 Infection and Their Relationship with Euthyroid Sick Syndrome

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Dear Editor

In the Medical Records Journal (2022;4(1):90-4), in our article titled "Assessment of Thyroid Function Tests in Patients with COVID-19 Infection and Their Relationship with Euthyroid Sick Syndrome" the number of patients was mistakenly written once in the material method section as 885. The number of patients who applied and were included between the specified dates is 473. In other parts of the article, it was stated that the study was conducted with 473 patients many times. The error in the number of patients made once in the material-method has been corrected.

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