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EDITORIAL

EDİTÖRYAL

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What is gray literature and how to search for it

Gri literatür nedir ve nasıl aranır

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ABSTRACT

The term gray literature refers to printed and/or electronic research that has either been published or remains unpublished, in non-commercial form. Many systematic reviews and meta-analysis do not include gray literature sources and studies published in languages other than English. Their inclusion increases accuracy and can reduce systematic errors. It is very important to include gray literature in the screening of sources while conducting scientific studies, in order to obtain evidence-based results. The Acta Medica Alanya journal includes gray literature, in particular in its compilation and editorial writings, and supports citing articles from our country, including those written in Turkish, in its research articles.

Keywords: Gray literature, review, research

ÖZ

Gri literatür terimi, yayınlanmamış ya da ticari olmayan basılı ve/veya elektronik araştırmaları ifade eder. Birçok sistematik derleme ve metaanalizi, gri literatür kaynaklarını ve İngilizce dışındaki dillerde yayınlanan çalışmaları içermez. Bunların dahil edilmesi kesinliği artırır ve sistematik hataları azaltabilir. Gri literatürün bilimsel çalışmalar yaparken kaynaklar arasında taramaya katılması, kanıta dayalı sonuçlar elde etmek açısından çok önemlidir. Acta Medica Alanya dergisi özellikle derleme ve editöryal yazılarında gri literatüre yer vermekte ve araştırma yazılarında Türkçe dahil ülkemiz kaynaklı makalelere atıfta bulunmayı desteklemektedir.

Anahtar Kelimeler: Gri literatür, derleme, araştırma

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The term gray literature refers to printed or electronic research that has either been published or remains unpublished, in non-commercial form [1]. This literature includes documents such as this paper, dissertations, committee statements, government policy reports, conference papers, ongoing academic research and non-English research results. [1-4].

While systematic reviews are important tools for analyzing and disseminating evidence, they offer good guidance for clinical decision-making [5], but many of these, as well as meta-analysis, do not include gray literature sources and studies published in languages other than English. Their inclusion increases accuracy and can reduce systematic errors [2,6,7] and gray literature is a rich source of evidence for thorough systematic

reviews and meta-analysis [7]. It has been shown that 26 to 41% of the evidence found in some systematic reviews exists in gray literature, and that publications such as conference summaries and papers can increase citation rates by approximately 10% [8]; the mere fact that 10% of the sources in Cochrane reviews consist of meeting presentations, supports the fact that gray literature may be crucial for evidence-based medicine [9]. No doubt, gray literature actually contains more studies that can be considered insignificant, have no significant differences between groups, or contain negative results and are considered difficult to publish [8], and studies with significant differences in their results tend to be published in journals with a globally available and relatively higher impact factor in English. For all these reasons, it is very important to include gray literature in the screening among the sources while conducting scientific studies, in order to obtain complete and thorough evidence-based results [1].

Meanwhile, there are some disadvantages with regard to the use of gray literature. An example of this would be “think tanks” that publish readily available reports, but that are likely to have bias reflecting their political or social views [3]. It is also possible that there may be discrepancies between titles, indexing information and summaries in the gray literature [10]. Additionally, even though access to most of this literature is free of charge and large libraries usually collect a great deal of writings – which can be accessed in a virtual environment with a simple search engine [3] – there is, however, no standard method for a detailed gray literature review and very few specific guidelines are available. Therefore, even though sorting through gray literature can sometimes be challenging [2,8,11], conference papers have been included in supplements of several journals and library catalogs in recent years, and sites that index and collect gray literature, such as the Bielefeld Academic Search Engine (BASE), NGO Search and Open Gray, are also increasing in number [3].

The Acta Medica Alanya journal endeavors to include gray literature, in particular in its compilation and editorial writings. It supports citing articles from our country of “Türkiye”, including Turkish, in its research articles.

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RESEARCH ARTICLE

ARAŞTIRMA

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Echocardiographic evaluation may provide more accurate patient selection for polysomnography in patients with obstructive sleep apnea: Predicting the severity of disease by echocardiography

Tıkayıcı uyku apnesi olan hastalarda ekokardiyografik değerlendirme polisomnografi için daha doğru hasta seçimi sağlayabilir: Ekokardiyografi ile hastalığın şiddetini tahmin etme

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ABSTRACT

Aim: Obstructive sleep apnea (OSA) may influence the cardiac function by several mechanisms. The aim of the present study was to evaluate the impact of OSA on left and right cardiac function and determine the echocardiographic parameters which can help to predict the severity of OSA.

Methods: In this cross-sectional analysis, 60 patients with suspected OSA were evaluated with transthoracic echocardiography before polysomnography between January and June 2017. On the basis of apnea-hypopnea index (AHI), the patients were classified into non-severe (AHI<30) (n = 30) and severe (AHI≥30) OSA (n = 30). The correlation between echocardiographic parameters and the apnea-hypopnea index (AHI) / Epworth Sleepiness Scale (ESS) was assessed.

Results: Regarding left ventricular (LV) echocardiographic parameters: left ventricular outflow (LVOT) proximal diameter, left ventricular mass index, posterior wall enddiastolic diameter (PWEDD) and interventricular septum enddiastolic diameter (IVSEDD) were significantly higher in severe OSA patients. With respect to right ventricular (RV) functional parameters: RV fractional area change (RVFAC) and myocardial performance index (MPI) values were significantly higher in severe OSA patients. We found significant positive correlations between AHI and LVOT proximal diameter, IVSEDD, RVMPI, RV E and A velocities, body mass index, neck circumference and ESS. By using the model created with 'PWEDD, LVOT diameter and RV A velocity' we were able to predict most of the patients' group correctly before polysomnography.

Conclusion: We conclude that we can predict the severity of the disease in patients with suspected OSA by using echocardiography.

ÖZ

Amaç: Tıkayıcı uyku apnesi (TUA) çeşitli mekanizmalarla kalp fonksiyonunu etkileyebilir. Bu çalışmanın amacı, TUA'nın sol ve sağ kalp fonksiyonu üzerindeki etkisini değerlendirmek ve TUA'nın ciddiyetini öngörmede yardımcı olabilecek ekokardiyografik parametreleri belirlemektir.

Yöntemler: Bu kesitsel analizde Ocak ve Haziran 2017 ayları arasında TUA şüphesi olan 60 hasta polisomnografi öncesi transtorasik ekokardiyografi ile değerlendirildi. Apne-hipopne indeksine (AHİ) dayanarak, hastalar ağır olmayan (AHI <30) (n=30) ve ağır (AHI≥30) TUA (n=30) olarak sınıflandırıldı. Ekokardiyografik parametreler ile apne-hipopne indeksi (AHİ) / Epworth Uykululuk Skalası (ESS) arasındaki korelasyon değerlendirildi. Regresyon analizi ile TUA ciddiyetini ön gördürebilecek model araştırıldı.

Bulgular: Sol ventrikül (LV) ekokardiyografik parametreler ile ilgili olarak; sol ventrikül çıkış akımı (LVOT) proksimal çapı, sol ventrikül kitle indeksi, arka duvar diyastol sonu çapı (ADDSÇ) ve interventriküler septum diastol sonu çapı (IVSDSÇ) ağır OSA hastalarında anlamlı olarak yüksek bulundu. Sağ ventrikül (RV) fonksiyonel parametrelerine göre; Sağ ventrikül fraksiyonel alan değişimi (SağVFAC) ve miyokardiyal performans indeksi (MPI) değerleri ağır OSA hastalarında anlamlı olarak yüksek bulundu. AHI ve LVOT proksimal çapı, IVSDSÇ, SağVMPI, SağV E ve A hızları, vücut kitle indeksi, boyun çevresi ve ESS arasında anlamlı pozitif korelasyon bulundu. "ADDSÇ, LVOT çapı ve SağV A hızı" ile oluşturulan modeli kullanarak, hastaların çoğunu polisomnografi öncesi doğru şekilde tahmin etmeyi başardık.

Sonuç: TUA şüphesi olan hastalarda ekokardiyografi kullanarak hastalığın ciddiyetini tahmin etmek mümkün olabilir.

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INTRODUCTION

Obstructive sleep apnea (OSA) is the most common form of sleep-related breathing disorders. It is characterized by repeated partial or complete closure of the pharynx, gasping episodes, unrefreshing sleep and excessive daytime sleepiness. It is defined by as the occurrence of more than five apneas / hypopneas per hour in polysomnography [1]. OSA is highly prevalent in the general population, affecting at least 9-15% of middle aged adults [2]. Definitions of OSA are based on respiratory and neurophysiological indices but recent data show that cardiovascular consequences may be more serious. It is associated with an increase in cardiovascular morbidity and mortality due to complications such as systemic and pulmonary hypertension, coronary artery disease, heart failure and arrhythmias [3]. The risk of cardiovascular complications appears to be mediated by the complex interaction between the mechanical and chemical effects (hypoxia, hypercapnia) or repetitive upper airway closure and its effect on the autonomic nervous system [4]. Studies have assessed the effects of OSA on the left ventricle (LV) [3]. Early determination of right ventricular (RV) dysfunction and pulmonary hypertension in patients with OSA is also important, although data on RV dysfunction and structural changes in this group of patients are limited. Recently, several echocardiographic studies have reported alterations in the structure and function of RV in patients with OSA, but the outcomes from these studies have been inconsistent [4]. Most of the studies were small and assessed few echocardiographic parameters, whereas large, randomized, controlled trials evaluating the impact of OSA on the alterations of the RV are lacking.

Accurate evaluation of RV morphology and function remains challenging in clinical practice due to its complex geometric shape. Although cardiac magnetic resonance imaging is considered as the gold standard for morphological and functional assessment of the right ventricle, conventional echocardiography remains the first-resort imaging modality in routine clinical practice due to its low-cost, safety, noninvasive nature and simplicity [5-6]. Novel techniques, including 2D and 3D speckle-tracking echocardiography, are very sensitive and can reveal alterations in RV structure and function in early disease stages. However, these techniques require expertise and have not been extensively validated for the assessment of RV function.

There is no 'gold standard' for the diagnosis of OSA, which makes it difficult to calibrate any test for diagnosis. Traditionally, polysomnography (PSG) in an attended setting (sleep laboratory) has been used as a reference standard for the diagnosis of OSA. Polysomnography measures several sleep variables, one of which is the apnea-hypopnea index (AHI), which is defined as the apneas and hypopneas per hour of sleep. The AHI has been widely used to diagnose OSA. The Epworth sleepiness scale (ESS), is a simple, self-administrated questionnaire which is shown to provide a measurement of the subject's general level of daytime sleepiness [7]. Polysomnography laboratories are very busy all over the world and patients have to wait for a long time to have the test. Therefore, a method that would facilitate proper patient selection for polysomnography would be very useful.

In this study, we aimed to investigate the impact of untreated OSA on left and right ventricular function as measured with echocardiography, the correlation between echocardiographic parameters and AHI/ESS and determine the echocardiographic parameters which can predict severe OSA. To the best of our knowledge, this is the first study that investigates the predictor echocardiographic parameters for severe OSA.

MATERIALS AND METHODS

Study population

Between January and June 2017, 60 patients with suspected OSA undergoing polysomnography were included in the study. They had symptoms including snoring, witnessed apnea and daytime sleepiness. All patients had to provide written, informed consent prior to inclusion in the study, which was approved by the local ethics committee.

Pulmonary function tests of all participants were evaluated. Individuals who had a sleep-related respiratory disease other than OSA, diagnosed pulmonary disease, left ventricular dysfunction (EF<50%), ischemic or valvular heart disease,

atrial fibrillation, or renal insufficiency (serum creatinine >2 mg/dl), were excluded.

All patients were subjected to a thorough clinical and laboratory evaluation. Echocardiographic examinations for the detection of LV/RV function were performed before the polysomnography and ESS evaluations. Echocardiographic examinations were performed exclusively for this study by two experienced physicians, with the exception of routine practice in patients scheduled for polysomnography. All patients underwent overnight polysomnography using a standard technique and the average AHI was calculated [8]. On the basis of AHI, patients were classified into non-severe (AHI < 30) and severe (AHI ≥ 30) OSA groups [9]. The ESS score was calculated for each patient using the Turkish version of the validated ESS questionnaire [10]. Body mass indices (BMI) of the patients were calculated as weight (kg) divided by the height-squared (m^2). Neck circumferences were also measured.

Echocardiography

Echocardiographic examinations were performed with a 2-4 MHz transducer attached to a Vivid S5 echocardiography machine (GE, Norway). Single lead electrocardiography was recorded continuously during the examination in the left lateral decubitus position. All measurements were taken at 3 consecutive cycles and the averages were recorded. Analysis was performed according to the recommendations found in the guidelines of the American Society of Echocardiography.

Left ventricular end-diastolic and end-systolic diameters (LVEDD, LVESD), interventricular septum and posterior wall end-diastolic diameters (IVSEDD, PWEDD) and left ventricular outflow tract (LVOT) proximal diameters were measured in the parasternal long axis view [11]. EF was calculated according to the Simpson formula. The left atrium (LA) diameters were calculated in the parasternal long axis and apical 4-chamber views. IVSEDD, PWEDD and internal diameters were used to calculate LV mass (LVM) using the following equation:

LVM = 1.04 x 0.8 [(LV Wall thickness + internal dimension) - (internal dimension)] + 10.6 [12].

BSA was calculated using the Sclich formula, which varies according to gender [13]. To evaluate the diastolic functions of the LV, the mitral inflow velocities were evaluated from the apical 4-chamber view. The early diastolic velocity of the lateral mitral annulus (Em) was recorded with tissue Doppler imaging (TDI).

Right ventricular diameters were measured in the parasternal long axis and apical 4-chamber views. Systolic pulmonary arterial pressure (sPAP), fractional area change (FAC), Sm velocity, tricuspid annular plane systolic excursion (TAPSE), TDI-derived myocardial performance index (MPI), tricuspid E wave velocity, A wave velocity, deceleration time (DT), E/A ratio, Ea velocity and Ea/Aa ratio were measured.

The maximal tricuspid regurgitation velocity was measured by continuous-wave Doppler echocardiography from the apical 4-chamber view. Systolic pulmonary pressure was calculated as follows:

4X (tricuspid systolic jet)^2 + right atrial pressure.

Early (E) and late (A) right ventricular inflow velocities were measured with pulsed wave Doppler by placing the sample volume in between the tips of the tricuspid valve in the apical 4-chamber view.

Pulsed wave TDI was obtained in the apical 4-chamber view by placing a 5-10 mm sample volume at the lateral side of the tricuspid annulus. Measurements were recorded during end-expiratory apnea [14]. On the TDI images annular peak systolic velocity (S'), early (Ea) and late (Aa) (peak annular diastolic velocities) and systolic velocity duration were measured as ejection time (ET), isovolumetric relaxation time (IVRT, time between the end of ET and the beginning of E') and isovolumetric contraction time (IVCT, time between the end of Aa and the beginning of ET) were measured. Tricuspid valve closure and opening time (TCO), which was measured from the cessation of the Aa wave to the beginning of the Ea wave, encompassed IVCT, ET and IVRT. The TDI-derived MPI, as a global estimate of both systolic and diastolic functions of the RV, was calculated with the following formula :

TDI-MPI = (TCO-ET)/ET [15].

TAPSE was calculated by placing an M-mode cursor through the tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole in the apical 4-chamber view.

RV FAC was obtained by tracing the RV endocardium both in end-systole and end-diastole from the annulus, along with the free wall to the apex, and then back to the annulus along with the interventricular septum in the apical 4-chamber view. RV FAC was calculated using the following formula:

FAC = (end-diastolic area - end-systolic area) / end-diastolic area x 100 [16].

Polysomnography Analysis

Full-night polysomnographic recording was applied with a Grass-telefactor - PMA AS40 in the sleep laboratory. Polysomnographies were scored manually by the same examiner. Measured parameters included electroencephalography (C4/A1, O2/ A1, F4/A1, F3/A2), electro-oculography, electrocardiogram, oronasal airflow - either by nasal cannula or thermal sensors - pulse oximetry, thoracoabdominal movements, submental and pretibial electromyography and snoring noises. Staging was performed according to the guidelines of the American Sleep Academy Association 2012 criteria [17].

Statistical Analysis: Data are presented as mean ± standard deviation for normally distributed continuous variables, median (minimum-maximum) for non-normally distributed continuous variables and count, percentages for categorical variables. The differences in categorical variables between groups were compared using the Chi-Square test. Normally distributed continuous variables were evaluated by the Student's t test. The degree of association between continuous variables was calculated by the Pearson's correlation coefficient. A multiple logistic regression was performed to identify the independent risk factors of outcome variable. Receiver operating characteristic (ROC) curves were used to describe the performance of diagnostics value of continuous variables. P-value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics: A total of 60 patients were enrolled in the study. Among the 60 patients included, the median age was 50.9 ± 13.7 years and 34 patients (56.6%) were male. The mean AHI value was 34.06 ± 25.3. The patients were classified as severe OSA (AHI≥30) (n= 30) and non-severe OSA (AHI<30) (n=30). Both study groups were similar with regard to age, gender, the prevalence of hypertension and diabetes, smoking year, blood pressure, body mass index (BMI) and heart rate values (p > 0.05). Neck circumference values were higher in the severe OSA group (40.2 ± 3.8 vs. 37.7 ± 4.4, p=0.021, respectively). The baseline demographic and clinical data are presented in Table 1.

Table 1. General characteristics of the patients

	AHI ≥30 n:30	AHI <30 n:30	P
Male gender (n, %)	20 (66.7)	14 (46.7)	0.118
DM (n, %)	9 (30.0)	8 (26.7)	0.774
HT (n, %)	13 (43.3)	7 (23.3)	0.100
Smoke (n, %)	16 (53.3)	15 (50.0)	0.796
FH (n, %)	6 (20.0)	11 (36.7)	0.152
Age (years)	53.6 ±14.0	48.2±13.0	0.130
Sys BP (mmHg)	143.3 ±22.6	136.0 ±25.2	0.241
Dia BP (mmHg)	90.0+14.6	84.3+12.3	0.110
BMI (kg/m2)	31.8 ± 6.9	28.9 ±5.4	0.064
Neck Circumference (cm)	40.2 ± 3.8	37.7 ± 4.4	0.021*
Heart Rate	81.2 ±10.3	75.9 ±11.4	0.063
ESS	6.63 ± 5.65	5.26 ± 4.68	0.313

BMI: Body Mass Index, DM: Diabetes Mellitus, Dia: Diastolic, ESS: Epworth Sleepiness Scale, FH: Family history, HT: Hypertension, Sys: Systolic

Conventional LV echocardiographic parameters: Regarding LV echocardiographic parameters, LVOT diameter, IVSEDD and PWEDD were significantly higher in severe OSA patients (22.25 ± 2.09 mm vs. 20.43 ± 4.23 mm, p=0.039; 11.13 ± 1.61 mm vs. 10.16 ± 1.46 mm, p=0.018; 11.10 ± 1.60 mm vs. 10.10 ± 1.42 mm, p=0.013 respectively). LVMI was also higher in this group (99.39 ± 25.51 gr/m² vs 87.71 ± 18.84 gr/m², p=0.048, respectively). There was a statistical trend for significance for left ventricular A velocity (p = 0.056) to be higher in the severe OSA group

(Table 2).

Conventional echocardiographic RV functional parameters: With respect to RV functional parameters, RVFAC and MPI values were significantly higher in severe OSA patients (47.94 ± 7.36% vs. 41.23 ± 12.18%, p=0.012; 0.43 ± 0.31 vs. 0.29 ± 0.16, p=0.034, respectively) whereas TAPSE and PVR values were similar in both groups. Right ventricular A velocity was also higher in the severe OSA group (0.58 ± 0.14 m/sn vs. 0.48 ± 0.13, p=0.008, respectively). No significant difference was determined between the two groups in terms of right atrial and right ventricular dimensions, right atrial area, and systolic pulmonary pressure (Table 3).

Table 2. Left ventricular echocardiographic parameters

	AHI ≥ 30 (n:30)	AHI < 30 (n:30)	p
PWEDD(mm)	11.10 ±1.60	10.10 ± 1.42	0.013*
IVSEDD(mm)	11.13 ±1.61	10.16 ± 1.46	0.018*
LVOT Diameter(mm)	22.25 ± 2.09	20.43 ± 4.23	0.039*
LVMI (gr/m^2)	99.39 ± 25.51	87.71 ± 18.84	0.048*
E (m/s)	0.61 ± 0.14	0.63 ± 0.18	0.726
A (m/s)	0.79 ± 0.15	0.70 ± 0.18	0.056
Em (cm/s)	9.81 ± 4.23	10.60 ± 4.90	0.505
Am (cm/s)	12.95 ± 5.19	11.67 ± 3.48	0.266
LAVI (mm/m^2)	21.1 ± 5.3	19.9 ± 4.4	0.336
LA D1(mm)	35.93 ± 4.46	34.50 ± 3.55	0.174
LVSD(mm)	26.5 ± 3.62	26.63 ± 4.05	0.894
LVDD(mm)	45.46 ± 3.56	44.73 ± 3.86	0.448
LVOT VTI	19.67 ± 5.09	20.91 ± 7.16	0.443
DT (ms)	232.16 ± 78.87	230.3 ± 90.31	0.932

A: Peak late diastolic mitral inflow velocity, Am: Late diastolic myocardial velocity, DT: Deceleration time, E: Peak early diastolic mitral inflow velocity, Em: Early diastolic myocardial velocity, IVSEDD: Interventricular septum end-diastolic diameter, , LVMI: Left ventricular mass index, LVDD: Left ventricular diastolic diameter, LVSD: Left ventricular systolic diameter, LVOT: Left ventricular outflow tract, LA D1:Left atrium anteroposterior diameter, PWEDD: Posterior wall end-diastolic diameter , Sys: Systolic, * p value < 0,05

Correlation analysis: We found significant positive but weak correlations between AHI and LVOT proximal diameter, IVSEDD, RVMPI, right ventricular E and A velocities, BMI, neck circumference and ESS. Within echocardiographic parameters, the absolute value of the correlations with RV A velocity, PWEDD, IVSEDD, LVOT diameter and RVMPI were higher than the one with ESS (Table 4).

Logistic regression analysis end regression model: The log regression model created with PWEDD, LVOT diameter and RV A velocity identified 73% of the patients' group correctly. 70% of the patients with severe OSA (AHI ≥ 30) were determined correctly and 76% of the other group of patients (AHI < 30) were predicted correctly by using this model (Table 5).

Table 3. Right Ventricular Echocardiographic Parameters

	AHI ≥ 30 (n:30)	AHI < 30 (n:30)	p
A (m/s)	0.58 ± 0.14	0.48 ± 0.13	0.008**
RVFAC (%)	47.94 ± 7.36	41.23 ± 12.18	0.012*
MPI	0.43 ± 0.31	0.29 ± 0.16	0.034*
DT (ms)	253.62 ± 89.44	246.81 ± 89.33	0.773
TR vel (cm/s)	1.88 ± 0.48	1.92 ± 0.61	0.823
PAP (mmHg)	15.49 ± 7.68	17.59 ± 9.31	0.382
TCO(s)	388.33 ± 60.42	385.6 ± 43.42	0.841
TAPSE(mm)	19.59 ± 10.22	20.00 ± 8.82	0.871
RA long axis (mm)	46.23 ± 5.09	46.06 ± 5.68	0.905
RA minor axis (mm)	37.26 ± 6.48	37.36 ± 6.05	0.951
RA area (cm^2)	14.17 ± 2.79	13.53 ± 3.70	0.451
RV diameter	27.03 ± 3.41	26.93 ± 3.36	0.909
RVOT (mm)	23.61 ± 2.88	23.0 ± 4.13	0.505
RVOT VTI	16.99 ± 5.27	17.0 ± 4.58	0.998
E (m/s)	0.518 ± 0.17	0.46 ± 0.13	0.177
Ea (cm/s)	10.83 ± 3.27	11.71 ± 3.67	0.333
Aa (cm/s)	16.6 ± 5.77	15.32 ± 3.92	0.321
Sa (cm/s)	14.47 ± 4.42	13.52 ± 3.61	0.365
PVR (dyn*s/cm5)	1.39 ± 0.84	1.32 ± 0.52	0.708

A: Peak late diastolic tricuspid inflow velocity, Aa: Late diastolic velocity of tricuspid lateral annulus, DT: Deceleration time E: Peak early diastolic tricuspid inflow velocity, Ea: Early diastolic velocity of tricuspid lateral annulus, MPI: Myocardial performance index , PAP: Pulmonary arterial pressure , PD: Peritoneal dialysis, PVR: Pulmonary vascular resistance, TR vel: Tricuspid regurgitation flow velocity, RA: Right atrium, RV: Right ventricle, RVOT: Right ventricle outflow tract, RVFAC: Right ventricular fractional area change, Sa: Systolic myocardial velocity of tricuspid annulus, TAPSE: Tricuspid plane systolic excursion, TCO: Tricuspid closure opening time. * p value < 0,05, **p value <0,01

DISCUSSION

To our knowledge, this is the first study to predict patients with severe OSA using conventional echocardiography and TDI. Various echocardiographic evaluations were found to be related to severity of many clinical conditions in previous studies [18]. We evaluated the patients with suspected OSA who were scheduled to undergo polysomnography. Echocardiographic examinations were performed

Table 4. Correlations between Echocardiographic/Clinical findings and AHI

RV Echocardiographic findings			LV Echocardiographic findings			General Clinical Findings		
	r	p		r	p		r	p
	r	p		r	p		r	p
MPI	0.33	0.010*	IVS	0.31	0.015*	ESS	0.29	0.027*
FAC	0.21	0.107	PW	0.32	0.012*	Neck Circumference	0.39	0.002
PVR	0.00	0.987	LVEDD	0.13	0.330	BMI	0.42	0.001**
TCO	0.07	0.595	LVEDD	0.03	0.826	Weight	0.40	0.002**
RV	0.17	0.191	LA D1	0.14	0.289	Boy	0.06	0.652
RVOT	0.19	0.142	LA D2	0.10	0.430	Age	0.22	0.089
RVOTVTI	-0.05	0.707	LA D3	0.12	0.375	Sys BP	0.16	0.223
Dia. Area	0.07	0.604	LAVI	0.23	0.859	Dia BP	0.23	0.079
Sys Area	-0.05	0.683	LVOT	0.34	0.008**	Heart rate	0.14	0.271
TAPSE	-0.02	0.852	LVOT VTI	0.00	0.983			
TR vel.	-0.14	0.294	LV E vel	-0.06	0.649			
PAP	-0.22	0.125	LV A vel	0.19	0.151			
RV E vel.	0.26	0.044*	Em	-0.16	0.217			
RV A vel.	0.35	0.006**	Am	0.09	0.475			
RV DT	0.09	0.510	LV DT	0.11	0.399			
Ea	0.21	0.101						
Aa	0.07	0.602						
Sa	0.04	0.738						
RA long axis	0.05	0.680						
RA minor axis	0.06	0.660						
RA area	0.02	0.909						

BMI: Body Mass Index, DM: Diabetes Mellitus, Dia: Diastolic, ESS: Epworth Sleepiness Scale, FH: Family history, HT: Hypertension, Sys: Systolic, Aa: Late diastolic velocity of tricuspid lateral annulus, Am: Late diastolic velocity of mitral lateral annulus , DT: Deceleration time , Ea: Early diastolic velocity of tricuspid lateral annulus , Em: Early diastolic velocity of mitral lateral annulus, IVSEDD: Interventricular septum end-diastolic diameter , LA D1:Left atrium anteroposterior diameter, LA D2:Left atrium long axis diameter, LV A vel: Peak late diastolic mitral inflow velocity, LV E vel: Peak early diastolic mitral inflow velocity, LVDD: Left ventricular diastolic diameter , LVMI: Left ventricular mass index , LVOT: Left ventricular outflow tract, LVSD: Left ventricular systolic diameter , MPI: Myocardial performance index , PAP: Pulmonary arterial pressure, PVR: Pulmonary vascular resistance , PWEDD: Posterior wall end-diastolic diameter, RV A vel: Peak late diastolic tricuspid inflow velocity, RV E: Peak early diastolic tricuspid inflow velocity, RA: Right atrium, RV: Right ventricle, RVOT: Right ventricle outflow tract, RVFAC: Right ventricular fractional area change, Sa: Systolic myocardial velocity of tricuspid annulus, Sys: Systolic , TAPSE: Tricuspid plane systolic excursion, TCO: Tricuspid closure opening time , TR vel: Tricuspid regurgitation flow velocity, * p value < 0,05 , **p value <0,01

Table 5. Log regression model

	OR	95,0% C.I.	P
PWEDD > 11 mm	5.05	1.28 - 19.94	0.021
LVOT D >21.5 mm	8.12	2.09-31.59	0.003
RV A vel. > 0.475 cm/s	5.18	1.28-20.96	0.021

LVOT: Left ventricular outflow tract, PWEDD: Posterior wall end-diastolic diameter, RV A vel: Peak late diastolic tricuspid inflow velocity

before polysomnographies. According to the results of our study, we found some structural and functional alterations in the left and right ventricles. The major new finding of our study is that we have shown the possibility of predicting the patients with severe OSA by the use of certain echocardiographic parameters. This could help in the selection of patients to undergo polysomnography primarily and determining the appropriate treatment.

We tried to create a regression model predicting severe OSA using the parameters associated with the severity of OSA in the t test and correlation analysis. In many model experiments, the most significant model was the one including 'PWEDD, LVOT proximal diameter and RV A velocity'.

The current gold standard for diagnosis and management of OSA is in-laboratory (in-lab) polysomnography, however the limited availability of testing options for patients has led to long wait times and increased disease burden within the population.

Tests that predict severe OSA may provide a priority ranking in sleep tests. Our predictive values are not an alternative to polysomnography, but can be helpful to identify patients who will be given priority in polysomnography [19].

In our study, it was found that the patients with severe OSA (AHI ≥ 30) showed a statistically significant increase in both IVSEDD and PWEDD compared to the patients with AHI <30. Additionally, severe OSA patients showed a significant increase in LVMI. This is in line with previous studies on this topic [20]. It is known that intermittent hypoxia causes left ventricular hypertrophy and also plays an important role in the cardiovascular complications of OSA [21]. Although the negative effect of intermittent hypoxia on the cardiovascular system has not been completely clarified, multiple mechanisms, including sympathetic overactivation, oxidative stress, inflammation, metabolic deregulation, and endothelial dysfunction have been suggested to be involved. Hypoxemia, hypercapnia and acidosis induced by chronic intermittent hypoxia in OSA patients, could activate the sympathetic nervous system. This results in increased LV afterload and heart rate, which promote myocardial oxygen demand and chronically contribute to LV hypertrophy and failure. In addition, systemic inflammation and free radical generation triggered by OSA, play important role in intermittent hypoxia-induced remodeling of LV [22]. In our study, we showed that severe OSA is associated with left ventricular hypertrophy. Hypertension prevalence and blood pressure values were similar in both groups in the study. Our findings showed the association between left ventricular hypertrophy and severe OSA, independent of hypertension. Hedner, J. et al. reported this association similarly [23] and the meta-analysis which evaluated the LV structure in OSA patients, also reported that OSA induces the cardiac abnormality independent of hypertension. In the analysis, they eliminated the effect of systemic hypertension by excluding the studies which hypertensive patients enrolled. We found that PWEDD ≥ 12 mm increases the likelihood of severe OSA fivefold, in a patient examined for the suspicion of OSA.

Unlike previous studies, we investigated the LVOT diameter and found it to be significantly higher in patients with severe OSA. To our knowledge, this is the first study which highlights the association between LVOT diameter and severe OSA. Although there is no data on the association between the increase in LVOT diameter and the severity of OSA, it could also be the result of LV remodeling and hypertrophy due to intermittent hypoxia. The normal value for the LVOT proximal diameter is 20.3 ± 2.3 mm [24]. Using ROC analysis, we determined 21.5 mm to be the maximum LVOT diameter. We found that a LVOT diameter > 21.5 mm increases eightfold the likelihood of severe OSA in a patient with suspected OSA.

The conclusions about the correlation between the severity of OSA and RV remodeling and function from various studies have differed. Several studies reported that OSA patients presented with right cardiac dysfunction but some others did not reveal any changes in RV morphology and function in OSA patients. Several mechanisms were considered to explain the association between RV dysfunction and OSA. Permanent pulmonary hypertension was thought to be an important factor, leading to RV overload and inducing the release of inflammatory factors and resulting with RV dysfunction [25]. Some other studies reported the increased venous return and overload due to the intrathoracic negative pressure against an occluded airway, resulted in remodeling of RV. In addition, stimulation of central and peripheral chemoreceptors and increase in sympathetic nerve activity by intermittent hypoxia and CO2 retention might be another mechanism of RV dysfunction.

In our study, there were no differences between the two groups in terms of right ventricular dimensions, right atrial area, PVR and systolic pulmonary pressure. With respect to right ventricular functional parameters, RVMPI and RVFAC values were significantly higher in the severe OSA group; whereas TAPSE and lateral TDI Sm values were similar in both groups. Maripov et al. demonstrated that RVMPI was significantly high in patients with OSA compared to the controls, in their meta-analysis including twenty-five studies [2]. They reported that patients with OSA had decreased TAPSE, RV Sm and RV FAC. The findings of the present study showed a similar increase in RV MPI but there were no differences in the TAPSE and RV Sm values of the two groups. Interestingly, there was an increase in RVFAC value in the severe OSA group in our study, which might be due to differences in study design. Most previous studies compared patients with OSA and healthy control groups, but we compared severe with non-severe OSA patients, so the mean AHI value of our control group was higher than those of previous studies. In addition, there are conflicting results about RVFAC and RV Sm values [2,26]. Dobrowolski et al. and Shivalkar et al. reported an increase in RV Sm; Kasikcioglu et al and Vitarelli et al. indicated that RV Sm was lower in patients with OSA [4,26-29]. The difficulty of accurate evaluation of RV morphology and function in clinical practice due to its complex geometric shape might be another reason for the discrepancy between the studies. When we examined the correlations between AHI and echocardiographic parameters, we found significant correlations between AHI and IVSEDD, PWEDD, LVOT diameter, RVMPI, right ventricular E and A velocities. None of the correlations were strong, although all but right ventricular E velocity were stronger than the correlation between AHI and ESS.

There is little data on the association between RV A velocity and the severity of OSA in previous studies. Kasikcioglu et al. reported an increase in RV A velocity in patients with severe OSA, but it was not statistically significant [4]. We found that RV A velocity was higher in the severe OSA group. The increase in RV A velocity was considered as a sign of RV diastolic dysfunction. The mean value of RV A velocity is 0,40 m/s and the upper reference value is 0,58 (0,55-0,60) m/s [15]. We accepted 0.475 m/s as the upper limit of RV A velocity that we determined using ROC analysis. We found RV A velocity > 0.475 m/s to increase the likelihood of severe OSA fivefold in a patient with suspected OSA.

Limitations: This was a cross sectional study including a relatively small number of patients with OSA. The small number of patients is an important limitation especially for predictive analysis. For more reliable results of the predicted values, the results should be examined in large-scale studies. We believe that this study should be a guide for larger studies to be carried out in the future.

Most of the patients with OSA have high BMI, which makes echocardiographic examination difficult. We tried to overcome this difficulty as the examinations were performed by experienced physicians.

Conclusion: To our knowledge, this is the first study that investigates the predictor echocardiographic parameters for severe OSA. Our findings indicate that we can predict 73% of patients with suspected OSA, whether they have severe OSA or not, before polysomnography. At this point, using echocardiography, it may be possible to select patients for polysomnography more accurately.

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Clinical and radiological features of traumatic orbital emphysema cases

Travmatik orbital amfizem olgularında klinik ve radyolojik özellikler

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ABSTRACT

Aim: In this study, we aimed to evaluate the clinical course and treatment requirements of orbital emphysema cases resulting from orbital trauma.
Material and Method: We included the 112 orbits of 82 patients who had presented to the emergency service of our hospital between 2016 and 2019 in this retrospective study. The common feature was severe orbital trauma due to various causes and referrals to the ophthalmology department with a preliminary diagnosis of ocular or orbital damage. The orbital computerized tomography images were evaluated for orbital emphysema and a classification was performed according to the location of the air as preseptal, extraconal, intraconal and intraocular.
Results: We included a total of 82 subjects consisting of 65 males and 17 females in the study. The mean age was 37.85 (3-78) years in general, 36.09 (3-78) years in the males, and 44.58 (15-78) years in the females. Emphysema was present in the preseptal area in 80 cases, the extraconal area in 26, and the intraconal area in 5 of the 112 orbits. Intraocular emphysema was detected in only a single case. The orbital compartment syndrome was not present in any of our cases.
Conclusion: Orbital emphysema is a common condition in orbital trauma. It may be associated with the orbital compartment syndrome. Orbital emphysema after orbital trauma is usually a benign, self-limiting condition.

Key Words: Orbital trauma, orbital tomography, orbital emphysema

ÖZ

Amaç: Çalışmamızda, orbita travmalarına bağlı görülen orbital amfizem (OA) olgularının klinik seyrini ve tedavi ihtiyaçlarını değerlendirmeyi amaçladık.
Gereç ve Yöntem: Bu retrospektif çalışmaya 2016-2019 yılları arasında hastanemiz acil servisine başvuran 82 hastanın 112 orbitası dahil edildi. Hastalarımızın ortak özelliği farklı nedenlerle ciddi yüz ve orbita travması yaşamış olmalarıydı. Glob veya orbita yaralanması ön tanısı ile göz hastalıklarına konsülte edilmiş bu hastaların orbita bilgisayarlı tomografileri (BT) OA yönünden değerlendirildi. Orbital havanın yerleşim yerine göre, preseptal, ekstrakonal, intrakonal ve intraoküler olarak sınıflandırıldı.
Bulgular: Çalışmaya dahil edilen 82 hastanın 65'i erkek, 17 tanesi ise kadındı. Hastaların genel yaş ortalaması 37,85 (3-78) idi. Cinsiyete göre bakıldığında erkek hastaların yaş ortalaması 36,09 (3-78), kadın hastaların yaş ortalaması ise 44,58 (15-78) olarak bulundu. 112 orbitanın 80 tanesinde preseptal sahada amfizem saptandı. Orbital havanın yerleşimi 80 gözde preseptal, 26 gözde ekstrakonal, 5 gözde intrakonal, 1 gözde ise intraokülerdi. Hiçbir hastamızda orbital kompartman sendromu tespit edilmedi.
Sonuç: Orbital amfizem orbita travmalarında sık karşılaşılan bir durumdur. Orbital kompartman sendromu ile ilişkili olabilir. Travma sonrası izlenen orbital amfizem genellikle iyi huylu kendini sınırlayan bir durumdur.

Anahtar Kelimeler: Orbital travma, orbita tomografisi, orbital amfizem

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INTRODUCTION

Orbital emphysema (OE) is the presence of air in the orbital or periorbital tissues. It is usually a result of orbital bone fractures due to trauma which result in air displacement from the paranasal sinuses to the orbit (1). OE is a common radiographic sign in orbital fractures and is the second most commonly associated with medial wall fractures following blunt trauma [2,3]. It can also be the result of forceful blowing of the nose, sneezing, weightlifting, retinal surgery, and exposure to air under pressure without an orbital fracture [4-8]. Palpebral emphysema may lead to unnecessary antibiotic treatment following a misdiagnosis of sinusitis or periorbital cellulitis, in non-trauma-related cases.

Orbitopalpebral emphysema can also develop if there is an orbital septum defect. Air collection in the orbit leads to increased intraorbital pressure and air can pass freely from the orbit to the eyelids if there is an orbital septum defect. Heerfordt injected air experimentally into cadavers and suggested that a mean intraorbital pressure of 40 to 50 mm Hg is required to perforate the septum [10]. Elderly persons' cadavers required a lower mean pressure than young ones for septum perforation, as the septum weakens with increasing age.

Orbital traumas are common ophthalmologic emergencies. Such trauma can lead to fractures in the bone structures of the orbital walls. Although there are many case reports about orbital emphysema in the literature, very few case series have been reported. We aimed to evaluate the clinical characteristics and follow-up process of OE cases due to orbital trauma in this study.

MATERIAL METHOD

We included the 112 orbits of 82 patients who presented to the emergency department of Alanya Alaaddin Keykubat University Training and Research Hospital between 2016 and 2019 in this retrospective study. The study was conducted in accordance with the principles of the Declaration of Helsinki, after the approval of the institutional ethics committee was obtained. The common characteristic of our patients was a history of severe orbital trauma because of various reasons. These patients were referred to the ophthalmology department with a preliminary diagnosis of orbital or globe injury and the orbital computed tomography (CT) was evaluated for OE. An anatomical classification of preseptal, extraconal, intraconal or intraocular was established, according to the location of the air. Patients who were found to have OE were evaluated for age, gender and etiology.

Cold compresses were recommended to the patients. The medical treatment consisted of a topical antibiotic (netilmicin sulphate 0.1%), topical steroid (dexamethasone disodium phosphate 0.3%) and an oral nonsteroidal anti-inflammatory drug (flurbiprofen 100 mg). A systemic antibiotic (amoxicillin clavulonate 875/175 mg) was added if a sinus infection finding was present.

RESULTS

The 82 patients included in the study consisted of 65 males and 17 females with a mean age of 37.85 (3-78) years. The mean age was 36.09 (3-78) years in the male patients and 44.58 (15-78) years in the females.

In our classification of the source of the orbital trauma, of the 55 cases of vehicular accidents, 37 cases suffered the injury from inside a vehicle, 4 from outside a vehicle, and 14 resulted from a motorcycle accident. One patient was found to have suffered the trauma after falling from a bicycle. A total of 15 patients had presented to the emergency department due to an injury sustained after an assault, 3 after falling from heights, and 8 due to trauma during sports activities (Figure 1).

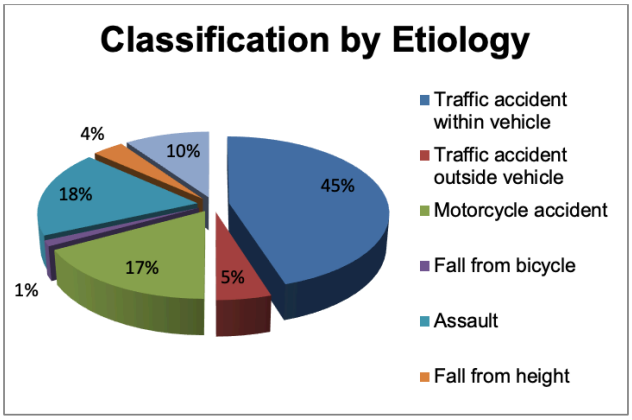

Fig1. Distribution of the orbital emphysema cases by etiology

The radiological distribution of our OE cases by

the location of the air is presented in Figure 2. Preseptal emphysema (Figure 3a) was found in 80 of the 112 orbits, while there were 26 extraconal (Figure 3b) and 5 intraconal (Figure 4a) emphysema cases, in addition to a single intraocular emphysema case (Figure 4b). There was no orbital compartment syndrome or central retinal artery occlusion in any patient. An intraocular foreign body due to a penetrating eye injury was detected in the patient with intraocular air and she was referred to a retina center for vitreoretinal surgery.

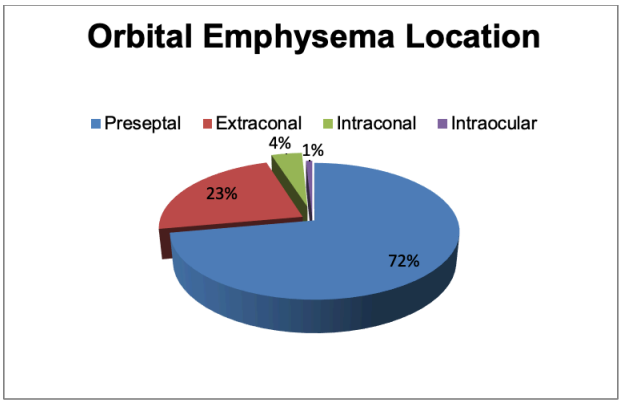

Fig 2. Distribution of the orbital emphysema cases by location

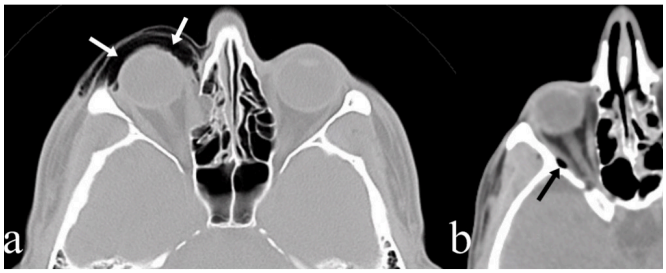

Fig 3. Computed tomographic images demonstrate preseptal (a: white arrow) and extraconal (b: black arrow) emphysema.

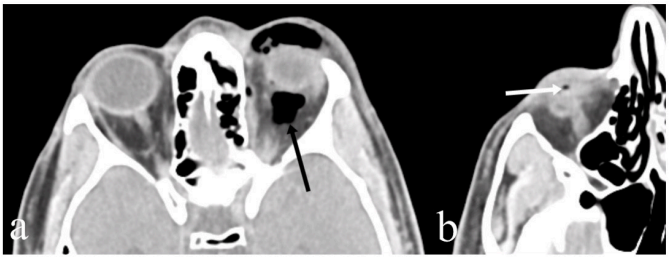

Fig 4. Computed tomographic images demonstrate intraconal (a: black arrow) and intraocular (b: white arrow) emphysema.

DISCUSSION

Orbital emphysema in the literature was described and classified by Heerfordt in 1904 [10]. This classification included palpebral emphysema, true orbital emphysema and orbitopalpebral emphysema. Isolated palpebral emphysema is rare. It may result from fracture of the lacrimal bone and secondary tear of the lacrimal sac in front of the orbital septum. Nasal air can then pass through the nasolacrimal drainage system and enter the eyelid tissues. Palpebral emphysema can also occur as a result of subcutaneous air spreading to the eyelids along the fascial plane. The air remains limited to the eyelid as long as the orbital septum is intact.

When planning our study, we wanted to emphasize that orbital fractures associated with blunt orbital trauma may cause OE, as the emphysema may also be associated with serious complications that can lead to permanent vision loss. Although it is often a minor problem and regresses with follow-up and medical treatment [1-3], it may occasionally be associated with more serious problems such as orbital compartment syndrome and central retinal artery occlusion [1]. Urgent orbital decompression may be required in the presence of compression signs, such as optic disc edema, weakening of the pupil reaction, a sudden decrease in visual acuity or limitation of eye movements [9].

There are only a few studies analyzing large orbital emphysema series. Moon et al. have found OA in 70 of their 348 patients with a medial orbital wall fracture. Intraorbital air was most commonly found (70%) in the superior extraconal region. In the current study, the main location was preseptal as seen in 80 (71.5%) of the 112 patients. Emphysema was present in a total of 32 cases (28.5%) in the extraconal, intraconal and intraocular regions.

A “blow-out” fracture is the most common fracture type following blunt orbital trauma [10,11]. These fractures are located on the bone structure separating the maxillary sinus from the orbital cavity and the maxillary sinus air can be displaced into the orbit. Another reported complication of orbital emphysema is a dramatic but temporary increase in intraocular pressure, up to 100 mm Hg in the case of trauma and/or barotrauma, where the integrity of the orbital septum is not impaired [12]. When the pressure in the upper

respiratory tract is artificially increased as seen with sneezing, coughing, vomiting, or blowing air through the nose - or following orbital fractures - air is forced from the sinus to the orbit [13]. The air can, similarly, easily exit from the fracture zone and a high intraorbital pressure is not maintained in most cases. However, if a unidirectional valve mechanism originating from a bone fragment or orbital fat at the fracture site is present, air may enter the orbit and become trapped [14]. The result is an increase in intraorbital pressure and sometimes an increase in intraocular pressure. Proptosis of the orbital content, rupture of the orbital septum or Tenon's capsule, and air escaping into the eyelids or conjunctival space act as preventive measures to reduce the intraorbital pressure. The intraorbital pressure can be monitored indirectly by measuring the intraocular pressure [15].

The diagnosis of OE can be made easily with the anamnesis, physical examination and orbital CT [14]. The latter should be the radiological imaging method of choice for patients presenting with orbital trauma to the emergency department [16].

In our previous study, at least one of the clinical signs of diplopia, laceration, afferent pupillary defect, hypoesthesia and exophthalmos was found to be present at a rate of 47.1% in traumatic orbital fractures. A statistically significant relationship between basal fractures and diplopia was also present in our previous study (p= 0.002). However, there was no significant relationship between other radiological and clinical findings [17].

In conclusion, orbital emphysema is a rare clinical condition. It is most commonly caused by orbital trauma and usually constitutes a coincidental and benign finding that improves over time. Careful observation is the only treatment required unless the orbital wall fracture involves an infected sinus, in which case oral prophylactic antibiotics may be administered.

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Conflict of Interest: The author has no conflict of interest related to this article.

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Are modified Gartland Type IV supracondylar humerus fractures different from Type III fractures? A retrospective clinical study

Modifiye Gartland Tip IV Suprakondiler Humerus Kırıkları, Tip III Kırıklardan Farklı mıdır? Retrospektif Klinik Çalışma

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ABSTRACT

Aim: The present study investigates whether surgical treatment of modified Gartland Type IV supracondylar humerus fracture is radiologically and clinically different from the treatment of Type III fractures.

Methods: The medical charts of 197 patients who underwent surgical treatment for pediatric supracondylar humerus fracture in our clinic between 2012 and 2015 were retrospectively reviewed, and 76 patients humerus Gartland Type III and unstable Type IV fractures regardless of neurovascular injury (49 males, 27 females) were included in the study as randomize. The patients were divided into two groups as patients with modified Gartland Type III (n=36) and patients with Type IV fractures (n=40). The mean age of the patients was 5.88±3.29 (1-15) years, and the mean duration of follow-up was 19.80±4.83 (12-29) months. All patients underwent surgery within the first 24 hours and closed reduction was first attempted. Posterior open reduction was performed in patients with failed attempts of closed reduction. The functional and cosmetic outcomes of the patients were evaluated according to the Flynn criteria. The Baumann's angle was measured on the X-rays obtained in the last control visit.

Results: The comparison of functional outcomes between the two groups revealed that satisfactory outcomes were obtained in 97.3% of patients in the Type III fracture group and 87.5% of patients in the Type IV fracture group; however, the difference was not statistically significant (p=0.509). The comparison of cosmetic outcomes showed that satisfactory outcomes have been obtained in 100% and 97.5% of the patients, and no significant difference was found between the two groups (p=0.495). There was no statistically significant difference between the two groups in terms of the need for open surgery, nerve injury, and Baumann's angle (p=0.776, p=0.108, p=0.069, respectively).

Conclusion: Modified Gartland Type IV pediatric supracondylar humerus fractures can be treated successfully just like Type III fractures with anatomical reduction, stable fixation and early initiation of joint movements.

Keywords: Supracondylar fractures of the humerus, pediatric fractures

ÖZ

Amaç: Bu çalışmada; modifiye Gartland tip IV suprakondiler humerus kırığı cerrahi tedavisinin klinik ve radyolojik olarak tip III kırıklardan farklı olup olmadığını araştırdık.

Yöntemler: 2012-2015 yılları arasında kliniğimizde çocuk suprakondiler humerus kırığı tanısıyla cerrahi tedavi uygulanan 197 hastanın dosyaları retrospektif olarak incelenip, nörovasküler yaralanma olup olmadığı bakılmaksızın 76 hasta (49 erkek, 27 kadın) randomize olarak çalışmaya dahil edildi. Modifiye Gartland Tip III (n=36) ve tip IV (n=40) olarak iki gruba ayrıldı. Yaş ortalaması 5.88±3.29 (1-15) yıl olan hastalar, 19.80±4.83 (12-29) ay süreyle takip edildi. Hastaların tamamı ilk 24 saat içinde ameliyata alındı ve kapalı redüksiyon öncelikli olarak denendi. Kapalı redükte edilemeyen hastalara posteriordan açık redüksiyon uygulandı. Hastaların fonksiyonel ve kozmetik sonuçları Flynn kriterlerine göre değerlendirildi. Son kontrollerindeki röntgenlerinden Baumann açısı ölçüldü.

Bulgular: İki grubun fonksiyonel sonuçları karşılaştırıldığında, tip III grubunda %97.3, tip IV grubunda ise %87.5 tatminkar sonuç elde edildi, aradaki fark istatistiksel olarak anlamlı bulunmadı (p=0.509). Kozmetik sonuçlar karşılaştırıldığında sırasıyla %100 ve %97.5 tatminkar sonuç elde edildi, iki grup arasında anlamlı fark bulunamadı (p=0.495). İki grup arasındaki açık cerrahiye gereksinim, sinir lezyonu ve Baumann açıları arasında istatistiksel olarak anlamlı fark bulunamadı (p değerleri sırasıyla, p=0.776, p=0.108, p=0.069).

Sonuç: Modifiye Gartland tip IV pediatrik suprakondiler humerus kırıkları, tip III kırıklar gibi anatomik redüksiyon, stabil tespit ve erken eklem hareketlerine başlanarak başarılı bir şekilde tedavi edilebilir.

Anahtar kelimeler: Suprakondiler humerus kırıkları, çocuk kırıkları

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INTRODUCTION

Pediatric supracondylar humerus fractures are classically defined as fractures proximal to the condyles of distal humerus that involve the olecranon fossa [1]. Supracondylar humerus fractures account for 16.6% of all fractures in children, 50% of elbow fractures in children and 85% of pediatric fractures requiring surgical therapy [1, 2]. It is usually more common in the 3-10 years age group and in males [2]. Typically, these fractures occur as a result of falling with the elbow extended while the hand is in open position [1, 3]. The main objective of therapy in such fractures is to obtain a functional joint through anatomical reduction, stable fixation and early initiating joint movements [4]. Pediatric supracondylar humerus fractures were first classified by Gartland et al. in 1959 and then modified in various ways [1]. Leitch et al. defined unstable fractures in flexion and extension as Type IV fractures [5].

The present study investigates whether surgical treatment of modified Gartland Type IV supracondylar humerus fracture is different from Type III fractures, in terms of clinical and radiological outcomes and the need for open surgery.

METHODS

The medical charts of 197 patients who underwent surgical treatment for pediatric supracondylar humerus fracture in our clinic between 2012 and 2015 were retrospectively reviewed, and 76 patients humeral Gartland Type III and unstable Type IV fractures regardless of neurovascular injury (49 males, 27 females) were included in the study as randomize. The patients were divided into two groups, namely as patients with modified Gartland Type III (n=36) and patients with Type IV fractures (n=40). The mean age of the patients was 5.88±3.29 (1-15) years, and the mean duration of follow-up was 19.80±4.83 (12-29) months. Age, side, etiological cause, treatment method, pin configuration, presence of nerve lesion, and fracture type were retrieved from the medical charts; the Baumann's angle was measured on the latest anteroposterior radiographs in the last control visit; and functional and cosmetic outcomes were recorded from the examination data in the patient files.

All children who were found to have supracondylar humerus fractures after admission to the emergency room underwent long arm splint applications with elbow flexed up to 110-120 degrees after traction, and then hospitalized in our clinic (Figure 1a, 1b). The limb was kept in an elevated position while continuing cold application, and patients underwent surgery at the earliest opportunity in a fasted state, after completion of preoperative preparation. All patients underwent surgery within the first 24 hours and, initially, closed reduction was attempted. Posterior open reduction was performed in patients with failed attempts of closed reduction. After the posterior exposure, the fracture line was reached at the medial and lateral sides of the triceps muscle. Fifty-eight patients underwent percutaneous pinning after closed reduction and eighteen patients underwent percutaneous pinning after open reduction (Figure 2a, 2b). The patient was evaluated as an unstable fracture in the operating room under lateral fluoroscopy with the elbow flexed, the anterior of the capitellum glenohumeral line and the posterior with the elbow extended. Patients with instability in all sides during surgery were classified as having Type IV fracture and this was noted on the patient chart. After the operation, all fractures underwent immobilization with a long arm splint for three weeks after which the splint was removed and joint movements were initiated. The K-wires were removed at the end of six weeks after surgery and joint movements were continued (Figure 3a, 3b).

The patients were classified according to the Modified Gartland classification system described by Leitch et al [6]. Cosmetic and functional evaluation criteria defined by Flynn et al. were used to evaluate the functional and cosmetic outcomes in the groups [7].

Patients with missing data in the medical charts, Type II fractures (n=18), metabolic bone sicks, accompanying another multiple fracture, patients (n=103) who were not noted as Type III or Type IV postoperatively, and those who did not regularly attend control visits within a 1-year period, were excluded from the study. The study was approved by the ethics committee of Kahramanmaras Sutcu Imam University Clinical Research. (Session:2018\15, Date:29.08.2018, Decision:23)

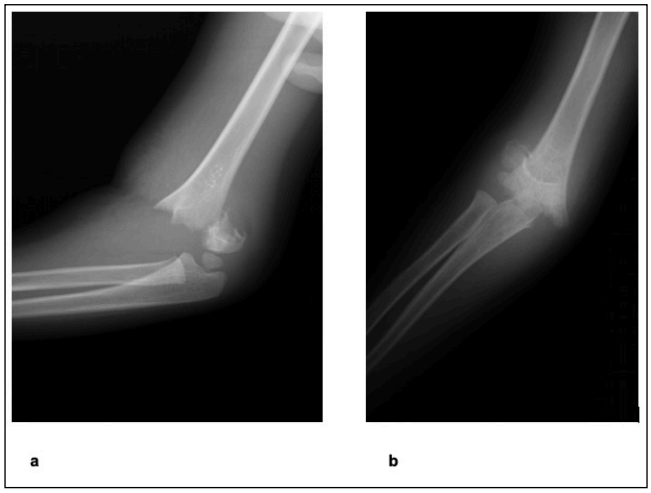

Figure 1a: Preoperative A-P radiography of pediatric supracondylar humerus fracture, b: Preoperative lateral radiography of pediatric supracondylar humerus fracture.

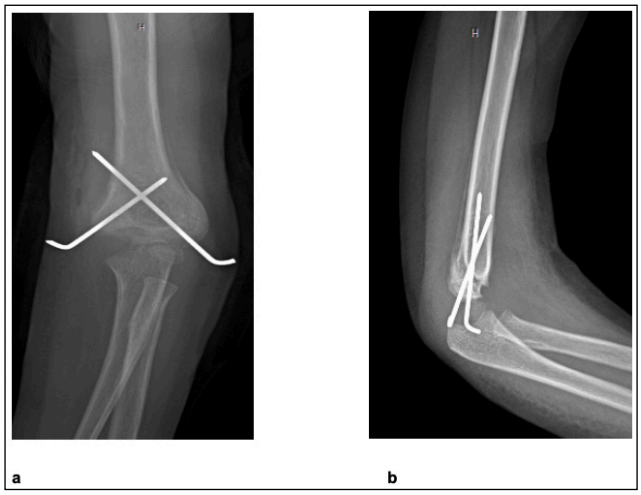

Figure 2a: Early postoperative A-P radiography of pediatric supracondylar humerus fracture, b: Early postoperative lateral radiography of pediatric supracondylar humerus fracture.

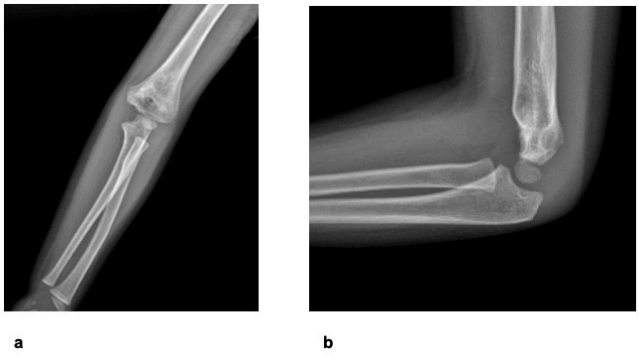

Figure 3a: A-P radiography of pediatric supracondylar humerus fracture three years later, b: Lateral radiography of pediatric supracondylar humerus fracture three years later

Statistical analysis

The data obtained in the study was analyzed using the SPSS (Statistical Package for Social Sciences) for Windows 25.0. The data collected from the patients was interpreted using descriptive statistics (frequency, percentage, mean and standard deviation). A Q-Q plot was used to evaluate fitness to normal distribution. Accordingly, age and Baumann's angle were found to have normal distribution.

A Chi-square test, independent samples T-test and F-test were used to evaluate whether the groups showed similar distribution or if there was a difference between the groups. The error rate was determined in all tests and a P-value of less than 0.05 was considered statistically significant.

RESULTS

Nerve lesion was detected in 11.8% (n=9) of patients, while the mean Baumann's angle was 72.96±7.63 degrees. In terms of functional outcomes, excellent outcomes were achieved in 59 patients, good outcomes were achieved in 11 and satisfactory outcomes were achieved in 70 patients (92.1%). The cosmetic outcome was excellent in 73 patients (96.1%). The demographic data of the patients participating in the study are shown in Table 1.

When the two groups are compared in terms of functional outcomes, the rate of satisfactory outcomes was 97.3% in the Type III fracture group and 87.5% in the Type IV fracture group, and the difference was of no statistical significance (p=0.509). A comparison of cosmetic outcomes showed that satisfactory outcomes were achieved in 100% and 97.5% of the patients, showing no significant difference between the two groups (p=0.495). There was no statistically significant difference between the two groups in terms of the need for open surgery, nerve lesion and Baumann's angle (p=0.776, p=0.108, p=0.069, respectively). The data for the comparison of the groups is shown in Table 2.

An improvement was noted in all patients within 6 weeks. Pin-track infection occurred only in three patients who recovered with oral antibiotherapy, and one patient underwent repeat closed reduction

with percutaneous pinning due to re-fracture after three months.

Table 1. Demographic characteristics of the patients participating in the study (n=76)

Specifications		Number	Percent
Age (year)		5.88±3.29 (1-15)	
Gender	Male	49	64.5
	Female	27	35.5
Side	Right	44	57.9
	Left	32	42.1
Etiology	Falls	69	90.8
	MVI	7	9.2
Fracture Type	Type III	36	47.4
	Type IV	40	52.6
Treatment	CRPP	58	76.3
	ORPP	18	23.7
Nerve lesions	Absent	67	88.2
	Median	1	1.3
	Radial	3	3.9
	Ulnar	5	6.6
Pin configuration	M1/L1	23	30.3
	M1/L2	42	55.3
	L2 or L3	11	14.5
Functional outcome	Excellent	59	77.6
	Good	11	14.5
	Moderate	2	2.6
	Poor	4	5.3
Cosmetic outcome	Excellent	73	96.1
	Good	2	2.6
	Poor	1	1.3
Baumann's Angle (degree)		72.96±7.63 (52-85)	
Following time (month)		19.80±4.83 (12-29)	

Abbreviations: MVI; Motor Vehicle Injury, CRPP; Closed Reduction Percutaneous Pinning, ORPP; Open Reduction Percutaneous Pinning, M1/ L1; Medial one pinning / Lateral one pinning, M1/L2; Medial one pinning / Lateral two pinning, L2 or L3; Lateral two pinning or Lateral three pinning.

DISCUSSION

In 1959, Gartland proposed a simple classification system based on the type of injury to emphasize the underlying principles of treatment in patients with supracondylar humerus fracture, and this system was later embraced as a practical and effective system [1].

In 2006, Leitch et al. proposed an additional Type IV injury that can be defined during, which they believed pose challenges in the treatment due to lack of a durable periosteal connection and presence of instability in multiple sides. They suggested that, despite their rare occurrence, these fractures are less stable than Type III fractures due to displacement of the fracture during flexion and extension [5].

Table 2. Data for the comparison of groups

Characteristics		Type III (n=36)	Type IV (n=40)	
Age (year)		4.69±2.93	6.95±3.26	t= -3.162 p=0.002
Side	Right	18 (50.0)	26 (65.0)	X2=1.746 p=0.186
	Left	18 (50.0)	14 (35.0)	
Treatment	CRPP	28 (77.8)	30 (75.0)	X2=0.081 p=0.776
	ORPP	8 (22.2)	10 (25.0)	
Nerve Lesions	Absent	34 (94.4)	33 (82.5)	X2=2.589 p=0.108
	Present	2 (5.6)	7 (17.5)	
Pin	M1/L1	11	12	X2=2.374 p=0.112
	M1/L2	21	21	
	L2 or L3	4	7	
Functional Outcome	Excellent	29 (80.6)	30 (75.0)	X2=2.905 p=0.509
	Good	6 (16.7)	5 (12.5)	
	Moderate	0 (0.0)	2 (5.0)	
	Poor	1 (2.8)	3 (7.5)	
Cosmetic Outcome	Excellent	36 (100.0)	37 (92.5)	X2=2.374 p=0.495
	Good	0 (0.0)	2 (5.0)	
	Poor	0 (0.0)	1 (2.5)	
Baumann's Angle (degree)		74.64±6.68	71.45±8.19	t=1.848 p=0.069
Duration of Follow-up (month)		21.97±4.80	17.38±3.59	t:-2.386 p:0.892

Abbreviations: CRPP; Closed Reduction Percutaneous Pinning, ORPP; Open Reduction Percutaneous Pinning, M1/ L1; Medial one pinning / Lateral one pinning, M1/L2; Medial one pinning / Lateral two pinning, L2 or L3; Lateral two pinning or Lateral three pinning.

The energy of injury is higher in Type IV fractures than in Type III fractures. The reduction of such fractures is difficult and they often require open surgery due to the presence of more extensive soft tissue injury. The complication rate after treatment is higher [8]. In our study, the rate of complications was numerically higher in the Type IV fracture group than in the Type III fracture group, but the difference between the groups was not statistically significant. Recent studies recommend conservative therapy in non-displaced or minimally displaced fractures (Type I, II). There is a tendency towards performing surgery in all displaced fractures (Types II, III, IV). There was no statistically significant difference between the

two groups in terms of the need for open surgery, but it was higher in the Type IV fracture group than in the Type III fracture group.

When Leitch et al. first identified Type IV fractures, 297/9 Type IV fractures were detected. However, it was stated that open fractures were not included in the study [5]. Stuart et al. compared 159 Type III and 39 Type IV fractures [9]. The reason why Type IV fractures in our study are more than Type III fractures; We think that we included open fractures in the study and accepted all high-energy supracondylar humerus fractures with vascular and nerve injuries from other medical centers.

Epidemiological studies revealed that the rate of such fractures increases in parallel to the activity level in the playgrounds, and the rate is higher in summer season, in the afternoon, at the weekends, in boys, and the majority occurs as a result of falls [10]. Similarly, in our study, these fractures were more common in boys who are physically more active and the fracture occurred after a fall in most cases.

Type IV supracondylar humerus fractures were seen in older age group than Type III fractures. We think that this may be due to the skeletal maturation resulting in decreased bone flexibility.

Nerve injuries are the most important complication of pediatric supracondylar humerus fractures, with a reported prevalence rate of 10-23%. The most commonly injured nerve is the anterior interosseous nerve, and the rate of neurological damage increases with increasing energy of trauma [8,11,12]. Consistent with the literature, neurological damage was also observed in the present study. Neurological damage was more frequent in the Type IV fracture group than in the Type III fracture group, but the difference between the groups was not statistically significant.

Although various open (open, medial, or lateral mini-open) and closed surgery and pinning methods have been described for surgical treatment of pediatric supracondylar humerus fractures, most studies have not shown superiority of one method to another [3,13-15].

The aim of surgical therapy in displaced pediatric supracondylar humerus fractures is to achieve functional recovery by performing anatomical reduction, stable fixation and initiating early joint movements. The studies have reported satisfactory outcomes (excellent-good) with closed reduction and percutaneous pinning in 88%, with medial mini-open technique in 94% of the patients, with anterior mini-open technique in 93% of the patients, with posterior open technique in 97% of patients, and with closed reduction followed by lateral or medial-lateral cross pinning in 99% of the patients. The results of the present study were found to be compatible with the literature, for both groups. [16-19].

In previous studies, it was stated that reduction of Type IV fractures is more difficult, more open surgery is needed and it is associated with worse clinical results [5, 9, 20]. Although Type IV fractures involve a higher energy trauma than Type III fractures, there was no statistically significant difference in functional and cosmetic outcomes in our study. The authors consider that the difference between the two groups would disappear with increasing team experience, good reduction, stable fixation and early initiation of range of joint motion exercises.

Limitations

Apart from retrospective study design, the present study is also limited by the small number of patients and the fact that operations were performed by two different surgeons.

CONCLUSION

Modified Gartland Type IV pediatric supracondylar humerus fractures can be treated successfully, just like Type III fractures, with anatomical reduction, stable fixation, and early initiation of joint movements. However, the authors believe that this observation must be supported by large case series and randomized trials.

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Retrospective comparison of the efficiency of sperm preparation methods in intrauterine insemination in unexplained infertility

Açıklanamayan İnfertilite Olgularında Uygulanan İntrauterin İnseminasyonlarda Sperm Hazırlama Yöntemlerinin Etkinliklerinin Geriye Dönük Karşılaştırılması

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ABSTRACT

Aim: To compare the effects on pregnancy rates of the sperm preparation methods used in intrauterine insemination (IUI) treatment in couples diagnosed with unexplained infertility.

Method: The study included 112 couples who presented at the Assisted Reproductive Techniques Clinic with no gynaecological problem observed in the female and semen analysis in the male showing features suitable for insemination, who were then diagnosed with unexplained infertility. The patients were evaluated in three groups according to the sperm preparation methods as Group 1 (Swim-Up), Group II (Gradient) and Group III (Microchip). The results were analyzed statistically and discussed in light of the relevant literature.

Results: No statistically significant difference was determined between the groups in respect to the age of the couples, duration of infertility, female basal FSH values, number of dominant follicles formed with ovulation induction, endometrium thickness during IUI, total number of motile sperm before sperm preparation, ratio of sperm with normal morphology (Kruger), motility rate after sperm preparation, and number of inseminated sperm (p>0.05 for all). The mean number of IUI attempts was 3.68 in the Microchip group, 1.86 in the Swim-Up group and 1.82 in the Gradient group. A statistically significantly higher number of IUI attempts was made in the Microchip group than in the other groups (p<0.01). In the comparison of the pregnancy rates, the highest rate of 22.73% was determined in the Microchip group, followed by 17.39% in the Gradient group and 15.91% in the Swim-Up group, with no statistically significant difference determined between the groups (p=0.064).

Conclusion: Although there was no apparent difference in success between the two methods most frequently used in sperm preparation in IUI cycles (Swim-Up, Gradient), the method of sperm selection with Microchip, which is being increasingly used, seems to be a promising alternative. There is a need for further, prospective, randomized studies with a greater number of cases and which include the pregnancy outcomes.

Key Words: Infertility, IUI, microchip

ÖZ

Amaç: Açıklanamayan infertilite tanısı almış çiftlerde, intrauterin inseminasyon (İUİ) tedavisi için kullanılan sperm hazırlama yöntemlerinin gebelik oranları üzerine etkilerinin karşılaştırılması.

Yöntemler: Çocuk istemi nedeniyle tüp bebek merkezi'ne başvurmuş, kadında herhangi bir jinekolojik problem gözlenmemiş, erkekte semen analizi aşılama için uygun özelliklerde olan ve açıklanamayan infertilite tanısı alan 112 çift çalışmaya dahil edilmiştir. Hastalar sperm hazırlama yöntemlerine göre Grup I (Swim-Up), Grup II (Gradient), Grup III (Mikroçip) olmak üzere üç grupta değerlendirilmiştir. Sonuçlar istatistiksel olarak analiz edilip literatür eşliğinde tartışılmıştır.

Bulgular: Çalışmaya dahil edilen çiftlerin yaşları, infertilite süreleri, kadınların bazal FSH değerleri, ovulasyon indüksiyonu ile oluşan dominant folikül sayısı, İUİ esnasındaki endometrium kalınlığı, sperm hazırlama öncesi total motil sperm sayısı, normal morfolojili (Kruger) sperm oranı, sperm hazırlama sonrası motilite oranı ve insemine edilen sperm sayıları arasında istatistiksel bir fark izlenmemiştir (Tüm p değerleri>0,05). Hastaların İUİ deneme sayısı Mikroçip grubunda 3,68 bulunmuş iken Swim-Up grubunda 1,86 ve Gradiyent grubunda 1,82 olarak tespit edildi. Mikroçip grubundaki daha fazla İUİ deneme sayısı diğer gruplara göre istatistiksel olarak yüksek bulundu (p<0,01). Gebelik oranları karşılaştırıldığında ise en yüksek oran %22,73 ile Mikroçip grubunda tespit edilirken (Swim-Up grubunda %15,91, Gradient Grubunda %17,39) arada istatistiksel olarak anlamlı fark görülmemiştir (p= 0,064).

Sonuç: IUI sikluslarında sperm hazırlamada en sık kullanılan iki method (Swim-Up, Gradient) arasında bariz bir başarı farklılığı olmamakla bereber, günümüzde kullanımı gittikçe artış gösteren Mikroçip ile sperm seçme yöntemi umut verici bir alternatif olarak görülmektedir. Bu konuda daha fazla vaka sayısı ile birlikte, gebelik sonuçlarının da dahil edildiği prospektif randomize çalışmalara ihtiyaç vardır.

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INTRODUCTION

Intrauterine insemination (IUI) is a method used in the treatment of couples with long-term infertility. For couples with unexplained infertility who are to undergo in vitro fertilization treatment, the female follicles are first stimulated with different protocols before the male semen sample treated with various washing methods is administered to the female [1].

There are several methods that have been used for many years for the preparation of the sperm sample, of which the most commonly used are the Gradient and the Swim-Up methods. Although several studies have compared the effect of washing methods on pregnancy success, there is insufficient evidence of which method is more successful in increasing pregnancy [2-5]. Microfluid systems are technology products formed from microchannels a few hundred micrometers in length which are used to differentiate small amounts of fluid and the particles within the fluid. These systems are a new method used in recent years in both IVF and IUI and have come into use with claims of the selection of sperm occurring with low DNA damage. The best known of these, which is used in our clinic, is the microchip method [6] which has come to the fore as an alternative sperm selection method usually applied to patients who have undergone IUI several times, but have not become pregnant. Although there are studies in the literature which have compared the success of this method with standard sperm selection methods in IVF cycles [7], there is limited data available in the literature related to IUI successes.

The aim of this study was to retrospectively show the effects on laboratory test results and pregnancy success in cases with unexplained fertility of sperm samples prepared with Gradient, Swim-Up and Microchip methods in couples diagnosed with unexplained infertility.

METHODS

Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaraş Sütçü Imam University (decision no: 02, session: 2019/15). The study included 112 patients who had presented at the Assisted Reproductive Techniques Center of Kahramanmaraş Sütcu Imam University between January 2016 and August 2018 because of their wish to conceive. The patients included had infertility ongoing for at least 1 year and were found to be suitable for IUI treatment with at least one tube open on hysterosalpingography (HSG), progressively motile sperm count of at least 10 million and/or a diagnosis of unexplained infertility. These 112 patients were separated into 3 groups according to the sperm preparation method:

Group I (Swim-Up) (n:44): The semen sample taken on the day of IUI was applied with the Swim-Up washing procedure to obtain high-quality sperm to be applied in IUI.

Group II (Gradient) (n:46): The semen sample was applied with the Gradient technique then IUI was applied after washing.

Group III (Microchip) (n:22): Sperm selection was made from the sperm sample using the Microchip method, then IUI was applied.

In the investigation of infertility etiology, transvaginal ultrasonography was performed on the 2nd or 3rd day of the cycle, and measurements were taken of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2). The couples included in the study had no chronic disease and were not using any drugs other than those in the IUI treatment.

The females in each couple were evaluated in respect of age, duration of infertility, gravida, abortus and parity, and the males were evaluated in respect of age and semen parameters. The demographic data and laboratory test results were recorded.

The females of the couples included in the study took Letrozole 2.5 mg (Femara, Novartis, Switzerland) twice a day for 5 days, starting on the 3rd or 5th day of the menstrual cycle, and were applied with ultrasound on the 3rd day after finishing the drug course. In patients where sufficient follicular development was not observed, a daily recombinant FSH (Gonal F, Merck Sereno, Modugno, Italy) injection was started. In the follicle follow-up measurements applied with ultrasound, on the day one of the follicles was seen to be >17mm, 6500 units recombinant human chorionic

gonadotropin (Ovitrelle, Merck Sereno, Modugno, Italy) was administered followed by the IUI procedure 36-48 hours later.

When preparing the semen samples for IUI, the sperm concentration, sperm count per ml, and total progressively motile sperm count were evaluated under contrast light microscope (Olympus CX41) before and after washing, and all the data were recorded. Positive beta HCG results at 14 days after the IUI procedure, and the outcomes of continued clinical pregnancy were recorded from a scan of the files.

Statistical analysis: Data obtained in the study were analyzed statistically using IBM SPSS for Windows, version 22.0 software (IBM statistics for Windows version 22, IBM Corporation, Armonk, NY, USA). Data were stated as mean± standard deviation (SD) values. Variance analysis (Repeated measures ANOVA with Bonferroni correction) was applied to repeated measurements. In the comparison of paired groups, the Tukey HSD was used. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

No statistically significant difference was determined between the cases in respect of female age, male age, duration of infertility, basal FSH values, dominant follicle count formed with ovulation induction, endometrium thickness during IUI, total motile sperm count and normal morphology (Kruger) before preparation, and number of sperm inseminated after preparation ($p>0.05$ for all) (Table 1). The number of IUI attempts was determined as 3.68 in the Microchip group, 1.86 in the Swim-Up group and 1.82 in the Gradient group (Table 1). The elevation in the microchip group was statistically significantly higher than the other groups ($p<0.01$). When the pregnancy rates were compared, the highest rate was determined in the Microchip group at 22.73% and the difference between the groups was not statistically significant, with 15.91% in the Swim-Up group and 17.39% in the Gradient group ($p=0.064$) (Table 2, Figure 1).

Table 1. Demographic characteristics of the cases.

	Swim-Up Group (n: 44)	Gradient Group (n: 46)	Microchip Group (n: 22)	P
Female age (years)	28.43 (min 21-max 35)	27.93 (min 20-max 36)	28.31 (min 21-max 35)	0.789
Male age (years)	29.20 (min 23- max 38)	29.82 8 (min 24 – max 39)	30.19 (min 22- max 38)	0.859
Duration of infertility (years)	2.15 ±0.86	2.19±0.85	4.4±1.1	0.081
Number of IUI attempts	1.86±0.71	1.82±0.70	3.68±0.89	0.002

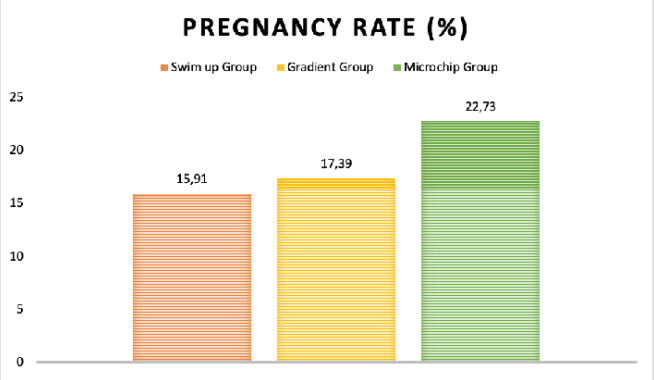

Figure 1. Pregnancy rates of the cases.

Table 2. Data of the cases related to follicular development, clinical course and pregnancy outcomes.

	Swim-Up Group (n: 44)	Gradient Group (n: 46)	Microchip Group (n: 22)	P
Dominant follicle count formed with induction	1.52±0.52	1.50±0.50	1.50±0.51	0.954
Endometrium thickness during IUI	10.68±1.21	10.56±1.12	10.90±1.19	0.966
Total motile sperm count before preparation	54x106± 36x106	57x106± 28x106	58x106± 25x106	0.876
Normal Morphology (Kruger) (%)	3.29±1.24	3.0±1.23	3.23±1.17	0.782
Motility rate after preparation (%)	98±1.1	93±3.23	88±4.91	0.875
Number of sperm inseminated after preparation	23x106± 13.16 x106	22 x106± 11.89 x106	19.18 x106± 7.22 x106	0.819
Pregnancy rate (%)	15.91	17.39	22.73	0.064

DISCUSSION

A total of 112 infertile patients treated with IUI in our center were evaluated in respect to pregnancy. The semen samples of patients with no chronic disease and no female or male factor during IUI treatment, were examined according to the manner of preparation. The most commonly used methods in IUI preparation are the Gradient and Swim-Up methods. The Microchip is a new sperm washing method used in IUI and IVF treatment [6].

When all the cases in the study were evaluated demographically, no significant difference was found. A difference was determined in respect of the IUI attempts (p=0.002). Compared to the Swim-Up and Gradient groups, the number of IUI attempts in the Microchip group was statistically significantly high (p=0.002). As the cost of the Microchip method is high and the State does not reimburse it, this method is not usually applied to patients planned to undergo IUI for the first time but is preferred for patients who have had several failed IUI attempts. However, even in the cases with relatively poor response in the cycles prepared by other washing methods, the pregnancy rate of 22.73% of the Microchip method is promising. When used in the first cycle, it is possible to reach higher pregnancy rates.

Previous studies that have compared sperm selection methods in IUI cases have focused on the Gradient and Swim-Up methods. Dodson et al. [8] examined the effect of these methods and reported that there was no significant difference in respect of sperm concentration and motility and pregnancy rates, and it was concluded that there was no superiority of one method over the other. Those results were similar to the findings of the current study. In contrast Depypere et al. [9] compared IUI methods in 117 cases and reported that the Gradient method was better than the Swim-Up method, in respect to both sperm parameters obtained after washing and pregnancy rates. In a prospective, randomized, controlled study by Posada et al. in 2005, the semen parameters and pregnancy outcomes of 82 patients were compared according to IUI preparation methods. Both before and after washing, the sperm parameters and the associated pregnancy rates were found to be significantly higher in the Swim-Up group than in the Gradient group [10]. In a review by Boomsa et al. in the Cochrane database which compared all methods except Microchip in 2011, none of the methods were found to have any significant effect on pregnancy and abortus [2]. One of the important studies related to sperm selection methods in assistive reproduction techniques was published by Sakkas et al. [11] in 2000 in Human Reproduction. In that study, the Swim-Up method was compared with the Gradient method in two different media (PureSperm and Percoll). The best method of sperm selection with the least nuclear DNA damage was investigated and it was concluded that both Gradient methods were more successful than the Swim-Up technique in the selection of sperm with less DNA damage [11].

In a well-designed study published in 2009, the presence of apoptotic and necrotic sperm was investigated with flow cytometry analysis after sperm preparation with the Swim-Up, and Gradient methods. The results of the study showed that both methods were successful in the selection of normal sperm. However, it was reported that healthier sperm could be selected quantitatively in the Gradient method and qualitatively in the Swim-Up method, and the appropriate method could be selected according to the treatment to be applied (IUI or IVF) [12].

As centrifugation is applied in Gradient methods, impairments in the sperm DNA structure are seen more often as a result of an increase in reactive oxygen products [13]. Consequently, microfluid channel systems (Microchip) were developed for the selection of sperm with less DNA damage. This system is a chip with microchannels that mimic the microenvironment of the cervix and vagina. Sperm obtained with this method can be used in both IVF and IUI.

Although there are only a few studies in the literature that have compared the success of other sperm preparation methods with microfluid systems, studies have shown that microfluid systems could be useful in the selection of better sperm. In a 2011 study by Zhang et al., it was suggested that when the negative aspects of other traditional sperm selection methods were taken into consideration, the microfluid system was a better method because of ease-of-use

and reliability [14]. It was also determined that the sperm obtained with this technique had significantly fewer radical oxygen products and less DNA fragmentation compared to the Swim-Up method [13,14]. There was found to be a single retrospective cohort study in literature, which was recently published with a similar design to that of the current study, which compared microfluid systems with other sperm preparation methods in IUI cycles. In that study, 133 IUI cases using sperm prepared with the microfluid system were compared with 132 cases with sperm prepared with the gradient method. The pregnancy rates were determined as 18.04% in the microfluid group and 15.15% in the density gradient group, and the difference was not found to be statistically significant. When the ongoing pregnancy rates were compared, the rate was determined as 15.03% in the microfluid group and 9.09% in the gradient group. This difference was determined to be statistically significant. In conclusion the authors emphasized that the use of the microfluid method could significantly increase the ongoing pregnancy rate [15]. The results of our study can be considered to be of value as although there are other studies in literature with as high a number of cases, this is the first study to have compared the microfluid system with the two most frequently used sperm preparation methods.

Limitations of this study could be considered to be the retrospective design and the low number of Microchip cases.

Conclusion: Although there was no apparent difference between the traditional methods of Swim-Up and Gradient used in sperm preparation in IUI cycles, the sperm selection method with Microchip is being used increasingly and seems to be a promising alternative. There is a need for more extensive, prospective, randomized studies, which would include pregnancy outcomes.

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RESEARCH ARTICLE

ARAŞTIRMA

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Can the serum Creatine Kinase (CK) level be a malnutrition parameter in patients with end-stage kidney failure?

Son Dönem Böbrek Yetmezliği Hastalarında Serum Kreatin Kinaz (Ck) Düzeyi Malnutrisyon Parametresi Olabilir Mi?

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ABSTRACT

Aim: The aim of this study was to investigate the relationship between serum CK levels and malnutrition parameters in patients undergoing hemodialysis (HD) and peritoneal dialysis (PD) for end stage renal disease (ESRD).
Methods: In this prospective study, 60 patients receiving HD and 30 patients receiving PD for ESRD were evaluated. The relationship between serum CK levels and Mini Nutritional Assessment (MNA) Test scores, albumin, C-Reactive Protein (CRP), arterial blood gas parameters, KT / V ratio, total body water, muscle mass, body mass index (BMI) and lean body mass (determined by Bioelectrical Impedance Analysis (BIA) were examined.
Results: No correlation was found between CK levels and age, dialysis duration and Ca values in HD and PD patients (p> 0.05). A positive correlation was found between CK levels and MNA scores and triceps skinfold thickness, lean body mass, body muscle mass and BMI values of PD and HD patients, and a significant negative correlation between total body water values (p <0.001).
Conclusions: It was determined that serum CK level was compatible with other parameters used in the determination and follow-up of nutritional disorder and sarcopenia in ESRD patients.

Key Words: End-Stage Renal Disease, Bioelectrical Impedance, Creatine Kinase, Sarcopenia, Malnutrition

ÖZ

Amaç: Bu çalışmanın amacı; Son Dönem Böbrek Yetmezliği (SDBY) nedeniyle hemodiyaliz (HD) ve periton diyalizi (PD) tedavisi alan hastalarda serum CK düzeyleri ile malnutrisyon parametreleri arasındaki ilişkiyi incelemektir.
Gereç ve Yöntem: Prospektif olarak yürütülen bu çalışmada, Türkiye' nin Ege bölgesinde hizmet veren bir hastanede SDBY nedeniyle HD tedavisi alan 60 hasta ve PD tedavisi alan 30 hasta değerlendirildi. Hastaların serum CK düzeyi ile Mini Nutrisyonel Değerlendirme Testi (MND)' nden aldıkları puanlar, albumin ve C-Reaktif Protein (CRP) gibi biokimyasal parametreler, arteriyel kan gazı değerleri, KT/V oranı, Biyoelektriksel İmpedans Analiz (BİA) yöntemiyle bakılan total vücut suyu, kas kütlesi, vücut kitle indeksi (VKİ) yağsız vücut kütlesi ve VYO (vücut yağ oranı) gibi değişkenler arasındaki ilişki incelendi.
Bulgular: HD ve PD hastalarında CK düzeyleri ile yaş, diyaliz süresi ve Ca değerleri arasında ilişki saptanmadı (p>0,05). HD ve PD hastalarının CK düzeyleri ve MND puanları ile BİA parametrelerinden yağsız vücut kütlesi, vücut kas kütlesi ve VKİ değerleri arasında pozitif yönde, TVS değerleri arasında negatif ilişki saptandı (p<0,001).
Sonuç: SDBY hastalarında serum CK düzeyinin, beslenme bozukluğu ve sarkopeninin belirlenmesi ve takibinde kullanılan diğer parametreler ile uyumlu olduğu görülmektedir.

Anahtar Kelimeler: Son Dönem Böbrek Hastalığı, Biyoelektriksel Empedans, Kreatin Kinaz, Sarkopeni, Malnütrisyon

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INTRODUCTION

Chronic renal failure (CRF) is an increasingly important public health problem in our country and in the world, and is defined as a pathological condition characterized by chronic, progressive and irreversible nephron loss due to various diseases (1). End-stage renal failure (ESRD) develops as a result of persistent kidney damage in patients followed up with the diagnosis of CRF. In this period, renal replacement treatment (RRT) is needed and the conservative approach consists of hemodialysis (HD), peritoneal dialysis (PD) and kidney transplantation (2). After starting dialysis treatment in patients with CRF, susceptibility to malnutrition occurs through factors such as the metabolic effects caused by dialysis in the body, chronic acidemia, chronic inflammation and oxidative stress (3).

Malnutrition means both poor nutrition and over nutrition and expresses the intake deficiency that will not meet the need and thereupon the developing pathological condition (4); it is an important problem leading to mortality and morbidity in CRF patients. Many biochemical and anthropometric measurements are used for the diagnosis of malnutrition (5). Bio-impedance Analysis (BIA) is the body composition analysis method which is used in the follow-up of malnutrition and the main principle of which is to measure the resistance of the tissues against the passage of the electrical current through the body tissues. Through the BIA method, various body components can be examined such as the body mass index (BMI), the lean body mass, the basal metabolic rate, the body fat ratio (BFR), and the total body water (TBW) (6). The Mini Nutritional Assessment (MNA) test is a fast, reliable, cheap and practical method used to determine the nutritional status of the elderly population and outpatients, which includes questions about the patient's lifestyle, mobilization and diet, as well as anthropometric measurements. It consists of four sections that provide the opportunity to determine the nutritional status in a subjective and general manner. These sections include questions about the patient's lifestyle, mobility, nutritional content and order, and anthropometric measurements (7).

Serum creatine kinase (CK) level is used in clinical practice in the diagnosis and follow-up of muscle-related diseases such as rhabdomyolysis, myocardial infarction, myositis and muscular dystrophy (8). CK enzyme that keeps the cell energy balance and have a key role in energy flow is closely associated with the parameters, reflecting the muscle mass directly, such as BMI and lean body mass, which are the known indicators of muscle mass in an organism (9). The aim of this study was to examine whether or not there is a correlation between the serum CK levels and other parameters (anthropometric measurements, biochemical values, MNA test, BIA) used in the follow-up of malnutrition in the patients receiving HD and PD treatment due to ESRD.

MATERIAL-METHOD

Study Model

This prospective study was conducted in a training and research hospital in the Aegean Region of Turkey, between April 2017 and April 2018, with 60 patients followed-up as a result of a diagnosis of ESRD and included in the routine HD program, and 30 patients in the PD program. We received the written, Informed Volunteer Consent Form (IVCF) of all patients and those who did not complete the IVCF, provided an inadequate answer to their anamnesis questions, were illiterate, had an additional psychiatric disease, were pregnant, were diagnosed with coronary artery disease, rhabdomyolysis and myopathy, had gone through a recent physical trauma, or were using statin drugs for hyperlipidemia, were excluded from the study. Approval to conduct the study was received from the clinical trials ethics committee of the hospital where the study was conducted (Date: 07.03.2017, Decision number: 10).

Data Collection

The laboratory findings specific to malnutrition measured in the last 3 months synchronously with CK were reached through the hospital information system, thanks to the routine follow-ups of the HD and PD patients, in order to assess the laboratory data for the nutritional condition of the patients. In the biochemistry laboratory of the hospital where the research was conducted,

laboratory examination data were obtained using the enzymatic method in the Olympus AO 5800 autoanalyzer. The patients were subjected to a four-part MNA check including 18 questions and were divided into three groups based on their MNA scores. The anthropometric evaluations (height, middle arm and calf circumference) in the first section were made using a tape measure with a sensitivity of 0.01 cm. The measurements were taken with the head upright, the soles of the feet flat on the ground, the knees stretched, the heels adjacent and the body taken upright. BMI values of the patients were calculated. The answers to the questions in the other three sections were filled in as a separate questionnaire for each patient and the scores were collected. Results were evaluated over 30 points and divided into three groups according to MND scores. It was considered that the nutritional status of patients obtaining the scores of > 24.0 in MNA was good, whereas patients obtaining a score between 17.0-23.5 were considered at risk for protein energy malnutrition (PEM); the presence of PEM was considered for patients obtaining a MNA score of 17.0.

BİA measurements were done with the Tanita-Body Composition Analyzer BC-420MA device. Patients were asked to stand on bare feet on the metal surface of the device and to release their arms parallel to the body. The measurement results were output from the device and the process required approximately 1-2 minutes for each subject.

Triceps skin fold thicknesses were measured with Holtain Skinfold Caliper device. With the patient standing upright, bending the left arm 90˚ from the elbow, the middle point between the acromion and olecranon protrusions was found, the arm was released and the layer was held with the left marker and thumb, and the right hands were measured from the place marked with the caliper.

Statistical Analyses

SPSS 25.0 packaged software was used in the analysis of variables. While the compatibility of the data with normal distribution was assessed with the Shapiro-Wilk test, the homogeneity of variances was evaluated using Levene's test. In the comparison of two independent groups based on qualitative data, Independent-Samples T test was used together with Bootstrap results and the Mann-Whitney U test was used using the Monte Carlo simulation technique. The correlations of the variables with each other were assessed using Pearson Correlation and Kendall's tau-b tests. In the comparison of the categorical variables, the Pearson Chi-Square and Fisher-Fisher Exact tests were performed using Exact results and the Fisher-Freeman-Holton test was performed using the Monte Carlo Simulation technique. The quantitative variables were shown as mean±SD (Standard Deviation) and median (Minimum / Maximum) and the categorical variables were shown as n (%) in the tables. The variables were examined at confidence level of 95% and the results with $p<0.05$ were determined to be significant.

RESULTS

The average age of the PD patients included in the study was 46.5 (28-73)/ years and was statistically significantly lower compared to the HD patients (58.0 (26-78) / years) ($p<0.001$). There was no significant difference between the groups in terms of gender and the presence of comorbid diseases ($p>0.05$) (Table 1).

Phosphor median value was 3.8 (1.8 - 5.7) mg/dl in HD patients and 4.8 (3.5 - 5.3) mg/dl in PD patients and it was observed to be statistically significantly lower in HD patients ($z=-4.022$, $p<0.001$). The Ca median value was 9.0 (7.7 - 11.0) mg/dl in HD patients and 10.0 (8.7 - 10.9) mg/dl in PD patients and it was statistically significantly lower in HD patients ($z=-5.300$, $p<0.001$). Mean pH value of venous blood was 7.3±0.1 in HD patients and 7.4±0.0 in PD patients and it was observed to be statistically significantly lower in HD patients ($t=-2.789$, $p=0.004$). Mean value of KT/V ratio was 1.5±0.1 in HD patients and 1.7±0.1 in PD patients and it was statistically and significantly lower in HD patients ($t=-11.993$, $p=0.001$). No statistically significant difference was determined between HD and PD patients in terms of albumin, HCO3, total cholesterol, LDL cholesterol and transferrin saturation percentage medians and CK, creatinine and CRP median values ($p>0.05$)(Table 2).

Median MNA score was determined to be 21.0 (15.0 - 28.0) and in HD patient group and 22.0

(15.0-26.0) in PD patient group and no statistically significant difference was determined between HD and PD patients in terms of MNA scores (z=-1.367; p=0.218). Based on MNA test scores, it was determined that there was malnutrition in 21.7% (n=13) of the HD patients, 60% (n=36) of them had risk in terms of malnutrition and 18.3% (n=11) had a normal nutrition status. It was determined that 13.3% (n=4) of the PD patients had malnutrition, 53.3% (n=16) were at risk of malnutrition, and 33.3% (n=10) had a normal nutrition status. In the intergroup comparison performed based on MNA test scores of HD and PD patients, no statistically significant difference was determined (p=0.218; X 2 =2.701) (Table 2).

Table 1. Sociodemographic characteristics of the patients undergoing hemodialysis and peritoneal dialysis

		Dialysis Type			
		Hemodialysis (n=60)	Peritoneal (n=30)		
		Median (Min.-Max.)	Median (Min.-Max.)	z-X2-t	p
Age		58.0 (26.0 - 78.0)	46.5 (28.0 - 73.0)	-4.507	<0.001a
		n (%)	n (%)		
Gender	Female	30.0 (50.0)	16.0 (53.3)	0.089	0.825 b
	Male	30.0 (50.0)	14.0 (46.7)		
Presence of Comorbid Disease	Yes	8.0 (13.3)	5.0 (16.7)	0.180	0.753 c
	No	52.0 (86.7)	25.0 (83.3)		
Comorbid Disease	Other	16.0 (30.8)	7.0 (28.0)	0.681	0.900 d
	DM	19.0 (36.5)	9.0 (36.0)		
	HT	13.0 (25.0)	8.0 (32.0)		
	PKD	4.0 (7.7)	1.0 (4.0)		
Time / year		Mean±SD	Mean±SD		
		5.4±1.9	4.9±1.2	1.275	0.209 e

a: Mann Whitney U test (Monte Carlo), b: Pearson Chi-Square Test (Exact), c: Fisher Exact Test (Exact), d: Fisher Freeman Halton Test (Monte Carlo), e: Independent Samples T test (Bootstrap), Min: Minimum, Max: Maximum, SD: Standard deviation, DM: Diabetes Mellitus, HT: Hypertension , PKD: Polycystic Kidney Disease

In the comparison of BIA values of HD and PD patients, no statistically significant difference was determined between the two groups in terms of body muscle index, BMI and TBW median values (p>0.05). The BFR median value was 26.3 (16.7 - 30.4) in HD patients and 27.2 (22.5 - 29.8) in PD patients and was statistically significantly lower in HD group (p=0.016; z=-2.594). While the mean value of lean body mass was 35.4 ± 4.1 in HD patients, it was 37.7±2.3 and statistically significantly higher in PD patients (p=0.001; t=-3.466) (Table 2). No statistically significant correlation was determined between CK levels and age, duration of dialysis, and Ca variables in HD and PD patients (p>0.05). While CK levels had a statistically significant positive correlation with albumin, phosphor, HCO3, HGB, total cholesterol, LDL, transferrin saturation, pH of arterial blood gas, KT/V ratio and creatinine values in HD and PD patients, they had a statistically significant negative correlation with CRP values (p<0.05) (Table 3).

There was a positive statistically significant correlation between CK levels and MNA scores, triceps skinfold thickness, lean body mass, body muscle mass and BMI values in HD and PD patients, and a negative statistically significant correlation between CK levels and TBW values (p<0.001) (Table 3).

DISCUSSION

When the correlation of serum CK levels with BIA data in HD and PD patient group was examined in the present study, it was determined that they had a positive statistically significant correlation with the variables such as BMI, BFR, lean body mass and body muscle mass (p<0.001) and a negative statistically significant correlation with TBW (p<0.001) in both patient populations. In the literature, Flahault et al., (2016) assessed retrospectively 1801 chronic kidney patients not undergoing dialysis in their study, where they stated that serum CK level had a significant correlation with BMI and muscle mass and that it may reflect the nutritional situation (8). In the present study, it was revealed that serum CK level was correlated with the parameters in BIA method that has been increasingly used recently, which is compatible with the literature.

MNA test is a method widely used in determination of malnutrition and it is recommended in determination and follow-up of malnutrition by international guidelines. A statistically significant correlation was determined between serum CK levels and MNA scores both in HD and PD patients (p<0.001). In the literature review, it was observed that there was a statistically significant correlation

Table 2. Comparison of the laboratory findings, MNA scores and bioimpedance analyses of patients undergoing hemodialysis and peritoneal dialysis.

		Dialysis Type			
		Hemodialysis(n=60)	Peritoneal (n=30)		
		Median(Min-Max)	Median(Min-Max)	z/t	p
Laboratory Findings	Albumin (g/dl)	3.5 (2.6 - 4.9)	3.8 (2.8 - 4.7)	-1.749	0.068 a
	Phosphor (mg/dl)	3.8 (1.8 - 5.7)	4.8 (3.5 - 5.3)	-4.022	<0.001 a
	HCO3 (mmol/L)	22.0 (17.0 - 28.0)	22.1 (17.9 - 25.8)	-0.433	0.649 a
	HGB (g/dl)	11.3 (8.6 - 12.7)	10.7 (9.8 - 11.9)	-2.241	0.018 a
	Ca (mg/dl)	9.0 (7.7 - 11.0)	10.0 (8.7 - 10.9)	-5.300	<0.001a
	Total Cholesterol (mg/dl)	126.5 (48.0 - 178.0)	124.0 (59.0 - 168.0)	-0.539	0.602 a
	LDL (mg/dl)	95.0 (52.0 - 128.0)	88.5 (64.0 - 130.0)	-1.426	0.153 a
	Transferrin sat (%)	18.9 (8.5 - 25.9)	20.5 (13.2 - 26.9)	-1.190	0.240 a
		Mean±SD	Mean±SD		
	CK (U/L)	75.1±36.5	88.1±31.5	-1.666	0.078 b
	pH	7.3±0.1	7.4±0.0	-2.789	0.004 b
	KT/V	1.5±0.1	1.7±0.1	-11.993	0.001 b
	Creatinine (mg/dl)	5.1±0.7	4.9±0.5	0.732	0.410 b
	CRP (mg/dl)	10.6±2.3	10.3±1.83	0.469	0.636 b
		n (%)	n (%)	x2 / Z	p
MNA Scores	Impaired	13.0 (21.7)	4.0 (13.3)	2.701	0.218 c
	Risky	36.0 (60.0)	16.0 (53.3)		
	Normal	11.0 (18.3)	10.0 (33.3)		
		Median(Min-Max)	Median(Min-Max)		
	MNA	21.0 (15.0- 28.0)	22.0 (15.0 – 26.0)	-1.367	0.166 d
		Mean±SD	Mean±SD	z/t	p
Bioimpedance Analyses	Lean body Mass	35.4±4.1	37.7±2.3	-3.466	0.001 b
		Median(Min-Max)	Median(Min-Max)		
	Body Muscle Mass	33.0 (20.1 - 41.8)	35.2 (27.8 - 41.9)	-1.793	0.076 a
	BMI	25.5 (19.7 - 30.7)	24.7 (21.3 - 28.9)	-1.875	0.056 a
	BFR	26.3 (16.7 - 30.4)	27.2 (22.5 - 29.8)	-2.594	0.016a
		27.8 (25.3 - 44.5)	27.4 (26.0 - 43.9)	-1.610	0.100a

a: Mann Whitney U test (Monte Carlo), b: Independent Samples T test (Bootstrap), c: Fisher Freeman Halton Test (Monte Carlo), d: Mann Whitney U test (Monte Carlo), SD: Standard deviation, Min: Minimum, Max: Maximum, MNA, Mini Nutritional Assessment, BMI: Body Mass Index, BFR: Body Fat Rate, TBW: Total Body Water

between MNA test and the other nutritional parameters, such as albumin and CRP (10,11). Similar to the literature, it was also revealed in the present study that the improvement in the nutritional situation in HD and PD patient groups was compatible with an increased serum CK level, which was considered to be an indicator of muscle mass and nutrition in the group of patients with ESRD.

In the present study, a positive statistically significant correlation was determined between serum CK levels and albumin in HD and PD patient groups ($p<0.001$). Similar to the present study, in their study Flahault et al., (2016) determined the existence of a positive statistically significant correlation between serum CK levels and albumin (8).

In addition to the use of CRP as acute phase reactant in the clinic, it was reported that it may be used in the follow-up of malnutrition in CRF (11). A previous study conducted in HD patient group revealed that CRP value was negatively associated with the reduced loss of muscle mass (12). In the present study, a negative significant correlation was determined between serum CK levels and CRP in HD and PD patient groups ($p<0.001$). This situation may be explained by the loss of muscle mass occurring after the inflammatory process was observed increasing in ESRD patients, resulting potentially from

decreased cytokine clearance, atherosclerosis, cardiac failure or a stubborn infection.

Table 3. The correlation between CK levels with sociodemographic characteristics, laboratory values, MNA scores and bioimpedance analyses of the patients undergoing hemodialysis and peritoneal dialysis

Correlation with CK						
	r	p	r	p	r	p
Age	-0.160	0.077	-0.037	0.846	-0.201	0.058
Duration of Dialysis	-0.036	0.786	0.051	0.790	-0.020	0.785
Albumin	0.737	<0.001	0.938	<0.001	0.758	<0.001
Phosphor	0.626	<0.001	0.708	<0.001	0.592	<0.001
HCO3	0.557	<0.001	0.750	<0.001	0.583	<0.001
HGB	0.625	<0.001	0.791	<0.001	0.511	<0.001
Ca	0.117	0.371	0.189	0.159	0.151	0.039
Total Cholesterol	0.697	<0.001	0.560	<0.001	0.660	<0.001
LDL	0.759	<0.001	0.760	<0.001	0.776	<0.001
Transferrin saturation	0.633	<0.001	0.615	<0.001	0.625	<0.001
pH	0.814	<0.001	0.834	<0.001	0.822	<0.001
KT/V	0.838	<0.001	0.885	<0.001	0.535	<0.001
Creatinine	0.811	<0.001	0.945	<0.001	0.811	<0.001
CRP	-0.837	<0.001	-0.820	<0.001	-0.827	<0.001
MNA	0.867	<0.001	0.767	<0.001	0.831	<0.001
Triceps skinfold thickness	0.755	<0.001	0.829	<0.001	0.716	<0.001
Lean body Mass	0.918	<0.001	0.853	<0.001	0.744	<0.001
Body Muscle Mass	0.710	<0.001	0.509	0.004	0.630	<0.001
BMI	0.786	<0.001	0.931	<0.001	0.611	<0.001
BFR	0.672	<0.001	0.615	<0.001	0.639	<0.001
TBW	-0.781	<0.001	-0.731	<0.001	-0.764	<0.001

Pearson Correlation Test, Kendall's tau-b Test r: Correlation Coefficient, CK: Creatine Kinase, HCO3: Bicarbonate, HGB: Hemoglobin, Ca: Calcium, LDL: Low density cholesterol, pH: potential hydrogen, CRP: C-reactive protein, MNA: Mini Nutritional Assessment, BMI: Body Mass İndex, BFR: Body Fate Ratio, TBW: Total Body Water

In the patients followed-up due to ESRD, serum creatinine levels have a very important place in the determination of the nutritional situation and muscle mass. It has been stated that the level of creatinine produced in skeletal muscle reflects muscle mass and is associated with survival (13). In the previous studies, it was revealed that low serum creatinine level was associated with malnutrition, showed low muscle mass, and was associated with increased mortality (14). In the present study, a positive statistically significant correlation was determined between serum CK levels and creatinine level in both of HD and PD patient groups ($p<0.001$). In a previous study, a positive statistically significant correlation was also determined between serum CK levels and creatinine level in patients with CRF not undergoing dialysis (8).

Limitations of the study

This research was conducted in a single-center study, therefore our results may not yet be applied universally.

CONCLUSION

Consequently, it is thought that measurement of serum CK level is compatible with other parameters used for the determination and follow-up of malnutrition and sarcopenia, in patients with ESRD. Since it is an inexpensive and reliable method that can be easily applied in clinical practice, there is a need for conducting more comprehensive studies with larger patient groups.

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RESEARCH ARTICLE

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Higher beta-2 microglobulin levels may predict the coronary slow flow phenomenon

Yüksek beta-2 mikroglobulin düzeyleri koroner yavaş akım fenomeni için öngördürücü olabilir

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ABSTRACT

Aim: To examine the association between plasma levels of β-2 microglobulin (β-2M), a protein previously associated with atherosclerosis, and the presence of coronary slow flow phenomenon (CSFP).
Material and Methods: 124 subjects who admitted to cardiology outpatient clinic with chest pain and directed to coronary angiography were investigated. Sixty-six of them had healthy coronary arteries and the others coronary slow flow. Venous blood samples were obtained to determine β-2M levels. TIMI frame count (TFC) was used to assess the classification of slow flow.
Results: Patients with coronary slow flow had higher levels of β-2M levels than healthy controls (2042.0 ± 660.2 and 1692.7 ± 403.4 ng / mL respectively) and the difference was statistically significant (p<0.001). β-2M levels were positively correlated with TFC (r=0.262, p= 0.003). Although groups were different in terms of β-2M, LDL and total cholesterol, Receiver operating characteristic (ROC) curve analysis demonstrated stronger predictive value of β-2M compared to LDL or total cholesterol in predicting the presence of CSF in our study population (area under curve [AUC] 0.748, 0.632 and 0.581; p<0.001, p=0.025 and p= 0.061 respectively).
Conclusion: High serum β-2M levels can be used as a biomarker to evaluate the slow flow.

Key words: beta-2 microglobulin, coronary slow flow

ÖZ

Amaç: Bu yazının amacı, daha önce ateroskleroz ile ilişkili olduğu saptanan bir protein olan β-2 mikroglobulin (β-2M) plazma seviyeleri ile koroner yavaş akım varlığı arasındaki ilişkiyi incelemektir.
Gereç ve Yöntemler: Göğüs ağrısı ile kardiyoloji polikliniğine başvuran ve koroner anjiyografiye yönlendirilen 124 olgu incelendi. 66'sında normal koroner arterler, diğerlerinde koroner yavaş akım vardı. β-2M seviyesini belirlemek için venöz kan örneklerinden elde edilen plazma numuneleri toplandı. Yavaş akım sınıflandırmasını değerlendirmek için TIMI kare sayısı (TFC) kullanıldı.
Bulgular: Koroner yavaş akımlı hastalarda beta-2 mikroglobulin düzeyleri sağlıklı kontrollere göre (sırasıyla 2042.0 ± 660.2 ve 1692.7 ± 403.4 ng / mL) daha yüksekti ve fark istatistiksel olarak anlamlıydı (p < 0.001). β-2M düzeyleri TFC ile pozitif korelasyon gösterdi (r= 0.262, p = 0,003). Gruplar β-2M, LDL ve total kolesterol açısından farklılık gösterse de, işlem karakteristik eğrisi (ROC) analizi, çalışma popülasyonumuzda koroner yavaş akım varlığını tahmin etmede LDL ve total kolesterole kıyasla β-2M'nin daha güçlü öngörücü değerini göstermiştir (ROC eğrisinin altında kalan alan [AUC] 0.632, 0.581 ve 0.748; p=0.025, p=0.061 ve p<0.001 sırasıyla).
Sonuç: Yüksek serum beta-2 mikroglobulin düzeyleri yavaş akım varlığını değerlendirmek için bir biyobelirteç olarak kullanılabilir.

Anahtar kelimeler: beta-2 mikroglobulin, koroner yavaş akım

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INTRODUCTION

The coronary slow flow phenomenon (CSFP) is an angiographic finding characterized by delayed distal vessel opacification in the absence of significant epicardial coronary disease. This phenomenon has clinical importance because it may be the cause of angina at rest or during exercise. In patients with CSFP, hospitalization and diagnostic catheterization rate is high due to chest pain, however the prognosis is as good as that of the normal population [1]. Although some underlying etiologies such as abnormally high microvascular resistance and widespread atherosclerosis of coronary arteries have been proposed, the exact pathophysiological mechanism of this phenomenon remains unclear. It is thought to be a form of microvascular circulation defect and a precursor of an occlusive epicardial artery disease [2].

There have been many studies in which the relationship between serum biomarkers and the presence and severity of CSFP was investigated. Considering that one of the underlying important mechanisms is endothelial dysfunction, beta-2 microglobulin (β-2M) levels, which have been found to be high in those with endothelial dysfunction recently and which are considered to be predominant in pathologies such as coronary artery disease and diabetic nephropathy, are unknown in CSFP [3-4]. Ballew et al. found that β-2M would provide better cardiovascular risk prediction than serum creatinine in chronic kidney disease [5]. In another study, Amighi and his colleagues determined that β-2M was independently associated with adverse cardiovascular outcome in asymptomatic carotid atherosclerosis [6].

In this study, we examined the association between coronary slow flow and plasma β-2M levels

MATERIAL AND METHODS

Study population

The cohort study, performed between January 2019 and September 2019, consisted of 58 patients with coronary slow flow and 66 patients with normal coronary arteries displayed with angiography. Normal coronary angiography was described as coronary epicardial vessels without any lesions including plaque and slow flow as epicardial vessels with the TFC levels above the determined limits, and without any other lesions. Chronic or acute renal disease, viral infections, history of any cancer type, multiple myeloma, hemodynamic factors that can decrease coronary flow such as hypotension or bradi-tachyarrhythmias, were exclusion criteria. The study protocol was approved by the Ethics Committee of Çukurova University Medicine School and performed in accordance with the Declaration of Helsinki.

Laboratory analysis

Laboratory analysis included routine complete blood count, kidney and liver function tests, lipid profile, C reactive protein (CRP) and sedimentation rate. 12 hours fasting venous blood samples were obtained and serum lipid levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol and triglycerides (TG) were measured with an automated chemistry analyzer (Abbott Aeroset, Minnesota, USA) using commercial kits (Abbott). LDL was measured with direct method and CRP concentration was measured by the nephelometric method. These routine tests were done before angiography. From patients with slow flow, beta-2 microglobulin levels were studied after angiography. Serum β-2M levels were examined using flow cytometry method.

Calculation of TIMI Frame Count

The time required for a coronary artery to reach a specified point distally from the beginning of filling was calculated as a cine-frame and named the TIMI frame count (TFC), which is used to standardize slow flow. The distal point is the distal bifurcation of the left anterior descending artery (LAD), the distal bifurcation of the longest branch for the circumflex artery (Cx), the first lateral branch of the posterolateral artery (PL) for the right coronary artery (RCA). The measurements showed that LAD was 1.7 times longer than RCA and Cx, and the calculated LAD frame number was divided by 1.7 and corrected. The slow and normal coronary flow pattern limits reported in the literature for each coronary artery were 36.2 ± 2.6 squares for LAD, 22.2 ± 4.1 squares for Cx and

20.4 ± 3 squares for RCA [7].

Statistical analysis

All statistical analysis were performed with an SPSS 17 (SPSS, Inc., Chicago, Illinois, USA). Continuous variables characterized by normal distribution were expressed as mean ± standard deviation (mean ± SD) and categorical variables as numbers and percentages. Comparisons of the continuous variables between groups were performed using the independent samples t-test and categorical variables with chi-square test as appropriate and correlations between variables using the Pearson product-moment correlation analyses. A two-tailed p value of less than 0.05 was considered as significant. A receiver operating characteristic (ROC) curve was constructed to determine the diagnostic accuracy of variables. The optimal cut-off of β-2M as well as the sensitivity and specificity of the test was calculated using the Youden index.

RESULTS

The control group with normal coronary arteries consisted of 31 males and 35 females, whereas the coronary slow flow group comprises 32 males and 26 females. The mean age of control group was 51± 8 years while it was 52 ± 7 years in the coronary slow flow group. The demographic characteristics of groups and laboratory tests are expressed in Table 1.

Inflammation markers such as sedimentation rate and CRP were similar (p=0.370 and 0.249) and there was no difference between whole blood counts between the groups. Coronary slow flow patients had higher levels of total cholesterol and LDL levels from controls and it was statistically significant (p<0.01).

The coronary angiography results showed that 30 patients (51%) had SCFP in LAD, 5 patients (9%) in Cx, 6 patients (10%) in RCA and 17 patients (30%) in two or more vessels. β-2M levels were higher at RCA slow flow than LAD or Cx. Mean β-2M levels were 2431.0 ± 885.6 ng/ mL for RCA, 2067.1 ± 692.7 ng/ mL for LAD and 2140.3 ±808.1 ng/ mL for Cx and the difference between subgroups was statistically significant (p= 0.001). Mean TIMI frame count of coronary slow flow patients was 31.24 ± 4.00 and 27.32 ± 2.99 for controls (p<0.001) (Figure A). β-2M was positively correlated with TFC (r= 0.262, p= 0.003) (Figure B). In subgroup analysis, non-RCA and RCA groups were differed in terms of TFC, but there was not any difference for other epicardial arteries (p= 0.013 for RCA, p=0.672 for LAD and p=0.812 for Cx).

Table 1-Demographic characteristics and laboratory results of groups, and statistical analysis

Variables	Control group (n=66)	Slow flow group (n=58)	p value
Female n, (%)	35 (53)	26 (45)	0.506
Age, years	51 ± 8	52 ± 7	0.193
Triglycerides (mg/dL)	201.5 ± 15.2	224.3 ± 19.4	0.472
HDL (mg/dL)	41.4 ± 8.1	42.4 ± 7.9	0.482
LDL (mg/dL)	121.1 ± 27.2	139.8 ± 33.0	0.002*
T.Cholesterol (mg/dL)	192.6 ± 45.9	214.3 ± 44.4	0.004*
Creatinine (mg/dL)	0.65 ± 0.13	0.67 ± 0.12	0.480
ALT (U/L)	19.9 ± 10.4	21.3 ± 10.4	0.445
WBC (x 103/mL)	8.1 ± 2.1	7.8 ± 1.6	0.451
HGB (mg/dL)	13.5 ± 1.6	13.7 ± 1.6	0.393
PLT (x 103/mL)	242.6 ± 52.8	257.3 ± 65.6	0.159
CRP (mg/L)	3.9 ± 4.8	5.1 ± 5.6	0.249
Sedimentation (mm/s)	9.4 ± 6.4	10.7 ± 8.8	0.370
Beta-2 microglobulin (ng/mL)	1692.7 ± 403.4	2042.0 ± 660.2	<0.001*

HDL: high density lipoprotein, LDL: low density lipoprotein, ALT: alanine transaminase, WBC: white blood count, HGB: hemoglobin, PLT: platelets, CRP: c- reactive protein, * statistically significant

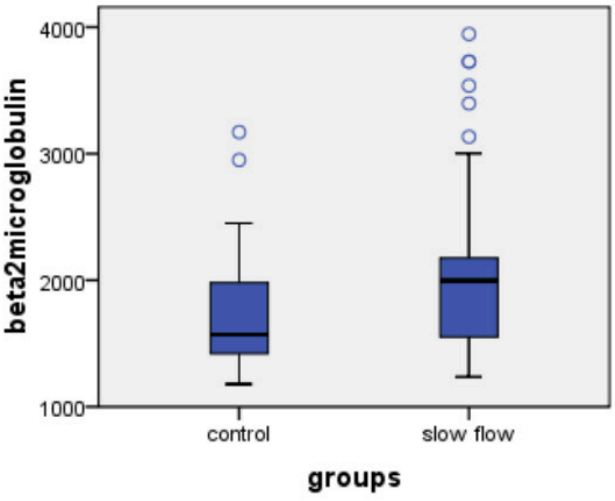


Figure A- Beta-2 microglobulin levels of groups

The coronary slow flow was positively correlated with LDL, total cholesterol and β-2M levels (p=0.002, r=0.295 ; p=0.009, r=0.233 and p<0.001, r=0.310 respectively). The correlation between coronary slow flow and β-2M was higher.

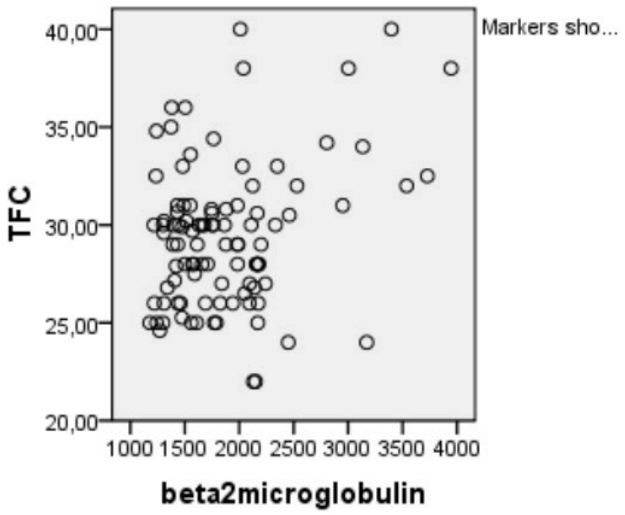
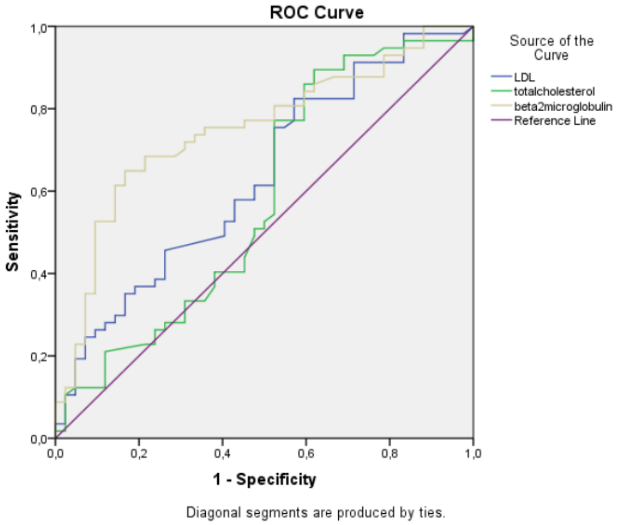


Figure B- Correlation between Beta-2 microglobulin and TFC

ROC curve analysis showed β-2M level moderately predicted diagnosis of CSFP with an area under the curve (AUC) of 0.748. The optimal cut-off value of β-2M for predicting CSF was 1551 ng/mL (75% sensitivity and 66% specificity, 95% CI: 0.650-0.846, p<0.001) (Figure C).



Variables	Area Under the Curve	95 % CI	p value
Beta-2 microglobulin	0.748	0.650-0.846	<0.001
LDL	0.632	0.522-0.743	0.025
Total cholesterol	0.581	0.462-0.700	0.061

Figure C- ROC plot for beta-2 microglobulin, LDL and total cholesterol

DISCUSSION

The coronary slow flow is the slow progression of contrast agent in the coronary bed, although there are normal or near-normal coronary arteries angiographically. Though the pathophysiology is not clear, microvascular disease is thought to be at the forefront. Patients with CSF may admit to the outpatient clinic with atypical chest pain, exercise angina, unstable angina pectoris, non-Q MI and Q wave MI [8]. The left anterior descending (LAD) artery is most often involved, followed by RCA and the Cx [9]. In our study, distribution of slow flow was similar to these results.

Some studies have reported male gender as a predictor of the coronary slow flow phenomenon, while others have found no relation between sex and slow flow [10]. 55% of the study population was male but there was no relation established between sex and CSFP in this paper. Although previous observational studies have concluded that these patients have good prognosis, Zhu et al. revealed that an age above 50 and dyslipidemia are associated with adverse outcome in patients with CSF [11]. The mean age of the CSF group was 53 and the groups differed in terms of LDL and total cholesterol levels in our study.

The coronary slow flow phenomenon is accepted as a spectrum of coronary artery disease and coronary artery endothelial dysfunction. The mechanism for the association between β-2M and coronary artery disease remains unclear, but the relationship between β-2M and immunity and inflammation disorders suggests that β-2M may play a role in vascular inflammation [12]. Several biomarkers such as omentin -1, endocan, adropin and sLOX-1 have been shown to be related to the presence and severity of coronary artery slow flow [13-14-15-16]. Lovren et al. stated that adropin levels were found to be lower in patients with coronary slow flow and negatively correlated with mean TFC. They claimed that adropin is expressed in coronary artery endothelial cells and it plays a potential endothelial protective role [16]. To the contrary of adropin, results of our study showed that increased β-2M levels may be a predictive biomarker for the coronary slow flow.

β-2M is a low-molecular-weight protein released by activated T and B lymphocytes. The estimated

half-life time is short (2 h) [17]. β-2M has been shown to increase in several inflammatory and hematologic disorders, such as systemic lupus erythematosus, acquired immunodeficiency syndrome, multiple myeloma, lymphoma and leukemia [18-19-20]. To our knowledge, β-2M in the coronary slow flow has not been evaluated. Our study is the first to investigate the relationship between β-2M and the coronary slow flow.

Serum beta-2 microglobulin is a well-established prognostic factor in multiple myeloma and follicular lymphoma [21]. Univariate analysis of prognostic factors revealed that poor performance status [Eastern Cooperative Oncology Group Performance scale (ECOG PS) ≥2] and elevated serum β-2M (≥1.8 g/mL) were significantly associated with shorter overall survival. Serum β-2M levels were significantly predictive of poor prognosis according to univariate analysis. Most studies defined a cut-off level of serum β-2M level between 2.0 to 3.5 and analysis showed 1.8 as the best cut-off level to establish a significant survival benefit [22]. Although the mechanism underlying the negative prognostic impact of elevated serum β-2M is unclear, a widely accepted hypothesis is that it is related to high tumor burden [23]. This data supports the role of inflammation and beta 2 microglobulin.

In our study, β-2M levels were higher in patients with the coronary slow flow than controls and β-2M was positively correlated with serum LDL and total cholesterol. β-2M had the most considerable effect on the coronary slow flow phenomenon. Furthermore, patients with the coronary slow flow in RCA had higher levels of β-2M and also higher TFC levels than others.

As a result, β-2M may reflect the prevalence of the coronary slow flow phenomenon and there was a weak correlation between β-2M levels and the severity of disease. β-2M could be a potential indicator of the CSFP.

Our study had some limitations namely that it was a single center study and had no follow-up period. Additionally, the study population was small and the groups differed in terms of LDL cholesterol that leads to endothelial dysfunction and microvascular disease. Finally, there was no designated treatment protocol.

CONCLUSION

We demonstrated that elevated serum β-2M levels were independently associated with the presence of angiographically proven coronary slow flow phenomenon, and a weak correlation between the severity of the disease and β-2M. Further studies are needed to support the usability of β-2M as a biomarker for the coronary slow flow.

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Conflict of Interest: The author has no conflict of interest related to this article.

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Effects of Paracetamol on Vascular Endothelial Growth Factor, Sclerostin and FETUIN-A in the Liver of Rat Fetuses

Sıçan Fetusların Karaciğerlerinde Parasetamolün Vascular Endothelial Growth Factor, Sclerostin ve FETUIN-A Üzerine Etkileri

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ABSTRACT

Aim: Paracetamol is widely used by important societal groups such as pregnant women and the elderly. Paracetamol, taken in high doses especially during pregnancy, causes liver failure. The aim of our study is to investigate the effects of paracetamol, which is widely used during pregnancy, on the fetal liver.

Methods: In our study, five groups of randomly selected rats from 10 Wistar Albino rats (n=2) were formed as control group, 50 mg / kg paracetamol group, 125 mg / kg paracetamol group, 250 mg / kg paracetamol group and 500 mg / kg paracetamol group. Paracetamol by gavage was given to pregnant rats in specified doses. Fetuses were taken by cesarean on the 20th day of pregnancy (10 fetuses were taken from each group). The fetus livers were then taken for biochemical analysis. Biochemically, vascular endothelial growth factor A (VEGF-A), FETU-A (FETUIN-A) (α2-heremans-schmid glikoprotein) and Sclerostin (SOST) values were examined.

Results: In this study, changes in liver hepatocyte cells are seen as the dose of paracetamol increases. Regular increase is observed in VEGF-A and FETU-A. SOST increased at a dose of 250 mg / kg and decreased in the group of 500 mg / kg paracetamol. ($p<0.05$).

Conclusions: As a result, it is seen that the use of high doses of paracetamol in pregnancy causes changes in the liver and many biochemical values on the fetus. We think that an overdosing of paracetamol, which is sold without prescription and used as an innocent analgesic during pregnancy, should be examined and this study will be a reference for other studies to be conducted.

Keywords: VEGF-A, paracetamol, liver, FETU-A, fetus

ÖZ

Amaç: Parasetamol gebe, çocuk ve yaşlılar gibi önemli gruplar tarafından yaygın olarak kullanılmaktadır. Özellikle gebelikte fazla dozda alınan parasetamol karaciğer yetmezliklerine neden olmaktadır. Çalışmamızın amacı gebelik döneminde yaygın olarak olarak kullanılan parasetamolün fetüs karaciğeri üzerine etkilerini biyokimyasal olarak araştırmaktır.

Yöntemler: Çalışmamızda 10 adet (n=2) gebe sıçanlardan Wistar Albino cinsi rastgele seçilen kontrol grubu, 50 mg/kg parasetamol grubu, 125 mg/kg parasetamol grubu, 250 mg/kg parasetamol grubu ve 500 mg/kg parasetamol grubu olmak üzere beş gruba ayrıldı. Gavaj yoluyla parasetamol, belirlenen dozlarda gebe sıçanlara verildi. Gebeliğin 20. gününde sezeryan ile fetüsler alındı (her gruptan 10 adet fetus alındı). Sonrasında fetus karaciğerleri biyokimyasal analiz için alındı. Biyokimyasal olarak vascular endothelial growth factor A (VEGF-A), FETU-A (α2-heremans-schmid glikoprotein) ve Sclerostin (SOST) değerleri incelendi.

Bulgular: Bu çalışmada parasetamol dozu arttıkça karaciğer hepatosit hücrelerinde değişiklikler görülmektedir. VEGF-A ve FETU-A'da düzenli artış görülmektedir. SOST ise 250 mg/kg dozunda yükselirken, 500 mg/kg parasetamol grubunda azalmıştır. ($p<0.05$)

Sonuç: Sonuç olarak gebelikte yüksek dozda parasetamol kullanımının fetüs karaciğerinde ve biyokimyasal değerde değişiklik meydana getirdiği görülmektedir. Bu çalışmada gebelikte masum analjezik olarak reçetesiz satılan ve çok kullanılan parasetamol'un yüksek dozda kullanımı konusunda dikkat edilmesi gerektiğini ve bu çalışmanın yapılacak diğer çalışmalara referans olacağını düşünmekteyiz.

Anahtar Kelimeler: VEGF-A, parasetamol, karaciğer, FETU-A, fetüs

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INTRODUCTION

Paracetamol has been widely used worldwide since its release in the mid-1950s due to its pain-relieving and antipyretic effects [1]. Nonsteroidal anti-inflammatory drugs are frequently used among pregnant women, preferred for its availability to be purchased without a prescription [2]. Paracetamol is a pain reliever that is widely used due to its reliability, cheapness and effectiveness [3]. However, unchecked use of paracetamol may affect fetus health negatively. Recent studies have reported that exposure to high doses of paracetamol before birth was linked to autism, attention deficit and hyperactivity [4]. Paracetamol taken in excessive doses passes through the placenta and causes both fetal and maternal hepatotoxicity [5]. As a weak acid, nonionized in the physiological pH range and weakly bound to plasma proteins, it crosses the placenta with the blood-brain barrier. The passage of substances dissolved in lipids from mother to baby is directly proportional to placental blood flow [6]. Although the use of standard doses of paracetamol in any trimester of pregnancy does not cause any side effects in fetal development, some studies on the use of paracetamol in pregnancy have attracted attention in recent years. Studies in humans have not shown a link between prenatal paracetamol exposure and complications such as miscarriage, low birth weight and preterm delivery. In addition, many studies argue that there is a positive link between paracetamol used during pregnancy and the risk of asthma in children, and there are publications both criticizing and supporting these views in the literature [7].

Along with increasing frequency of paracetamol use and overdose intake, an increase in liver toxicity and mortality rates are also observed. Paracetamol intoxication is responsible for about 500 deaths annually in the United States alone, causing hepatocellular necrosis. Although hepatotoxicity frequently develops in toxic doses of paracetamol intake, symptoms of renal failure, metabolic acidosis, coagulopathy, encephalopathy and recurrent gastrointestinal tract may also be seen. After taking paracetamol orally, it is converted into the toxic metabolite N-acetyl-p-benzoquinonimine by the cytochrome p450 enzyme system and detoxified with endogenous glutathione. In high doses, glutathione stores decrease, and liver toxicity occurs because toxic metabolites cannot be detoxified. N-Acetylcysteine is a glutathione precursor. It prevents the binding of toxic metabolites of paracetamol to hepatic macromolecules and refreshes reduced glutathione stores; it also reduces hepatic necrosis with antioxidant mechanisms. In acute paracetamol poisoning, it is reported that the N-Acetylcysteine applied within the first 8 hours following the intake largely prevents the development of toxicity [8].

Angiogenesis is a multifactorial and progressive process that leads to the formation of new blood vessels. It plays an important role in the development of the tumor. The most important and best-known factor affecting both physiological and pathological angiogenesis is VEGF-A [9].

It is a multifunctional growth factor family that has specific effects for endothelial cells [10]. While this growth factor plays a critical role in vascular formation, it has been found that it is necessary in many functions performed by endothelial cells [11].

FETU-A is a glycoprotein and is synthesized from the liver. Factors affecting it is secretion in humans have been reported to be in conditions such as severe liver injury, cirrhosis, acute viral, hepatitis and cancer [12].

SOST is a new biomarker associated with the bone-vascular axis. Zou et al. performed a study in which vascular effects of serum sclerostin level were examined [13].

In this study, we aimed to investigate the effects of high dose paracetamol use on the fetus during pregnancy, especially on the enzymes of the fetus liver.

MATERIALS AND METHODS

The approval for the study was received by the University Experimental Animals Ethics Committee on 16.11.2016 with the protocol number 16/145 Wistar albino rats aged at least 8 weeks old and with an average weight of 185-200 g, were obtained from Erciyes University Experimental Animals Clinical Research Center use in this study. Female rats were placed in the same cage with male rats at 17:00 in the evening

to launch the experiment. After the vaginal smear samples of the female rats were examined under a microscope at 7:00 am the next day, specimens with sperm in the vaginal smear were considered to be 0.5 days pregnant and kept in separate cages apart from male rats. Paracetamol doses were given to the pregnant rats in accordance with the literature and at the end of the experiment, livers of rat fetuses were analyzed. A total of 10 rat fetuses from each group were included in the study.

Experimental groups

In accordance with the literature [14] powdered paracetamol was dissolved with 1 ml SF (saline solution) and administered to the rats orally at 3.00 pm by gavage.

Control group: SF was administered to the rats by gavage 1-20 days of their pregnancy.

50 mg/kg paracetamol group: Paracetamol at a dose of 50 mg/kg was administered to the pregnant rats at 3.00 pm on 1-20 days of their pregnancy by gavage.

125 mg/kg paracetamol group: Paracetamol at a dose of 125 mg/kg was administered to the pregnant rats at 3.00 pm on 1-20 days of their pregnancy by gavage.

250 mg/kg paracetamol group: Paracetamol at a dose of 250 mg/kg was administered to the pregnant rats at 3.00 pm on 1-20 days of their pregnancy by gavage.

500 mg/kg paracetamol group: Paracetamol at a dose of 500 mg/kg was administered to the pregnant rats at 3.00 pm on 1-20 days of their pregnancy by gavage (Figure 1).

Homogenization and total protein concentration

Rat liver samples were weighed and homogenized in phosphate-buffered saline solution (PBS). Then homogenates were centrifuged at 10 000 RPM for 15 minutes at 4°C, and supernatants were collected and analyzed immediately. The total protein concentration was determined in each sample using direct colorimetric measurements of total protein with Bio-Rad reagents (Bio-Rad laboratories GmbH, Munchen, Germany) and bovine serum albumin as the standard.

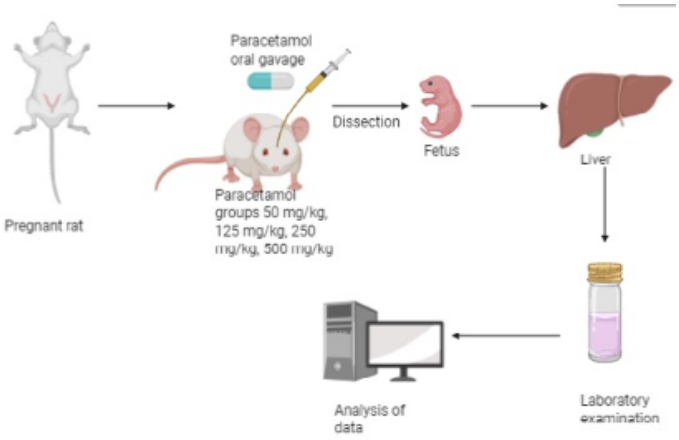

Figure 1. Summary diagram of the whole study. Biochemical analyzes of liver tissues were performed in five different groups

VEGF-A, SOST and Fetu-A Levels

The concentrations of VEGF-A, SOST and Fetu-A were assayed in rat liver homogenates by ELISA method (8-point standard worked) according to the protocol booklet of the manufacturers of the ELISA kits for VEGF-A (Elabscience Rat VEGF-A ELISA kit catalog No: E-EL-R2603, Elabscience (Wuhan, China)), SOST (Elabscience Rat SOST ELISA kit catalog No: E-EL-R2427, Elabscience (Wuhan, China)) and FETU-A (Elabscience Rat FETU-A ELISA kit catalog No: E-EL-R2451, Elabscience (Wuhan, China)) assay kit instructions in duplicates. The absorbances were measured using Multiskan GO plate reader (Thermo Scientific, U.S.A) and calibrated according to standard curves. The results obtained were calculated for liver homogenate total protein contents in mg.

Statistical Analysis

All analyses were performed with an SPSS version 23.0 (IBM Co., NY, USA) and data was given as mean (standard deviation). In the data obtained, 5 parameters were evaluated (kurtosis), skewness, mean-standard deviation ratio, Gauss curve, Shapiro-Wilko test) and normal distribution analysis was performed. When 3.5 + points out of 5 parameterswere obtained, we accepted that our data was distributed normally and parametric tests were applied a one-way Anova test for the same day in multi-group comparisons Tukey test, since variances are equal in post hoc evaluations.

RESULTS

VEGF-A, FETU-A and SOST levels were measured in accordance with the protocol, fetus livers samples by ELISA method. When the levels of VEGF-A were examined, it was found that the paracetamol 500 mg / kg group was statistically higher than the other groups (Figure 2). In the FETU-A group, the paracetamol was also higher in the 500 mg / kg group (Figure 3). In the SOST level, paracetamol was more common in the 250 mg / kg group than in the other groups (Figure 4). In groups with liver damage, sclerostin level increased.

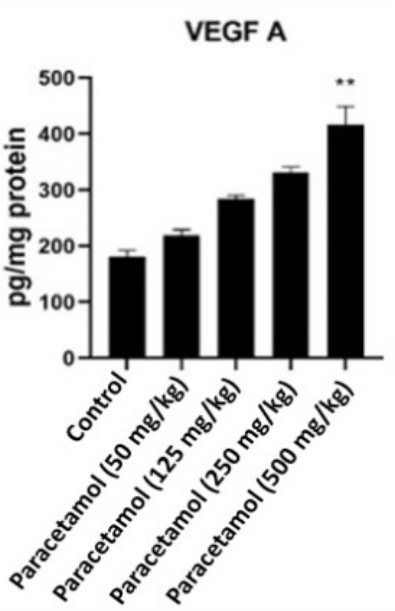

Figure 2. Levels of VEGF-A by experiment groups. One-way ANOVA, post hoc Tukey test (**p<0.01)

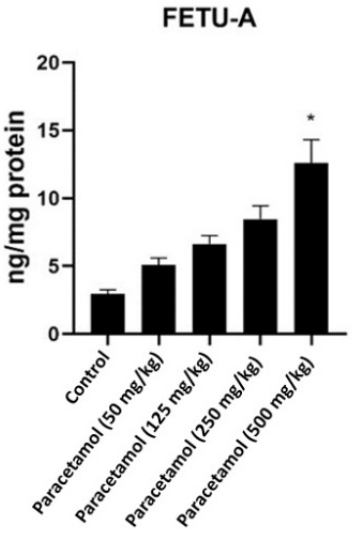

Figure 3. Levels of FETU-A by experiment groups. One-way ANOVA, post hoc Tukey test (* p<0.05)

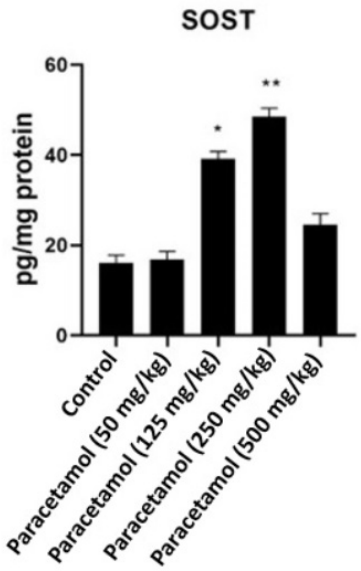

Figure 4. Levels of SOST (Sclerostin) by experiment groups. One-way ANOVA, post hoc Tukey test (*p<0.05, **p<0.01)

DISCUSSION

Excessive drug consumption may result in health problems in the liver and kidneys and cause acute insufficiency. Analgesic and non-steroidal drugs are used very frequently today [15] and over-the-counter medications are widely used in mild and moderate pain. Paracetamol in particular is a pain medication in use at large in the population by the elderly, for children and in pregnancyt [16]. Despite this, its effects on the fetus, especially in pregnancy, are not fully known. In experimental studies, paracetamol given for the purpose of treatment caused changes in the cognitive abilities and behaviors of animals [17]. It is a reliable drug when used in prescription dosage, however, when taken in doses above 4000 mg daily, it causes liver damage [18].

Schilling et al. determined that high doses of paracetamol would damage the liver and that some patients may experience liver damage at doses slightly above the recommended daily limit of 4 grams [19].

In another study, Holm et al. applied 50 mg / kg and 150 mg / kg paracetamol to the rats by gavage until the 7th day after mating. When the ovaries of the female offspring were examined 7 weeks after birth, they found that the number of primordial follicles decreased by approximately 50% in groups exposed to paracetamol, and that there was a significant decrease in the number

of primary and secondary follicles. Based on these data, the author points out that exposure to prenatal paracetamol subsequently leads to decreased fertility [20].

In a study by Momma et al., analysis was performed of the potential effect of paracetamol given to Wistar rats on the cardiovascular system on the 21st day of their pregnancy, which reported that paracetamol, ductus arteriosus caused narrowing in the inner diameter, increase in the volume of the ventricles and heart failure. In another study, it was reported that glutathione concentration decreased in the fetal mouse liver without any malformation due to the paracetamol application to the mice between the 6th and 13th days of their pregnancy [21]. Oxidative stress stimulates the formation of mitochondrial peroxynitritis, which triggers mitochondrial DNA damage, and hepatic macrophages advance liver damage from paracetamol [2].

There are studies indicating that when paracetamol is taken in overdose, it causes a decrease in the activity of antioxidant enzymes. At the same time, pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α can cause apoptosis, necrosis of hepatocytes, and liver damage by stimulating oxidative stress [22].

Chronic paracetamol poisoning occurs at doses of more than 60 mg/kg daily, intakes more than a week. In particular, drug use takes place mostly in the first three months of pregnancy, and some expectant mothers use drugs prior to being aware of their pregnancy. In the late period of pregnancy, fetal kidneys start to work quite effectively and quickly eliminate hydrophilic drugs. Since the urine of the fetus passes into the amniotic fluid, hydrophilic drugs are less likely to pass to the mother, even though the maternal plasma concentration is reduced. Therefore, amniotic fluid can be considered as a reservoir for hydrophilic drugs [23]. The risk of toxicity is increased because the blood-brain barrier permeability is higher in the fetus than the adult and the detoxification function of the liver is less effective. In individuals with chronic liver disease, SOST level increases [24]. This result is similar to our study where we that VEGF-A and FETU-A ratios increased in 500mg/kg paracetamol group and SOST amount increased in 250mg/kg paracetamol group. Considering the literature, it was seen that high doses of paracetamol in the liver increased VEGF-A, FETU-A and SOST levels compared to the control group.

Paracetamol crosses the blood-brain wall in the fetus during pregnancy. In our study, growth factors in fetus livers were investigated in pregnant rats given paracetamol. Depending on the dose of paracetamol, VEGF-A, FETU-A and SOST values increased and the VEGF-A and FETU-A were found to be similar to other studies [25]. More clinical and experimental studies are needed to determine the extent to which paracetamol affects the organs and development of the fetus in pregnant women.

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Conflict of interest: The authors declare that there are no conflicts of interest.

Limitations: Lack of cell viability test in the fetal liver and failure to look at different growth parameters constitute the limitations of the study.

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RESEARCH ARTICLE

ARAŞTIRMA

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Can portal vein pulsatility index be used as predictive parameter with hepatic artery resistive index for liver fibrosis in nonalcoholic hepatosteatosis?

Nonalkolik hepatosteatozda portal ven pulsatilite indeksi hepatik arter rezistif indeksi ile karaciğer fibrozisi öngörüsü için prediktif parametre olarak kullanılabilir mi?

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ABSTRACT

Aim: Nonalcoholic fatty liver disease (NAFLD) is a clinical entity with a broad spectrum of isolated liver steatosis, steatohepatitis and even cirrhosis. In the development of hepatitis or cirrhosis, flow changes in the hepatic artery and portal vein may be detected. The aim of this study was to investigate the significance of the changes in hemodynamic findings according to the steatosis grade in patients with nonalcoholic hepatosteatosis.
Materials and Methods: the study was performed with B-mode and Doppler ultrasonographic (US) measurements of patients who applied to the radiology department for abdominal ultrasonography examination between February and September 2018. Hepatic artery resistive index (HARI) and portal vein pulsatility index (PVPI) were evaluated. Thirty patients without steatosis and 30 patients from each 3 hepatosteatosis grade were included into the study. As the criteria for inclusion of patients in the study, there was no history of additional disease. p<0.05 values were considered statistically significant.
Results: HARI was significantly lower in grade 3 steatosis than the control group, grade 1 and 2 steatosis (p<0.05). In grade 3 steatosis, portale vein diameter was significantly wider than the control group, grade 1 and 2 steatosis (p<0.05). PVPI was significantly lower in grade 2 steatosis than the control group and grade 1 steatosis (p<0.05). Significant hemodynamic changes were detected in the hepatic artery and portal vein when compared with control and patients groups.
Conclusion: The evaluation of PVPI is considered as a noninvasive valuable method as if HARI in the evaluation of liver parenchymal damage in NAFLD.

Keywords: nonalcoholic, hepatosteatosis, hepatic artery resistive index, portal vein pulsatility index

ÖZ

Amaç: Nonalkolik yağlı karaciğer hastalığı (NAYKH); izole karaciğer yağlanması, steatohepatit hatta siroza kadar uzanan geniş bir spektrumu barındıran klinik antitedir. Hepatit ya da siroz gelişiminde hepatik arter ve portal vendeki akım değişiklikleri saptanabilir. Çalışmanın amacı nonalkolik hepatosteatozlu hastalarda steatoz evresine göre hemodinamik bulgulardaki değişikliğin anlamlı olup olmadığının araştırılmasıdır.
Gereç ve Yöntem: Çalışma Şubat-Eylül 2018 tarihleri arasında Radyoloji Bölümüne batın ultrasonografi tetkiki için başvuran hastalardan bakılan B-mod ve Doppler ultrasonografik ölçümlerle yapılmıştır. Hepatik arter rezistif indeksi (HARİ) ve portal venin pulsatilite indeksi (PVPİ) değerlendirildi. Steatozu olmayan 30 hasta ve her 3 hepatosteatoz evresinden 30'ar hasta çalışmaya dahil edildi. Hastaların çalışmaya dahil edilme kriteri olarak ek hastalık öyküsünün olmamasına bakıldı. <0.05 değerler istatistiksel olarak anlamlı kabul edildi.
Bulgular: Evre 3 steatozda HARİ kontrol grubu, evre 1 ve 2 steatozdan anlamlı olarak daha düşüktü (p< 0.05). . Evre 3 steatozda, portal ven çapı evre 0, evre 1, evre 2 den anlamlı (p<0.05) olarak daha yüksekti. Evre 2 steatozda, PVPİ kontrol grubu ve evre 1 steatozdan anlamlı olarak daha düşüktü (p<0.05). Kontrol ve hasta grupları ile karşılaştırıldığında hepatik arter ve portal vende anlamlı hemodinamik değişiklikler saptanmıştır.
Sonuç: PVPİ, NAYKH'de parankim hasarının değerlendirilmesinde, HARİ gibi noninvaziv değerli bir yöntem olarak görülmektedir.

Anahtar Kelimeler: nonalkolik, hepatosteatoz, hepatik arter rezistif indeks, portal ven pulsatilite indeksi

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common health problem, developed generally as a complication of obesity [1, 2]. NAFLD can progress and become the cause of hepatitis, whereas Nonalcoholic steatohepatitis (NASH) is an inflammatory form and can progress to fibrosis, cirrhosis or hepatocellular carcinoma (HCC) [3]. Clinical examinations and biochemical laboratory tests, including transaminases, are not sufficient in differentiating hepatitis, cirrhosis and HCC. Biopsies are the gold standard for differential diagnosis but they incur some risks and complications [4, 5], therefore, noninvasive methods may be useful in the evaluation of parenchyma involvement. Doppler ultrasonography (US) parameters such as hepatic artery resistive index (HARI), have been used for evaluating fatty liver and follow up microcirculatory resistance of liver, and can give information about formation of NASH [6] . On the other hand, portal vein pulsatility index (PVPI) can also give similar information about NASH formation [7] though HARI is useful in evaluating the development of fibrosis, since hemodynamic evaluations don't provide a definitive diagnosis. We think that an additional hemodynamic parameter will strengthen the diagnostic approach and therefore, the purpose of this study was to investigate the significance of the changes in hemodynamic findings according to the steatosis grade in patients with nonalcoholic hepatosteatosis.

MATERIALS AND METHODS

This retrospective and randomized study was conducted with the patients who applied to radiology departments for abdominal ultrasonography (US) evaluations between February-September 2018. Patients were informed for consent and the required approval was received from the Institutional Review Board (IRB) application (dated 06.11.2019 and numbered 596). The patients were questioned about the history of alcohol use were examined for HbA1c and fasting blood glucose and those with diabetes were excluded from the study. Patients with a history of malignancy or cardiac diseases and drug use that can cause liver steatosis, such as steroids, were also excluded from the study. Free of additional diseases, 30 patients without steatosis and 30 patients from each 3 hepatosteatosis grade were included into the study and were evaluated by the Doppler US in terms of HARI, PVPI and other hepatic artery and portal vein velocities. The B-mode US was used for spleen and liver dimensions. Ultrasound examination was done by two radiology specialists with Toshiba Aplio 500 (Toshiba, Tokyo, Japan) ultrasound device and 6.0-1.9 MHz convex transducer. As a standard position for evaluation, the patients were in the supine position with breath held during inspiration. Resistive index and pulsatility index were calculated with the formulas [(Peak systolic velocity - End diastolic velocity) / Peak systolic velocity] and [(Peak systolic velocity - End diastolic velocity) / Average velocity], respectively.

Statistical analysis

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov–Smirnov test. The Kruskal-Wallis, Mann-Whitney U test was used for the analysis of quantitative independent data. The Chi-squared test was used to analyze qualitative independent data. For statistical significance, $p<0.05$ values were accepted. $p<0.05$ values were considered statistically significant.

RESULTS

The patients' ages were between 36 and 57 years and the mean age was 44.2±4.5 (sd). The age of the patients in the control group was significantly lower than the patients in all three groups with steatosis. There was no significant difference for age between grade 1-2-3 steatosis patients. The number of female and male patients were equal and no significant difference was found between the control group and the patients groups, in terms of gender distribution.

Portal vein diameter (PVD) was significantly higher in grade 3 hepatosteatosis patients than in the control group and in grade 1-2 hepatosteatosis patients. PVD was significantly higher in grade 2 hepatosteatosis patients than in the control group and the grade steatosis 1 patients. There was no significant difference for PVD between grade 1 steatosis patients and the control group.

Liver and spleen size, hepatic artery and portal vein end-diastolic and peak-systolic velocities, PVD, portal vein mean velocity, minimum-maximum-median-mean values for HARI and PVPI are shown in Table 1.

Table 1: Maximum, median and mean values for liver and spleen size, hepatic artery and portal vein end-diastolic and peak-systolic velocities, PVD, portal vein mean velocity, HARI and PVPI

	Min-Max	Median	Mean±sd
Hepatic Artery End Diastolic Velocity	5.6-52.6	14.6	15.2±4.5
Hepatic Artery Peak Systolic Velocity	28.8-88.0	47.0	48.0±9.2
Hepatic Artery Resistive Index	0.47-0.84	0.68	0.68±0.1
Diameter of Portal Vein	7.5-12.2	10.0	9.9±1.1
Portal Vein End Diastolic Velocity	8.3-16.2	12.4	12.2±1.8
Portal Vein Peak Systolic Velocity	10.3-19.5	15.4	15.4±1.9
Portal Vein Average Speed	9.5-17.8	13.8	13.8±1.7
Portal Vein Pulsatility Index	0.08-0.49	0.21	0.23±0.09
Spleen size (mm)	69.0-115.0	93.5	92.9±10.4
Liver size (mm)	130.0-175.0	148.0	150.4±10.6

HARI was significantly lower in grade 3 steatosis patients than the grade 1-2 steatosis patients and the control group, and significantly lower in patients with grade 2 steatosis than the control group and the grade 1. There was no statistically significant difference between the grade 1 steatosis patients and the control group in terms of HARI.

PVPI was significantly lower in grade 3 steatosis than in the control group and grade 1 steatosis patients, and significantly lower in grade 2 steatosis patients than in the control group and grade 1 steatosis patients. There was no statistically significant difference in PVPI values between grade 1 steatosis patients and the control group, and between grade 2 and 3 steatosis groups.

Table 2 shows the statistical comparison between hepatic artery end-diastolic and peak-systolic velocity values, PVD and mean velocity, portal vein end-diastolic and peak-systolic velocity values, liver and spleen dimensions.

DISCUSSION

NAFLD is the involvement of steatosis in liver without the other common causes of steatosis, such as alcohol, drugs, other metabolic conditions or hereditary disorders [5,6]. Although the diagnosis is confirmed radiologically, the definitive diagnosis is made histopathologically [8]. NAFLD includes non-alcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), the latter of which may progress to fibrosis, cirrhosis or hepatocellular carcinoma [9].

NAFLD is the most common cause of chronic liver disease. It is thought that one fourth of chronic liver disease in the world is caused by steatosis [10]. There were few studies about the prevalence of hepatic steatosis in Turkey, however, important data has emerged in recent studies about the prevalence of hepatosteatosis in this country. According to a review study, published in 2019, the prevalence of NAFLD in Turkey is considered to be about or above 30% [6].

Biopsy is a valuable method to show the presence of NASH and the degree of fibrosis, as well as to evaluate the prognosis of the disease [8]. On the other hand, US and Doppler US are generally used in the evaluation of fatty liver as a cheap, simple and rapid assessment method. In addition, hepatic artery flow studies were performed with Doppler US to evaluate the development of fibrosis in hepatosteatosis patients [10].

In a study by Tana C et al., HARI was significantly lower in NAFLD patients than controls and, likewise, significant differences were found between subgroups [10]. In another study, Mihmanli I et al. found HARI value significantly lower in fatty liver patients [11]. In our study, HARI was also significantly lower in grade 2 and 3 steatosis patients than the lower grade and control groups. On the other hand, no statistically significant difference was found between grade 1 steatosis patients and the control group. These radiological findings suggest that there is no significant development of fibrosis in the early stage, though histopathological and radiological comparisons are needed to confirm this hypothesis.

There are also studies examining the effectiveness of Doppler US in the evaluation of hepatosteatosis

Table 2: Statistical evaluation results of HARI, HVPI, hepatic artery end-diastolic and peak-systolic velocity values, PVD and mean velocity, portal vein end-diastolic and peak-systolic velocity values, liver and spleen size

		Control group	Grade 1	Grade 2	Grade 3	p value	Control group-Grade 1	Grade 0-2	Grade 0-3	Grade 1-2	Grade 1-3	Grade 2-3
Hepatic Artery End Diastolic Velocity	Mean±sd	12.0±1.8[23]	12.8±4.6[23]	16.8±2.8[3]	19.1±3.8	0.000[K]	1.000	0.000	0.000	0.000	0.000	0.016
	Median	11.8	11.6	16.2	18.5							
Hepatic Artery Peak Systolic Velocity	Mean±sd	49.9±8.8	46.3±10.4	49.0±10.0	46.8±5.9	0.266[K]	0.062	0.372	0.165	0.337	0.383	0.848
	Median	48.4	42.8	47.3	46.9							
Hepatic Artery Resistive Index	Mean±sd	0.75±0.06[23]	0.72±0.08[23]	0.64±0.06[3]	0.59±0.07	0.000[K]	0.221	0.000	0.000	0.000	0.000	0.005
	Median	0.75	0.75	0.64	0.59							
Diameter of Portal Vein	Mean±sd	9.0±0.5[23]	9.3±0.9[23]	10.6±0.8	10.7±0.8	0.000[K]	0.290	0.000	0.000	0.000	0.000	0.776
	Median	9.0	9.0	11.0	10.9							
Portal Vein End Diastolic Velocity	Mean±sd	12.7±1.6[1]	11.2±1.9	12.8±1.3[1]	12.4±1.6[1]	0.002[K]	0.001	0.663	0.455	0.001	0.014	0.325
	Median	12.6	10.7	12.9	12.3							
Portal Vein Peak Systolic Velocity	Mean±sd	16.6±1.4[123]	14.6±2.1	15.6±1.4	15.0±1.8	0.000[K]	0.000	0.005	0.001	0.052	0.451	0.186
	Median	16.7	14.2	15.2	14.6							
Portal Vein Average Speed	Mean±sd	14.7±1.4[1]	12.9±1.9	14.2±1.3[1]	13.7±1.7	0.001[K]	0.000	0.149	0.052	0.003	0.107	0.228
	Median	14.8	12.5	14.2	13.4							
Portal Vein Pulsatility Index	Mean±sd	0.27±0.09[23]	0.27±0.11[23]	0.20±0.05	0.19±0.06	0.001[K]	0.626	0.002	0.001	0.026	0.012	0.647
	Median	0.28	0.24	0.20	0.18							
Spleen Size (mm)	Mean±sd	90.8±11.2	96.2±9.3	93.2±11.0	91.2±9.4	0.186[K]	0.081	0.510	0.841	0.257	0.045	0.390
	Median	92.5	95.5	95.0	91.5							
Liver Size (mm)	Mean±sd	138.8±3.2[123]	147.9±9.1[23]	152.8±7.0[23]	161.9±5.5	0.000[K]	0.000	0.000	0.000	0.009	0.000	0.000
	Median	139.0	147.0	154.0	162.0							

K Kruskal-Wallis (Mann-Whitney u test) / X^2 (Chi-squared) test

[1] Difference with grade 1 p<0.05 / [2] Difference with grade 2 p<0.05 / [3] Difference with grade 3 p<0.05

in children. In the study of Hizli S et al., decreasing in HARI values in children was correlated with the fatty liver and development of fibrosis [12]. It should be noted that pediatric patients were excluded from our study.

Although HARI has been evaluated in similar studies, PVPI has rarely been evaluated to predict the development of fibrosis. In a study evaluating NAFLD patients, a statistically significant difference was found in terms of PVPI value when compared with the control group, although there was no significant difference between steatosis grades [7]. In our study, PVPI was significantly lower in patients with grade 2 and 3 steatosis than the lower grades and the control group. There was no statistically significant difference in PVPI between grade 1, the control group and between grade 2-3 groups. Therefore, it may not be meaningful to evaluate fibrosis between closer groups and at low stages.

In another study, with the examining portal vein flow changes in NAFDL patients, no significant correlation was found between portal vein velocity and hepatosteatosis grades [13]. In our study, although a significant decrease was observed in grade 1 hepatosteatosis patients compared to the control group, no statistically significant difference was found in higher grades.

In one study, HARI and portal vein velocity were significantly decreased with increasing steatosis stage and the mean portal vein velocity was significantly lower with increasing of stage [14].

The presence of additional diseases are likely to affect the portal flow measurements. In many studies, it is stated that heart diseases change portal vein flow [15,16] and portal vein flow measurements in one particular study with type 1 and 2 diabetics, differed from non-diabetic patients [17]. Therefore, patients with additional diseases, such as diabetes and heart diseases, were excluded from our study.

According to another result of our study, PVD increases with steatosis stage and this finding is consistent with the literature. It should be noted that the limitation of our study is that the definitive diagnosis of fibrosis development was not made by biopsy.

In conclusion; HARI is a Doppler US parameter that has been proposed by many researchers for a long time, to predict the development of fibrosis in NAFLD patients. Similarly, in our study, HARI showed significant changes with increased steatosis. For PVPI, a limited number of studies are found in the literature and some studies have not yielded significant results. However, in our study, statistically significant changes were observed for PVPI with increasing steatosis stage, and we think that it can be used as a Doppler US parameter as well as HARI for predicting fibrosis development.

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Correlation of functional and radiological results with three-dimensional gait analysis in patients with unilateral slipped capital femoral epiphysis

Femur başı epifiz kayması tanılı hastalarda klinik ve radyolojik sonuçların yürüme analizi ile korelasyonu

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ABSTRACT

Aim: The aim of this study was to evaluate the correlation between gait analysis and clinical and radiographic results in patients operated for slipped capital femoral epiphysis (SCFE).

Materials and Methods: This study included 31 patients with unilateral SCFE. The mean follow-up time was 3.3 ± 1.4 years. Harris hip score (HHS) and the Pediatric Outcomes Data Collection Instruments (PODCI) scores were collected. Slip-angle, alpha-angle, lateral femoral head ratio (LFHR), articulotrochanteric distance (ATD), anteroposterior plane femoral head ratio (AP-FHR), anterior head-neck offset ratio (HNOR), and neck-shaft angle (NSA) were measured. An age-matched control group consisting of 20 healthy individuals was used for comparison.

Results: Transfer and basic mobility subscale of PODCI was correlated with pelvis tilt ROM ($r = -0.7$, $p < 0.001$), foot progression angle (FPA) ROM ($r = -0.4$, $p=0.02$), and mean spine tilt ($r=-0.6$, $p<0.001$). FPA was also correlated with the HHS ($r=-0.5$, $p<0.001$) and pain/comfort subscale of PODCI ($r=-0.5$, $p=0.015$). Significant correlations were detected between LFHR and mean hip flexion ($r=-0.5$, $p<0.001$), pelvic tilt ($r=-0.4$, $p=0.04$), and mean spine tilt ($r=0.6$, $p<0.001$). Correlations between ATD and mean internal rotation of the hip ($r=0.5$, $p=0.03$) and mean dorsal ankle extension ($r=-0.4$, $p=0.03$) were also significant. No significant correlation was found between the alpha angle, AP-FHR, and HNOR with the kinematic values.

Conclusion: Clinical scores of patients treated for SCFE were mostly correlated with pelvic tilt ROM, FPA, and spine tilt. LFHR and ATD were observed as the most critical radiological measurements related to a patient's gait function.

Key Words: Gait analysis, slipped capital femoral epiphysis, radiologic correlation, clinical correlation, impingement

ÖZ

Amaç: Bu çalışmanın amacı femur başı epifiz kayması (FBEK) nedeniyle opere edilen hastalarda yürüme analizi ile klinik ve radyolojik sonuçların korelasyonunu değerlendirmekti.

Hastalar ve Yöntem: Bu çalışmaya ortalama takibi 3.3 ± 1.4 yıl olan tek taraflı FBEK tanısıyla opere edilen 31 hasta dahil edildi. Klinik değerlendirme Harris kalça skoru (HKS) ve Pediatrik Veri Toplama Aracı (PVTA) skoru ile yapıldı. Radyolojik değerlendirme için kayma açısı, alpha alçısı, lateral femur başı oranı, artikulotrokanterik mesafe (ATM), ön-arka planda femur başı oranı, anterior baş-boyun offset oranı ve boyun şaft açısı ölçümü yapıldı. Yaş eşleşmeli 20 sağlıklı bireyden kontrol grubu oluşturuldu.

Bulgular: PVTA transfer ve temel mobilite alt ölçeği; pelvis tilt eklem hareket açıklığı (EHA) ($r = -0.7$, $p <0.001$), ayak ilerleme açısı EHA ($r =-0.4$, $p=0.02$) ve ortalama omurga tilti ($r=-0.6$, $p<0.001$) ile anlamlı korelasyon gösterdi. Ayrıca ayak ilerleme açısı ile HKS ($r=-0.5$, $p<0.001$) ve PVTA ağrı/konfor alt ölçeği anlamlı korelasyon gösterdi ($r=-0.5$, $p=0.015$). Lateral femur başı oranı ile ortalama kalça fleksiyonu ($r=-0.5$, $p<0.001$), pelvik tilti ($r=-0.4$, $p=0.04$) ve ortalama omurga tilti ($r=0.6$, $p<0.001$) koreleydi. ATM ile ortalama kalça iç rotasyonu ($r=0.5$, $p=0.03$) ve ortalama ayak bileği ekstansiyonu ($r=-0.4$, $p=0.03$) koreleydi. Alfa açısı, Ön-arka femur başı oranı ve anterior baş boyun ofsetinin kinematik değerlerle korelasyonu gösterilemedi.

Sonuç: FBEK nedeniyle opere edilen hastalarda klinik skorlar çoğunlukla pelvik tilt EHA, ayak ilerleme açısı ve omurga tilti ile korelasyon gösterirken, radyolojik sonuçlardan lateral femur başı oranı ve ATM'nin yürüme fonksiyonu ile ilişkili olduğu anlaşılmıştır.

Anahtar kelimeler: yürüme analizi, femur başı epifiz kayması, eklem kinematiği, radyolojik korelasyon, klinik korelasyon, sıkışma

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INTRODUCTION

Slipped capital femoral epiphysis (SCFE) is one of the most common hip joint pathologies during the adolescence period [1]. After in situ pinning, three planar residual deformities occur according to the degree of slip [2]. Residual deformities can be summarized as femoroacetabular impingement, shortening of the femoral neck, femoral anteversion loss, and metaphyseal changes in the anterior and superior part of the neck [3]. These deformities affect the functional capacity of patients and pose a risk for hip osteoarthritis [3]. Major operations, such as osteotomy or debridement, are performed to treat newly occurred deformities after slippage, with the guidance of clinical examination and radiological evaluation. However, imaging is a static measure and range of motion tests are not performed under loaded activities of daily living. Afterwards, for surgeries (including in situ pinning and thereafter osteotomy or debridement), patient scores are useful in addressing short-term benefits, but require subjective patient feedback for their assessment and might not be useful indicators of longer-term outcomes [4-6]. All these issues cause the functional outcome of treatment to be ignored [7]. After the closure of the epiphysis, current assessment methods are inadequate to evaluate first, the effect of functional outcomes, and then the impact of residual deformity in the proximal femur on movement [8,9].

Gait is the most common repetitive voluntary movement of the lower limbs and essential activity of daily living. Correlation of the clinical and radiological results of deformity after slippage with gait analysis (GA), which provides a better understanding of the functional results, may lead to a better evaluation of indications of future joint preservation surgeries. There are a limited number of studies on the evaluation of patients with SCFE by objective methods such as GA [8, 10-12].

The aim of this study was to evaluate the correlation between GA and clinical and radiographic results in patients operated for SCFE.

MATERIALS and METHODS

Between 2005 and 2013, the records of patients who underwent in situ pinning surgery with a diagnosis of SCFE were analyzed retrospectively on a computerized patient record system. Thirty-one patients with chronic unilateral SCFE (Figure 1.) were included in the study, and 45 patients were excluded. Criteria for exclusion were as follows: clinically or radiologically bilateral slip at the time of first admission or follow-up (n = 14), open reduction or osteotomy (n = 11), history of revision surgery, less than 2 years of follow-up (n = 6), presence of musculoskeletal system disease developing primary or secondary gait disturbance such as fracture or scoliosis (n = 3), development of avascular necrosis (AVN) (n = 3), and chondrolysis (n = 1) complications. We also excluded two patients who did not take the GA test and five patients who did not visit the outpatient clinic regularly. In addition, the study was approved by the Institutional Review Board (IRB) (2014).

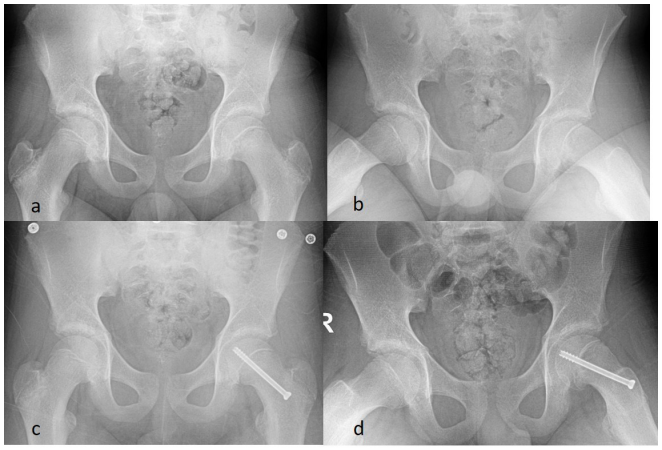

Figure 1 - One of our patients treated with in situ pining. a-b: preoperative anteroposterior and lateral view of healthy and slipped hips. c-d: postoperative anteroposterior and lateral view of healthy and slipped hips.

A full body GA was performed using a the Vicon Bonita System (Oxford Metrics Ltd., Oxford, England) in all patients. Three records that were compatible with each other and the highest patient compliance were included in the study. Averages of these three selected records were used in statistical calculations. The minimum and maximum values were calculated from the peak values in the direction of movement in the stance phase.

The mean age of patients when gait analyses were performed was 16.5 ± 2.5 years, and mean body mass index (BMI) was 27.78±5.6 kg/m2. A control group was formed of volunteers whose

mean age was 17.84 ± 1.47 years (range, 16-20), with a mean BMI of 27.72±2.61 kg/m2. The SCFE and control groups were similar in age (p = 0.51) and BMI (p = 0.21). The control group (7 females, 13 males) consisted of healthy individuals without any gait-influencing disorder. The neurological examination, including spasticity and motor strength, as well as the limb length discrepancy were also evaluated before the gait exam in both groups. A scoliosis screening test, examination for tibia rotational deformity, hip, knee and ankle joint contractures were routinely performed in both groups. We also evaluated hip, knee, ankle, and foot joints angular measurements with goniometer. Hip flexion, hip joint flexion contracture, hip internal rotation (IR) and hip external rotations (ER), and hip abduction and adduction exams were performed in the supine position, whereas hip extension and femoral anteversion were assessed in the prone position. The two groups were clinically examined on the same day as the GA, by an experienced physiotherapist and senior orthopedic surgeons.

The Harris Hip Score (HHS) and the Pediatric Outcomes Data Collection Instruments (PODCI) score were used to measure the quality of life and physical function of patients.

The deformity analysis of the proximal femur was performed by the following x-ray views:

1.Slip-angle: anteroposterior (AP) and Lateral (LAT) view of hip [13]

2. Femoral head ratio (FHR): AP view of pelvis AP (Figure 2.) [3]

3. Lateral femoral head ratio (LFHR): LAT view of hip (Figure 2.) [14]

4. Alpha angle: AP and LAT view of hip (Figure 3.) [15, 16]

5. Anterior femoral head-neck offset ratio (HNOR): LAT view of hip (Figure 3.) [17]

6. Articulotrochanteric distance (ATD): AP view of pelvis; and

7. Femoral neck-shaft angle (NSA): AP view of hip [18]

Southwick slip-angles were measured both preoperatively and 6 months postoperatively, whereas other radiological measurements were performed while x-rays were being taken on the same day of GA.

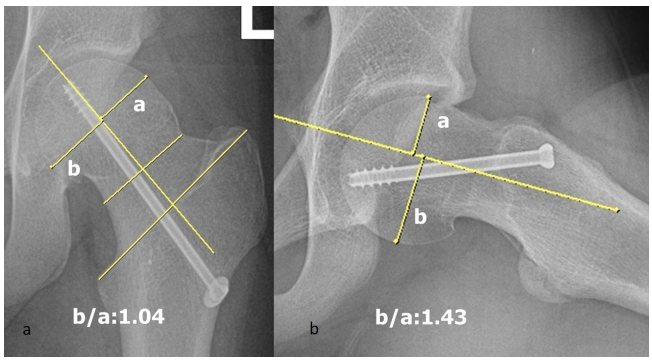

Figure 1 - One of our patients treated with in situ pining. a-b: preoperative anteroposterior and lateral view of healthy and slipped hips. c-d: postoperative anteroposterior and lateral view of healthy and slipped hips.

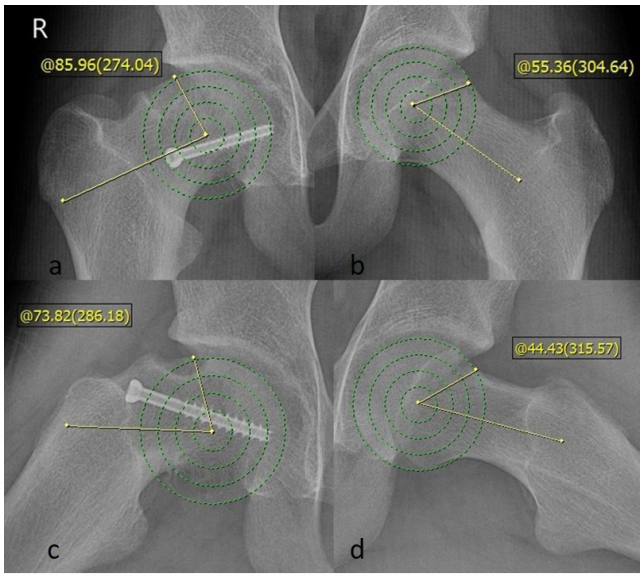

Figure 3 - a-b: Alpha angle measurement method on anteroposterior plane of slipped hip and healthy hip. c-d; Alpha angle measurement method on lateral plane of slipped hip and healthy hip.

Replicate measurements correlated significantly between observers. Values of correlation coefficients between two different measurements that ranged between 0.88 and 0.99 were acceptable.

Statistical analysis

The resulting data was analyzed using the IBM Statistics 19.5 (SPSS Inc., IBM, IL, USA). Kurtosis and skewness values were used to analyze the distribution of data. Kinetic and kinematic data of the SCFE and control groups were compared with an independent t-test. All GA data was correlated

Table 1. Statistically significant gait deviations between SCFE patients after epiphysis closure and control group

Kinematic variables	Group	Mean (SD)	Mean Difference	95% CI of the Difference	Sig. (2-tailed)
Pelvis tilt ROM	SCFE	3.5 (1.5)	1.2	0.5 / 1.8	<0.01
	Control	2.3 (0.5)			
Hip flexion ROM	SCFE	35.1 (3.7)	-4.6	-6.8 /-2.3	<0.01
	Control	39.8 (4.6)			
Min. pelvic obliquity	SCFE	-3.1(1.9)	2.7	1.7 / 3.8	<0.01
	Control	-5.7 (1.8)			
Max. pelvic obliquity	SCFE	2.4 (1.8)	-1.2	-2.3 / -0.1	0,02
	Control	3.6 (1.9)			
Pelvis obliquity ROM	SCFE	5.5 (2.3)	-3.9	-5.4 / -2.5	<0.01
	Control	9.5 (2.8)			
Min. Hip abduction	SCFE	-4.01 (3.1)	3.6	1.8 / 5.4	<0.01
	Control	-7.6 (3.5)			
Hip abduction ROM	SCFE	10.8 (2.9)	-2.1	-3.8 / -3.3	0,02
	Control	12.9 (3.4)			
Max. knee abduction	SCFE	10.8 (5.8)	1.8	-1.9 / 5.5	0,03
	Control	6.5 (7.9)			
Knee Abduction ROM	SCFE	15.2 (6.1)	4.4	0.9 / 7.9	0,01
	Control	10.7 (6.9)			
Mean FPA	SCFE	-11.1 (7.7)	-5.9	-9.9 / -1.9	0,01
	Control	-5.2 (6.5)			
Min. FPA	SCFE	-14.2 (8.1)	-5.9	-10.2 / -1.6	<0.01
	Control	-8.3 (7.5)			
Max. FPA	SCFE	-6.3 (8.1)	-5.5	-9.4 /-1.6	0,02
	Control	-0.9 (6.1)			
Ankle rotation ROM	SCFE	31.2 (1.7)	8.2	3.4 / 13.1	0,01
	Control	22.9 (6.7)			
Mean thorax tilt	SCFE	5.6 (5.4)	4.2	1.5 / 6.9	<0.01
	Control	1.4 (4.4)			
Min. thorax tilt (towards swinging limb)	SCFE	3.7 (5.9)	4.9	2.2 / 7.7	<0.01
	Control	-1.2 (4.4)			
Max. thorax tilt (towards supporting limb)	SCFE	7.4 (5.7)	4	1.2 / 6.9	<0.01
	Control	3.4 (4.3)			
Spine tilt ROM	SCFE	5.1 (3.3)	-2.8	-4.5 / -0.9	0,02
	Control	7.8 (3.4)			

The joint kinematic values of the SCFE patients and control group were compared between the axial, frontal, and sagittal planes, but statistically significant differences were noted only in the table. SD= standard deviation; CI = Confidence interval; ROM = range of motion; FPA = foot

with radiological and clinical findings using Pearson's correlation test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The mean age of patients (1 female, 30 males) at the time of surgery who were included in the study was 13.5 ± 2.2 years and mean follow-up was 3.3 ± 1.4 years.

At the last follow-up, the slip side hip range of motion (ROM) was measured as follows: mean hip flexion 118.2^0(100–140), mean hip extension 280(20–35), mean hip abduction 50.1^0(45–60), mean hip adduction 45.4^0(35–50), mean hip internal rotation (IR) 28^0(0–50), mean hip external rotation (ER) 51^0(45-60).

According to the control group, statistically significant gait deviations are presented in Table 1. We did not observe any statistically significant difference in kinetic measurements, cadence, step

Table 2. Significant correlations of patient scores with gait analyses Statistically significant correlations were noted only in the table.

Patient scores	Mean score (SD)	Pearson Correlation	Pelvis tilt ROM	Min. hip flexion	FPA ROM	Ankle rotation ROM	Mean spine tilt	Min. spine tilt towards supporting limb	Max. spine tilt towards swinging limb	Step width
Transfer & Basic Mobilitya	97 (4)	Coef.	-0.7**		-0.4*		-0.6**	-0.5**	-0.5**	
		Sig. (2-tailed)	<0.01		0.02		<0.01	<0.01	<0.01	
Sports and Physical Functioninga	85 (12)	Coef.	-0.6**		-0.5**	-0.4*	-0.6**	-0.6**	-0.5**	
		Sig. (2-tailed)	<0.01		<0.01	0.04	0	<0.01	<0.03	
Pain/Comforta	75 (17)	Coef.			-0.5*					
		Sig. (2-tailed)			0.015					
Happinessa	82 (17)	Coef.			-0.5*					
		Sig. (2-tailed)			0.01					
Global functioninga	9 (8)	Coef.	-0.6**		-0.5**		-0.5**	-0.5**	-0.4*	
		Sig. (2-tailed)	<0.01		<0.01		<0.01	0.01	0.02	
Harris hip score	96 (6)	Coef.		0.4*	-0.5**					-0.4*
		Sig. (2-tailed)		0.04	0.01					0,05

aAdolescent (parent and self report) Pediatrics Outcomes Data Collection Instrument-Lower extremity outcome scales of standardized means; SD= standard deviation; ROM = range of motion; FPA = foot progression angle; min.= minimum; max = maximum. * = Correlation is significant at the 0.05 level (2-tailed). **= Correlation is significant at the 0.01 level (2-tailed).

Table 3. Radiologic correlations with kinematic parameters

Kinematic parameters	Lateral femoral head ratio		Articulo-trochanteric Distance		Femoral neck – shaft angle	
	Pearson Correlation	Sig. (2-tailed)	Pearson Correlation	Sig. (2-tailed)	Pearson Correlation	Sig. (2-tailed)
Min. Pelvic tilt	-0.4*	0.04				
Mean hip flex	-0.5**	<0.01				
Min. hip flex	-0.4*	0.02				
Max. hip flex	-0.5**	<0.01				
Mean knee flex	-0.4*	0.01				
Min. knee flex	-0.4*	0.02				
Mean dorsal ankle extension			-0.4*	0.03		
Max. dorsal ankle extension	-0.4*	0.03				
Max. knee abd. angle			0.4*	0.02		
Knee abd. ROM			0.4*	0.03		
Mean internal rotation of hip			0.5*	0.03	0.4*	0.04
Min. internal rotation of hip			0.4*	0.04		
Max. internal rotation of hip			0.4*	0.04	0.4*	0.04
Mean spine tilt	0.6**	<0.01				
Min. Spine tilt towards supporting limb	0.6**	<0.01				
Max. spine tilt towards swinging limb	0.6**	<0.01				

ROM = range of motion; FPA = foot progression angle; min.= minimum; max = maximum; abd =abduction; flex = flexion; CC; * Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

width, and gait velocity.

The PODCI score standardized means with HHS obtained at the patient's last controls and the correlations of these scores with the GA, are shown in Table 2. Our results demonstrated that pelvis tilt ROM, FPA ROM, mean spine tilt, min. and max. spine tilt, were significantly correlated with at least three subscales of PODCI scores. In addition, min. hip flexion, FPA ROM, and step width were significantly correlated with HHS.

In the radiological deformity analysis, measurement of variables represented as mean ± standard deviation were as follows: pre-operative AP Southwick slip-angle was 19.7±14.2, pre-operative lateral Southwick slip-angle was 32.7±16, post-operative AP Southwick slip-angle

was 14.5±9, post-operative lateral Southwick slip-angle was 23.4±15.29, AP Femoral Head Ratio was 1.3 ±0.2, lateral Femoral Head Ratio was 1.9±0.7, articulotrochanteric distance was 11.8±6.79, AP plane alpha angle was 73.4±15.9, lateral plane alfa angle was 64.8±16.1, anterior Head-Neck Offset Ratio was 0.04±0.07, femoral neck-shaft angle was 127.8±6.1. A significant correlation was found between the AP plane Southwick slip-angle and mean knee flexion ($r = -0,357$ $p < 0.05$), thorax tilt ROM ($r = 0.385$, $p < 0.05$), and walking speed ($r = 0.379$, $p < 0.05$). A significant correlation was found only with walking speed ($r = 0.514$, $p < 0.01$) for the lateral plane Southwick slip-angle. No significant correlation was found between the AP and Lat. plane of the alpha angle, AP-FHR, and HNOR with kinematic values. Correlations of ATD, NSA, and LFHR with the transverse plane, sagittal plane, and spinal kinematics were notable (Table 3).

DISCUSSION

According to our current knowledge, in patients with chronic SCFE, complex deformity occurs after in situ pinning [2]. The femoral neck becomes shorter due to premature epiphysiodesis, and the greater trochanter continues to grow. Another controversial subject is the femoral neck/shaft angle measurement, and alpha angle measurement in these patients whose femoral head's center of rotation has changed. These measurements should be different from the traditional description because in the latter, the femoral head is centralized on the femoral neck, whereas in SCFE patients, the femoral head is not centralized on the femoral neck [19]. This situation has not been questioned and discussed previously in the literature in patients with SCFE. The determination of gait disorders by GA and identification of which gait abnormalities correlate with the radiological deformity will enable the radiological deformity to both target and guide treatment.

In our patient group, whereas the pelvis tilt ROM increased, the hip flexion-extension ROM, max. knee flexion, knee flexion-extension ROM significantly decreased. Although differences in mean, minimum, and maximum hip flexion were observed, they were not statistically significant. These differences, however, resulted in a statistically significant difference in hip flexion/extension ROM. While the coronal plane of pelvis ROM and hip ROM decreased significantly, a significant increase in coronal plane knee abduction-adduction ROM was detected. In addition, our findings seem to be consistent with studies with a similar group of patients that was operated on for SCFE. Westhoff et al. reported a significant increase in pelvis sagittal ROM, and significant decreases in both hip sagittal and knee flexion ROM [8]. While Sangeux et al. found slight gait deviations from the normal in the sagittal plane during the entire gait cycle, they reported an increase in pelvic obliquity during the swing phase [12]. Song et al. observed that as long as the degree of slip increased, pelvic obliquity also increased [10]. The most notable gait deviation in the transverse plane was detected in the rotation of the foot in our study. The increase in foot rotation ROM was not significant, but a significant increase in the foot mean-max-min. ER was detected. The increase in the FPA may have been caused by retroversion of the proximal femur and the orientation of the hip toward ER posture to protect itself from metaphyseal impaction of the proximal femur [20]. There was a significant increase in the mean and min.-max. tilt in thorax kinematics, but a significant decrease was found in thorax tilt ROM. The significant decrease in spine tilt ROM in our study was similar to the study by Westhoff et al. who reported a significant decrease in spine ROM compared with the pelvis [8].

The inverse correlation of PODCI and HHS scores with kinematic data especially with pelvic tilt ROM, FPA ROM, and spine tilt is remarkable. In Westhoff et al.'s study, clinical dissatisfaction was found to be positively correlated with the decrease in sagittal plane hip ROM and the decrease in pelvic obliquity [7]. However, in this study, the variety of treatments, especially osteotomy, may have caused differences in the expected proximal femoral deformity in patients. Song et al. observed that patients with mild and severe slip who had in situ pinning, showed correlation with both pain and function in the patients grouped according to the degree of slippage, but this was not statistically significant [10]. The impact of remodeling or metaphyseal changes in both hip joint kinematics and acquired patient scores may

explain this besides the slip-angle [21].

In our study, the slip-angle in the AP plane showed a positive correlation with the mean knee flexion, thorax tilt ROM, and gait velocity, but it showed a positive correlation with only gait velocity in the lateral plane. The highest correlation between GA and radiological measurements was found between the LFHR and the ATD in our study. In a similar study, Song et al. reported that as the slip-angle increased, both pelvic obliquity and trunk obliquity increased, and during the gait cycle, the hip was mostly in the extension, adduction, and ER posture [10]. They also found a decrease in knee flexion and an increase in ER of foot progression with increased slip-angle. Westhoff et al. noted that the strength of the correlation between step size, sagittal pelvis ROM, and FPA increased with the poor radiological index [8]. In a similar study in which patients with a slip-angle less than 30° were excluded, Sangeux et al. reported that kinematic values were not correlated with radiometric measurements (i.e., alpha angle, slip-angle) [12]. This might be, as they expressed, because of the exclusion of patients with a mild slip from the study, which may have led to the accumulation of high levels of radiological deformity measurements. In previous studies, in patients with cam morphology, NSA has been shown to cause increased stress on the hip and has been reported to have smaller values in patients with symptomatic impingement syndrome. Our findings demonstrated that NSA had a positive correlation with only min. hip IR and mean hip IR of the kinematic values. The reason for this may be that the post-slip deformity does not consist only of the impingement deformity, it is because the femoral head and femoral neck are not on the same plane due to sliding and consequently, the hip's center of rotation has changed [22].

In our study, no correlation was found between kinematic and kinetic values and the alpha angle, which is one of the most important radiologic impingement criteria widely used in clinical practice. It seemed that the alpha angle did not correlate with gait functions. There are two possible reasons for this. One of them is the measurement method, and the other one is about the compensation mechanism. In the description by Nötzli, which is widely cited in studies, the center of the femoral neck and the center of the femoral head are on the same axis [16]. However, the femoral neck axis does not pass through the center of the femoral head after an epiphyseal slip. In this case, the line parallel to the femoral neck axis can be used. However, this measurement yields different results than the angular values measured by the line connecting the midpoint between the narrowest level of the femoral neck and the center of the femoral head [16,23]. Therefore, we must be careful when planning surgical treatment of head-neck deformity with open or arthroscopic osteoplasty.

Clinical examination and radiological findings, as it is in patients with SCFE, may not affect the patient's score and quality of life on the short term. In this dynamic deformity seen in the growth phase, hip motions and patient scores are not related only to the slip-angle. For example, in patients with SCFE with moderate and severe slip, the decrease in hip joint ROM was found to be the same, which was linked to metaphyseal changes in the femoral neck during remodeling [24]. In addition to this information, it has been demonstrated that both short-term improvement in patient's score and radiologic deformity can be achieved with corrective osteotomies [23]. It has also been shown that a corrective osteotomy may be useful to prevent possible hip arthrosis in long-term follow-ups [24]. However, these treatments may continue to be ineffective. Diab et al. could not detect differences in follow-up scores of in situ pinning from osteotomy groups after 7 years of follow-up [25]. Proximal femoral osteotomy surgery that provides alignment without correcting the contour of the head and neck junction may be the reason. Open or arthroscopic removal of the metaphyseal hump in the head and neck junction after a slight slip that does not cause serious alignment deformity may provide adequate joint motion and most importantly impingement treatment. However, both the provision of head and neck contour and alignment surgery may be considered in the surgical planning of patients with severe slip. Since patients show both radiological and clinical normalization due to remodeling in follow-ups, it makes treatment choices more complicated. Therefore, a clear understanding of the effect of this dynamic deformity on hip function through reliable radiologic and functional

measurements, is of critical importance before any surgical intervention.

The main limitation of this study was that most patients in our study group did not have severe slipped epiphysis. The mean slip-angle of our study population was relatively moderate. However, we applied the same treatment to these patients and evaluated a relatively homogeneous patient population compared with a matched control group. In addition, we evaluated all aspects of hip deformity in patients with SCFE such as slip-angle, alpha angle, tilt indexes (lateral and anteroposterior femoral head ratio), articulotrochanteric distance, and femoral neck/shaft angle. This study is the first in the literature evaluating all aspects of hip deformity and its correlation with three-dimensional GA compared with healthy individuals. Our study may guide further studies when evaluating the association between gait function and patients' clinical and radiological outcomes.

Conclusion: According to our results, the clinical scores of patients treated for SCFE were mostly correlated with pelvic tilt ROM, FPA, and spine tilt. Compensatory mechanism in pelvic tilt and spine tilt, as well as external rotation of the foot, is significantly associated with clinical scores. LFHR and ATD were observed as the most essential radiological measurements related to the patient's gait function.

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RESEARCH ARTICLE

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Efficacy of prophylactic calcium dobesilate in renal ischemia-reperfusion injury in rats

Ratlarda böbrek iskemi-reperfüzyon hasarında proflaktik kalsiyum dobesilatın etkinliği

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ABSTRACT

Aim: In this study, the objective was to investigate the protective effect of calcium dobesilate, which has antioxidant and anti-inflammatory properties, on the experimental renal ischemia-reperfusion injury (IRI).
Methods: Twenty-four male Wistar-Albino rats were divided into three groups: Sham group (Group 1), ischemia-reperfusion group (Group 2), and treatment group (Group 3). Before the ischemia-reperfusion procedure, rats in Group 3 received calcium dobesilate through gavage (100mg/kg/day) for 10 days. Groups other than the sham group underwent ischemia for 45 minutes and reperfusion for 24 hours. Plasma urea and creatinine levels, erythrocyte superoxide dismutase and glutathione peroxidase enzyme activity levels were measured. In addition, histopathological changes that may be related to ischemia-reperfusion injury in the renal tissue, were investigated.
Results: The median glutathione peroxidase and superoxide dismutase enzyme levels were higher in Group 2 compared to Groups 1 and 3. However, the differences were not statistically significant. The creatine levels were statistically lower in Group 3 compared to Group 1 and Group 2. The median urea levels were lower in Group 3 than in Group 1 and Group 2, but the differences were not statistically significant. The histopathological examination showed that parameters such as cellular necrosis, flattened tubular epithelial cells, cytoplasmic vacuolization, tubular lumen obstruction, and chronic inflammation, which are indicators of the ischemia-reperfusion injury, were statistically less common in the treatment group compared to the control group.
Conclusion: Our study demonstrated that prophylactic calcium dobesilate had a protective effect on ischemia-reperfusion injury.

Keywords: Renal, ischemia-reperfusion, calcium dobesilate, prophylactic.

ÖZ

Amaç: Çalışmamızda, antioksidan ve antienflamatuvar özellikleri olduğu bilinen, kalsiyum dobesilatın deneysel böbrek iskemi-reperfüzyon hasarı (IRI) üzerindeki koruyucu etkisini araştırmayı amaçladık.
Yöntemler: 24 adet erkek Wistar-Albino rat üç gruba ayrıldı; sham grubu (grup 1), iskemi-reperfüzyon grubu (grup 2) ve tedavi grubu (grup 3). İskemi-reperfüzyon işlemi öncesi Grup 3'e 10 gün boyunca 100 mg/kg/gün kalsiyum dobesilat gavaj yolu ile verildi. Sham grubu haricindeki gruplara 45 dakika iskemi ve 24 saat reperfüzyon uygulandı. Plazma üre ve kreatinin düzeyleri, eritrosit süperoksit dismutaz ve glutatyon peroksidaz enzim aktivite düzeyleri çalışıldı. Ayrıca böbrek dokusundaki iskemi-reperfüzyon hasırına ait olabilecek histopatolojik değişiklikler incelendi.
Bulgular: Grup 2'de ortanca glutatyon peroksidaz ve süperoksit dismutaz enzim düzeyleri Grup 1 ve Grup 3'den daha yüksekti, ancak istatistiksel anlamlı değildi. Grup 3'de kreatinin düzeyleri Grup 1 ve Grup 2'den istatistiksel olarak anlamlı derecede daha düşüktü. Ortanca üre değerleri Grup 3'de Grup 1 ve Grup 2'den daha düşüktü ancak istatistiksel olarak anlamlı değildi. Histopatolojik incelemede; kontrol grubu ile kıyaslandığında tedavi grubunda, hücre nekrozu, tübüler epitelyal hücre düzleşmesi, sitoplazmik vakuolizasyon, tübüler lümen obstrüksiyonu ve kronik inflamasyon gibi iskemi-reperfüzyon hasarının göstergesi olan bu parametrelerin istatistiksel olarak anlamlı derecede daha az olduğu gözlendi.
Sonuç: Çalışmamız, proflaktik kalsiyum dobesilatın böbrek iskemi-reperfüzyon hasarında koruyucu etkilerinin olduğunu göstermiştir.

Anahtar Kelimeler: Renal, iskemi- reperfüzyon, kalsiyum dobesilat, proflaktik

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INTRODUCTION

In the recent years, a pathological condition called ischemia-reperfusion injury (IRI) became a common discussion topic depending on the gradually increasing popularity of surgeries like kidney transplantation, nephron-sparing surgery, renal artery surgery, and aorta surgery, which cause a transient decrease in the renal blood flow.

The blood flow to the kidneys is temporarily obstructed during various surgical interventions comprising the clamping of the renal artery or aorta above the renal artery and kidney transplantation [1]. This obstruction may cause ischemic injury in kidneys. Although organ reperfusion following ischemia may decrease the existing injury, it may adversely affect several cellular processes emerging due to the reperfusion. The severity of the injury may lead to organ dysfunctions [2, 3]. Hypoxia, inflammatory cytokines, and free oxygen radicals are the underlying factors of the renal IRI. The involvement of the increased free oxygen species and inflammation lead to cell death [4,5]. Therefore, inflammatory cytokines, free radicals, and oxidative damage are the target of the therapeutic approaches [6].In this context, several agents had been investigated up to the present.

Calcium dobesilate (CD) (calcium 2,5-dihydroxybenzene sulfonate, CLS 2210) is currently used in three major indications (chronic venous insufficiency, diabetic retinopathy, and hemorrhoidal attacks) depending on its angioprotective and antioxidant properties [7]. It is classified under the venotonic and vasculoprotector agents [8]. In Turkey, calcium dobesilate (Doxium®, 500mg capsule, Abdi İbrahim İlaç Sanayi) is approved for the chronic venous insufficiency and used in the treatment of lower extremity venous insufficiencies and diabetic retinopathy for approximately 30 years. Besides, it is used as an adjuvant agent in the treatment of arteriovenous circulation disorders and hemorrhoidal disorders.

Depending on its protective effect against IRI in the skeletal muscle, small intestine and liver, several studies had been conducted to investigate the effects of CD on the preservation of the ischemic skin flaps, diabetic retinopathy, myocardial infarct, and the heart muscle during the cardiac surgery and erectile disfunction. However, there is no study in the literature related to its protective effects against renal ischemia-reperfusion injury. In our study, our objective was to investigate the effects of CD on antioxidants like superoxide dismutase (SOD) and glutathione peroxidase (GPx); on renal function test parameters like urea and creatine and the histopathological changes in respect of IRI.

MATERIAL AND METHOD

This experimental study was approved by the Local Ethics Committee for the Animal Research of the Medical Faculty at AbantİzzetBaysal University by written permit numbered (2009/35).

Twenty-four adult male Wistar-Albino rats (300-360g) were enrolled in our study. The animals were exposed to 12-hour light and 12-hour darkness and followed in separated cages under room temperature (22°C). All subjects were fed with standard rat food and tap water for 10 days. The cages were cleaned regularly.

The anesthesia induction was performed with intramuscular ketamine HCl (40mg/kg; 50mg/cc; Ketalar®; Parke-Davis) and 2% xylazine HCl (10mg/kg; 23.32mg/cc; Rompun®; Bayer) combination. After the first laparotomy, postoperative paracetamol (1-2mg/ml added to drinking water; Parol®; AtabayKimya) was added to the analgesic effect of xylazine HCl. Renal ischemia was created with an atraumatic microvascular clamp placed on the right renal artery. Blood samples were taken from vena cava inferior for the measurement of hemoglobin, GPx, SOD enzyme, urea, and creatine levels. The samples were stored in a deep-freezer at -80°C.

GROUP 1 (n=8, sham group) and GROUP 2 (n=8, control=ischemia-reperfusion group) were monitored without administration of any treatment for 10 days. GROUP 3 (n=8, treatment group) received calcium dobesilate with a dose of 100mg/kg/day, which was dissolved in 0.5cc drinking water and administrated through intragastric gavage for 10 days. After 10 days, only in GROUP 1, laparotomy was performed with a laparotomic incision and right nephrectomy was carried after 24 hours following blood collection. Ischemia was performed in the renal artery in GROUP

2 and GROUP 3 for 45 minutes. 24 hours later blood samples were obtained from all subjects before the right nephrectomy. Tissue samples were inserted in a 10% formaldehyde solution for the histopathological examination. After the experiment, all animals were sacrificed with decapitation.

Urea and creatinine levels (mg/ml) were measured in an autoanalyzer (Abbott Architect Ci 8200, Chicago, IL, USA) using the kits manufactured by Abbott (Chicago, IL, USA). The erythrocyte enzyme activity was measured with the commercial kitRansod (Randox Laboratories Ltd., SD125 Ransod, UK), the erythrocyte GSH-Px activities were measured in an autoanalyzer (Olympus AU-600, Tokyo, Japan) with the commercial kit Ransel (Randox Laboratories Ltd., 505 Ransel, UK) in U/g Hb.

Regarding the histopathological examination, tissue samples stored in a 10% formaldehyde solution were embedded in paraffin blocks and cut at 5μm thickness. All sections were stained with hematoxylin-eosin and examined under a light microscope by an investigator blinded for the samples. The scoring was done according to a modification of the semiquantitative scale described by Paller et al. for the assessment of the changes in the acute renal failure [9].

According to this scale:

1-Chronic inflammation (none/mild, moderate, severe/diffuse)

2-Flattened tubular epithelial cells (none/mild, moderate, severe/diffuse)

3-Cytoplasmic vacuolization (none/mild, moderate, severe/diffuse)

4-Cellular necrosis and ischemic changes (none/mild, moderate, severe/diffuse)

5-Tubular lumen obstruction (none/mild, moderate, severe/diffuse)

The Statistical Analysis

The normal distribution of the measured levels was analyzed with the Shapiro-Wilk test. We determined that parameters other than SOD and GPx values were not normally distributed. The descriptive statistics were expressed according to the compatibility with the normal distribution and quantitative variables were expressed with mean±standard deviation or median (deviation between quarter values; Interquartile Range-IQR) and qualitative variables were expressed with numbers. The 5-point scoring system, which had been used in the histopathological examinations, was converted to a 3-point scale to enable statistical analysis and facilitate interpretation (0=none or mild change; 1=moderate change; 2=severe/diffuse change). During the intergroup comparisons, normally distributed variables were analyzed with the one-way analysis of variance (ANOVA) and non-normally distributed variables with the Kruskal-Wallis variance test with the non-parametric correspondence. To assess the origin of the detected differences, paired comparisons were performed with the Bonferroni posthoc test or Bonferroni-corrected Mann-Whitney U test. For the intergroup comparison of the categorical variables, Chi-square or likelihood ratio values were used. Statistical analysis was done with SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software package. A score of $P \leq 0.05$ was considered as statistically significant.

RESULTS

We determined that the mean SOD value was higher in the control group compared to the sham group. Even though the mean SOD value was lower in the treatment group than the control group, there was no statistically significant difference. We found that the mean GPx value was higher in the control group than the sham group and lower in the treatment group than the control group. However, there was no statistically significant difference between the groups for the GPx value. Urea levels were highest in Group 1 and lowest in Group 3, which was the treatment group. However, there was no statistically significant difference between the three groups. The creatine levels were higher in Group 2 compared to Group 1 and Group 3. The median creatine level was lower in the treatment group than the sham group (Table 1). It was determined that the median creatine value at least in one of the experimental groups was statistically higher compared to other groups. According to the results of the post hoc paired comparison of the creatine levels in the experimental groups, there

was a statistically significant difference between control and sham and treatment groups (Table 2).

Table 1. The SOD, GPx, urea, and creatinine levels in the study groups.

	Urea level (Median/ IQR)	Creatine level (Median/ IQR)	SOD level (mean±SD)	GPx level (Mean±SD)
Group 1	36/32.5	0.54/0.53	2036.39 ± 103.81	20.58 ± 12.54
Group 2	37.5/34.0	0.57/0.55	2168.97 ± 192.52	24.87 ± 14.16
Group 3	34.5/26.5	0.53/0.50	2076.15 ± 204.88	22.19 ± 8.98
X2*	2.239	11.105		
F**			1.237	0.262
P	0.326	0.004	0.311	0.772

Abbreviations: SOD, superoxide dismutase; GPx, glutathione peroxidase; SD, standard deviation; IQR, Interquartile Range

* The result of the Kruskal-Wallis non-parametric variance analysis

* * The result of the ANOVA one-way variance analysis

Table 2. Post hoc paired comparison of the creatine level per experiment groups

	Group 2		Group 3	
Group 1	Z	P	Z	P
Group 2	2.774	0.005	1.333	0.195
Group 3			2.743	0.005

We found also that there was a statistically significant difference between the groups for the distribution of all histopathological variables (Table 3).

Chronic inflammation: While there was a statistically significant difference between sham and control groups (X2=6.904; p=0.009); and between the control and treatment groups (X2=4.857; p=0.028), there was no statistically significant difference between the sham and treatment groups (X2=0.255; p=0.614). The chronic inflammation scores of the treatment and shame groups were similar. While the control group had the highest chronic inflammation score, the chronic inflammation score of the treatment group was considerably close to the score of the Sham group.

Flattened tubular epithelial cells: While there was a statistically significant difference between the Sham and control groups (X2=22,181; p<0.001); and between the control and treatment groups (X2=15,451; p<0.001), there was no statistically significant difference between the sham and treatment groups (X2=3,059; p=0,080).

Table 3. The distribution of the histopathological changes per experiment groups

		Group 1 (n:8)	Group 2 (n:8)	Group 3 (n:8)	P
Chronic inflammation	None/mild	4	0	3	0.026
	Moderate	4	8	5	
	Diffuse	0	0	0	
Flattened tubular epithelial cells	None/mild	8	0	6	<0.001
	Moderate	0	5	2	
	Diffuse	0	3	0	
Cytoplasmic vacuolization	None/mild	5	0	0	<0.001
	Moderate	3	2	6	
	Diffuse	0	6	2	
Cellular necrosis	None/mild	8	0	1	<0.001
	Moderate	0	5	6	
	Diffuse	0	3	1	
Tubular lumen obstruction	None/mild	8	0	4	<0.001
	Moderate	0	2	4	
	Diffuse	0	6	0	

Cytoplasmic vacuolization: There was a statistically significant difference between the Sham and control groups (X2=15,451; p<0.001); between the control and treatment groups (X2=10,723; p=0,005); and between the sham and treatment groups (X2=4,186; p=0,041).

Cellular necrosis: While there was a statistically significant difference between the sham and control groups (X2=22,181; p<0.001); and between the control and treatment groups (X2=15,902; p<0.001), there was no statistically significant difference between the sham and treatment groups (X2=2,524; p=0,283).

Tubular lumen obstruction: There was a statistically significant difference between the sham and control groups (X2=22,181; p<0.001); between the control and treatment groups (X2=6,904; p=0,009); and between the sham and treatment groups (X2=14,543; p=0,001).

DISCUSSION

IRI is an adverse process that may lead to acute renal failure [10]. IRI may emerge as a result of certain surgical interventions [1]. The re-establishment of blood flow to the tissue following ischemia may only completely prevent the development of injury

but also may increase the tissue injury related to the reperfusion [11]. Regarding the prevention of IRI, several methods such as inhibition of the calcium diffusion into the cells, bonding to calcium, inhibition of the development of the free oxygen radicals, suppression of the neutrophil functions, and inhibition of the lipoxygenase and cyclooxygenase pathways had been suggested [12]. In these context; several agents like antioxidants, carnitine, aminoguanidine, calcium channel blockers, immunosuppressants, PDE3 inhibitors, and vitamin E had been investigated.

Some studies conducted with CD, which is classified under the venotonic and vasculoprotective agents, showed that CD has free oxygen species scavenging and decreasing properties along with the antioxidant capacity [13, 14]. It increases NOS activity in macro- and microvascular endothelial cells and decreases the capillary endothelial cell desquamation depending on its effects on the NO synthesis and release [15]. Furthermore, it inhibits the platelet aggregation, decreases the blood viscosity, erythrocyte aggregation, and rigidity. As a result of these effects, it may prevent blood stasis, vascular obstruction, and ischemia [16, 17].

Several studies had been conducted with CD to demonstrate its effects on the ischemia-reperfusion injury in different doses in organs like heart, eye, lung, muscle, and penis with conflicting results. However, there is no published study in the literature related to its effects on renal ischemia-reperfusion injury. In our study, we preferred a dose range of 100mg/kg/day based on a study on antioxidant and angioprotective effects of CD in diabetic rats [13].

Cihan et al. [18] investigated the effects of CD on the myocardial ischemia-reperfusion injury and observed that the change in the mean coronary artery pressure was significantly higher in the group, in which patients had undergone calcium dobesilate perfusion. They reported that this effect might be explained with the increase of the vasodilator substances originating from the endothelium. In their study, İşkesen et al. [19] investigated the prevention of the myocardial injury during the cardiac surgery and observed that the levels of CK, CK-MB, myoglobin, and troponin-T, which are biochemical markers for the myocardial injury, were lower in the group, in which patients received oral calcium dobesilate for 14 days, compared to the control group. In addition, the lactate level in the blood samples taken after the reperfusion was significantly lower. They concluded that calcium dobesilate had positive effects regarding the reduction of the myocardial injury and preservation of myocardium.

In their study, Rota et al. [20] administered 100mg/kg/day calcium dobesilate to diabetic rats for 10 days and showed that the retinal albumin leak decreased about 70% and retinal VEGF expression about 69.4%. They suggested that calcium dobesilate stabilized the blood-retina barrier in diabetic retinopathy depending on it's in situ antioxidant activity. In a similar study conducted by Szabo et al. [21] on diabetic rats, it was concluded that calcium dobesilate was effective in the prevention of the retinal injury mediated by free oxygen radicals and induced by ischemia-reperfusion.

In a study conducted on Guinea pigs, inflammation was created with the subdermal implantation of microscope glass and then CD was administered to observe its anti-inflammatory effects. They concluded that CD had an anti-inflammatory effect probably depending on the blocking of the activity of the macrophage-activating factors and more probably depending on the stimulation of the faster production of the macrophage-deactivating factors like TGF beta-1 and 2, which decreases the number of the circulating monocytes [22].

In our study, we observed that the plasma levels of urea and creatine, which are indicators of the renal glomerular dysfunction, were lower in the treatment group compared to the control group. These low levels were statistically significant for creatine but not for urea. The SOD and GPx enzyme activities were at the highest level in the control group. This finding depended on that the control group was exposed to the highest level of ischemic injury compared to other groups. Although the SOD and GPx enzyme activities were not statistically significant, their level in the treatment group was lower than the control group and higher than the sham group. As a result of this, it might be suggested that the treatment group

was less exposed to IRI than the control group. Histopathologically; cellular necrosis, flattened tubular epithelial cells, cytoplasmic vacuolization, tubular lumen obstruction, and chronic inflammation, which are markers of the ischemic changes, were less severe in the treatment group compared to the control group. They were similar to the sham group in the treatment group (Figure 1).

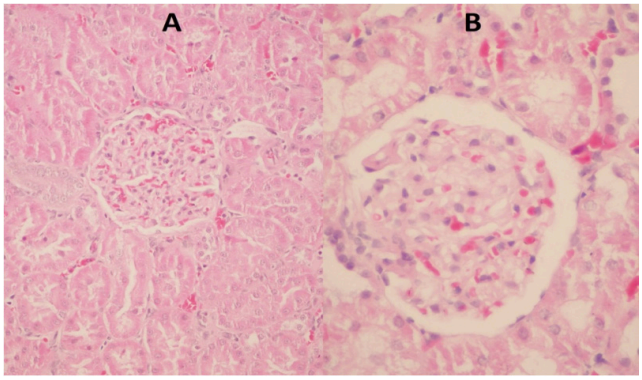

Figure 1:The Sham group showed normal renal cortical tissue structure(HE x 100) (A), Histopathological findings similar to sham group in the treatment group (HE x 200) (B).

The most important limitation of our study is that we did not measure the SOD and GPx levels in the tissue samples. Another limitation of the study is the experimental study.

CONCLUSION

Although there is no study in the literature focused on the prophylactic calcium dobesilate use in the renal ischemia-reperfusion injury yet, the results of our study indicated that prophylactic calcium dobesilate might be used for the reduction of the renal injury caused by ischemia-reperfusion. Further studies with different posology and duration are needed to support our results.

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Conflict of Interest: The author has no conflict of interest related to this article.

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Risk factors and surgical treatment methods in femoral hernia

Femoral Hernide Risk Faktörleri ve Cerrahi Tedavi Yöntemleri

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ABSTRACT

Aim: Femoral hernias are more common in the right groin and in the female population. Elective hernia surgery after diagnosis is the most suitable option for femoral hernias, due to fewer complications and shorter length of hospitalization. In this study, we analysed the factors affecting clinical outcomes in patients undergoing urgent or elective early surgery, due to femoral hernia.

Materials and methods: In this retrospective study, all elective and urgent femoral hernias that were operated between January 2017 and January 2020 were analysed. Routine imaging tests were not applied to the patients and ultrasonography (USG) was applied in the presence of clinical suspicion.

Results: 38 femoral hernia patients were operated on during the 3 years observation period. According to the type of surgery, 30 patients underwent hernia repair with mesh and 8 patients underwent suture repair. Of the 28 patients operated electively, 5 were male and 23 were female. 17 of the patients were right and 11 were left femoral hernia. Of the 10 patients who were operated urgently due to strangulation or incarceration, 4 were male and 6 were female. 7 of the patients were right and 3 were left femoral hernia. 3 of the urgently operated patients underwent intestinal resection due to strangulation.

Conclusion: Femoral hernias were more common in women and especially in the right side, and emergent femoral hernia surgery resulted in more intestinal resection and longer patient hospitalization. In particular, we think that the application of USG with physical examination in women will increase the diagnosis rates of femoral hernias. In addition, we think that the diagnosis of preoperative femoral hernia will decrease recurrence rates by choosing the right surgical technique.

Keywords: Hernia, femoral hernia, inguinal hernia

ÖZ

Amaç: Femoral fıtıklar sağ kasıkta ve kadınlarda daha sık görülürler. Daha az komplikasyon ve yatış süresi sebebiyle femoral fıtık olgularında teşhis sonrası erken elektif fıtık cerrahisi en uygun seçenektir. Bu çalışmada femoral fıtık nedeniyle acil ya da elektif erken ameliyat edilen hastalarda klinik sonuçlara etki eden faktörleri araştırdık

Gereç ve yöntemler: Bu retrospektif çalışmada Ocak 2017-Ocak 2020 tarihleri arasında ameliyat edilen femoral fıtıklar incelendi. Hastalara rutin pre-op görüntüleme yöntemleri kullanılmamakla beraber klinik şüphe varlığında ultrasonografi (USG) uygulandı.

Bulgular: 3 yıllık süre içinde 38 femoral fıtık hastası ameliyat edildi. Ameliyat tipi olarak 30 hastaya yamalı onarım, 8 hastaya yamasız onarım uygulandı. Elektif olarak ameliyat edilen 28 hastanın, 23'ü kadın 5'i erkekti. Hastaların 17'si sağ 11'i sol femoral fıtıktı. Acil olarak ameliyat edilen 10 hastanın 6'sı kadın, 4'ü erkekti. Hastaların 7'si sağ 3'ü sol femoral fıtıktı. Hastaların post-operatif ortalama hastane yatış süresi 143 saatti. Hastaların 3'üne strangülasyon nedeniyle bağırsak rezeksiyonu uygulandı.

Sonuç: Femoral fıtıklar kadınlarda ve özellikle sağ kasıkta daha sık saptanmış; acil uygulanan femoral fıtık cerrahisi daha fazla bağırsak rezeksiyonu ve uzun hasta yatış sürelerine yol açmıştır. Özellikle kadınlarda USG'nin fizik muayene ile birlikte uygulanması gözden kaçabilecek femoral fıtıkların teşhis oranlarını artıracağını düşünmekteyiz. Ayrıca preoperatif femoral fıtığın teşhisinin, doğru ameliyat tekniği seçimiyle nüks oranlarını da düşüreceğini düşünmekteyiz.

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INTRODUCTION

Inguinal hernias are 9 to 12 times more common in males than females, but femoral hernias occur 4 times more in females [1]. This difference can be explained by the longer distance between pubic tubercle and the internal inguinal ring and a wider rectus abdominis muscle in women [2].

Inguinal and femoral hernias are more common in the right groin. This situation is thought to be caused by the delay of closure of the processus vaginalis, due to the later descending of the right testicle to the scrotum during fetal development. It is also thought that the position of the sigmoid colon reduces the development of hernia on the left, by creating a barrier in front of the left femoral canal.

Diagnosis of femoral hernias is difficult [3,4] and although only a physical examination is sufficient for deciding on surgery for a groin hernia, ultrasonography (USG) helps in cases such as obesity, occult hernias, femoral hernias and concurrent hernias [5]. USG also shows high sensitivity for inguinal - femoral hernia separation, in particlular in groin hernias in women. But even in cases where physical examination and ultrasound are combined, femoral hernias can be overlooked [3,4,6].

Since strangulation and incarceration are more common in femoral hernias, “close follow-up” is not among the treatment options, unlike inguinal hernias. Elective hernia surgery after diagnosis is the most suitable option for femoral hernias due to less complications and length of hospitalization [7-13].

In this study, we analysed the factors affecting clinical outcomes in patients undergoing urgent or elective early surgery, due to a femoral hernia.

MATERIALS AND METHODS

The present study was a single-center retrospective analysis and after obtaining permission from the hospital ethics committee with the certificate number 2018/0139, groin hernias operated on between 2017 and 2020 were examined. There were 38 femoral hernia patients among 1650 emergency and elective operated groin hernias, and these patients were included in the study. All patients over the age of 18 who were operated for an urgent, elective, recurrent or primary femoral hernia (Figure 1) were included in the study. Age, gender, hernia type and side, imaging method used for the diagnosis of hernia, ASA scores and surgical procedures were analyzed from the hospital system and patient files. All patients were invited for outpatient control at post-op 1st week, 1st month and 6th month. The control method was a physical examination, but in case of clinical suspicion, other imaging methods, primarily USG (Figure 2), were also used.

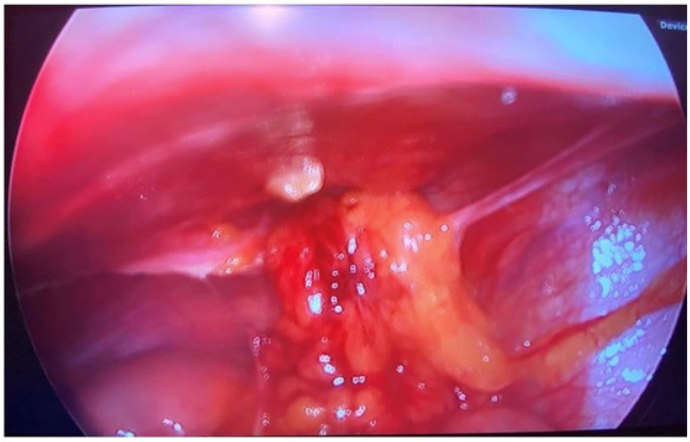

Figure1. Laparoscopic view of omental strangulation

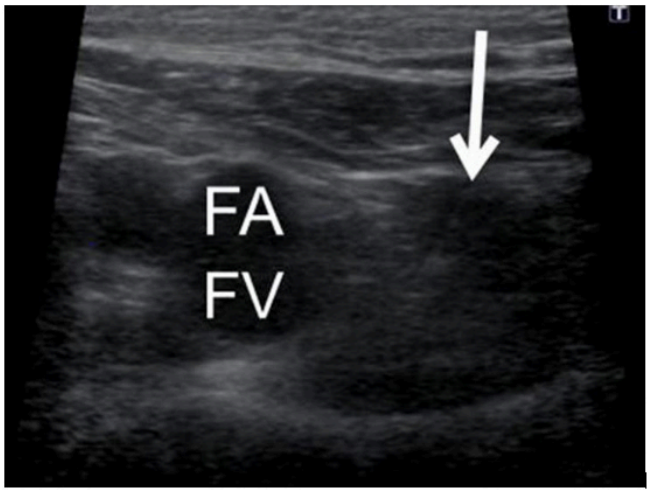

Figure 2. US imaging below inguinal ligament in the axial plane demonstrate herniation sac protursion (arrow) just medial to the femoral artery/vein (FA/FV)

The patients were divided into two groups, one as emergency and the other as elective. Data collected between both groups were analyzed comparatively. Data was analyzed with the SPSS Statistics Version 26 using student t test and $P<0.05$ was considered statistically significant.

RESULTS

During the course of three years, 38 femoral hernia patients were operated on. The ratio of all femoral hernia surgeries performed in our clinic to all hernia surgeries was 2.3%. Of the 28 patients operated electively, 5 were male and 23 were female, whereas 17 of the patients were right and 11 were left-sided femoral hernias. 76.3% of the cases were women (p = 0.002) and 63.2% of the hernias were on the right side (p = 0.001), whereas 4 of the patients were operated on due to a recurrent hernia. Preoperative USG examination was performed in 13 of the patients and the rate of preoperative femoral hernia diagnosis with USG was 23%. Surgery was decided upon for 14 patients following only a physical examination. There was no patient who underwent intestinal resection in the elective group. The mean post-operative hospital stay of these patients were 31.3 hours. The mean age of the patients was 59.25 ± 14.7. When ASA risk assessment of all femoral hernia patients was performed, 8 patients were seen as ASA I, 17 patients as ASA II, and 3 patients as ASA III. There was no ASA IV patient. According to the type of surgery, 22 patients underwent hernia repair with mesh and 6 patients underwent suture repair. Regarding the method for surgery with mesh, 8 patients had a Lichtenstein repair, 11 patients had plug mesh repair, and 3 patients had laparoscopic repair (Table 1). In the classification of hernias, 26 of the femoral hernias were Stage I, two were Stage II femoral hernias whereas 4 patients in stage I group were recurrent femoral hernias (Table 2).

Of the 10 patients who were operated urgently due to strangulation or incarceration, 4 were male and 6 were female, 7 of the patients were right and 3 were left sided femoral hernia. One of the patients was operated on due to recurrent hernia and 6 of the patients underwent preoperative USG. The rate of preoperative femoral hernia diagnosis with USG was 17%. One patient was determined to be operated on only following a physical examination, and 3 of the urgently operated patients underwent intestinal resection due to strangulation. The average postoperative hospital stay of these patients was 143 hours. The length of hospital stay was longer in the emergent group and it was statistically significant (p = 0.001). The mean age of the patients was 63.4 ± 17.3 years. When ASA risk assessment of all femoral hernia patients was performed, 9 patients were seen as ASA I,one patient as ASA III and there was no ASA II and ASA IV patients. According to the type of surgery, 8 patients underwent hernia repair with mesh and 2 patients underwent suture repair. All the patients in this group had surgery with plug mesh method (Table 1). In the classification of hernias, 9 of the femoral hernias were Stage I and one was Stage II femoral hernia, whereas one patient in stage I group was recurrent femoral hernia (Table 2).

Table 1: Patients operated with the diagnosis of femoral hernia

		Group 1: Elective	Group 2: Emergent	P Value
Number of patients,(n)		28	10	
Gender	Female	23	6	0,002
	Male	5	4	
Mean age,(y)		59,25±14,7	63,4±17,3	
Hernia Side,(n)	Right	17	7	0,001
	Left	11	3	
Patients performed USG,(n)		13	6	
Femoral hernia diagnosed with USG,(n)		3	1	
Intestinal resection,(n)		0	3	
Length of stay,(h)		31,3±19,2	143±55,6	0,001
ASA Score,(n)	I	8	9	
	II	17	0	
	III	3	1	
Types of hernia repair,(n)	Mesh	22	8	
	Suture repair	6	2	
Types of surgery,(n)	Suture repair	6	2	
	Liectenstein repair	8	0	
	Plug mesh repair	11	8	
	Laparoscopic repair	3	0	

DISCUSSION

Femoral hernias constitute 2 to 4% of all elective and emergent groin hernia surgeries [1]. In our study, the femoral hernia rate was 2.3%. Femoral hernias occur more often in women and on the right groin and similarly, in our study, they were

indeed observed more frequently in women and in the right groin. Unlike inguinal hernias, follow-up is not recommended in femoral hernias since complications and intestinal resections are higher. Elective repair is strongly recommended [8-11]. We also do not recommend follow-up for femoral hernias in our clinic. There were no patients who were being followed up in the emergent group.

Table 2: Distribution of patients according to EHS hernia classification.

	F		R	
	Elective	Emergent	Elective	Emergent
I	22	8	4	1
II	2	1	0	0
III	0	0	0	0

F: Femoral, R: Recurrence, I: <2cm, II: 2-4cm, III: >4cm

Of the patients who had emergent femoral hernia surgery, more intestinal resection and longer hospitalization was observed [7,12,13]. In our study, intestinal resection was performed in 3 cases in the emergent group, which also experienced a longer hospital stay.

In obesity, occult hernias, femoral hernias, and concurrent hernias, USG can be used in addition to physical examination to help diagnosis [5], where it demonstrates a high sensitivity for the diagnosis of femoral hernia, aspecially in women. In our study, preoperative femoral hernia was successfully diagnosed in 18 patients by physical examination and USG together.

However femoral hernias can be missed, even when physical examination and USG are combined [3,4,6]. There may be cases where the presence of inguinal hernia is diagnosed, but the femoral hernia is overlooked or not observed. When we analysed of the groups, 15 of the patients could not be diagnosed with physical examination, and 19 of them, with the combination of physical examination and USG both.

In our study, the diagnosis was inguinal hernia in the previous operation in 4 of the recurrent cases.

Unlike inguinal hernia repair, suture repair is still an acceptable option in femoral hernia repair [5]. There are centers with similar results in terms of recurrence between the two methods [22], as well as series indicating less recurrence rate in mesh repair [17,20]. In our clinic, 30 patients underwent hernia repair with mesh and 8 patients underwent suture repair. Notably, all recurrent hernia cases had undergone repair ith mesh and in such surgeries, there was no difference found between plug mesh and flat mesh repair in terms of recurrence and mesh reaction [20-22]. However, plug mesh fares worse in terms of patient comfort in the following years, causing pain and mass sensation [23,24] and plug mesh has a higher risk of mesh erosion than flat mesh. At the same time, mesh migration is more common in plug mesh than the flat mesh in the first 2 to 3 years. While the mesh shrinkage can be seen up to 20% in flat mesh [25,26], this rate can be up to 90% in plug mesh. Here, ease of use of the plug mesh method for the surgeon comes to the fore. In our study, the plug mesh method was used in 63.3% of hernia mesh surgeries and no recurrence was observed in these patients.

After the anterior repair of inguinal hernias, re-operation is more common in women and femoral hernia was found in about 40% of re-operation cases. These recurrences may be femoral hernias that have been overlooked in the first operation [14-19]. Therefore, laparoscopic repair should be preferred in women and mesh should be placed in such a way that both inguinal and femoral areas are covered[27]. In addition, the recurrence rate of laparoscopic repairs is lower than open repairs [17,20]. We also performed laparoscopic repair in 3 patients and none of these patients were diagnosed with femoral hernias preoperatively.

Limitations: Our inability to compare the repair methods we use in femoral hernias because of the low rate of patients who underwent femoral hernia repair in all groin hernia repairs, can be considered a limitation of this study, however, in literature, large series are not encountered in this regard. Additionnaly, since this study was performed retrospectively, physical examination and USG examinations of the patients were not performed by the same surgeon and radiologist, making the study heterogeneous.

Conclusion: Delays in the treatment of femoral hernias can lead to morbidity and mortality. Surgery should be performed immediately in these patients following diagnosis. Although physical examination alone is considered sufficient in the

diagnosis of femoral hernia, we think that the application of USG pre-operatively in all women and right groin hernias will increase the diagnosis rates of femoral hernias, thereby reducing re-operation rates. In addition, we think that the diagnosis of preoperative femoral hernia will decrease recurrence rates by choosing the right surgical technique.

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Conflict of Interest: The author has no conflict of interest related to this article.

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RESEARCH ARTICLE

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Mid to long term results of surgical fixation of mid-shaft clavicle fractures

Klavikula cisim kırıklarının cerrahi tedavisinin orta-uzun dönem sonuçları

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ABSTRACT

Aim: The aim of the study is to represent surgical and functional outcomes of plate fixation of mid-shaft clavicle fractures (MCF) via anatomical locking plate, in a large patient population including highly active patients.
Methods: We retrospectively evaluated 94 patients surgically treated for MCF between May 1st 2011 and October 30th 2017. Patients with minimum one-year of follow-up were included to the study. The mean follow-up was 42 ± 27.7 months (12 to 83) months. All patients were followed up until radiological and clinical healing was achieved. All fractures were classified according to the OTA classification. Medical charts were retrospectively reviewed for demographic data, cause of injury, time to surgery, athletic activity, operative complications, radiographic and functional healing time. Constant score was applied to patients at final follow-up to evaluate functional outcomes.
Results: The mean age at the time of injury was 31.4±15.4 (11 to 74) years. Ninety-one clavicles (96.8%) demonstrated radiologic and functional healing in a mean of 62 ± 33 days. The mean Constant score at the final follow-up was 91 ± 6.6 (76 to 100). The major underlying cause was sports related injuries (n=53, 56.3%) followed by motorcycle accidents (n=17,18.0%) and low falls (n=12, 12.7%). Forty-three patients (45.7%) were involved in regular athletic activity at least 3 times weekly. The overall complication rate was 19.1% (n=18). The most common complication was implant irritation in 11 patients (11.7%), 6 of which underwent implant removal surgery. The overall non-union rate was 3.2% (n=3).
Conclusion: Operative treatment of displaced mid-shaft clavicle fractures with precontoured locking plate provides high union rates and satisfactory mid to long-term functional outcomes. However, one should consider the significant, potentially serious operative complications.

Key words: mid-shaft clavicle fracture, treatment, anatomical locking plate, athlete, complication

ÖZ

Amaç: Bu çalışmanın amacı klavikula cisim kırıklarında cerrahi tedavinin orta-uzun dönem sonuçlarını, aktivite seviyesi yüksek hastaların dahil olduğu geniş bir popülasyonda değerlendirmektir.
Yöntemler: Klavikula cisim kırığı nedeniyle 1 mayıs 2011 ile 30 ekim 2017 tarihleri arasında cerrahi olarak tedavi edilmiş, en az bir yıl takipli 94 hasta retrospektif olarak incelendi. Ortalama takip suresi 42 ± 27.7 (12 – 83) aydı. Hastalar radyolojik ve klinik iyileşme sağlanana kadar takip edildi. Tüm kırıklar OTA sınıflamasına göre sınıflandı. Hasta dosyaları demografik bilgiler, yaralanma nedeni, ameliyata kadar geçen süre, komplikasyonlar, radyolojik ve fonksiyonel iyileşme zamanları açısından tarandı. Fonksiyonel sonuçları değerlendirmek için hastalara Constant skorlama sistemi uygulandı.
Bulgular: Yaralanma anındaki ortalama yaş 31.4 ± 15.4 (11-74) yıl idi. Doksan-bir klavikula (%96.8) ortalama 62 ± 33 günde radyolojik ve fonksiyonel iyileşme gösterdi. Son takipteki ortalama Constant skoru 91 ± 6.6 (76 -100) idi. En sık altta yatan sebep sporla ilişkili yaralanmalar (n=53, %56.3) ardından motosiklet kazaları (n=17, %18.0) ve düşmeler (n=12, %12.7) olarak saptandı. 43 (%45.7) hastanın haftada en az 3 defa sportif aktivitede bulunmaktaydı. Genel komplikasyon oranı %19.1 (n=18) idi. En sık görülen komplikasyon implant irritasyonu (n=11, %11.7) idi. Bu hastaların altısında implant çıkarma ameliyatı uygulandı. Kaynamama oranı %3.2 (n= 3) olarak hesaplandı.
Sonuç: Klavikula cisim kırıklarının anatomik kilitli plaklar ile cerrahi tedavisi yüksek kaynama oranı ve orta-uzun dönemde başarılı fonksiyonel sonuç sağlamaktadır. Ancak, cerrahi planlanmasında potansiyel ciddi komplikasyonlar göz önüne alınmalıdır.

Anahtar kelimeler: klavikula cisim kırığı, tedavi, anatomik kilitli plak, sporcu, komplikasyon

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INTRODUCTION

Clavicle fractures are seen in approximately 2.6% of all adult fractures and the incidence is rising among adults (1, 2). Sports related injuries account for 45% of clavicle fractures (3) and the treatment of displaced mid-shaft clavicle fractures (MCF) has been evolving in last decades. Traditionally, MCF were treated non-operatively (4), however treatment trends have shifted towards surgery as a result of a non-union rate of up to 15% following non-operative treatment (5, 6). Additionally, surgical treatment results in faster return to activity (7) and non-union and malunion of MCF cause a significant functional deterioration of the shoulder girdle (8). Surgical treatment of MCF allows the anatomical reduction of the clavicle and has been shown to decrease non-union rates and increase the functional outcomes (9). Thus, surgical treatment of MCF is recommended in highly active individuals (10).

Anatomic locking plates are the most widely used implants for surgical treatment (11), although few studies have reported the surgical results of these on high-demand patients (12). Despite the successful results in the treatment, little is known about long-term functional results and complication rates (13). The aim of the study was to represent the mid to long-term functional results of open reduction and internal fixation (ORIF) of MCF, via anatomical locking plate, in a large population that included athletes and high-demand patients.

MATERIALS AND METHODS

The study included patients treated with ORIF for MCF by 5 different orthopedic surgeons between May 1, 2011 and October 30, 2017 in our institution. The Institutional Review Board (IRB) approval was obtained prior to the start of the investigation (IRB: 1/4/2019, 2018-7932). The inclusion criteria were displaced MCF, closed fracture, surgery within four weeks of injury and a minimum one-year of follow-up. Patients with open fractures or a concomitant serious injury causing delayed surgery were excluded. Medical charts were retrospectively reviewed for demographic data, smoking status, athletic activity, cause of injury, time to surgery, operative complications, radiographic and functional healing time. The Orthopaedic Trauma Association (OTA) clavicle fracture classification was used to evaluate MCF on preoperative radiographs (Figure 1) (14). Indications for surgical treatment were displaced/angulated or comminuted fractures and non-unions after 6 months of conservative treatment. Constant shoulder score was used to evaluate functional outcome (15). Patients who had regular workouts 3 times weekly or more was considered as athletes (competitive or recreational) and 94 patients fulfilled the criteria. Patients and their families were informed about surgical and conservative treatment options and they selected the treatment options themselves, after the nature of the procedure was fully explained.

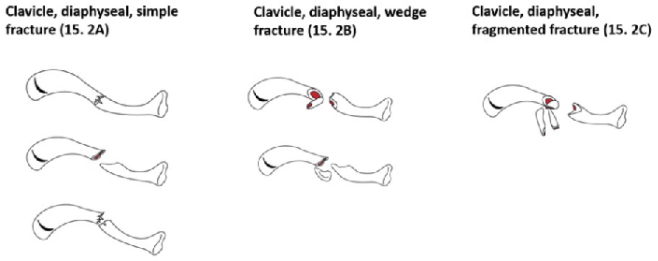

Figure 1. OTA Classification of mid-shaft clavicle fractures

The procedure was performed under general anesthesia in beach-chair position with a pad behind the ipsilateral scapula. A horizontal incision was centered over the fracture site. The supraclavicular nerve, if seen, was dissected and preserved during exposure. The fracture was anatomically reduced and a 3.5 mm anatomical locking plate was applied on the superior side (Depuy Synthes, Rynham, Massachusetts) and interfragmentary screws were used in the presence of a third fragment. The plate was fixed to the clavicle via 3 screws on each end. The quality of reduction and clavicle length was confirmed with the non-operative side on intraoperative radiographs.

Postoperatively, the operative arm was immobilized in a sling for 2 weeks. Pendulum exercises started immediately for 4 times a day, whereas shoulder elevation over 90 degrees and heavy lifting (over 10 pounds) was avoided for the first three weeks. Patients were followed at 1st, 4th and 6th week and then monthly, until the fracture consolidation was obtained (Figure 2). Radiologic evaluation was performed anterior-posterior with a 45 degrees up-tilted radiograph.

Three bridging cortices in these two radiographs were needed for radiographic healing (16). The criteria for functional healing were a non-tender fracture site and painless ROM (17) and once achieved, strengthening exercises were allowed. Return to sports criteria were radiographic and clinical fracture healing, full shoulder ROM and shoulder strength near 100% compared to the uninjured side. Non-union was considered to be the absence of bony bridging at the 6th month's follow-up.

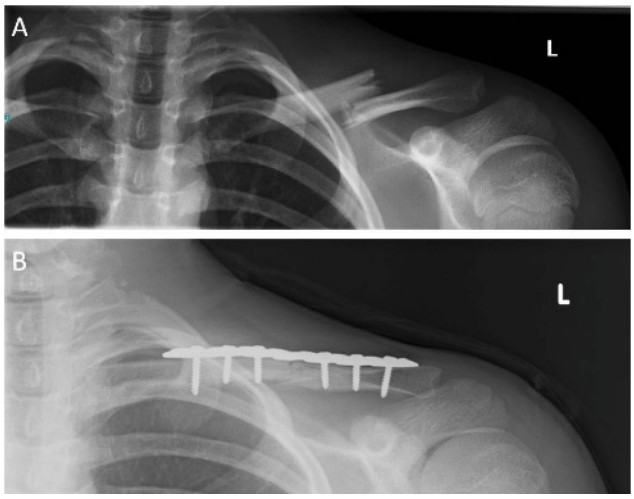

Figure 2. A) Radiograph of a 14-year-old male patient demonstrating OTA 15.2B mid-shaft clavicle fracture with significant shortening. B) Surgical fixation with pre-countered anatomical plate at postoperative 4th week showing bony bridging.

Statistical analysis: Descriptive statistics of continuous numerical variables were expressed as mean ± standard deviation, while categorical variables were expressed as number of patients and percentage.

RESULTS

There were 73 males (77.6%) and 21 females (22.4%) in our study. The left clavicle was fractured in 57 patients (60.6%) and the right clavicle in 37 patients (39.4%). The mean age at the time of injury was 31.4 ± 15.4 years (11 to 74 years old). According to the OTA classification, 11 fractures were classified as subtype 15.2A, 36 fractures were classified as subtype 15.2B and 47 fractures were classified as subtype 15.2C. There were no open fractures and neurovascular injuries at the time of the surgery. The mean time to surgery was 6.6 ± 3.3 days. Forty-three patients (45.7%) had 3 or more regular workouts weekly and were considered to be athletes. Tobacco smoking was noted in 22 of the patients (23.4%) (Table 1).

Table 1. Demographics of the patients

Gender	73 (77.6%) male
Operative side	57 (60.6%) left
Age	31.4 ± 15.4 (11 to 74) years
Athletic status	43 (45.7%) athlete
Smoking status	22 (23.4%) smoker
Classification of fractures	
15.2A	11
15.2B	36
15.2C	47

Sports related injuries was the primary underlying cause (n=53, 56.3%) followed by motorcycle crashes (n=17, 18.0%), motor vehicle accidents (n=12, 12.7%) and low falls (n=12, 12.7%). Associated injuries were noted in 26 patients (27.6%). Rib fractures (n=11, 11.7%) were the most common associated injury followed by pneumothorax (n=5, 5.3%) and scapula fracture (n=4, 4.2%) (Table 2).

Tablo 2. Distribution of the patients according to mode of injuries and additional injuries

Cause of injury	Number (%)
Sports related	53 (56.3%)
Motorcycle crush	17 (18.0%)
Motor vehicle accidents	12 (12.7%)
Low fall	12 (12.7%)
Associated injuries	26 (27.6%)
Rib fracture	11 (11.7%)
Pneumothorax	5 (5.3%)
Scapula fracture	4 (4.2%)
Femur shaft fracture	2 (2.1%)
Iliac wing fracture	2 (2.1%)
Hemothorax	1 (1.0%)
Glenohumeral dislocation	1 (1.0%)
Tibia plateau fracture	1 (1.0%)
Sternum fracture	1 (1.0%)

The mean follow-up was 42 ± 27.7 months (12 to 83 months). Ninety-one patients (96.8%) showed radiologic and functional healing at the final follow-up. The mean time to radiologic union was 62 ± 33 days. The mean Constant score at the latest follow-up was 91 ± 6.6 (76 -100). The mean Constant score was 90.4 ± 6.5 among smokers. One of the 22 smoking patients (4.5%) underwent revision surgery for non-union at 6th month.

Table 3. Distribution of operative complications in study cohort

	N (%)
Complications	18 (19.1%)
Implant irritation	11 (11.7%)
Non-union	3 (3.2%)
Deep infection leading non-union	2 (2.1%)
Hypertrophic non-union	1 (1.0%)
Implant failure	2 (2.1%)
Superficial skin infection	1 (1.0%)
External jugular thrombophlebitis	1 (1.0%)
Brachial plexopathy	1 (1.0%)
Hypertrophic scar	1 (1.0%)

The overall complication rate was 19.1% (n=18) in this study (Table 3). The most common complication was implant irritation in 11 patients (11.7%), 6 (6.4%) of which underwent implant removal surgery. Refracture was noted in 1 patient 3 weeks after the implant removal surgery, that was successfully treated with ORIF. Non-union was observed in 3 patients (3.2%). Two of them suffered a deep infection: those requiring removal of the plate, decortication of the union site, irrigation and debridement. The patients received intravenous antibiotics for 6 weeks and revision ORIF with an iliac bone graft was performed, once the infection was eradicated. One patient suffered hypertrophic non-union at the 6th month and treated with removal of the plate and decortication of the union site: a longer precontoured plate was applied with an iliac bone graft. The most serious complication was an external jugular vein thrombophlebitis in one of the infected patients. Brachial plexopathy was noted in 1 patient following surgery, that was attributed to prolonged preoperative immobilization of the shoulder; nerve symptoms resolved after 6 months of oral gabapentin and physical therapy. Hyperthrophic scar formation was observed in 1 patient. A superficial propionibacterium acne skin infection was treated with intravenous antibiotics in 1 patient. Implant failure was observed in 2 patients, one of which suffered from a mental disability and failed to follow the instructions, whereas the other resulting from a deep infection at the postoperative 2nd week.

DISCUSSION

The treatment of displaced MCF still remains controversial. Since suboptimal outcomes following non-operative treatment methods have been published, surgical treatment methods have become increasingly popular. Recent meta-analyses comparing surgical versus non-operative treatment methods following displaced MCF, revealed lower non-union and malunion rates and superior functional outcomes (18).

We aimed to evaluate mid to long term functional outcomes and examine complications of plate fixation in a population that included patients with a high degree of activity. We found a 96.8% union rate in a mean of 62 ± 33 days. The functional results were satisfactory in mean Constant score (91) at mean follow-up of 42 months. All fractures consolidated at final follow-up and this finding is predictable and parallel to the literature (6, 19). Guerra et al. published a recent meta-analysis of 14 randomized controlled trials comparing surgical versus non-operative treatment of displaced clavicle fractures. They reported lower risk of non-union (10%; 95% CI, 6%-18%, P<0.001) and 5.1 weeks shorter time to union with surgery (P= 0.007). Additionally, long-term functional scores were significantly better in the surgery group: the overall Constant score mean difference was 5.3 points (P<0.001), and the DASH index mean difference was 4.3 points (P =0.04) (20).

The factors affecting the clavicle fracture healing were previously demonstrated (21-23): tobacco smoking, age, female gender and fracture comminution were associated with delayed healing and non-union following clavicle fractures (21). Murray et. al found a 3.76 folds increased risk of non-union in smokers (22). Moreover, Napora et al. reported decreased American Shoulder and Elbow Surgeons (ASES) scores (83.6±18.4 versus 74.1±23.0) indicating that smoking is responsible for decreased functional outcomes following clavicle fractures (23). In our study the rate of tobacco smoking was 23.4%. The mean Constant score was 90.4 ± 6.5 and the complication rate was 22.7% among smokers. However, our study was not designed to study the effect of smoking on fracture healing and outcomes.

Treatment of MCF in highly active individuals and athletes deserves special attention. The aim is always to obtain fracture union and fast return

to activity (10), however, anatomic reduction is mandatory as shortening of the clavicle deteriorates shoulder girdle mechanics and decreases shoulder strength (24). Ranalletta et. al reported a 98% union rate, a mean Constant score of 94.1 and a 94% return to sports rate in 68 days (5 to 180) following plate fixation of 54 displaced MCF (12). Mckee et al. conducted a meta-analysis comparing the functional outcomes of operative and non-operative treatment of MCFs. There were 3 studies using the Constant score. The average Constant score for the operative group was 94.3, and the average Constant score for the non-operative group was 90.2 (n = 222 total patients) at one year (25). In our study, the mean Constant score for surgical treatment for MCF was 91 ± 6.6 at 42 ± 27.7 months follow-up.

Despite the decreased non-union/malunion rates and satisfactory functional outcomes, surgical treatment is associated with a high risk of complications (7) (11) (26). Fridberg et al. reported 30% implant-related complications with non-anatomical locking plates (27). Verborg et al. published a 90% union rate, however this included an 18% wound infection rate and a 5% refracture rate following surgical treatment of the clavicle fracture. In our study, the overall complication rate was 19.1% and the most common complication was implant irritation in 11.7% of patients, that led implant removal surgery in 6.4% of them. The refracture rate was 1.1% and the postoperative infection rate was 3.2% (3 patients). The most serious complication was an external jugular venous thrombophlebitis caused by deep cervical infection in one patient. Overall, 11 patients (11.7%) required secondary surgeries due to operative complications.

Our study has some limitations, the most important one of which was its retrospective design. Additionally, the study lacked a control group and our study cohort was heterogeneous, including trauma patients, motor vehicle accidents and athletes. Surgical indications in different groups might vary, as our threshold for surgical treatment in athletes, for instance, is lower. The strength of our study was a large number of patients from a tertiary center with midterm and long-term functional outcomes. It should be noted that although the study population included many athletes, no sports specific evaluation was performed.

In conclusion, operative treatment of displaced clavicle fractures with precontoured locking plate, provides high union rates and satisfactory midterm/long-term functional outcomes. However, one should consider the significant, potentially serious operative complications.

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Anxiety, protective behaviors and related factors during the COVID-19 outbreak: A cross-sectional study

COVID-19 Salgını Sırasında Anksiyete, Koruyucu Davranışlar ve İlişkili Faktörler: Kesitsel Bir Çalışma

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ABSTRACT

Aim: This study aims to determine the anxiety, personal protective behaviors, and related factors in Turkish society during the COVID-19 pandemic.
Patients and Methods: The sample consisted of 617 volunteer participants aged 18 to 75, living in the community and literate. Research approval, purpose, and questions were delivered to individuals in an online environment using a link and forms were collected by asking the participants to send back the completed questionnaires to the online environment. A COVID-19 data form and the State-Trait Anxiety Inventory (STAI-State) were used to collect the data.
Results: The study evaluated data from the 617 participants: 59.48% (n = 367) of the study participants were female and 40.52% (n = 250) were male. We found increased anxiety levels in the participants, with high levels of anxiety in 30.79% (n = 190). The main personal protective behavior was "washing hands frequently" (84.76%). Personal distance and mask usage rates were low (8.6% and 5.02%, respectively). We found higher anxiety levels in men (p = 0.008), people with chronic diseases (p = 0.003), the elderly (p<0.001) and those with lower education levels (p<0.001). We found higher levels of anxiety in those showing avoidance behaviors.
Conclusions: The results of our study show that psychological consequences should be considered in addition to the physical outcomes of the COVID-19 outbreak and that some subgroups have a higher risk of anxiety. People who require professional support should be identified and psychological support should be planned.

Keywords: COVİD-19, pandemics, anxiety, protective behavior

ÖZ

Amaç: Bu çalışmada COVİD-19 pandemisi sırasında Türk toplumunda anksiyete, kişisel koruyucu davranışlar ve ilişkili faktörleri incelemeyi amaçlanmıştır.
Hastalar ve Yöntem: Örneklemimizi 18-75 yaş arası, okur-yazar, çalışmaya gönüllü 617 birey oluşturmuştur. Araştırma onamı, amacı ve sorular soft ortamda bireylere bir link vasıtasıyla ulaştırılmış ve formlar yine soft ortamda cevaplanan anketlerin iletilmesiyle toplanmıştır. Verilerin toplanmasında, araştırmacılar tarafından oluşturulan COVİD-19 ile ilgili soruları ve sosyo-demografik verileri içeren form ve Durumluk-Sürekli Kaygı Envanteri (STAI-Durumluk) kullanıldı.
Bulgular: Çalışmada 617 gönülle değerlendirilmiştir. Çalışmaya katılanların %59.48 (367)'i kadın, %40.52 (250)'si erkekti. Katılımcıların % 30.79 (190)'unda yüksek seviyede kaygı düzeyleri saptanmıştır. Başlıca gerçekleştirilen kişisel koruyucu davranış yüksek oranda elleri sık sık yıkama şeklindedir. (%84.76). İkinci sıklıkta ise insanlarla en az bir metre mesafe koyma davranışıdır. (%8.6). Katılımcıların %5.02 (31)'i maske takmakta, %1.62 (10) kişi ise hiçbir koruyucu önlem almamaktadır. Çalışmada erkeklerde (p=0.008), tanılanmış kronik hastalığı olanlarda (p=0.003), yaşlılarda (p<0.001) ve daha düşük eğitim düzeyi olanlarda (p<0.001) daha yüksek kaygı düzeyleri saptanmıştır. Kişisel koruyucu davranışlardan kaçınıcı davranış yüksek kaygı düzeyi ile ilişkili bulunmuştur.
Sonuç: Çalışmamızın sonuçları, COVID-19 salgınının fiziksel sonuçlarına ek olarak, psikolojik sonuçların da dikkate alınması gerektiğini göstermektedir. Çalışmamızda bazı alt gruplarda kaygı riski daha yüksek belirlenmiştir. Profesyonel desteğe ihtiyaç duyan insanlar tanımlanmalı ve psikolojik destek planlanmalıdır.

Anahtar kelimeler: COVİD-19, pandemi, anksiyete, koruyucu davranışlar

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INTRODUCTION

Unrecognized pneumonia cases in the city of Wuhan, in the Hubei province of China, were reported in late December 2019 and a new coronavirus with the same origin but different genetic features as the coronavirus that causes of SARS (severe acute respiratory syndrome), was identified [1, 2]. This new coronavirus (2019-nCoV) is thought to have been first transmitted from an intermediate host, likely a bat, to humans, however the facts that the virus has travelled beyond the first place of occurrence and is seen in healthcare workers, confirmed interpersonal transmission through droplets [3]. The International Committee on Taxonomy of Viruses (ICTV) announced the name of this new virus as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) on February 11, 2020 [4]. On January 30, 2020, the World Health Organization (WHO) named it Coronavirus Disease 2019 (COVID-19) and declared it an internationally alarming public health situation, as a pandemic, on March 11, 2020 [5].

COVID-19 spread rapidly all over the world after the first case in China on December 19. In Turkey, the first case was reported on March 10, 2020 and as of April 4, 2020, a total of 24,934 cases had been reported and the number of deaths due to COVID-19 infection was reported to be 501.

This is not the first epidemic the world has recently faced. Previously, epidemics of SARS in 2003, Influenza A H1N1 (swine flu) in 2009, MERS in 2012, Ebola in 2014 and Zika in 2015, have occurred. Studies on anxiety and related factors were also conducted in previous epidemics as pandemic viral diseases are associated with increased anxiety in populations [6, 7]. A study conducted in 2009 with the participation of 6,249 online participants reported high anxiety related to the pandemic emotional variables, such as self-reported anxiety over the epidemic to mediate the possibility of participatory protective behaviors [8]. A community-based study conducted with 1,210 participants in China reported 53.8% of the participants were psychologically affected at different levels, ranging from moderate to severe, in the course of the COVID-19 epidemic [9].

Psychological reactions during a pandemic have the particular potential to cause fear and fear-related behaviors, to accelerate the spread of disease, to reduce life-saving interventions, to intensify psychological distress and to compound psychosocial outcomes [10]. The psychological effects of an epidemic can be more common than its somatic effects, be more destructive, and last longer. In fact, previous research has revealed that the fear of epidemics has more negative effects than the epidemic itself [11].

In the literature, the possibility of people adhering to health recommendations has been reported as being higher if they believe the disease has serious consequences, if the probability of being affected by the epidemic is high, if the disease is difficult to treat, if the proposed behaviors are effective, and if the government provides clear and adequate information about the epidemic; they become more confident in their determination to control the spread of the infection [12, 13].

Although close results have been reported about pandemic-related psychiatric and behavioral responses in different societies, psychological reactions and behavioral responses have been reported to conceivably differ among cultures in pandemic cases [14-16]. As such, studies to be carried out in different cultures in epidemic situations may help in obtaining data from that culture and in taking culture-specific measurements. In this study, we aimed to examine anxiety levels, personal protection behaviors and related factors during the COVID-19 epidemic.

MATERIALS AND METHODS

This cross-sectional study was conducted online, using snowball sampling techniques, from March 23 to March 28, 2020. The online survey was developed using Google Docs and the data was collected through various techniques from social media, namely, Twitter, Facebook and WhatsApp. In total, 617 participants took part in the survey, which allowed for only one response per person. Electronic informed consent was obtained from each participant prior to starting the investigation and participants were able to withdraw from the survey at any moment, without providing any justification. The study was approved by the ethics committee of Alanya Alaaddin Keykubat University Clinical Research. (05.06.2020/19-16).

Instruments and data collection

Data form. This is structured in three parts. The first part involved socio-demographic characteristics (e.g., gender, age, and education level). The second part involves health and disease characteristics (diagnosed diseases). The third part is about characteristics of COVID-19 (information and protection methods).

The State-Trait Anxiety Inventory (STAI): The original inventory was developed in 1970 by Spielberger et al. and consists of 40 items. It has two subscales that measure State and Trait anxieties using a 4-point Likert-type scale. The Turkish validity and reliability study for the scale was performed by Öner and Le Compte in 1985 [17]. Total scores can range from 20 to 80, whereas a higher score obtained on the scale shows higher anxiety and worry levels.

Ercan et al.'s study aimed to determine a cut-off score for the STAI state and trait anxiety subscales to differentiate between healthy adults and those with anxiety disorders. This study found a cut-off value of 41 to be optimal (sensitivity = 78.3; specificity = 71.2) for the STAI-State [18].

In our study, only the State Anxiety Scale was used because of its allowance for describing how the individual feels at a certain time and under certain conditions, and takes into account one's feelings about the situation.

Data Analysis

Frequency and percentage values were calculated for the categorical variables. The Kruskal-Wallis H test was used to compare continuous, independent variables between the two groups and the Mann-Whitney U test was used to compare two independent and non-normally distributed variables. The latter is used for comparing between the two groups whereas the former is used for further group comparisons. Probability ratios and 95% confidence intervals were calculated: p values <.05 were regarded as statistically significant. IBM's (2013) SPSS Statistics for Windows (Version 22.0, Armonk, NY) was used for data analysis.

RESULTS

The participants (N = 617) in the study were categorized according to their age and the majority were in the group of 18 to 25 years old (45.37%). The majority of respondents were female (59.48%), single (58.5%), university graduates (48.75%), with mid-range incomes (48.78%) and no children (60.61%). Some 3% of the participants had traveled abroad in the previous month (see Table 1), whereas 21.55% of the participants were diagnosed with a chronic disease.

Table 1: Participants' Socio-Demographic Characteristics (N = 617)

		n	%
Gender	Female	367	59.48
	Male	250	40.52
Age	18-25	280	45.37
	26-35	101	16.35
	36-45	133	21.55
	46-55	60	9.76
	56 or older	43	6.97
Marital Status	Married	256	41.5
	Single	361	58.5
Economic Status	Income less than expenses	177	28.69
	Income and expenses equal	301	48.78
	Income more than expenses	139	22.53
Education Status	Literate / Secondary school	49	7.94
	High school	179	29.01
	University	301	48.75
	Master and above	88	14.30
Having children	Yes	243	39.39
	No	374	60.61
Traveling abroad in the last 1 month	Yes	18	3
	No	599	9

The responses from the participants regarding their information status and protective behavior regarding COVID-19 are shown in Table 2: 69.21% (n = 427) of the participants declared having low anxiety whereas 30.79% (n = 190) reported having high anxiety.

The participants' mean STAI-State score was 39.44, with the average STAI-State score for men was 39.79. Men declared having higher anxiety levels than women and this gender difference is statistically significant (p = 0.08)

The lower a participant's education level, the higher their anxiety levels. Here again, the difference was statistically significant (p<0.001).

Participants whose income is higher than their expenses had statistically significantly higher anxiety levels than those with worse economic situations (p = 0.022). Those diagnosed with any chronic disease are found to have higher anxiety levels and the difference was statistically significant (p = 0.003) and having knowledge about COVID-19 was associated with having higher anxiety rates (p = 0.017).

The participants were separated into two groups: those with protective behaviors (frequent hand washing) and those with avoidance behaviors (social distancing, wearing mask/gloves). Participants with avoidance behaviors had higher anxiety levels than participants with protective behaviors (p<0.001). When evaluating STAI-State scores in terms of the other variables, no statistically significant relationship was found (see Table 3).

Table 2: Participants' Information Status on COVID 19 (N = 617)

		N	%
Information level on COVID19	None	25	4.05
	Little	243	39.39
	A lot	349	56.56
My primary source of information on COVID 19*	TV	105	17.01
	Internet	324	52.51
	Scientific article	179	29.01
	Friend/relative	9	1.47
The main action taken for protection *	Nothing	10	1.62
	Mask and distance	84	13.62
	Frequent hand washing	523	84.76
COVID 19 affects my mental health	Agree	358	58
	Do not agree	259	42

* Participants could not make more than one selection.

DISCUSSION

As previous studies have shown differences in the psychological reactions and behavioral responses between societies and cultures to be revealed in pandemic situations [15], we aimed to examine anxiety, personal protective behaviors and related factors in Turkish society during the COVID-19 pandemic. our study revealed a high level of anxiety in 30.79% of the participants, which is a result compatible with studies conducted during the COVID-19 infection. Qiu et al.'s study detected psychological stress in 35% of the participants [19] whereas Rubin et al. (2009) reported 23.8% to have major concerns in response to the epidemic in the early stages of the H1N1 influenza outbreak [20].

We found male participants to have higher anxiety levels than the female participants and the difference was statistically significant. Previous studies have found higher levels of anxiety in female participants, which has also been associated with a higher level of anxiety sensitivity in women [19, 20]. The result we obtained may result from the fact that men are often the principal income providers of the family, that they undertake the economic burden and feel responsible for the potential economic consequences of the epidemic. Additional studies are required to further examine these correlations.

A study examining psychological reactions and factors related to the COVID-19 epidemic reported anxiety, depression and stress to be significantly related to chronic diseases [9]. In accordance with the current literature, our study revealed that having a chronic disease significantly relates to anxiety levels; the COVID-19 virus having more negative outcomes for people with advanced age or chronic disease in particular may explain this result.

We found the Internet to be the most common source of information about COVID-19 (52.51%) and this is compatible with other current studies [9]. In addition, the information in these regarding the increase of cases experiencing recovery has been found to be significantly associated with a decrease in stress levels [9].

The studies examining the relationship between anxiety levels and preventive measures have revealed confusing results. Increased anxiety has been positively associated with the possibility of participating in proposed behavioral changes, such as washing hands and disinfecting door handles [21]. One study conducted during the 2003 SARS epidemic found preventative behaviors to positively and significantly relate to moderate anxiety, whereas a recent study during the COVID-19 pandemic has revealed opposite results [9, 22].

Our study has unexpectedly found a relationship between the levels of self-reported knowledge about COVID-19 and anxiety: it appears that as

Table 3: Distribution of Participants' STAI-State Scores (N = 617)

			n	Anxiety Level		Z	p
				Low	High		
Gender		Female Male	367 250	269 158	98 92	-2.665	.008**
Marital Status		Single Married	361 256	247 180	114 76	-0.501	.216
Having children		Yes No	243 374	167 260	76 114	0.209	.835
Traveling abroad in the last 1 month		Yes No	18 599	10 417	8 182	-1.272	.203
Diagnosed with any chronic disease Diagnosed with any chronic disease		Yes No	133 484	74 335	59 149	-2.931	.003**
Attending any training about COVID 19		Yes No	60 557	38 371	22 186	-0.434	.664
Mann-Whitney U, p < 0.001; ** 0.001 ≤ p < 0.01; * 0.01 ≤ p < 0.05							
					Chi-Square	df	p
Age	-25 26-35 36-45 46-55 55 and above	280 101 133 60 43	183 75 94 43 14	97 26 39 17 29	24.747	6	<.001***
Education level	Literate / Secondary school High school University Master and above	49 179 301 88	22 109 216 62	27 70 85 26	18.338	3	<.001***
Economic status	Income less than expense Income and expense equal Income more than expense	177 301 139	107 213 89	70 88 50	7.657	2	.022*
Information level on COVID19	Have not Some Have	25 243 349	15 176 270	10 67 79	10.144	3	.017*
My primary source of info. on COVID 19*	TV, Friend Internet Scientific article	114 324 179	75 220 116	39 104 63	.841	3	.840
The main action taken for protection	Nothing Mask and Distance Frequent hand washing	10 84 523	9 39 361	1 45 162	18.310	2	<.001***
Kruskal Wallis Test, *** p < 0.001; ** 0.001 ≤ p < 0.01; * 0.01 ≤ p < 0.05 STAI: State-Trait Anxiety Inventory (STAI)"							

knowledge about COVID-19 increases, so do anxiety levels. Previous studies have reported similar results on the relationship between zika virus-related information and anxiety [23]. Considering the cross-sectional structure of our study, this may be the result of some participants who already have anxiety about it are coping by seeking additional information about COVID-19. It should be noted that we did not measure actual levels of knowledge about COVID-19 in our participants.

Anxiety levels for individuals with low education levels were significantly higher statistically than those with high education levels and similar results have been reported in previous studies [29]. This result may have different causes, including the possibility that low education levels may foster economic concerns associated with having a low socioeconomic level, and therefore indirectly with the epidemic.

In our study, we have found hand washing to be the most common personal protective behavior and that the use of masks and social distancing between people had rarely been applied. Where protective measures are concerns, different practices emerge from different cultures; for

example, a study conducted in China in 2004 reported the use of masks for protection from the epidemic to be 62.1%, whereas in our study, we found it to be 5.02%. Elsewhere, a community-based study on swine flu in the UK reported that 72% of people did not change the frequency of their hand washing [24]. Additionally, we found higher levels of anxiety in those who exhibited avoidance behaviors and this result is compatible with previous studies in our country, during the swine flu [25].

Our study incurred some limitations, including the fact that the data emerged from cross-sectional studies and that causality cannot therefore be determined. As a result, the associations should be interpreted with caution, as reverse causality cannot be dismissed. Additionally, no psychiatric evaluation was performed on the participants, no details were sought regarding the chronic diseases and measurements were performed using self-reporting scales, which raises the limitations of common method bias.

As a result of our study, however, we have found the existence of a highly increased level of anxiety during a pandemic. As far as we know from previous pandemic studies, the psychological effects of a such an event continue long after it ends, therefore support programs may be needed for those requiring psychological professional help: online during the course of the epidemic and face-to-face afterward. We also showed that the participants had obtained information on the epidemic mostly from the Internet. As shown in previous studies, emphasis on the number of recovery cases and correct information reduces anxiety levels, therefore this type of information flow over the Internet should be provided. In general, we found that the participants mostly performed personal protective behaviors, with hand washing being the most prevalent. More emphasis should be placed on social distancing and the use of masks and gloves.

Strategies such as vaccination and antiviral treatment, hygienic practices, and social distancing are known to play a vital role in controlling the spread of disease during a pandemic. As no effective treatment or vaccine is available yet for COVID-19, hygiene, preventive behaviors, and social isolation have become more important and this also requires changing existing habits and replacing them with specific social behaviors. It also requires the public authority to render important decisions for serious protective measures.

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CASE REPORT

OLGU SUNUMU

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Management of the type-1 heparin induced thrombocytopenia (HIT) in the course of acute inferior myocardial infarction with high thrombus burden

Yüksek trombüs yükü olan akut inferior miyokart enfarktüsü seyrinde gelişen tip-1 heparin ilişkili trombositopeni vakasının yönetimi

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ABSTRACT

Heparin-induced thrombocytopenia (HIT) is a difficult clinical presentation to deal with and we know little about the management of these patients. Stopping of heparin is essential in treatment but some patients may need anticoagulation in the follow-up; however, we do not have enough data about the patients with a need of anticoagulant usage. We want to present a myocardial infarction patient who developed type I HIT after exposure to unfractionated heparin with a need of anticoagulation at the same time.

Keywords: myocardial infarction, heparin administration, heparin induced thrombocytopenia

ÖZ

Heparin ilişkili trombositopeni (HİT) başa çıkılması zor bir klinik tablodur ve bu hastaların yönetimiyle ilgili bilgimiz sınırlıdır. Heparin'in kesilmesi tedavinin esasıdır ancak bu hastaların bir kısmında antikoagülan kullanım ihtiyacı doğabilir ve takibinde antikoagülan ihtiyacı olan hastalarla ilgili net bir veri bulunmamaktadır. Bu yazımızda anfraksiyone heparin sonrasında tip I HİT gelişen ve aynı zamanda antikoagülan kullanım ihtiyacı bulunan miyokart enfarktüsü hastamızın sunumunu yapmayı amaçladık.

Anahtar sözcükler: miyokart enfarktüsü, heparin kullanımı, heparin ilişkili trombositopeni

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INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a challenging clinical disorder, but we have limited data about the management of these patients. Diagnosis is depending on the decreasing of platelet count under 150 000 per mm3 or lower than 50% of the basal level. There are two different types of HIT and they differ from each other regarding prevalence, mechanisms of development, times of onset and clinical presentations. Type II HIT has an immunological mechanism and presents with the development of HIT antibodies. Prevalence of type II HIT is as low as 0.2% in the literature [1]; however, type I HIT can be experienced after the procedures needing high active clotting time levels, such as coronary artery bypass grafting or mechanical valve surgeries. Prevalence of type II HIT is higher and reaches up to 30% after open-heart surgeries [2]. Type I HIT develops as a result of direct toxic effect of heparin on platelets. Type I HIT generally develops in the first few days after heparin exposure; on the other hand, type II HIT is known to have a later onset and starts after 5 days following heparin administration. Clinical presentations also differ between these two types of HIT: type I HIT presents with bleeding, whereas type II HIT presents with typical, reactive thrombosis complications. Stopping of heparin-derived anticoagulants is essential, but we have little evidence about the management of these patients, especially if they need oral anticoagulation in the follow-up. In this paper, we want to present a case of type I HIT patient with a need of oral anticoagulation.

CASE REPORT

A 66 years old male patient admitted to the emergency department with syncope. On his admission electrocardiography (ECG), acute inferior myocardial infarction (MI) with complete AV block was detected. A diagnostic coronary angiography was performed emergently with a temporary percutaneous pacing lead. The right coronary artery (RCA) revealed aneurysmatic anatomy with global thrombosis, and we performed iterative percutaneous balloon angioplasties with diameters of 3.0 and 4.0mm coronary balloons. We were unable to achieve a flow so we administered an intracoronary tirofiban via a microcatheter for perfusion of distal coronary bed. A TIMI-2 flow appeared following the tirofiban bolus, and sinus rhythm was accessed; we noticed ST-segment resolution on 12-lead ECG. We decided to continue the tirofiban infusion and planned a control coronary angiography. On his control coronary angiography, the RCA was still globally thrombosed, but near TIMI-3 flow existed in the distal coronary bed. We planned an oral anticoagulation for high thrombotic burden in the long term.

At the 36th hours of unfractionated heparin administration, the patient developed massive gastrointestinal bleeding, bleeding from the femoral access site, and subcutaneous bleeding from venous indwelling. His hemoglobin level was 6.7gr/dL, and thrombocyte count was 39 000/mm3. Following these results, type-1 heparin-induced thrombocytopenia (HIT) was diagnosed, and all antiplatelet and anticoagulant therapies were stopped, and 5 000IU protamine sulfate was given to him. We replaced four units of whole blood, and the patient became stable hemodynamically. Follow-up hemoglobin and thrombocyte counts were expressed in Figures1 and 2. We started clopidogrel 1x75mg on the day of the thrombocyte count at >50 000/mm3 and rivaroxaban 1x15mg with a thrombocyte count >100 000/mm3. The patient recovered excellently, and we stopped clopidogrel because of severe allergic reaction while continuing with rivaroxaban 1x20mg at the end of the 1st month.

DISCUSSION

Coronary aneurysms can be congenital or can develop secondarily to various conditions such as atherosclerosis, trauma, previous coronary interventions, Kawasaki's disease, mycotic emboli, or systemic lupus erythematosus [3]. Aneurysmatic anatomy disrupts the laminar pattern of coronary blood flow, and this may result in the formation of coronary thrombus. In the setting of acute coronary syndromes following the correction of the blood flow of the distal coronary bed, in most cases with coronary aneurysm, we are not be able to perform stenting because of inappropriate vessel size [4]. Some authors offer the administration of thrombolytic therapy in cases where distal blood

Figure-1: Timeline of hemoglobin follow-up

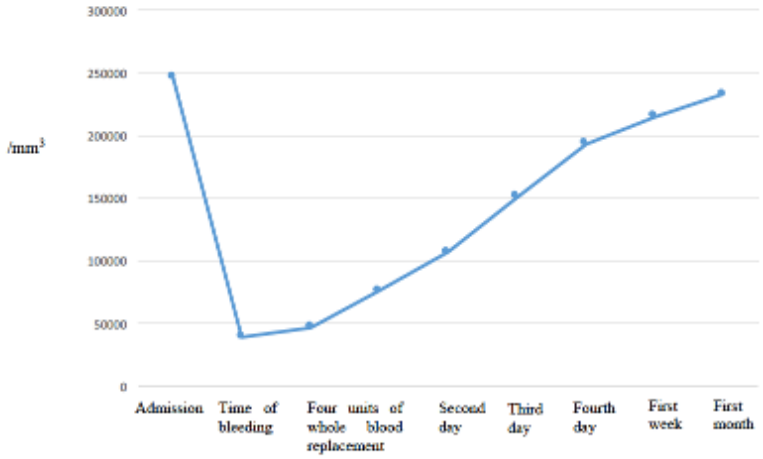

Figure-2: Timeline of thrombocyte count follow-up

flow fails to restore with traditional percutaneous balloon angioplasty techniques [5]. In our patient, the coronary anatomy revealed diffuse aneurysmal dilatation starting from the proximal portion of the RCA and extending distal part of it. We measured the diameter of the RCA as 5.7mm, and we decided that the stenting of this highly thrombosed, long segment aneurysm, might not be the optimal treatment choice. On the other hand, we evaluated the restoration of normal sinus rhythm, resolution of ST-segment elevation, and cessation of chest pain as the signs of successful reperfusion of distal coronary bed, so long-term oral anticoagulation was decided as the follow-up treatment.

Heparin-induced thrombocytopenia (HIT) resembles two distinct clinical presentations in clinical practice as type I and type II. The main difference between them is the time of development of thrombocytopenia [2]. Type I HIT generally develops in the first 5 days after exposure to heparin. In our case, thrombocytopenia developed at 36th hour after heparin administration. These two types of HIT also have different clinical features. Type I HIT is a non-immunological pathology and generally presents with bleeding. Type II HIT is a rare, immune-mediated disorder and shows a paradoxical thrombogenic status despite profound thrombocytopenia [6]. Massive gastrointestinal bleeding was the clinical presentation in our case. We were unable to search HIT antibodies by the time of the onset of thrombocytopenia and clinical presentation, as bleeding directed us to type I HIT as a definitive diagnosis. Oral anticoagulation is highly recommended for type II HIT because of the prevention of future thrombosis. But there is not enough data about the management of type I HIT patients, especially if they have the need

for an oral anticoagulation, as in our case. The main concern rises from the risk of bleeding which is already highly prevalent in type I HIT patients. Previous studies offer the bridging with a non-heparin parenteral anticoagulant within the period of the recovery of thrombocyte count and after thrombocyte count exceeds 150 000/mm3, starting with a vitamin-K antagonist oral anticoagulant in type II HIT patients; but no data exists about type I HIT patients [7].

We have limited choices for non-heparin parenteral anticoagulants, the likes of bivalirudin and fondaparinux, and these treatments require laboratory monitoring and have high costs in practice, as well as the fact that access to these medications may not be easy. Recently, some studies have been published about the role of direct oral anticoagulants (DOAC) in the HIT treatment. There is strong evidence for the use of DOACs safely in the HIT patients, and rivaroxaban has the most significant proof among them [8, 9]. The authors claim that there is no need for bridging with another non-heparin parenteral anticoagulant in the case of rivaroxaban usage and recommend the start of rivaroxaban at the time of diagnosis of HIT. They report that the possibility of thrombosis declines as low as 2.2% with the rivaroxaban treatment [10]. Of course, these recommendations are proven for type II HIT patients. There is no universal consensus for the management of the type I HIT. We encounter type I HIT, especially in the first few days of open-heart surgeries, and in most cases, cessation of heparin treatment can be enough for the recovery. But we do not have any previous data about the management of the type I HIT patients who need long term oral anticoagulation, such as in our case.

CONCLUSION

Differential diagnosis of two different types of HIT is essential in the management of HIT patients. Oral anticoagulation is essential in the treatment of type II HIT disorders, but the need of bridging therapy with a non-heparin parenteral anticoagulant can be problematic for physicians. We do not have any clinical data about the efficacy and safety of oral anticoagulation in type I HIT patients who already present with high bleeding risk. Novel oral anticoagulants are promising choices regarding the efficacy and safety in the treatment of HIT patients, but we need further clinical studies in this area.

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REVIEW

DERLEME

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COVID-19: A Current Brief Review

COVID-19: Güncel Kısa Bir Derleme

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ABSTRACT

Coronavirus infection has become an important public health concern because of its increasing prevalence, serious complications and mortality. The previous pathogenic coronaviruses severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) were mortal virus infections in past 15 years. Today the current epidemic caused by a new coronavirus (SARS-COV-2) is called coronavirus disease of 2019 (COVID-19). The virus causes different illness, from upper respiratory tract infections like the common cold, to lower respiratory tract infections such as bronchitis, pneumonia, and SARS. The coronavirus can be transmitted through small infected droplets from a person with COVID-19 during coughs or exhales. Additionally, it can also be transmitted from contaminated environment or objects. A number of precautions to prevent transmission of COVID-19 have been applied to stop the current outbreak. There is no certain treatment of the disease but the studies on vaccines and treatment continue. In this review, we aimed to give a brief information about COVID-19.

Keywords: COVID-19, SARS-COV-2, pandemia

ÖZ

Koronovirüs enfeksiyonu artan prevalansı, ciddi komplikasyonları ve mortalitesi nedeniyle önemli bir halk sağlığı sorunu haline gelmiştir. Son 15 yıl içinde bundan önceki patojenik ölümcül koronavirüsler ciddi akut solunum sendromu koronavirüs (SARS-CoV) ve Orta Doğu solunum sendromu koronavirüs (MERS-CoV) enfeksiyonlarıydı. Bugün yeni bir koronavirüsün (SARS-COV-2) neden olduğu mevcut salgın 2019 yılının koronavirüs hastalığı (COVID-19) olarak adlandırılmaktadır. Hastalık soğuk algınlığına benzeyen üst solunum yolu enfeksiyonlarından bronşit, pnömoni ve hatta SARS enfeksiyonlarına kadar değişik derecelerde hastalığa neden olabilir. Damlacıklar veya doğrudan temas yoluyla insandan insana bulaşarak yayılabilir. Ayrıca kontamine olmuş cisimler veya çevre ile de bulaşabilir. Mevcut salgını kontrol etmek için; COVID-19'un kişiden kişiye bulaşmasını azaltmak önemli ve bunun için kapsamlı önlemler gerekmektedir. Hastalığın kesin tedavisi bilinmemektedir ancak aşılar ve tedavi ile ilgili çalışmalar devam etmektedir. Bu derlemede COVID-19 ile ilgili kısa bir bilgi verilmesi amaçlanmıştır.

Anahtar kelimeler: COVID-19, SARS-COV-2, pandemi

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Introduction

Coronavirus was called first by June Almeida and David Tyrrell. They investigated and studied on human coronaviruses during 1930 when an acute respiratory infection of animals shown to be caused by infectious bronchitis virus [1]. Coronaviruses are big, spherical particles with surface projections. The diameter of the virus particles is aproximately 125 nm. The diameter of the envelope is 85 nm and the spikes are 20 nm long [2]. In electron microscope the envelope of the virus seen as a distinct pair of electron-dense shells. The scientific name for coronavirus is Orthocoronavirinae or Coronavirinae [3]. They are grouped in two subgroups. Alphacoronaviruses and betacoronaviruses infect mammals. Gammacoronaviruses and deltacoronaviruses infect birds [4]. Even all these viruses have a genetic relationship; they can cause different diseases with different severities. Some can kill more than 30% of the infected patients such as MERS-CoV, and some are relatively benign, such as the common cold. Coronaviruses can cause colds with major symptoms, such as fever, headache and sore throat. Moreover; they can lead to pneumonia (viral pneumonia or secondary bacterial pneumonia) and bronchitis [4,5]. On the other hand, the coronavirus can also cause extrapulmonary disease such as cardiovascular, neurological, renal and hepatic diseases [6,7-9].

The World Health Organization office of China was informed of cases of pneumonia of unknown etiology in Wuhan City, Hubei Province, on the last day of 2019 [9]. A novel coronavirus currently termed coronavirus disease of 2019 was announced as the causative agent by Chinese authorities. According to the different reports, the COVID-19 symptoms ranged from mild to severe diseases that can ultimately lead to death. The symptoms usually appear in two weeks time after viral exposure which includes fever, cough, shortness of breath and pneumonia. The severe cases showed respiratory, hepatic, gastrointestinal and neurological complications that can leads to mortality. The transmission of COVID-19 can ocur via respiratory droplets or from contaminated environment and objects [5,6,10-12].

Epidemiology

The virus spreads rapidly more than 200 countries in a short time. Aproximately 7 million infected cases of COVID-19 with a total of 400857 deaths were reported as of June 8, 2020. The numbers of infected cases and death associated with the disease increased daily (figure 1). In Turkey 170132 infected cases and 4632 associated deaths were reported (figure 2) [10,13]. A total of 2039194 tests were performed and 127943 patients recovered from disease. There are still 31429 patients with active disease. The number of disease is correlated with the number of tests performed. All these data can vary according to the regions, quality of healthcare system, treatment options, prevention methods, awareness of the people. The characteristics of the patients such as age, sex, and overall health also effect the results. The men, older people and patients with chronic diseases were reported as more prone to disease in some studies [14,15].

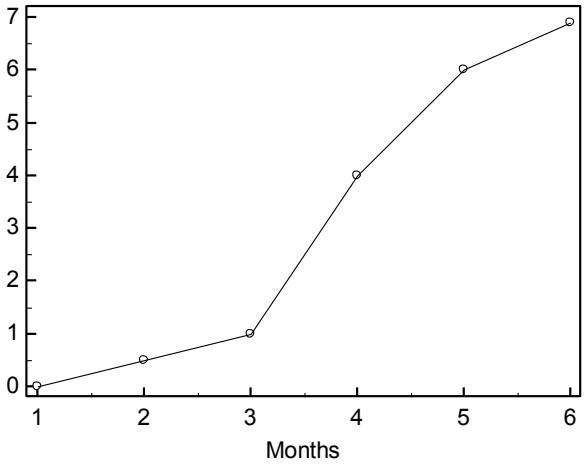

Figure 1: The total COVID-19 cases throughout the world between January 2020-June 2020. (MedCalc v19.2.6, licenced to Şakir Özgür Keşkek) 1-6: January 2020 –June 2020 (https:// https://covid19.who.int/. Access date 08.06.2020.)

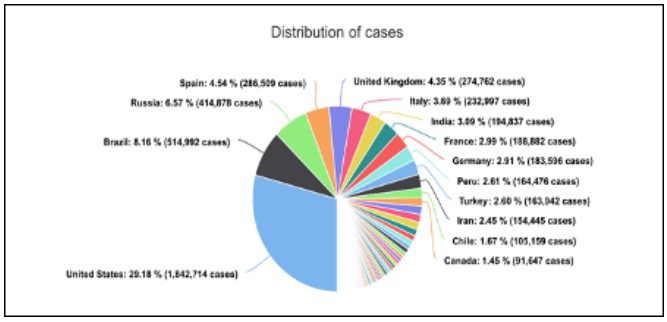

Figure 2: Distribution of cases according to the countries (https://www.worldometers.info/coronavirus/#countries. Access date 01.06.2020.)

Virus structure

Coronaviruses are enveloped, non-segmented, positive-sense single-stranded RNA virus genomes with size ranging from 26 to 32 kilobases, According to the best knowledge, today the biggest viral RNA genome is belonging to the coronavirus genome. It is characterized by club-like spike sprojecting from its surface [16]. The genetic analyses of SARS-CoV-2 genomes and classified out two prevalent evolvement types of SARS-CoV-2, L type (~70%) and S type (~30%). The strains in L type, derived from S type, are more thrusting and contagious [17]. The virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid protein. The interaction of receptor binding domain located in the S protein and target receptor on the host cell surface such as Angiotensin converting enzyme 2 (ACE2) are important for infection [4,6,17,18].

Clinic

The symptoms of COVID-19 infection come out after an incubation period of near one week. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days. The characteristics of the patient; age, sex, immune system and co-morbidities effect the incubation period [4,12,19]. Fever is the most common symptom, but it is highly variable according to the patient status. On the other hand, critically ill and older patients may not have fever. Most of the COVID-19 patients have similar symptoms, in addition to the fever such as cough, loss of appetite, fatigue, myalgia and headache (table 1). Sneezing, runny nose, sore throat, and skin lesions are less common symptoms. Loss of smell was reported in 30% of cases in some countries. Majority of patients with SARS-CoV-2 infection presented with mild flu-like symptoms and a few patients are in critical condition and rapidly develop acute respiratory distress syndrome, respiratory failure, multiple organ failure, even deaths [12,19-22]. A small number of cases do not have any symptoms associated with COVID-19 in any time [23].

Symptomatic, pre-symptomatic and asymptomatic transmissions are three ways for transmission of COVID-19. Symptomatic transmission occurs via close contact through respiratory droplets, contact with the infected individuals or from environment due to the contaminated objects and surfaces. Pre-symptomatic transmission may ocur when viral load is high enough to enable transmission just before the symptoms appear [18,20].

Table 1: Frequency of symptoms in COVID-19 [17].

Symptom	Range
Fever	83–99%
Cough	59–82%
Loss of appetite	40–84%
Fatigue	44–70%
Shortness of breath	31–40%
Coughing up sputum	28–33%
Muscle aches and pains	11–35%

The complications of the disease are pneumonia, acute respiratory distress syndrome, multi-organ failure, septic shock, and death [24]. Cardiovascular complications may include heart failure and arrhythmias. Increased blood coagulation may be a hematological manifestation [25]. One of four patients with COVID-19 have elevated liver enzymes due to the liver injury [26]. Central nervous system complications may include seizure, stroke, encephalitis, and Guillain Barre syndrome [27].

Diagnosis

Identification, examination and confirmation of pathogens can be achieved by laboratory studies. For diagnosis of coronavirus, respiratory materials including nasopharyngeal swabs, oropharyngeal swabs, stool sample, tissue biopsies, blood sample, urine sample can be tested. Real-time Reverse transcription PCR (RT-PCR) is the best way for the detection of virus today [19].

Blood samples of COVID-19 have included lymphopenia with reduction of CD4 and CD8 lymphocytes, prolonged prothrombin time, elevated lactate dehydrogenase, d-dimer, alanine transaminase, ferritine and creatinine kinase [4,5]. Patients with severe illness had higher plasma level of cytokines [25]. There are some difficulties for the diagnosis of COVID-19 because laboratory detections and radiographic images are not always in agreement with clinical features and contact histories of patients [19].

Radiological findings of COVID-19 pneumonia

are multiple lung opacities, multiple types of the opacity. Especially bilateral lower lobes of the lungs are involved [26]. Diagnosis of COVID-19 has to be depend on detailed understanding of clinical features, radiographic features, and laboratory detection [19].

Treatment

Today, we have no any effective approved vaccine or anti-viral therapeutic agents to treat COVID-19. The disease management focuses on supportive care which may include fluid therapy, oxygen support, and supporting other affected vital organs. Lifestyle management with healthy diet, exercise and body hygiene are recommended to improve immunity. Many type of medications are being evaluated for the treatment of COVID-19including remdesivir, favipiravir, chloroquine, hydroxychloroquine, lopinavir/ritonavir, and lopinavir/ritonavir combined with interferon beta [27].

The effective treatment options against COVID-19 can either based on the use of broad-spectrum anti-viral drugs. Remdesivir is an RNA polymerase inhibitor and inhibits SARS-CoV-2 in vitro tests and clinical recovery was observed in patients treated with the remdesivir [28].

Favipiravir is an RNA dependent RNA polymerase inhibitor. It exerts an antiviral action more potent than lopinavir/ritonavir in the treatment of COVID-19, and that there are no serious adverse reactions reported for this drug [29].

Chloroquine, an antimalarial agent with anti-inflammatory and immunomodulatory activities, has achieved to an important position as a potential therapeutic option for the management of COVID-19 [30]. Chloroquine increases endosomal pH of the cell and block virus infection.

Tocilizumab, also known as atlizumab, is an immunosuppressive drug. It is a monoclonal antibody against the interleukin-6 receptor. Tocilizumab can prevent cytokine storm in severe coronavirus disease [31].

Peptidic fusion inhibitors, antiSARS-CoV-2 neutralizing monoclonal antibodies, anti-ACE2 monoclonal antibodies and protease inhibitors may be a choice in the future [32-34].

Antibodies of the patients recovered from COVID-19 is being investigated for a passive immunisation. The FDA has approved the using of blood plasma from patients who have recovered from COVID-19 [35].

Prognosis

The symptoms, clinical properties of COVID-19 can differ in wide spectrum. The disease may occur with a few or no symptoms, similar with other common respiratory diseases infectious such as the common cold. Non serious cases may recover in two weeks time, while those with severe diseases may take three weeks to two months to recover. The duration of the disease from the onset of the symptoms to death has ranged from two to eight weeks [36].

Hypertension, diabetes mellitus, obesity and cardiovascular disease are common in most of the patients who die of COVID-19. ARDS was found the common cause of death in autopsy series [36,37].

Smokers were more likely to have severe symptoms of COVID-19 and they also more likely to die according to the non-smokers. approximately 2.4 times more likely to require intensive care or die compared to non-smokers. Mortality rate is lower in patients younger than 50 years compared to patients older than 70 years [36,38].

Prevention

The WHO has stipulated strict recommendations to reduce and prevent the spread of the disease. Wearing of a mask is convenient for persons who have symptoms of COVID-19. Health caregivers and other health workers should also wear mask when they faced with suspected covid 19 patients [39]. The cleaning of hands frequently with an alcohol-based hand rub, and wash with soap for at least 20 seconds. Avoid touching eyes, nose and mouth. Objects and surfaces should be kept clean and disinfected in the environment. At least 1 meter distance between the persons should be maintened. Finally, it is very important to stay at home during pandemia [10,40].

Conclusion

COVID-19 is the current pandemia caused

by a new coronavirus today. The previous coronaviruses and the last one have a genetic relationship but they cause different diseases with different levels of severities. The virus spread to more than 200 countries with Turkey in a short time. The numbers of infected cases and death associated with the disease increased daily. Although, fever, headaches, myalgia, and coughing are common symptoms of the disease the infection can presented with different clinical spectrum vary from mild flu-like symptoms to acute respiratory distress syndrome. Diagnosis of COVID-19 has to be based on detailed understanding of clinical features, radiographic features, and laboratory detection. There is no any effective approved vaccine or anti-viral therapeutic agents to treat COVID-19 today. Many type of medications are being evaluated for the treatment including remdesivir, favipiravir, chloroquine, hydroxychloroquine etc. The current approach to disease management focuses on supportive care. Both developed and developing countries should work for the advance and update of their health systems. Cooperation between these countries is important for disease prevention [41]. There are many ways for admission of the diseae. It should not be forgotten that to reduce and/or prevent the spread of the disease is the most significant way of protection now [42].

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LETTER TO EDITOR

EDİTÖRE MEKTUP

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Letter to Editor, Comments on "Scientificity and H-Index."

Editöre Mektup: Bilimsellik ve H-Endeksi hakkında yorum

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Dear Editor

We have read with great interest the editorial paper written by Karahan O. and Aslan A., published in your journal in Volume 4, Number 1, 2020 titled "Scientificity and H-Index" [1]. Firstly, we are thanking the authors, and we entirely agree with their sentiments on the importance of h-index. This index freely available through Google Scholar and Scopus and helps the individual researchers to evaluate and benchmark their outputs as well as that of peers. Various analytical sources are used to measure the output of scientific journals, authors and institutions, etc. [2]. As h-index was discussed in detailed at the handled paper, we aimed to mention several different metrics which are used to measure and evaluate the quality of scientific publications:

The Impact Factor: This factor is a quantitative tool for categorizing, ranking, evaluating, and comparing the journals. This scientometric index reflects the frequency which an "average article" in a journal has been cited in a certain period. The use of impact factor as an individual -or article-level metric is controversial because, within a single journal, there is a wide variation of citations from article to article [3-5].

The Immediacy Index: This index is calculated for a journal by dividing the number of all citations to articles published in a specific year by the number of articles published in a given year. Also, this index can provide a useful perspective on comparing journals specialized in cutting-edge research [3-5].

Journal Cited Half-life: After all citations during one year counted, the median article publication date calculated for a journal. Half of the cited article was published before this time, and the other half were published subsequently. For example, for the year 2020, a cited half-life of 4 years means that half of all cited articles were published before 2016, and half were published afterward. This measure used to evaluate the current interest in

a journal [3-5].

Eigenfactor Score: Although the calculation is complicated, the Eigenfactor scores freely viewed from http://www.eigenfactor.org/, where they calculated. This tool can measure the importance of the journal into the scientific community. Because of the Eigenfactor measures the total number of citations, it is no surprise that the chronicles which are publishing pretty much articles have a higher Eigenfactor [3-5].

The Article influence score: This score also available from http://www.eigenfactor.org/, and it shows the average influences per article. For the journal, it is calculated by dividing the Eigenfactor score by the number of papers published [3-5].

I-10 index: This is a straightforward measure as an index to rank the author impact. It is created by Google Scholar and refers to the number of publications with ten or more citations [3-5].

Citation impact: It is one of the most basic citation metrics for an individual author. It is obtained by dividing all citations by the number of all publications of the researcher [4-6].

Journal Citation Reports: This annual journal report provides information about the journal’s value. This report includes various article-level data to provide information about the reciprocal relationship between the article and the journal. The editor understood how their journal is performing and easily benchmarks their journal against the others [3-6].

Essential Science Indicators: Data collected from surveys that are obtaining information from more than ten thousand journals, and this data using for rank the authors, institutions, and countries based on publication and citation performances. This tool sourced by the Science Citation Index and includes bi-monthly updates to rankings and citation counts [4-6].

Percent articles in Citable Items: This tool highlights the rates of “original article” publishing. The sum of the various types of academic papers gives the number of citable items. The percentage of the original articles should be high in this sum. [6].

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LETTER TO EDITOR

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Diploma Mills

Diploma Fabrikaları

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Dear Editor,

With respect to the previous publications in your journal on predatory publishers and congresses [1,2], I write this letter to also call your attention, as well as the attention of the readers, about the rising frequency of 'diploma mills' in the global community.

By way of definition, a diploma mill is a company or organization that claims to be a tertiary academic institution but awards fake academic qualifications, such as degrees, diploma, and certificates to people [3]. According to the World Education Services Inc, in 2017, a total of 2,615 diploma mills are in the world, of which 38.5% of them were from the USA. In fact, at least 400 PhD degree-awarding diploma mills had been identified in the USA [4].

Without mincing words, diploma mills are fake tertiary academic institutions. The diploma mills are highly proficient in using strategic methods to win the interests of tertiary school education seekers towards enrolling for their so-called academic programs. Some of these strategies includes the: use of scholarship scams [3]; use of academic internet address (i.e. ".edu") [3]; obtaining accreditation from fake accrediting agencies [3]; and use on online social media platforms, e-mails and short message service (SMS) to advertise their academic programs. [5].

Pertinently, the need for acquisition of post-secondary school academic qualifications is an important issue that cannot be overemphasized; as such qualifications are needed to be a competitive candidate in the job market. Hence, every tertiary school education seeker must be meticulous when it comes to enrolment in tertiary institutions, so that they do not fall a prey of diploma mills.

However, every problem has its solution. In order to avoid falling a prey of a diploma mill, a tertiary school education seeker must ensure that he/she: checks for the details (such as name, address, and ownership) of their intending institution in the master list of the national/regional accrediting agency of the country where the institution is situated; make in-depth enquiries about the

institution in question from the current students and alumni of such institution and compare the information obtained with other well-known traditional governmental institutions; research on the comments made by people on social media and news media about the institution in question; and physically visit the institution for further enquiries and observations.

Ideally, a diploma mill cannot be included in the master list of an authentic national/regional accrediting agency. Also, comments made by students and alumni of a diploma mill as well as the general public are usually controversial, questionable and not in line with other traditional tertiary academic institutions. In fact, some of them use fake addresses, with locations that are not befitting.

If the above-recommended discerning strategies are adopted in verifying the authenticity and credibility of an academic institution, I strongly believe that a tertiary school education seeker will not fall a prey of a diploma mill

Finally, like the way predatory journals, publishers and congresses exist, so also fake academic tertiary institutions exist. Hence, we need to be very cautious whenever we want to: publish our scientific works; participate in scientific conference; or acquire additional educational qualifications.

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