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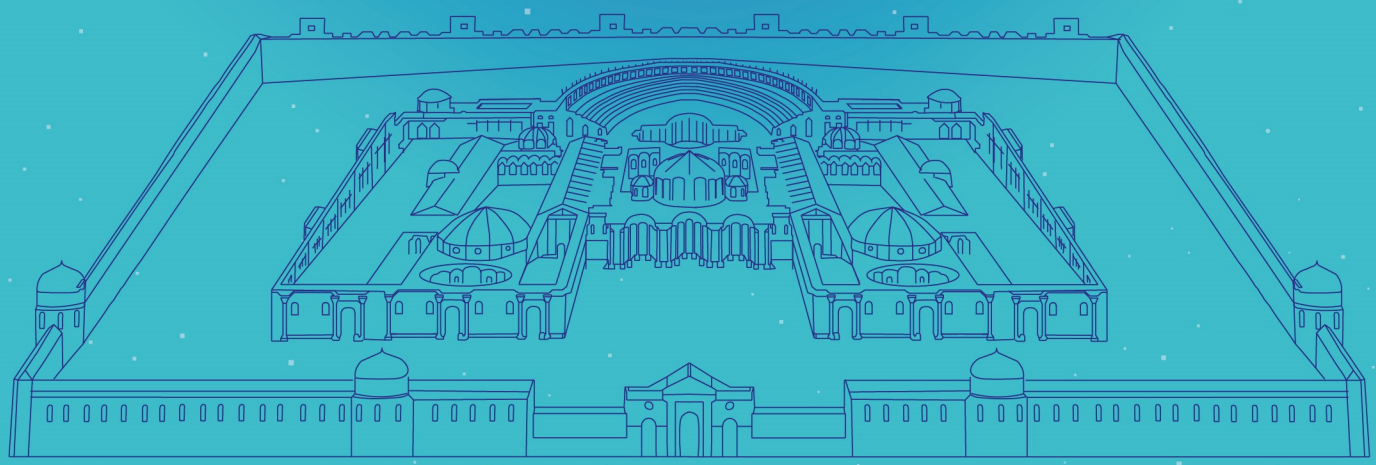

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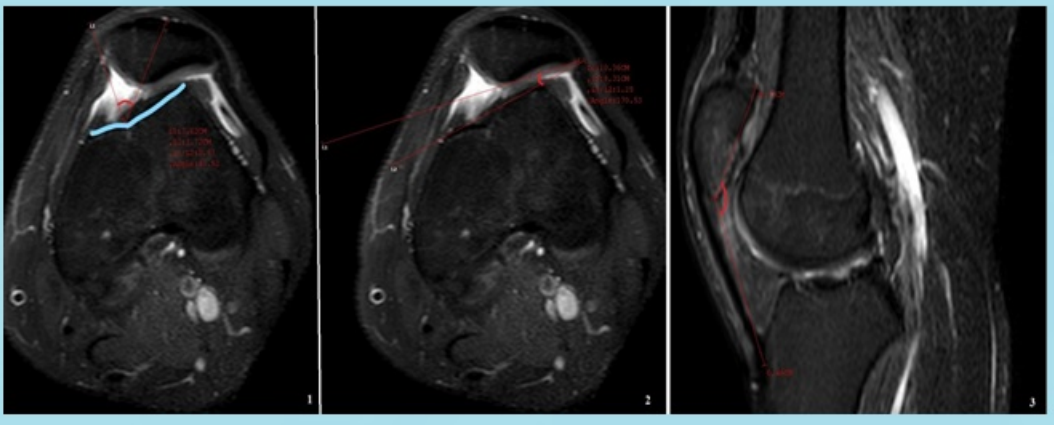

The congruence angle (1), the lateral patellofemoral angle (2) and patellar height (3)

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Research Article | Araştırma Makalesi

EVALUATION OF UPPER EXTREMITY VENOUS THROMBOSIS WITH DOPPLER ULTRASONOGRAPHY IN PERIPHERAL VENOUS LINE APPLIED PATIENTS

PERİFERİK VENÖZ KATATER UYGULANAN HASTALARDA ÜST EKSTREMİTE VENÖZ TROMBOZUNUN DOPPLER ULTRASONOGRAFİ İLE DEĞERLENDİRİLMESİ

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Abstract

Objective: Peripherally inserted venous lines (PVL) may increase the risk of venous thrombosis due to vessel wall disarrangement. Aim of this study is to identify the cases of upper extremity venous thrombosis (UEVT) related to PVL since most of the PVLs applied to upper extremities.

Methods: Sixty-nine hospitalized patients with previous or present PVL insertions were included in this prospective study. Upper extremity Doppler compression ultrasonography (USG) examination were performed to on all patients. The cases with detected UEVTs were evaluated as group 1 and the remaining cases were evaluated as group 2. Demographic parameters, PVL applications, intravenous treatments were compared between the groups.

Results: UEVT was diagnosed by Doppler USG in 26 (37.7%) patients out of 69 patients. Lower extremity thrombosis was found in 10 (14.49%) patients. UEVT was observed in cephalic vein in 14 (53.8%) and in basilic vein in four (15.4%) out of 26 (37.7%) patients. Axillary and brachial deep UEVT was located in two (2.9%) cases. Superficial UEVT was found in 24 (34.8%) cases. Ceftriaxone, cefoperazone/sulbactam and esomeprazole were the mostly associated treatments with UEVT. UEVT was detected in five patients with PVL that were inserted only for drawing blood.

Conclusion: PVL is a risk factor for UEVT since almost 1/3 of the patients revealed UEVT. When PVL is no longer needed or the need for intravenous therapy decreases, oral therapy should be planned and PVL should be removed. Removal of PVL appears to be necessary to avoid UEVT.

Keywords: Peripheral venous line, upper extremity venous thrombosis, Doppler ultrasonography, intravenous therapy

Öz

Amaç: Periferik venöz kataterler (PVK), damar duvar hasarı nedeniyle venöz tromboz riskini artırabilir. Çalışmanın amacı, PVK'lerin çoğu üst ekstremitelere uygulandığı için, PVK'ya bağlı üst ekstremite venöz tromboz (ÜEVT) vakalarını belirlemektir.

Yöntem: Bir aylık süreçte göğüs hastalıkları kliniğinde yatan hastalardan PVK'sı olan veya başvurusundan önce hastane yatışında PVK öyküsü olan 69 hasta bu prospektif çalışmaya dahil edildi. PVK'ya bağlı trombüs oluşumunu değerlendirmek için tüm hastalara üst ekstremite Doppler, kompresyon ultrasonografi (USG) tetkiki yapıldı. ÜEVT olan olgular grup 1, ÜEVT olmayan olgular ise grup 2 olarak değerlendirildi. Demografik parametreler ve intravenöz tedaviler (İV) gruplar arasında karşılaştırıldı.

Bulgular: Altmış dokuz hastanın 26'sında (%37,7) Doppler USG ile ÜEVT tanısı kondu. On hastada (%14,5) alt ekstremite ven trombozu tespit edildi. Yirmi altı hastanın 14'ünde (%53,8) sefalik vende ve dört hastada (%15,4) bazilik vende ÜEVT görüldü. Derin ÜEVT iki olguda (%2,9) aksiller ve brakiyal venlerde; yüzeyel ÜEVT 24 olguda (%34,8) izlendi. Seftriakson, sefoperazon / sulbaktam ve esomeprazol, ÜEVT ile en çok ilişkili İV tedavilerdi. Sadece kan almak için PVK uygulanan beş hastada ÜEVT izlendi.

Sonuç: Çalışmamızın sonuçları, hastaların yaklaşık 1/3'ünde Doppler USG incelemesi ile ÜEVT tespit edildiği için PVK'nın ÜEVT için bir risk faktörü olduğunu göstermiştir. PVK'ya gereksinim kalmadığında veya intravenöz tedavi ihtiyacı azaldığında, oral tedavi planlanmalı ve PVK çıkarılmalıdır. ÜEVT'den kaçınmak için PVK'nın çıkarılması gerekli görünmektedir.

Anahtar Kelimeler: Periferik venöz katater, üst ekstremite ven trombozu, Doppler ultrasonografi, intravenöz tedavi

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Introduction

Peripheral venous line (PVL) is applied to most of the hospitalized patients in order to facilitate blood intake and intravenous (IV) therapy. Peripheral venous line is mostly applied to superficial upper extremity veins. Healthcare workers often witness visible complications of PVL such as pain and swelling on the trace of the vein. Many studies, especially that are in intensive care units, have shown that central venous catheters cause upper extremity venous thrombosis.[1,2]

Superficial and deep vein thrombosis (DVT) can be seen in the upper extremities as well as in the lower extremities. Upper-extremity deep vein thrombosis (UEDVT) accounts for just about 10%-25% all DVT cases.[3] Proximal UEDVT is defined as thrombosis involving the axillary or more proximal deep veins, and distal UEDVT is defined as thrombosis of the brachial veins. Axillary and subclavian veins are most frequently affected.[3] Upper-extremity vein thrombosis (UEVT) is divided into two as primary and secondary. While primary UEVT does not have a defined underlying reason, secondary UEVT occurs on a ground of a preexisting cause such as malignancy, central venous catheter (CVC), surgery, and thrombophilia.[3,4] The causes of upper extremity superficial thrombosis are mostly iatrogenic. Injury, stasis, and foreign material in the lumen of the vein itself lead to thrombosis. However, lower extremity superficial thromboses are mostly caused by varicose veins.[5]

We could not find any previous paper in literature that investigated venous thrombosis occurrence as a result of PVL and the location of the thrombosis with Doppler compression ultrasonography (USG). In our study, we aimed to investigate the rate of thrombus formation caused by PVL application in the upper extremities and the relationship of the thrombus with IV treatments or other applications.

Methods

Study Design and Patient Selections

This prospective, cross-sectional study was conducted in the Department of Pulmonary Diseases. Seventy-nine patients that were hospitalized in the pulmonary diseases inpatient clinic for 1 month were evaluated and 69 of them were included in the study. Patients hospitalized with pre-diagnosis of pneumonia, chronic obstructive pulmonary disease (COPD), asthma, respiratory failure, pulmonary embolism and malignancy, and who underwent PVL were included in the study. Pregnant women, patients who were immobile, hospitalized in intensive care unit and/or did not have previous or present PVL insertions were excluded from the study. Ethical approval was obtained from the local ethics committee (Clinical Research Ethics Committee decision number 2014/120; date: July 16, 2014). Informed consents were obtained from all participants.

Ages, genders, comorbidities, and smoking habits of 69 patients were recorded. Complaints of the patients' on admission were noted. History of venous thrombosis of the patients had been questioned and recorded. Previous admission to hospital of the patients and the history of venous line insertion were investigated. Diagnosis of patients and treatments were recorded. In order to determine the time of radiological examination, hospitalization times were recorded. The location of PVL and the given treatment were noted. Anticoagulant therapy was administered to patients with a diagnosis of pulmonary embolism (PE). Other patients were given prophylactic doses of anticoagulant treatment with low molecular weight heparin during their hospitalizations.

Upper extremity Doppler USG examinations were performed to all patients by Logiq9 brand ultrasound machine to examine the thrombus formation. All of the Doppler USG examinations were conducted by the same radiologist. The number of Doppler USG examinations and the day of hospitalizations were noted when the thrombi were detected. Doppler USG was applied to both lower and upper extremities during the first five days of hospitalization if the pre-diagnosis of the patient was PE or DVT. It was also applied to both upper extremities 5 days after venous line insertion and hospitalization.

Statistical Analysis

The findings of the study were assessed for statistical analysis using SPSS 21.0 program (IBM, Armonk, New York, United States). Descriptive statistics were computed for each of the analyzed variables. Results are presented as mean ± standard deviation (SD). The normal distribution of the data was tested by the Shaphiro Wilks test. In order to compare the different groups stratified by age and sex, the independent samples t-test and Chi-squared test were used. The Mann–Whitney U test was used for the parameters without normal distributions when comparing two independent groups. P-value < 0.05 was considered significant.

Results

Sixty-nine patients who were hospitalized in the pulmonary diseases inpatient clinic for 1 month were included in the study. The patients were divided into two subgroups: group 1 and 2. Group 1 consisted of 21 cases with sole UEVTs and 5 cases of UEVT and LEVTs. Cases without UEVTs formed group 2 and patients with sole LEVTs were included in this group. The mean age of the patients was 67.63 ± 17.25 (20-96) and 27 of them were female and 42 were male. Forty-one (59.4%) of the patients were smokers, 28 (40.6%) were non-smokers. Comparison of the demographic parameters between group 1 and group 2 is presented in Table 1.

Venous thrombosis was detected in total of 36 patients (52.2%). UEVT was observed in the 26 (37.7%) patients and 5 of them had both UEVT and LEVT. Pure LEVT was found in 10 patients. UEVT was observed in cephalic vein in 14 patients, in basilic vein in 4 patients and in antecubital vein in 1 patient. Brachial UEVT was detected in 2 cases (2.9%) (Table 2). Superficial UEVT was found in

92% of the UEVT patients. Only 8% of UEVT cases had deep UEVT. Doppler USG repetition was performed in only one patient after the 5th day and no thrombus was detected. The patient was included in Group 2.

Table 1. Comparison of the demographic parameters according to the groups.

	Group 1 The patients with UEVT n = 26 (21+5) (37.7%)	Group 2 The patients without UEVT n = 43 (62.3%)	P value
Age (mean± sd)	65.73 ± 18.43	68.79 ± 16.62	0.472
Gender			0.550
Female	9 (34.6%)	18 (41.9%)	
Male	17 (65.4%)	25 (58.1%)	
Smoking			0.929
Smoker	16 (61.5%)	25 (58.1%)	
Non-smoker	10 (38.5%)	18 (41.9%)	

UEVT: upper extremity venous thrombosis, SD: standard deviation

Table 2. Results of Doppler USG of bilateral upper and lower extremities in the patients that participated in the study (n = 69)

Results of Doppler USG	n (%)
Upper extremity VT	**21 (30.4%)**
Superficial venous thrombosis	
Basilic vein	4 (5.8%)
Cefalic vein	14 (20.3%)
Antecubital vein	1 (1.4%)
Deep venous thrombosis	
Axillar vein	-
Brachial vein	2 (2.9%)
Upper + lower extremities VT	
Femoral vein+Cefalic vein	3 (4.3%)
Poplital vein+Cefalic vein	1 (1.4%)
Vena saphena parva+Cefalic vein	1 (1.4%)
Lower extremity VT	**10 (14.5%)**
Superficial venous thrombosis	
Vena saphena magna	3 (4.3%)
Vena saphena parva	-
Deep venous thrombosis	
Femoral vein	2 (2.9%)
Popliteal vein	3 (4.3%)
Crural vein	2 (2.9%)
Total VT	**36 (52.2%)**

USG: ultrasonography, VT: venous thrombosis
USG: ultrasonography, VT: venous thrombosis

Thrombosis was detected in 13 patients who were diagnosed with PE or DVT during the first 5 days of their hospitalizations. Thrombosis was also found in 23 patients after 5 days of PVL insertions. 42 patients (60.9%) had previous hospital admissions and 28 of the 42 had been given intravenous therapy in their previous hospitalizations. PVLs were inserted in the right upper extremities in 36 patients (52.2%) and left upper extremities in 33 patients (47.8%) for their current treatments.

Diagnoses of the patients were noted according to the groups. Only 2 patients had PE in group 1. Since LEVT patients were in group 2, 10 patients were diagnosed with PE in this group. The most seen diagnosis was pneumonia in group 1 (Table 3). Intravenous esomeprazole was given to 34 patients, ceftriaxone to 25, cefoperazone/sulbactam to 16, furosemide to 10, methylprednisolone to 7, theophylline to 8, paracetamol and metoclopramide to 3 patients. Acetylcysteine, hyosine butylbromide, piperacillin/tazobactam, and imipenem were prescribed to 1 patient.

Table 3. Diagnosis of 69 patients with and without UEVT

Diagnosis	Group 1 The patients with UEVT n = 26 (37.7%)	Group 2 The patients without UEVT n = 43 (62.3%)	Total n = 69
COPD	5 (19.2%)	5 (11.6)	10 (14.5%)
PE	2 (7.7%)	10 (23.2%)	12 (17.4%)
Pneumonia	15 (57.7%)	19 (44.2%)	34 (49.3%)
Lung Cancer	1 (3.8%)	2 (4.6%)	3 (4.3%)
Asthma	2 (7.7%)	4 (9.3%)	6 (8.7%)
NMD	1 (3.8%)	-	1 (1.4%)
OSAS	-	1 (2.3%)	1 (1.4%)
Heart Failure	-	1 (2.3%)	1 (1.4%)
ILD	-	1 (2.3%)	1 (1.4%)

UEVT: upper extremity venous thrombosis, COPD: chronic obstructive pulmonary disease, PE: pulmonary embolism, NMD: neuromuscular disease, OSAS: obstructive sleep apnea syndrome, ILD: interstitial lung disease.

Thrombus development was evaluated according to the treatments the patients were receiving. In the groups receiving cefaperazone/sulbactam, ceftriaxone, and esomeprazole patients developed UEVT more than other groups (Table 4).

Discussion

Hospitalization itself is a risk factor for numerous morbidities like infections and complications of several invasive procedures. As seen in our study as well, patients hospitalized in pulmonary inpatient clinics mostly require IV antibiotic treatment because of severe pneumonia and/or COPD attacks. Therefore, most of the hospitalized patients need PVL for their treatment or diagnosis. Placement of peripheral lines is shown to be the most commonly performed invasive procedure in acute healthcare settings with as many as 80% of hospital inpatients requiring intravenous access at some stage during their admission, and worldwide more than one billion lines are used annually.[6,7] Generally, PVLs attached to peripheral arm veins are sufficient for these purposes. Once inserted, a well-functioning line can remain in use for several days if required.

Table 4. The relationship between the UEVT and PVL applications/treatments in 69 patients

Given therapy from the PVL	Total n (%) n = 69	Group 1 The patients with UEVT n = 26 (37.7%)	Group 2 The patients without UEVT n = 43 (62.3%)	P value
Ceftriaxone	25 (36.2%)	11	14	0.414
Cefoperazone/sulbactam	16 (23.2%)	6	10	0.986
Tazocin	1 (1.4%)	1	-	
Imipenem	1 (1.4%)	-	1	
Esomeprazole	34 (49.3%)	15	19	0.277
Paracetamol	3 (4.3%)	3	-	
Furosemide	10 (14.5%)	3	7	
Metoclopramide	3 (4.3)	-	3	
Theophylline	8 (11.6%)	3	5	
Methylprednisolone	7 (10.1%)	2	5	
Only serum	3 (4.3%)	1	3	
Only for blood taking	12 (17.4%)	5	7	0.754
PVL applied only in previous hospitalisation	3 (4.3%)	1	2	
PVL applied also in previous hospitalisation	28 (40.6%)	9	19	0.433

PVL: peripheral venous line, UEVT: upper extremity venous thrombosis.

Common side effects of PVL application are redness, pain, and edema on the applied arm. There are previous studies that have evaluated these symptoms and demonstrated the relationship between catheter applications and thrombus formation [1,2,8] However, those studies were mostly related to intensive care settings and deep catheter procedures. Best of our knowledge, no study that conducted by using USG to examine PVL that is attached to the superficial veins in the upper extremities to show thrombus, was found in the English literature. UEVT was shown by Doppler USG in 37.7% of the patients in our study.

The major systemic risk factors for upper extremity thrombosis is the presence of malignancy.[9,10] The mechanisms by which malignant tumors promote thrombosis were vary. In malignancies, pro-inflammatory cytokines released from the expression of tumor antigens increase the release of thrombotic substances in the blood, leading to hyper viscosity. Stasis develops secondary to compression of the veins in the thrombosed site and venous thrombosis progresses. Frequent hospitalizations, chemotherapy and additional aggressive supportive treatments are also defined as an important risk factor for the development of thrombosis in cancer patients. Although chemotherapeutic agents are frequently administered through the central venous catheter, other treatment is also delivered via with a peripheral catheter.[11] One of our three patients with lung cancer had upper extremity thrombosis.

Local factors may play a dominant role in UEVT compared with LEVT. Foreign material in the lumen of the arm veins is led to thrombosis. The highest reason of thrombosis is most frequently indwelling central venous catheters and pacemaker. The odds ratio in patient with UEVT by intravascular devices like central venous catheters eightfold increased risk of venous thrombosis of the arm.[2,12] The specific features of central venous catheters which are the catheter type, technique, course and level of insertion may affect thrombosis occurrence. In addition, the duration of catheterization, recurrent PVL insertion, recurrent hospitalization, the fluid administered, number of punctures during catheter insertion and catheter related infections may have an effect on the presence of thrombosis in patients with peripherally catheters. Less is known about the relation between peripherally catheters in patients with hospitalization and UEVT. The risk of arm vein thrombosis were significantly increased due to implanted port a catch systems and pacemaker.[13,14] The major problem appears to be the thrombogenicity of the foreign material itself. Other potential risk factors include damage to the vascular wall and impaired blood flow due to hyper viscosity, according to Virchow triad.[15] The presence of thrombophilia also increases the risk of UEVT. The previous investigations were found that the most common thrombophilia's, the factor V Leiden mutation and the prothrombin G21020A mutation, among patients related to UEVT.[16-18] In our study, PVL was usually applied to the right cephalic vein. Upper extremity deep venous thrombosis was detected in two of 26 cases with UEVT, others were upper extremity superficial venous thrombosis. Superficial thrombi were mostly observed in the cephalic vein. Upper extremity deep venous thrombosis was seen in axillary and brachial veins.

Superficial UEVT sometimes may lead to deep UEVT so the cases that were found as superficial UEVT may have a risk of developing deep UEVT if the PVL duration time is prolonged and some drugs continue to be administered. Some studies showed that superficial LEVT patients have more risk of developing deep venous thrombosis.[19,20] In European Society and Cardiology (ESC) Guideline of PE 2019; superficial venous thrombosis is considered as moderate risk factor which is two to nine fold increased risk of venous thromboembolism.[21]

In patients using ceftriaxone, cefoperazone/sulbactam as IV form antibiotics and esomeprazole, UEVT was significantly higher than other drugs in our study. Esomeprazole is a proton pump inhibitor and is widely used in the treatment of stomach ulcers and gastric protective treatment. The choice of IV treatment of this drug, instead of oral form, may increase the risk of UEVT. The limitations of our study were the relatively small sample size and the presentation of a single-centered

experience. In addition, a second Doppler USG could not be performed in patients with prolonged PVL duration.
In conclusion, UEVT was detected by Doppler USG in 1/3 of the patients in our study. PVL appears to be a risk factor for the occurrence of UEVT. Although most of the UEVTs in our study were superficial, they also may pose a risk for pulmonary embolism. Therefore, to take off the PVL when the IV treatment and the need is over and to consider oral treatment form of the drugs, seems to be necessary to avoid from UEVT.

Compliance with Ethical Standards
Ankara Yildirim Beyazit University Faculty of Medicine Ethics Committee approved this study (decision number 2014/120; date: July 16, 2014). Informed consent was obtained from all participants.

Conflict of Interest
The authors declare no conflicts of interest.

Author Contribution
Authors contributed equally to this work.

Financial Disclosure
Financial disclosure none.

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ANTHROPOMETRIC STUDY OF PROXIMAL HUMERUS AND CAVITAS GLENOIDEALIS: NORMAL GLENOHUMERAL RELATIONSHIPS

PROKSIMAL HUMERUS VE CAVITAS GLENOIDEALIS'İN ANTROPOMETRİK ÇALIŞMASI: NORMAL GLENOHUMERAL İLİŞKİLER

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ABSTRACT

Objective: The shoulder joint has a complex anatomical structure due to its unique irregular shape. The anatomy of the shoulder joint should be known in detail for surgical treatment of shoulder joint disorders and surgical interventions such as arthroscopic procedures. In addition, knowing whether there are racial or gender-related morphometric differences in the shoulder joint can be useful in anthropology and some clinical areas, especially in forensic medicine. However, despite the importance of the subject, there are few studies on the quantitative anatomy of the shoulder joint. The aim of this study is to present the measurements of the shoulder joint in detail.

Methods: A total of 107 people (54 men, 53 women) were measured. 18 measurements were performed, 6 in the proximal humerus and 12 in the cavitas glenoidealis. An MRI device was used in the measurements. The shape of Cavitas Glenoidalis was evaluated (teardrop, pear-shaped, round, ovoid, inverted comma-shaped) and their percentages were calculated.

Results: All values in the proximal humerus were higher in men ($p < 0.05$). In comparisons by age (> 40 and <40), all values except the vertical diameter of the humerus and BF length were found to be higher over 40 years of age.

Conclusion: These findings can provide a reproducible reference point for articulatio humeri in osseous anthropometry, offer a valuable reference in shoulder replacement surgery and help characterize osseous glenohumeral instability.

Keywords: Proximal humerus, cavitas glenoidealis, anthropometry, shoulder arthroplasty

ÖZ

Amaç: Omuz eklemi benzersiz düzensiz şekli nedeniyle karmaşık bir anatomik yapıya sahiptir. Omuz eklem bozukluklarının cerrahi tedavisi ve artroskopik işlemler gibi cerrahi müdahaleler için omuz ekleminin anatomisinin detaylı olarak bilinmesi gerekir. Ayrıca omuz ekleminde ırk veya cinsiyete bağlı morfometrik farklılıkların olup olmadığının bilinmesi antropoloji ve bazı klinik alanlarda özellikle adli tıpta faydalı olabilir. Ancak konunun önemine rağmen omuz ekleminin kantitatif anatomisine ilişkin az sayıda çalışma bulunmaktadır. Bu çalışmanın amacı omuz eklemi ölçülerini detaylı olarak sunmaktır.

Yöntem: Toplam 107 kişiye (54 erkek, 53 kadın) ölçüm yapıldı. 6'sı humerus proksimalinde ve 12'si cavitas glenoidealis'te olmak üzere 18 ölçüm yapıldı. Ölçümlerde MR cihazı kullanıldı. Cavitas Glenoidalis'in şekli (gözyaşı damlası, armut biçimli, yuvarlak, oval, ters virgül biçimli) değerlendirildi ve yüzdeleri hesaplandı.

Bulgular: Humerus proksimalindeki tüm değerler erkeklerde daha yüksekti ($p<0.05$). Yaşa göre karşılaştırmalarda (>40 ve <40), humerus vertikal çapı ve BF uzunluğu dışındaki tüm değerler 40 yaş üzerinde daha yüksek bulundu.

Sonuç: Bu bulgular kemik antropometrisinde articulatio humeri için tekrarlanabilir bir referans noktası sağlayabilir, omuz replasman cerrahisinde değerli bir referans sunabilir ve kemikli glenohumeral instabiliteyi karakterize etmeye yardımcı olabilir.

Anahtar Kelimeler: Proksimal humerus, cavitas glenoidealis, antropometri, omuz artroplastisi

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Introduction

Few anatomical data are available to support the need for humeral hand glenoid prosthetic components in a wide range of sizes and shapes. For total shoulder arthroplasty, the widespread gold standard suggests one radius curvature for the head of the humerus and glenoid, with two humeral offsets.[1-15] This study has a twofold purpose: to develop a specific, reproducible, computerized measurement technique to define the osseous anatomy of the proximal humerus and glenoid and to describe the osseous anatomical relationships between the normal proximal humerus and glenoid regarding total shoulder arthroplasty design.

Methods

The research method of this study was approved by our institutional review board and by the ethics committee (2019/2125). Written informed consent was obtained from all individuals before the MRI examination. This study is based on a retrospective evaluation of MRI in 107 (54 males and 53 females) individuals consecutively between March 2019 and October 2019. The patients with congenital, pathological, or traumatic lesions were excluded from the study. Patients were randomly selected and informed consent was received from all patients before participating in the study.

1.5 T (Aera, Siemens, Erlangen, Germany) device was used for magnetic resonance imaging. Fat-suppressed proton density images in the axial plane, fat-suppressed T1 and T2-weighted images in the coronal oblique plane, and fat-suppressed T2-weighted images in the sagittal plane were evaluated. Anatomical measurements were made precisely at the highest magnification possible by an experienced radiologist at the Syngo via (Siemens, Healthcare, Erlangen, Germany) workstation over the existing images. Each measurement was made 3 times and these measurements were averaged (Figure 1-4). The intra-observer agreement values for repeated measurements were found between 0.894 and 0.983 which showed a higher agreement level. The anthropometric measurements of the proximal humerus and the glenoid cavity were shown in Figures 1- 4. In the figures, it can also be followed the abbreviations of the measured parts of the proximal humerus and the glenoid cavity.

Statistical Analysis

SPSS 20.0 (IBM Inc., Chicago, IL, USA) software was used in order to analyze the study. Descriptive statistics were presented as frequencies and percentages for categorical variables and mean±SD and percentile values for numerical variables. Student t-test was used for two independent samples, and a one-way analysis of variance was used for several independent samples. Pearson correlation coefficients were calculated between measurements and gestational age. The Intraclass Correlation Coefficient (ICC) analysis was performed for agreement of repeated measurements. $P<0.05$ was considered statistically significant as a 5% type-I error.

Results

The data obtained from measurements on art. humeri were statistically evaluated. The calculations of Mean±SD and *P* values of these parameters were performed according to gender (male-female) and lateralization (right-left) and presented in tables. There were 54 males and 53 females (nearly half of the total individuals) enrolled in the study. The mean age of females was 49.67±12.57 years and 46.87±14.53 years for males.

A significant difference was identified in values of each proximal humerus between genders except for AB ($p<0.05$) (Table 1). All values were observed to be significantly higher in males.

Table 1. Distribution of the morphometric measurements of the proximal humerus by gender (in cm)

Parameters	N	Male Mean±SD	N	Female Mean±SD	p
AB	54	9.31±2.08	53	9.12±1.93	0.612
BD	54	14.97±2.42	53	13.13±2.31	0.001*
BF	54	43.67±3.96	53	38.16±3.14	<0.001*
EF	54	30.04±4.44	53	27.62±3.84	0.003*
VC	54	40.66±3.56	53	36.37±3.21	<0.001*
TC	54	49.70±3.87	53	44.24±3.06	<0.001*

*Significant at 0.05 level according to Student t-test

Comparison results of right and left proximal humerus measurements were given. Except for BF, EF all measurements were found higher on the right side than on the left side (Table 2-4).

Table 2. Distribution of morphometric measurements of proximal humerus by lateralization (in cm)

Parameters	N	Right Mean ± SD	N	Left Mean ± SD	p
AB	50	9.25±2.00	57	9.12±2.02	0.884
BD	50	15.11±2.70	57	13.14±1.97	<0.001*
BF	50	40.50±4.09	57	41.33±4.85	0.342
EF	50	28.26±4.11	57	29.35±4.45	0.192
VC	50	48.68±4.10	57	45.52±4.20	0.001*
TC	50	38.13±3.84	57	38.89±4.15	0.326

*Significant at 0.05 level according to Student t-test

For Cavitas glenoidalis, AB, AC, CD, DM, and IJ averages were found to be higher in males (Table 5) and the right side values were smaller than the left side (Table 6). All measurements except for JL, IJ, and KL in Cavitas glenoidealis were significantly different between the sides of each gender (Tablo 7). Most of the measurements did not differ between the age groups of 40 years (Table 8). 65.05% of Cavitas glenoidalis were

pear-shaped, 24.27% were oval-shaped and 10.68% were reversed comma-shaped. All abbreviations stated in the results were shown in Figure 1-4.

Table 3. Distribution of measurements made in the anteroposterior view of proximal humerus by gender and lateralization (right: 50, left: 57) (in cm)

	Male			Female		
	Right	Left		Right	Left	
Parameters	Mean ± SD	Mean ± SD	p	Mean ± SD	Mean ± SD	p
AB	9.24±2.18	9.39±2.04	0,841	9.26±1.85	8.99±2.03	0.597
BD	16.13±2.59	13.99±1.77	0,823	14.11±2.47	12.26±1.80	0.725
BF	26.26±3.49	44.07±3.98	0,008*	37.79±1.79	38.50±4.00	0.913
EF	29.26±3.49	30.73±5.10	0,765	27.27±4.51	27.93±3.19	0.620
VC	51.63±3.14	48.05±3.71	0,653	45.74±2.53	42.90±2.92	0.586
TC	40.47±3.88	40.84±3.34	0,992	35.80±1.93	36.89±3.99	0.538

*Significant at 0.05 level according to Student t-test

Table 4. Distribution of morphometric measurements of proximal humerus by age (in cm)

Parameters	N	>40 years Mean ± SD	N	<40 years Mean ± SD	p
AB	77	9.47±2.03	30	8.56±1.80	0.028*
BD	77	14.27±2.55	30	13.53±2.42	0.162
BF	77	40.57±4.41	30	41.88±4.68	0.193
EF	77	29.00±4.12	30	28.42±4.83	0.564
VC	77	47.22±4.36	30	46.43±4.63	0.423
TC	77	38.50±4.30	30	38.62±3.17	0.872

*Significant at 0.05 level according to Student t-test

Table 5. Distribution of morphometric measurements in Cavitas Glenoidealis by gender (male, female) (in cm)

Parameters	N	Male Mean ± SD	N	Female Mean ± SDd	p
AB	54	32.38±5.18	53	29.31±4.96	0.002*
AC	54	16.56±3.60	53	14.16±2.69	<0.001*
BC	54	15.69±2.83	53	15.12±3.19	0.338
CD	54	3.70±1.59	53	3.00±1.42	0.018*
EF	54	24.87±6.44	53	22.58±5.59	0.051
GH	54	34.50±9.89	53	31.18±7.79	0.056
AI	54	11.16±1.22	52	11.11±1.24	0.828
IG	54	11.03±1.03	52	11.01±1.51	0.907
BF	54	11.84±1.65	52	11.59±1.20	0.382
FH	54	10.29±1.04	52	10.29±1.84	0.981
DI	53	34.29±5.76	52	30.93±4.03	<0.001*
IJ	54	17.69±5.36	52	13.60±2.44	<0.001*
GH	54	12.80±17.83	52	7.62±2.24	0.039

*Significant at 0.05 level according to Student t-test

Table 6. Distribution of measurements in the shoulder joint, cavitas glenoidealis by lateralization (right, left) (in cm)

Parameters	N	Right Mean ± SD	N	Left Mean ± SD	p
AB	50	35.36±3.44	55	26.84±2.91	<0.001*
AC	49	17.90±2.99	55	13.12±1.83	<0.001*
BC	50	17.32±2.65	55	13.71±2.25	<0.001*
CD	50	4.69±1.09	55	2.19±0.74	<0.001*
EF	50	20.81±3.41	55	26.46±6.84	<0.001*
GH	50	27.42±2.63	55	38.01±9.88	<0.001*
AE	49	10.42±0.57	55	11.73±1.31	<0.001*
IG	49	10.30±0.24	55	11.65±1.50	<0.001*
BF	49	10.75±0.49	55	12.53±1.50	<0.001*
FH	49	10.65±1.05	55	9.97±1.73	0.017*
DI	49	30.28±4.56	54	34.75±5.03	<0.001*
IJ	55	16.95±3.60	55	14.51±5.22	0.006*
GH	49	12.72±18.79	55	8.13±2.37	0.096

*Significant at 0.05 level according to Student t-test

Table 7. Distribution of morphometric measurements in Cavitas glenoidealis by gender and lateralization (right, left) (in cm)

	Male			Female		
Parameters	Right Mean ± SD	Left Mean ± SD	p	Right Mean ± SD	Left Mean ± SD	p
AB	37.05±3.38	28.33±2.23	<0.001*	33.68±2.63	25.41±2.80	<0.001*
AC	19.62±2.55	13.99±2.10	<0.001*	16.25±2.44	12.,30±1.01	<0.001*
BC	17.26±3.08	14.34±1.78	<0.001*	17.39±2.21	13.11±2.52	<0.001*
CD	5.06±1.23	2.56±0.73	<0.001*	4.32±0.80	1.83±0.56	<0.001*
EF	21.63±3.73	28.11±7.00	<0.001*	20.01±2.92	24.88±6.41	<0.001*
GH	28.86±2.55	40.30±11.11	<0.001*	25.98±1.82	35.82±8.16	<0.001*
AE	10.48±0.70	11.72±1.28	<0.001*	10.38±0.42	11.74±1.37	<0.001*
EG	10.33±0.26	11.67±1.11	<0.001*	10.27±0.24	11.64±1.83	<0.001*
BF	10.72±0.46	12.78±1.76	<0.001*	10.79±0.53	12.29±1.19	<0.001*
FH	10.58±0.88	10.05±1.12	0.527	10.74±1.22	9.91±2.20	0.603
DE	31.61±5.11	36.99±5.40	<.0001*	28.90±3.51	32.67±3.67	<0.001*
EF	19.00±3.70	16.55±6.50	0.836	14.83±1.87	12.55±2.40	0.920
GH	16.67±2.85	9.53±2.10	0.312	8.61±2.36	6.78±1.79	0.293

*Significant at 0.05 level according to Student t-test

Table 8. Distribution of morphometric measurements in Cavitas glenoidealis by age (in cm)

Parameters	N	>40 years Mean ± SD	N	<40 years Mean ± SD	p
AB	77	31.65±5.22	30	28.84±4.95	0.012*
AC	76	15.70±3.34	30	14.50±3.41	0.108
BC	77	15.82±3.09	30	14.34±2.53	0.013*
CD	77	3.56±1.61	30	2.84±1.22	0.015*
EF	77	23.98±6.42	30	23.12±5.30	0.483
GH	77	33.10±9.08	30	32.24±9.01	0.660
AE	76	11.03±1.01	30	11.42±1.62	0.228
EG	76	11.04±1.41	30	10.97±0.89	0.780
BF	76	11.61±1.40	30	11.99±1.54	0.253
JH	76	10.41±1.56	30	9.98±1.23	0.136
DI	76	32.17±5.18	30	33.82±5.30	0.157
IJ	76	15.74±3.58	30	15.54±6.71	0.879
GH	76	10.76±15.28	30	9.00±2.90	0.340

*Significant at 0.05 level according to Student t-test

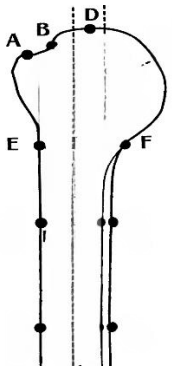

Figure 1. Proximal humerus for morphometric measurements (anterior view) (*Adapted from McPherson et al., 1997).*

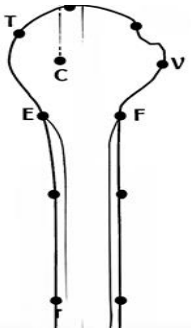

Figure 2. Proximal humerus for morphometric measurements (lateral view). (TD: Transverse diameter, VD: Vertical diameter) (*Adapted from McPherson et al., 1997*)

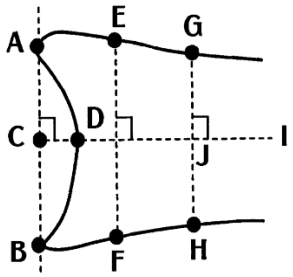

Figure 3. Glenoid fossa for morphometric measurement (anterior view) (*Adapted from McPherson et al., 1997*)

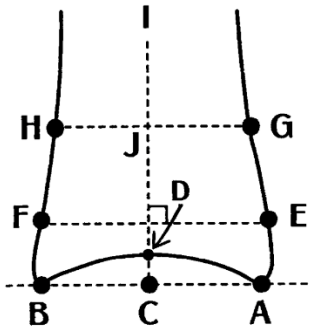

Figure 4. Glenoid fossa for morphometric measurement (lateral view) (*Adapted from McPherson et al., 1997*)

Discussion

The importance of precise reconstruction of the normal three-dimensional anatomy has been stressed by newly introduced designs for prosthetic replacement of the proximal part of the humerus. However, so far, the external three-dimensional anatomy of the proximal part of the humerus has been reported in only a few studies. As far as we know, no researchers have directly measured intramedullary proximal humeral morphology or associated it with extramedullary morphology.

The glenoid version describes the orientation of the glenoid cavity with respect to a plane perpendicular to the scapular body. The glenoid version is between 2^0 of anteversion and 9^0 of retroversion on normal shoulders.[16-20] Since version abnormalities have been correlated with glenohumeral instability [21,22], osteoarthritis[23,24], rheumatoid arthritis[18], and subcoracoid impingement[19], knowledge of glenoid version is fundamental. The glenoid version may also serve a function in shoulder replacement surgery. The latest studies have indicated that excessive glenoid component version is linked with abnormal loading of a glenoid component[25] and with poor clinical results.[26]

The modern era of shoulder arthroplasty began in 1951 with the introduction of Kruger's vitallium humeral head replacement and Neerer's similar humeral head implant.[27-29] Since then, a wide range of prosthetic designs have been developed, and clinically implanted and various successful results have been obtained.[30-33] These prosthetic systems consist of designs ranging from minimally constrained such as the Neer prosthesis to constrained or fixed fulcrum devices such as the Bickel, Jefferson, Reeves, Leeds, and Stanmore.

The efficacy of a minimally or nonconstrained shoulder design should be dependent on recreating the exact and complicated mechanical connections between the proximal humerus and glenoid fossa. The following is essential for the creation of a durable total shoulder prosthesis tolerating the functional ranges of the normal human shoulder:

(1) Knowledge of glenohumeral kinematics and the mechanical forces that interact at the shoulders within the functional range of motion. This information has been rigorously researched and carefully defined and explained in the literature.[34-40]

(2) Knowledge of the properties and performance of biomaterials present for the use of total shoulder arthroplasty in humans. These data have been obtained from extensive studies of total hip and knee implants.[41-42]

(3) Knowledge of the accurate osseous anatomy and anatomical relationships of the normal proximal humerus and glenoid.[43-46]

Unlike the hip and knee, few anthropometric data are available highlighting the osseous anatomy of the human shoulder.[30,32,40,44,45] When using minimally constrained shoulder implants, it is essential to recreate normal anatomical relationships. Unlike the hip joint, where the osseous anatomy resembles a ball-and-socket providing inherent stability, glenohumeral articular stability depends primarily on the surrounding musculotendinous soft-tissue unit acting in a smooth synchronous pattern to provide a resultant stabilizing force towards the glenohumeral joint.[31,34-36,38-40] The osseous anatomy and

normal anatomical relationships of the glenohumeral joint need to be reconstructed in every individual undergoing minimally restricted resurfacing shoulder arthroplasty in order to enable the complex movements of the 17 muscles surrounding the shoulder joint to function properly. Furthermore, when an uncemented procedure is used, a close match between the bone and the implant is essential. This is supported by histological data suggesting that before bone ingrowth occurs on porous impaled surfaces the relative motion between an implant and bone must be decreased to 50 µm or less.[47] In addition, the strength and rigidity of cancellous bone increase significantly within 2 to 5 mm of the cortical Wall.[48] Therefore, it is only possible to directly support the humeral component with the strongest available bone if instruments and implants closely representing endosteal geometry are designed.

The anatomic parameters described and measured in this study provided an accurate reference for proximal humerus and glenoid implant designs. In general, the anthropometric data obtained in this study are in line with the latest results of Lannotti et al.[44] and Maki and Gruen.[45] The anatomic relationships discussed in this study also provide further insight into human glenohumeral geometry.

If the purpose of prosthetic replacement of the proximal part of the humerus is to reconstruct normal anatomy, it is crucial to provide a three-dimensional understanding of normal extramedullary and intramedullary humeral morphology. Prosthetic sizing, positioning, and design may be influenced by this information. Extramedullary anatomy may affect fixation and the position of the articular surface. In order to properly approximate normal anatomy with proximal humeral arthroplasty, this relation between the two anatomical considerations requires concurrent knowledge of both extramedullary and intramedullary morphology. A review of the literature on the morphological and morphometric properties of the glenoid cavity reveals the incredible variety of existing forms and parameters.[49-54] It appears that the morphology of the scapula and the glenoid cavity is extremely diverse. There is, however, a consensus on the role of the glenoid cavity that an osseous base is provided for the stability of the glenohumeral joint both sagittally and vertically.[51] The most significant factor that contributes to this stability was recently identified by Itoi et al.[55] indicating that a bone loss of more than %21 of the superior-inferior glenoid length would lead to instability in spite of correct soft-tissue recovery.[54] This was confirmed by Burkhart et al.[56], who clarified the definition of bone loss: assuming that the inferior glenoid is in the form of a circle to the anterior rim of less than 6mm (loss of %25) would be the sign for a bony surgical stabilizing procedure. Anatomists describe the shapes of the glenoid cavity as teardrop, pear-shaped, round, ovoid, or inverted comma shape. The anteroposterior (AP) width of the upper half of the glenoid cavity in this shape is less than the lower half. In addition, the supero-inferior (SI) diameter is greater than the largest AP diameter.[57-60] Normal variations in the anatomical dimensions of the glenohumeral surfaces should be known for the design and selection of prosthetic components for shoulder arthroplasty.[59] Reestablishment of normal glenohumeral relationships is achieved by restoring normal skeletal anatomy, selecting appropriate size prostheses, and their correct placement.[59] When Cavitas glenoidalis measurements were compared between genders, a significant difference was observed. This feature was mentioned in the studies of both Von Schroeder et al.[57] and Mallon et al. In their study on cavitas glenoidalis, Prescher and Klümpen[58] stated in their citation from Acsadi Nemesceri (1970) that the main bones used in gender determination were pelvis and skull bones, and they also investigated whether the use of cavitas glenoidalis is appropriate. The surface area of cavitas glenoidalis was reported as 9.87 ± 1.23cm² in males and 7.18 ± 0.89 cm² in females. He also indicated that this area is associated with the maximum length and width of the scapula. Nevertheless, the same researcher stated that 60% of men and 36% of women can be correctly detected by cavitas glenoidalis and it can thus only be used as an aid in the presence of other bones.[58]

Conclusion

1. A precise/reproducible system has been developed for the comprehensive examination of the osseous anatomy of the human shoulder.
2. Many osseous parameters have been identified by a meticulous anthropometric study of the glenoid and proximal humerus, which can be used to fit the prosthesis to the anatomical geometry of a patient.
3. Anatomical relationships of the humeral head and glenoid have been described as conformity, constraint, and canal flore useful to understand the geometry of the glenohumeral joint.
4. Correlations that are beneficial for the design and sizing of prosthetic components exist between many parameters.

Compliance with Ethical Standards

Ethics committee approval for the study was obtained from the University of Necmettin Erbakan Research Ethics Committee (2019/2125).

Conflict of Interest

There is no conflict of interest between the authors.

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Research Article | Araştırma Makalesi

INHIBITORY EFFECT OF CELL PHONES AGAINST HUMAN BREAST CANCER AND MYELOID LEUKEMIA CELLS GROWTH IN CULTURE MEDIA

KÜLTÜR ORTAMINDA İNSAN MEME KANSERİ VE MİYELOİD LÖSEMİ HÜCRELERİNİN PROLİFERASYONUNA KARŞI CEP TELEFONLARININ İNHİBİTÖR ETKİSİ

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Abstract

Objective: There is current news that emerges regarding the relationship between the magnetic effects of cell phones and some types of cancer. In spite of the studies carried out, the level of evidence of this news is low, and also the relationship between the magnetic effects of cell phones and other types of cancer is not certain except for brain cancer. In this study, it is aimed to examinethe effects of magnetic field of cell phones on the samples of breast cancer human myeloid leukemia cell growth.

Methods: In the study, breast cancer MCF-7 and leukemia K562 cell lines were used as the source of cancer cells. During the six-day cell culture, cancer cells were subjected to the effects of cell phone by using a telephone call program (Automated outbound call software). The system made 6 calls for 1 minute for each call once in 144 minutes from a fixed line. The number of cultured cells and proliferation capacities of the two types of tumor cells in the control and experimental groups were assessed.

Results: The number of cancer cells, which were subjected to the effects of cell phone as a result of the culture of tumor cells, was found lower when compared with control group (7500000 ± 100000 vs 6625000 ± 225000 for MCF-7; 15412500 ± 112500 vs 13700000 ± 250000 for K562; $P < 0.05$ for both). In MTT test, it was found out that two types of cell proliferation were inclined to slow down with the effect of cell phone.

Conclusion: The results can be translated that cell phone may inhibit neoplastic transformation, and this observation may promote to initiate new clinical studies both for healthy people and for patients with cancer.

Keywords: Cancer cells, Magnetic fields, Cell phone, Proliferation

Öz

Amaç: Cep telefonlarının manyetik etkileri ile bazı kanser türleri arasındaki ilişkiye dair güncel haberler bulunmaktadır. Yapılan araştırmalara rağmen bunların kanıt düzeyi düşüktür. Ayrıca cep telefonlarının manyetik etkilerinin beyin kanseri dışında diğer kanser türleri ile ilişkisi kesin değildir. Bu çalışmada, insan meme kanseri ve miyeloid lösemi hücre örneklerinin proliferasyonu üzerinde cep telefonlarının manyetik alanının etkilerinin incelenmesi amaçlanmıştır.

Yöntem: Çalışmada kanser hücresi kaynağı olarak meme kanseri MCF-7 ve lösemi K562 hücre dizileri kullanıldı. Altı günlük hücre kültürü sırasında kanser hücreleri, bir telefon arama programı (otomatik giden arama yazılımı) kullanılarak cep telefonunun etkilerine maruz bırakıldı. Sistem sabit hattan 144 dakikada bir her aramada 1'er dakika süreyle 6 arama yaptı. Kontrol ve deney gruplarındaki iki tip tümör hücresinin kültürlenen hücre sayısı ve çoğalma kapasiteleri değerlendirildi.

Bulgular: Tümör hücrelerinin kültürü sonucunda cep telefonu etkisine maruz kalan kanser hücrelerinin sayısı kontrol grubuna göre daha düşük bulundu (7500000 ± 100000 vs 6625000 ± 225000 MCF-7 için; 15412500 ± K562 için 112500 vs 13700000 ± 250000; her ikisi için $P < 0,05$). MTT testinde iki tip hücre çoğalmasının cep telefonunun etkisiyle yavaşlamaya meyilli olduğu tespit edildi.

Sonuç: Sonuçlar, cep telefonunun neoplastik dönüşümü engelleyebileceği şeklinde tercüme edilebilir ve bu gözlem hem sağlıklı insanlar hem de kanserli hastalar için yeni bir klinik çalışma başlatmayı teşvik edebilir.

Anahtar Kelimeler: Kanser Hücreleri, Manyetik Alan, Cep telefonu, Proliferasyon

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Introduction

With a view to maintain life in a healthy way, there should be a balance between the reproduction and death of the human cells that form the living being. During life, some cells assign their duties to some other cells. The cells that should die according to genetic programming are destroyed in a certain order.[1] To set an example for cell death during natural course of life, it can be assumed as the disappearance of some structures, which emerge while the living being is growing mature in ovum or mother's womb, in maturation process. To give another example, cell death might be the disappearance of overstimulated immune cells to avoid damaging familiar cells.[2-4]

As a result of the stimulus such as hormones, some chemical substances and radiations coming from environment when the natural course continues, DNA damage can occur in cells. If the cell cannot repair DNA damage, the cells carrying abnormal characters disappear in a programmed way (apoptosis). In this way, hazardous possibilities such as the spread of damaged cells and cancer genesis are prevented.[4,5]

There is a weak side of the cells that have the potential of fast reproduction and accelerated cycle. This weak point is that they are quite sensitive to environmental effects. These environmental effects can cause abnormal maturation of cells and deviations in their differentiation processes. These deviations result in some unwanted events such as disabilities, damages in tissues and organs, and genetic diseases.[6,7]

Some technological devices such as cell phone, which have been ever increasingly produced and used in recent years, result in electro-magnetic pollution by producing electro-magnetic waves. The observations and studies carried out up until now indicate that electro-magnetic waves may increase the frequency of brain cancer formation.[6,8] However, the effects of electro-magnetic waves on the other types of cancer are not certain. The possible effects of electro-magnetic waves on cells were also examined in laboratory environment; however, the effects of electro-magnetic waves on cancer cells are limited.[9-11] The observations should be supported with sufficient laboratory studies. In the first instance, knowing these effects can make people more sensitive regarding the protection of people from magnetic effects. Also, it can shed light on the formation mechanisms of some types of cancer and draw the attention of patients receiving cancer treatment.

In this study, it was aimed to examine the effect of cell phones on the growth of cancer cells of different embryonic layers, epidermal and mesenchymal origin in culture, and thus at drawing the attention on both fast-dividing cells demonstrating malign character.

Methods

Study design

The study was planned as an experimental study and carried out in the Hematology Research Laboratory, Başkent University Adana Turgut Noyan Application and Research Center. In the study, breast cancer cells were used as an example for the cancer cell of epidermal origin, while human myeloid leukemia cells were used as an example for the cancer cells of mesenchyma layer origin. The K562 (German Collection of Microorganisms and Cell Cultures (Braunschweig, Germany) cell line was obtained for our previous studies and stored in the freezer was also used for this study. The MCF cell line was obtained from the Ministry of Agriculture and Forestry Alum Institute. The samples of both types of cancer cells were cultured into six cell culture plaques. Three of these plaques were subjected to the magnetic field of cell phone during the cell culture, while the other three were set as control plaques. In this way, study groups with three plaques were constituted.[12]

After six-days cancer cell culture and before applying 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) test used to determine cytotoxicity/cell viability, culture plaques were monitorized in inverted microscope (Nikon EclipseT100, Tokyo, Japan) when they were viable. After then, MTT test was conducted and the proliferation capacities of the cells in each culture plaque were observed.[13] And then, the number of cells present in each plaque and similarly the condition of viability of the cells were analyzed.

Cell Culture

RPMI-1640 (Stem Cell Technology, Vancouver, Canada) was used as the medium for the cultures. 10% fetal bovine serum, L-glutamine and antibiotic were added into feed lot. The cells frozen for the culture were resolved in water bath at a temperature of 37°C and prepared for the culture. After the count, cell solutions were transferred to 75 cm^2 culture flasks (BD, Le Ponte d'claix, France) as 100.000 cell/10 mL. The culture flasks incubated in environment with 5% CO2, 95% moisture and at temperature of 37 °C for 6 days. The process mentioned above was performed with control groups first, repeated for experimental groups with cell phone after. 1 mL sample (after trypsinization for MCF-7) was taken from the plaque on the last day of the culture for control and experimental groups and this sample was used for cell count and viability.[13,14]

Cell Count, Viability Test and MTT Test

By taking 10 µL of the obtained cell solution, the cells were counted under the light microscope (Olympus BX51, Tokyo, Japan) using the Thoma cell counting chamber (Arat et al., 2008). Acridine Orange (Sigma, A6014, Germany) viability assay was used to measure the viability of cells. Examined under a fluorescent microscope (Nikon, Eclipse E600, Tokyo, Japan). Green cells were considered viable, while orange cells were considered dead.

In the MTT test, 5000 cells/100 microliter per well were seeded in 96-well culture plates for each group. Control groups of both cell lines were analyzed first, and then test groups with mobile phone were analyzed. Culture plates were incubated for 96 hours at 5% CO2, 95% humidity and 37 °C. At the end of the experiment 10 µL (5 mg/mL

concentration) MTT solution for each was added into all of these wells. It was left for incubation of four hours again. In the end of incubation, DMSO was added into each well and left for incubation in the mixer for 15 minutes. And then, it was read in plate ELISA reader at a wavelength of 570 nm (reference wavelength is 630 nm).[13]

Creating Electromagnetic Effect

In order to create electromagnetic field during the study, the relationship between human being and cell phone was imitated. To this end, 1800 MHz GSM (Vodafone, Hong-Kong, China) device used frequently among people was used. The cell phone was placed in carbon dioxide incubator, in which cell culture was carried out, in a way that it can have contact with culture plaques.

With a view to provide standard calls, a fixed telecom line connected with a computer and analog modem was used. In the project, 6 calls for 1 minute for each, once in 144 minutes were made from fixed line in order to obtain data and use the cell phone (GSM; global system for mobile communication) device in the call process through "Automated Outbound Call Software" present in the web site titled "http://www.nch.com.au/ivm/outbound.html". The calls were recorded.

The cell phone was charged every morning between 8.00 o'clock and 9.00 o'clock. If it is considered that the cells caught infection during the culture of the tumor cells (according to their appearance and smell), these cells would be excluded from the study. It was also planned that if there is any difficulty in measurements and analyses technically, the study would be repeated. With a view to carry out the project, permission was received from Başkent University Adana Application and Research Center Directorate.

Statistical Analysis

In the statistical analysis of data, GraphPad Prism vs 9.0.0 (GraphPad Software, San Diego, CA, USA) program was used. The effect of the cell phone in study groups that contained both types of tumor cells was assessed by noting the number of cells obtained after the culture and their values read in ELİSA device and the percentages of viable cells. Student's t test was used in comparing the continuous measurements between the groups. A value of $p < 0.05$ was considered statistically significant.

Results

Cells of a million were initially seeded in each culture flask. Adequate growth was observed after 6 days in cell cultures generated with control groups and experimental groups of cell lines. Technical problems such as color change and odor did not occur in the culture plates.

Table 1 and Figure 1 shows the number of cells obtained after cell culture in control and test groups. The number of cells, which were subjected to the effects of cell phone as a result of the culture of tumor cells, was found lower when compared with the control group. This difference was found statistically significant both for MCF-7 breast cancer cells and K562 leukemia cells (7500000 ± 100000 vs 6625000 ± 225000 for MCF-7; 15412500 ± 112500 vs 13700000 ± 250000 for K562; $P < 0.05$ for both).

Table 1. The number of cells obtained after cell culture in control and experimental groups

Study groups		Number of Cells Day 6	
		MCF-7	K562
Control	N	3	3
	SD	100000	112500
	Median	7500000	15412500
	Bottom	7400000	15300000
	Top	7600000	15525000
Test Groups	N	3	3
	SD	225000	250000
	Median	6625000	13700000
	Bottom	6400000	13450000
	Top	6850000	13950000
	P value	0.0035	0.0004

In spite of the difference in the number of cells, the viability rates in control and experimental groups did not change (94.3±0.6 % for control group; 95.6±0.6 % for experimental group, $p > 0.05$). Table 2 and Figure 2 show the proliferative capacity of the cells cured in control and experimental groups which were exposed to MTT test.

Examining the absorption values of the samples which were taken from wells by carrying out MTT test in culture plaques and read in ELISA, it was determined that as a result of they were subjected to the effects of cell phones in the culture environment, the proliferative capacities of both MCF-7 breast cancer cells and K562 leukemia cells were inclined to be lower when compared to the controls. However, this difference was statistically significant only for K562 cells ($p< 0.05$).

Table 2. The proliferative capacity of the cells cured in control and experimental groups which were exposed to MTT test

Study groups		% Proliferation	
		MCF-7	K562
Control	N	3	3
	SD	3,781	3,392
	Median	100	100
	Bottom	96,22	96,61
	Top	103,8	103,4
Test Groups	N	3	3
	SD	0.9778	2.056
	Median	94.98	93.32
	Bottom	94	91.26
	Top	95.96	95.38
	P value	0.09	0.043

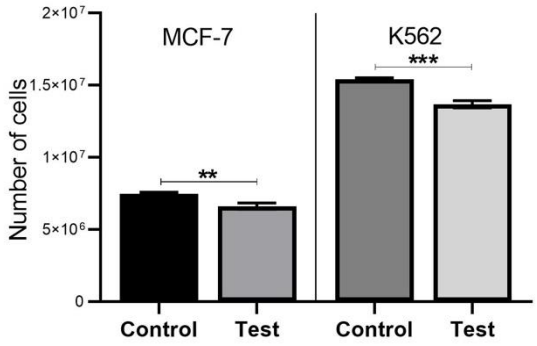

Figure 1. The number of cells obtained after cell culture in control and experimental groups

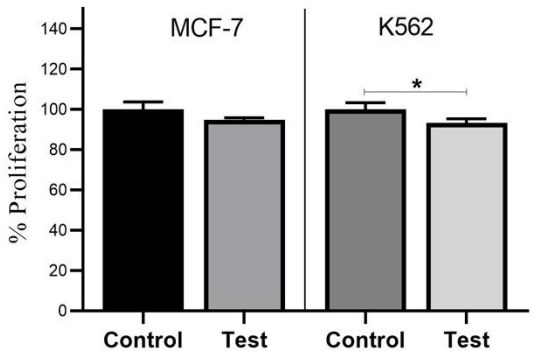

Figure 2. The proliferative capacity of the cells cured in control and experimental groups which were exposed to MTT test

Discussion

Each living being might be damaged as a result of the environmental effects in the place it is present. Chemical effects such as pesticides, roughly, biological effects such as microbes and physical effects such as accidents can be counted among these effects. With the developments in technology, the importance of electromagnetic pollution among these physical effects is gradually increasing day by day. And cell phones have been the technological devices which produce magnetic pollution and commonly used among people. They have become an integral part of daily life.[10,15]

There is much news of media, newspapers in particular, regarding the harmful effects of cell phones on human health.[9-11] The most important of this news in scientific terms can be counted as the INTERPHONE study which includes 5115 people with the participation of 13 countries.[16] Brain cells are the cells that have slow proliferative capacity and thus, their renewal ability is restricted. The results of the studies indicate mostly that cell phones may cause brain tumors stemming from brain cells.[16-18] It is also asserted that the harmful effects of cell phones to brain cells may originate from the heat effect occurring when they are kept close to brain, except for magnetic field.[17]

It was indicated in scientific sources that there may be some differences among individuals in terms of being negatively affected from cell phones.[19] It was reported that age is an important factor and the highest exposure can be seen in children and early adults. A human being's being at home, in workplace, travelling on a bus or a train or being in a rural area while using cell phone can change his/her level of exposure.[4,18] This effect increases in relation to the proximity to base stations and high voltage transmission lines.[19] The distance of cell phones to human body was also found out to be important for magnetic exposure. Even the firms that produce cell phone added warnings in the instructions of the device regarding its harmful effects. These warnings indicate that the device should be kept away from human body about 2.5 cm. It is a known fact that use frequency and duration of cell phones are important regarding exposure. The presence of cell phone radio frequency and other electric household appliances along with cell phone was found important regarding exposure.[18,19]

Cell phones are generally carried in the pockets of shirts which are close to breast region or in back pockets of pants which are close to the area where the bone marrow is intensive. The tumor cells of breast and bone marrow which have neighbor relations with these regions were chosen as the material of the study as the cells which are of ectoderm and mesoderm layers origin and have fast proliferative capacity. The fact that these cells have cell chains that can be obtained commercially provided the opportunity to carry out the study in culture environment. In our study, it was determined that the proliferative capacities of breast and bone marrow neoplasm cells, which were subjected to the effect of cell phone during the culture, slowed down in comparison to the other cells even though it was not certain. The fact that this slowing down was observed in both types of tumor cells stemming from different layers may support the idea that the effect is independent from the type of tumor and formed as a result of a general environmental effect (magnetic field). As mechanism, it is claimed that the inhibitory effect of electromagnetic waves of mobile phones (<300 GHz) on cell proliferation is related to the T-type Ca2+ channel subunit expressed in malignant cells, especially MCF-7 breast cells, and Ca2+ uptake into breast cells is affected by the electromagnetic field and sensitizes tumor cells.[20] Alteration of intracellular Ca2+ level affects apoptosis, proliferation, mitochondrial activity, and gene transcription of cells.[21,22] Another mechanism could be probable epigenetic influence. Further studies are needed on this subject.[23]

In this study, cells in the same number were cultured in each culture plaques. Culture study was carried out on the cells in experimental groups in the same duration, the same environment and conditions. In order to reduce margin of error, each experiment was repeated in three different culture plaques. With a view to test the effect of cell phone, the cell phone was placed in incubator in a way that it was close to the plaques. In the INTERPHONE study, calls were standardized in a way that corresponds to the intensive use duration defined as the use of cell phone more than half an hour in a day and cell phone calls in the same frequency and duration were made.

MTT test, which is an acceptable method for researching the effect of environmental effects on the reproduction of cells, and viability tests were used.[13]

The study has some limitations. First, the period of cell culture and subjection to the effects of cell phone could be kept longer. Second, the electromagnetic field of subjection cannot have a numerical measurement. This measurement could have been possible by using the devices utilized in experiments and creating fixed magnetic field. Third, studies on the mechanism are required, such as apoptosis study. In this study however, the basic thought was to examine the effect of cell phone on cancer cells by simulating the use of cell phone as in daily life.

In conclusion**,** the results obtained in our study support the idea that the proliferative capacities of breast cancer and leukemia cells of different embryonic layer origins can be affected when they are subjected to the effects of cell phone in laboratory environment. The fact that these effects are inclined to slow down the proliferation of cancer cells may encourage researchers for carrying out further studies on mitigating the concerns about tumor genesis.

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Compliance with Ethical Standards

This study does not have a design on biomaterials directly sourced from humans or animals. The study was performed with a commercially available cell line. Therefore, ethical committee approval is not required.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

The project idea was put forward by BB and MA. BB, MA, and EM jointly designed and conducted the laboratory phases of the study. IK provided laboratory support. The writing phase of the study was done by all the authors.

Financial Disclosure

Financial disclosure none.

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Research Article|Araştırma Makalesi

ASSESSMENT OF ENDOTHELIAL DYSFUNCTION AND VASCULAR STIFFNESS AFTER CHOLECALCIFEROL ACCORDING TO DIALYSIS MODALITY

KOLEKALSİFEROL SONRASI ENDOTEL DİSFONKSİYONU VE DAMAR SERTLİĞİNİN DİYALİZ MODALİTESİNE GÖRE DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: The risk of developing cardiovascular disease (CVD) increases significantly in children with chronic kidney disease (CKD) especially with low serum 25- hydroxyvitamin D (25OHD) levels. Herein; we aimed to compare the effects of vitamin D deficiency and the impact of cholecalciferol treatment on endothelial functions and vascular stiffness in children with CKD receiving hemodialysis (HD), peritoneal dialysis (PD) and non-dialysis (ND).

Methods: HD (n=7), PD (n=7) and ND (n=27) patient groups consisting of 41 children totally with low 25OHD levels were compared among each other in regards of biochemical parameters, flow-mediated dilatation (FMD) and local arterial stiffness before and after a single dose of 300.000 units of cholecalciferol treatment.

Results: There was no difference in FMD and local arterial stiffness values between HD, PD and ND patient groups before vitamin D supplementation. Significant increase in endothelium-dependent FMD was observed in all patient groups after intervention with cholecalciferol; however the improvement in endothelium-independent FMD and local arterial stiffness measurements was demonstrated in patients with PD and ND. Baseline parathormon level was higher in patients on dialysis; at the end of the study, significant decrease was detected only in patient group not receiving dialysis.

Conclusions: Endothelial dysfunction and impaired vascular stiffness were determined in children with CKD with low 25OHD levels regardless of the disease severity. Recovery with cholecalciferol therapy revealed that vitamin D deficiency should be corrected even in early stages of CKD to prevent the development of CVD.

Keywords: Vascular stiffness, endothelial dysfunction, chronic kidney disease, cholecalciferol

ÖZ

Amaç: Özellikle serum 25-hidroksivitamin D (25OHD) seviyeleri düşük kronik böbrek hastalığı (KBH) olan çocuklarda kardiyovasküler hastalık (KVH) gelişme riski önemli ölçüde artmaktadır. Bu çalışmada; KBH olan ve hemodiyaliz (HD), periton diyalizi (PD) ve diyaliz dışı (ND) tedavi alan çocuklarda D vitamini eksikliğinin etkilerini ve kolekalsiferol tedavisinin endotel fonksiyonları ve damar sertliği üzerine olan etkilerini karşılaştırmayı amaçladık.

Yöntem: Serum25OHD düzeyi düşük toplam 41 çocuktan oluşan 7 HD, 7 PD ve 27 ND hasta grupları; 300.000 ünite tek doz oral kolekalsiferol öncesi ve sonrası biyokimyasal parametreler, akım aracılı dilatasyon (FMD) ve lokal arter sertliği açısından kendi aralarında karşılaştırıldı.

Bulgular: D vitamini takviyesi öncesi HD, PD ve ND hasta grupları arasında FMD ve lokal arteryel sertlik değerlerinde farklılık yoktu. Kolekalsiferol tedavisi sonrası tüm hasta gruplarında endotel bağımlı FMD de önemli artış gözlendi; ancak endotel bağımsız FMD ve lokal arteryel sertlik ölçümlerinde iyileşme sadece PD ve ND hastalarında gösterildi. Diyaliz olan hastalarda (HD, PD) başlangıç parathormon düzeyi daha yüksekti; çalışma sonunda ise sadece diyalize girmeyen hasta grubunda anlamlı azalma olduğu tespit edildi.

Sonuç: KBH olan ve 25OHD düzeyi düşük çocuklarda hastalığın şiddetine bakılmaksızın endotel fonksiyon bozukluğu ve artmış damar sertliği saptanmıştır. Kolekalsiferol tedavisi ile gözlenen iyileşme, KVH gelişimini önlemek için D vitamini eksikliğinin KBH nın erken evrelerinde bile düzeltilmesi gerektiğini ortaya koymuştur.

Anahtar Kelimeler: Damar sertliği, endotel disfonksiyonu, kronik böbrek hastalığı, kolekalsiferol

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Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in children with end-stage renal disease (ESRD).[1] Hypertension, disturbed calcium-phosphorus metabolism, elevated serum intact parathyroid hormone (iPTH) and dysregulated renin-angiotensin-aldosterone axis have been associated with cardiac dysfunction and increased vascular stiffness in chronic kidney disease (CKD) patients.[2] Left ventricular hypertrophy, systolic or diastolic dysfunction have been detected even in early stages of renal impairment.[3]

Endothelial dysfunction as an initial sign of atherosclerotic process has also been demonstrated in children with early stages of CKD.[4] Flow-mediated dilatation (FMD) of the brachial artery which has been validated to assess endothelial dysfunction and determination of an increased carotid intima media thickness (cIMT) have been used as an indicator for cardiovascular events in patients with CKD.[5,6]

Previous studies revealed that low level of serum 25-hydroxyvitamin D3 (25OHD) in CKD patients has been associated with higher cardiovascular mortality,endothelial dysfunction and increased arterial stiffness.[7,8] In recent years, vitamin D has been demonstrated to prevent ventricular hypertrophy,suppress vascular smooth muscle cell proliferation and inhibit systemic inflammation in CKD.[9-11] As vitamin D deficiency has been reported to be more prevalent in this population,especially in patients on peritoneal dialysis, prompt vitamin D supplementation is crucial for improved cardiovascular status.

In the present study, we evaluated the efficacy of oral cholecalciferol on left ventricular hypertrophy, arterial stiffness and brachial artery FMD, in addition to the markers of inflammation and calcium-phosphorus metabolism and we compared the results between hemodialysis (HD), peritoneal dialysis (PD) and pre-dialysis patients.

Methods

Patients

Serum 25OHD levels of forty-four children with CKD including those on dialysis therapy who had been followed up by the department of pediatric nephrology were investigated. Its levels were classified according to the KDOQI Guidelines. Serum 25OHD levels between 16 and 30 ng/ml were described vitamin D insufficiency, while <15ng/ml and <5 ng/ml deficiency and severe deficiency, respectively.[12] The study protocol was approved by University Ethics Committee in accordance with the Declaration of Helsinki. Written informed consent for participation was taken from all patients and/or their parents.

Patients who had sufficient serum vitamin D levels (25OHD>30 ng/ml), inflammation, heart disease, hepatic disease and malignancy were excluded from the study.

Of the 44 patients with CKD, 41 patients with low vitamin D levels were recruited for the study.

Laboratory

After a fasting period of at least 8 hours, venous blood samples were obtained. At baseline, serum creatinine, urea nitrogen (BUN), glucose, albumin, calcium, phosphorus, alkaline phosphatase (ALP), total cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), iPTH and 25OHD were measured. C-reactive protein (CRP) and fibrinogen were evaluated for inflammatory status. All the blood samples were collected one day before hemodialysis session.

Echocardiography

All children with CKD underwent 2-D M-mode echocardiography using a Vivid 7 system (GE Vingmed, UltrasoundAS, Horten, Norway) with a 3 MHz transducer. The cardiovascular assessment was performed by an experienced pediatric cardiologist after the subjects had rested for at least 10 minutes and the parameters were estimated according to guidelines of American Society of Echocardiography.[13] Left ventricular mass index (LVMI) was calculated with the formula described by De Simone et al.[14] Left ventricular hypertrophy was defined as LVMI greater than 38.6 g/$m^{2.7}$.

Flow-Mediated Dilatation

Flow-mediated, endothelium-dependent vasodilatation was performed by the same physician for fasting subjects in a quiet room. Caffeine and exercising for at least 8 hours were avoided. After 10 minutes of resting period, B-mode ultrasound images were obtained using 10 MHz linear array according to the method that was described by Celermajer et al.[15] Firstly, diameter of the right brachial artery was measured on antecubital fossa. After the placement of a pneumatic tourniquet above the cubital region, it was inflated to a pressure of 300 mmHg for 5 minutes. The diameter of the brachial artery was obtained again for reactive hyperemia, 45-60 seconds after the cuff deflation. Fifteen minutes later, it was remeasured for basal and for 5 minutes after 400 µg sublingual glyceryltrinitrate.

Distensibility

Distensibility of carotid arteries is a sensitive marker for the functional changes of vascular tree which predicts cardiovascular disease (CVD) risk earlier than increased cIMT. It is defined with distensibility coefficient (DC), stiffness index (β), incremental elastic modulus (E_{inc}) and determines local arterial stiffness.[16]

A pediatric cardiologist who was blinded to the patients' clinical situation performed echocardiography and vascular ultrasound. Intraobserver coefficient of variation was 2.1% for FMD.

Intervention

After initial assessments of biochemical and cardiovascular results, 41 children with CKD having low 25OHD levels (<30 ng/ml) were given single dose of 300.000 IU oral cholecalciferol. All laboratory tests and cardiovascular measurements were repeated after 12 weeks. The effects of vitamin D supplementation were compared between HD, PD and pre-dialysis patients.

Statistical Analysis

Mean ± standart deviation was used for continuous and normally distributed variables, median for skewed variables. One-way ANOVA or Kruskall-Wallis test was performed for the comparison of multiple categories. Significant difference before and after cholecalciferol was calculated with paired *t*test or Wilcoxon test. Statistical analysis was performed using Statistical Package for the Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA) and p value of 0.05 or lower was significant.

Results

Patient Characteristics

Forty-four CKD patients (24 girls) were screened. Forty-one of 44 children (93.2%) had low levels of serum 25OHD. Of the 41 patients, median age was 14.9 years (10.9-16.5). 13 of them (31.7%) had vitamin D insufficiency and 28 (68.3%) had deficiency. Severe deficiency was found in 5 patients (12.2%). The patients were grouped according to their dialysis modality such as HD (n=7), PD (n=7) and pre-dialysis groups (n=27). All of the HD patients were dialyzed for 3-4 hours thrice weekly using bicarbonate based dialysate and all PD patients received automated peritoneal dialysis. During the study period, 21 patients (51.2%) were treated with calcium-based phosphate binders whereas 8 patients (19.5%) with sevalemer. Calcitriol was prescribed for 16 children. There were no differences with regards to age, gender, duration of kidney disease, time on dialysis and BMI between HD, PD and pre-dialysis groups. The mean duration of dialysis were 2.93±2.48 and 4.3±3.15 years, in HD and PD patients, respectively (p=0.38). Table1 summarizes demographic characteristics of the patients. Mean glomerular filtration rate (GFR) of the children in pre-dialysis group was significantly higher than those in HD and PD groups (p<0.001). Baseline systolic blood pressure did not differ among the groups but diastolic blood pressure was significantly higher in HD patients when compared to others (p=0.046). No significant change was observed in blood pressure values after cholecalciferol supplementation.

Vitamin D and Bone Mineral Metabolism

Baseline mean serum 25OHD levels were similar in HD (12.6±8.3 ng/ml), PD (9.9±5.5 ng/ml) and pre-dialysis patients (13.1±5.48 ng/ml) (p=0.46). No significant differences were observed in baseline values of serum calcium, phosphorus, calcium-phosphorus product, albumin and LDL-cholesterol between the study groups. The patients in HD and pre-dialysis groups had significantly higher ALP levels than those in PD group (p=0.007). Serum iPTH levels were significantly elevated in HD group when compared to the patients in pre-dialysis group (p=0.034) (Table1). After the supplementation of vitamin D, 25OHD increased significantly in each group. Serum 25OHD levels increased from10.9 to 27.6 ng/ml (p=0.028), 9.9 to 21.9 ng/ml (p=0.043) and 13.1 to 32.8 ng/ml (p<0.001) in HD, PD and pre-dialysis patients, respectively (Figure 1) No significant change was observed in calcium, phosphorus, calcium-phosphorus product, albumin and LDL-cholesterol levels in either groups before and after cholecalciferol treatment. However, significant decreament in ALP and iPTH levels were detected only in pre-dialysis patients. Mean ALP levels decreased from 238.2 to 184.5 U/l (p=0.003) and median iPTH decreased from 200.4 to 127.3 pg/ml (p=0.005). There was a trend towards a decline in ALP and iPTH in HD and PD groups that was not significant.

Endothelial and Inflammatory Markers

Both median CRP (0.66 mg/dl vs 0.12 mg/dl, p=0.04) and mean fibrinogen values (4.6±0.9 g/l vs 3.75±0.8 g/l, p=0.035) significantly elevated in HD group when compared with pre-dialysis group. However, no change was observed in CRP and fibrinogen levels among the groups following cholecalciferol supplementation. Regarding the indicators for endothelial dysfunction, baseline endothelium-dependent (p=0.42) and independent FMD measurements (p=0.54) were similar between patients having HD, PD and no replacement therapy. After vitamin D treatment, there was a significant increase in mean endothelium-dependent FMD from 5.58% to 7.85% (p<0.001), 5.7% to 8.5% (p=0.016) and 7.23% to 9.77% (p<0.001) in HD, PD and pre-dialysis patients, respectively. Although mean endothelium-independent FMD improved significantly in PD (12.48±5.81% vs 13.4±5.26%, p=0.036) and pre-dialysis groups (13.99±4.96% vs 15.38±5.18%, p=0.022) after cholecalciferol supplementation, the increase in HD patients from 12.05±2.21% to 12.77±1.95% did not reach statistical significance (p=0.14) (Table 2).

Cardiac Function

Patients on HD had significantly higher mean LVMI than those in pre-dialysis group (59.1±34.6 vs39.4±11.7 g/$m^{2.7}$, p=0.04). Eventually, vitamin D therapy had no effect on LVMI within the study groups.

Carotid Artery Structure and Function

DC, β and E_{inc} values of both CCA were similar between HD, PD and pre-dialysis patients. Following vitamin D treatment, significant improvement was observed in DC, β and E_{inc}values of the patients in PD and pre-dialysis groups whereas no recovery was noted in hemodialyzed children (Table 3-4).

Table 1. Baseline demographic, biochemical and cardiovascular parameters

	HD (n=7)	PD (n=7)	Nondialysis (n=27)	p value
Age, years	15.1±1.6	15.2±3.3	12.9±4.2	NS
Height SDS	-4.62* (-8.81 --2.67)	-1.76 (-3.93 -1.13)	-1.63 (- 3.8 - 0.67)	0.034
BMI	19.34±7.46	17.52±3.61	18.1±2.86	NS
BMI SDS	0.86±3.63	- 0.41±1.56	0.32±1.2	NS
Duration of CKD, years	6.22±2.93	4.42±3.04	4.52±3.12	NS
SBP, mmHg	120(107-155)	120(96-120)	107(100-120)	NS
DBP, mmHg	81.86±23.54**	62.57±13.26	67.52±12.7	0.046
Creatinin (mg/dl)	5.21 (4.6-7.19)*	5.69(5.53-9.12)*	1.64(1.18-3.18)	0.000
eGFR (ml/min/1.73m^2)	14.11±3.67*	14.08±5.35*	46.45±24.43	0.000
25OHD (ng/ml)	12.6±8.39	9.91±5.54	13.13±5.48	NS
iPTH (pg/ml)	531.6(238.9-945)*	229.4(109.2-323.3)	200.4(111.7-387)	0.034
Calcium (mg/dl)	9.8(9-10.1)	9.7(9-9.9)	9.5(9.2-9.8)	NS
Phosphorus (mg/dl)	4.9(4.7-5.4)	4.3(3.1-5.6)	4.5(4.2-4.8)	NS
Ca x P product	47.9±6.2	41.6±15	41.8±6.4	NS
Total cholesterol (mg/dl)	167(144-230)	189(175-203)	168(143-192)	NS
LDL cholesterol (mg/dl)	91.1±34	112.6±27.3	96.1±31.8	NS
CRP (mg/dl)	0.66(0.29-1.97)*	0.07(0.03-0.56)	0.12(0.05-0.34)	0.04
Fibrinogen (g(l)	4.6±1.32*	4.58±0.9*	3.75±0.83	0.035
LVMI (gr/m$^{2.7}$)	59.15±34.61*	41.72±12.44	39.48±11.79	0.04
RCCA				
DC (kPa^{-1}10^{-3})	42.07±11.82	52.31±25.99	53.9±20.67	NS
β	3.99±1.53	4±1.55	3.53±1.22	NS
E_{inc} (kpa 10^3)	0.31±0.09	0.26±0.1	0.24±0.09	NS
LCCA				
DC (kPa^{-1}10^{-3})	42.24±10.97	49.41±20.37	54.33±21.24	NS
β	3.91±1.43	4.22±1.96	3.57±1.48	NS
E_{inc} (kpa 10^3)	0.27±0.08	0.27±0.11	0.24±0.10	NS
ED - FMD (%)	5.58±2.09	5.70±4.19	7.23±3.8	NS
EI - FMD (%)	12.05±2.21	12.48±5.81	13.99±4.96	NS

Data are expressed as mean±SD and median (interquartile range)

HD hemodialysis, *PD* peritoneal dialysis, *SDS*standart deviation score, *BMI* body mass index, *CKD* chronic kidney disease, *SBP* systolic blood pressure, *DB*diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *25OHD* 25-hydroxyvitaminD, *iPTH* intact parathyroid hormone, *LDL* low-density lipoprotein, *CRP*: C-reactive protein, *LVMI* left ventricular mass index, *RCCA* right common carotid artery, *LCCA* left common carotid artery, *DC*distensibility coefficient, *β* stiffness index, E_{inc}elasticity increment model, *ED-FMD* endothelium-dependent flow-mediated dilatation, *EI-FMD* endothelium-independent FMD, *NS* not significant.

* p<0.05 vs nondialysis; ** p<0.05 vs PD and nondialysis

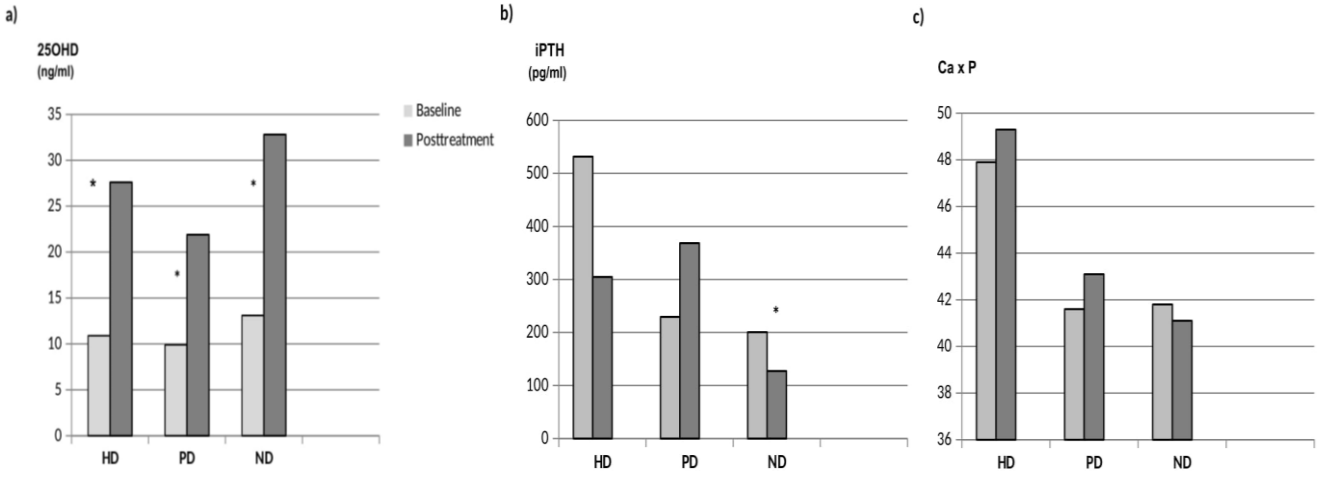

Figure 1. Changes in median 25-hydroxyvitamin D (25OHD), intact parathyroid hormone (iPTH) and in mean calcium phosphorus product (Ca x P) values in children with hemodialysis (HD), peritoneal dialysis (PD) and nondialysis (ND) before and after cholecalciferol. * p<0.05

Table 2. Cardiovascular measurements in hemodialysis patients before and after cholecalciferol

	Baseline	Post-treatment	p value
RCCA			
DC ($kPa^{-1}10^{-3}$)	42(31.5-55.8)	41.9(27.7-68.6)	NS
β	3.99±1.53	4.2±2.18	NS
E_{inc} (kpa 10^3)	0.31±0.09	0.29±0.14	NS
LCCA			
DC ($kPa^{-1}10^{-3}$)	42.224±10.97	47.26±16.89	NS
β	3.91±1.43	3.8±1.3	NS
E_{inc} (kpa 10^3)	0.27±0.08	0.26±0.1	NS
ED - FMD (%)	5.58±2.09	7.85±2.2	0.000
EI - FMD (%)	12.05±2.21	12.77±1.95	NS

RCCA right common carotid artery, *LCCA* left common carotid artery, *DC*distensibility coefficient, *β* stiffness index, E_{inc} elasticity increment model, *ED-FMD* endothelium-dependent flow-mediated dilatation, *EI-FMD* endothelium-independent FMD, *NS* not significant.
p<0.05 statistical significance

Table 3. Cardiovascular measurements in peritoneal dialysis patients before and after cholecalciferol

	Baseline	Post-treatment	p value
RCCA			
DC ($kPa^{-1}10^{-3}$)	52.3(25.9-75.8)	61.8(49.6-68.5)	NS
β	4±1.55	2.78±0.85	0.044
Einc (kpa 10^3)	0.26±0.1	0.2±0.06	0.043
LCCA			
DC ($kPa^{-1}10^{-3}$)	49.41±20.37	64.73±18.37	0.017
β	4.22±1.96	2.74±0.92	0.016
E_{inc} (kpa 10^3)	0.27±0.11	0.19±0.06	0.014
ED - FMD (%)	5.70±4.19	8.5±3.56	0.016
EI - FMD (%)	12.48±5.81	13.4±5.26	0.036

RCCA right common carotid artery, *LCCA* left common carotid artery, *DC*distensibility coefficient, *β* stiffness index, E_{inc} elasticity increment model, *ED-FMD* endothelium-dependent flow-mediated dilatation, *EI-FMD* endothelium-independent FMD, *NS* not significant.
p<0.05 statistical significance

Table 4. Cardiovascular measurements in nondialyzed patients before and after cholecalciferol

	Baseline	Post-treatment	p value
RCCA			
DC ($kPa^{-1}10^{-3}$)	52.75(38.09-60.19)	55.66(45.56-74.39)	0.029
β	3.53±1.22	3.2±1.05	NS
E_{inc} (kpa 10^3)	0.24±0.09	0.21±0.07	0.047
LCCA			
DC ($kPa^{-1}10^{-3}$)	54.33±21.24	57.9±21.83	NS
β	3.57±1.48	3.5±1.1	NS
E_{inc} (kpa 10^3)	0.24±0.10	0.22±0.08	NS
ED - FMD (%)	7.23±3.8	9.77±3.88	0.000
EI - FMD (%)	13.99±4.96	15.38±5.18	0.022

RCCA right common carotid artery, *LCCA* left common carotid artery, *DC*distensibility coefficient, *β* stiffness index, E_{inc} elasticity increment model, *ED-FMD* endothelium-dependent flow-mediated dilatation, *EI-FMD* endothelium-independent FMD, *NS* not significant.
p<0.05 statistical significance

Discussion

Considering that cardiovascular events are the most frequent causes of death in children with CKD, it should be aimed to review and eliminate risk factors with early interventions.[17,18] In the present study, we found remarkable improvement in ED-FMD after cholecalciferol supplementation in children with hemodialysis, peritoneal dialysis and pre-dialysis groups.

FMD as a surrogate marker for endothelial dysfunction has been associated with obesity, hypercholesterolemia and low 25OHD levels.[19] It has also been reported that deterioration in endothelial function begins even in the milder stages of CKD.[4] Decreased nitric oxide bioactivity by reduced synthesis or inhibition via endogenous substances have been shown to contribute to this process.[20,21] After cholecalciferol, we observed statistically significant improvement in ED-FMD value, along with a significant increase in low 25OHD levels in hemodialysis, peritoneal dialysis and pre-dialysis groups whose age, gender, BMI, systolic, diastolic pressure measurements, serum calcium, phosphorus, calcium-phosphorus product, LDL-cholesterol and 25OHD levels

were not statistically different among each other before and after cholecalciferol therapy.

In adult patients having grade 3-4 CKD; Chitalia et al reported improved brachial artery FMD with two doses of 300.000 units of cholecalciferol although changes in pulse wave velocity and augmentation index predicting central arterial stiffness did not reach statistical significance.[22]

Arterial stiffness seen with increased frequency due to aging and hypertension enhance pre-existing CVD and mortality risk in CKD patients because of the alterations of mineral metabolism, hyperparathyroidism, microinflammation, overactivity of sympathetic system and renin-aldosterone axis, abnormalities of nitric oxide system and arterial wall calcification.[17,23,24] Moreover, London et al and Shroff et al have demonstrated increased vascular stiffening in dialyzed adults and children having low 25OHD.[5,25]

Although it was reported that central arterial stiffening increases as kidney functions worsen, similar to Patange et al, who had also revealed 25OHD as a risk factor for vascular stiffness in children receiving hemodialysis; we did not find a difference between hemodialysis, peritoneal dialysis and pre-dialysis groups about DC, Einc and β values indicating our patients' severely affected local arterial stiffening.[8] Therefore, these results which allow us to predict the development of CVD and mortality risk, were demonstrated to be equally impaired in all stages of kidney disease regardless of glomerular filtration rate and it was an important finding revealing that cardiovascular health began to deteriorate even from the initial phase of kidney damage. However significant amelioration in these parameters after 25OHD treatment were only detected in peritoneal dialysis and pre-dialysis groups when compared to hemodialysis patients.

Consistent with a double-blind, randomized study by Marckmann et al who had reported lowered iPTH in non-HD patients compared to HD group after cholecalciferol; decrease of iPTH levels in our study group was significantly detected only in pre-dialysis patients.[26] Thus, it was emphasized the effectiveness of nutritional vitamin D use in mild to moderate CKD for preventing secondary hyperparathyroidism. Regarding its effects on cardiomyocytes and elevated blood pressure resulting in cardiac hypertrophy, iPTH monitorisation is also essential to reduce CVD risk in CKD.[2]

Our study failed to demonstrate any significant change in LVMI, CRP and fibrinogen values among each group after 25OHD intake; whereas in HD patients as expected, it has been shown to have raised levels of these markers at baseline assessment compared to others. The chronic inflammatory environment, caused by the release of cytokines which are increased in the process of CKD, has been associated with cardiac calcification and arteriopathy.[21,27] There are conflicting results about the efficacy of nutritional vitamin D on inflammatory status in CKD. Kalkwarf et al described negative association between CRP and 25OHD levels in 182 children and adolescents with CKD in the age of 5 to 21 years.[28] In this context, Stubbs et al reported a favourable decline in IL-6 levels in seven HD patients after cholecalciferol use.[11] Conversely, in one study conducted with 54 CKD patients older than 18 years of age, no impact of vitamin D supplementation given 40.000 units per week for 8 weeks was observed on inflammatory indicators.[26] Their results were consistent with our data.

In addition to its classical role on bone mineral metabolism, vitamin D has also anti-inflammatory properties,suppresses cardiac hypertrophy,inhibits vascular muscle cell remodeling and renin aldosteron axis.[27,29] Widespread distribution of vitamin D receptors along various cells including endothelium, lymphocytes, vascular smooth muscle cells and myocardium explains the possible mechanisms for preventing the development of CVD.[30]

FMD and local arterial stiffness predicting high CVD and mortality, were found to be severely and equally affected in HD, PD and pre-dialysis groups. Despite the lack of any change within variables that may affect vascular stiffening throughout the study, significantly improved ED-FMD in all groups and decreased arterial stiffness in PD and pre-dialysis groups only with vitamin D intake could be explained by the effects of vitamin D on endothelial and vascular smooth muscle cells.

The failure of significant improvement in EI-FMD, local arterial stiffness and LVMI in hemodialysis patients after intervention may be explained by the prevalent chronic inflammation or other predisposing factors not yet fully elucidated.

The limitations of our study are small sample size, lack of 1,25-hydroxyvitaminD measurements and using only CRP and fibrinogen as proinflammatory markers.

In conclusion; low 25OHD levels in CKD children, may contribute further to the endothelial dysfunction and arterial stiffness which are already present since the early stages of kidney disease. Therefore, intervention with nutritional vitamin D can be considered as a good option in preventing the increased CVD and mortality risk in patients with CKD. Larger randomized trials are needed to confirm these findings.

Compliance with Ethical Standards

Ethical approval was granted by Kocaeli University Ethics Committee with the approval number of 11-6/5-18032014.

Conflict of Interest

The authors declare no conflict of interest.

Author Contribution

MBA: Study design; MAO, KD, MD and OK: Material preparation, data collection and analysis; MBA: Writing first draft of the article; MBA and KB: Critical review of the article, finalization and publication process. All authors read and approved the final version of the manuscript.

Financial Disclosure

None.

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Research Article | Araştırma Makalesi

ANALYSIS OF THE RELATIONSHIP BETWEEN MENISCAL TEARS AND MEDIAL PATELLOFEMORAL RUPTURE ACCORDING TO THE TREATMENT METHOD AND GENDER

MENİSKÜS YIRTIKLARI İLE MEDİAL PATELLOFEMORAL RÜPTÜR ARASINDAKİ İLİŞKİNİN TEDAVİ YÖNTEMİ VE CİNSİYETE GÖRE ANALİZİ

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ABSTRACT

Objective: The purpose of this study was analysis of the relationship between meniscal tears and medial patellofemoral rupture according to the treatment method and gender.

Methods: This study was planned as retrospective study between January 2010 and January 2021. Magnetic resonance images of 60 individuals (37 knees were left, and 23 were right) were obtained for analysis. Patellar morphology, patellar height and patellar alignment and evaluation lateral and medial meniscus tears were evaluated. Knee MRI protocol including axial T2-weighted turbo spin echo was used.

Results: There was a significant difference patellar height (surgery; 1.21±0.27 and conventional; 0.99±0.16), the congruence angle (surgery; -4.94±4.72 and conventional; 4.93±5.72), the lateral patellofemoral angle (surgery; -35.61±16.62 and conventional; 10.93±15.00), except for age parameter (surgery; 27.06±6.20 and conventional; 27.47±5.33) between the conventional and surgical treatment groups ($p<0.05$). Moreover, we found that 29 patients of the patients with medial patellofemoral rupture had a lateral meniscus tear, 11 patients had a medial meniscus tear, and 8 patients had both lateral and medial meniscus tears.

Conclusion: We found that relationship between meniscal tears and medial patellofemoral rupture will affect the treatment course. Also, this study will contribute to evaluate the radiological and clinical correlations, patello-femoral positioning in patients who medial patellofemoral rupture.

Keywords: Anatomy, patellofemoral ligament, meniscus tears,

ÖZ

Amaç: Bu çalışmanın amacı menisküs yırtıkları ile medial patellofemoral rüptür arasındaki ilişkinin tedavi yöntemi ve cinsiyete göre incelenmesidir.

Yöntem: Bu çalışma Ocak 2010 ile Ocak 2021 tarihleri arasında retrospektif olarak gerçekleştirildi. Analiz için 60 kişiye (37 diz sol taraf ve 23 diz ise sağ taraf) ait manyetik rezonans görüntüleri alındı. Patellar morfoloji, patellar yükseklik ve patellar hizalama ve lateral, medial menisküs yırtıkları değerlendirildi. Aksiyel T2 ağırlıklı turbo spin eko içeren diz MRG protokolü kullanıldı.

Bulgular: Konvansiyonel ve cerrahi tedavi grupları arasında yaş parametresi hariç (cerrahi tedavi yapılanlarda; 27,06±6,20 ve konvansiyonel tedavi yapılanlarda; 27,47±5,33), patellar yükseklik (cerrahi tedavi yapılanlarda; 1,21±0,27 ve konvansiyonel tedavi yapılanlarda; 0.99±0.16), uyum açısı (cerrahi tedavi yapılanlarda; -4,94±4,72 ve konvansiyonel tedavi yapılanlarda; 4,93±5,72), lateral patellofemoral açı (cerrahi tedavi yapılanlarda; -35,61 ve konvansiyonel tedavi yapılanlarda; 10,93±15,00) parametrelerinde anlamlı fark bulundu ($p<0,05$). Ayrıca medial patellofemoral yırtığı olan hastaların 29'unda lateral menisküs yırtığı, 11'inde medial menisküs yırtığı ve 8'inde hem lateral hem de medial menisküs yırtığı tespit ettik.

Sonuç: Menisküs yırtıkları ile medial patellofemoral rüptür arasındaki ilişkinin tedavi sürecini etkileyeceğini bulduk. Ayrıca bu çalışma, medial patellofemoral rüptürü olan hastalarda radyolojik ve klinik korelasyonların, patello-femoral pozisyonların değerlendirilmesine katkıda bulunacaktır.

Anahtar Kelimeler: Anatomi, patellofemoral ligament, menisküs yırtıkları

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Introduction

Patella dislocations occurs in 3% of all knee injuries. It is common in the young population and women. The incidence of patellar instability is 5.8 per 100,000 and 29 per in the general population.[1] the most important etiyology in the development of patellar instability is medial patellofemoral ligament (MPFL) rupture.[2] The anatomic structures of femur, tibia and the ligaments of the knee are important risk factors to develop patellofemoral instability.[3]

Patients with MPFL rupture were included in the study. We evaluated these patients according to treatment method (surgical and conventional), anatomical parameters, the presence or absence of lateral and medial meniscus tears, age and gender. Since our study examined MPFL rupture, which is rare condition, and it includes more patients with MPFL rupture than studies in the literature, it will make a significant contribution to the literature. There is no study in the literature evaluating the treatment method and meniscus tears in patients with MPFL rupture. So we think that our study will provide a different perspective on this issue. Because the meniscus structure provides resistance against impacts and also contributes to stabilization on the knee joint. Also, the meniscus is responsible for the lubrication, nutrition, and proprioception of articular cartilage. Moreover, knowing these differences in patellofemoral anatomy will help the orthopedic surgeon to determine the appropriate physical therapy methods and to choose the appropriate treatment by showing the individual mechanism of patellar instability.[4] Therefore, we think that the addition relationship between meniscal tears and MPFL rupture will affect the treatment course. The aim of our study was analysis of the relationship between meniscal tears and medial patellofemoral rupture according to the treatment method and gender.

Methods

Participants

This study was planned as retrospective study between January 2010 and January 2021. All the test procedures were performed according to the Helsinki Declaration of Principles. Necessary permissions for the study were obtained from Cukurova University Faculty of Medicine, Non-invasive clinical research Ethic Board with conclusion number 105/30. Magnetic resonance images (MRI) of 60 knees (37 knees were left, and 23 were right) were obtained for analysis. The subjects of experimental group were selected patients with operated for patellofemoral ligament rupture and the subjects of control group were selected patients with no operated for patellofemoral ligament rupture. Moreover, exclusion criteria for subjects were history of oncologic, orthopedic and neurological signs.

Evaluation of MRI Images

The slices used for measurements were standardized and performed by the same orthopedist. In addition, although the number of participants provided sufficient statistical power, the number of men and women in our study was similar.

The congruence angle; The angle measured between these two lines like in the Figure 1. If the apex of the patellar joint ridge is lateral to the zero line, then the congruence angle is positive. If it is medial, then the angle is negative. [5]

The lateral patellofemoral angle; measure is calculated as the angle between a horizontal line across the peaks of the 2 femoral condyles and a line along the lateral patellar facet (Figure 1).[5]

Patellar height; we evaluated on lateral radiographs by using Insall-Salvati index (Figure 1).[6]

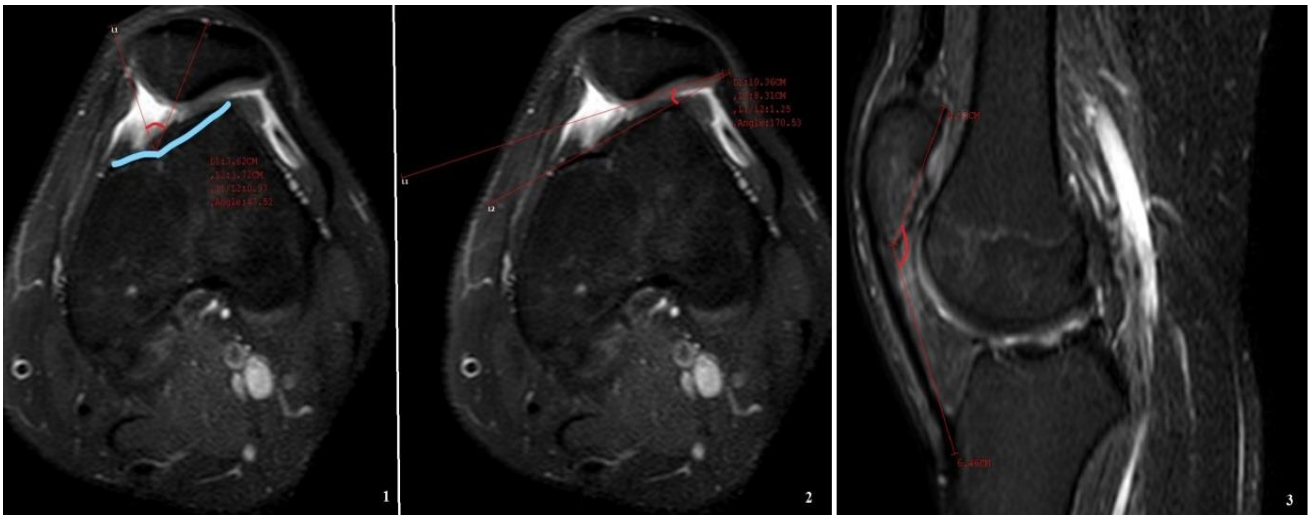

Figure 1. The congruence angle (1), the lateral patellofemoral angle (2) and patellar height (3)

Lateral and medial meniscus tears; Arthroscopic classification of Dorfmann et al. was used for classification.

Grade 1; It is the change in the structure of the meniscus without any deterioration in its integrity. The meniscus is homogeneous but loses its normal appearance. It

becomes darker, its surface becomes irregular and wavy. This type is called meniscosis.
Grade 2; It is characterized by the build-up of calcium inside the body and surface of the meniscus (meniscocalcinosis).
Grade 3; Horizontal cleavage tear.
Grade 4; The radial tear originates from the inner edge of the medial meniscus, with an oblique course at the junction of the meniscus body and the posterior horn.
Grade 5; Existence of unidentified complex lesion. It is rare, but occurs in osteoarthritic knees.

Statistical Analysis

Statistical analysis was performed using the SPSS v.22 package. Furthermore, skewness and kurtosis was used to determine whether the data showed normal distribution or not and to decide which test to use (parametric or non-parametric tests). According to the skewness and kurtosis values, the data showed a normal distribution. Independent Samples T Test was chosen from parametric tests (statistically significant as $p<0.05$).

Results

The ages of sixty patient with patellofemoral rupture (29 females and 31 males) were 18-36 years over a period of eleven years between January 2010 and January 2021. Patellar height, the congruence angle, the lateral patellofemoral angle, situation of lateral and medial meniscus tears were measured. The distribution of the assessment parameters of the patients with medial patellofemoral ligament rupture according to conventional and surgical treatment is shown in Table 1. There was a significant difference except for age parameter between the conventional and surgical treatment groups. In addition the evaluation of measurement parameters of patients with medial patellofemoral ligament rupture according to gender is shown in Table 2. A significant difference was found between genders in parameters except age and the lateral patellofemoral angle parameters. Moreover, we found that 29 patients of the patients with medial patellofemoral rupture had a lateral meniscus tear, 11 patients had a medial meniscus tear, and 8 patients had both lateral and medial meniscus tears (Table 3). The distribution of parameters in patients with and without lateral meniscal tear is shown in Table 4. Significant differences were found between both groups except age parameter. In addition, Table 5 shows the distribution of parameters according to whether there is a medial meniscus tear or not. Significant differences were found between groups except for age and the congruence angle parameters. The relationship between those with and without both lateral and medial meniscal tears is given in Table 6. Significant differences were obtained between groups except age and the congruence angle parameters.

Table 1. Conventional and surgical treatment evaluations of patients with medial patellofemoral ligament rupture

Parameters	Surgery (n=31) Mean±SD	Conventional (n=29) Mean±SD	p
Age	27.06±6.20	27.47±5.33	0.787
Patellar height	1.21±0.27	0.99±0.16	0.000
The congruence angle	-4.94±4.72	4.93±5.72	0.000
The lateral patellofemoral angle	35.61±16.62	10.93±15.00	0.000

SD: Standard Deviation

Table 2. Evaluations of patients with medial patellofemoral ligament rupture by gender

Parameters	Male (n=31) Mean±SD	Female (n=29) Mean±SD	p
Age	28.32±5.47	26.17±5.90	0.144
Patellar height	1.17±0.27	1.04±0.21	0.046
The congruence angle	2.87±7.19	-3.13±5.88	0.001
The lateral patellofemoral angle	21.58±23.55	25.43±15.80	0.458

SD: Standard Deviation

Table 3. Condition of meniscus tears (lateral/medial) according to gender and treatment method

	Surgery		Conventional		Total
	Male (n)	Female (n)	Male (n)	Female (n)	
Lateral meniscus tears	12	13	0	3	28
Medial meniscus tears	8	0	0	3	11
Total	20	13	0	6	39

Table 4. Distribution of parameters according to whether there is a lateral meniscus tear or not

Parameters	Patients With Lateral meniscus tear (n=29) Mean±SD	Patients Without Lateral meniscus tear (n=31) Mean±SD	p
Age	26.48±5.74	27.97±5.74	0.317
Patellar height	1.20±0.26	1.02±0.20	0.004
The congruence angle	-4.52±4.90	3.94±6.58	0.000
The lateral patellofemoral angle	37.55±14.77	10.72±15.07	0.000

SD: Standard Deviation

Table 5. Distribution of parameters according to whether there is a medial meniscus tear or not

Parameters	Patients With Medial meniscus tear (n=11) Mean±SD	Patients Without Medial meniscus tear (n=49) Mean±SD	p
Age	27.64±5.03	27.18±5.93	0.814
Patellar height	1.30±0.23	1.06±0.23	0.003
The congruence angle	-2.55±2.94	0.46±7.74	0.212
The lateral patellofemoral angle	50.00±11.62	17.64±16.48	0.000

SD: Standard Deviation

Table 6. Distribution of parameters according to whether there is a lateral and medial meniscus tears or not

Parameters	Patients With Lateral and Medial meniscus tears (n=8) Mean±SD	Patients Without Lateral and Medial meniscus tear (n=52) Mean±SD	p
Age	29.75±4.17	26.89±5.88	0.191
Patellar height	1.42±0.12	1.06±0.22	0.000
The lateral patellofemoral angle	53.75±11.57	18.91±16.82	0.626
The congruence angle	-1.25±2.31	0.09±7.66	0.000

SD: Standard Deviation

Discussion

The young active population is the most affected by patellar instability and is an important source of morbidity.[7] It is necessary to have precise and accurate information about the anatomy and morphometry of the patellofemoral joint for the understanding, correct diagnosis and treatment of anomalies in the joint. There are many studies in the literature describing the relationship of patellofemoral instability with anterior knee pain, patellar dislocation, patellofemoral osteoarthritis and patellar chondromalacia. However, studies evaluating the relationship between morpho-radiological measurements of the joint between gender and meniscus tears are limited.

In knee mechanics, the source of stabilizing power of the knee is 50-60% MPFL. In rare cases of MPFL rupture, anatomical MPFL reconstruction is commonly used.[8,9] It is also applied in conservative treatment for MPFL rupture. However, it has been reported in the literature that patellar dislocation recurs at a rate of 15 to 44% as a result of conservative treatment.[10-12] In general, there is no study in the literature comparing the surgical and conservative treatment procedures of medial patellofemoral ligament reconstruction.[13] The principles of surgical methods for patellofemoral instability are based on releasing tense contracted tissues, transferring or strengthening medial stabilizing structures, and changing the attachment site of the patellar tendon. The meniscus is vital for the continuation of knee functions. Meniscus has a supportive effect on joint stability, shock absorption effect, effect on balanced load transmission by increasing femur and tibia joint surface compatibility, effects on deep sense and positive effects on cartilage nutrition. Meniscus tears can be classified according to different features such as the localization of the tear, the shape of the tear, and the duration of the injury. The right approach to the treatment of meniscal tears is possible by understanding the types of meniscus tear. For example, longitudinal tears are usually accompanied by anterior cruciate ligament damage. Oblique, longitudinal and degenerative tears are more common; radier, horizontal tears are less common.[14,15]

In our study, 31 patients with medial patellofemoral rupture received surgical treatment, while 29 patients received conventional treatment. When the anatomical factors affecting the treatment method were examined, we concluded that the congruence angle and the lateral patellofemoral angle factors affected the treatment method. When the patients in our study were evaluated in terms of meniscal tears, it was found that 29 patients (12 male and 16 female) had lateral meniscus tears and 11 patients (8 male and 3 female) had medial meniscus

tears. While 13 of the female patients who underwent surgery had a lateral meniscus tear, 3 female patients received conventional treatment. While 12 male patients who underwent surgery had a lateral meniscus tear, 8 male patients had a medial meniscus tear. In addition, 26 of the patients with medial patellofemoral rupture who underwent surgery had a lateral meniscus tear, while 3 of the patients with patellofemoral rupture who received conventional treatment had a lateral meniscus tear. It was determined that 8 patients with medial patellofemoral tears had both lateral and medial meniscus tears. In female patients with lateral meniscus tear, 7 patients had a grade 4 tear, while 6 patients had a grade 3 tear and 6 patients had a grade 5 tear. It was found that 2 of the patients with medial meniscus tears were grade 4 and 6 of them were grade 3. While 6 of the patients had grade 3 lateral meniscus tear, 6 of the patients had grade 5 lateral meniscus tear and 14 of the patients had grade 4 lateral meniscus tear treated in underwent surgery, 3 of the patients treated with conventional treatment had grade 4 lateral meniscus tears. In addition, 2 of the patients who underwent surgery had a grade 4 and 6 of the patients who underwent surgery had a grade 3 medial meniscus tear, while 3 of the patients receiving conventional treatment had a grade 4 medial meniscus tear. These results reveal that lateral meniscal tears are more common in patients with medial patellofemoral rupture. Thus, we can say that the situations in which the lateral meniscus is overloaded and the gender factor produce a risk for the predisposition to rupture of the medial patellofemoral ligament. Another important factor is patellofemoral alignment. The patella slides outward as it moves in the femoral groove. With this shift, one side of the cartilage under the patella is exposed to more pressure. Over time, this abnormal pressure can damage the articular cartilage. Thus, patellofemoral alignment is demaged. There were also measures describing the relationship between the lateral patellofemoral angle, congruence angle. These measures have all been used in previous studies to assess patellar alignment. We evaluated the congruence angle (patellofemoral compliance) and lateral patellofemoral angle (patellar inclination) parameters in our study as an indicator of patellofemoral alignment. In our study, when we made a comparison according to the treatment method, it was found that patellofemoral compliance was significantly lower in those who underwent surgery, while patellar inclination was found to be significantly higher (Table 1). Moreover, when we compared the genders, patellofemoral compliance fit was found to be significantly higher in men, while patellar inclination was found to be significantly lower in our study (Table 2). In addition, patellofemoral compliance was found to be significantly lower in patients with lateral and medial meniscal tears, while patellar inclination was found to be significantly higher (Table 6). At the same time, we evaluated patellar inclination with the lateral patellofemoral angle parameter. The lateral patellofemoral angle is also important in determining the treatment method. If the angle is greater than 16 degrees, surgical treatment may be preferred since the probability of recurrence will be very high.[16] This study reported the average lateral patellofemoral angle to be 35.61±16.62 in patients with surgical treatment and 10.93±15.00 in patients with conventional treatment (Table 1). Moreover, while there is a significant difference (p=0.000) in the lateral meniscus tear, there is no significant difference (p=0.212) was found in the medial meniscus tear for the congruence angle parameter (Table 4-5). However, a significant difference (p=0.000) was obtained in the congruence angle parameter compared to groups with/without both medial and lateral meniscus rupture (Table 6). We think that this is due to the fact that the number of patients with only medial meniscus rupture is 11 people. When the literature is examined, Indelli et al., in their study found that patellar congruence angle was −3° (range,−11° to +9°) with respect to an average pre-operative value of 10.3° (range, +1.5° to +25.5°) ($p<0.05$).[17] In another study, Kan et al., found that subjects with patellar dislocation had laterally deviated congruence angles (20° (SD 28°)), while control subjects had slightly medially deviated congruence angles (−9° (SD 12°)) (p=0.04).[18] Aksu et al., found the congruence angle parameter to be 10.94±10.15 with patellar tendinopathy and 14.99±6.72 with patellar tendinopathy in their study on professional dancers. They also found the congruence angle as 13.78±5.44 with quadriceps tendinopathy and 10.80±11.12 with quadriceps tendinopathy.[19] Yang et al., in their study, they found that the mean congruence angle was 43.30±11.04 before the operation and 16.64±9.98 after the operation.[20] In another study, Grimm et al., found a significant difference between the ages, but they didn't find a significant difference between the genders (p=0.81 for sex, p=0.06 for age).[21] In one study, Lullini et al. demonstrated that all measures of patellofemoral stability and alignment were more consistent in weight-bearing cone-beam computed tomography than in conventional computed tomography in MPFL rupture reconstruction.[22]

We used to measure patellar height is Insall-Salvati index. Ergun's study showed that there was a strong correlation between female gender and advanced age. The results of the study revealed that female gender and advanced age were high patellar height, which predisposes to patellofemoral malalignment.[23] In the study by Arun and Ganesan in 200 people (100 male and 100 female), they found the patellar height to be 1.41 on average in men and 1.28 in women. They stated the general mean as 1.34.[24] Leung et al., found that in the Southern Chinese population, the position of the patella is 15% to 20% higher than in western populations. They stated that a patella alta index of >3.4 is considered abnormal in this population.[25] In our study, patellar height was found to be higher in male and patients with lateral and medial meniscus tears. In addition, our study was revealed that patellar height was higher in patients with surgical treated. This result supported the literature that high patellar height factor is a risk factor for patellar instability.

Conclusion

Clinical studies have shown that non-anatomical MPFL reconstruction is closely related to postoperative complications.[26] Different patello-femoral designs in total knee arthroplasty is important for orthopedists and prosthetic manufacturers.We think that this study will contribute to implant design and modern femoral implants. Also, this study will contribute to evaluate the radiological and clinical correlations, patello-femoral positioning in patients who medial patellofemoral rupture.

There were several limitations in the present study. Since our study includes a wide time period, surgeons who perform surgical operations and surgical methods are different. Therefore, an evaluation could not be made according to surgical methods. For this reason, we recommend performing studies that evaluate parameters according to surgical methods.

Compliance with Ethical Standards

Ethical approval was obtained from Cukurova University, Non-invasive clinical research Ethic Board with conclusion number 105/30.

Conflict of Interest

There are no conflicts of interest.

Author Contribution

AGK: Study idea, hypothesis, study design; AGK, MGB and VTT: Material preparation, data collection and analysis;AGK and MGB: Writing the first draft of the article; AGK, MGB and VTT: Critical review of the article finalization and publication process.

Financial Disclosure

None.

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Research Article | Araştırma Makalesi

ARTIFICIAL INTELLIGENCE BASED RATING OF CARPAL TUNNEL SYNDROME EFFICACY IN CLINICAL DIAGNOSIS

KARPAL TÜNEL SENDROMUNUN DÜZEYİNİN YAPAY ZEKA TEMELLİ DERECELENDİRİLMESİ

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ABSTRACT

Objective: The most common entrapment neuropathy seen by the clinician is Carpal tunnel syndrome (CTS). CTS is graded as mild, moderate, and severe according to the results obtained on electroneuromyography (ENMG) by clinicians. We aimed to show the effectiveness of the use of artificial intelligence in clinical diagnosis in the grading of CTS.

Methods: In our study, the data of 315 people with a pre-diagnosis of CTS were used and classified into four classes based on AI as CTS grade. Machine Learning (ML) algorithms Ensemble, Support Vector Machine (SVM), K-Nearest Neighbor (KNN), and Decision Tree (Tree) algorithms were used in classification processes. 10% Hold-out validation was used and the learning rate was determined as 0.1. As a result of the classification, accuracy, precision, sensitivity, specificity, and F1-score performance values were obtained.

Results: SVM made the best estimation and KNN made the worst estimation in the 0 class. The best estimate in class 1 belongs to the Support Vector Machine. Ensemble and Tree made the best guesses in the 2nd and 3rd grades. In our study, the best algorithm with an overall success rate is SVM with 93.55%.

Conclusion: The results showed that ML algorithm models consistently provided better predictive results and would assist physicians in determining the medical treatment modality of CTS. Artificial intelligence (AI) techniques are reliable methods that assist clinicians to deliver quality healthcare.

Keywords: Carpal Tunnel Syndrome, Electromyography, Artificial Intelligence, Grading

ÖZ

Amaç: Karpal tünel sendromu (KTS), median sinirin karpal tünelde sıkışması sonucu en sık görülen tuzak nöropatisidir. Elde edilen veriler sonucunda hastada mevcut KTS kliniği hafif, orta ve ağır olarak gradelenir. KTS derecelendirmesinde klinik tanıda yapay zeka kullanımının etkinliğini göstermeyi amaçladık.

Yöntem: Çalışmamızda KTS ön tanısı ile başvurmuş ve electroneuromyography yapılmış olan 315 bireyin, demografik ve electroneuromyography sonuçlarından elde edilmiş sinir ileti verileri kullanılmıştır. Sınıflandırma işlemlerinde makine öğrenmesi algoritmalarından Topluluk, Destek Vektör Makinesi, K-En Yakın Komşu ve Karar Ağacı algoritmaları kullanılmıştır. %10 bekletme doğrulaması kullanılmış ve öğrenme oranı 0.1 olarak belirlenmiştir. Sınıflandırma sonucunda doğruluk, kesinlik, duyarlılık, özgüllük ve F1-skor performans değerleri elde edilmiştir.

Bulgular: Çalışmamızın sonucunda 0 sınıfında en iyi tahmini Destek Vektör Makinesi, en kötü tahmini K-En Yakın Komşu yapmıştır. 1. sınıfda en iyi tahmin Destek Vektör Makinesine aittir. 2. ve 3. sınıflarda en iyi tahmini Topluluk ve Karar Ağacı yapmıştır. Çalışmamızda, genel başarı oranı en iyi algoritma %93,55 ile Destek Vektör Makinesidir.

Sonuç: Makine öğrenme algoritma modellerinin tutarlı bir şekilde daha iyi tahmin sonuçları sağladığını ve doktorlara KTS'nin tıbbi tedavi yöntemini belirlemede yardımcı olacağını gösterdi. Yapay zeka teknikleri, klinisyenlerin kaliteli sağlık hizmeti sunmalarına yardımcı olan güvenilir yöntemlerdir.

Anahtar Kelimeler: Karpal tünel sendromu, elektromiyografi, yapay zeka, derecelendirme

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Introduction

Neurological diseases are acute, chronic or progressive clinical manifestations that occur as a result of neurodegeneration in the central and peripheral nervous system. The increase in the elderly population and the inadequacy of treatments in chronic processes increase the cost of neurological diseases day by day. In recent years, deep learning algorithms have been used to increase the early diagnosis and treatment possibilities of neurologists.[1] The recognition of artificial intelligence (AI) dates back to the 1950s.[2] AI aims to develop a method for capturing and solving complex problems based on large amounts of data.[3] It also has the effect of changing the current model in the diagnosis, treatment, prediction, and economics of neurological diseases.[2] It has been understood that with the use of artificial intelligence, it becomes easier to diagnose permanent neurological damage and even guides the prevention of diseases.[1] Studies in stroke, dementia, epilepsy and movement disorders have shown that machine learning will contribute greatly to the future of neurologic diseases[4], but there has not been enough studies on peripheral nerve diseases yet. Carpal tunnel syndrome is one of the most common peripheral neuropathies in the active working adult population, affecting daily activities and reducing work efficiency. It occurs by compression of the median nerve in the carpal tunnel and causes sensory and motor complaints in the first three fingers of the hand.

It is known that the common risk factors of CTS are; female gender, high body mass index (BMI), advanced age, and repetitive hand movements.[5] The incidence of CTS is approximately 3.0% in women and 2.1% in men.[6] Electroneuromyography (ENMG) is the most frequently used auxiliary diagnostic tool in the diagnosis of CTS. It is also helpful in following up on the disease progress by grading the severity of median nerve compression.[7-11] The severity of CTS is graded as mild, moderate, or severe based on the results of the data obtained in ENMG.[12] The treatment option is mostly determined according to this grading result.[13] The treatment options for CTS are, in order, from mild to severe; medical treatment, rest splints and surgical treatments. If severe CTS is left untreated, it can cause irreversible damage of median nerve, causing atrophy and weakness in the hand muscles.

Before AI systems can be used in healthcare applications, they need to be trained using data from clinical activities such as screening, diagnosis, treatment assignment, etc., so that similar subject groups and relationships among them can be learned. Machine learning (ML) creates data analytics algorithms to extract features from data.[14,15] The use of algorithms with high predictive power and success rate increases the accuracy of early diagnosis. The studies on this subject and the success of the applied devices emphasize the importance of machine learning in the field of medicine.[16] It enables ENMG to be used as a guide in following the course of the disease and determining the treatment method. However, the reliability of the ENMG test can be very variable due to factors such as the experience of the person performing the test, the technical characteristics of the device used, and the patient's compliance with the test. Considering these factors, there are studies conducted with machine learning algorithms.[14]

There are several algorithms in different libraries of machine learning. The ML algorithms used in this study are Ensemble, Support Vector Machine (SVM), K-Nearest Neighbor (KNN), and Decision Tree (Tree).

The ensemble can improve classification performance. Findings of classifiers with varying accuracies are combined with an ensemble-based approach.[17] Even when using multiple sets of measures with ML algorithms, classification performance may not necessarily improve. In this context, Ensemble methods are multi-classifier systems in which individual weak classifiers are combined to create a more robust classification system.[18]

SVM is a fairly robust classification method for disease diagnosis.[19] According to other machine learning algorithms; It is widely used in medical research due to its many advantages such as being effective in cases where the sample size in the study is less than the number of dimensions, using different kernel functions in the decision mechanism, having unbalanced data, giving more effective and successful results in big data, and working with a large number of independent variables.[15,20,21]

KNN is a lazy learning approach as there is no clear training process. There is a K value determined in the study to classify KNN, and this value indicates the number of elements that the algorithm will look at in the data set. It is a statistics-based method.[17,18] It is one of the highly preferred machine learning algorithms because of its simplicity and resistance to complex training data.[17]

Decision Tree is an algorithm whose structure is based on probability and statistics. Decision trees consist of general-specific and downward-trained data.[22,23] Classification of data in decision trees consists of two stages, namely learning and classification. The training data known before the learning phase is examined by the classification method to reveal the model. This learned model is specified as classification rules. In the second stage, the classification stage, the test data is used to query whether the decision tree is correct.[21,23]

Hold-out validation is recommended to eliminate the overfitting problem. Here, the data is divided into two non-overlapping parts and one is trained while the other is tested with the trained model. People often don't understand this very clearly, and they consider waiting for validation to be dividing data into two equal parts. While it's true that it could be called a hold verification, it's a very specific standby verification case where 50% of the data held for testing is. Therefore, wait validation may have different percentages.[24]

Methods

In our study, the original data of 315 people who applied to Electroneuromyography laboratory of Sakarya University Training and Research Hospital with a preliminary diagnosis of CTS and underwent electromyography examination were used. Demographic data such as age, gender, height, weight, dominant hand, body mass index (BMI) and EMG conductions were recorded by the author M.A. and database were prepared by him. BMI is classified according to the criteria determined by the World Health Organization.[25] The motor and sensory latency, sensory and motor amplitude, and conduction velocity values of the median and ulnar nerves were evaluated by EMG, and CTS was graded by the clinician. NCSs were made by a specialist neurologist using the same EMG device at 24°C using standard conduction procedures. CTS grading was performed by the same specialist neurologist according to the electrophysiological parameters stated by Padua.[26] From the Carpal Tunnel Syndrome data used in the experimental study, it was classified based on artificial intelligence in 4 classes as CTS grade (0 normal, 1 mild, 2 moderate, 3 severe). Ensemble, Support Vector Machine (SVM), K-Nearest Neighbor (KNN), and Decision Tree (Tree) algorithms from ML algorithms were used in classification processes. 10% Hold-out validation was used and the learning rate was determined as 0.1.

Table 1. Dataset

Attribute	Definition
Age	
Gender	Male / Female
Height	cm
Weight	kg
Dominant Hand	Right / Left
Side	Right / Left
BMI	Body mass index
BMI Group	18 underweight weak 18.6-25 normal 25.1-30 overweight 30.1-35 degree obese 35.1-40 2. degree obese 40.1'in üstü 3. degree obese
Median SNAP	>6 mV
Median SCV	>49 m/s
Median MDL	<4.20 ms
Median CMAP	>4,5 mV
Median MCV	>50 m/s
Ulnar SNAP	>4 mV
Ulnar SVC	>49 m/s
Ulnar MDL	<4,0ms
Ulnar CMAP	>5.0 mV
Ulnar MCV	>47m/s

The data set is explained in Table 1 above. Carpal Tunnel Syndrome (CTS) severity data;

GRADE 0: 157 pieces of data with zero intensity (normal)
GRADE 1: 92 data at an intensity (mild)
GRADE 2: 55 pieces of data in two (moderate)
GRADE 3: 11 data at three severity (severe)

In the figure 1 below, the ratio of the total number of female/male samples to the overall sample number is given.

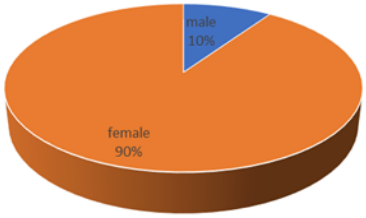

Figure 1. Gender distribution

BMI distribution is given in figure 2 below.

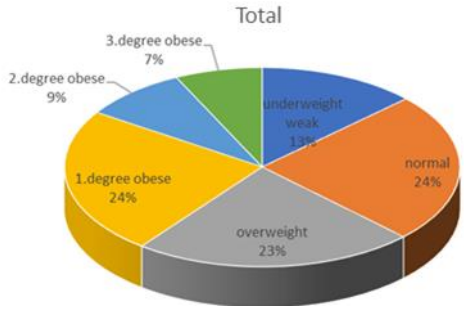

Figure 2. BMI distribution

Simulation Results and Performance Evaluation

As a result of the classification in the experimental study, accuracy, precision, sensitivity, specificity, and F1-score performance values were obtained. To better present these results, ROC (Receiver Operating Characteristic) curves graphics were drawn. The complexity matrix shown in Table 2 is used to calculate performance metrics (Table 2).

Table 2. Confusion Matrix

Predicted Class	Actual Class	
	Positive	Negative
True	[1]TP	[2]TN
False	[3]FP	[4]FN

[1]True Positive, [2]True Negative, [3]False Positive, [4]False Negative

Mathematical equations of performance metrics used in the study are given in equations 1, 2, 3, 4 and 5 given below.

$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN}$$

$$Precision = \frac{TP}{TP+FP}$$

$$Sensitivity = \frac{TP}{TP+FN}$$

$$Specificity = \frac{TN}{TN+FP}$$

$$F1-score = \frac{2*TP}{2*TP+FP+FN}$$

The complexity matrix obtained as a result of the study is shown in Figure 3. In this matrix, each algorithm is classified into 4 different groups as the CTS grade of the algorithm (0 normal, 1 mild, 2 modarete, 3 severe).

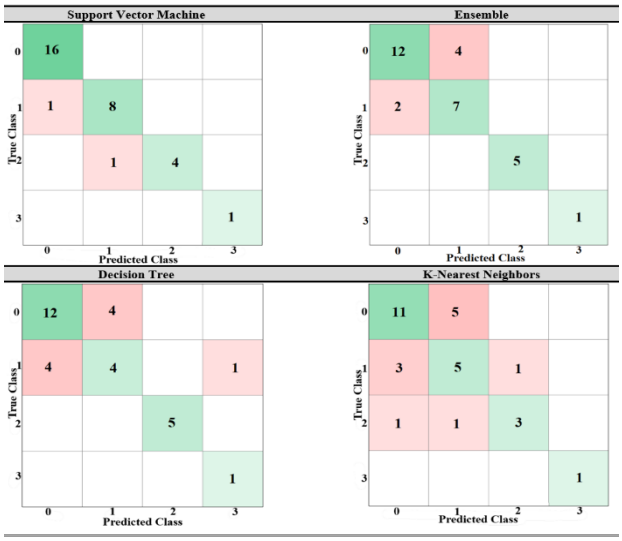

Figure 3. Confusion matrix

While the SVM algorithm correctly classified all the data in the "0 normal" class, the Ensemble and Tree algorithms predicted 4 of the data in the "1 mild" grade and misclassified them, while KNN predicted 5 of them in the "1 mild" class and classified them incorrectly. Likewise, their performance in other classes can be seen in Figure 3 (Figure 3). If we evaluate the results in Figure 3 in general, SVM made the best prediction in 0 grade and KNN made the worst prediction. The best estimate in grade 1 belongs to SVM. Ensemble and Tree made the best guesses in the 2nd and 3rd grades. Using the numerical values obtained from the complexity matrix given in Figure 3, when substituting in equations 1, 2, 3, 4, and 5, the overall performance results of the Carpal tunnel syndrome grade classification data are calculated in Table 3 (Table 3).

Table 3. Carpal tunnel syndrome performance results of the classification

Classifier	Accuracy (%)	Precision (%)	Sensitivity (%)	Specificity (%)	F1-score (%)
Support Vector Machine	93.55	95.75	92.22	97.20	93.69
Ensemble	80.65	87.34	88.19	92.12	87.50
Decision Tree	70.97	68.75	79.86	87.95	72.18
K-Nearest Neighbours	64.52	73.45	71.08	85.55	71.91

When we evaluate Table 3, the best overall success is SVM with 93.55%. This is followed by Ensemble with 80.65%, Tree with 70.97%, and KNN with 64.52%. Besides, the Carpal tunnel syndrome ROC curve graph is shown in Figure 4. Data classification performances of classification algorithms are clearly shown on this graph.

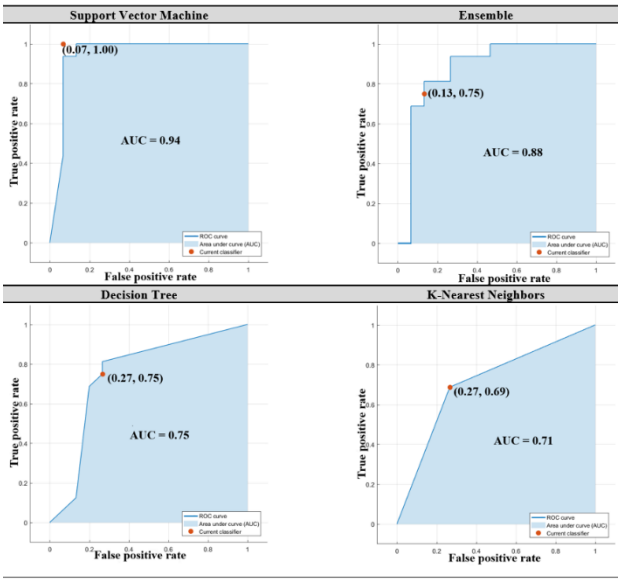

Figure 4. Carpal tunnel syndrome ROC curve graph

It is seen that SVM has the best area in the ROC curve graph, which is a different graph showing the performances of the algorithms (Figure 4). This is followed by Ensemble, Tree, and KNN, respectively.

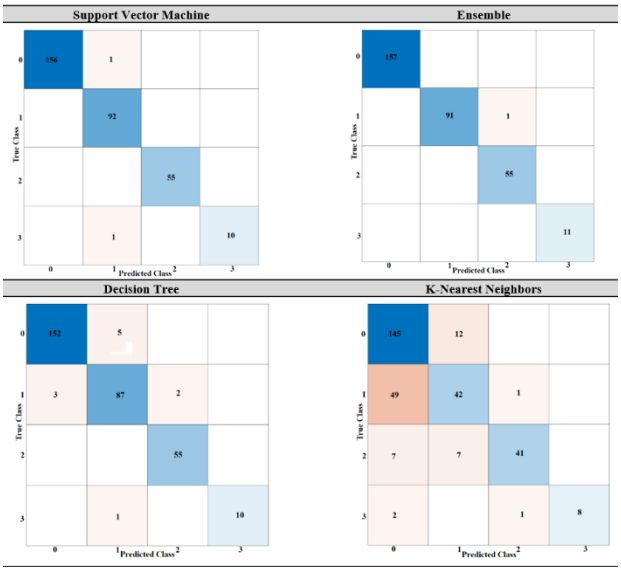

Figure 5. Training confusion matrix

The confusion matrix obtained at the end of training the data is shown in Figure 5 (Figure 5). When the confusion matrices obtained at the end of the trainings were compared, SVM predicted 156 data belonging to the zero class correctly, while it predicted only one data to be one class incorrectly. Likewise, while it correctly predicted ten data belonging to three classes, it achieved a high performance by estimating only one data as one class incorrectly. Likewise, while Ensemble correctly predicted 91 data belonging to the 1 class, only 1 data was incorrectly predicted to have two classes. He predicted

all other data correctly. The performances of other algorithms are as seen in Figure 5.
Datasets analyzed during the current study are available from the corresponding author by appropriate request.

Discussion

ENMG is used not only to determine the treatment modality in CTS but also to determine the severity of median nerve entrapment. This enables the usage of ENMG in following up on the progress of the disease and guiding the determination of the treatment modality. However, the reliability of the ENMG test can be very variable due to factors such as the experience of the person performing the test, the technical characteristics of the device used, and the patient's compliance with the test. In addition, the value of the test may vary according to the purpose of the test, for example, the sensitivity of the test should be maximized in order not to miss any case in the CTS screening to be performed in the industry sector.[27] The exponential increase in publications on AI in recent years and the focus on artificial intelligence in professional and scientific meetings in recent years emphasize the importance of this issue.[14] Diagnosing and managing diseases is a difficult task that cannot be obtained from textbooks or classroom information. It is gradually acquired through years of observation and experience.[28] CTS is an entrapment neuropathy with a wide range of symptoms and signs. Accurate grading of CTS is important, as choosing the right treatment option may vary depending on the severity of CTS.[29,30] Using computer-assisted techniques in medical applications can reduce cost, time, human expertise, and medical error.[28]
Kunhimangalam et al. reported that by designing an expert system, they were able to diagnose CTS and its severity using fuzzy logic to help the patient take appropriate therapeutic measures before the severity of CTS increases. They believe that the system they developed can help the GP or specialist to diagnose and predict the patient's condition.[28]
Park et al. using an ML-based modeling approach to investigate the feasibility of determining the severity of CTS based on personal, clinical, and sonographic characteristics, as in electrodiagnostic techniques, reported that the best ML models yielded greater than 70% accuracy. While ML-based models performed well in classifying mild and severe grades, model accuracies were relatively low when classifying moderate grades. They stated that Extreme Gradient Boosting (XGB) has the best performance among the evaluated ML algorithms.[31]
Faeghi et al. analyzed the accuracy of CTS diagnosis based on ML modeling by applying segmentation processes to sonographic images obtained at wrist level from CTS and control groups. They reported that the diagnostic accuracy of radiologists increased when the computer-assisted diagnosis was applied.[32]
Wei et al. determined that hand kinematics is important for CTS diagnosis and severity grading using Random Forest (RF) for hands with mild to moderate CTS in controls, in ML-based CTS assessment with predictive accuracy reaching 90.3%.[11]
Yaman et al. compared bagging and boosting ensemble learning methods to automatically classify EMG signals. Their experimental results showed that group classifiers perform better in diagnosing neuromuscular disorders. The results of the study reported that AdaBoost achieved 99.08% accuracy with the Random Forest Ensemble method, therefore using a smaller dataset provides a performance advantage.[22]
In our study, the best estimation was SVM and the worst estimation was KNN in the grade zero. Our best guess in grade 1 belongs to SVM. Ensemble and Tree made the best guesses in the 2nd and 3rd grades. SVM is the best algorithm with an overall success rate of 93.55%. As can be understood from the results of the algorithms we used in our study, the data type should be more to increase the success rate of the algorithms.
It is possible to talk about some difficulties in using machine learning in electrophysiological measurements. For example, the devices from which we receive the messages are not standardized and the data obtained according to the height, weight, gender and other demographic characteristics of the patients cannot be standardized. Similar limitations are seen in the studies of distinguishing neurologic and psychological diseases in machine learning.[33]
It should be kept in mind that AI can be used in different methods and in different combinations while diagnosing the disease, and it has different limitations and abilities in every direction.[34]
Although it facilitates clinical diagnosis, it is the best used It should be known that even AI algorithms tend to avoid negative side effects and test results, and it should not be overlooked that the safety of the patient cannot be fully ensured.[35]

Conclusion

The results of our study showed that the ML algorithm models provided better optimal training and prediction results, consistent with previous studies. Our ML-based classification system was able to accurately predict the severity of CTS using patient baseline, clinical information, and nerve conduction results. We believe that our study can play a supportive role in the clinic, allowing the surgeon or physician to determine the severity of CTS and decide on surgical or medical treatment accordingly, with minimal discomfort to the patient. The use of artificial intelligence can achieve very successful results in proportion to the regular and detailed recording of patient data in the digital system. However, it should be clearly known that; Artificial intelligence usage algorithms without positive findings obtained as a result of the examination by the clinician will always be incomplete in the diagnosis and treatment process.

Ethics approval

This study was carried out taking into account the principles of the Declaration of Helsinki. The study was approved by the Non-Interventional Ethics Committee of Sakarya University Faculty of Medicine with the date 04/03/2022 and number 52.

Conflict of Interest

The authors declare no competing interests.

Author Contributions

MA, YE and ESD designed the study, ESD and MA collected data, SU analyzed the data and ESD and YE wrote the study. MA and SU checked the results.

Financial support

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Araştırma Makalesi | Research Article

ÜNİVERSİTE HASTANESİNDE ÇALIŞAN DOKTOR VE HEMŞİRELERİN İZOLASYON ÖNLEMLERİNE UYUMLARININ DEĞERLENDİRİLMESİ

EVALUATION OF COMPLIANCE OF PHYSICIANS AND NURSES WITH ISOLATION PRECAUTIONS IN UNIVERSAL HOSPITAL

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ÖZ

Amaç: İzolasyon önlemleri hastane enfeksiyonlarının azaltılmasında büyük rol oynamaktadır. Bu çalışma çalışan doktor ve hemşirelerin izolasyon önlemlerine uyumlarını değerlendirmek amacıyla yapılmıştır.

Yöntem: Çalışma Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi'nde çalışan 100 sağlık personeli (54 doktor, 46 hemşire) ile tanımlayıcı olarak yapılmıştır. Veriler katılımcıların sosyodemografik özelliklerini içeren anket formu ve izolasyon önlemlerine uyum ölçeği kullanılarak toplanmıştır. Ölçekten alınması beklenen minimum puan 18, maksimum puan 90'dır. Yüksek puan sağlık çalışanlarının izolasyon önlemlerine uyumunun arttığını göstermektedir. Veriler SPSS (Statistical Package for the Social Sciences) 22.0 istatistik paket programı aracılığı ile analiz edilmiştir.

Bulgular: Araştırmaya katılan hekim ve hemşirelerin yaş ortalamaları 25,99±5,13 olup %66'sı kadındır. İzolasyon önlemlerine uyum ölçeğinden kadın personel %73,8±10,17 ve erkek personel %66,52±14,82 puan almıştır. İzolasyon önlemlerine uyum hemşirelerde daha yüksek oranlarda bulunmuştur. Katılımcıların %72'sinin izolasyon önlemlerine ilişkin eğitim aldığı saptanmıştır. Çalışmamızda eğitim alan sağlık personellerinin izolasyon önlemlerine uyum oranı %71,95±13,39 saptanmıştır. Eğitim alan sağlık personellerinde izolasyon önlemlerine uyum oranı daha yüksek bulunmuştur.

Sonuç: Çalışmada izolasyon önlemleri konusunda eğitim alanların ölçekten yüksek puan aldıkları belirlenmiştir. İzolasyon önlemleriyle ilgili eğitim programları geliştirilmeli ve bu eğitim tüm sağlık çalışanlarına verilmelidir.

Anahtar Kelimeler: İzolasyon önlemleri, hastane enfeksiyonu, uyum

ABSTRACT

Objective: Isolation measures play a major role in reducing hospital infections. This research was carried out to evaluate the compliance of physicians and nurses with isolation precautions.

Methods: This study was conducted with a total of 100 health staff (56 doctors and 46 nurses) working at Afyonkarahisar Health Sciences University. Data were collected using the sociodemographic characteristics and the compliance with isolation precautions scale. The minimum and maximum possible scores anticipated to be obtained from the scale were 18 and 90 points respectively. High scores indicated that the health staff's compliance with isolation precautions is high.

Results: The mean age of participants in the study was 25.99±5.13 years with 66% female. The mean scores of female and male staff were 73.8±10.17% and 66,52±14.82% respectively. Compliance with isolation precautions was found to be higher in nurses. The mean scores of health staff who had education on isolation were 71.95±13.39%. The health staff who had education on isolation obtained to be higher mean scores from compliance with isolation precautions.

Conclusion: It was determined that the ones who had received training on isolation precautions achieved a high score. Training programs should be developed and this training should be provided for the health staff.

Keywords: Isolation precautions, nosocomial infection, compliance

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Giriş

Hastane enfeksiyonları tüm dünyada olduğu gibi ülkemizde de önemli bir sağlık sorunudur. Hastalar hastaneye başvurduktan sonra gelişen ve başvuru anında inkübasyon döneminde olmayan veya hastanede gelişmesine rağmen bazen taburcu olduktan sonra ortaya çıkan enfeksiyonlardır. Hastalık Kontrol ve Korunma Merkezi (Centers for Disease Control and Prevention (CDC))'e göre yaklaşık olarak hastanede yatan her 20 hastadan 1'inde hastane enfeksiyonu geliştiği bildirilmektedir.[1,2] Hastane enfeksiyonları nedeniyle artan morbidite ve mortalite oranlarına bağlı olarak yaşam kalitesinde bozulma, hastanede yatış süresinde uzama ve maliyet artışı görülebilmektedir.[3,4] Bunun sonucunda hasta güvenliğinin sağlanmasında enfeksiyon kontrolü ve gelişiminin önlenmesi giderek önem kazanmaya başlamıştır.

Hastane enfeksiyonlarının azaltılmasında sağlık çalışanlarının izolasyon önlemlerine uyumunun rolü büyüktür. İzolasyon önlemleri, hastanede bulunan tüm hastaları kapsayan standart önlemler ve bulaşma yoluna yönelik önlemler olmak üzere iki şekilde sağlanmaktadır. Standart önlemler, kan ve vücut sıvılarıyla bulaşabilecek etkenlere yönelik önlemleri kapsar ve hastanın tanısına, enfeksiyon olup olmadığına bakılmaksızın hastanede bulunan tüm hastalara uygulanması gereken önlemlerdir. CDC'nin 2019 yılında güncellediği 'İzolasyon Önlemleri' kılavuzunda belirtilen standart önlemler incelendiğinde, en önemli standart önlemin ter dışında her tür kan, vücut sıvı ve sekresyonu ile temas sırasında steril olmayan eldiven giyilmesi ve temas sonrasında eldivenlerin çıkarılarak el hijyeninin sağlanması olduğu ifade edilmiştir. Bulaşma yoluna yönelik önlemler, tanımlanmış veya şüphe edilen, epidemiyolojik olarak önemli, enfekte veya kolonize hastalara standart önlemlere ek olarak uygulanan önlemlerdir. Bulaşma yoluna yönelik önlemler; hava yolu önlemleri, damlacık önlemleri ve temas önlemleri olmak üzere üç grupta incelenmektedir.[5] Ülkemizde yapılan çalışmalar incelendiğinde, çoğunlukla hemşirelerin izolasyon önlemlerine uyumunun incelendiği hekim ve hemşirelerin izolasyon önlemlerine uyumunun birlikte değerlendirildiği çalışmaların çok az sayıda olduğu görülmektedir.[4-9] Hasta ile temas halinde olan sağlık personellerinden hemşire ve doktorların izolasyon önlemlerine uyumu, doğru yöntemlerle ve belli aralıklarla değerlendirilmelidir. Bu bilgiler ışığında araştırmamız hastanemizde çalışan doktor ve hemşirelerin izolasyon önlemlerine uyumlarını değerlendirmek amacıyla yapılmıştır.

Yöntem

Çalışmamız Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi'nde 5 Dâhili, 3 Cerrahi yoğun bakım ünitesi ve 9 Dahili, 2 Cerrahi servisinde çalışan 100 sağlık personeli (24 Asistan Doktor, 30 İntörn Doktor, 20 Sorumlu hemşire ve 26 Öğrenci hemşire) ile tanımlayıcı olarak yapılmıştır. Veriler katılımcıların demografik özelliklerini içeren anket formu ve İzolasyon Önlemlerine Uyum Ölçeği (İÖUÖ) kullanılarak toplanmıştır. Araştırmaya başlamadan önce ölçeğin geçerlilik ve güvenirlilik çalışmasını yapan Tayran ve Ulupınar'dan ölçeğin kullanımına ilişkin izin alınmıştır. Tayran ve Ulupınar tarafından geliştirilen, geçerlilik ve güvenilirliği 2011 yılında yapılan bu ölçek; hekim ve hemşirelerin izolasyon önlemlerine uyumunu ölçmeyi amaçlamaktadır. İzolasyon önlemlerine uyumu etkileyen faktörleri belirlemeye yönelik 18 maddeden oluşan 5'li likert tipte bir ölçektir.[10] Ölçekteki maddeler bulaşma yolu (3, 8, 9, 10, 11. maddeler), çalışan-hasta güvenliği (2, 5, 12,14, 16, 17. maddeler), çevre kontrolü (1, 13, 15, 18. maddeler) ve el yıkama ve eldiven kullanımı (4., 6., 7. maddeler) olmak üzere dört alt boyutta bulunmaktadır. Ölçekte, kesinlikle katılıyorum 1, katılmıyorum 2, fikrim yok 3, katılıyorum 4 ve kesinlikle katılıyorum 5 puan olarak değerlendirilmektedir. İzolasyon önlemlerine uyum, toplam puan hesaplanarak değerlendirilmektedir. En düşük 18, en yüksek 90 puan alınan bu ölçekte puan arttıkça uyum da artmaktadır. Araştırmaya katılan hekim ve hemşirelere araştırma öncesinde araştırma hakkında bilgilendirme yapılarak ve yüz yüze görüşme tekniği ile veriler toplanmıştır. Katılımcıların sosyodemografik verileri frekans ve yüzdeler ile gösterilmiştir. Veriler SPSS (Statistical Package for the Social Sciences) 22.0 istatistik paket programı aracılığı ile analiz edilmiştir.

Bulgular

Araştırmaya katılan hekim ve hemşirelerin yaş ortalamaları 25,99±5,13 olup %66'sı kadındır. Katılımcıların %72'si izolasyon önlemlerine ilişkin eğitim aldığını, %28'i ise eğitim almadığını ifade etmiştir. Araştırmaya katılan personelin eğitim alıp almama durumuna bakılmaksızın %82'si eğitim almak istemektedir. Sağlık personelinin demografik özelliklerine göre dağılımı Tablo 1'de değerlendirilmiştir.

Araştırmaya katılan kadın personelin izolasyon önlemlerine uyum oranı %73,8±10,17 ve erkek personelin izolasyon önlemlerine uyum oranı %66,52±14,82 olarak bulunmuştur. Araştırmaya katılan personelden yaşa göre izolasyon önlemleri uyumuna baktığımızda 25 yaş ve altı çalışanların uyum oranı %73,01±10,56 ve 25 yaş üstü çalışanların uyum oranı %68,9±14,39 olarak bulunmuştur. Araştırmaya katılan personelden 0-1 yıl çalışma süresi olanların izolasyon önlemlerine uyum oranı %73,25±10,64; 2-5 yıl çalışma süresi olanların izolasyon önlemlerine uyum oranı %73,17±8,39; 6-10 yıl çalışma süresi olanların izolasyon önlemlerine uyum oranı %60,66±18.,6; 11 yıl ve üstü çalışma süresi olanların izolasyon önlemlerine uyum oranı %47,66±18,5 olarak bulunmuştur. Araştırmaya katılan asistan doktorların izolasyon önlemlerine uyum oranı %69,16±9,56; intörn doktorların izolasyon önlemlerine uyum oranı %70,23±8,48; sorumlu hemşirelerin izolasyon önlemlerine uyum oranı %68,95±18,27 ve öğrenci hemşirelerin

izolasyon önlemlerine uyum oranı %76.42±12.16 olarak bulunmuştur. Çalışmamızda eğitim alan sağlık personellerinin izolasyon önlemlerine uyum oranı %71,95±13,39 iken eğitim almayanların 69,71±9,30 saptanmıştır. Eğitim alanlarda izolasyon önlemlerine uyum oranı daha yüksek bulunmuştur. Araştırmaya katılan sağlık personelinin bazı özelliklerine göre izolasyon önlemleri uyum ölçeği puan ortalamaları Tablo 2'de gösterilmiştir.

Tablo 1. Sağlık Personelinin Demografik Özelliklerine Göre Dağılımı

Özellikler		Sayı (n)	Yüzde (%)
Yaş	<25	59	59
	≥25	41	41
Cinsiyet	Kadın	66	66
	Erkek	34	34
Meslek Grubu	Asistan Doktor	24	24
	İntörn Doktor	30	30
	Öğrenci Hemşire	26	26
	Sorumlu Hemşire	20	20
Çalışılan Birim	Cerrahi Yoğun Bakım	13	13
	Dâhiliye Yoğun Bakım	8	8
	Cerrahi Servis	29	29
	Dâhili Servis	50	50
Eğitim Durumu	Eğitim Almış	72	72
	Eğitim Almamış	28	28
Görevde Çalışma Süresi	0-1 yıl	60	60
	2-5 yıl	28	28
	6-10 yıl	9	9
	≥11	3	3
Eğitimin Alındığı Yer	Kongre/Kurs	1	1
	Hizmet İçi Eğitim	20	20
	Okul Eğitimi	49	49
	Oryantasyon Eğitimi	2	2
Eğitim Alma İsteği	İsteyen	82	82
	İstemeyen	18	18

Tablo 2. Sağlık Personelinin Bazı Özelliklerine Göre İzolasyon Önlemleri Uyum Ölçeği Puan Ortalamaları

Özellikler		Sayı	Toplam Puan±SS
Yaş	<25	59	73,01±10,56
	≥25	41	68,9±14,39
Cinsiyet	Kadın	66	73,8±10,17
	Erkek	34	66,52±14,82
Meslek Grubu	Asistan Doktor	24	69,16±9,56
	İntörn Doktor	30	70,23±8,48
	Öğrenci Hemşire	26	76,42±12,16
	Sorumlu Hemşire	20	68,95±18,27
Çalışılan Birim	Cerrahi Yoğun Bakım	13	66,07±16,99
	Dâhiliye Yoğun Bakım	8	70,62±11,50
	Cerrahi Servis	29	73,86±8,67
	Dâhili Servis	50	71,34±12,87
Eğitim Durumu	Eğitim Almış	72	71,95±13,39
	Eğitim Almamış	28	69,71±9,30
Görevde Çalışma Süresi	0-1 yıl	60	73,25±10,64
	2-5 yıl	28	73,17±8,39
	6-10 yıl	9	60,66±18,96
	≥11	3	47,66 ± 18,50

SS: Standart Sapma

Tartışma

Hastane enfeksiyon oranları, sağlık hizmetlerinin güvenli ve kaliteli bir şekilde sunulmasında önemli bir göstergedir. Hastanın bakım ve tedavisinden sorumlu olan hekim ve hemşirelerin izolasyon önlemlerine uyumunun artması hastane enfeksiyon oranlarının azaltılmasında oldukça etkilidir. CDC tarafından belirlenen izolasyon önlemlerinin sağlık çalışanları tarafından doğru bir şekilde uygulanması hastane kaynaklı enfeksiyonları %30 oranında azaltabilir.[6] Araştırma sonuçlarımızı değerlendirdiğimizde, sağlık çalışanlarından hemşirelerin İÖUÖ toplam puanının, doktorların İÖUÖ toplam puanından daha yüksek düzeyde olduğu saptanmıştır. Ülkemizde yapılan çalışmalarda izolasyon önlemlerine uyum çalışmamızda olduğu gibi hemşirelerde daha yüksek oranlarda bulunmuştur.[7-9]

Suliman ve arkadaşlarının yaptığı bir çalışmada hemşirelerin izolasyon önlemlerine uyumu ile öğrenim durumu arasında fark olmadığı belirtilmektedir.[11] Çalışmamızda ise öğrenci hemşirelerde sorumlu hemşirelere göre daha yüksek uyum oranları saptanmış olup, bunun nedeni mezuniyet sonrası hemşirelerin çalıştıkları birimlerde iş yükünün fazla olması ve hemşire sayısının yetersiz olması dolayısıyla bir hemşirenin hastaya ayırdığı zamanla ilişkili olabilir. Bu konu ile ilgili olarak yapılan bir çalışmada hemşirelerin çoğunda çalışma koşullarının memnuniyeti düşük saptanmıştır.[12]

Bazı çalışmalarda, cinsiyet ile İÖUÖ puan ortalaması arasındaki korelasyonlar saptanmıştır. Cinsiyet ile izolasyon önlemlerine uyumun farklılık gösterdiği bu çalışmalarda kadınların uyumunun daha yüksek olduğu belirtilmektedir.[6,8] Kadın sağlık personelinin toplam ölçek puanının erkeklerden fazla olması, kadınların erkeklere oranla izolasyon önlemlerine uyumunun daha iyi olduğunu göstermektedir.

Literatürde, deneyimlere bağlı olarak yaş ve çalışma süresi arttıkça izolasyon önlemlerine uyumun da arttığı bildirilmektedir.[13] Karahan ve ark.'larının çalışmasında da İÖUÖ puan ortalaması ile çalışma yılı arasında anlamlı fark olmadığı belirtilmektedir.[3] Çalışmamızda ise yaş ve çalışma süresi arttıkça izolasyon önlemlerine uyum azalmaktadır. Bu bulgu araştırmamızda çalışmaya katılan bireylerin daha çok eğitimlerini yakın zamanda tamamlamış genç popülasyon olmaları, dolayısıyla bilgi düzeyleri ve farkındalıklarının daha fazla olması ile açıklanabilir.

Hastanelerde hastane infeksiyonlarının en fazla görüldüğü, stres ve iş yükünün en fazla olduğu klinikler arasında yoğun bakım üniteleri yer almaktadır. Bu durum yoğun bakım ünitelerindeki deneyimli eleman sayısını sınırlamakta, çalışmamızda da olduğu gibi uyum oranlarını düşürmektedir.[14,15] Çalışanların bireysel motivasyonunu etkileyen çalışma koşulları nedeniyle aynı kurumdaki yoğun bakım üniteleri gibi farklı kliniklerde izolasyon önlemlerine uyumun da farklı olacağı düşünülmektedir.

İzolasyon önlemlerine uyumda eğitimin rolü çok büyüktür. Sağlık çalışanlarına periyodik eğitim verilmesi, denetimlerle ve geri bildirimlerle desteklenmesi, izolasyon önlemlerine uyumu ve hasta bakım kalitesini

arttıracaktır.[16-18] Çalışmamızda bunu destekler şekilde eğitim alanlarda izolasyon önlemlerine uyum oranı eğitim almayanlara göre daha yüksek oranlarda saptanmıştır.

Sonuç

Sonuç olarak araştırmamızda eğitimin izolasyon önlemlerine uyumu arttırdığı saptanmıştır. İzolasyon önlemleriyle ilgili eğitim programları geliştirilmeli ve bu eğitim tüm sağlık çalışanlarına verilmelidir. Sağlık personelinin izolasyon önlemleri eğitim programlarında mezuniyet sonrasında da hizmet içi eğitimlerle bilgilerinin tazelenmesi sağlanmalıdır. Aynı zamanda sağlık personelinin çalışma koşullarının iyileştirilmesi ve memnuniyetlerinin değerlendirilmesi ile hekim ve hemşirelerde izolasyon önlemlerine uyumunun artması beklenmektedir.

Etik Standartlara Uygunluk

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Bu çalışmada herhangi bir kişi/kurum ile çıkar çatışması bulunmamaktadır.

Yazar Katkısı

HT: Fikir, Tasarım, Veri Toplama, İstatistiksel Analiz, Yazım

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Araştırma Makalesi | Research Article

GEBELERİN DEPRESYON, ANKSİYETE, STRES DÜZEYLERİNİN GENİTAL HİJYEN DAVRANIŞLARI ÜZERİNE ETKİSİ

THE EFFECT OF DEPRESSION ANXIETY, STRESS LEVELS OF PREGNANTS ON GENITAL HYGIENE BEHAVIORS

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ÖZ

Amaç: Bu çalışmanın amacı gebelerin depresyon, anksiyete ve stres düzeyleri ile genital hijyen davranışları arasındaki ilişkinin belirlenmesidir.

Yöntem: Tanımlayıcı ve ilişki arayıcı nitelikteki bu çalışma, bir devlet hastanesinin kadın hastalıkları ve doğum poliklinikleri ile doğum servisine Eylül 2021-Kasım 2021 tarihlerinde başvuran (n=369) gebe bireylerle yürütüldü. Çalışmada Kişisel Bilgi Formu, Genital Hijyen Davranışları Ölçeği ve Depresyon Anksiyete Stres Ölçeği kullanıldı. Araştırmadan elde edilen veriler SPSS 21 programında analiz edildi. Tanımlayıcı istatistiksel yöntemlerde; ortalama, standart sapma, frekans ve yüzde dağılımı, ölçek puanlarının karşılaştırılmasında ise Pearson Korelasyon analizi uygulandı.

Bulgular: Araştırmaya katılan gebelerin çoğunluğunu 18-25 yaş grubu oluşturdu. Gebelerin %43,6'sının depresyon, %90'ının anksiyete ve %71'inin stres belirtilerini farklı düzeylerde (hafif, orta, ileri ve çok ileri) yaşadığı saptandı. Buna göre, gebelerin yarıdan fazlasının (%57,2'sinin) çok ileri düzeyde ve %16,8'inin de ileri düzeyde anksiyete belirtileri yaşadığı bulundu. Gebelerin depresyon ve stres düzeyleri ile genital hijyen davranışları arasında istatistiksel olarak negatif yönde anlamlı bir ilişki olduğu saptandı. Anksiyete düzeyleri ile genital hijyen davranışları arasında ise anlamlı fark bulunmadı.

Sonuç: Gebelerin depresyon ve stres düzeyleri arttıkça genital hijyen davranışları azalmaktadır. Gebelerin psikososyal sağlık durumlarının iyi olmaması sadece gebelik süreci olumsuz etkilemekle kalmamakta; kadının genital hijyen davranışlarını da olumsuz etkilemektedir.

Anahtar Kelimeler: Anksiyete, depresyon, gebe, genital hijyen, stres

ABSTRACT

Objective: This study aims to determine the relationship between depression, anxiety, and stress levels of pregnant women and genital hygiene behaviors.

Methods: This descriptive and relationship-seeking study was conducted with pregnant individuals (n=369) who applied to the obstetrics and gynecology outpatient clinics of a state hospital and the obstetrics service between September 2021 and November 2021. Personal Information Form, Genital Hygiene Behaviors Scale, and Depression and Anxiety Stress Scale were used in the study. The data obtained from the research were analyzed in the SPSS 21 program. In descriptive statistical methods, Pearson Correlation analysis was used to compare mean, standard deviation, frequency, percentage distribution, and scale scores.

Results: Most of the pregnant women participating in the study were in the 18-25 age group. It was determined that 43.6% of the pregnant women experienced depression, 90% anxiety, and 71% stress symptoms at different levels (mild, moderate, severe, and very severe). Accordingly, it was found that more than half of the pregnant women (57.2%) experienced very advanced anxiety symptoms, and 16.8% had severe anxiety symptoms. It was determined that there was a statistically negative and significant relationship between depression and stress levels of pregnant women and genital hygiene behaviors. No significant difference was found between anxiety levels and genital hygiene behaviors.

Conclusion: As the depression and stress levels of pregnant women increase, their genital hygiene behaviors decrease. The poor psychosocial health status of pregnant women does not only negatively affect the pregnancy process; It also negatively affects the genital hygiene behaviors of women.

Keywords: Anxiety, depression, pregnant, genital hygiene, stress

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Giriş

Genital hijyen davranışları, bir bireyin bilgi, inanç ve alışkanlıkları doğrultusunda gerçekleştirdiği öz bakım uygulamalarındandır. Bu uygulamalar bireyler arasında sıklık ve yöntem açısından farklılık gösterebilmektedir. Kadın sağlığını korumak için genital hijyen uygulamaları büyük önem taşımaktadır. Aynı zamanda kadınların sosyal olarak rahat hissetmesi, cinsel yolla bulaşan hastalıklardan kaçınması için de genital hijyen bakım davranışları gereklidir. Nitekim, genital hijyen yetersizliğine bağlı olarak kadınlarda genital ve üriner sistem enfeksiyonları sıklıkla görülebilmektedir.[1,2] Genital hijyen yetersizliğine ek olarak gebelik durumu da kadınların genital enfeksiyon yaşama riskini arttırmaktadır. Gebelikte görülen anatomik, fonksiyonel değişimler, idrar içeriğinin değişmesi, hormonal ve fizyolojik farklılıklar gebelikte genital enfeksiyona neden olabilmektedir.[3,4] Gebelikte görülen genital enfeksiyonlar çoğu zaman belirtisiz ya da basit bir sistit şeklinde görülebilmekle beraber, düşük doğum ağırlığı, piyelonefrit, erken doğum, hipertansiyon, preeklampsi ve perinatal ölüm insidansında artış gibi ciddi komplikasyonlara da neden olabilmektedir.[5,7] Nitekim, enfeksiyon hastalıklarının önlenmesinde kişisel hijyen alışkanlıklarının çok önemli olduğu vurgulanmaktadır.[8] Genital enfeksiyonlara neden olan kötü hijyen alışkanlıkları arasında el yıkama alışkanlığının olmaması, uygun iç çamaşırı kullanılmaması ve tuvalet sonrası genital hijyenin sağlanmaması sıralanabilir.[9] Diğer yandan, ruh sağlığının da hijyen davranışlarını etkilediği belirtilmiştir.[10] Yapılan çalışmalarda, depresyon anksiyete ve stres yaşayan bireylerin hijyen alışkanlıklarında azalma olduğu bildirilmiştir.[1,11,12] Anneliğe geçiş süreci olan gebelik dönemi de, kadınların ruh sağlıklarında olumsuz değişimlere neden olabilen zorlu bir süreçtir. Bu süreçte yaşanan depresyon, aksiyete ve stres durumu, anne ile fetüs sağlığını etkilemekte, gebelik, doğum ve doğum sonrası dönemlerde ciddi komplikasyonlara neden olabilmektedir.[13] Dolayısıyla, gebelerin de depresyon, anksiyete ve stres yaşama durumlarının genital hijyen alışkanlıklarını etkileyebileceği düşünülmektedir. Ancak literatürde gebelerin yaşadığı depresyon, anksiyete ve stresin genital hijyen alışkanlıkları üzerine etkisini inceleyen çalışmaya henüz rastlanılmamıştır. Bu araştırma gebelerin yaşadığı depresyon stres ve anksiyetenin genital hijyen davranışları üzerine etkisini incelemek amacıyla planlanmıştır.

Araştırma Soruları

1. Gebelerin depresyon, anksiyete ve stres düzeyleri nedir?
2. Gebelerin genital hijyen davranış düzeyleri nedir?
3. Gebelerin depresyon, anksiyete ve stres düzeyleri ile genital hijyen davranışları arasında ilişki var mıdır?

Yöntem

Araştırmanın Tipi, Evren ve Örneklemi

Tanımlayıcı ve ilişki arayıcı alan araştırmanın evrenini bir devlet hastanesinin kadın hastalıkları ve doğum polikliniklerine Eylül 2021 - Kasım 2021 tarihleri arasında başvuran çalışmaya gönüllü olarak katılmak isteyen gebeler oluşturdu. Kuruma Haziran 2021 - Ağustos 2021 tarihleri arasında başvuran 8076 kadın sayısı evren olarak kabul edildi. Buna göre araştırma örneklemi, evreni bilinen örneklem yöntemine göre (a=0,05; H=±0,05 ve oranlar p=0,5; q=0,5) 367 gebe olarak belirlendi.[14] Araştırma verileri olasılıksız rastgele yöntemlerinden biri olan gelişigüzel örnekleme yöntemi kullanılarak toplandı. Araştırmaya 18 yaşından büyük, 2.trimesterde olan, kendinde ve fetüste herhangi bir komplikasyon olmayan, çalışmaya katılmayı kabul eden ve konuşma problemi olmayan gebeler dahil edildi. Araştırma verileri araştırmacı tarafından katılımcılar ile yüz yüze konuşularak yaklaşık 15-20 dakikada toplandı. Araştırmanın yapıldığı tarihte hastane gelen toplam 369 gebe ile çalışma tamamlandı.

Veri Toplama Araçları

Veriler kişisel bilgi formu, Depresyon, Anksiyete, Stres Ölçeği ve Genital Hijyen Davranışları Ölçeği kullanılarak toplandı.

Kişisel Bilgi Formu

Bu form araştırmacılar tarafından literatür bilgisi dahilinde hazırlanmış olup yaş, boy, kilo, aile tipi, eğitim seviyesi, gebelik sayısı, mesleği ve gelir durumunu belirleyen 15 sorudan oluşmaktadır.[3,8]

Depresyon, Anksiyete, Stres Ölçeği (DASÖ-42)

Lovibond ve Lovibond (1995) tarafından depresyon, anksiyete ve stresi değerlendirmek amacıyla geliştirilmiş 42 maddelik bir ölçektir. Depresyon, anksiyete ve stres olmak üzere üç boyuttan oluşmuştur ve her bir boyut 14 madde içermektedir.[15] Ölçeğin Türkçe uyarlaması Akın ve Çetin (2007) tarafından yapılmıştır. Yüksek puanlar depresyon, anksiyete ve stres düzeylerinin arttığını göstermektedir. Ölçeğin Cronbach Alpha iç tutarlılık sayısı 0,89 olarak bildirilmiştir.[16] Bu çalışmada Cronbach Alfa Katsayıları ölçeğin tamamı için 0,95, depresyon, anksiyete ve stres alt boyutları için ise sırasıyla 0,92, 0,86 ve 0,91 olarak bulunmuştur.

Genital Hijyen Davranışları Ölçeği (GHDÖ): Ege ve Eryılmaz (2005) tarafından genital hijyen davranışlarını değerlendirmek için 27 maddelik ölçek geliştirilmiş ve geçerlik ve güvenirlik çalışması yapılmıştır.[17] GHDÖ ölçeği 2017 yılında Karahan tarafından 23 maddeye dönüştürülmüş ve geçerlik ve güvenirlik çalışması yapılmıştır. GHDÖ ölçeği beşli Likert tipi ve üç alt boyutta 23 maddeden oluşmaktadır. Ölçeğin alt boyutları "genel hijyen" (ilk 12 madde), "menstrüel hijyen" (madde 13-20) ve "anormal bulgu farkındalığı" (madde 21-23)" şeklindedir. Ölçekten alınabilecek en düşük puan 23, en yüksek puan 115 olup, yüksek puanlar olumlu genital hijyen davranışına işaret etmektedir.[18] GHDÖ ölçeğinin

Cronbach alfa değeri bu çalışmada 0,77 olarak bulunmuş olup bu değerler genel hijyen alt boyutu için 0,62, menstrüel hijyen alt boyutu için 0,62 ve anormal bulgu farkındalığı için 0,65 olarak bulunmuştur.

İstatistiksel Analiz

Elde edilen veriler Statistical Package for the Social Sciences 21.0 programı ile analiz edilmiştir. Araştırmada verilerin analizinde sayı, yüzde, ortalama ve standart sapma gibi tanımlayıcı özellikler kullanılmıştır. Verilerin normal dağılıma uygunluğu çarpıklık ve basıklık değerleri ile değerlendirilmiştir. Depresyon Anksiyete Stres Ölçeği'nin (çarpıklık: 0,482, basıklık: -0,426) ve Genital Hijyen Davranış Ölçeği'nin (çarpıklık: -0,738, basıklık: 0,717) normal dağılım gösterdiği belirlendi.[19] Depresyon, anksiyete, stres ve genital hijyen davranışları arasındaki ilişkiyi incelemek için Pearson korelasyon analizi kullanılmıştır. Çalışmada korelasyon gücü hesaplanırken zayıf veya düşük korelasyon (r = 0-0,29), orta korelasyon (r = 0,30-0,64), güçlü korelasyon (r =0,65-0,84), ve çok güçlü korelasyon (r = 0,85-1,0) referans olarak alındı.[14] Gebelerin depresyon, anksiyete ve stres düzeylerine düzeylerine göre Genital Hijyen Davranış Ölçeği puan ortalamalarının karşılaştırılmasında ise Tek Yönlü Varyans Analizi (ANOVA) kullanılmıştır. Farklılığın hangi gruplardan kaynaklandığının tespit edilmesinde ise Post-hoc testlerden Tukey testi kullanılmıştır.

Etik Boyut

Araştırmanın yürütülebilmesi için bir devlet üniversitesinin Etik Kurulu'ndan 18.06.2021 tarih ve 2021/15-04 sayılı Karar No'su ile etik onay alınmıştır. Bilgilendirilmiş onamları alınan, araştırmaya katılmaya gönüllü olan gebelere araştırmada toplanan bilgilerin gizli kalacağı açıklanmıştır. Çalışmada kullanılan ölçeklerin kullanım izni ilgili yazarlardan alınmıştır. Araştırma "Helsinki Deklarasyonu Prensiplerine ve yayın etiğine uygun olarak" yapılmıştır.

Bulgular

Araştırmaya katılan gebelerin %43,4'ü 18-25 yaş aralığındadır. Yarıdan fazlasının (%62,3'ünün) eğitim durumu lise ve üzeri olup, (%89,7'si) çekirdek aileye sahiptir. Gebelerin %36,3'ü gelir durumlarının orta düzeyde olduğunu belirtmiştir. Katılımcıların büyük çoğunluğu (%82,1'i) ev hanımıdır, %48,5'inin bir gebeliği mevcut olup, %42,5'i fazla kiloludur (Tablo 1).

Çalışmaya katılan gebelerin Depresyon Anksiyete Stres Ölçeği ile Genital Hijyen Davranış Ölçek puan dağılımları Tablo 2'de verilmiştir. Buna göre, gebelerin DASÖ toplam puan ortalaması 95,07±28,08 ve GHDÖ toplam puan ortalaması 90,50±12,16 olarak bulunmuştur (Tablo 2).

Tablo 1. Gebelerin tanıtıcı özellikleri (n=369)

Değişkenler	Sayı	%
Yaş grubu		
18-25	160	43,4
26-34	142	38,5
35 ve üzeri	67	18,2
Eğitim durumu		
İlkokul veya altı	139	37,7
Lise veya üzeri	230	62,3
Aile tipi		
Çekirdek	331	89,7
Geniş	38	10,3
Algılanan gelir durumu		
Kötü	108	29,3
Orta	134	36,3
İyi	127	34,4
Meslek		
Ev hanımı	303	82,1
Çalışan	66	17,9
Gebelik Sayısı		
1	179	48,5
2	77	20,9
3	49	13,3
4 ve üzeri	73	17,3
BKİ		
Normal	139	37,7
Fazla kilolu	157	42,5
Obez	73	19,8

Tablo 2. Gebe kadınların DASÖ ve GHDÖ ile alt boyutlarından aldıkları puan ortalamaları (n:369)

Ölçek	Madde Sayısı	Min-Maks	Ortalama ±SS
Depresyon	14	42-81	51,72±9,69
Anksiyete	14	0-42	21,53±9,89
Stres	14	0-42	21,81±11,35
DASÖ Toplam Puan	42	42-161	95,07±28,08
Genel Hijyen	12	20-60	46,93±6,69
Anormal Bulgu Fark.	3	3-15	12,31±2,88
Adet Hijyeni	8	10-40	31,25±5,74
GHDÖ Toplam Puan	23	49-115	90,50±12,16

Min: Minimum, Maks: Maksimum, SS: Standart sapma

Gebelerin depresyon, anksiyete, stres düzeylerinin dağılımı incelendiğinde %43,6'sının depresyon, %90'ının anksiyete ve %71'inin stres belirtilerini farklı düzeylerde (hafif, orta, ileri ve çok ileri) yaşadığı saptanmıştır. Buna göre, gebelerin yarıdan fazlasının (%57,2'sinin) çok ileri düzeyde ve %16,8'inin de ileri düzeyde anksiyete belirtileri yaşadığı görülmektedir (Tablo 3).

Tablo 3. Gebelerin depresyon, anksiyete, stres düzeylerinin dağılımı (n:369)

DASÖ alt boyut düzeyleri	Depresyon		Anksiyete		Stres	
	Sayı	%	Sayı	%	Sayı	%
Normal	208	56,4	37	10,0	107	29,0
Hafif	51	13,8	13	3,5	51	13,8
Orta	43	11,7	46	12,5	81	22,0
İleri	27	7,3	62	16,8	54	14,6
Çok İleri	40	10,8	211	57,2	76	20,6

Gebelerin DASÖ ve GHDÖ puan ortalamaları arasındaki ilişkiyi belirlemeye yönelik yapılan Pearson korelasyon analiz sonucu Tablo 4'te verilmiştir. Buna göre, gebelerin DASÖ ile GHDÖ puan ortalamaları arasında istatistiksel olarak zayıf düzeyde negatif yönde anlamlı bir ilişki olduğu saptanmıştır (r = -0,114, p<0,05). Gebelerin GHDÖ ortalama puanları ile DASÖ alt boyut puanları korelasyonunda ise depresyon (r = -0,191, p<0,05) ve stres düzeyleri (r = -0,089, p<0,05) ile istatistiksel olarak zayıf düzeyde negatif yönde anlamlı ilişki olduğu bulunmuştur. Gebelerin anksiyete düzeyleri ile GHDÖ puan ortalamaları arasında ise istatistiksel olarak anlamlı bir ilişki saptanmamıştır (r = - 0,034, p>0,05) (Tablo 4). Buna göre, çalışmaya katılan gebelerin depresyon ve stres düzeyleri arttıkça genital hijyen davranışlarının zayıf düzeyde azaldığı bulunmuştur. Anksiyete düzeyleri arttıkça da genital hijyen davranışlarının azaldığı saptanmıştır; ancak bu sonuç istatistiksel olarak anlamlı değildir (p>0,05).

Gebelerin DASÖ alt boyutlarının düzeylerine (normal, hafif, orta, ileri, çok ileri) göre GHDÖ puan ortalamalarının karşılaştırılması Tablo 5'te verilmiştir. Buna göre, anksiyete ve stres alt boyut derecelerine göre GHDÖ puan ortalamalarında istatistiksel olarak anlamlı farklılık saptanmazken, depresyon alt boyut düzeyleri ile GHDÖ puan ortalamalarında istatistiksel olarak anlamlı farklılık tespit edilmiştir (F=3,561, p=0,007). Bu farklılığın hangi depresyon düzeyinden kaynaklandığını belirlemek için yapılan Tukey analizi sonucuna göre depresyon düzeyi normal olan gebelerin, GHDÖ puan ortalamaları depresyon seviyesi çok ileri olan gebelere göre daha fazla bulunmuştur (p<0,05). Buna göre, depresyon düzeyi çok ileri olan gebelerin genital hijyen davranışlarının depresyon düzeyi normal olan gebelere kıyasla daha olumsuz olduğu görülmektedir.

Tablo 4. Depresyon, Anksiyete, Stres ve Genital Hijyen Davranış Ölçeği arasındaki ilişki

Ölçekler	1	2	3	4	5	6	7	8
Depresyon (1)	1							
Anksiyete (2)	r = 0,590 p = 0,000	1						
Stres (3)	r = 0,721 *p = 0,000	r = 0,875 *p = 0,000	1					
DASÖ Toplam (4)	r = 0,844 *p = 0,000	r =0,909 p = 0,469	r = 0,961 *p = 0,000	1				
Genel Hijyen (5)	r = -0,172 *p = 0,001	r = -0,039 p = 0,451	r = -0,088 p = 0,090	r =- 0,109 *p = 0,036	1			
Anormal Bulgu Farkındalığı (6)	r = −0,182 *p = 0,001	r = 0,132 *p = 0,011	r = -0,008 p = 0,872	r = -0,020 p = 0,707	r = 0,300 *p = 0,000	1		
Adet Hijyeni (7)	r = −0,112 *p = 0,032	r = −0,093 p = 0,074	r = −0,081 p = 0,120	r = −0,104 *p = 0,046	r = 0,487 *p = 0,000	r = 0,381 *p = 0,000	1	
GHDÖ Toplam Puan (8)	r = −0,191 *p = 0,000	r = −0,034 p = 0,509	r = −0,089 *p = 0,039	r = −0,114 *p = 0,029	r = 0,852 *p = 0,000	r = 0,582 *p = 0,000	r = 0,831 *p = 0,000	1

*p<0,05

Tartışma

Araştırmaya katılan gebelerin yarıya yakını depresyon, tamamına yakını anksiyete ve büyük çoğunluğunun stres belirtilerini farklı düzeylerde (hafif, orta, ileri ve çok ileri) taşıdığı saptanmıştır. Nitekim, literatürde de kadınların gebelikte oluşan fizyolojik, psikolojik, sosyal değişimlere uyum sağlarken çeşitli düzeylerde duygulanım bozuklukları yaşayabildikleri bildirilmiştir.[13,20] Ulusal ve uluslararası yapılan çalışmalar incelendiğinde ise özellikle kullanılan ölçek, çalışmanın yapıldığı kültür ve trimesterlere göre duygulanım bozukluğu prevelansının değiştiği görülebilmektedir.

Tablo 5. Depresyon, Anksiyete Stres düzeylerine göre Genital Hijyen Davranış Ölçeği puanlarının karşılaştırılması

DASÖ alt boyutları	Düzey	X	SS	F	p
Depresyon	Normal[a]	91,93	12,49	3,561	0,007*
	Hafif[b]	92,07	10,43		a>e**
	Orta[c]	88,55	12,05		
	İleri[d]	87,11	10,59		
	Çok İleri[e]	85,45	11,97		
Anksiyete	Normal[a]	91,59	12,27	0,181	0,948
	Hafif[b]	89,61	15,75		
	Orta[c]	89,95	12,95		
	İleri[d]	89,79	12,56		
	Çok İleri[e]	90,70	11,69		
Stres	Normal[a]	91,32	13,48	0,861	0,487
	Hafif[b]	92,11	10,49		
	Orta[c]	90,59	11,38		
	İleri[d]	89,98	13,57		
	Çok İleri[e]	88,55	10,95		

Analizlerde ANOVA ("F") ile Tukey testi kullanılmıştır. *p<0,05

Gelişmekte olan Orta Amerika ülkesi Nikaragua'da çalışmaya katılan gebelerin %41'inin anksiyete ve %57'sinin depresyon belirtileri taşıdığı bildirilirken[21], Şangay'da 2813 örneklem ile yapılan çalışmada ise gebelerin %11,1'nin anksiyete ve %10,3'ünün depresyon belirtileri gösterdiği saptanmıştır.[22] Hindistan'da gebelerin depresyon, anksiyete ve stres durumlarını belirlemek amacıyla yapılan toplum temelli benzer çalışmada, gebelerin %25,5'inde depresyon, %63'ünde anksiyete ve %23'ünde stres belirtileri bildirilmiştir.[11] Yüksel ve ark.'nın (2020) aynı ölçeği (DASÖ) kullanarak gebeler ile yaptıkları araştırmada, çalışmamıza paralel olarak gebelerin %55,7'sinin depresyon, %83'ünün anksiyete ve %39,7'sinin stres belirtilerini farklı düzeylerde (hafif, orta, ileri ve çok ileri) gösterdikleri bulunmuştur.[23] Diğer yandan, literatürde, gebelerde görülen depresyon, anksiyete ve stres belirtilerinin farklı düzeylerde olmasının; yaşanan coğrafi bölge (bölgeler/uluslararası kültür farkı), toplumun ve eşin gebeye yaklaşımı, kullanılan ölçme aracı gibi çok çeşitli değişkenler ile ilişkili olabileceği düşünülmektedir.

Araştırmaya katılan gebelerin Genital Hijyen Davranış Ölçeği toplam puan ortalaması 90,50 (SS 12,16) olarak bulunmuştur. Gebe olan ve olmayan kadınların genital hijyen davranışlarını belirlemek amacıyla yapılan karşılaştırmalı bir çalışmada, GHDÖ puanı gebe olan kadınlarda 74,87 (SS 11,08), gebe olmayan kadınlarda ise 75,01 (SS 11,63) olarak bildirilmiştir.[24] Türkiye'nin yedi farklı coğrafi bölgesinde yaşayan 3106 kadının genital hijyen davranışlarını belirlemek amacıyla yapılan çalışmada GHDÖ toplam puan ortalaması 78,96 (SS 11,65) olarak bulunmuştur.[25] Arıkan'ın (2019), Nevşehir'de 20-37. gebelik haftasında olan 365 gebe ile yaptığı çalışmada GHDÖ toplam puan ortalaması 64,42 (SS 10,44) olarak bildirilmiştir.[26] Gebelerin genital hijyen davranışlarının kırsal ve kentsel bölgelere göre belirlendiği araştırma da ise kırsal kesimde yaşayan gebelerin GHDÖ puan ortalaması 77,98 (SS 12,19) iken kentsel bölgelerde yaşayan gebelerin GHDÖ puan ortalaması 81,29 (SS 11,22) olarak bulunmuştur.[8] Gebelerde genital hijyen eğitiminin idrar yolu enfeksiyonu semptomlarına etkisini belirlemek amacıyla İzmir'de gebeler ile yapılan çalışmada GHDÖ toplam puan ortalaması 71,36 (SS 14,75) olarak bildirilmiştir.[27] Çalışmalarda verilen genital hijyen eğitimi istatistiksel olarak kadınların GHDÖ puan ortalamalarını artırdığı saptanırken, verilen eğitim ile kadınların genital hijyen farkındalıklarının arttığı vurgulanmıştır.[3,27] Nitekim, koruyucu sağlık hizmetlerinin en önemli boyutlarından biri bireylere verilen sağlık eğitimidir. Gebelere verilen prenatal sağlık eğitimi kapsamında genital hijyen uygulamalarına yer verilmesi kadında oluşabilecek enfeksiyonların önlenmesi açısından oldukça önemlidir. Dolayısıyla kadınların farkındalık kazanmaları ve genital hijyen davranışlarının olumlu olması anne-bebek sağlığının gelişimine katkı sağlayacaktır.[3]

Bu çalışmada, gebelerin genital hijyen davranışları ile depresyon ve stres düzeyleri arasında negatif yönde zayıf düzeyde anlamlı bir ilişki saptanmıştır. Buna göre, gebelerin depresyon ve stres düzeyleri arttıkça genital hijyen davranışlarının azaldığı bulunmuştur. Bununla birlikte, depresyon düzeyi çok ileri olan gebelerin genital hijyen davranışlarının da depresyon düzeyi normal olan gebelere kıyasla daha olumsuz olduğu belirlenmiştir. Literatürde bu iki ölçek arasındaki korelasyonu değerlendiren çalışmaya henüz rastlanmamış olması tartışma için bir sınırlılık oluşturmakla birlikte, araştırmadan elde edilen sonuçlar sonraki araştırmalar için kaynak oluşturacaktır. Nitekim, depresyon ve stres gibi ruhsal sorunlar kişilerin baş etme becerilerini olumsuz etkilemekle birlikte günlük yaşam aktivitelerinin devam ettirilmesine de engel oluşturabilmektedir.[28] Günlük yaşamın bir parçası olan hijyen gereksinimlerinin yerine getirilememesi depresyonun sıklıkla görülen belirti ve bulgularındandır.[29] Bu doğrultuda, çok ileri düzeyde depresyonu olan gebelerin de genital hijyen davranışlarının yetersiz olması öz bakımlarını sağlamada

yetersizlik ve isteksizliğe bağlı davranışsal değişimlerden kaynaklı olabileceği düşünülmektedir.

Gebelikte yaşanan depresyon, anksiyete ve stres gibi duygu durum bozukluklarının düşük doğum ağırlığı, yüksek preterm eylem, intrauterin gelişim geriliği, olumsuz maternal bağlanma gibi gebelik, doğum ve doğum sonu komplikasyonlarını artırdığı açıklanmaktadır.[30] Dolayısıyla, gebelerin rutin sağlık izlemleri kapsamında psikososyal sağlıklarının da değerlendirilmesi, depresyon, anksiyete ve stres düzeylerinin belirlenmesi olumlu genital hijyen davranışlarının geliştirilmesi açısından da önemli yer tutmaktadır. Bu durum, özelde anne-bebek sağlığı açısından, genelde ise toplum sağlığı açısından oldukça önemlidir.

Sonuç ve Öneriler

Gebelerin depresyon, anksiyete, stres düzeyleri ile genital hijyen davranışları arasındaki ilişkinin incelenmesi amacıyla yapılan araştırma sonucunda gebelerin depresyon ve stres düzeyleri arttıkça genital hijyen davranışlarının zayıf düzeyde azaldığı bulunmuştur. Diğer yandan, anksiyete düzeyleri ile genital hijyen davranışları arasında ise anlamlı fark saptanmamıştır. Dolayısıyla, gebelik sürecinde yaşanılan depresyon ve stres düzeylerinin de genital hijyen davranışını etkileyebilecek faktörler arasında tartışılabilir; ancak bu konuda daha fazla araştırmaya ihtiyaç bulunmaktadır. Gebelerin psikososyal sağlık durumlarının iyi olmaması sadece gebelik sürecini olumsuz etkilemekle kalmamakta genital hijyen davranışlarını da olumsuz etkileyebilmektedir. Nitekim, sağlık profesyonelleri tarafından gebelerin psikososyal sağlık durumunlarının düzenli olarak değerlendirilmesi, buna ilişkin standart ölçek ve modellerin kullanılması, prenatal eğitimlerin ve gebe okullarının ruh sağlığının korunması/güçlendirilmesi ve doğru genital hijyen davranışlarını kapsayan eğitim faaliyetlerini içermesi önerilmektedir. Böylece özelden genele, toplum sağlığının da korunması amaçlanmış olacaktır. Literatürde gebelerin depresyon, anksiyete ve stres düzeylerine ilişkin çeşitli değişkenler ile yapılan çalışmalar mevcut olmakla birlikte, genital hijyen davranışları ile ilişkisinin incelendiği çalışmalar henüz çok yetersizdir. Bu doğrultuda, bu çalışmanın sonuçları literatüre sağladığı katkı açısından da oldukça önemlidir.

Etik Standartlara Uygunluk

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Research Article | Araştırma Makalesi

INVESTIGATION OF SUBSTANTIA NIGRA HYPERECHOGENICITY BY TRANSCRANIAL SONOGRAPHY IN PATIENTS WITH ESSENTIAL TREMOR

ESANSİYEL TREMOR HASTALARINDA TRANSKRANİYAL SONOGRAFİ İLE SUBSTANTİA NİGRA HİPEREKOJENİTESİNİN ARAŞTIRILMASI

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ABSTRACT

Objective: Essential tremor (ET) is the most common movement disorder. ET diagnosis may precede future Parkinson's disease. Substantia nigra hyperechogenicity in transcranial sonography (TCS) is associated with Parkinson's disease. The underlying etiology of substantia nigra hyperechogenicity remains unclear. In this study, we aimed to investigate the significance of the substantia nigra hyperechogenicity in patients with essential tremor.

Methods: A total of 55 patients with ET and 60 matched controls underwent TCS. The hyperechogenic area was measured in the SN. Approximately ten years after their baseline TCS, all patients were inquired about their current condition, treatment, and medications to determine whether they had received a diagnosis of PD.

Results: A total of 15 subjects were excluded due to insufficient image acquisition. The echogenic area of the SN ranged from 0.01 to 0.86 cm^2 (mean 0.25±0.15) in the patient group and from 0.02 to 0.72 cm^2 (mean 0.15±0.16) in the control group. Patients with ET had a significantly larger echogenic area than controls (p=0.001). 47% (26/55) of the patients have hyperechogenic SN, whereas only 15 % (9/60) of healthy controls have hyperechogenicity in the substantia nigra. None of the patients reported having a change in their diagnoses of ET.

Conclusions: The results of this study show that SN hyperechogenicity is increased in patients with ET. Transcranial sonography may contribute to understanding the pathophysiology of ET.

Keywords: Essential tremor, parkinson's disease, substantia nigra hyperechogenicity, transcranial sonography

ÖZ

Amaç: Esansiyel tremor (ET) en sık görülen hareket bozukluğudur. ET ayrı bir hastalık olarak kabul edilse de, klinik takipte ET tanılı vakaların Parkinson Hastalığına (PH) ilerleyebildiği bilinmektedir. Transkraniyal sonografide (TKS) Substantia nigra (SN) hiperekojenitesi saptanması, PH ile ilişkili bulunmuştur. Ancak bu radyolojik bulgunun etiyolojisi ve klinik anlamı belirsizliğini korumaktadır. Biz de bu çalışmada esansiyel tremorlu hastalarda SN hiperekojenisitenin önemini araştırmayı amaçladık.

Yöntem: Bu çalışmada ET tanısı olan toplam 55 hastaya ve yaşları benzer 60 kontrole TKS uygulandı ve SN hipekojeniteleri ölçüldü. Başlangıç TKS'lerinden yaklaşık on yıl sonra, tüm hastalara tekrar ulaşıldı ve PD teşhisi alıp almadıkları, mevcut durumları, tedavileri ve ilaçları hakkında sorular soruldu.

Bulgular: Çalışmaya dahil edilen 115 hastadan 15'i yetersiz görüntü kalitesi nedeniyle çalışmadan dışlandı. SN'nin ekojenik alanı hasta grubunda 0,01 ile 0,86 cm^2 (ortalama 0,25±0,15), kontrol grubunda ise 0,02 ile 0,72 cm^2 (ortalama 0,15±0,16) arasında değişiyordu. ET'li hastalarda kontrollere göre anlamlı ölçüde daha büyük bir ekojenik alan ölçüldü (p=0,001). Hastaların %47'si (26/55) hiperekojenik SN'ye sahipken, sağlıklı kontrollerin sadece %15'i (9/60) substantia nigra'da hiperekojeniteye sahipti. Hastaların hiçbiri takipte ET tanılarında bir değişiklik olduğunu bildirmedi.

Sonuç: Bu çalışmanın sonuçları, ET'li hastalarda SN hiperekojenitesinin arttığını göstermektedir. Transkraniyal sonografi ET patofizyolojisini anlamaya katkı sağlayabilir.

Anahtar Kelimeler: Esansiyel tremor, parkinson hastalığı, substantia nigra hiperekojenitesi, transkraniyal sonografi

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Introduction

Essential tremor (ET) is the most common movement disorder in adults [1]. It is characterized by action tremor of the arms, which may progress in severity, spreading to the limbs or head and becoming disabling. There is still an ongoing debate on the pathology underlying the disease. Essential tremor has been proposed to be a neurodegenerative condition considering its insidious onset, progressive course, and association with an increased risk for Parkinson's disease (PD) and Alzheimer's disease. In addition, autopsy findings of loss of Purkinje cells in the cerebellum and Lewy bodies in the locus coeruleus supported the neurodegenerative nature of ET [2]. However, there have been claims that ET might be a disorder of a thalamocorticocerebellar network rather than a degenerative condition [3]. In addition, in some ET subgroups, a transformation from ET to PD has been reported [4]. The diagnosis of ET is based on a thorough patient history-taking and clinical examination, with particular attention given to differentiating from PD. However, due to the overlapping clinical features, it may be challenging to distinguish ET from PD, even for expert neurologists in movement disorders.

Currently, the differentiation between ET and PD may be possible by dopamine transporter imaging, which can demonstrate presynaptic neurodegeneration consistent with PD [2]. However, this imaging modality is expensive and only available at some facilities. Transcranial sonography (TCS) is a non-invasive and inexpensive tool used to assess the presence of hyperechogenicity of the substantia nigra, indicating a degenerative course in PD or alike, and recognized as an additional diagnostic tool in PD [5,6]. Previous studies showed significant hyperechogenicity in the area of SN in patients with PD compared with ET and healthy controls [7]. Hyperechogenic SN is defined if the calculated hyperechogenic SN area is greater than the determined cut-off value for SN echogenicity, which may differ from center to center [5]. Consistent with the guidelines, a cut-off value of 0.21 cm^2 for SN hyperechogenicity was determined in our center to differentiate PD from healthy controls [8]. In addition, several studies also assessed SN hyperechogenicity in ET patients and reported a wide range of incidences from 0% to 33% [7,9–14]. SN hyperechogenicity in ET was attributed to the close anatomical relation of the nucleus ruber to the SN, with a consideration of a linkage between ET and PD which is the increased risk of ET transforming to PD [7,14,15]. In addition, a recent longitudinal study suggested that increased substantia nigra hyperechogenicity may be a risk marker in determining the early Parkinson's signs in ET patients [16]. However, other studies found no difference in SN hyperechogenicity between ET and controls [7]. In order to address these gaps, we investigated ET patients with TCS for the evaluation of SN hyperechogenicity and, after 10 years, inquired into their clinical status about the risk for transformation to PD.

Methods

The present study involved fifty-five consecutive patients in a prospective design diagnosed with ET from June 2008 to 2010. In all patients, the diagnosis was based on the criteria of the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET)[17]. Informed consent was obtained from each patient. The study was approved by the institutional review board of Göztepe Training and Research Hospital.

Demographic data and clinical characteristics of the patients were recorded. A detailed family history was taken. The duration of the disease and age of disease onset was inquired. ET was classified as mild, moderate, or severe based on the WHIGET criteria.

All patients underwent transcranial sonography performed by the same experienced radiologist who was blinded to the diagnosis of the patients, using a 1-4 MHz transducer (Siemens Antares Medical System, Munich, Germany). The penetration depth was 16 cm, with a dynamic range between 40-60 dB. The transducer was placed on the preauricular region of the temporal bone in the axial plane so that the butterfly-shaped hypoechogenic midbrain could be visualized. After acquisition, the image of the midbrain was frozen, the mesencephalic tegmentum was marked and the echogenicity of the substantia nigra was depicted. The marked echogenic area was calculated in cm^2 automatically by the device. Images with insufficient acquisition were excluded. The results obtained from ET patients were analysed according to the disease duration and severity of ET and in comparison, with 60 age- and sex-matched healthy controls who had visited the neurology outpatient clinic for various reasons and who had been found to have no neurologic problem during the enrolment period.

In addition, patients were contacted via telephone calls about 10 years after their baseline TCS examinations for their current condition, treatment and medications and to determine whether they had received a diagnosis of PD. Those with increased SN values above the cut-off values of the present study and the cut-off values reported for PD patients [8] were particularly inquired with respect to transformation risk from ET to PD.

Statistical Analysis

Continuous variables were expressed as mean (±standard deviation) and categorical variables were expressed as number and percentages. as well as one-way analysis of variance for comparisons between groups, Tukey multiple comparison test for subgroup comparisons, independent t test for comparison of paired groups, chi-square test for comparison of qualitative data were used.

Sensitivity, specificity, positive predictive value, negative predictive value, LR were calculated in determining the cut-off points for SN+ (hyperechogenicity of substantia nigra), and the area under the ROC curve was calculated. The results were evaluated at the significance level of $p < 0.05$, at a 95% confidence interval.

Results

Of 55 patients with ET and of 60 controls, 10 and 5 subjects, respectively, were excluded due to insufficient image acquisition. Demographic and clinical characteristics of the patients are summarized in Table 1. The patient and control groups were similar in age and gender (p>0.05). The mean age of the patients was 55.2±15.2 the mean duration of the disease 10.5±10.3 years, and the mean age of onset 55.2 ±15.2 years. There was a male predominance (36/19).

Table 1. Clinical and demographic characteristics of the patients and the control group

		ET n:55	Control n:60
Age (years)		62.52±6.23	65.05±9.49
Sex	**Male**	36 (65.5%)	32 (53.3%)
	Female	19 (34.5%)	28 (46.7%)
Disease Duration (years)		10.47 ± 10.32	N/A
Family history of ET (n)		32 (58.1%)	N/A

Abbreviations: ET, essential tremor; n, number; N/A, not applicable

The estimated echogenic area of the SN ranged from 0.01 to 0.86 cm^2 (mean 0.25±0.15) in the patient group and from 0.02 to 0.72 cm^2 (mean 0.15±0.16) in the control group. Patients with ET had a significantly larger echogenic area than controls (p=0.001). Transcranial sonography findings are shown in Table 2. No significant corelation was found between the echogenic SN area and sex, age, family history, duration and age of the disease onset, and disease severity. Nearly half of the patients (26/55) have hyperechogenic SN whereas only 15 % (9/60) of healthy controls have hyperechogenic SN.

Table 2. Transcranial sonography findings of the ET patients and control group

	ET N:55	Control N:60	P value
MB (cm^2)	2.63±0.41	2.76±0.53	0.052
SN (cm^2)	0.25±0.15	0.15±0.16	**0.001**
SN/MB	0.10±0.07	0.05±0.06	**0.001**

Significant p-values are shown in bold. Abbreviations: MB, Midbrain; SN, Substantia nigra.

In ROC analyses, the area under the curve was 0.753 (Figure 1). A cut-off value of 0.13 cm^2 for the hyperechogenic SN area in ET represented a sensitivity of 78.3%, a specificity of 70.9%, a positive predictive value of 68.4% and a negative predictive value of 80.2%.

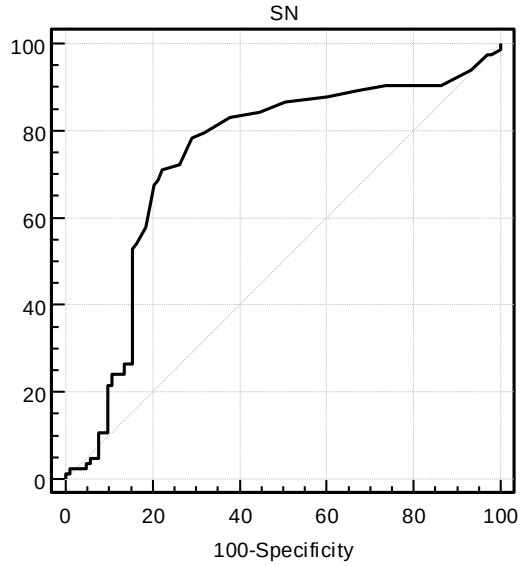

Figure 1. ROC curve of the cut-off value of hyperechogenic SN
Area Under Curve: 0.753±0.037 (0.683 – 0.815)

After a period of nearly ten years from baseline TCS evaluations, 20 patients were available to follow-up controls. Among them, 7 patients who had been considered to have hyperechogenic SN based on both the cut-off values of the present study and the cut-off values reported for PD patients. None of the responding patients reported having a change in their diagnoses of ET.

Discussion

In the present study, SN hyperechogenicity was seen significantly higher in ET patients than healthy controls. SN hyperechogenicity indicating the striatal degeneration suggests an association between ET and PD.

In a follow-up study, of 70 ET patients with baseline TCS findings 54 were examined after a mean of 6.16 years for a new-onset diagnosis of PD with clinical features and TCS. Strikingly seven of 18 patients (38.8%) who had SN hyperechogenicity developed PD on ET supporting the increased risk of PD development on ET[15]. Despite numerous investigation on the relation between ET and PD including epidemiologic, imaging, pathologic and genetic studies, the association has not been defined clearly [3,4,15]. Our data may create a base for investigating ET converting to PD. Further follow-up studies may be combined with multimodal assessment methods such as DAT SCAN or instrumented motion analysis.

Not surprisingly, similar to PD patients in the literature, SN echogenicity showed no correlation with the clinical features of the patients [5]. The exact reason underlying this echogenicity in SN remains unclear, but studies claim increased iron accumulation during the degenerative process of the disease, indicating the vulnerability of the region [6,18]. Thus, our results are important for showing a possible link between the ET and the radiological findings of sonographic evaluation of SN.

The limitation of the study may be the selection of the patients. The diagnosis of ET is made based on clinical features.

Conclusion

Our results demonstrate that SN hyperecogenicity is significantly increases in ET group compared to healthy controls. Although, the follow-up study did not support the relation between conversion of ET to PD in the patients with larger SN hyperecogenicity, undoubtful difference with healthy controls still prove the value of transcranial sonography studies in the diagnosis and as well as enlightening the mechanisms of ET.

Compliance with Ethical Standards

The study was approved by the institutional review board of Göztepe Training and Research Hospital (No:01.06.2009; 57/N2)

Conflict of Interest

All authors declare that they have no conflicts of interest.

Author Contribution

OOC: Design the study collect the data and wrote the manuscript; FC, IAC, SA, AO, EO, NI: Contributed to the scientific content, statistical analysis and manuscript writing. All authors read and approved the final version of the manuscript.

Financial Disclosure

There are no financial conflicts of interest to disclose.

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Araştırma Makalesi | Research Article

KARIN AĞRISI NEDENİ İLE ÇOCUK GASTROENTEROLOJİ VE ÇOCUK ROMATOLOJİ POLİKLİNİKLERİNE YÖNLENDİRİLEN HASTALARIN ÖZELLİKLERİ

CHARACTERISTIC OF PATIENTS WITH ABDOMINAL PAIN REFERRED TO A PEDIATRIC GASTROENTEROLOGIST AND PEDIATRIC RHEUMATOLOGIST

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ÖZ

Amaç: Çocukluk çağında en sık hastane başvuru nedenlerinden biri karın ağrısıdır. Amacımız genel pediatri polikliniklerinden karın ağrısı nedeniyle çocuk gastroenteroloji ve romatoloji polikliniklerine yönlendirilen hastaların özelliklerini değerlendirmektir.

Yöntem: Karın ağrısı nedeni ile genel pediatri polikliniklerinden Çocuk Gastroenteroloji veya Çocuk Romatoloji polikliniklerine yönlendirilen hastalar elektronik sistemden tarandı. Çalışmaya başvuru dışında en az 1 kez kontrol vizit yapılmış, 18 yaş altı hastalar dahil edildi. Dahil edilen hasta sayısı 209'du. Hastaların klinik özellikleri, laboratuvar sonuçları, son tanıları ve tedavileri yönlendirilen kliniğe göre incelendi.

Bulgular: Hastaların yaş ortalaması 10,95±4,73 yıl ve median 11 yıl (1,42-18 yıl) idi. Hastaların 115'i (%55) kızdı. Karın ağrısı başlangıç süresi medyan değeri 12 aydı ve 5 gün-10 yıl arasındaydı. 117 hasta (%56) yalnızca çocuk gastroenteroloji polikliniğine, 43 hasta (%20,6) yalnızca Çocuk Romatoloji polikliniğine, 49 hasta (%23,4) ise her ikisine yönlendirilmişti. Hastaların 125'inde (%59,8) karın ağrısı her gündü ve 106'ında (%50,7) ağrı 1 saatten kısa süreliydi. Ağrı 86'ında (%41,1) yaygın, 67'inde (%32,1) periumblikal, 36'ında (%17,2) epigastrik yerleşimliydi. En sık eşlik eden semptom 94'ünde (%45) yemeklerle artan ağrıydı. Ateş, eklem bulgusu, döküntü, miyalji, oral aft, tonsilit, ailede ailevi Akdeniz ateşi (AAA) varlığı yalnızca Çocuk Gastroenteroloji polikliniğine yönlendirilen anlamlı olarak azdı (p<0,05). Konulan tanılar 56'ında (%26,8) iritable barsak sendromu (İBS), 44'ünde (%21,1) AAA, 44'ünde (%21,1) gastrit, 37'inde (%17,7) kabızlık, 30'unda (%14,4) gastroözefageal reflüydü (GÖRH) ve 29'unda (%13,9) patoloji saptanmadı.

Sonuç: Karın ağrısı nedeni ile Çocuk Gastroenteroloji ve Çocuk Romatoloji polikliniklerine yönlendirilen hastalarda başlıca saptanan hastalıklar İBS, AAA, gastrit, kabızlık, GÖRH idi. Hastaların yarısından fazlasında genel pediatri kliniklerinde takip edilebilecek hastalıklar mevcuttu.

Anahtar Kelimeler: Karın ağrısı, ailesel Akdeniz ateşi, fonksiyonel gastrointestinal bozukluklar, pediatrik, sevk klinikleri

ABSTRACT

Objective: We aim to investigate the characteristics of patients with abdominal pain who were referred from general pediatric to pediatric gastroenterology and rheumatology.

Methods: We searched patients with abdominal pain who were referred from general pediatric to pediatric gastroenterology and rheumatology in the registry system. Under 18 years, patients whose at least one visit was done after the first admission were included. The number of patients is 209. We assessed clinical characteristics, laboratory results, final diagnoses, and treatments according to admission to subdivision clinics.

Results: The mean age was 10.95±4.73 years, and the median was 11 years (1.42-18). One hundred fifteen (55%) were girls. The duration of onset of abdominal pain was between 5 days and ten years; its median was 12 months. The number of patients who were referred only to pediatric gastroenterology was 117 (56%), to pediatric rheumatology was 43 (20.6%), and to both clinics was 49 (23.4%). Abdominal pain was lasting every day in 125 (59.8%), and episode duration was less than one hour in 106 (50.7%). The location of pain was generalized in 86 (41.1%), periumbilical in 67 (32.1%), and epigastric in 36 (17.1%). The most common accompanying symptom was meal-related pain in 94 (45%). Fever, joint findings, rashes, myalgia, oral aphthae, tonsillitis, and familial Mediterranean fever (FMF) in the family were significantly less in referred to pediatric gastroenterology (p<0.05). The diagnosis was irritable bowel syndrome (IBS) in 56(26.8%), FMF in 44 (21.1%), gastritis in 44 (21.1%), constipation in 37(17.7%), gastroesophageal reflux disease (GERD) in 30 (14.4%), and no pathology in 29 (13.9%).

Conclusion: The most common diagnoses were IBS, FMF, gastritis, constipation, and GERD, and almost half of the patients had diagnoses that could follow in general pediatrics.

Keywords: Abdominal pain, familial Mediterranean fever, functional gastrointestinal disorders, pediatric, referrals clinics

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Giriş

Karın ağrısı genel pediatri polikliniklerine başvuru nedenleri arasında sık görülmektedir. Okul çağı ve adölesan çocuklarının %10-25'i karın ağrısı yaşamaktadır ve %2-4'ü bu nedenle doktora başvurmaktadır. Karın ağrısına neden olan altta yatan bir çok neden vardır. Karın ağrısının akut ve kronik olmasına göre nedenleri değişiklik göstermektedir. Kronik karın ağrısı tanımı 3 aylık süreçte en az 3 karın ağrısı dönemi olması olarak belirtilmiştir. Kronik karın ağrısı nedenleri arasında organik nedenler nadirdir ve çoğunlukla fonkisyonel karın ağrısı görülmektedir. [1] Akut karın ağrısı nedenleri arasında ise akut gastroenterit, idrar yolu enfeksiyonu ve üst solunum yolu enfeksiyonu en sık görülenlerdir. [2] Ayrıca karın ağrısı periyodik ateş sendromlarında görülen majör bulgulardandır.[3]

Periyodik ateş 6 aydan uzun süren nedeni bilinmeyen tekrarlayan ateş atakları olarak tanımlanmıştır. Bu durum tekrarlayan enfeksiyonlar ile karışabilmektedir.[3] Periyodik ateş sendromlarından ülkemizde en sık görüleni Ailevi Akdeniz Ateşidir (AAA). Karın ağrısı tekrarlayan ateşten sonra AAA'nın en sık saptanan bulgusudur. Karın ağrısı sıklığı AAA'da %70-%90 olarak bildirilmiştir.[4–6] Tekrarlayan ateş AAA hastalarında her zaman karın ağrısı ile birlikte saptanmayabilir. Bu hastalarda karın ağrısı sıklığı ateş sıklığından daha fazla bulunmaktadır[6] AAA'daki bulgular seröz zarların rekürren, kendi kendini sınırlayan inflamasyonuna bağlı ortaya çıkmaktadır. Karın ağrısı da peritonite bağlı olarak ortaya çıkmaktadır.[7] Karın ağrısı AAA dışındaki diğer periyodik ateş sendromlarının da ana bulgularından biridir. Örneğin genetik geçişli olmayan PFAPA sendromunda karın ağrısı tanı kriteri olmamasına rağmen %20-%60 sıklıkla görülmektedir. Diğer monojenik periyodik ateş sendromları olan Tümör Nekrozis Faktör Reseptör ilişkili periyodik sendrom ve Hiperimmunoglobulin D sendromu hastalarının çoğunluğunda da karın ağrısı ortaya çıkmaktadır.[8,9] Bu nedenle tekrarlayan karın ağrısı olan çocuklar çocuk romatoloji polikliniklerine de yönlendirilmektedir.

Karın ağrısı etyolojisinde bir çok nedenin bulunması bazen gereksiz incelemelere ve yönlendirmelere yol açarken bazen de tanı gecikmesine neden olmaktadır.[10] Bunu en aza indirmek için çocuklarda karın ağrısının özelliklerinin iyi irdelenmesi gerekmektedir.

Bu çalışmanın amacı genel pediatri hekimlerinin karın ağrısına yaklaşım açısından güncel yaklaşımlarının ve bu hastaları yandal polikliniklerine yönlendirirken dikkate aldıkları unsurların belirlenmesidir.

Yöntem

Çalışma populasyonu

Karın ağrısı nedeni ile genel pediatri polikliniklerinden Bursa Şehir Hastanesi Çocuk Gastroenteroloji veya Çocuk Romatoloji polikliniklerine yönlendirilen hastalar 01.06.2020-01.09.2020 arsında geriye dönük olarak tarandı. Çalışma retrospektif vaka kontrol çalışması olarak dizayn edildi. Örneklem büyüklüğü çocukluk çağında karın ağrısı sıklığı %15 olarak varsayıldığında %95 güvenle, kabul edilebilir örnekleme hatasının d=0.01 değerini aşmayacak şekilde 195 olarak hesaplandı. 18 yaş altındaki, ilk başvuru sonrasında en az 1 kez kontrol viziti yapılmış, tıbbi incelemeleri sonuçlanmış ve kesin tanısı konulmuş hastalar çalışmaya dahil edildi. Daha önce başka bir çocuk gastroenteroloji veya çocuk romatoloji bölümü tarafından değerlendirilmiş tıbbi dosyasında eksik bilgi olanlar dışlandı. Sonuç olarak çalışmaya 209 hasta dahil edildi. Hastaların demografik verileri, karın ağrısı paterni, süresi, eşlik eden semptomları, aile öyküsü, fizik muayene bulguları, laboratuvar ve görüntüleme sonuçları, kesin tanıları, tedavileri incelendi.

İstatistik Analizi

Sürekli değişkenlerinin normal dağılıma uygunluğu Kolmogorov Smirnov testi ile değerlendirildi. Normal dağılıma uyan sürekli değişkenler ortalama ± standart sapma olarak ifade edildi ve Student's t-test ile karşılaştırıldı. Normal dağılıma uymayan sürekli değişkenler ise ortanca (minimum-maksimum) olarak belirtildi ve Mann-Whitney U test ile karşılaştırıldı. Kategorik değişkenler frekans ve yüzde olarak ifade edildi. Kategorik değişkenlerin gruplar arası karşılaştırması ki-kare ve Fisher's exact testi ile yapıldı. İstatistiki anlamlılık $p<0,05$ olarak kabul edildi. İstatsitik analizleri SPSS (version 20.0, SPSS, Chicago, IL, USA) bilgisayar paket programı ile yapıldı.

Etik Durum

Hastalardan ve ebeveynlerinden bilimsel çalışmalarda tıbbi verilerinin kullanımı için yazılı onam alındı. Etik onayı Bursa Şehir Hastanesi Etik Kurulu tarafından verildi.

Bulgular

Toplam hasta sayısı 209'du. Hastaların yaş ortalaması 10,9±4,7 yıl, ortanca değer 11 (1,4-18) yıl idi. Cinsiyet 115'inde (%55) kızdı. Hastalarda karın ağrısının başlangıç süresi ortanca değer 12 ay (5 gün-10 yıl) idi. Başvuru klinikleri değerlendirildiğinde 117 (%56) hasta yalnızca çocuk gastroenteroloji polikliniğine, 43'ü (%20,6) yalnızca çocuk romatoloji polikliniğine, 49'u (%23,4) ise her iki polikliniğe yönlendirilmişti.

Karın ağrısının süresi 106 (%50,7) hastada bir saatten kısa, görülme sıklığı 125 (%59,8) hastada her gün, lokalizasyonu 86 (%41,1) hastada yaygındı. Karın ağrısının diğer özellikleri Şekil 1'de verilmiştir. En sık eşlik eden bulgu 111 hastada (%53,1) yemekler ilişkili artan ağrıydı, ardından sırasıyla 104'ünde (%49,8) kabızlık, 83'ünde (%39,7) dispepsi ve 81'inde (%38,8) bulantı gelmekteydi (Tablo 1). Hangi polikliniklere yönlendirildiklerine göre bulguların sıklığındaki farklılıklar Tablo 1'de ayrıntılı olarak verilmiştir. Bulantı, kabızlık, dispepsi, ağız kokusu yalnızca çocuk gastroenteroloji polikliniğine yönlendirilenlerde çocuk romatoloji polikliniğine yönlendirilenlere göre daha fazla iken, her iki polikliniğe yönlendirilenlerle farklı değildi. Yemeklerle ilişkili olan ve her gün olan karın ağrısı yalnızca çocuk gastroenterolojiye gönderilenlerde diğer iki

gruptakilerden fazla idi. Ateş, eklem bulgusu, USYE bulgusu ve ailede AAA olması ise yalnızca çocuk romatoloji polikliniğine gönderilenlerde diğer iki gruptakilere göre daha fazla idi. Ancak miyalji, oral aft, döküntü, tonsilit yalnızca çocuk romatoloji polikliniğine gönderilenlerde çocuk gastroenteroloji polikliniğine gönderilenlere göre daha fazla iken, her iki polikliniğe gönderilerle farklı değildi. İshal, kusma, göğüs ağrısı sıklığı üç grupta da benzerdi.

Tablo 1. Hastaların yönlendirildikleri polikliniğe göre eşlik eden bulguların değerlendirilmesi

Eşlik eden semptomlar	Çocuk Gastroenteroloji n =117 (%100)	Çocuk Romatoloji n=43 (%100)	Her iki poliklinik n=49 (%100)	p
Bulantı	62 (%53)[a]	6 (%13,9)[b]	13 (%26,5)[a.b]	**<0,001**
Kusma	15 (%12,8)	9 (%20,9)	9 (%18,4)	0,37
Kabızlık	70 (%59,8)[a]	11(%25,6)[b]	23 (%46,9)[a,b]	**<0,001**
İshal	35 (%29,9)	12 (%27,9)	22 (%44,9)	0,13
Dispepsi	67 (%57,3)[a]	1 (%2,3)[b]	15 (%30,6)[a,b]	**<0,001**
Yemeklerle ilişkili olma	94 (%80,3)[a]	2 (%4,6)[b7]	15 (%30,6)[c]	**<0,001**
Ağız kokusu	67 (%57,3)[a]	1 (%2,3)[b]	10 (%20,4)[a,b]	**<0,001**
Ateş	3 (%2,6)[a]	31 (%72,1)[b]	23 (%46,9)[c]	**<0,001**
Eklem bulgusu	1 (%0,9)[a]	15 (%34,9)[b]	17 (%34,7)[c]	**<0,001**
Döküntü	3 (%2,6)[a]	8 (%18,6)[b]	7 (%14,3)[b]	**0,001**
Miyalji	1 (%0,9)[a]	18 (%41,9)[b]	8 (%16,3)[a,b]	**<0,001**
Oral aft	2 (%1,7)[a]	12 (%27,9)[b]	9 (%18,4)[a,b]	**<0,001**
Göğüs ağrısı	13 (%11,1)	2 (%4,6)	7 (%14,3)	0,31
Tonsilit	2 (%1,7)[a]	7 (%16,3)[b]	8 (%16,3)[b]	**<0,001**
ÜSYE bulguları	4 (%3,4)[a]	8 (%18,6)[b]	0[a]	**<0,001**
Ailede AAA varlığı	0[a]	11 (%25,6)[b]	7 (%14,3)[c]	**<0,001**
Hergün ağrı olması	106 (%90,6)[a]	4 (%9,3)[b]	15 (%30,6)[c]	**<0,001**

AAA: Ailevi Akdeniz ateşi, ÜSYE: Üst solunum yolu infeksiyonu
*Aynı harf ile belirtilen sonuçlar birbiri ile benzerdir.

Tablo 2. Karın ağrısı nedeni ile hastalara yapılan tetkikler ve saptanan sonuçlar

Yapılan tetkikler	n (%)
Akut faz reaktanı	184 (%88)
En az bir akut faz rekatan yüksekliği	65 (%31,1)
Kan sayımı	203 (%97,1)
Anemi	14 (%6,7)
Lökositoz	15 (%7,2)
Tam idrar analizi	201 (%96,2)
Piyüri	5 (%2,4)
Hematüri	3 (%1,4)
Proteinüri	2 (%1)
İdrar kültürü	139 (%66,5)
Üreme yok	134 (%64,1)
Üreme var	5 (%2,4)
Gaita tetkikleri	59 (%28,2)
Gaitada parazit	2 (%1)
Gaitada gizli kan	4 (%1,9)
Gaitada kültüründe üreme	1 (%0,5)
Batın ultrasonografi	152 (% 72,7)
Apendiks çapında artış	3 (%1,5)
Batın içi serbest sıvı	3 (%1,4)
Dalak boyutlarında artış	2 (%1)
Hepatosteatoz	2 (%1)
İnvajinasyon	1 (%0,5)
Karaciğer boyutu artmış, dalak boyutu artmış	1 (%0,5)
	24 (%11,5)
Mezenterik lenfadenit	114 (%54,6)
Normal	1 (%0,5)
Polikisitik over	2 (%1)
Terminal ileum ve çekumda kalınlaşma	
Çölyak hastalığı antikorları	87 (% 41,6)
Normal	85 (%40,7)
Doku transglutaminaz IgA	1 (%0,5)
EMA IgA ve Doku transglutaminaz IgA	1 (%0,5)

EMA: endomisyum antikoru, IgA: İmmunglobulin A

Hastaların 203'ünde (%97,1) kan sayımı tetkiki yapılmış, 14'ünde (%6,7) anemi, 15'inde (%7,2) lökositoz saptanmıştır. Tam idrar analizi 201'inde (%96,2) çalışılmış, 10'unda (%4,8) anormal sonuç saptanmıştır. Akut faz reaktanlarına (AFR) 184 (%88) bakılmıştır, 65'inde (%31,1) en az bir AFR yüksekliği vardır. Hastalarda yapılan diğer tetkikler ve sonuçları Tablo 2'de belirtilmiştir. 71 (%34) hastaya endoskopi yapılmıştı. Bunların 58'ine üst gastrointestinal sistem (GİS) endokopisi, 12'ine üst ve alt sistem endoskopisi, birine yalnızca alt GİS endokopisi yapılmıştı ve hepsinden biyopsi alınmıştı. Bu hastaların 12'inde (%16,9) endoskopi normaldi ve 9'unda (%12,7) biyopside patoloji yoktu (Tablo 3. MEFV gen analizi çalışılan hasta sayısı 67 (%32,1) idi. Exon 10'da homozigot veya heterozigot mutasyon 23 (%11) hastada bulundu (Tablo 4).

Karın ağrısı nedeni olarak hastalarda en sık saptanan durum 56 (%26,8) hastada irritable barsak sendromuydu (İBS). Ardından 44'er (%21,1) hastada AAA ve nonspesifik gastrit, 37 (%17,7) hastada kabızlık, 30 (%14,4) hastada gastroözofajial reflü vardı (Tablo 5). Birden fazla tanı konulan hasta sayısı 75 (%45,9) idi. Hastaları genel pediatri bölümünün takip edebileceği hastalığa sahip olanlar ve yandal polikliniklerinden takip edilmesi gereken hastalığa sahip olanlar olarak iki gruba ayırdık. Hastaların 125'inde (%59,8) genel pediatri hekiminin takip edebileceği hastalıklar mevcuttu. Bu iki grubu karın ağrısına eşlik eden bulgular açısından karşılaştırdık (Tablo 6). Bulantı, kabızlık, dispepsi, yemeklerle ilişkili artan ağrı, ağız kokusu, tetikleyici besin varlığı genel pediatri bölümünün takip edebileceği hasta grubunda daha fazladı. Ateş, eklem

bulgusu, döküntü, miyalji, oral aft, tonsilit, ailede AAA varlığı yandal poliklinikleri tarafından takip edilmesi gereken hasta grubunda fazla idi. Yandal poliklinikleri tarafından takip edilmesi gereken hasta grubunda yaş daha küçük, karın ağrısı başlangıç süresi, ağrı süresi daha uzundu (sırasıyla 9,13 (2,9-17,8) yıl vs 12 (1,422-18) yıl, 24 (0,16-120) ay vs 12 (0,10-120) ay, 2 (0-7) gün vs 0,04 (0,04-1) gün; sırasıyla p=0,01, p=<0,001, p=<0,001). Tedavi olarak verilen ilaçlar Şekil 2'de verilmiştir. Yalnızca 15 (%7,2) hastaya tedavi verilmedi.

Tablo 3. Endoskopi yapılanlarda saptanan endoskopi bulguları ve biyopsi sonuçları

Hasta sayısı	**n=71 (% 100)**
Endoskopi bulguları	
Nonspesifik gastrit	33 (% 46,5)
Nodüler pangastropati	23 (% 32,4)
Duodenogastrik safra reflüsü	15 (% 21,1)
Reflü özofajiti	12 (% 17)
Normal	12 (% 16,9)
Aktif kolit	6 (% 8,5)
Terminal ileumda nodüler hiperplazi	3 (% 4,2)
Biyopsi sonuçları	
Nonspesifik bulgular	27 (% 38)
Gastrit	21 (% 29,6)
Normal	9 (% 12,7)
Eosinofilik inflamasyon	4 (% 5,6)
Alkalen reflü	3 (% 4,2)
Terminal ileit	2 (% 2,8)
Çölyak hastalığı	2 (% 2,8)
Aktif kolit	2 (% 2,8)

Tablo 4. MEFV gen analizi yapılanlardaki mutasyonlar

MEFV gen analizi	**n=67 (% 32,1)**
M694V/M694V	2 (%3)
M694V/M680I	2 (%3)
M694V/V726A	3 (%4,5)
M680I/V726A	1 (%1,5)
M694V/-	12 (%17,9)
V726A/-	1 (%1,5)
A744S/-	2 (%3)
E148Q/R202Q	1 (%1,5)
R202Q/R202Q	4 (%6)
E148Q/-	5 (%7,5)
P369S/-	1 (%1,5)
R202Q/-	13 (%19,4)
Normal	20 (%29,4)

Tablo 5. Karın ağrısına nedeni olarak bulunan durumlar

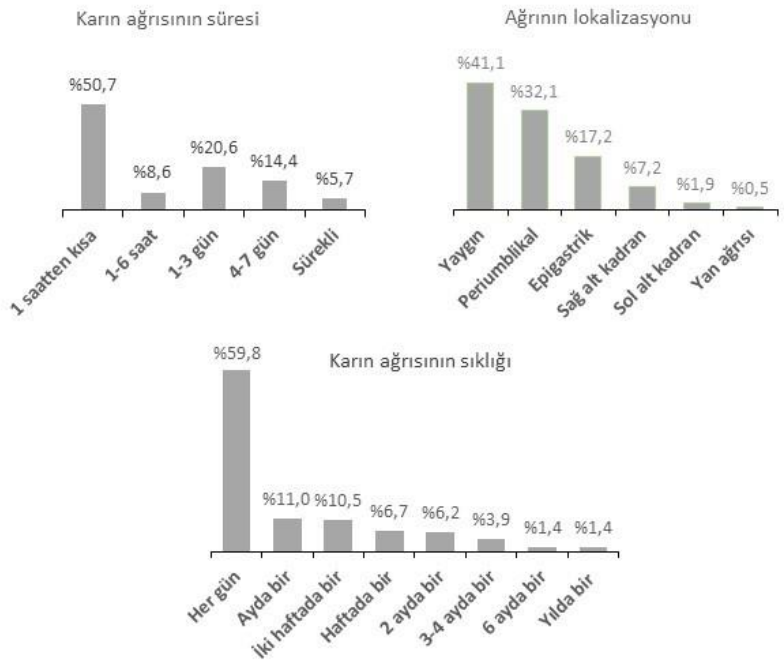
Tanı	**Hasta sayısı n (%)**
İrritable barsak sendromu	56 (%26,8)
Ailevi Akdeniz ateşi	44 (%21,1)
Gastrit	44 (%21,1)
Helicobacter pylori gastriti	28 (13,4)
Kabızlık	37 (%17,7)
Gastroözofajial reflü hastalığı	30 (%14,4)
Patoloji yok	29 (%13,9)
Tekrarlayan ÜSYE'ye bağlı mezenterik lenfadenit	6 (%2,9)
Eosinofilik gastrointestinal hastalıklar	5 (%2,4)
İdrar yolu infeksiyonu	4 (%1,9)
Tanımlanmamış otoinflamatuar hastalık	4 (%1,9)
İnflamatuar barsak hastalıkları	4 (%1,9)
Abdominel migren	3 (%1,4)
Henoch Schenlein purpurası	3 (%1,4)
Akut apandisit	2 (%1)
Akut gastroenterit	2 (%1)
Çölyak hastalığı	2 (%1)
İnek sütü protein allerjisi	2 (%1)
PFAPA	2 (%1)
Apandikste nöroendokrin tümör	1 (%0,5)
Parazit enfeksiyonu	1 (%0,5)

Birden fazla tanısı bulunan hasta sayısı 75 (%45,9) idi.
PFAPA: Periyodik Ateş, Aftöz Stomatit, Farenjit ve Servikal Lenfadenit Sendromu, ÜSYE: Üst solunum yolu infeksiyonu

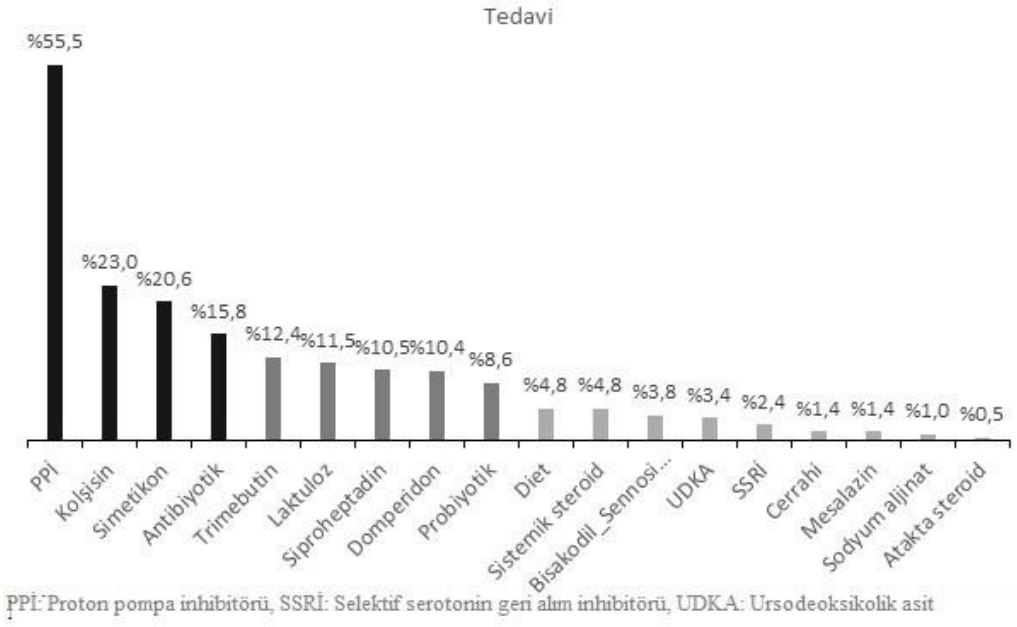
Tablo 6. Yandal polikliniği takibini gerektiren tanılı hastaların klinik özelliklerinin gerektirmeyenler ile karşılaştırılması

Özellikler	**Yandal polikliniği takibi gerekenler n=84 (%100)**	**Yandal polikliniği takibi gerektirmeyenler n=125 (%100)**	**p**
Yaş (yıl)	9,12 (2,92-17,83)	12 (1,42-18)	**0,010**
Kız cinsiyet	44 (%52,4)	71 (%56,8)	0,530
Başlangıç süresi (ay)	24 (0,16-120)	12 (0,1-120)	**<0,001**
Ağrı süresi (gün)	2 (0,04-7)	0,04 (0,04-1)	**<0,001**
Bulantı	18 (%21,4)	63 (%50,4)	**<0,001**
Kusma	18 (%21,4)	15 (%12)	0,070
Kabızlık	26 (%31)	78 (%62,4)	**<0,001**
İshal	33 (%39,3)	36 (%28,8)	0,110
Dispepsi	12 (%14,3)	71 (%56,8)	**<0,001**
Yemekle ilişkili olma	11 (%13,1)	100 (%80)	**<0,001**
Ağız kokusu	11 (%13,1)	67 (%53,6)	**<0,001**
Ateş	43 (%51,2)	14 (%11,2)	**<0,001**
Eklem bulgusu	27 (%32,1)	6 (%4,8)	**<0,001**
Döküntü	14 (%16,7)	4 (%3,2)	**0,001**
Miyalji	24 (%28,6)	2 (%2,4)	**<0,001**
Oral aft	21 (%25)	2 (%1,6)	**<0,001**
Göğüs ağrısı	8 (%9,5)	14 (%11,2)	0,700
Tonsilit	15 (% 17,9)	2 (%1,6)	**<0,001**
ÜSYE bulguları	4 (%3,2)	8 (%9,5)	0,054
Ailede AAA öyküsü	17 (%20,2)	1 (%0,8)	**<0,001**
Anemi	4 (%4,8)	10 (%8,4)	0,310
Lökositoz	11 (%13,1)	4 (%3,4)	**0,009**
AFR yüksekliği	40 (%52,6)	25 (%23,1)	**<0,001**
Gaitada gizli kan	4 (%19)	0 (%0)	**0,014**

AAA: Ailevi Akdeniz ateşi, ÜSYE: Üst solunum yolu infeksiyonu
Normal dağılıma uymayan sürekli değişkenler ortanca (minimum-maksimum) olarak ifade edildi.



Şekil 1: Hastalardaki karın ağrısının özellikleri



Şekil 2: Hastalarda tedavi olarak kullanılan ilaçlar

Tartışma

Karın ağrısı olan bir çocukta ileri inceleme gerektiren alarm bulguları olabilir. Kilo kaybı, bulantı, kusma, , disfaji, dışkılama aciliyeti, kronik ishal, gastrointestinal (Gİ) kanama bulgusu, gece semptomları, açıklanamayan, ateş, hepatosplenomegali, artrit, döküntü, oral aft, büyüme geriliği, anal fissür, lökositoz, hipoalbunemi, anemi, artmış akut faz belirteçleri, ailede inflamatuar barsak hastalığı öyküsü alarm bulgularından bazılarıdır.[11] Bizim çalışmamızda, çocuk gastroenteroloji veya romatoloji polikinik takibi gereken hastalarda bu alarm bulgularından ateş, eklem bulgusu, döküntü, oral aft, lökositoz, artmış akut faz belirteci, dışkıda gizli kan daha fazla olarak saptandı. Çocuk gastroenteroloji ve romatoloji bölümlerinden birinin takibini gerektiren hastalarımızda inflamasyon varlığını gösteren bulgular fazla olmasına rağmen Gİ bulgulardan herhangi biri bu grupta baskın değildi.

Karın ağrısına eşlik eden bulguları yönlendirildikleri polikliniğe göre değerlendirdiğimizde genel pediatristlerin yemeklerle ilişkili karın ağrısı ve her gün olan karın ağrısını sadece çocuk gastroenteroloji bölümüne yönlendirdiğini bulduk. Bu tip karın ağrıları fonksiyonel karın ağrısı bozuklukları (FKAB) ve İBS dediğimiz değişen bağırsak hareketleri ile karakterize bağırsak-beyin ekseni bozukluklarında yaygındır. Bu bozuklukların pediatrik popülasyonda tahmini prevalansı %1,6 ile %41,2 arasında değişmektedir ve altında yatan patofizyoloji iyi anlaşılmamıştır. FKAB'ler multifaktöryeldir ve genetik

yatkınlık, çocuk istismarı, stres veya depresyon gibi psikolojik kaygı bozuklukları, gıda ürünlerine aşırı duyarlılık ve bağırsak mikrobiyota değişiklikleri sonucu gelişebilir.[12] Pediatrik FKAB Roma IV tanı kriterleri tarafından tanımlanan, İBS, fonksiyonel dispepsi, karın migreni ve başka türlü tanımlanamayan fonksiyonel karın ağrısını içerir.[13] Gİ bulgulardan bulantı, kabızlık, dispepsi, ağız kokusu varlığında ise genel pediatristler her iki polikliniğe birlikte yönlendirme kararı almışlardı. Kronik karın ağrısı oluşturan ve sürdüren farklı organik ve psikososyal sebeplerin zaman ayrılarak sorgulanması gerekmektedir. Biz bu sorgulamanın genel pediatri hekimleri tarafından farklı nedenlerden dolayı yeterince yapılamadığını düşünüyoruz.

Tekrarlayan karın ağrısı atakları gördüğümüz AAA'nın çocuklarda kullanılan tanı kriterleri Yalçınkaya ve Özen tanı kriterleridir. Bu kriterler en az 3 kez olan ateş, karın ağrısı, göğüs ağrısı, artrit atağı ve ailede AAA öyküsü olmasıdır.[7] Ülkemizde AAA sıklığı bölgelere göre değişmekle birlikte yaklaşık 1/1000'dir.[14] Ateş, eklem bulgusu ve ailede AAA varlığı olanların çocuk romatoloji polikliniğine yönlendirilenlerde daha fazla olması AAA'nın tanı kriterlerinin genel pediatri hekimleri tarafından çok iyi bilindiğini göstermektedir. Tonsilit ve oral aft ise PFAPA'nın temel bulgularıdır. PFAPA'da karın ağrısı tanı kriteri olmasa da görülmektedir.[15] TRAPS, HIDS, CAPS gibi diğer otoinflamatuar hastalıklarda, karın ağrısı ve ateş ile birlikte miyalji, oral aft, döküntü görülebilmektedir ve bu hastalıklar çok nadir hastalıklardır.[3] Sonuçlarımıza göre miyalji, oral aft, tonsilit, döküntü bulguları olanlar ise her iki polikliniğe yönlendirilmekteydi. Bu bulgulardan oral aft ve döküntü aynı zamanda inflamatuar barsak hastalıklarında da ortaya çıkabilir.[16] Bu nedenle genel pediatristlerin oral aft ve döküntüsü olanları her iki bölüme göndermeleri uygundur. Ancak tonsilit ve miyaljinin üzerinde yeterince durmadıklarını düşünmekteyiz.

Ülkemizde yapılan çalışmalarda karın ağrısı olan çocukların %9-30'unda etyolojide ÜSYE saptanmıştır.[17,18] Türkiye Sağlık Araştırması verilerine göre ÜSYE sıklığı 0-6 yaş arasında %35 ve 7-14 yaş arasında %30'dur.[19] ÜSYE bulguları olanların ise genel pediatri polikliniğinde takip edilmesi beklenir. Bizim verilemizde karın ağrısı olanların %5'inde ÜSYE bulgusu ve %3'ünde tekrarlayan ÜSYE'ye bağlı mezenterik lenfadenit vardı.

Akut karın ağrısı ani başlayan (≤3 gün), klinik seyrin dakikalar ve saatler içinde değişebildiği, bazen cerrahi müdahalede gerekebilen ağrı olarak tanımlanmaktadır.[20] Kronik karın ağrısı en az 1-3 aydır süren ve tekrarlayan karın ağrısı ise en az 3 ayda, en az 3 kez tekrarlayan karın ağrısı olarak belirtilmiştir.[21] Çalışmamızda karın ağrısı şikayetinin başlangıç süresi ortanca değeri 12 ay, minumum 5 gün ve maksimum 10 yıl olarak saptanmıştır. Çocuk gastroenteroloji ve çocuk romatoloji bölümü takibi gerektirenlerde bu süre gerektirmeyenlere göre daha uzundur. Ayrıca karın ağrısının süresi de yandal poliklinik takibi gerektirenlerde daha uzun saptanmıştır. Karın ağrısı süresi hastalarımızın yarısında bir saatten ve neredeyse tamamında 7 günden daha kısaydı. Fonksiyonel karın ağrısı olan okul çocuklarında karın ağrısı ataklarının süresi %90'ında 10 dakika ile 4 saat arasında saptanmıştır.[22] AAA atağında ise karın ağrısı 6-72 saat sürmektedir.[7]

Karın ağrısı olan hastalarda Gİ endoskopi organik değişiklikleri ekarte etmek için kullanıldığı için önemli bir tetkiktir. Ancak her hastaya invaziv bir işlem olan endoskopi planlamak kabul edilen bir görüş değildir. En uygun endikasyonlar; çocuğun ailesinde peptik ülser ve/veya H. pylori öyküsü, ailede inflamatuar barsak hastalığı öyküsü ile alarm semptomları olan istemsiz kilo kaybı, büyüme geriliği, belirgin kusma, kronik ve belirgin ishal, Gİ kan kaybı, sağ üst veya alt kadranda kalıcı hassasiyet ve açıklanamayan ateş olarak vurgulanmıştır.[23] Bizim çalışmamızda hastaların yaklaşık üçte birine endoskopi yapılmıştı. Bu hastaların çoğunluğunda nonspesifik gastrit saptandı ve patoloji de nonspesifik inflamasyon bulguları vardı. Ülkemizde yapılan bir çalışmada kronik karın ağrısı nedeni ile ösefagogastroduodenoskopi yapılan çocuklar incelenmiştir. Biyopsi sonuçlarında en sık saptanan patoloji %35,2 sıklık ile H. pylori gastriti olmuştur.[24] Bizim sonuçlarımızda da benzer şekilde endoskopi yapılmış hastaların %39'unda H. pylori gastriti mevcuttu.

Sonuçlarımıza göre tedavide en sık verilen ilaçlar proton pompa inhibitörleriydi. Proton pompa inhibitörlerinin gastroenterolojik hastalıkların birçoğunda endikasyonu mevcuttur. Bu hastalıkların başlıcaları; semptomatik gastroözofajial reflünün kısa süreli tedavisi, eroziv özofajit, peptik ülser hastalığı tedavisi, Helicobacter pylori eradikasyonu ve eozinofilik özofajit hastalığıdır.[25] Bu tanılar bizim hastalarımız arasında da ilk sıralardaydı. Hastalarımıza ikinci sıklıkta verilen ilaç ise kolşisindi. Kolşisin AAA'da atakların ve amiloidozisin önlenmesinde tek tedavi yöntemidir.[26] Ayrıca PFAPA ve sınıflandırılamayan otoinflamatuar hastalıklarda da kolşisin kullanılabilir.[27,28]

Sonuç

Karın ağrısı nedeni ile Çocuk Gastroenteroloji ve Çocuk Romatoloji polikliniklerine yönlendirilen hastalarda başlıca saptanan hastalıklar İBS, AAA, gastrit, kabızlık, GÖRH idi. Hastaların yarısından fazlasında genel pediatri kliniklerinde takip edilebilecek hastalıklar mevcuttu. Bu durum son yıllardaki savunmacı tıp yaklaşımının öne geçmesine ve yandal kliniklerine erişimin kolaylaşmasına bağlı olabilir. Ancak tıbbi giderlerin artmasına ve hastaların gereksiz yere hastanede zaman geçirmelerine neden olmaktadır. Bu nedenle yandal polikliniklerine sevk endikasyonlarının genel pediatri hekimlerine meslek içi eğitimlerle sürekli olarak anlatılmasının yararlı olacağını düşünmekteyiz.

Etik Standartlara Uygunluk

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Çıkar Çatışması Beyanı
Yazarların konuyla ve/veya herhangi başka bir yazar ile ilgili maddi veya manevi bir çıkar çatışması yoktur.

Yazar Katkısı
Yazarlar eşit katkı sağlamışlardır.

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Kaynaklar

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Research Article | Araştırma Makalesi

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF OUR OSTEOPOROSIS PATIENTS WITH FRAGILITY FRACTURES

FRAJİLİTE KIRIKLI OSTEOPOROZLU HASTALARIMIZIN KLİNİK VE DEMOGRAFİK ÖZELLİKLERİ

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ABSTRACT

Objective: Due to the high recurrence risk and mortality rate in fragility fractures, we aimed to investigate the characteristics of individuals with fragility fractures evaluated in our clinic.

Methods: The files of male and postmenopausal female patients over the age of 50 who had a fragility fracture of the vertebra, forearm, proximal humerus and hip in the last 2 years were reviewed retrospectively.

Results: Of the 121 patients, 86 (71.1%) were female, 35 (28.9%) were male, and the mean age of the patients was 68.49±9.85. The fracture site was hip in 36 (29.8%) patients, forearm in 35 (28.9%) patients, and vertebra in 26 (21.5%) patients; multiple fractures were present in 21 (17.4%) patients. While 25 (20.6%) patients had a previous fragility fracture. 22 (18.2%) patients had adequate dietary calcium, 47 (38.8%) had adequate dietary protein intake. The parents of 16 (13.2%) patients had hip fractures. 52 (43%) of the patients had comorbidity that increased the risk of osteoporosis, and 62 (51.2%) had drug use that increased the risk of osteoporosis. 92 (76%) patients were not receiving any osteoporosis treatment at the time of fracture, and 5 (4.1%) patients developed fractures while under medical treatment. The median 25(OH)VitD3 of the patients was 16.5 µg/L (3.0/156.0). In bone mineral density evaluations, the median of the femoral neck T score was -1.5 (-4.2/2.2), the median of the femoral total T score was -1.0 (-4.1/0.90), and the median of the lumbar total T score was -2.2 (-4.3/2.6).

Conclusion: Knowing the factors associated with fragility fractures will facilitate the identification of high-risk individuals and will also provide an idea in terms of preventive measures and systematic approaches to be taken.

Keywords: Clinical features, demographic data, fragility fracture, osteoporosis

ÖZ

Amaç: Frajilite kırıklarındaki yüksek tekrarlama riski ve mortalite oranı nedeniyle, çalışmamızda kliniğimizde değerlendirilen frajilite kırıklı bireylerin özelliklerini araştırmayı amaçladık.

Yöntem: Son 2 yıl içerisinde vertebra, ön kol, proksimal humerus ve kalçasında frajilite kırığı olan 50 yaş üstündeki erkek ve postmenapozal kadın hastaların dosyaları retrospektif olarak incelendi.

Bulgular: 121 hastanın 86'sı (%71,1) kadın, 35'i (%28,9) erkekti ve hastaların yaş ortalaması 68,49±9,85 idi. Hastaların 36'sının (%29,8) kırık yeri kalça, 35'inin (%28,9) ön kol, 26'sının (%21,5) vertebra, 21'inin (%17,4) proksimal humerusken; 3 (%2,5) hastada multiple kırık mevcuttu. 25 (%20,6) hastada daha önce geçirilmiş frajilite kırığı vardı 22 (%18,2) hastada diyette yeterli kalsiyum, 47 (%38,8) hastada diyette yeterli protein alımı mevcuttu. 16 (%13,2) hastanın ebeveyninde kalça kırığı vardı. Hastaların 52 (%43)'sinde osteoporoz riskini artıran komorbidite, 62 (%51,2)'sinde osteoporoz riskini artıran ilaç kullanımı vardı. 92 (%76) hasta kırık sırasında herhangi bir osteoporoz tedavisi almamaktaydı, 5 (%4,1) hastada ise medikal tedavi altındayken kırık gelişmişti. Hastaların 25(OH)VitD3 ortancası 16,5 µg/L (3,0/156,0) idi. Kemik mineral yoğunluğu değerlendirmelerinde femur boyun T skoru ortancası -1,5 (-4,2/2,2), femur total T skoru ortancası -1,0 (-4,1/0,90), lomber total T skoru ortancası -2,2 (-4,3/2,6) idi.

Sonuç: Frajilite kırıkları ile ilişkili faktörlerin bilinmesi yüksek riskli kişilerin belirlenebilmesini kolaylaştıracak, alınacak koruyucu önlemler ve sistematik yaklaşımlar açısından da fikir verecektir.

Anahtar Kelimeler: Klinik özellikler, demografik veriler, frajilite kırığı, osteoporoz

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Introduction

Osteoporosis is the most common chronic bone disease, resulting in an increased risk of fracture as a result of low bone mass and deterioration of the microarchitecture of bone tissue.[1]

Fragility fractures occur spontaneously or occur after low-energy trauma (such as coughing, sneezing, or falling from a height that does not exceed one's own height) that would not normally result in a fracture of healthy bone. It is estimated that one out of every three women and one in every five men will have a fragility fracture after the age of 50.[2-4]

Osteoporosis and its complications, especially hip fractures, create a physical, psychological, social and economic burden.[5] According to the results of the large population-based FRACTURK study conducted in 12 centers, it is estimated that the number of hip fracture cases in Turkey will reach 64000 in 2035.[6] In a systematic review, it was determined that there was an 8-36% increase in mortality in the first year after hip fracture, and it was also emphasized that mortality in men was higher than in women in the same review.[7]

While the risk of having a new fracture increases two to three times in those with a fracture, it is observed that 23% of women over 50 years of age develop a secondary fracture within one year after the first fracture.[2,3] It has been reported that 50% of recurrent fractures can be prevented and mortality is reduced with appropriate treatment.[8,9] Despite this, only 20% of women with fragility fractures were found to receive osteoporosis treatment.[10] Therefore, knowing the risk factors for fractures is very important in terms of guiding the patient by taking precautionary measures.

In this study, we aimed to investigate the demographic and clinical characteristics of individuals with fragility fracture who applied to our outpatient clinic and to reveal the risk factors associated with fracture.

Methods

In this study, patients with fragility fractures who applied to the Physical Medicine and Rehabilitation Clinic of our hospital between October 2021 and July 2022 were included. The files of the patients were reviewed retrospectively. Before the study, the approval of our hospital's Ethics Committee dated 06.06.2022 and numbered 139/29 was obtained, and our study was conducted in accordance with the principles of the Declaration of Helsinki.

Our study included those with fragility fractures in the vertebra, forearm, proximal humerus and hip, among male and postmenopausal female patients over 50 years old who had a fragility fracture in the last 2 years. Pathological fractures (such as osteogenesis imperfecta, osteomalasia, Paget's, bone tumor, multiple myeloma) were not included in our study.

121 patients who met the study criteria and had complete file data were included in our study.

Demographic data of all patients (age, gender, education and working status, marital status, body mass index (BMI)), comorbidities, diseases and drugs that may cause secondary osteoporosis, fracture site, previous fragility fracture history and location, detailed osteoporosis treatment histories, smoking, alcohol use, dietary calcium, protein, caffeine intake, adequate physical activity, menopausal age for women, presence of hip fracture in the mother or father, and the number of falls in the last year were noted. Among the latest bone mineral density (BMD) values, lumbar total T score, lumbar total BMD (gr/cm2), femur total T score, femur neck T score, femur total BMD (gr/cm2) and 25(OH)VitD3, calcium, phosphorus, alkaline phosphatase (ALP), parathormone (PTH) levels were recorded from their files.

SPSS version 28.0 was used for statistical analysis. The suitability of the data to the normal distribution was evaluated by visual and analytical methods (Kolmogrov-Smirnov test). Categorical data were presented as n (%), non-normally distributed numerical data and ordinal data were presented as median (min-max), and normally distributed numerical data as mean±SD.

Results

Of the 121 patients included in the study, 86 (71.1%) were female, 35 (28.9%) were male, and the mean age of the patients was 68.49±9.85. The demographic data of the patients are presented in Table 1, and the risk factors associated with fracture are presented in Table 2.

Table 1. Demographic Data of Patients (n=121)

Age, mean (SS)		68.49 (9.85)
BMI, mean (SS)		29.23 (5.7)
Gender, n (%)	Woman	86 (71.1)
	Man	35 (28.9)
Educational status, n (%)	İlleterate	29 (24.0)
	Literate	10 (8.2)
	0-5 years	44 (36.4)
	5-8 years	10 (8.3)
	8-12 years	17 (14.0)
	≥12 years	11 (9.1)
Working status, n (%)	Unemployed	111(91.7)
	Employed	10 (8.3)
Marital status, n (%)	Married	80 (66.1)
	Single	2 (1.7)
	Other	39 (32.2)
Living place, n (%)	City center	107 (88.4)
	Village	14 (11.6)
Living condition, n (%)	With spouse or children	106 (87.6)
	Alone	13 (10.7)
	Other	2 (1.7)

SS: Standard deviation, BMI: Body mass index

Table 2. Risk Factors for Fracture (n=121)

Alcohol consumption, n (%)	No	119 (98.3)
	Yes	2 (1.7)
Somking, n (%)	No	98 (81.0)
	Yes	23 (19.0)
Daily caffee consumption, n (%)	<4 cups/day	119 (98.3)
	≥4 cups/day	2 (1.7)
Dietary calcium intake, n (%)	Inadequate	99 (81.8)
	Adequate*	22 (18.2)
Dietary protein intake, n (%)	<1 g/kg/day protein	74 (61.2)
	≥1 g/kg/day protein	47 (38.8)
Physical activity, n (%)	Inadequate	91 (75.2)
	Adequate**	30 (24.8)
Age of menopause, mean (SS)		45.45
Parental history of hip fracture, n (%)	No	105 (86.8)
	Yes	16 (13.2)
Number of falls in the last year, median (min-max)		1 (0-25)
Comorbidity that can lead to OP, n (%)	No	69 (57.0)
	Yes***	52 (43.0)
Drug that can lead to OP, n (%)	No	59 (48.8)
	Yes****	62 (51.2)

SS: Standard deviation, OP: Osteoporosis, *The calculation system recommended by the International Osteoporosis Foundation was used (http://www.iofbonehealth.org/calcium-calculator), **People who do at least 3 days a week and at least 30 minutes at a time by walking, cycling, resistive exercise ***Diabetes Mellitus, rheumatic diseases, celiac disease, inflammatory bowel disease, kidney or liver disease, immunodeficiency, hypogonadism, hyperthyroidism, hyperparathyroidism ****Proton pump inhibitors, glucocorticoids, antiepileptics, thyroid hormone drugs, immunosuppressives, antineoplastics, anticoagulants

The fracture site was hip in 36 (29.8%) patients, forearm in 35 (28.9%) patients, and vertebra in 26 (21.5%) patients; multiple fractures were present in 21 (17.4%) patients. While 96 (79.4) patients did not have a history of previous fragility fracture, 25 (20.6%) patients did. The first fracture site of patients with previous fragility fractures was hip in 9 (36%) patients, forearm in 9 (36%), proximal humerus in 4 (16%), and vertebra in 3 (12%) patients. The secondary fracture site was hip in 8 (32%) patients, forearm in 5 (20%), proximal humerus in 4 (16%), vertebra in 3 (12%), and ankle and tibia in 5 (20%) patients. 92 (76%) patients were not receiving any osteoporosis treatment at the time of fracture, 8 (6.6%) patients had previously used calcium or vitamin D but stopped, 6 (5.0%) patients developed fractures while using calcium or vitamin D, 10 (% 8.3) patients had previously used bisphosphonates for various periods (3 months-5 years) and stopped. Fractures developed in 5 (4.1%) patients while under osteoporosis treatment (1 patient using alendronic acid, 1 patient using ibandronic acid, 1 patient using zolendronic acid, and 2 patients using denosumab). Current fracture-related features are presented in Table 3, laboratory data in Table 4, and BMD-related data in Table 5.

Table 3. Clinical Features Associated with Existing Fracture (n=121)

Fracture site, n (%)	**Hip**	36 (29.8)
	Forearm	35 (28.9)
	Vertebrae	26 (21.5)
	Proximal humerus	21 (17.4)
	Multiple	3 (2.5)
Previous fragility fracture history, n (%)	**None**	96 (79.4)
	Hip	5 (4.1)
	Forearm	5 (4.1)
	Proximal humrerus	4 (3.3)
	Vertebrae	3 (2.5)
	Pelvis	1 (0.8)
	Others	5 (4.1)
	Multiple	2 (1.7)
OP treatment history, n (%)	**None**	92 (76)
	Has stopped using calcium or Vitamin D	8 (6.6)
	Have suffered a fragility fracture while using Calcium or Vitamin D	6 (5.0)
	Has stopped using bisphosphonate/ denosumab/ teriparatide	10 (8.3)
	Have suffered a fragility fracture while using isphosphonate/denosumab/teriparatide	5 (4.1)

OP: Osteoporosis

Table 4. Laboratory Data of Patients (n=121)

25(OH)VitD3 µg/L, median(min/max)	16.5 (3.0/156.0)
Calcium mg/dl, mean (SS)	9.35 (0.55)
Phosphorus mg/dl, mean (SS)	3.62 (0.65)
ALP U/L, median(min/max)	94.0 (38.0/393.0)
PTH ng/L, median(min/max)	41.9 (9.8 /289.0)

ALP: Alkaline phosphatase, PTH: Parathormone

Table 5. Bone Mineral Density Measurements of Patients

n=121	**Median(min/max)**
Femoral neck T score	-1.5 (-4.2/2.2)
Femoral total T score	-1.0 (-4.1/0.90)
Lumbar total T score	-2.2 (-4.3/2.6)
Femoral total BMD	0.90 (0.48/1.02)
Lumbar total BMD	0.81 (-2.5/1.42)

BMD: Bone Mineral Density

Discussion

In the current study, clinical and demographic data of 121 patients who were followed up and treated with the diagnosis of fragility fracture in the Physical Medicine and Rehabilitation Clinic of our hospital are presented.

The effect of body weight on fracture has been studied in various studies. In a study examining the characteristics of patients with osteoporotic hip fractures, it was shown that 49% of the patients had low body weight.[11] Similar results were obtained in two other studies, and it was

thought that reduction of protective adipose tissue and malnutrition were effective in this situation.[12,13] On the other hand, the mean BMI of the patients was found within the normal range. The effect of BMI on fracture risk has generally been studied in studies of hip fracture. Wardlaw GM et al.[14] defined the actual effect of BMI on the risk of non-hip fractures as uncertain. The fact that our study included patients with fractures not only in the hip but also in the vertebrae, forearm, proximal humerus and forearm regions, and differences in the number of patients in the studies may have been effective in obtaining different results.

The environmental characteristics and the lack of family support are among the factors that can lead to fragility fracture. In our study, it was observed that 13% of the patients lived alone, and in a previous study, this rate was 17%, similar to ours.[11] In the literature, it is emphasized that fragility fractures of the vertebrae are less associated with falls or trauma, unlike hip and forearm fractures.[15] In our current study, although factors were not analyzed separately for each region of fracture, when all patients were examined, the median number of falls in the last year was 1, and 43% of patients had comorbidities that increased the risk of osteoporosis.

Drugs such as glucocorticoids, proton pump inhibitors, aromatase inhibitors, thyroid hormone preparations, antiepileptics, warfarin, and nucleotide reverse transcriptase inhibitors are known to induce osteoporosis.[16] 62 (51.2%) of all patients evaluated in our study, 12 (%46.1) of those with vertebral fractures were using at least one of these drugs. These data are consistent with studies that draw attention to etiological factors other than falls in fragility fractures.[15,17]

Previous fracture increases risk of new fracture regardless of bone density.[18] When all fractures are taken together, having an osteoporotic fracture increases the risk of developing new fractures 2.2 times.[19] There are various studies investigating the characteristics of recurrent fragility fractures.[20,21] In the study of Dang DY et al.[20], patients with fragility fractures were followed up for three years, and it was found that vertebral fractures, followed by proximal humerus fractures, were most associated with secondary fractures, considering all initial fracture types. It was observed that the secondary fracture site was mostly the hip. Focusing more on the fracture healing process in upper extremity fractures and ignoring follow-up and treatment for the prevention of secondary fractures may be important in achieving this result. In a study by Viprey M et al.[22], 455 patients with proximal humerus and distal radius fractures who did not receive osteoporosis treatment before the fracture were examined. In the first year after the fracture, it was observed that only 29.4% of them received calcium/vitamin D support treatment, and 9.4% received pharmacological osteoporosis treatment (bisphosphonate, strontium ranelate, hormone replacement therapy, raloxifene).[22]

In our study, it was seen that the first fracture site associated with recurrent fracture was the forearm and hip, with the most 9 (36%) patients. The difference in this result from the literature may have been due to the change in the number of patients examined. In our study, it was also seen that 25 (20.6%) patients had a previous fragility fracture and the secondary fracture site was the hip with a maximum rate of 32%, similar to the literature. Considering that the mortality of hip fracture is high, when a fracture is encountered, whether this fracture is a fragility fracture, the risk of recurrence, the importance of close follow-up and treatment should be considered once again.

In a study comparing the characteristics of patients with osteoporosis with vertebral fractures, hip fractures and no fractures, no statistically significant difference was found between the number of chronic diseases and family history of fracture, BMI, menopause ages, smoking, dietary calcium intake, coffee and alcohol consumption.[23] In the same study, it was observed that the vertebral T-scores of the group with vertebral fractures and the hip T-scores of the group with hip fractures were lower.[23] This is consistent with studies stating that BMD in a region is the best indicator of the fracture probability of that region.[24,25] On the other hand; there are also studies emphasizing that the majority of fractures are seen in women with normal bone mineral density.[26,27] In our study, however, T scores were not compared according to the fracture site; however, medians of both lumbar total T score and femoral neck T score were better than other studies. It was remarkable that although most patients had fragility fractures, their BMD was not osteoporotic. In addition, our patients had low vitamin D levels, dietary calcium and protein intakes, and most of the patients did not have sufficient physical activity levels. This situation highlights the necessity of questioning the risk factors, drugs used and other fracture-related factors in postmenopausal women and men over 50 years of age.

When studies investigating the treatment of osteoporosis after hip fracture were examined, it was observed that the rates of initiation of osteoporosis treatment after fracture ranged from 5% to 30%.[6] Regular follow-up of patients with fragile fractures is therefore very important for the prevention of recurrent fractures. Fracture liaison units have recently been established for this purpose in the world and in our country, and individuals with fragility fractures have been closely followed up and treated.[28]

Our study has some limitations such as being a retrospective file review study and small number of patients. We think that the effective factors in fragility fractures can be revealed in more detail with multicenter and multidisciplinary studies in which more patients are examined.

In conclusion; osteoporosis is an important public health problem that can affect the quality of life of patients and lead to complications that require long-term and expensive treatments and even death. Although patients with fractures are not always severely osteoporotic, secondary causes of osteoporosis such as low vitamin D levels, insufficient dietary calcium and protein intake, inadequate physical activity, and the use of various drugs

stand out. Early diagnosis of osteoporosis by questioning the risk factors, and when fragility fractures are detected, providing appropriate pharmacological and non-pharmacological treatments and closely monitoring these patients are very important. Knowing the factors associated with fragility fractures will facilitate the identification of high-risk individuals and will provide an idea for preventive measures and systematic approaches.

Compliance with Ethical Standards

Ethics committee approval for the study was obtained from the University of Health Sciences Diskapi Yildirim Beyazit Education and Research Hospital Clinical Research Ethics Committee (139/29).

Conflict of Interest

There is no conflict of interest between the authors.

Author Contribution

Z.K.U., A.E.Ş., Y.Ö.G. and E.Ü.A. data collection, Z.K.U., A.E.Ş. and Y.Ö.G. data proceessing, Z.K.U. and D.C. analysis, D.C. and E.Ü.A. supersivion and all authors have read and accepted the article.

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Research Article | Araştırma Makalesi

ASSOCIATION BETWEEN LEFT ATRIAL APPENDAGE THROMBUS FORMATION AND MONOCYTE/HDL RATIO IN PATIENTS WITH ACUTE ISCHEMIC STROKE

AKUT İSKEMİK İNME GEÇİREN HASTALARDA SOL ATRİAL APPENDAJ TROMBÜS OLUŞUMU VE MONOSİT/HDL ORANI ARASINDAKİ İLİŞKİ

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Abstract

Objective: There is an apparent link between thrombus formation and inflammation. Monocyte/high density lipoprotein ratio has been determined as an inflammatory marker and associated with many cardiovascular disorders like coronary artery disease, acute coronary stent thrombus, coronary thrombus burden and atrial fibrillation. The aim of this study was to clarify the correlation between Monocyte/high density lipoprotein ratio and left atrial appendage thrombus formation in individuals who have suffered from an acute ischemic cerebral infarction.

Methods: The study retrospectively included a total of 69 patients who had been diagnosed with acute ischemic cerebral infarction. The patients' demographic, clinical, and echocardiographic information were gathered from their records in a retrospective manner. Monocyte/high density lipoprotein ratio and neutrophil/lymphocyte ratio were calculated from admission laboratory data.

Results: Thirteen patients had a LAATF (11 male; 64±14.5 years); 14 patients had spontaneous echo contrast stage 3 or 4 (11 male; 62.3±9.7 years) and 42 patients (29 males; 61.0±11.1 years) did not have left atrial appendage thrombus formation or SEC. With the exception of atrial fibrillation, the baseline demographic and clinical characteristics of the three groups were similar (p<0.001). Further, monocytes were significantly lower in the thrombus negative group compared to other groups (p<0.001). MHR was different in all three groups (p<0.001). This parameter was significantly increased in patients with left atrial appendage thrombus formation and spontaneous echo contrast findings.

Conclusion: Our study showed that an increased MHR is associated with left atrial appendage thrombus formation.

Keywords: Monocyte/HDL ratio; left atrial appendage; atrial fibrillation

Öz

Amaç: Trombüs oluşumu ve enflamasyon arasında kuşkusuz bir bağlantı bulunmaktadır. Monosit/yüksek yoğunluklu lipoprotein oranı bir enflamasyon göstergesi olup, koroner arter hastalığı, akut koroner stent trombozu, koroner trombüs yükü, atriyal fibrilasyon gibi birçok kardiyovasküler hastalıkla ilişkilidir. Çalışmamızın amacı akut iskemik inme geçirmiş bireylerde monosit/yüksek yoğunluklu lipoprotein oranı ve sol atriyal apendiks trombüsü arasındaki ilişkiyi değerlendirmektir.

Yöntem: Akut iskemik inme teşhisi olan toplam 69 hasta retrospektif olarak bu çalışmaya dahil edildi. Demografik, klinik ve ekokardiyografik veriler hasta dosyalarından retrospektif olarak toplandı. Monosit/yüksek yoğunluklu lipoprotein oranı ve nötrofil/lenfosit oranları hastane başvurusuna ait olan laboratuvar bulgularından hesaplandı.

Bulgular: On üç hastada sol atriyal apendaj trombüsü teşhisi konuldu (11 erkek; yaş 64,1±14,5); 14 hastada evre 3 veya 4 spontan eko kontrast saptandı (11 erkek; yaş 62,3±9,7); 42 hastada ise ne sol sol atriyal apendaj trombüsü ne de spontan eko kontrast görüntüsü mevcuttu (29 erkek; yaş 61,0±11,1). Atriyal fibrilasyon (p<0,001) haricinde 3 grup arasında demografik ve klinik bulgularda anlamlı bir fark saptanmadı. Monosit seviyesi trombüs negatif olan grupta diğer gruplara kıyasla daha düşüktü (p<0,001). Monosit/yüksek yoğunluklu lipoprotein oranı her grup için anlamlı bir fark gösterdi (p<0,001). Bu parametre sol atriyal apendaj trombüsü ve spontan eko kontrast saptanan hastalarda anlamlı yüksekti.

Sonuç: Çalışmamız yükselmiş Monosit/yüksek yoğunluklu lipoprotein oranının sol atriyal apendaj trombüsü oluşumu ile ilişkili olduğunu gösterdi.

Anahtar Kelimeler: Monosit/yüksek yoğunluklu lipoprotein oranı, sol atriyal apendiks, atriyal fibrilasyon

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Introduction

Cardiac thrombus embolization from the left atrium (LA) has a major impact on the etiology of ischemic stroke, especially in patients with AF.[1] The pathogenesis of thrombus formation is considered to be multifactorial and is not fully elucidated yet.[2]

Over more than one century ago Virchow suggested three abnormalities that contribute to thrombus formation: blood stasis, endothelial dysfunction, and clotting activation.[3,4] Although this triad is completely fulfilled in patients with AF, emerging evidence suggests that inflammation may also play an important role in the genesis of thrombus formation.[5-7]

Monocytes play a fundamental part in the inflammation process by secreting pro-oxidant cytokines.[8,9] High-density lipoprotein-Cholesterol (HDL-C) on the other hand has a protective effect in terms of antioxidation and also by limiting monocyte activation.[10,11] Consequently, MHR could serve as an alternative indicator of inflammation and oxidative stress and this parameter has been widely explored in the field of cardiovascular diseases.[12,13] An elevated MHR was linked to adverse outcomes. Besides, it was also an indicator of high rates of major adverse cardiovascular events such as acute thrombosis of a stent and thrombus burden in individuals with ST-segment elevation myocardial infarction (STEMI).[6,7]

The aim of this study was to elucidate the association between MHR and thrombus formation in the left atrial appendix (LAA) of patients who had suffered an AICI.

Methods

A total of 69 individuals with the diagnosis of AICI were retrospectively included in this investigation between January 2019 and June 2021.

Previous medications, anthropometric characteristics, cardiovascular history, and risk factors were obtained from the patients' medical records. The definition of arterial hypertension used in this study was a systolic blood pressure reading ≥140 mmHg and/or diastolic blood pressure reading ≥90 mmHg, as documented in at least two separate occasions.[14] The diagnosis of diabetes mellitus was based on either a fasting serum glucose concentration ≥126 mg/dl or >200 mg/dl at any testing or the use of an anti-hyperglycemic medication.[15] The criteria for dyslipidemia were derived from the 2019 European Guidelines, which defined the condition as either the use of lipid-lowering therapy or a confirmed diagnosis of dyslipidemia as documented in the patient's medical records.[16] The smoking status classification was current smoker or non-smoker. Individuals who reported using tobacco regularly in the last six months were also classified as current smokers. The definition of coronary artery disease was treated with anti-ischemic drugs, antiplatelet therapy after coronary angiography; coronary stenting performed in the past, or coronary revascularization surgery. Heart failure was considered as systolic dysfunction with an ejection fraction <50%. None of the patients had diastolic dysfunction more than grade II. Paroxysmal AF was defined as AF that resolves on its own or with intervention within one week of beginning.[17] Permanent AF was specified according to the 2020 ESC Guidelines.[17] A calculation of the body mass index (BMI; weight (kg)/ height square [m^2]) was performed on all participants.

The suspected diagnosis of AICI was verified by cranial tomographic imaging and simultaneous diffusion magnetic resonance imaging immediately after the neurological examination of the attending neurologist. Ultrasound of carotid and vertebral arteries was used to determine the etiology of AICI within one day of the occurrence. In this context, only non-complex atherosclerotic plaques without any significant stenosis have been diagnosed. The definition of noncomplex was: (a) an even and uniform surface texture and (b) homogenous and identical echocardiographic imaging or predominant echogeneity with limited territories of echolucency (<25%). Further, echocardiographic scans were conducted by a single expert examiner who was unaware of the clinical and laboratory findings. Transthoracic echocardiography examinations were performed with a commercially available ultrasound system having a 2.5-3.5 MHz transducer (ie33, Phillips Medical system, Bothell, Washington, USA). Patients lay on their left side in a resting position, and apical four-chamber and parasternal images of the LA and left ventricle (LV) were recorded. The cardiac chambers were evaluated using echocardiographic images, and the following parameters were measured: The modified Simpson's method was utilized to determine the ejection fraction of the LV.[18] To calculate the LA volumes, the area-length technique was employed from the apical four and two-chamber views at end-systole, which was just before the opening of the mitral valve. The LA volume index was computed by dividing the LA volumes by the body surface area.[19] In the apical four-chamber view, pulsed-wave Doppler of trans-mitral LV inflow was conducted, with the sample volume positioned at the level of the mitral tips. Tissue Doppler mitral annular velocity was ascertained from the four-chamber view by positioning the sample volume on the lateral annulus, close to the insertion site of the mitral valve.[20] The LV diastolic function was evaluated by measuring peak early (E) and early diastolic mitral annular velocity (E'). To determine the LV filling pressures, the E/E' ratio was employed as an index.

All patients also underwent 2-and 3-dimensional transesophageal echocardiography (TEE) (ie33, Phillips, or Vivid I, GE Healthcare) within three days of the AICI occurrence. Various images of the LAA were acquired using different perspectives, including a continuous sweep between 0 and 180 degrees in both short and long-axis views, which were taken from the mid-esophageal position. The observation of LAATF (an intra-cavity mass identified and characterized as uniformly echo-dense and well-defined, clearly separate from the surrounding endocardium and pectinate muscles, and

visible in multiple image planes) was recorded and the peak velocity at which the LAA empties (utilizing a Pulse wave Doppler placing the probe one cm deep into the appendage's orifice) determined.[21] The visibility of SEC was enhanced by adapting the gain settings to eliminate low-amplitude echo images, thus improving image clarity. SEC severity was evaluated none, when there was no smoke-like echogenicity present; stage 1 was defined as small amount of echogenicity observed in the LAA or sparsely dispersed in the main LA; stage 2 was a more concentrated whirling configuration than stage 1 was observed, along with SEC distributed in a comparable pattern; stage 3 was documented, when throughout both the main LA and the LAA, a concentrated whirling configuration was noted; and stage 4 finally, showed a more significant echo density and the whirling configuration was very slow, surpassing stage 3 in intensity .[22] All cardiac imaging was initiated upon request of the neurology department of our hospital.

Blood samples were obtained from an antecubital vein by venous needle puncture after a 12-hour fast. We used blood samples taken the next morning after the admission date of the patients. A commercially available automated hematology analyzer (Sysmex XT-1800i, Kobe, Japan) that provided complete blood count was utilized for computing hemoglobin, white blood cell, neutrophil, lymphocyte and platelet values. Further, the levels of biochemical markers in the blood, such as baseline lipid profile, creatinine and plasma glucose, were measured to assess the metabolic state of the subjects. These parameters were calculated using an auto-analyzer (Abbot Architect ci4100, Holliston, MA, USA). MHR was obtained by dividing the number of monocytes by HDL cholesterol level. The value of NLR was determined by dividing the number of neutrophils by the number of lymphocytes present in the blood.

The criteria for exclusion from the study were established as follows: Decompensated heart failure; congenital or pulmonary disease or critical valve dysfunction; patients with prosthetic valves; renal or hepatic dysfunction; clinical evidence of cancer; blood dyscrasiasis; auto-immune diseases; acute or chronic infections or inflammatory conditions; current therapy with corticosteroids and/or non-steroidal anti-inflammatory drugs.

The research protocol adhered to the principles outlined in the Declaration of Helsinki and received approval from the Institutional Ethics Committee of Istanbul Okan University (No: 23.06.2021; 139/24)

Statistical Analysis

Statistical evaluation of the obtained data was done with SPSS for Windows 11.5 (Chicago, INC). To compare continuous data between the three groups, One-way ANOVA and Bonferroni tests were used, and for comparing qualitative data, the Chi-Square test was employed. The statistical significance boundary was accepted as 0.05.

Results

This study included 69 patients who had been diagnosed with AICI. The participants were categorized into three groups based on the presence or absence of LAATF and SEC.

Table 1 displays the baseline characteristics of the study sample. The age and gender distribution of the patients did not differ significantly. Body mass index, systolic and diastolic blood pressure were comparable. Smoking habits, chronic diseases, and use of medication did not show any statistical significance. Patients with AF had statistically significant more LAATF than patients with normal sinus rhythm.

Table 1. Basic characteristics of the study population

Parameters	Thrombus (+) n=13	SEC stage 3-4 n=14	Thrombus (-) n=42	p-Value
Age (mean±SD)	64.1±14.5	62.3±9.7	61.0±11.1	0.688
Male	11(84.6%)	11(78.6%)	29(69.0%)	0.485
NSR	2(15.4%)	11(78.6%)	28(66.7%)	0.001
PAF	2(15.4%)	2(14.3%)	11(26.2%)	0.001
AF	9(69.2%)	1(7.1%)	3(7.1%)	0.001
BMI (mean±SD)	29.4±1.2	30.2±1.5	29.8±1.5	0.367
SBP (mean±SD)	137.6±12	138.2±6.6	133.3±9.5	0.205
DBP (mean±SD)	89.2±8.6	94.2±12.3	94.4±11.7	0.346
CAD	7(53.8%)	8(57.1%)	18(42.9%)	0.579
Heart failure	5(38.5%)	8(57.1%)	19(45.2%)	0.606
Smoking	7(53.8%)	7(50.0%)	21(50.0%)	0.969
Diabetes	3(23.8%)	2(14.5%)	12(28.6%)	0.556
AHT	5(38.5%)	6(42.9%)	22(52.4%)	0.624
AHTM	5(38.5%)	6(42.9%)	22(52.4%)	0.624
BB/CCB	6(46.2%)	6(42.9%)	15(35.7%)	0.757
ATM	7(53.8%)	8(57.1%)	17(40.5%)	0.465
ALM	7(53.8%)	8(57.1%)	14(33.3%)	0.186

SEC, spontaneous echo contrast; NSR, normal sinus rhythm; PAF, paroxysmal atrial fibrillation; AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; AHT, arterial hypertension; AHTM, antihypertensive medication; BB, beta-blocker; CCB, calcium channel blocker; ATM, antithrombotic medication; ALM; antilipidemic medication

Comparison of the laboratory findings are represented in Table 2. In contrast to other groups, the Thrombus (-) group exhibited significantly lower levels of monocytes. All other laboratory parameters did not demonstrate any significant differences between the groups.

Table 2. Laboratory findings of the study population

Parameters	Thrombus (+) n=13	SEC stage 3-4 n=14	Thrombus (-) n=42	p-value
Hgb g/dl)	14.4±1.51	14.2±1.73	13.8±1.75	0.75
WBC (10^9/L)	8.6±1.7	9.8±2.5	9.1±1.6	0.62
Neutrophiles (10^3 /μl)	9.2±3.5	8.3±1.2	8.7±2.1	0.70
Lym(10^3 /μl)	3.5±1.4	2.8±2.1	3.2±1.2	0.72
Monocytes (10^3 /μl)	0.83±0.36	0.81±0.24	0.64±0.3	0.001
Platelets (10^3 /μl)	269.5±84.6	254.5±70.2	256.3±75.3	0.28
Triglyceride (mg/dl)	197.9±50.7	195.5±83.1	197.5±54.7	0.90
HDL (mg/dl)	39.8±9.7	39.6±9.5	38.8±7.3	0.92
LDL (mg/dl)	130.0±34.5	129.9±53.7	131.8±41.2	0.19
Glucose (mg/dl)	126.2±52.8	127.7±42.1	119.7±37.3	0.08
Creatinine (mg/dl)	1.01±0.4	0.97±0.3	1.03±04	0.3

SEC, spontaneous echo contrast; WBC, white blood cells; HDL, high density lipoprotein; LDL, low density lipoprotein; Hgb, hemoglobin; Neu, Neutrophiles; Lym, Lymphocytes

Table 3 displays MHR, NLR, and echocardiographic findings of the study sample. A significant difference was observed between the three groups with regards to MHR ($p<0.001$ between the groups). NLR levels were comparable between Thrombus (+) and SEC group. But in comparison to other groups, it was statistically reduced in the Thrombus (-) group. LAA Ev showed statistically significant difference between all groups: Thrombus (+)-SEC: $p<0.008$; Thrombus (+)-Thrombus (-): $p<0.001$; SEC-Thrombus (-): $p<0.001$).

Table 3. MHR, NLR and echocardiographic findings of the study population

Parameters (mean±SD)	Thrombus (+) n:13	SEC stage 3-4 n:14	Thrombus (-) n:42	p-value
MHR	0.59±0.24	0.45±0.20	0.22±0.09	<0.001
NLR	7.9±6.0	6.8±4.6	3.4±3.8	0.002
LVEF	45.9±10.4	41.8±9.5	46.0±7.8	0.40
LAVI	43.8±7.1	43.3±3.9	42.7±2.2	0.86
E/E'	13.4±3.3	13.3±3.9	12.7±2.2	0.72
LAA Ev	26.0±7.7	28.8±8.3	34.8±9.0	0.004

SEC, spontaneous echo contrast; MHR, monocyte to high-density lipoprotein cholesterol ratio; NLR, neutrophil to lymphocyte ratio; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; LAA Ev, left atrial appendix emptying velocity.

Discussion

One of the primary results of this research was that patients who had a LAATF demonstrated a considerably higher MHR value. Further, a significant correlation was found between MHR and NLR. As far as we are aware, this is the initial study that highlights the connection between MHR and LAATF.

Monocytes have a crucial impact on the progression of chronic inflammation and cardiovascular disorders by modulating inflammatory cytokines and adhesion molecules.[23] These prooxidant cytokines are promoting coagulation and inhibit fibrinolysis.[24] HDL-C on the other hand has some cardioprotective effects improving endothelial function via its anti-inflammatory and antioxidative effects.[25] HDL-C inhibits the transmigration of monocytes into the endothelium and prevents monocyte activation.[26] Therefore, it seems to be reasonable to use MHR as an inflammation parameter by proportioning these two markers.

In many studies, MHR and NLR were found to be important vascular inflammatory markers and reliable predictors for atherosclerosis formation and also for cardiovascular outcomes.[27] In one study for example Avci et al. investigated the effectiveness of MHR in 269 patients with the diagnosis of pulmonary embolism for predicting in-hospital mortality. Here, compared to the group without mortality, the group that experienced mortality had significantly higher MHR values.[28] Another investigation by Isik et al. revealed that patients with angiographically isolated coronary artery ectasia had significantly elevated NLR values when compared to patients with normal coronary angiograms. They concluded a strong association between increased NLR values and the occurrence of isolated coronary artery ectasia.[29]

The main focus of the current research was on investigating the correlation between LAATF and MHR which is considered relevant marker of inflammation. Virchow suggested more than a century ago that the formation of a thrombus requires the presence of three conditions: Flow disturbances, endothelial dysfunction, and clotting activation.[30] Since most of our patients with LAATF had AF, the mentioned Virchow triad is fulfilled in many aspects: The absence of atrial systole leads to stagnation of blood within the LA, which can be seen on transesophageal echocardiography as SEC.[31] Further, in our study individuals with LAATF or SEC had a substantial reduction in LAA ejection velocity compared to patients without LAATF underlining this flow abnormality. Endothelial dysfunction is also detected in patients with AF. Numerous studies have verified this by evaluating various markers of endothelial dysfunction, including von Willebrand factor (vWF) and E-selectin.[32] Finally, abnormal changes in coagulation are also present. Many investigations have demonstrated an elevation in serum concentrations of F1+2, fibrinogen, and D-dimer in patients with AF.[33] But still, the pathophysiology of thrombus formation in patients with AF remains multi-factorial and the precise mechanisms by which this might occur are uncertain.[2] Increasing evidence suggests that inflammation may contribute to this hypercoagulable state as well.[34] Studies have shown that plasma levels of C-reactive protein (CRP) and interleukin-6 are linked to thrombotic state in patients with AF.[35] CRP is also associated with SEC formation in LA or LAA.[36] Further, one investigation demonstrated elevated expression of vWF in the endocardium of patients with AF with correlation to adherent platelet thrombus formation.[37] Thrombosis can be induced by inflammation through a mechanism that involves vWF-mediated process such as endothelial activation, the release of vWF, and the formation of hyper adhesive vWV strands and fibrils.[38]

Nakamura et al. demonstrated in one study high expression of tissue factor in the LA endocardium showing that local inflammation is involved in the genesis of thrombus.[39] Of note, two of our patients with normal sinus rhythm and elevated MHR values had a thrombus formation in the LAA, too. This may suggest that not only the classical triad of Virchow is responsible for thrombus formation in the LAA. Inflammation of the endocardium with generation of a prothrombotic state even in non-AF patients may contribute to thrombus formation. In this context, MHR may indicate this prothrombotic state of the LA endocardium due to local inflammation. Yamashita et al. found that monocytes and macrophages within atrial specimens of patients with AF expressed cytokines leading to an 'occult myocarditis' with further recruitment of monocytes and macrophages.[40] Arisoy et al demonstrated the association between MHR and the extent of thrombus formation in patients with STEMI.[5] A total of 414 individuals diagnosed with STEMI were included in the study population. The participants were classified into two categories based on the extent of thrombus formation by performing a primary percutaneous coronary intervention (PCI). MHR values were significantly elevated in the group with a high extent of thrombus formation. Another study by Cetin et al. showed that MHR predicts stent thrombosis after PCI in patients who were followed up for 37.2 months. During this period of time 112 patients developed stent thrombosis. Here MHR was an independent predictor of stent thrombosis in this patient group.[6] These studies reveal that a pro-inflammatory state of the endothelium seems to play an important role in the genesis of thrombus formation demonstrated by the inflammation-marker MHR.[41] Additionally, in our study MHR values were also significantly increased in patients with SEC stage 3 and 4 compared to patients without any thrombus in the LAA. This again underscores the inflammatory milieu. In one study Maehema et al. investigated inflammation and formation of thrombus in the LA of individuals with non-rheumatic AF. They enrolled 190 patients with non-rheumatic AF who underwent a TEE examination. All participants were examined for the existence or non-existence of LAATF via the above-mentioned method. Additionally, CRP values of the study population were measured. They found that systemic inflammation, represented by elevated CRP levels, was related to thrombus formation in this patient group. Further, they concluded that this prothrombotic state, in addition to the Virchow triad, may be associated with SEC.[4]

Our study should be evaluated with its inherent limitations. To begin with, this study is retrospective in nature and has a relatively small sample size. Further, the occurrence of LAATF in individuals who recently suffered from an embolic event may have been underestimated due to the possibility of LAATF being previously embolized and thus not detected. Finally, other inflammation markers such as sedimentation, C-Reactive Protein or high-sensitive C-Reactive Protein were not included in this study due to lack of data.

In Conclusion, this study focused on the relationship between MHR and LAATF. MHR is considered a novel biomarker representing both inflammation and oxidative stress. Thus, it appears that inflammation has a significant impact on the occurrence of LAATF. Based on our findings, additional prospective investigations with a more extensive participant pool would yield more comprehensive insights.

Compliance with Ethical Standards

The research protocol adhered to the principles outlined in the Declaration of Helsinki and received approval from the Institutional Ethics Committee of Istanbul Okan University (No: 23.06.2021; 139/24)

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

Authors contributed equally to this work.

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Araştırma Makalesi | Research Article

BİLATERAL DİSTAL TİP NAZOLAKRİMAL KANAL TIKANIKLIKLARINDA EŞ-ZAMANLI BİLATERAL ENDOSKOPİK MEKANİK DAKRİYOSİSTORİNOSTOMİ

SIMULTANEOUS BILATERAL ENDOSCOPIC MECHANICAL DACRYOCYSTORHINOSTOMY IN BILATERAL DISTAL TYPE NASOLACRIMAL CANAL OBSTRUCTIONS

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ÖZ

Amaç: Eş zamanlı bilateral olarak uygulanan mekanik endoskopik dakriyosistorinostomi (EN-DSR) operasyonunun başarı oranının, cerrahi süresinin ve komplikasyonlarının araştırılması amaçlandı.

Yöntem: Bu retrospektif çalışmaya bilateral nazolakrimal kanal tıkanıklığı şikayeti ile başvuran ve eş zamanlı bilateral mekanik EN-DSR operasyonu uygulanan 14 hastanın 28 gözü dahil edildi. Her gözün operasyon sürelerine ek olarak, 1. hafta, 1. ay, 3. ay ve 6. ay kontrollerindeki anatomik ve fonksiyonel başarı oranları ve komplikasyon oranları değerlendirildi.

Bulgular: Hastaların yaş ortalaması 51,0 ± 8,5 ve kadın/erkek cinsiyet oranları (9/5 [%64,3/35,7]) olarak izlendi. Her iki göz için ortalama ameliyat süresi 73,93 ± 7,64 dakika (min-maks: 60-90) olarak bulundu. Anatomik başarı oranı 1. hafta, 1. ay, 3. ay ve 6. ay için %100, %96,4, %92,9 ve %92,9 olarak bulunurken, fonksiyonel başarı oranları sırasıyla, %96,4, %96,4, %92,9 ve %89,3 olarak izlendi. Postoperatif komplikasyon olarak, 4 gözde (%14,3) lakrimal kese bölgesinde hematom, 2 gözde (%7,1) basit müdahale ile kontrol altına alınabilen epistaksis ve 2 gözde (%7,1) ise 1 haftalık erken dönemde silikon tüp ekstrüzyonu görüldü. Sağ ve sol göz arasında cerrahi süresi, anatomik ve fonksiyonel başarı oranları arasında anlamlı fark izlenmedi (sırasıyla, p=0,130, p=0,142, p=0,541).

Sonuç: Bilateral nazolakrimal kanal tıkanıklığı olan hastalarda kısa cerrahi süresi, yüksek başarı ve düşük komplikasyon oranları ile eş zamanlı bilateral mekanik EN-DSR önerilebilecek bir yöntemdir.

Anahtar Kelimeler: Nazolakrimal kanal tıkanıklığı, dakriyosistorinostomi, endoskopik, eş zamanlı, bilateral

ABSTRACT

Objective: To investigate the success rate, duration of surgery, and complications of simultaneous bilateral mechanical endoscopic dacryocystorhinostomy (EN-DSR) operation.

Methods: This retrospective study included twenty-eight eyes of 14 patients who presented with bilateral nasolacrimal duct obstruction and underwent simultaneous bilateral mechanical EN-DCR operation. In addition to the operation times of each eye, anatomical and functional success rates and complication rates at the 1st week, 1st month, 3rd month, and 6th-month follow-ups were evaluated.

Results: The mean age of the patients was 51.0 ± 8.5, and the female/male sex ratio was 9/5 [64.3%/35.7]. The mean operation time for both eyes was 73.93 ± 7.64 minutes (min-max: 60-90). Anatomical success rates were found to be 100%, 96.4%, 92.9%, and 92.9% for the 1st week, 1st month, 3rd month, and 6th month, while the functional success rates were 96.4%, 96.4%, 92.9%, and 89.3%, respectively. Postoperative complications were hematoma in the lacrimal sac region in 4 eyes (14.3%), epistaxis that could be controlled with simple intervention in 2 eyes (7.1%), and silicone tube extrusion in the early period of 1 week in 2 eyes (7.1%). There was no significant difference between the right and left eyes in terms of surgery time, anatomical and functional success rates (respectively, p=0.130, p=0.142, p=0.541).

Conclusion: Simultaneous bilateral mechanical EN-DCR is a method that can be recommended in patients with bilateral nasolacrimal duct obstruction, with short surgical time, high success, and low complication rates.

Keywords: Nasolacrimal duct obstruction, dacryocystorhinostomy, endoscopic, simultaneous, bilateral

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Giriş

Lakrimal drenaj sistemi punktum, kanaliküller ve ortak kanalikülü kapsayan proksimal, lakrimal kese ve nazolakrimal kanalı kapsayan distal tip olarak ikiye ayırılır.[1] Epifora, çapaklanma ve dakriyosistit ile sonuçlanabilen distal tip nazolakrimal kanal tıkanıklığı (NLKT) en sık görülen tipidir.[2]

Distal tip NLKT'nin tedavisi dakriyosistorinostomidir (DSR).[3] DSR cerrahisi için geleneksel uygulanan altın standart tedavi burun ile medial kantus bölgesi arasından veya gözyaşı oluğu bölgesinden yapılan bir kesi ile gerçekleştirilen eksternal cerrahi (EKS-DSR) yöntemdir. Bununla birlikte, dışardan kesi olmaksızın burun içerisinden uygulanan farklı endoskopik DSR (EN-DSR) yöntemleri de literatürde tanımlanmıştır. EN-DSR yöntemleri içinde en sık kullanılan kemik dokunun çıkartıldığı ve lakrimal kese ile nazal mukoza arasında anastomuzun sağlandığı mekanik EN-DSR ve sınırlı kemik doku ve mukoza penceresi içerisinden işlem gerçekleştirilen lazer-destekli EN-DSR teknikleri bulunmaktadır.[4] Yayınlanan bir meta-analizde mekanik EN-DSR'nin EKS-DSR ile benzer başarı oranına sahipken, komplikasyon oranının daha düşük olduğu gösterilmiştir.[4] Bilateral NLKT'nin insidansı tam bilinmemekle birlikte, daha önceki çalışmalarda %9-18 oranlarında görülebildiği bildirilmiştir.[5] Eş zamanlı bilateral EKS-DSR uygulaması ile ilgili ilk çalışma 1989 yılında yayınlanmış[6] ve ilerleyen dönemlerde farklı araştımacılar tarafından eş zamanlı bilateral EKS-DSR'nin komplikasyon oranları düşük, hızlı ve başarılı bir yöntem olduğu gösterilmiştir. [5,7-10]

EN-DSR daha az zaman alan bir cerrahi olması ve cilt kesisi olmaması nedeniyle postoperatif dönemde daha hızlı iyileşme göstermesi sayesinde bilateral NLKT'lerde eş zamanlı olarak uygulanması konusunda araştırılmıştır.[11] Sonrasında gelen farklı çalışmalar ile birlikte eş zamanlı bilateral EN-DSR'nin güvenli, hızlı uygulanabilir ve başarılı sonuçlarının olduğu gösterilmiştir.[10-12] Buna ek olarak, eş zamanlı uygulanacak cerrahinin maliyeti düşürmesi ve daha önemlisi hastanın anestezi hazırlığı ve anestezi süresini kısalttığı bildirilmiştir.[11] Postoperatif dönemde daha hızlı normal hayata dönüş süresi sağlayan bir cerrahi olması ve yara izi riski olmaması nedeniyle hastalar EN-DSR'yi EKS-DSR'ye tercih etmektedir.[13] Bu nedenle son yıllarda kullanımı giderek yaygınlaşan EN-DSR'nin bilateral NLKT'de eş zamanlı her iki göze uygulanması hakkında literatürün daha fazla veriye ihtiyacı vardır.

Bu çalışmada, bilateral NLKT'de uygulanan eş zamanlı EN-DSR'nin farklı takip zamanlarındaki fonksiyonel ve anatomik başarı sonuçları, komplikasyon oranları ve cerrahi süresinin araştırılması amaçlanmıştır.

Yöntem

Bu çalışma girişimsel, retrospektif olarak dizayn edildi ve Marmara Üniversitesi Tıp Fakültesi Göz Hastalıkları Anabilim Dalı Oküloplastik ve Orbital Cerrahi biriminde Ocak 2021 ve Mart 2022 tarihleri arasında yürütüldü. Çalışma Helsinki Deklarasyonu Prensiplerine uygun olarak planlandı ve Marmara Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından 2022.1369 sayılı onay alındı.

Çalışmaya 18 yaşından büyük, semptomatik bilateral epiforası bulunan, nazolakrimal kanal muayenesinde distal tip tıkanıklık olduğu görülen olgular dahil edildi. Geçirilmiş DSR, travma, sino-nazal kanser, hastalık veya patoloji, burun içi cerrahi öyküsü olanlar, kafa kemiklerinde anomalliğe neden olabilecek sendromlu olgular ve tek taraflı epifora şikayeti olan hastalar çalışmadan dışlandı. Buna ek olarak, oküler yüzey hastalığına, punktal veya kanaliküler tıkanıklığına, kapak gevşekliği veya malpozisyonuna bağlı epiforası olan olgular da çalışmaya dahil edilmedi.

Hastalara görme keskinliği, göz içi basınç ölçümü, fundus muayenelerine ek olarak, ön segment ve punktum patolojilerini ekarte etmek için tam oftalmolojik muayene uygulandı. Proksimal tip NLKT'leri ekarte etmek için punktum genişletici ile punktum muayeneleri ve sondalama teli ile kanalikül muayeneleri yapıldı. NLKT tanısını doğrulamak için hastalara florosein boya kaybolma testi ve 26 ölçeklik lakrimal kanül ile nazolakrimal kanal lavajı uygulandı. Cerrahi öncesinde hastaların kullandıkları antiagregan ve antikoagülan kan sulandıcılar cerrahinden en az 5 gün önce kesildi ve tüm hastalar anestezi hekimi tarafından operasyona uygunluk açısından değerlendirildi.

Cerrahi Teknik

Bilateral EN-DSR'lerin tümü genel anestezi altında solak bir cerrah (VD) tarafından uygulandı. Operasyon öncesinde %1'lik lidokain ve 1:100,000'lik adrenalin emdirilmiş pamuklar ile burun tamponlandı. Endoskopik görüntüleme başladıktan sonra orta konkanın lateraline ve lakrimal kesenin medialine denk gelen burun mukozasına 20mg/ml lidokain HCI ve 0,00125mg/ml epinefrin içeren kombine lokal anestezik solüsyon 4ml uygulandı. Daha sonra, 15 numara bistüri ile nazal mukoza tabanı superiora bakan U şeklinde insize edildi ve periost elavatoru yardımıyla altındaki kemik yapıdan diseke edilerek mukozal flep oluşturuldu. Mukozanın altında kalan lakrimal kemik ve maksiller kemiğin frontal çıkıntısı arasından Kerrison kemik kesici yardımıyla girilerek lakrimal kesenin medialini örten kemik dokular uzaklaştırıldı. Üst ve alt punktumlar dilate edilerek, uygun büyüklükte prob ile lakrimal kese içine girildi ve kesenin burun içine doğru çadır şeklinde ittirilmesi sonrasında 12 numara bistüri yardımıyla lakrimal kese mukozasında kesi gerçekleştirildi ve kesinin kenarları superior ve inferiora doğru kesilerek burun içine doğru marsupialize edildi. Üst ve alt punktumdan ilerletilen silikon tüpler burun içinden çıkartılarak bağlandı. Cerrahi sonrası kanamayı azaltmak için operasyon öncesinde uygulanan tamponlardan burun içine tekrar uygulanarak operasyona son verildi. Cerrahi süresi ilk kesi yapılması ile cerrahinin sonlandırılması arasında geçen süre olarak ölçüldü.

Başarı Kriteri

Tüm hastalar operasyon sonrası 1. Hafta, 1. Ay, 3. Ay ve 6. Ayda tekrar değerlendirildi. Kontrollerde tüm oftalmolojik

muayeneye ek olarak lakrimal lavaj uygulandı. Tüm hastaların silikon tüpleri 3. Ayda çekildi. Lakrimal lavaj muayenesi patent olan hastalar *Anatomik başarılı*, olmayanlar *Anatomik başarısız* olarak değerlendirildi. Hastanın sulanma şikayetlerinin devam etmesine göre ise sübjektif olarak *Fonksiyonel başarı ve başarısız* olarak ayrıldı. Şikayetleri azalmasına rağmen sulanmanın devam etmesi durumunda hasta *Fonksiyonel başarısız* olarak değerlendirildi.

Verilerin analizi için Statistical Package for Social Sciences (SPSS) versiyon 24.0 kullanıldı. Verilerin dağılımı için Shapiro-Wilks testi uygulandı. Kategorik veriler sayı (yüzde) olarak, parametrik veriler ortalama ± standart sapma ve parametrik olmayan veriler ortalama ± standart sapma (min-maks) olarak verildi. Parametrik olmayan verilerin karşılaştırılması için Mann-Whitney U testi kullanıldı. $p<0,05$ olan değerler anlamlı olarak kabul edildi.

Bulgular

Çalışmaya 14 hastanın 28 gözü dahil edildi. Hastaların yaş ortalaması 51,0 ± 8,5 ve kadın/erkek cinsiyet oranları (9/5[%64,3/35,7]) olarak izlendi. Toplam 28 gözün 9'unda (%32,1) geçirilmiş dakriyosistit öyküsü bulunmaktaydı. Gözlerin semptom başlama süreleri ile son başvuru süreleri arasında ortalama 9,4 ± 3,9 ay bulunmaktaydı. Hastaların takip sürelerine göre *Anatomik* ve *Fonksiyonel* başarı oranları Tablo 1'de verilmiştir.

Göz başına ortalama ameliyat süresi 37,5 ± 6,6 dakika (min-maks: 25-50) her iki göz için ise ortalama ameliyat süresi 73,93 ± 7,64 dakika (min-maks: 60-90) olarak bulundu. Gözler ayrı olarak değerlendirildiğinde sağ göz ortalama ameliyat süresinin 35,7 ± 6,8 dakika (min-maks: 25-50), sol göz ortalama ameliyat süresinin 39,3 ± 6,2 dakika (min-maks: 30-50) olduğu görüldü (p=0,130). Cerrahilerin hiçbirinde intraoperatif komplikasyon izlenmedi. Postoperatif komplikasyonlar incelendiğinde 4 gözde (%14,3) lakrimal kese bölgesinde hematom, 2 gözde (%7,1) basit müdahale ile kontrol altına alınabilen epistaksis, 2 gözde (%7,1) ise 1 haftalık erken dönemde silikon tüp ekstrüzyonu görüldü. Aynı anda *fonksiyonel ve anatomik başarısız* olan gözlerden birinde erken dönemde tüp ekstrüzyonu mevcuttu. Altıncı ayda *fonksiyonel başarısız* olan gözlerden iki göz sol, bir göz sağ taraflı iken (p=0,541), *anatomik başarısız* gözlerden her ikisi de sol gözdü (p=0,142).

Tablo 1. Farklı takip zamanlarına göre gözlerin *Anatomik* ve *Fonksiyonel* başarı oranları

	1. Hafta	1. Ay	3. Ay	6. Ay
Anatomik Başarı, n Başarı oranı	28/28 (%100)	27/28 (%96,4)	26/28 (%92,9)	26/28 (%92,9)
Fonksiyonel Başarı, n Başarı oranı	27/28 (%96,4)	27/28 (%96,4)	26/28 (%92,9)	25/28 (%89,3)

Tartışma

Bu retrospektif çalışmada, bilateral eş zamanlı uygulanan mekanik EN-DSR'nin ciddi komplikasyon olmaksızın hızlı şekilde uygulanabilen, başarı oranları yüksek bir yöntem olduğu gösterilmiştir.

EN-DSR, EKS-DSR'ye göre bazı avantajları sayesinde son yıllarda popülerliğini arttırmaktadır. EN-DSR'nin avantajları, yüzde bir kesi izi skarı bırakmaması, orbikülaris oküli kasına zarar verilmemesinden dolayı lakrimal pompa fonksiyonun korunması ve postoperatif dönemde hızlı iyileşme sağlaması olarak sıralanabilir.[14] Hastaların tercihi açısından bakıldığında, yapılan bir çalışmada bir gözüne EN-DSR diğer gözüne ise EKS-DSR uygulanan hastaların tümü (n=5) retrospektif olarak sorgulandıklarında EN-DSR'yi tercih ettiklerini belirtmişlerdir.[13]

EN-DSR ve EKS-DSR'nin başarı oranları literatürde sık olarak ele alınan konu başlıklarından biridir. EKS-DCR'nin başarı oranı farklı çalışmalarda %70-95 arasında bildirilirken, EN-DSR için %63-96 arasında başarı oranı bildiren çalışmalar mevcuttur.[15] EN-DSR için farklı sonuçlar bildirilmesinin bir nedeni endonazal yaklaşım uygulanırken mekanik (kemik turu ve Kerrison kemik kesici), veya lazer-destekli farklı tekniklerin kullanılmasıdır.[16,17] Cochrane veritabanı ile yapılan bir sistemik derlemede mekanik EN-DSR ile EKS-DSR'nin anatomik başarı oranları her iki cerrahi için de %90 bulunmuştur.[15] Fakat aynı çalışmada endonazal lazer-destekli DSR'nin anatomik başarı oranı %63, EKS-DCR'ın oranı %91 olarak bildirilmiştir.[15] Yayınlanan farklı bir meta-analizde ise, çalışmamızda kullanılan mekanik EN-DSR yöntemi ile %84 oranında, EKS-DSR ile %87 oranında (p=0.43) benzer başarı bildirilmiştir.[4] Fakat endonazal-lazer destekli DSR'nin başarı oranı %77 olarak EKS-DSR'den daha düşük olduğu gösterilmiştir (p<0,001). Enfeksiyon ve kabul edilemez skar gelişimi ise EKS-DSR'de EN-DSR'ye göre anlamlı olarak yüksek bulunmuştur (sırasıyla; p<0,001, p<0,001).[4] Mevcut çalışmadaki komplikasyonların hepsi basit müdahale ile kontrol edilmiştir ve hiçbir hastada postoperatif enfeksiyon izlenmemiştir.

Bilateral eşzamanlı uygulanan EKS-DSR'nin kanama, enfeksiyon gibi komplikasyonları arttırabileceği düşünülebilir. Fakat daha önce yapılan çalışmalarda eşzamanlı girişimin komplikasyon oranlarını etkilemediği gösterilmiştir.[5,7-10] Bu çalışmalarda bilateral eşzamanlı EKS-DSR ile başarı oranları %61,3 – %97 arasında bildirilmiştir.[5,8-10] Bu oranlar literatürde tek taraflı yapılan cerrahi ile benzerlik göstermektedir. Yapılan bir çalışmada eş zamanlı bilateral ile tek taraflı EKS-DSR başarı oranları arasında anlamlı fark gösterilmemiştir (sırasıyla, %75 ve %82, p>0,05).[10] Tek taraflı EKS-DSR'nin operasyon süresi hakkında farklı sonuçlar bulunmakla birlikte Tarbet ve Custer çalışmalarında cerrahi süresini 52-100 dakika olarak bildirilmiştir.[18] Bilateral EKS-DSR ile ilgili yayınlarda Yazıcı ve ark.[5] cerrahi süresini iki göz için ortalama 89 dakika, Yüksel ve ark.[8] 86 dakika, Weiberger ve ark.[10] ise anestezi süresini ortalama 130 dakika, cerrahi süresini ortalama 90 dakika olarak bildirilmiştir.

EN-DSR daha hızlı bir cerrahi süresine imkan vermesi, komplikasyon oranlarının daha düşük olması ve iyileşme süresinin daha hızlı olması sayesinde bilateral NLKT'da eşzamanlı uygulanması açısından üzerine çalışılmalar yürütülmüştür. Bu çalışmaların sonucunda %91[10,11] ve %92,3[12] şeklinde farklı başarı oranları bildirilmiştir. Mevcut çalışmada 28 göz üzerinde uygulanan eşzamanlı cerrahide bulduğumuz %91 anatomik ve %89 fonksiyonel başarı oranları literatürde bildirilenler ile benzerlik göstermektedir. Bununla birlikte, çalışmada iki göz için ortalama ameliyat süresi 73 dakika olarak bulunmuştur. Bu sonuç, Weiberger ve ark.[10] ile benzerlik gösterirken (76 dakika) ve Herzallah ve ark.'nın[12] 155 dakika olarak bildirdiği toplam ameliyat süresine göre kısa, Bayraktar ve ark.[11] bildirdiği ortalama cerrahi süresine (44 dakika) göre ise daha uzundur. Bayraktar ve ark. çalışmasında cerrahiyi uygulayan kişinin endoskopik cerrahiye aşina bir kulak burun boğaz uzmanı tarafından uygulanıyor oluşu cerrahi süreyi etkileyen bir faktör olabilir. Yine de çalışmada bulunan cerrahi sürenin EKS-DSR çalışmalarına göre daha kısa olduğu söylenebilir. Cerrahi sürenin kısalmasının maliyeti azaltacağını ve tek seans ile uygulanan cerrahinin operasyon maliyetinde %25, toplamda %28'lik bir azalma sağladığı belirtilmiştir.[11]

Bunlara ek olarak, endoskopi kamerasının non-dominant elde, işlem yapılacak aletlerin ise dominant elde tutulmasından dolayı, sağ elini kullanan cerrahlar için sol göze ve solak cerrahlar için sağ göze uygulanacak işlemlerin daha kolay olacağı düşünülmektedir. Mevcut çalışmada cerrahiler solak bir cerrah tarafından uygulanmış ve sağ göz ortalama operasyon süresi daha kısa bulunmasına rağmen aradaki fark anlamlı bulunmamıştır. Buna ek olarak, sağ ve sol gözler arasında başarı oranları arasında da anlamlı fark gösterilmemiştir.

Çalışmanın kısıtlılıklarından bir tanesi hastaların sadece 6 ay takip edilmesi ve uzun süre takip sürelerinin olmayışıdır. Çalışmada silikon tüpler 3. ayda çıkartıldıktan sonra bir hastanın 6. ay kontrolünde fonksiyonel ve anatomik başarısızlık meydana gelmiştir. Fakat takip süresinin kısa olması nedeniyle, bu hastaların uzun dönemdeki fonksiyonel ve anatomik başarılarındaki değişim hakkında yorum yapılamamaktadır. Buna ek olarak, bilateral NLKT'nin tek taraflı tıkanıklığa göre daha nadir görülmesi nedeniyle çalışmadaki hasta sayısının az olduğu söylenebilir. Son olarak, çalışmada eş zamanlı bilateral EKS-DSR grubu ile karşılaştırma yapılamadığı için bu iki cerrahi arasındaki başarı, komplikasyon ve süre gibi parametreler üzerine yorum yapılamamaktadır. Gelecekte daha fazla hasta sayısı, daha uzun takip süresi ve EKS-DSR'yi de içeren bir kontrol grubu ile yapılacak çalışmalar, bilateral eşzamanlı uygulanacak EN-DSR operasyonun başarısı ve uzun dönemdeki takibi açısından aydınlatıcı bilgiler verebilir.

Sonuç olarak, bu çalışmanın sonuçları bilateral nazolakrimal kanal tıkanıklığı olan hastalarda eşzamanlı uygulanacak mekanik EN-DSR ile yüksek oranda başarı sağlanabildiği, bu cerrahi yöntemin basit müdahale ile giderilebilen düşük komplikasyon oranları ve kabul edilebilir cerrahi süresi olduğunu göstermiştir. Bu nedenle bilateral tıkanıklığı olan ve iki farklı cerrahiye hazırlanmakta zorluk yaşanabilecek özellikle yaşlı, ek hastalığı olan hastalarda ve tek seferde her iki gözün ameliyat olmasını isteyen olgularda, bilateral eşzamanlı mekanik EN-DSR yüksek başarı ve düşük komplikasyon oranlarıyla önerilebilecek bir yöntemdir.

Açıklamalar

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Research Article | Araştırma Makalesi

EXPRESSION LEVELS OF ACE2 AND TMPRSS2 IN DIFFERENT CELL LINES

ACE2 VE TMPRSS2 GENLERİNİN FARKLI HÜCRE HATLARINDAKİ İFADE DÜZEYLERİ

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ABSTRACT

Objective: ACE2 and TMPRSS2 proteins have received increased attention with the outbreak of pandemic COVID-19. These proteins have roles in respiratory and hypertension disorders as well as cardiovascular and renal diseases. The objective of this work was to examine the mRNA and protein levels of ACE2 and TMPRSS2 in cell lines derived from various tissue origins.

Methods: After the growth of 14 different cell lines, protein and mRNA were isolated from the cell pellets. The amounts of mRNAs and proteins were then determined and quantified using qRT-PCR and ELISA.

Results: Findings showed that VERO, HEK293T, and VERO E6 cell lines significantly differed from others in the mRNA levels of both the ACE2 and TMPRSS2 genes. In protein levels obtained using ELISA, PNT1A cell line had the highest level of ACE2 protein expression, while for TMPRSS2, A549 had the highest level of protein expression.

Conclusions: It has found in this study how the expressions levels of ACE2 and TMPRSS2 depend on the cell type. This may be an explanation for why virulence entrance differs in different types of tissues. It is speculated that HEK293T cells with high levels of both genes may be a suitable option for studies at the RNA level by using these two genes. MCF7 may be a good candidate for studies at the protein level. Given the high levels of mRNA expression of both genes, it may be inferred that cells derived from the kidney were among those that were most susceptible to virus entry.

Keywords: ACE2, TMPRSS2, COVID19

ÖZ

Amaç: ACE2 ve TMPRSS2 proteinleri, COVID-19 pandemisi ile birlikte önem kazanmıştır. Bu proteinlerin solunum ve hipertansiyon bozukluklarının yanı sıra kardiyovasküler ve renal hastalıklarda rolleri vardır. Bu çalışmanın amacı, çeşitli dokulardan üretilen hücre hatlarında ACE2 ve TMPRSS2'nin mRNA ve protein seviyelerini belirlemektir.

Yöntem: 14 hücre hattı kültürde çoğaltıldıktan sonra, hücre pelletlerinden protein ve mRNA izole edildi. Ardından mRNA seviyeleri qRT-PCR ve protein seviyeleri ise ELISA metotları kullanılarak ölçüldü.

Bulgular: Çalışmanın sonuçları, ACE2 ve TMPRSS2 genlerinin mRNA seviyelerinin VERO, HEK293T ve VERO E6 hücre hatlarında, diğer hücre hatlarına kıyasla, önemli ölçüde yüksek olduğunu göstermiştir. ELISA kullanılarak elde edilen protein seviyelerinde, PNT1A hücre hattı en yüksek ACE2 protein ifadesine sahipken, TMPRSS2 için A549 en yüksek protein ekspresyonuna sahip olarak bulunmuştur.

Sonuç: Bu çalışmada ACE2 ve TMPRSS2 gen ifadelerinin hücre tipine göre farklılaşabileceği gösterilmiştir. Bu sonuç, farklı doku tiplerinde virüs girişinin neden farklı olduğunun bir açıklaması olabilir. Her iki genin de yüksek düzeyde bulunduğu HEK293T hücrelerinin, bu iki gen kullanılarak RNA düzeyinde yapılacak çalışmalar için uygun bir seçenek olabileceği düşünülmektedir. MCF7 hücre hattı ise protein seviyesindeki çalışmalar için iyi bir seçenek olabilir. Her iki genin yüksek mRNA ekspresyon seviyeleri göz önüne alındığında, böbrekten üretilen hücre hatlarının virüs girişine en duyarlı olanlar arasında olduğu sonucuna varılabilir.

Anahtar Kelimeler: ACE2, TMPRSS2, COVID19

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Introduction

In late 2019, a novel coronavirus, named lately as coronavirus disease 2019 (COVID-19), has started to outbreak and affected many people throughout the world. More than 762 million people were affected so far in the World and 6.9 million patients were died due to the disease.[1] Because of the growing number of studies examining the disease's mechanism and how the coronavirus 2 (SARS-CoV-2) invades healthy cells, angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) proteins have gained prominence.

In healthy cells, by regulating blood pressure and maintaining electrolyte balance, ACE2 plays a key role in the renin-angiotensin system (RAS) of the regulation of cardiovascular and renal functions[3], In COVID-19, ACE2 was discovered as a gate in the virus entrance mechanism. It has been shown that the transmembrane protein ACE2 serves as a receptor for the spike (S) protein of the SARS-CoV-2 virus.[4-7] This S protein consists of two subunits as S1 and S2. When S1 binds to ACE2, S2 is cleaved by transmembrane serine protease 2 (TMPRSS2) and the virus is taken inside the cells by invagination of the cell membrane.[7-10]

Regulations in ACE2 protein levels have been linked to different diseases such as cardiovascular diseases[11], hypertension[12], lung injuries[13,14] and, respiratory system diseases.[3,15] It has been shown in studies that SARS-CoV, which caused more than 800 deaths in 2003, uses the ACE2 receptor for cell entry.[16-19] Since ACE2 is linked to many diseases including COVID-19, it is important to determine both RNA and protein levels of this enzyme in different types of cells.

TMPRSS2 is a type II transmembrane serine protease. Even though its biological function is not clear, it is thought that TMPRSS2 is responsible for the initiation of extracellular matrix (ECM) proteolysis.[21] Additionally, the androgen receptor (AR) is a transcription factor in for TMPRSS2 gene and it promotes gene expression. Upon increased expression of the gene, viruses primed into the cells with the help of protease activity of that gene.[22] TMPRSS2 proteins appear vital for the entrance of different types of viruses into cells such as H1N1 and H7N9 influenza viruses, SARS-CoV, MERS-CoV, and finally SARS-CoV 2 coronaviruses.[23] In androgen receptor-dependent prostate cancer cells, mRNA levels of TMPRSS2 gene were found to be increased.[24-26]mRNA expression level of TMPRSS2 was demonstrated in different tissues such as prostate, breast, kidney, and colon.[24,25,27]

Although there are many *in vivo* and clinical studies investigating the expression of ACE2 and TMPRSS2 in different types of tissues[16,28,29], *in vitro* studies on the expression of these genes are very limited. In the recent study, ACE2 and TMPRSS2 levels were compared with the RT-PCR method using various cell lines, it was shown that both genes were expressed in HUVEC, A549 and HaCaT cells.[30] In another study, it has been demonstrated that ACE2 expression was found in 16HBE and VeroE6 cells, while it was not expressed in BEAS2B and A549 cells.[31] In a different study, high-throughput mRNA sequencing was used to identify potential cell lines for ACE2 analysis. Nevertheless, expression could not be confirmed in some cell types including Alveolar type II cells such as A549.[32] In another study in which primary cells were used, it was reported that airway epithelial cells highly expressed ACE2 and TMPRSS2 proteins.[33] However, primary epithelial cells are not a good option for *in vitro* studies due to disadvantages such as being expensive and having a restricted proliferative capacity. Some other *in vitro* studies have used Caco-2[34], Calu-3[35], HEK293T[36], and Huh7[35] cells and have been shown to express varying levels of ACE2 and/or TMPRSS2. Studies with a limited number of cell lines have shown that the cell line with the highest expression level of ACE2 is VeroE6[16,30,36].

Studies on ACE2 and TMPRSS2 appear to focus more on tissues than cells. Additionally, most studies seem to be predominantly conducted at the RNA level. It is noteworthy that protein expression levels of those genes are typically not verified. Since the results collected from various studies are both insufficient and conflicting, it is clear that determining both RNA and protein levels of these genes in different cell types is necessary in order to provide data for future *in vitro* investigations.

In this study, it was aimed to compare the levels of ACE2 and TMPRSS2 in cell lines of different tissue origins at both mRNA and protein levels. The results of this research will contribute to studies those investigating the roles of ACE2 and TMPRSS2 in diseases such as COVID-19 either separately or together. Additionally, this research may be used as a benchmark when investigating the processes or mechanisms connected to these genes. These findings will contribute to studies examining the involvement of ACE2 and TMPRSS2 in diseases, separately or together, as well as contribute to the elucidation of the pathways and mechanisms related to these genes.

Methods

Briefly, after fourteen different cell lines were cultured, proteins and mRNAs were isolated from the cell pellets. Then, the levels of mRNAs and proteins were determined by using qRT-PCR and ELISA, respectively (Figure 1).

Cell Lines and Culture Conditions

Fourteen different cell lines were used in this study (Table 1). Vero, Vero E6, HEK293, MRC5, A549, DMS114, MCF7, HeLa, SHSY5Y, BJ and HUVEC cells were incubated in Dulbecco's modified Eagle's medium (DMEM, Thermo Fisher Scientific, USA), PNT1A, DU145, LNCaP cells were incubated in Roswell Park Memorial Institute 1640 medium (RPMI, Thermo Fisher Scientific, USA). All media contained 10% fetal bovine serum (FBS) (Gibco, Thermo Fisher Scientific, USA) and 1% penicillin/streptomycin (Gibco, Thermo Fisher Scientific, USA). Cells were cultured in a 37°C incubator (Thermo Fisher Scientific, USA) with 5% CO_2.

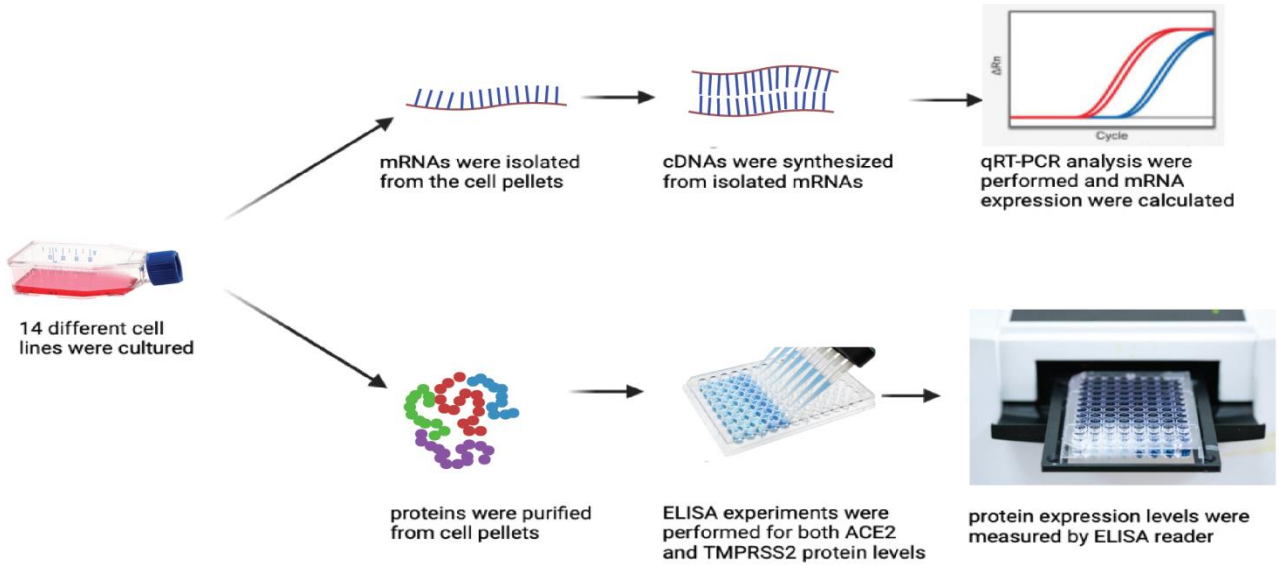

Figure 1. Schematic workflow of experimental methodology

Table 1. Properties of the cell lines that were used in the study

Cell line	Organism	Tissue	Cell type	Disease
Vero	*Cercopithecus aethiops*	Kidney	Epithelial	Normal
Vero E6	*Cercopithecus aethiops*	Kidney	Epithelial	Normal
HEK293	*Homo sapiens*	Embryonic Kidney	Epithelial	Normal
PNT1A	*Homo sapiens*	Prostate	Epithelial	Normal
DU145	*Homo sapiens*	Prostate	Epithelial	Carcinoma
LNCaP	*Homo sapiens*	Prostate	Epithelial	Carcinoma
MRC5	*Homo sapiens*	Lung	Fibroblast	Normal
A549	*Homo sapiens*	Lung	Epithelial-Like	Carcinoma
DMS114	*Homo sapiens*	Lung	Epithelial	Carcinoma
MCF7	*Homo sapiens*	Mammary Gland	Epithelial	Adenocarcinoma
HeLa	*Homo sapiens*	Cervix	Epithelial	Adenocarcinoma
SHSY5Y	*Homo sapiens*	Bone Marrow	Epithelial	Neuroblastoma
BJ	*Homo sapiens*	Skin	Fibroblast	Normal
HUVEC	*Homo sapiens*	Umbilical	Endothelial	Normal

RNA Isolation and Real-Time Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR)

Total RNA was isolated from the pellets of cultured cells using the QIAGEN ® RNeasy Mini Kit (QIAGEN, USA) according to described by Yanar and her colleagues.[37] The purity and concentration of the isolated RNAs were determined by Nanodrop (Thermo Scientific, USA). Then, cDNA was synthesized using RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, USA). From the obtained cDNAs, a qRT-PCR reaction was set up using ACE2 and β -actin primers (QIAGEN, USA). Using SYBR™ Green PCR Master Mix (ThermoFisher Scientific, USA) and the commercially obtained primers listed in Table 2, reactions were performed in accordance with the manufacturer's instructions using a Roche Light Cycler 480 System (Roche, USA). β-actin was used as a reference gene. Each experiment was set up as three replicates.

Table 2. Primers used in qRT-PCR experiments

Primer	Source	Annealing Temperature	Product size (Bp, length)	Gene Globe ID
ACE2	NM_021804 RT² qPCR Primer Assay, QIAGEN, USA	60˚C	3519	PPH 02572A-200
TMPRSS2	NM_005656 RT² qPCR Primer Assay, QIAGEN, USA	60˚C	3212	PPH 02262C-200
β-actin	NM_001101 RT² qPCR Primer Assay, QIAGEN, USA	60˚C	1582	PPH 00073G-200

Protein Isolation and Enzyme-Linked Immunosorbent Assay (ELISA)

Protein isolation was performed according to as described by Albayrak with small modifications.[38] Cell pellets were suspended in MPER buffer (Pierce Inc., USA) and then SSB14B 1.4 mm stainless steel beads and protease inhibitor cocktail were added. After they were homogenized with Next Advance homogenizer (Bullet Blender, Next Advance, Troy, NY, USA) the samples were centrifuged at 20,000 ×g for 30 min at 4°C and the supernatant containing the proteins was taken into fresh tubes. Concentrations of protein samples were measured and calculated using the Bradford Assay (Bio-Rad, USA) using a Nano Drop ND-1000 spectrophotometer (Thermo Scientific, USA). Proteins were stored at -80°C until used in experiments.

ELISA tests were performed using 200 µg of each protein sample. The amount of ACE2 and TMPRSS2 proteins were analyzed using commercial ELISA kits (Elabscience, E-EL-H0281 and E-EL-H1418 USA) according to the manufacturer's instructions.

Each experiment was performed in three replicates. Briefly, 100 µl sample was added to each well and incubated at 37°C for 90 minutes. After the liquid was removed, 100 µl of biotinylated detection solution was added to each well and incubated at 37°C for 1 hour. After washing for three times, 100 µl of HRP conjugate was added to each well this time and incubated at 37°C for 30 minutes. After the liquid was taken out, washing was done for five times and 90 µl of substrate solution was added and incubated at 37°C for 15 minutes. Finally, 50 µl of stop solution was added and the OD at 450 nm was measured with an ELISA plate reader. The results were evaluated for further studies.

Results

The aim of the study was to determine the expression levels of the ACE2 and TMPRSS2 genes in fourteen different type of cell lines. For the investigation of transcription levels, mRNA expressions were determined by qRT-PCR analysis. In that analysis, β-actin gene was used as reference gene and the mRNA expression was calculated based on their CT values (Figure 2).

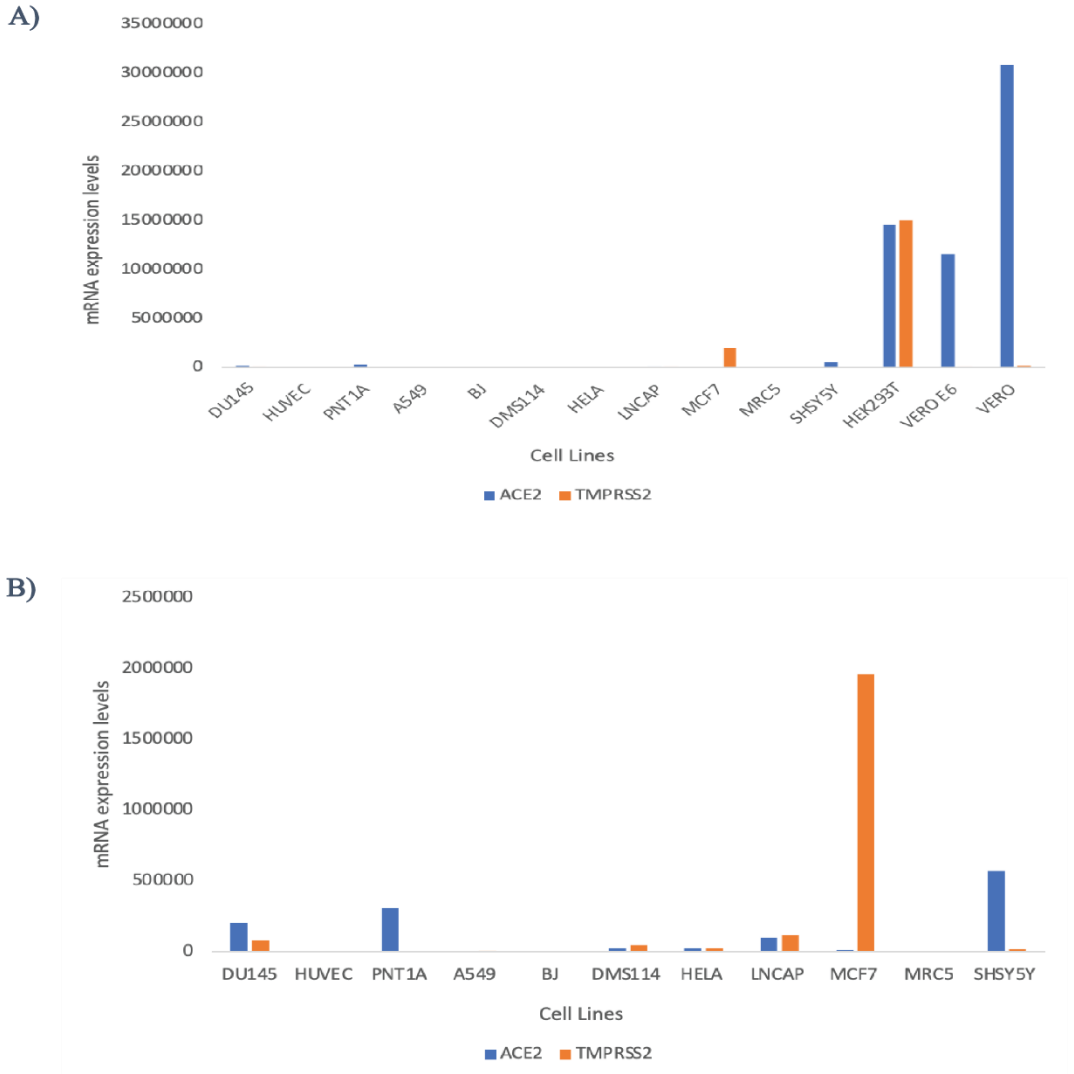

Figure 2. Bar graph of mRNA levels of cell lines A) mRNA levels of ACE2 and TMPRSS2 in 14 cell lines. B) mRNA levels of ACE2 and TMPRSS2 in 11 cell lines after Vero, Vero E6 and HEK293T were excluded) (Blue bars: ACE2, orange bars: TMPRSS2)

According to the results, there was a dramatic difference in the mRNA levels of both ACE2 and TMPRSS2 genes in VERO, HEK293T and VERO E6 cell lines, compared to the other eleven cell lines. When these fold increases were displayed in a single bar graph, other cell lines were hardly detected (Figure 2A). When these three cell lines were removed and a bar graph was generated again, the mRNA levels continued in order as SHSY5Y, PNT1A, and DU145 for ACE2 and MCF7, and LNCaP for TMPRSS2 (Figure 2B). The mRNA levels of both genes were highest in the HEK293T cell line when two genes were evaluated together.

After the mRNA levels of the genes were determined by using qRT-PCR, determination and calculation of the protein levels of ACE2 and TMPRSS2, ELISA experiments were performed afterwards protein purifications from all cell lines (Figure 3). According to Figure 3, ACE2 protein expression was highest in PNT1A cell line and MCF7, HEK293T, HELA and SHSY5Y were following in order whereas for TMPRSS2, A549 has the highest in protein expression and MCF7 and PNT1A were following.

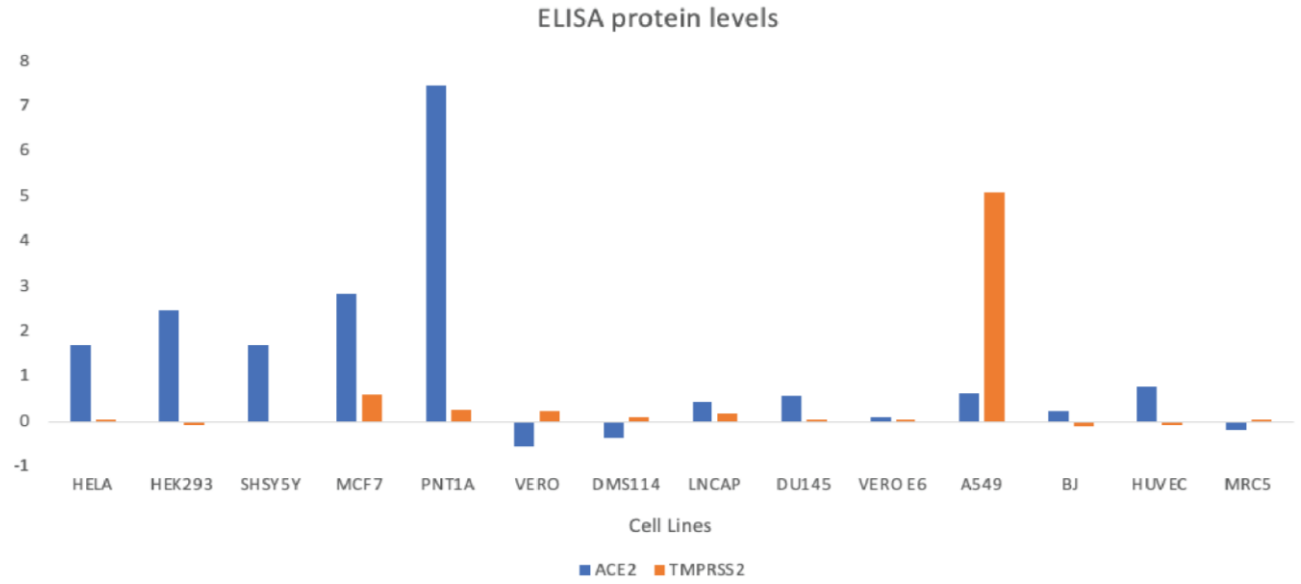

Figure 3. ACE2 and TMPRSS2 protein levels of the cell lines detected by ELISA (blue bars for ACE2 protein levels while red bars for TMPRSS2)

Since TMPRSS2 is a key enzyme in prostate cancer[39], prostate cancer cell lines were evaluated separately. As seen in figure 4, while TMPRSS2 expression was higher in LNCaP cells compared to DU145 cells, ACE2 expression was the opposite (Figure 4A). Same trend was observed for the protein level in ELISA (Figure 4B).

Discussion

With the global COVID-19 disease outbreak, researches related to the mechanism of how SARS-CoV-2 virus enters and spreads within cells has been accelerated in speed and increased in tendency. According to the findings, ACE2 and TMPRSS2 proteins estimated to have a role in the virus entrance to the cells; however, it is still a bottleneck to make conclusion from these studies[40]. These proteins function in different cellular mechanisms in healthy cells and their expression levels have been associated with diseases like hypertension, cardiac or lung injuries.[24] The studies investigating the protein expression levels are mostly in tissue samples not in cell lines. Additionally, there are some inconsistences in the expression levels of ACE2 and TMPRSS2 between different studies.[41-44] To make contribution to the literature and offer data for future *in vitro* studies, protein and mRNA levels of ACE2 and TMPRSS2 in fourteen different cell lines were investigated in this study.

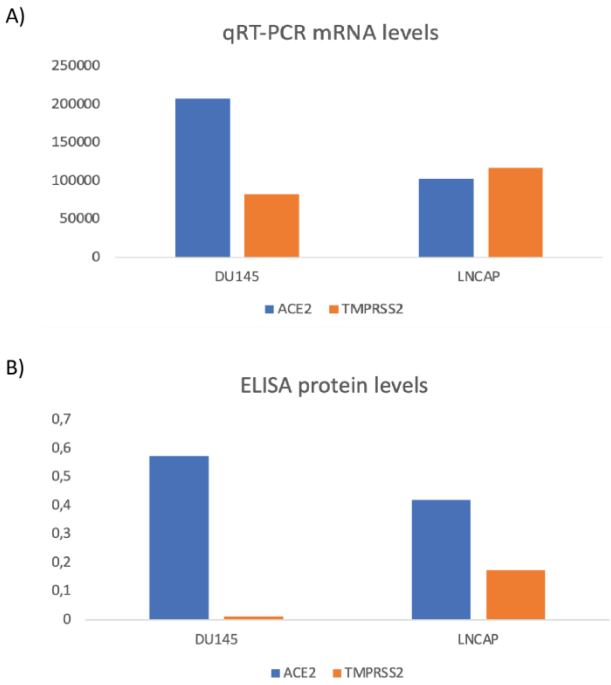

Figure 4. ACE2 and TMPRSS2 expression levels for DU145 and LNCaP cell lines A) mRNA levels detected by qRT-PCR, B) Protein levels detected by ELISA

We have demonstrated using our experimental study that how the expressions of ACE2 and depend on the cell

type. Some of the cell lines did not express one or even both of the proteins, while some others showed significant expression levels. This may be an explanation for why virulence entrance differs in different types of tissues. In COVID-19 Disease, for SARS-COV2 virus to enter the cells, ACE2 protein functions as a gate for the virus. TMPRSS2 seems to act as protease responsible for the S2 protein of the virus cleavage. However, TMPRSS2 route is not the only way for the virus to invade. Apart from the TMPRSS2, the SARS-CoV-2 fusion can be activated via cathepsin-mediated systems together with ACE2 receptor binding.[45] It can be speculated that, the expression of TMPRSS2 is not vital for virus infection however the presence of both ACE2 and TMPRSS2 at the same time may increase the pathogenicity and susceptibility of the virus infection.[46] For that reason, it is important to determine which type of cells express ACE2 or TMPRSS2 alone or together.

According to our findings, highest mRNA expression of ACE2 gene was found in Vero, Vero E6 and HEK293T cells. Vero and Vero E6 cell lines originated from the kidney tissue of a species of monkey called Cercopithecus aethiops. Those cell lines are mostly used in virus replication and investigation studies. Especially, Vero E6 is often preferred for replication of viruses because of its fast growth rate, low probability of malignancy, their sensitivity to a variety of viruses.[47,48] However, the mRNA expression of TMPRSS2 gene is significantly low in these cell lines. If mRNA levels of both proteins are expected to be higher amounts for investigations of the functions of those genes or associated mechanisms, it might not be suitable to use those cell lines for a model cell. Additionally, employing such cell lines to research diseases with human origins may not produce accurate results due to their dissimilar origin, it might be required confirmation using cell lines having human origins. In the ELISA data in Figure 3, protein expression levels of the genes in these cell lines are not found significant. Moreover, since those cell lines were originated from different species, the results of the mRNA levels of those genes do not represent the human kidney data. HEK293T cell lines may possible candidate for as represent the human kidney data, since both ACE2 and TMPRSS2 genes were expressed in roughly comparable amounts in mRNA level and at maximum level compared to other cell lines originated from human tissues. For that reason, HEK293T cells might be suitable for to investigate mechanisms related to mRNA of ACE2 and/or TMPRSS2 genes. However, TMPRSS2 is much lower in protein level than ACE2, and this discrepancy may be explained by the possibility that TMPRSS2 protein turnover is higher than that of ACE2 protein. Furthermore, since highest mRNA levels of both genes were found in cell lines originated from kidney tissues in, it can be estimated that that kidney tissue is much more susceptible for virus entrance. According to meta-analysis data of Gkogkou, it is also indicated that both ACE2 and TMPRSS2 are highly expressed in kidney tissues.[49] According to the study investigating RT-PCR expression levels of ACE2 and TMPRSS2 genes in mouse ocular and systemic tissues, kidney had the highest expression levels for both genes.[30] Our observations are consistent with the literature; therefore, it can be assumed that kidney-originating cells were among those that were most vulnerable to virus entry because of the high levels of both genes' mRNA expression.

TMPRSS2 is a frequently altered gene in prostate cancer mostly in fused form with ERG gene.[50,51] TMPRSS2 expression was significantly increased in response to androgens in cDNA microarray analysis.[25] Similarly, it was reported that androgen regulates both ACE2 and TMPRSS2 expression levels in mouse tissues and androgen levels may be targeted for alternative COVID-19 treatment.[52] In this study, in order to reveal the correlation of androgen receptors with ACE2 and TMPRSS2 expression levels, prostate cancer cell lines were evaluated separately. Besides a healthy prostate cell line PNT1A, we have used two prostate cancer cell line as LNCaP for androgen dependent[53] and DU145 for androgen independent.[54] According to our findings, which are in line with the literature, TMPRSS2 mRNA levels in the LNCaP cells were higher than those in the DU145 cells. The situation was the opposite for ACE2 mRNA levels, though. The level was higher in DU145 cell line compared to LNCaP (Figure 4). This is because there is no clear evidence that ACE2 gene expression is altered by androgen receptor. However, apart from androgen receptor expression, there might be other factors affecting ACE2 expression. In the study of Baratchian and his colleagues, it is reported that the suppression of ACE2 expression with anti-androgen drugs depended on sex differences.[55] Mjaess and his colleagues also stated that because of the androgen dependence, the risk for cardiovascular diseases or COVID-19 may increase in male patients.[56]

It is quite expected that protein expression levels might differ from mRNA levels. The amount of protein produced from an mRNA molecule varies depending on many factors such as translation rates, post-translational modifications such as alternative splicing and RNA methylations, protein damage or degradation, protein half-lives, and stability of the proteins. In addition, another reason for the lack of correlation in RNA-protein levels may be related to the fact that ACE2 protein is a membrane protein. Membrane proteins are mostly flexible and unstable. Therefore, they cause difficulties in studies such as expression, solubilization, purification, and crystallization.[57] On the other hand, in general, the obtained data from the cell lines is consistent with the data obtained from the tissues in the literature. Generally, both in the tissues of kidney, prostate and breast and the cell lines obtained from those adjacent tissues, expressions of both genes were elevated. The differences might be due to the difference between cell lines and the characteristics of the tissues.[49]

In conclusion, in light of the data we have obtained, it is thought that HEK293 cells with high levels of both genes may be a suitable option for studies to be carried out at the RNA level by using these two genes. MCF7 may be a good option for studies at the protein level. Although the

TMPRSS2 protein level in A549 cells is higher than MCF7, its usage is not recommended because the ACE2 level remains too low compared to MCF7. It would be appropriate to decide which gene is at the forefront for studies to be conducted at both the RNA and protein levels, in which both genes will be studied. We think that it may be appropriate to use HEK293 cells in studies where ACE2 will be at the forefront, and MCF7 cells in studies where TMPRSS2 will be at the forefront. Based on the literature, ACE2 and TMPRSS2 may be a gate for the entrance of coronavirus species. Therefore, the data obtained here will be a source for future studies not only for COVID-19 but also possible future coronavirus species. Additionally, ACE2 and TMPRSS2 became popular with COVID-19 pandemic, yet those genes are related to severe diseases like lung, renal or cardiac disorders. For this reason, it is important to obtain protein and mRNA levels of them in different tissues for further studies related to those diseases. This study is offering the data in which the protein and mRNA levels of ACE2 and TMPRSS2 genes in different types of cell lines for the researchers who would like to study either virus related studies like COVID-19 or the genes related diseases like cardiac, renal or lung diseases. For researchers who are interested in studying either virus-related studies like COVID-19 or gene-related disorders like cardiac, renal, or lung ailments, this study is providing data on the protein and mRNA levels of ACE2 and TMPRSS2 in various types of cell lines. It will be appropriate to support these data with further studies such as investigating protein stability, crystallography, or function to validate mRNA-protein consistency.

Compliance with Ethical Standards

Since this study was in vitro cell line study, there were no need for ethical approval.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

MGBA, SY: Study idea, hypothesis, study design; MGBA, SY, MK, GA: Material preparation, data collection and analysis; MGBA, SY: Writing the first draft of the article; GA, MK: Critical review of the article finalization and publication process.

Financial Disclosure

Financial disclosure none.

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Research Article | Araştırma Makalesi

ANXIETY AND ASSOCIATION WITH COVID-19 VACCINATION-RELATED HEADACHE SYMPTOMS

COVID-19 AŞISINDAN SONRA YAŞANAN BAŞ AĞRISI SEMPTOMLARININ KAYGI DÜZEYİ İLE İLİŞKİSİ

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Abstract

Objective: To prevent the pandemic, widespread vaccination work continues in Turkey. We aimed to determine the level of pain, headache, and anxiety among the neuropsychiatric symptoms after the vaccination was given to the healthcare workers.

Methods: Healthcare workers who have received the COVID-19 vaccine were given a questionnaire through the internet after the second dose of the vaccination. A form consisting of 34 questionnaire questions about their demographic characteristics, whether they experienced pain or headache after vaccination and the Beck Anxiety scale was to be filled.

Results: The data of 484 participants were examined in our study. 31.1% of the participants reported experiencing a headache after the vaccination. In the analysis using a single variable model, it was found that individuals with mild anxiety symptoms had a 2.6-fold increased risk of experiencing headaches. For those with moderate anxiety symptoms, the risk was 4.5 times higher, while individuals with severe anxiety symptoms faced a 7.2-fold increased risk. Additionally, the study observed that patients with a history of previous headaches had a 2-fold higher risk compared to those without such a history in the single variable model.

Conclusion: We suggest that the assessment of anxiety levels during vaccination after COVID-19 vaccination can be an important indicator in predicting the development of headaches. Further studies on this will be important in optimizing vaccination programs and ensuring social immunity.

Keywords: Anxiety, COVID-19, Headache, SARS-CoV-2, Vaccine

Öz

Amaç: Pandemiyi önlemek amacıyla Türkiye'de yaygın aşılama çalışmaları devam etmektedir. Bu çalışmada sağlık çalışanlarına aşı yapıldıktan sonra nöropsikiyatrik semptomlardan ağrı, baş ağrısı ve anksiyete düzeylerinin belirlenmesi amaçlandı.

Yöntem: COVID-19 aşısı olan sağlık çalışanlarına aşının ikinci dozundan sonra internet üzerinden anket verildi. Demografik özellikleri, aşı sonrası ağrı ya da baş ağrısı yaşayıp yaşamadıkları ve Beck Anksiyete Ölçeği ile ilgili 34 sorudan oluşan bir form doldurulması istendi.ve mikroskobik görüntüler değerlendirilmiştir**.**

Bulgular: Çalışmamızda 484 katılımcının verileri incelenmiştir. Katılımcıların %31,1'i aşılamadan sonra baş ağrısı yaşadığını bildirdi. Tek değişkenli modelde hafif kaygı belirtileri 2,6 kat, orta düzeyde kaygı belirtileri 4,5 kat ve şiddetli kaygı belirtileri 7,2 kat daha yüksek baş ağrısı riski taşıyordu. Benzer şekilde, önceden baş ağrısı olan hastaların tek değişkenli modelde olmayanlara göre 2 kat daha fazla risk taşıdığı gözlendi.

Sonuç: COVID-19 aşısı sonrası aşılama sırasındaki kaygı düzeyinin değerlendirilmesinin baş ağrısı gelişimini öngörmede önemli olduğu gözlenmiştir. Bununla ilgili ileri çalışmalar aşılama programları sonrası baş ağrısının yönetilmesi ve toplumsal bağışıklığın sağlanması açısından önemli olacaktır.Anahtar

Anahtar Kelimeler: Anksiyete, COVID-19, Baş Ağrısı, SARS-CoV-2, Aşı

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Introduction

The severe acute respiratory failure syndrome caused by SARS-CoV-2, the COVID-19 pandemic, has been on a large scale not seen since the 1918 influenza pandemic. Although the predominant clinical picture is associated with respiratory disease, neurological signs are increasingly recognized.[1]

Clinical evidence from COVID-19 patients indicates that the virus causes damage to endothelial cells in various organs, including the lungs, heart, kidneys, liver, and intestines. This multi-organ involvement sets COVID-19 apart from other viral infections such as the H1N1 influenza and SARS, which primarily affect the lungs.[2]

SARS-CoV-2, the virus that causes COVID-19, demonstrates neurotropism, meaning it has an affinity for the nervous system. This is attributed to the presence of ACE2 receptors in endothelial cells, which are also found in the brain, including glial cells and neurons. Consequently, the virus can potentially target and affect the nervous system. The neurotropic nature of COVID-19 aligns with the wide range of neurological, psychiatric, and psychological symptoms and syndromes observed in individuals throughout the course of the infection. [2,3]

Moriguchi et al. observed viral RNA in the cerebrospinal fluid of a patient with aseptic encephalitis, and Paniz-Mandolfi et al. reported the presence of SARS-CoV-2 viral particles in neuronal and capillary endothelial cells in the frontal lobe tissue in a postmortem study. Therefore, SARS-CoV-2 neuroinvasion, neuroinflammation, and impairment of the blood-brain barrier (BBB) have been suggested to be responsible for neurological symptoms. [4-6]

To prevent the pandemic, vaccination studies have gradually commenced in Turkey. Priority is accorded to healthcare workers and most of them have received the second dose of vaccination. The vaccine, administered in Turkey, is inactivated with Beta-propiolactone and contains alum adjuvant. It belongs to Sinovac and is of Chinese origin. Looking at the side effect profile, it resulted in a low side effect rate - no different from a placebo. [7-9]

A study conducted in Turkey in 2021 involving 780 healthcare workers revealed that 62.5% of them experienced at least one side effect following COVID-19 vaccination. The most frequently reported side effect was injection site pain, which was reported by 41.5% of the participants. Fatigue was experienced by 23.6% of the individuals, and headache was reported by 18.7%, making them the next most common side effects.[10]

Vaccines are successful in providing immunization, despite being inactive. Due to COVID-19's ability to affect the nervous system, cause neuroinflammation, and potentially disrupt the blood-brain barrier, it is expected that neuropsychiatric symptoms may arise following vaccination. Our objective is to assess these symptoms, particularly pain, headache, and anxiety. To achieve this, we have planned to administer a questionnaire on headache and pain, as well as an anxiety scale, to healthcare professionals after they have received the full vaccine dosage.

Methods

The study complies with the Helsinki Declaration requirements and received local ethics committee approval (Sakarya University, Ethics Committee Decision Letter No E-71522473-050.01.04-14843/122). For the survey for the assessment of pain, headache, and anxiety in healthcare professionals after the COVID-19 vaccination in 2020, the healthcare workers who completed the 2nd vaccination program and who willingly participated in the study were given a questionnaire form and Beck Anxiety Scale prepared on the internet. The vaccination program applied to healthcare workers in Turkey is in the form of two doses at a one-month interval. Our questionnaire form consisted of two parts and a total of 34 questions. In the first part, there were 24 questions, demographic data such as age, gender and duty, vaccination, and whether they experienced pain in general, and if they experienced pain, the region and severity were questioned. The pain experience location question has multiple-choice options. In the second part of the study, only patients with headaches were included. They were asked about the duration, characteristics, analgesic requirements, and severity of their headaches. Additionally, the Beck Anxiety scale was administered online as a continuation of the questionnaire. Participants who chose to take part in the survey provided informed consent. Individuals under the age of eighteen and those who did not complete the necessary data form were excluded from the study. Our study is an observational questionnaire study conducted in a cross-sectional manner.

Statistical analysis

The data were evaluated by uploading it to the computer environment via SPSS for Windows 21.0 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as mean (±) standard deviation, median (minimum-maximum), frequency distribution, and percentage. The conformity of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk Tests). To predict treatment response using defined sociodemographic and clinical data, a logistic regression model with a retrospective elimination method was applied. The statistical significance level was accepted as $p < 0.05$.

Results

In our study, the data of 484 participants were examined. It reported that 443 of its participants had completed two doses of the vaccine. The mean age of the participants was 40.1±8.9, 76.6% were women and 60.3% were working as doctors. The sociodemographic characteristics of the study group are given in Table 1.

Table 1. Sociodemographic features

Study Parameters		n (%) (n=443)
Gender	Male	103 (23.3%)
	Female	340 (76.7%)
Education	High School	4 (0.9%)
	University	252 (56.9%)
	Doctorate / Specialist Physician	187(42.2%)
Job	Doctor	267 (60.3%)
	Dentist	88 (19.9%)
	Nurse	47 (10.6%)
	Staff	20 (4.5%)
	Anesthesia Technician	12 (2.7%)
	Medical secretary	9 (2.0%)
Working place	University Hospital	136 (30.7%)
	Training and Research Hospital	118 (26.6%)
	Public Hospital	87 (19.6%)
	Freelance	31 (7.0%)
	Other Public Institutions	25 (5.6%)
	Family Health Center	24 (5.4%)
	Private Hospital	22 (5.0%)

Table 2. COVID-19 and vaccine-related data

Study Parameters		n (%)
Have you had COVID-19 before?	Yes	67 (14.9)
	No	376 (85.1)
How long has it been if you've had COVID-19?	1 month and less	5 (1.1)
	2-4 months	37 (8.4)
	5-6 months	7 (1.6)
	More than 6 months	17 (3.8)
	I did not have the disease	376 (84.9)
How long ago did you get the first dose of COVID-19 vaccine?	21-35 days	49 (11.1)
	36- 45 days	224 (50.6)
	More than 45 days	170 (38.4)
Have you had any pain after the first COVID-19 vaccine?	Yes	195 (44.0)
	No	248 (56.0)
How long ago did you get the second dose of COVID-19 vaccine?	10-20 days	323 (72.9)
	21-35 days	115 (26.0)
	36- 45 days	3 (0.7)
	More than 45 days	2 (0.5)
Did you have any pain after the second COVID-19 vaccine?	Yes	203 (45.8)
	No	240 (54.2)
Did you feel the need to use painkillers after the COVID-19 vaccine?	Yes	109 (24.6)
	No	210 (47.4)
	No Pain	124 (28.0)
Did your pain that started after the COVID-19 vaccine worry you about getting the disease?	Yes	52 (11.7)
	No	391 (88.3)
Have you applied to the health institution regarding your pain that started after the COVID-19 vaccine?	Yes	6 (1.4)
	No	437 (98.6)
In which area did the pain occur?	Vaccinetion site	140 (31.6)
	Head	138 (31.1)
	Arms	67 (15.1)
	Neck	54 (12.0)
	Chest	32 (7.2)
	Back	29 (6.5)
	Legs	23 (5.2)
	No pain	248 (56.0)

Notably, 44% of the participants (n: 195) reported any pain after the first vaccine and 45.8% (n: 203) after the second vaccine. 24.6% (n: 109) of them used painkillers due to this pain. In addition, 1.4% (n: 6) stated that they applied to a health institution after the vaccination due to pain. Table 2 shows data related to COVID-19 and vaccines.

According to the findings of our study, 31.1% of the participants reported having a headache after vaccination, and 21.0% used painkillers for the headache. When the duration of pain was questioned, the highest rate (11.1% in the whole group) reported that the pain lasted for 2-4 hours, and when they scored it out of 10, the median score was 4 (Q1:2-Q3:6). 24.2% of the participants reported that they were diagnosed with a headache-related disease before vaccination. Table 3 shows headache-related data.

Table 3. Headache data

Study Parameters		n (%)	(n:443)
Have you had a headache after the COVID-19 vaccine	Yes	138 (31.1)	138
	No	305 (68.8)	305
Have you used painkillers for your headache?	Yes	93 (21.0)	93
	No	45 (10.0)	45
	No headache after vaccination	305 (68.8)	305
How long was the headache without taking painkillers?	<2 hours	17 (3.8)	17
	2-4 hours	49 (11.1)	49
	4-24 hours	42 (9.5)	42
	24-72 hours	24 (5.4)	24
	More than 72 hours	6 (1.4)	6
	No pain	305 (68.8)	305
How was the headache severity?	Mild	16 (7.0)	16
	Moderate	75 (16.9)	75
	Severe	47 (10.6)	47
	No headache after vaccination	305 (68.8)	305
Is there a migraine, tension type or other headache previously diagnosed by a doctor?	Yes	107 (24.2)	107
	No	336 (75.8)	336

Upon the examination of the Beck Anxiety scale scores, it was observed that the median score of the participants was 5 (Q1: 2-Q3: 11). According to the classification, 20.1% (n: 89) had mild anxiety, 5.4% (n: 24) reported moderate anxiety and 2.0% (n: 9) reported severe anxiety.

The forecast the occurrence of headaches within the entire group of participants (n: 443), a model was developed using the backward elimination method. The significant variables included gender, previous COVID-19 history, previous headache-related diagnosis, and anxiety classification (Chi-square: 25.832, p: 0.001). This model explained 39% of the variance (Nagelkerke R2: 0.398) and achieved a 70% correct classification rate. In the univariable model, individuals with mild anxiety symptoms had a 2.6 times higher risk of experiencing headaches, while those with moderate anxiety symptoms had a 4.5 times higher risk, and those with severe anxiety symptoms had a 7.2 times higher risk (Table 4).

Additionally, patients with previous headaches were twice as likely to be at risk in the univariable model compared to those without.

Table 4. Multivariable Logistic regression model to predict having headache after vaccination

		Multivariable Model			
		B	**S.H.**	**p**	**OR**
Beck Anxiety Inventory	No worries (0-7)	Reference category			
	Mild Level (8-15)	0.648	0.253	0.010	1.912
	Moderate Level (16-25)	1.262	0.441	0.004	3.532
	Severe (26-35)	1.656	0.725	0.022	5.237
Having previously been diagnosed with a headache-related disease	No	Reference category			
	Yes	0.551	0.239	0.021	1.736

*In Step 1, the variables of Age, Gender, Beck Anxiety Classification, Previous COVID and Previous headache-related diagnosis were entered. Step 4 shown in the table.

Discussion

This study shows that participants who have anxiety symptoms tender to have headaches after vaccination. In addition, previous headache is important for post vaccination headache. Sekiguchi et all also showed that patients with pre-existing headaches were more likely to suffer from headaches after COVID-19 vaccination. Both migraine and non-migrainous headache groups were found to have significantly higher rates of headaches after vaccination. But they mentioned that the majority of their participants were women so caution shouldn't be missed when applying results to the general population.[11] Similarly our participants were more likely women and it is one of our study's key limitations. Göbel et all studied headache characteristics after vaccination BNT162b2 mRNA. Their results showed that this type of headache was similar to neither migraine nor tension type. If there is a pre-existing primary headache such as migraine, the hyperexcitability of trigeminovascular neurons can increase pain as the reason for the long duration and intensity of pain in patients with post-vaccine headaches. Also, post-vaccine headaches can be triggered by the immune responses of the protein. The pathomechanisms of headaches after vaccination against COVID-19 are not yet understood. [12]

Regardless of the precise mechanisms by which SARS-CoV-2 enters the central nervous system (CNS) and how sensitively it exerts its pathogenetic effects, a wide variety of neuropsychiatric symptoms have been reported in COVID-19 patients affecting both the CNS and the peripheral nervous system (PNS).[13] Early neurological symptoms include loss of sense of smell and taste, as well as body aches, headache, and myalgia. Anosmia, fever, and myalgia are considered the strongest independent predictors of positive SARS-CoV-2 tests. At the same time, the percentage of patients suffering from these complications varies widely between different studies, assessment time points, and geographic locations even though the involvement of both CNS and PNS is now well documented. [2,14]

Another fundamental aspect of SARS-CoV-2 infection in the (CNS) is the induction of high levels of systemic inflammation and disruption in the blood-brain barrier (BBB). This high inflammation promotes neuroinflammation in conditions such as sepsis, which ultimately significantly impairs brain homeostasis and leads to neuronal apoptosis. [15,16] Interestingly, in one study, the total blood lymphocyte counts were significantly lower in patients with CNS-related (eg headache, dizziness, ataxia) or muscular (eg, myalgia) symptoms. Immunological findings were in the same line in COVID-19 patients with neurological symptoms. [17] A study from Wuhan noted that 36% of the patients admitted to a hospital for SARS-CoV-2 infection had neurological features, mostly mild symptoms such as dizziness and headache, but these symptoms may be more specific neurological syndrome than a systemic disease. [18,19]

Whittaker et al. conducted a comprehensive review of existing published literature and found that headache and anosmia are frequently observed neurological symptoms associated with SARS-CoV-2. [20] In the study conducted by Mao et al. in Wuhan, neuronal complications were found at a rate of 36.4%, and headache at a rate of 13.1% [19]. Currently, world science is focused on the development of a vaccine against SARS-CoV-2. The need to develop vaccines during pandemic periods poses a major challenge to science and medicine. [21,22]

The Sinovac Biotech vaccine, used in Turkey, is based on a platform initially developed for pre-SARS-CoV-1. It involves growing the virus in Vero cells and then inactivating it using beta-propiolactone. Two versions of this inactivated vaccine, adjuvanted with alum or CpG108, have been developed. In a Phase II human trial involving 600 healthy adults (NCT04352608) aged 18-59 years, the vaccine demonstrated 90% seroconversion after the second dose, with the presence of neutralizing antibodies. Interestingly, the production method for the virus differed between the Stage I and II trials, which may have contributed to increased immunogenicity. The study, which included a placebo control group, did not observe any side effects such as headache. [7-9]

In a study in which side effects after Moderna and Pfizer-Biontech vaccinations in the USA were published,

headache was found at a rate of 22.4% and it was one of the most frequently mentioned side effects. [23] In the review made by Maury et al., it was stated that one of the most common symptoms in COVID-19 patients was a headache at a rate of 20.4%. [24]

In the BNT162b2 mRNA COVID-19 vaccine Safety and Efficacy study by Polack et al., the most frequently reported systemic events were fatigue and headache (after the second dose, 59% and 52% among young vaccines; 51% and 39% among older ones, respectively). However, fatigue and headaches have also been reported by many people taking a placebo. (After the second dose, 23% and 24%, respectively, among the young vaccines; 17% and 14% among the older ones).[25]

The most common adverse events were found to be injection site pain, headache, and fatigue following each vaccination in both age groups in the preliminary report of a randomized controlled phase 2 trial on the safety and immunogenicity of the MRNA-1273 SARS-CoV-2 vaccine. After the first vaccination, the most common adverse events were headaches in young adults 50 mg (29%) and 100 mg (25%), placebo in young, and placebo in older adults.[26]

In the first human study of Zhu et al.'s recombinant adenovirus type-5 vectored COVID-19 vaccine, the most common side effects were found to be fever, fatigue, and muscle pain, whereas the most common headache rate was at 39%. [27] In the rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine study conducted for two different forms of lyophilized and frozen in Russia, the most common side effects were stated as pain in the vaccine area, hyperthermia and headache (42%). [28] In a study in which symptoms were evaluated after vaccination in India, the headache was found at a rate of 28% in the population where different types of vaccines were used. [29]

In our study, headache was observed with a rate of 31.1%. Looking at the pain areas, it was seen that the most common site of pain was the arm where the vaccine was administered and the headache. In a review by Tolebeyan et al., it was stated that headache is one of the most common neurological manifestations in SARS-CoV-2 patients and its prevalence varies between 6-71%. One meta-analysis noted that 12.1% of patients with SARS-CoV-2 reported headaches or dizziness. In another meta-analysis of 38 studies of patients with SARS-CoV-2 infection, the prevalence of headache was reported in 15.4% of all patients. [30,31] The consistency of headache prevalence following vaccination was observed across multiple studies. It would have been valuable to compare the prevalence of headaches after different vaccines, such as Pfizer and Janssen. However, at the time of our study, only the Sinovac vaccine was available in Turkey.

While the efficacy of a vaccine primarily relies on factors related to the vaccine itself, it is crucial to consider the individual characteristics of the vaccinated person. Psychological, social, and behavioural factors can have a notable impact on the immune response triggered by the vaccine. Glaser et al. conducted studies suggesting that the response to vaccination might be influenced by conditions such as depressive disorder or stress anxiety. Participants exhibiting higher levels of depressive symptoms were found to have elevated levels of IL-6 both before and following vaccination compared to those reporting fewer symptoms. They stated that humoral or cellular immunity may change with stress levels after vaccination. [32-34] In their review of the effects of stress on antibody response by Cohen et al., [35] in contrast to the relative lack of evidence for the primary immune response, promising evidence was found for an association between stress and secondary immune response. A lower secondary antibody response was found among patients with chronically high-stress levels. This situation was more pronounced in the elderly. Furthermore, it was observed that individuals who reported acute stress or negative affect showed a diminished secondary immune response. However, this association was specifically observed in studies measuring secretory immunoglobulin A (sIgA) antibodies, where psychological factors and antibody levels were closely linked over time.

In a study by Szmyd et al., it was stated that anxiety about the side effects of vaccination such as headache and depressive symptoms decreased the desire for vaccination in healthcare workers.[36] In addition, they reported that there was a significant relationship between concerns before vaccination and post-vaccination side effects and that the side effects increased.[36] In a study by Zarobkiewicz et al., healthcare workers were found to have significantly less anxiety about vaccination. It has been suggested that this may be due to more knowledge and realization in this field acquired during the training process. However, healthcare professionals also reported concerns about short-term side effects such as fever or malaise. [37] Therefore, this anxiety situation will increase the possibility of a headache that may occur after vaccination. In our study, in addition to the above studies, we found that severe anxiety increased the probability of a headache by 7.2 times, moderate anxiety increased that probability by 4.5 and mild anxiety by 2.6 times in predicting people with post-vaccination headaches.

Our study had several limitations. Firstly, we did not collect data on past medical histories, such as alcohol or smoking habits, and comorbidities like Diabetes Mellitus or Hypertension. Additionally, the type of headache experienced before vaccination and the type of pain after vaccination could have provided valuable information, but we were unable to categorize the headaches as participants self-reported their pain without evaluation by a clinician. Moreover, the majority of our participants were women, and it is known that women are more prone to anxiety disorders, which could have influenced our findings. Another limitation is that we only included participants who had completed the second dose of the Sinovac vaccine, and we did not compare the first and second doses. Furthermore, at the time of our study, only the Sinovac vaccine was available in Turkey, so we were unable to compare the effects of different vaccines. We

also did not analyse or correlate pain in other parts of the body with headaches and anxiety. These limitations should be considered when interpreting our findings.

In conclusion, our study suggests that assessing anxiety levels during COVID-19 vaccination can be an important indicator for predicting the development of headaches. Therefore, providing information about headaches and addressing vaccination concerns may help prevent neuropsychiatric symptoms associated with vaccination. Neuropsychiatric manifestations potentially caused by vaccination can encompass a wide range of serious conditions. Headaches can also be influenced by subjective factors. Post-vaccine headaches following COVID-19 vaccination may represent a distinct headache type, and its characteristics will be important for classification. Diagnostic criteria should be carefully defined. Anxiety could act as a trigger or comorbidity and may vary depending on the vaccine type.

There is a need for more extensive research on post-vaccine headaches and anxiety levels. Further studies investigating neuropsychiatric symptoms associated with COVID-19 vaccination are crucial for optimizing vaccination programs and ensuring community immunity.

Compliance with Ethical Standards

The study complies with the Helsinki Declaration requirements and received local ethics committee approval (Sakarya University, Ethics Committee Decision Letter No E-71522473-050.01.04-14843/122).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

Authors contributed equally to this work.

Financial Disclosure

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Araştırma Makalesi | Research Article

KISA BACAK ATEL FAALİYET MALİYETİNİN ZAMAN SÜRÜCÜLÜ FAALİYET TABANLI MALİYETLEME İLE HESAPLANMASI

CALCULATION OF SHORT LEG SPLINT ACTIVITY COST WITH TIME DRIVEN ACTIVITY BASED COSTING

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ÖZ

Amaç: Sağlık kurumları, optimum maliyetle, zamanında, kaliteli ve sürdürülebilir sağlık hizmeti sunmayı amaçlamaktadır. Geri ödeme sistemleri de Sağlık Uygulama Tebliğ (SUT)'inde listelenen sağlık hizmet fiyatlarını doğru tespit etmeyi amaçlamaktadır.

Doğru hesaplanan sağlık hizmetleri fiyatları ve sağlık hizmeti maliyetleri ile olumsuz sapmaların önüne geçilerek yönetilebilir bir sistem kurulabilir. Bu çalışmanın amacı sağlık hizmetlerinin maliyetini güncel bir yaklaşım olan zaman sürücülü faaliyet tabanlı maliyetleme (ZSFTM) yöntemi ile hesaplayan bir model ortaya koymaktır.

Yöntem: İkinci basamak ilçe devlet hastanesi acil servisinde, kısa bacak atel sağlık hizmetinin maliyeti ZSFTM yöntemi ile hesaplanmıştır. Araştırma 2020 yılını kapsayan retrospektif bir vaka çalışmasıdır. Sağlık hizmetlerinin maliyetlerinin, SUT'ta açıklanan fiyatı ile karşılaştırma yapılabilmesi için hastanede gerçekleştirilen tüm giderler hesaplamaya dahil edilmiştir.

Bulgular: Kısa bacak atel faaliyetinin, direkt ilk madde ve malzeme birim maliyeti 43.68 TL, faaliyet maliyeti 61,40 TL, toplam birim maliyeti ise 105,08 TL olarak hesaplanmıştır. 2020 yılında SUT'da kısa bacak atel faaliyeti liste fiyatı ortalama olarak birim başına 28,9 TL'tir. Çalışmada faaliyet maliyeti 61,40 TL olarak hesaplanmıştır. Çalışmaya göre, hastane kısa bacak atel faaliyetinden birim başına 32,5 TL zarar etmektedir.

Sonuç: Çalışmaya göre, hastane kısa bacak atel faaliyetinden zarar etmektedir. ZSFTM yöntemi, sağlık hizmeti maliyetlerini, güvenilir, doğru ve kolay hesaplayarak, sağlık hizmetlerinin kaliteli, zamanında ve sürdürülebilir olarak sunulmasını olanaklı hale getirdiği tespit edilmiştir.

Sağlık hizmetlerinin maliyeti tek tek bu yöntem ile hesaplanarak, hangi faaliyetlerden kar, hangi faaliyetlerden zarar ettiği tespit edilerek gerekli önemler alınabilir.

Anahtar Kelimeler: Sağlık hizmetleri, zaman sürücülü faaliyet

ABSTRACT

Objective: Health institutions aim to provide timely, quality and sustainable health services at optimum cost. Reimbursement systems also aim to accurately determine the health service prices listed in the Health Implementation Communique (HIC). A manageable system can be established with correctly calculated health care costs. The aim of this study is to present a model that calculates the cost of health services with the time driven activity based costing (TDABC) method.

Methods: The cost of the short leg splint in the emergency department of the second level state hospital was calculated by the TDABC method. The research is a retrospective case study covering the year 2020. In order to compare the costs of health services with the price announced in the HIC, all expenses incurred in the hospital are included in the calculation.

Results: direct material cost of the short leg splint was calculated as 43.68 TL, the activity cost as 61.40 TL and the total unit cost as 105.08 TL. In 2020, the list price of short leg splint activity in HIC is 28.9 TL on average.. According to the study, the hospital loses 32.5 TL per unit from the short leg splint activity.

Conclusion: According to the study, the hospital suffers from short leg splint activity. It has been determined that the TDABC method makes it possible to provide quality, timely and sustainable health services by calculating health care costs in a reliable, accurate and easy way. Correct management decisions can be made with correctly calculated costs.

Keywords: Healthcare, time driven activity based costing, strategic cost management

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Giriş

Nüfusun ve ortalama yaşam süresinin artması, yeni teknolojiler ile yeni tedavi yöntemlerinin gelişmesi sağlık harcamalarını her geçen gün arttırmaktadır.[1,2] TÜİK 2021 yılı sağlık istatistiklerine göre, Türkiye'de toplam sağlık harcaması 2020 yılına göre %41,6 artmıştır. Toplam sağlık harcamalarının devlet payı %79,2 özel sektörün payı %20,8 dir. Sağlık harcamaları içeriğindeki yatırımlar ise bir önceki yıla göre %36,4 artmıştır. Sağlık sunucularına yapılan sağlık harcamaları incelendiğinde ise ilk sırayı %49,5 oran ile hastaneler almıştır. Kişi başına düşen sağlık harcamaları ise 2021 yılında bir önceki yıla göre %40,3 oranında artmıştır.[3] Kıt kaynakların olduğu bir ortamda sağlık hizmetlerine olan talebin sürekli artması, sağlık hizmeti arzının etkin bir şekilde sürdürülebilirliği için maliyet yönetiminin önemi artırmaktadır.[4] Sağlık kurumları, hasta kişilere veya hasta gruplarına sağlık hizmeti sağlayan, yönetim kurulu, yönetici ve uzman kişilerden oluşan idari bir yapıdır.[5] Dünya da olduğu gibi ülkemizde de sağlık kurumları yöneticileri en yüksek kalitede hizmeti minimum maliyetle sunmaya çalışmaktadır. Bu amacı gerçekleştirebilmeleri için maliyetleri etkin bir şekilde yönetebilmeleri gerekmektedir.[6] Sağlık hizmetlerinin maliyetini hesaplamak, sağlık hizmetlerinin özelliklerinden dolayı zor ve karmaşıktır. Sağlık hizmetlerinin maliyetinin hesaplanmasında iyi bir maliyet modeli tercih edilir ise, kıt kaynaklar etkin ve verimli bir şekilde yönetilebilir, maliyet kontrolü sağlanabilir ve harcama yükü azaltılabilir.[7] Maliyet hesaplanma yöntemleri ise üretim şekillerindeki değişikliklerden etkilenerek zaman içinde farklılıklar göstermiştir.[8] Sağlık hizmeti sunan kurumların sundukları hizmetlerin maliyetlerinin hesaplanması ve değerlendirilmesi, yöneticilerin aldıkları kararları desteklenmesi iyi bir maliyet muhasebesi sistemi ile mümkün olmaktadır.[9]

Doğru ölçülemeyen bir maliyetleme ile sürecin doğru yönetilememesi de kaçınılmazdır. Sağlık sisteminin diğer bir parçası olan geri ödeme sistemlerinin de etkin bir şekilde işleyebilmesi ve sürdürülebilir olması için hizmet başı maliyetlerin doğru hesaplanması gerekmektedir. Aksi takdirde geri ödeme sistemleri, bazı hizmetlere gereğinden fazla ödeme yaparken bazı hizmetlere ise olması gerekenden daha az ödeme yaparak yanlış kararlar alınmasına neden olabilir. Bu durum ise sistemin sürdürülebilirliğini olumsuz yönde etkileyecektir.[10] Finansal çıktılardan faydalanarak maliyetlerin hesaplanabilmesi için öncelikle maliyetlerin maliyet merkezlerine uygun bir şekilde tahsis edilmesi, sonrasında ise maliyet merkezlerindeki hizmetlerin birim maliyetlerinin doğru bir şekilde hesaplanması gerekmektedir.[11] Ancak sağlık hizmetlerinin maliyetini doğru bir şekilde hesaplamak, sağlık hizmeti sunumunun karmaşık bir yapıda olması sebebi ile zordur. Sağlık hizmetinin içeriğinin farklı nitelikteki personel, makine, teçhizat, ekipman ve malzeme içermesi sebebi ile zor ve karmaşık bir süreçtir.[10]

Çalışmanın amacı, zor ve karmaşık bir süreç olan sağlık hizmetlerinde maliyetleme sürecini kolay yönetebilmek amacıyla zaman sürücülü faaliyet tabanlı maliyetleme yönteminin uygulanabilirliğini ortaya koymaktır. Bu amaçla çalışmada kısa bacak atel sağlık hizmeti maliyetinin hesaplanması için ZSFTM model önerisi yapılmıştır.

Literatür Araştırması ve Kavramsal Çerçeve

Bu başlık altında, stratejik maliyet yönetimi aracı olan, faaliyet tabanlı maliyetleme (FTM) ve FTM yönteminin günümüzde uygulama alanını genişletme amacıyla ortaya atılan ZSFTM yöntemi hakkında bilgi verilmiştir. Ayrıca, sağlık kurumlarında ZSFTM konusunda yapılmış bazı çalışmalara yer verilmiştir.

Stratejik maliyet yönetimi, işletmelerin mevcut durumlarını sürekli geliştirirken maliyetlerini de düşürmek amacıyla yönetim sürecinde, maliyet yönetim tekniklerini dikkate almasıdır.[12] Stratejik maliyet yönetimi işletmelerin stratejisini de dikkate alarak, işletmelere maliyet yönetimi sağlamaktadır.[13] Stratejik maliyet yönetiminin bir aracı olan FTM yöntemi, Cooper ve Kaplan tarafından, 1980'lerin ortalarında geleneksel maliyetleme yöntemlerine alternatif olarak ortaya atılmıştır.[14] FTM, bireysel faaliyetleri temel maliyet nesneleri olarak tanımlayarak bir maliyetlendirme sistemini geliştirir.[15] 1990'ların başında FTM geleneksel maliyetlemeye göre daha doğru sonuçlar verdiğinden dolayı kullanımı yaygınlaştı.[16] FTM, geleneksel maliyetlemeye göre daha doğru sonuçlar verse de , artan üretim miktarları ve ürün çeşitliği ile FTM modeli için bilgilerin işlenmesi zaman alıcı aynı zamanda da maliyetli bir işlem olmaya başlamıştır. Ayrıca FTM modeli atıl kalan kapasitenin yönetilmesine de olanak sağlamamaktadır.[17]

Zaman alan ve maliyetli bir süreç olmaya başlayan FTM yöntemine alternatif olarak ZSFTM modeli Kaplan ve Anderson tarafından önerilmiştir.[16] ZSFTM, bir süreçte ihtiyaç duyulan, ekipman, insan kaynağı gibi her bir kaynağın gerektirdiği zamanı ve zaman birimi başına maliyetini tahmin eder. Doğru bir şekilde giderleri ölçmek ve maliyet hesaplamalarının zorluklarının üstesinden gelebilmek için yenilikçi bir modeldir.[18]

ZSFTM modelinde ilk olarak faaliyet merkezlerine ait giderler faaliyet merkezlerine atanır. Faaliyet merkezlerinde ilgili giderler toplandıktan sonra, ilgili faaliyet merkezinde çalışan insan kaynağı ve cihaz kaynağı kapasite süreleri hesaplanır. Faaliyet merkezi gideri ile ilgili merkez için hesaplanan kaynak kapasite süresi bölünerek kapasite maliyet oranı tespit edilir. Tespit edilen kapasite maliyet oranı maliyet objesinin üretilmesi için gerekli olan süre ile çarpılmak suretiyle, maliyet objesinin maliyeti hesaplanır.[17]

Sağlık kurumlarında stratejik maliyet yönetiminin uygulanabilirliği konusunda yapılan çalışmaların bazıları şöyledir;

Yaman[19], Özen [20], Karakullukçu [21], Çarıkçı ve Acar [22], Çil Koçyiğit ve ark. [23], Erli [24], stratejik maliyet yönetiminin hastanelerde uygulanabilirliği değerlendirilmiştir. Sağlık kurumlarında stratejik maliyet yönetiminin uygulanabilir olduğu sonucuna varmışlardır. Bekçi ve Özal[25], ise sağlık kurumlarında stratejik maliyet yönetiminin uygulanamaz olduğu sonucuna varmıştır.

Sağlık kurumlarında, ZSFTM yönteminin uygulanmasına yönelik yapılan çalışmalardan bazıları şöyledir;
Ting ve ark.[26], pediatrik yeşil dal kırıklarının tedavi maliyeti, Anzai ve ark.[27], karın ve pelvis bilgisayarlı tomografi faaliyet maliyeti, Tseng ve ark.[28] fatura ve sigorta ile ilgili olan faaliyetlerin maliyeti, Shankar ve ark.[29], acil servise başvuran karın ağrılı hastaların maliyeti, Kaçak (2021)[8], bir hastanenin yoğun bakım bölümünde yatan hasta maliyeti ölçümünde, ZSFTM yöntemini kullanmıştır. Yun ve ark.[30], acil serviste mevcut maliyetleme yöntemleri ve ZSFTM yöntemi kıyaslamıştır. Berthelot ve ark.[31], acil serviste bakım maliyetleri geleneksel ve ZSFTM yöntemi ile kıyaslamıştır. Çalışmalarda geleneksel maliyet hesaplama yönteminin kesin ve güvenilir olmadığı, ZSFTM yönteminin atıl kapasiteyi dikkate alan ve kolay uygulanabilen bir yöntem olduğunu vurgulamıştır. Deal ve ark.[33], acil serviste yaptıkları çalışmada ZSFTM yönteminin faydalarını vurgulamışlarıdır.

Yöntem

Çalışmanın uygulaması Sağlık Bakanlığı'na bağlı ikinci basamak bir devlet hastanesinin acil servis departmanının cerrahi müdahale bölümünde gerçekleştirilmiştir. Çalışmanın amacı sağlık hizmeti sunan kurumların ve geri ödeme sistemlerinin alacağı kararları kolaylaştırmak, etkili bir yönetim için hizmet başı maliyetlerin ZSFTM yöntemi ile hesaplanabilirliğini bir model ile ortaya koymaktır.
Acil servis departmanında, cerrahi müdahale bölümünde gerçekleştirilen kısa bacak (diz altı) atel faaliyet maliyetinin hesaplanmasında retrospektif bir vaka çalışması gerçekleştirildi. Modeli ortaya koyarken faydalanılan veriler 2020 yılına aittir. 2020 yılında kısa bacak atel sağlık hizmetini gerçekleştirmek için gerekli olan faaliyetler, kaynaklar ve sarf malzemeler tespit edildi. Veriler, gerçek değerlere yakın olarak simüle edildi. Sağlık hizmetlerinin maliyetlerinin, Sağlık Uygulamaları Tebliği'nde açıklanan fiyatı ile karşılaştırma yapılanabilmesi için destek faaliyetlerin ve ikincil faaliyetlerin maliyetleri de dikkate alınmıştır.
Faaliyet kaynaklarının tespit edilmesi, zaman denklemlerinin oluşturulması, süreç haritalarının oluşturulması gibi tüm maliyetleme sürecinde doğrudan gözlem yapılmakla birlikte, hastanenin veri kayıtlarından ve il sağlık müdürlüğü istatistik kayıtlarından faydalanılmıştır.
Çalışmanın yapıldığı hastanenin acil servis departmanının cerrahi müdahale bölümü, 18 m^2'lik bir alana sahiptir. Haftada 7 gün 24 saat hizmet vermektedir. 24 saatlik zaman diliminde, 2 yardımcı sağlık personeli (YSP), 1 hekim, 1 tıbbi sekreter çalışmaktadır. Bir ayda toplam 3 hekim, 6 YSP, 3 tıbbi sekreter çalışmaktadır. Yılda yaklaşık 1.500 adet kısa bacak atel sağlık hizmeti gerçekleştirilmektedir. Cerrahi müdahale bölümünde, demirbaş olarak, sedye, tepe lambası, ilaç dağıtım aracı, ilaç dolabı, bilgisayar kasası ve monitörü, barkod ve lazerli yazıcı, çalışma koltuğu ve taburesi bulunmaktadır. Acil servis departmanı, cerrahi müdahale bölümünde gerçekleştirilen kısa bacak atel hizmetinin maliyetini hesaplamak için seçilen ZSFTM yönteminin uygulanmasında, Kaplan ve Porter'in[10] yazdığı, "Sağlıkta Maliyet Krizi Nasıl Çözülür?" isimli makalesinde önerdiği modelin adımları dikkate alınmıştır. Önerilen adımlar şöyledir;
Adım 1: Maliyeti hesaplanacak sağlık hizmetinin tespit edilmesi
Adım 2: Sağlık hizmet sunumunun değer zincirinin tanımlanması
Adım 3: Sağlık hizmetinin süreç haritasının oluşturulması ve her bir süreç için zaman tahminlerinin hesaplanması
Adım 4: Kaynak maliyetinin tespit edilmesi
Adım 5: Kaynağın kapasite ve kapasite maliyet oranlarının tespit edilmesi
Adım 6: Sağlık hizmetinin toplam faaliyet maliyetinin tespit edilmesi

Bulgular

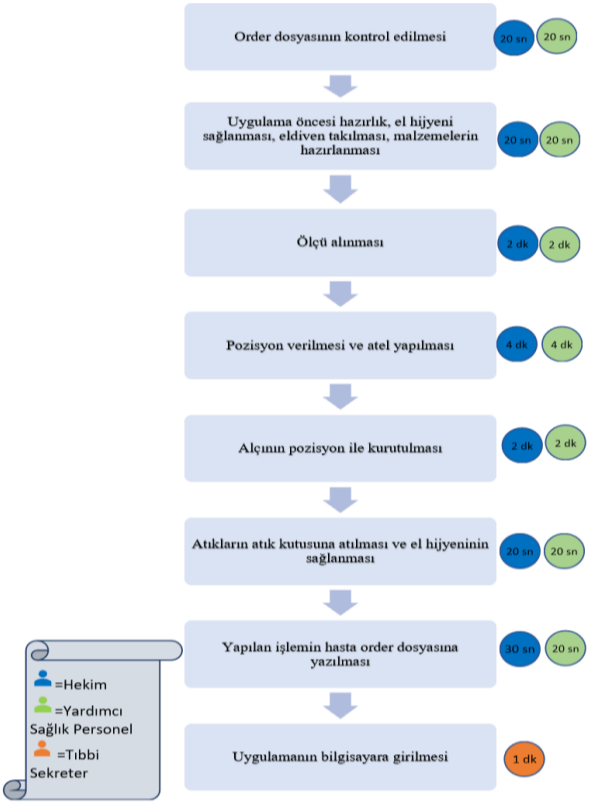
Adım 1: Maliyeti Hesaplanacak Sağlık Hizmetinin Tespit Edilmesi
Maliyeti hesaplanacak sağlık hizmeti, acil servis departmanında cerrahi müdahale bölümünde gerçekleştirilen "kısa bacak (diz altı) atel" hizmeti olarak seçilmiştir. Kısa bacak atel, ayak bileği, lateral malleol, medial malleol, posterior malleol, ayak karpal kemikleri ve metatarsal seviyelerinde olan yaralanmalarında kullanılmaktadır. Metatarsal bir yaralanma varsa atel, parmak ucundan baldıra kadar uzanır. Metatarsal bir yaralanma değilse atel, metatars distal ucundan baldır bitimine kadar uzanır.

Adım 2: Sağlık Hizmet Sunumunun Değer Zincirinin Tanımlanması
Faaliyetlerin sınıflandırılmasında Baker (1998:35)'in [34] sağlık kurumlarında önerdiği yapı dikkate alınmıştır. Baker, sağlık kurumlarında faaliyetleri birincil faaliyetler, ikincil faaliyetler ve destek faaliyetler olmak üzere üç bölümde kategorize edilebileceğini ifade etmiştir.
Birincil faaliyetler, icra edilmesi için hastanın da olması gereken hasta bakım faaliyetleridir. Hasta ile doğrudan teması gerektirmektedir. İkincil faaliyetler, yine hasta bakımı ile alakalı olan fakat icrası için hasta ile temas gerektirmeyen faaliyetlerdir. Destek faaliyetler ise hasta bakımı ile alakalı olmayan hasta bakım faaliyetlerini destekler nitelikte olan faaliyetlerdir.
Uygulama kapsamında acil servis departmanın cerrahi müdahale bölümünde sunulan kısa bacak atel hizmeti ele alınmıştır. Kısa bacak atel sağlık hizmeti bakım faaliyet sunumun değer zinciri göz önüne alındığında faaliyetler şöyle kategorize edilmiştir;

- Birincil Faaliyet: Kısa Bacak Atel Hizmet Faaliyeti
- İkincil Faaliyet: Veri Kayıt
- Destek Faaliyetler; Acil Denetim, Acil Temizlik, Genel Yönetim, Yemekhane, Özlük, Mutemetlik, Bilgi İşlem.

Adım 3: Sağlık Hizmetinin Süreç Haritasının Oluşturulması ve Her Bir Süreç İçin Zaman Tahminlerinin Hesaplanması

Şekil 1'de kısa bacak atel hizmet sunumunun yerine getirilmesi için gerekli faaliyet ve alt faaliyetleri gösteren süreç haritası gösterilmektedir.



Şekil 1. Kısa Bacak Atel (Diz Altı) Faaliyet Süreci.

Kısa bacak atel sağlık hizmeti sunum süreci; ilk olarak faaliyeti gerçekleştirecek olan personel order dosyasını kontrol eder. Uygulama öncesi el hijyeni sağlanır ve eldiven takılır. İhtiyaç duyulan malzemeler hazırlanır. Hastaya uygun pozisyon verilir. Yüzüstü yatırılır. Ayak bileği 90 derece konumuna getirilir. Uygun ölçü alınır. Alçı altı pamuk sarılır. Alçı sargısı bir kovada ıslatılarak alçı altı pamuk üzerine sarılır. Sargı bezi ile sabitlenir. Ayağa uygun pozisyon verilir. Ayak bileği 90 derecede kuruması beklenir. Kullanılan sarf malzemeler atık kutusuna atılır. El hijyeni sağlanır. Uygulama hizmeti gerçekleştiren personel tarafından order dosyasına işlenir, tıbbi sekreter tarafından bilgisayara girilir.

Tablo 1'de kısa bacak atel sağlık hizmet sunumu için ilgili personelin (insan kaynağının) harcadıkları süre gösterilmektedir. Hekim 9 dk 30 sn (570 sn), YSP, 9 dk 30 sn (570 sn), tıbbi sekreter ise 1 dk (60 sn) harcamaktadır.

Tablo 1. Kısa Bacak (Diz Altı) Atel Sağlık Hizmet Sunumunun Süreleri

İnsan Kaynağı	Hekim	YSP	Tıbbi Sekreter
Süre (dk/br)	9 dakika 30 sn	9 dakika 30 sn	1 dk
Süre (sn/br)	570 sn	570 sn	60 sn

Adım 4: Cerrahi Müdahale Bölümü Kaynak Maliyetinin Tespit Edilmesi

Cerrahi müdahale bölümüne ikinci dağıtım ile yüklenen hastane giderleri tutarları ve her bir gider kalemi için uygun dağıtım ölçüsü Tablo 2'de gösterilmiştir. Cerrahi müdahale bölümünün ikinci dağıtım sonrası toplam gideri 3.045.558,85 TL/Yıl olarak hesaplanmıştır.

Adım 5: Kaynağın Kapasitesinin ve Kapasite Maliyet Oranlarının Tespit Edilmesi

Acil servis, cerrahi müdahale bölümünde faaliyette bulunan insan kaynağının (hekim, YSP, tıbbi sekreter) kapasitesinin ve kaynak maliyetinin tespit edilerek, kaynak maliyetinin kaynak kapasitesine bölünmesi suretiyle kapasite maliyet oranı hesaplanmıştır.

Tablo 3'te dağıtım ölçüleri olarak belirlenen, personel sayısı, personelin kullandığı alanın metrekare ölçüsü, personel grubuna ait bilgisayar, telefon ve ampul sayısı, bilgisayar ve ampullerin yıllık olarak tükettiği enerji KW ölçüsü ile gösterilmiştir.

Cerrahi müdahale bölümü toplam kaynak gideri 3.045.558,85 TL/Yıl olarak hesaplanmıştır. Hekim gideri toplam, 855.585,28 TL/Yıl, YSP gideri 1.530.209,83 TL/Yıl, tıbbi sekreter gideri 659.763,74 TL/Yıl, olarak hesaplanmıştır. Kaynak giderlerinin kaynak gruplarına ataması Tablo 4'te gösterilmiştir.

Acil servis 365 gün 24 saat hizmet vermektedir. Cerrahi müdahale bölümünde 1 hekim, 2 YSP ve 1 tıbbi sekreter 365 gün 24 saat mesai çalışması yapmaktadır. Aylık ise 3 hekim, 6 hemşire, 3 tıbbi sekreter bu döngüyü tamamlamaktadır. Her bir çalışan için günlük çalışma süresinden zorunlu duraksamalar (mola ve dinlenme) düşüldükten sonra teorik kapasite hesaplanmıştır. İnsan kaynağının pratik kapasitesi ve kapasite maliyet oranı hesaplanması, Tablo 5'de gösterilmektedir.

Hekim pratik kapasitesi, 15.689.700 sn/yıl, YSP, pratik kapasitesi 31.379.400 sn/yıl, tıbbi sekreter pratik kapasitesi 15.689.700 sn/yıl olarak gerçekleşmiştir. Personellere atanan maliyetler, personellerin pratik kapasitelerine bölünmesiyle hesaplanan kapasite maliyet oranı, hekim için 0,0545 TL/sn ((855.585,28 TL/Yıl)/(15.689.700 sn/yıl)), YSP için 0,0488 TL/sn, tıbbi sekreter için ise 0,0421 TL/sn olarak hesaplanmıştır.

Adım 6: Sağlık Hizmetinin Toplam Maliyetinin Tespit Edilmesi

Adım 3'te kısa bacak atel sağlık hizmetinin süreç haritası oluşturarak her bir süreç için zaman ölçümleri tespit edilmişti. Tablo 1'de ise her bir insan kaynağının kısa bacak atel sağlık hizmeti için harcadığı süre gösterilmişti. Tablo 5'te gösterilen insan kaynaklarının kapasite maliyet oranı ile, insan kaynaklarının kısa bacak atel sağlık hizmeti için harcadıkları süreler çarpılmak sureti ile kısa bacak atel sağlık hizmetinin faaliyet maliyeti hesaplanmıştır.

Hekim ;0,0545 (TL/Sn)*570 (Sn/Br)=31,08(TL/Br)
YSP ;0,0488(TL/Sn)*570(Sn/Br)=27,79(TL/Br)
Tıbbi Sekreter ;0,0421(TL/Sn)*60(Sn/Br)=2,52(TL/Br)

Kısa bacak atel sağlık hizmeti toplam faaliyet maliyeti ise 31,08(TL/Br)+27,79(TL/Br)+2,52(TL/Br=61,40(TL/Br) olarak hesaplanmıştır. Kısa bacak atel sağlık hizmetinde

kullanılan ilk madde ve malzemeler hastadan hastaya değişmektedir. Uzman görüşüne göre ortalama olarak tespit edilen direkt ilk madde ve malzemeler ve giderleri Tablo 6'da gösterilmiştir.

Hesaplanan faaliyet birim genel imalat maliyeti 61,40 TL/adet dir. Hesaplanan birim direkt ilk madde ve malzeme maliyet 43,68 TL dir. Toplam birim maliyet ise 105,08 TL/adet olarak hesaplanmıştır. 2020 yılında hastane de 1.162 adet kısa bacak atel sağlık hizmeti sunulmuştur. Yıllık toplam maliyet ise 122.102,96 TL/Yıl olarak gerçekleşmiştir. Kısa Bacak Atel Sağlık Hizmetinin Toplam Maliyeti Tablo 7'de gösterilmiştir.

Tablo 2. Cerrahi Müdahale Kaynak Giderleri ve Kaynak Dağıtım Ölçüleri

Gider Türleri	Tutar	Dağıtım Ölçüsü
Hekim Maaş Ücret ve Ekleri	278036,08	İlgili Personel
Hekim Sabit Döner ve Ekleri	107539,53	İlgili Personel
Hekim Sabit Dışı Döner ve Ekleri	89181,27	İlgili Personel
Hekim Nöbet Ücreti Ekleri	17885,07	İlgili Personel
YSP Maaş Ücret ve Ekleri	417054,12	İlgili Personel
YSP Sabit Döner ve Ekleri	161309,29	İlgili Personel
YSP Sabit Dışı Döner ve Ekleri	133771,91	İlgili Personel
YSP Nöbet Ücreti Ekleri	41538,63	İlgili Personel
Tıbbi Sekreter Maaş Ücret ve Ekleri	186204,54	İlgili Personel
Tıbbi Sekreter Sabit Döner ve Ekleri	48667,54	İlgili Personel
Tıbbi Sekreter Sabit Dışı Döner ve Ekleri	6118,81	İlgili Personel
Tıbbi Sekreter Nöbet Ücreti Ekleri	27893,89	İlgili Personel
Kırtasiye	2816,97	Personel Sayısı
Demirbaş Amortismanı	1857,68	Personel Sayısı
Aydınlatma Elektrik Gideri	2500,06	Ampul Kw
Bilgisayarların Tükettiği Elektrik Gideri	8952,58	Bilgisayar Kw
Bina Bakım Onarım Gideri	120,49	m^2
Isınma Gideri	1167,69	m^2
Su Gideri	286,06	m^2
Güvenlik Gideri	36796,62	Personel Sayısı
İlaçlama, Dezenfeksiyon Gideri	79,17	m^2
Temizlik Malzemesi Gideri	815,15	m^2
Haberleşme Gideri	651,78	Telefon Sayısı
Diğer Müşavir Firma Gideri	89,20	Personel Sayısı
Lisans Belge Düzenleme Hizmet Alımı	255,20	Personel Sayısı
Bilgisayar Hizmet Alımı	4356,51	Bilgisayar Sayısı
Bilgisayar Sistemleri ve Yazılımlarının Kiralanması	169,51	Bilgisayar Sayısı
Yemekhane Faaliyetinden Gelen Pay	26591,59	Personel Sayısı
Özlük Faaliyetinden Gelen Pay	5698,02	Personel Sayısı
Mutemetlik Faaliyetinden Gelen Pay	27487,64	Personel Sayısı
Bilgi İşlem Faaliyetinden Gelen Pay	5263,03	Bilgisayar Sayısı
Genel Yönetim Faaliyetinden Gelen Pay	1313741,31	Personel Sayısı
Denetim Faaliyetinden Gelen Pay	86934,35	Yardımcı Sağlık Personeli
Temizlik Faaliyetinden Gelen Pay	3727,54	m^2
Toplam	3045558,83	

Tablo 3. Cerrahi Müdahale Bölümü Kaynak Giderlerinin Kaynak Dağıtım Ölçüleri

Dağıtım Ölçüleri	Toplam	Hekim	YSP	Tıbbi Sekreter
Mesai Saatinde Personel Sayısı	4	1	2	1
m^2	32	10	18	4
Bilgisayar Sayısı	3	1	1	1
Ampul Sayısı	12	4	6	2
Bir Ampulün Yıllık Tükettiği KW		876	876	876
Tüm Ampullerin Yıllık Tükettiği KW	10512	3504	5256	1752
Bir Bilgisayarın Yıllık Tükettiği KW		4204,8	4204,8	4204,8
Tüm Bilgisayarların Yıllık Tükettiği KW	12614,4	4204,8	4204,8	4204,8
Telefon Sayısı	4	2	1	1

Tablo 4. Kaynak Giderlerinin Kaynak Gruplarına Atanması

Kaynak Giderleri	Toplam	Hekim	YSP	Tıbbi Sekreter
Hekim Maaş Ücret ve Ekleri	278036,08	278036,08		
Hekim Personeli Sabit Döner ve Ekleri	107539,53	107539,53		
Hekim Sabit Dışı Döner ve Ekleri	89181,27	89181,27		
Hekim Nöbet Ücreti Ekleri	17885,07	17885,07		
YSP Maaş Ücret ve Ekleri	417054,12		417054,12	
YSP Personeli Sabit Döner ve Ekleri	161309,29		161309,29	
YSP Sabit Dışı Döner ve Ekleri	133771,91		133771,91	
YSP Personeli Nöbet Ücreti Ekleri	41538,63		41538,63	
Tıbbi Sekreter Maaş Ücret ve Ekleri	186204,54			186204,54
Tıbbi Sekreter Sabit Döner ve Ekleri	48667,54			48667,54
Tıbbi Sekreter Sabit Dışı Döner ve Ekleri	6118,81			6118,81
Tıbbi Sekreter Nöbet Ücreti Ekleri	27893,89			27893,89
Kırtasiye	2816,97	704,24	1408,49	704,24
Demirbaş Amortismanı	1857,68	464,42	928,84	464,42
Aydınlatma Elektrik Gideri	2500,06	833,35	1250,03	416,68
Bilgisayarların Tükettiği Elektrik Gideri	8952,58	2984,19	2984,19	2984,19
Bina Bakım Onarım Gideri	120,49	37,65	67,78	15,06
Isınma Gideri	1167,69	364,90	656,82	145,96
Su Gideri	286,06	89,39	160,91	35,76
Güvenlik Gideri	36796,62	9199,16	18398,31	9199,16
İlaçlama, Dezenfeksiyon Gideri	79,17	24,74	44,53	9,90
Temizlik Malzemesi Gideri	815,15	254,73	458,52	101,89
Haberleşme Gideri	651,78	325,89	162,94	162,94
Diğer Müşavir Firma Gideri	89,20	22,30	44,60	22,30
Lisans, Belge Düzenleme Hizmet Alımı	255,20	63,80	127,60	63,80
Bilgisayar Hizmet Alımı	4356,51	1452,17	1452,17	1452,17
Bilgisayar Sistemleri Ve Yazılımlarının Kiralanması	169,51	56,50	56,50	56,50
Yemekhane Faaliyetinden Gelen Pay	26591,59	6647,90	13295,80	6647,90
Özlük Faaliyetinden Gelen Pay	5698,02	1424,51	2849,01	1424,51
Mutemetlik Faaliyetinden Gelen Pay	27487,64	6871,91	13743,82	6871,91
Bilgi İşlem Faaliyetinden Gelen Pay	5263,03	1754,34	1754,34	1754,34
Genel Yönetim Faaliyetinden Gelen Pay	1313741,31	328435,33	656870,66	328435,33
Denetim Faaliyetinden Gelen Pay	86934,35		57956,24	28978,12
Temizlik Faaliyetinden Gelen Pay	3727,54	931,89	1863,77	931,89
Toplam	3045558,85	855585,28	1530209,83	659763,74

Tablo 5. Acil Servis, Cerrahi Müdahale Bölümü İnsan Kaynaklarının Pratik Kapasitesi

Faaliyet Merkezi	Açıklama	Hekim	YSP	Tıbbi Sekreter
Faaliyet Merkezi Maliyeti	(TL/Yıl)	855585,28	1530209,83	659763,74
Çalışan Sayısı	(Kişi/Gün)	3	6	3
Yıllık Gün Sayısı	(Gün/Yıl)	365	365	365
Hafta Sonu ve Bayram	(Gün/Yıl)	116,5	116,5	116,5
Yıllık İzin	(Gün/Yıl)	20	20	20
İdari İzinli ve Raporlu Gün Sayısı	(Gün/Yıl)	5	5	5
Kişi Başı Net Yıllık Çalışma Gün Sayısı	(Gün/Yıl)	223,5	223,5	223,5
Günlük Çalışma Süresi	(Saat/Gün)	8	8	8
Mola ve Dinlenme	(Saat/Gün)	1,5	1,5	1,5
Kişi Başı Net Günlük Çalışma Süresi	(Saat/Gün)	6,5	6,5	6,5
Kişi Başı Net Yıllık Çalışma Süresi	(Saat/Gün)	1452,75	1452,75	1452,75
Toplam Net Yıllık Çalışma Süresi (Pratik Kapasite)	(Dk/Yıl)	261495	522990	261495
Toplam Net Yıllık Çalışma Süresi (Pratik Kapasite)	(Sn/Yıl)	15689,700	31379,400	15689,700
Kapasite Maliyet Oranı	(TL/Dk)	3,27	2,93	2,52
Kapasite Maliyet Oranı	(TL/Sn)	0,0545	0,0488	0,0421

*Kapasite Maliyet Oranı: İnsan Kaynağı Maliyet Toplamı (Tablo5)/İnsan Kaynağı Pratik Kapasitesi

Tablo 6. Kısa Bacak Atel Sağlık Hizmeti İlk Madde ve Malzeme Gideri

Malzeme Adı	Adet	Birim Fiyat	Tutar
Alçı Sargı 15 Cm	10	1,44	14,4
Alçı Altı Pamuk 10 Cm/1,5m	5	0,49	2,45
Sargı Bezi 10cm/10m	12	1,85	22,2
Hipoallerjenik Flaster 5cmx5cm	1	1,39	1,39
Nonsteril Eldiven	4	0,81	3,24
Birim Direkt Malzeme Maliyeti		43,68	

Tablo 7. Kısa Bacak Atel Sağlık Hizmetinin Toplam Maliyeti

Kısa Bacak Atel Maliyeti	Açıklama	Tutar
Birim Direkt İlk Madde ve Malzeme Maliyeti	TL/Adet	43,68
Birim Faaliyet Gideri	TL/Adet	61,40
Toplam Birim Maliyet	TL/Adet	105,08
İşlem Sayısı	Adet/Yıl	1162
Toplam Yıllık Maliyet	TL/Yıl	122102,96

Tartışma

Günümüzde artan arz talep ile birlikte üretim şekillerinin değişmesi neticesinde yetersiz kalan geleneksel maliyetleme yöntemlerine alternatif olarak stratejik maliyet yönetimi kapsamında FTM yöntemi ortaya atılmıştır. Ancak uygulanmasının ve devamlılığının zor olması nedeni ile güncel bir yönetim muhasebesi aracı olamamıştır. ZSFTM ise FTM yönteminin uygulanması ve devamlılığının sağlanmasındaki zorlukları gidermiştir.[17] ZSFTM yöntemi ile sağlık kurumlarında hem daha doğru maliyetleme yapılacağı , hem de daha doğru yönetim kararları alınabileceği düşünülmektedir. [32]

Literatürde ZSFTM yöntemi ile sağlık kurumlarında yapılmış olan çalışmalar değerlendirildiğinde,

Ting ve ark.[26], pediatrik yeşil dal kırıklarının tedavi maliyeti, Anzai ve ark.[27], karın ve pelvis bilgisayarlı tomografi (AP BT) faaliyet maliyeti, Tseng ve ark.[28] fatura ve sigorta ile ilgili olan idari faaliyetlerin maliyetini ZSFTM ile hesaplamıştır. Shankar ve ark.[29], acil servise başvuran karın ağrılı hastaların tedavi süreçlerini maliyetini düşürmek için ZSFTM yöntemi ile incelemiştir. Kaçak (2021)[8], bir hastanenin yoğun bakım bölümünde yatan hasta maliyeti ölçümünde, geleneksel yöntem, FTM ve ZSFTM yöntemini kıyaslayarak yatan hasta maliyetini hesaplamış ve sağlık uygulama tebliği fiyatları ile kıyaslamıştır. Yun ve ark.[30], acil serviste mevcut maliyetleme yöntemleri ve ZSFTM yöntemlerini belli bir sağlık hizmeti maliyetini ölçmeden, süreçleri ele alarak kıyaslamıştır. Berthelot ve ark.[31], acil serviste İdrar yolu enfeksiyonu durumdaki yetişkin hastalara bakım faaliyetleri maliyetini geleneksel ve ZSFTM yöntemi ile kıyaslamıştır. Deal ve ark.[33], acil serviste yaptıkları çalışmada ZSFTM yönteminin faydalarını vurgulamışlarıdır. Akbulut ve Gençtürk[32], tıbbi onkoloji bölümünde, dört kanser türünde maliyetleri, geleneksel, FTM, ZSFTM bazında kıyaslamışlardır. Çalışmalarda ZSFTM yönteminin sağlık kurumları için, atıl kapasiteyi dikkate alan, doğru maliyetleme yapan ve kolay uygulanabilen bir yöntem olduğu vurgulanmıştır.

Çalışmada diğer çalışmalardan farklı olarak, tüm hastane giderlerini, ikincil faaliyetleri ve destek faaliyetlerin maliyetlerini de dikkate alarak kısa bacak atel hizmet faaliyetinin sunum sürecine ZSFTM yöntemi uygulanmıştır. Kaçak[8], Akbulut ve Gençtürk[32] gibi elde edilen sonuçlar, sağlık uygulamaları tebliğinde belirtilen fiyatlar ile kıyaslanmıştır.

İkinci basamak bir devlet hastanesinin acil servis departmanı, cerrahi müdahale bölümünde gerçekleştirilen çalışmada, kısa bacak atel faaliyetinin, direkt ilk madde ve malzeme birim maliyeti, 43,68 TL, faaliyet maliyeti ise 61,40 TL, toplam birim maliyeti ise 105,08 TL olarak hesaplanmıştır. Yılda 1.162 adet kısa bacak atel sağlık hizmeti sunulmuş olup, hastane için yıllık malzeme 50.712,48 TL, faaliyet maliyeti 71.287,74 TL, toplam maliyet ise 122.102,96 TL olarak hesaplanmıştır.

2020 yılında hastanenin SGK ya fatura ettiği ortalama kısa bacak atel faaliyet satış fiyatı ise birim başına ortalama 28,9 TL'dir. Çalışmada kullanılan verilerin gerçeğe yakın olarak simüle edildiği unutulmamakla birlikte, çalışmada bu maliyet 61,40 TL olarak tespit edilmiştir. Çalışmaya göre, hastane kısa bacak atel faaliyetinden birim başına 32,5 TL zarar etmektedir.

Sağlık alanında bütçe açığı vermemek, etkin maliyet kontrolü için tüm sağlık hizmetleri maliyetinin hesaplanması ve SUT liste fiyatlarının hesaplanan maliyetlere göre güncellenmesi gerekmektedir. Aksi takdirde bazı hizmetlere maliyetin altında bazı hizmetlere ise maliyetinin çok üzerinde fiyat belirlenebilir bu durum ise maliyet yönetimini imkansız hale getirmektedir.

ZSFTM yöntemi yöneticilere alacakları kararlarda güvenilir, hızlı ve sürdürülebilir bir şekilde yardımcı olmaktadır. Ayrıca ZSFTM yöntemi, süreç haritaları ile gereksiz faaliyetleri azaltmayı ve atıl kapasite yönetimini de mümkün kılmaktadır.

Gelecekteki çalışmalarda, hastanede gerçekleştirilen tüm hizmet maliyetlerinin ZSFTM yöntemi ile hesaplanması

önerilmektedir. Ayrıca süreklilik ve kolaylık sağlaması amacı ile maliyet sisteminin kurumsal kaynak planlama sistemlerine entegre edilmesi önerilmektedir.

Etik Standartlara Uygunluk

Sakarya Üniversitesi Rektörlüğü Sosyal ve Beşeri Bilimler Etik Kurulunun 08.03.2023 tarihli ve 55 sayılı toplantısında alınan "38" nolu karar ile çalışmanın etik açıdan uygun olduğuna oy birliği ile karar verildi.

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Bu çalışmanın herhangi bir kişi/kurum ile çıkar çatışması yoktur ve yazarlar arasında çıkar çatışması bulunmamaktadır.

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Research Article | Araştırma Makalesi

PULMONER HYDATID CYST SURGICAL TREATMENT, SINGLE CENTER EXPERIENCE

AKCİĞER HİDATİK KİSTİ CERRAHİ TEDAVİSİ, TEK MERKEZ DENEYİMİ

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ABSTRACT

Objective: Lung hydatid cyst is an infectious disease caused by the parasite Echinococcus granulosus. Surgery is the main treatment of the disease in lung hydatid cysts. In our article, we aimed to share our experiences with our patients who underwent surgical treatment for hydatid cysts of the lungs.

Methods: The data of 41 patients who underwent surgical treatment for pulmonary hydatid cysts in our clinic were analyzed retrospectively. The factors affecting the success of surgical treatment were analyzed.

Results: Eighteen (43.9%) of the patients were male and 23 (56.1%) were female. There was no statistically significant difference between the size groups in terms of length of hospital stay (p=0.070). No statistically significant correlation was found between the number of lesions and postoperative complications (p=0.367).

Conclusion: Lung hydatid cysts are a public health problem that can be seen in all age groups. Although different symptoms and complications related to the disease are encountered in lung hydatid cysts, surgery is an effective treatment method with low recurrence, morbidity and mortality.

Keywords: Echinococcus granulosus, lung hydatid cyst, surgical treatment

ÖZ

Amaç: Akciğer hidatik kisti Echinococcus granulosus cinsi parazit tarafından oluşturulan bir enfeksiyon hastalığıdır. Akciğer hidatik kistlerinde hastalığın esas tedavisini cerrahi oluşturmaktadır. Makalemizde akciğer hidatik kisti nedeni ile cerrahi tedavi uyguladığımız hastalarımızla ilgili deneyimlerimizi paylaşmayı amaçladık.

Yöntem: Kliniğimizde akciğer hidatik kisti nedeni ile cerrahi tedavi uyguladığımız 41 hastanın verileri retrospektif olarak incelendi. Cerrahi tedavi başarısını etkileyen faktörler analiz edildi.

Bulgular: Hastaların 18'i (%43,9) erkek, 23'ü (%56,1) kadındı. Hastanede kalış süresi açısından lezyon boyut grupları arasında istatistiksel olarak anlamlı fark saptanmadı (p=0,070). Lezyon sayısı ile postoperatif komplikasyonlar arasında istatistiksel olarak anlamlı bir ilişki bulunmadı (p=0,367).

Sonuç: Akciğer hidatik kisti her yaş grubunda görülebilen bir halk sağlığı sorunudur. Akciğer hidatik kistlerinde hastalığa bağlı farklı semptom ve komplikasyonlarla karşılaşılsa da cerrahi, düşük nüks, morbidite ve mortalite ile etkili bir tedavi yöntemidir.

Anahtar Kelimeler: Echinococcus granulosus, akciğer hidatik kisti, cerrahi tedavi

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Introduction

Lung hydatid cyst is an infectious disease caused by the parasite Echinococcus granulosus. Human is the intermediate host in this disease, it becomes infected by intake parasite eggs.[1,2] Geography and occupation, especially animal husbandry, is a risk factor.[3] Lung is the second most frequently involved organ after the liver, and lung involvement is more common in the pediatric age group.[4] Surgery is the main treatment of the disease in lung hydatid cysts. Medical treatment is applied after surgical treatment or in cases where surgery cannot be performed for different reasons and in some patient groups. In our article, we aimed to share our experiences with our patients who underwent surgical treatment for hydatid cysts of the lungs.

Methods

Patient Selection and General Features

The data of 55 patients who were operated for pulmonary hydatid cyst in Kocaeli University Hospital Thoracic Surgery Clinic between March 2005 and April 2022 were scanned retrospectively. Patients who had insufficient data and were not followed up regularly in our clinic were excluded from the study, and the data of the remaining 41 patients were analyzed. The data used in our study were accessed from patient files, hospital radiological imaging systems, and telephone interviews with patients. Age, gender, side, number, symptom, occupation, size, localization, simultaneous liver involvement, radiological features, rupture status, surgical procedure, drain follow-up, hospitalization time, postoperative complications, mortality, additional procedures-interventions performed by other branches analyzed. Lesions were divided into 4 groups according to their radiological size as 0-3≤cm (Group I), 4-5≤cm (Group II), 6-8≤cm (Group III), 9 cm and above (Group IV). The size of the largest lesion was taken into account in multiple/bilateral lesions. The first 30 days were considered as early, and the period after 30 days were considered as late postoperative complications.

Surgical Procedure and Follow-up

The diagnoses of the patients were mainly made by radiological imaging (chest radiography, thorax tomography, abdominal usg) and clinical correlation. Serological tests were not performed by us, except for the diagnostic serological tests that were already available before the patients applied to us. Patients whose cysts ruptured into the intrapleural space were operated urgently with appropriate medical treatment, while other cases were operated in the early period. All patients were operated with a posterolateral thoracotomy, 40 patients underwent cystotomy + capitonage and enucleation, while wedge resection was performed in 1 patient. Two patients with bilateral lesions were operated with consecutive thoracotomy. After the operation, albendazole treatment was given to the patients, and liver function tests were performed at 4-week intervals. After discharge, the patients were followed up with physical examination and radiological imaging.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Shapiro-Wilk's test was used to assess the normality assumption. Continuous variables were presented with median (interquartile range). Categorical variables were presented with counts and percentages. Comparisons between groups were performed using Mann-Whitney U test and Kruskal-Wallis test. Associations between categorical variables were examined by Chi-square test. A p-value <0.05 was considered statistically significant.

Results

Eighteen (43.9%) of the patients were male and 23 (56.1%) were female. The median age of the patients was 30 years (min: 7, maximum: 76). 14 (34.1%) patients were housewives, 9 (22%) patients were self-employed, 8 (19.5%) patients were students, 7 (17.1%) patients were workers, 2 (4.9%) patients were shepherds-farmer, 1 (2.4%) patient was not engaged in any work.

Thirty-five (85.4%) of the patients were symptomatic (Table 1).

Tablo 1. Symptoms

	n (%)
Asymptomatic	6 (14.63)
Chest Pain	16 (39)
Cough	12 (29.3)
Hemoptysis	8 (19.5)
Dyspnea	7 (17.1)
Sputum expectoration	6 (14.6)
Weakness	5 (12.2)

While hydatid cyst was considered in 30 (73.2%) patients in preoperative radiological imaging, abscess or non-specific cyst was considered in 11 (26.8%) patients. 33 (80.5%) of the patients had a single hydatid cyst and 8 (19.5%) had multiple hydatid cysts. The cyst was most commonly observed in the right hemithorax and lower lobes (Table 2). Sizes of the lesions were between 0-3 cm in 5 (12.2%) patients, between 4-5 cm in 10 (24.4%) patients, between 6-8 cm in 16 (39%) patients, and 9 cm or more in 10 (22.5%) patients. Simultaneously, 16 (39%) of the patients had hydatid cysts in the liver. Percutaneous biopsy was performed on liver lesions of 2 (4.9%) patients. The liver lesions of 7 (17.1%) patients were operated by the general surgery team.

Rupture was detected in 10 (24.4%) of the patients, 4 of them in the intrapleural area and 6 of them in the bronchial area. While cystotomy+capitonage or

enucleation was performed in 40 (97.6%) patients, wedge resection was performed in 1 (2.4%) patient. Diaphragm was opened in 5 (12.2%) patients, liver was intervened in 4 and spleen in the other. Additional tube thoracostomy was performed to 2 (4.9%) patients due to expansion defect. No mortality was observed.

The median number of drains was 2 (min: 1, maximum: 3). The median drain time and hospital stay were 5 days (min: 3, maximum: 74) and 7 (min: 4, maximum: 54) days, respectively.

There was no statistically significant difference between genders in status of rupture (p=0.300). Rupture was found in the right hemithorax in 4 (16%) patients and in the left hemithorax in 4 (28.6%) patients, while at least one hemithorax was found in 2 patients with bilateral lesions. Considering the relationship between size and rupture status, there were 2 (40%) rupture in Group 1, 1 (10%) in Group 2, 4 (25%) in Group 3, and 3 (33.3%) in Group 4. Rupture was found in 7 (25.9%) patients without postoperative complications, while rupture was found in 3 (23.1%) patients with postoperative complications. No statistically significant correlation was found between postoperative complication and rupture status (p=1.00) (Table 3). The median hospital stay was 7 days in the group with and without rupture. No statistically significant difference was found between the groups with and without rupture in terms of length of hospital stay (p=0.656).

There were 1 (7.7%) postoperative complication in the 1st group, 3 (23.1%) postoperative complications in the 2nd group, 6 (46.2%) postoperative complications in the 3rd group, 3 (33.3%) postoperative complications in the 4th group. Postoperative median hospital stay was 7 days in the 0-3 cm group, 5 days in the 4-5 cm group, 8 days in the 6-8 cm group, and 7.5 days in the 9 cm and above group. There was no statistically significant difference between the size groups in terms of length of hospital stay (p=0.070). No statistically significant correlation was found between the number of lesions and postoperative complications (p=0.367).

Table 2. Cyst Localizations

	n (%)
Hemithorax	
Right	25 (61)
Left	14 (34.1)
Bilateral	2 (4.9)
Lobe	
Right up	9 (22)
Right middle	3 (7.3)
Right lower	23 (56.1)
Left up	4 (9.8)
Left lower	4 (9.8)
Diaphragm	2 (4.9)

Table 3. Postoperative Complications

	n (%)
Expansion defect	3 (7.3)
Atelectasis	2 (4.9)
Dyspnea	2 (4.9)
Prolonged air leakage	2 (4.9)
Arrhythmia	1 (2.4)
Hemoptysis	1 (2.4)

Discussion

Lung hydatid cyst is a public health problem mainly caused by the parasite Echinococcus granulosus. It can affect any age group and its main treatment is surgery. Successful results are obtained with surgical treatment. In our study, demographic characteristics, characteristics related to lesions, surgical treatment results and factors affecting them were analyzed.

In three studies conducted in our country, it was observed that the patients were young and the mean age was 21.5-45.8 years.[3,5,6] Lung hydatid cyst is more common in male gender (52%-69%).[3,5] The median age in our study was 30 years. In our study, the rate of female gender was higher (56.1%). Considering the occupational risk factor, while most of the patients are expected to be engaged in animal husbandry,[3,5] housewives were more common in our study. We explain this situation as the expected occupational distribution will be different from normal due to the fact that our region is an industrial city and the animal husbandry sector is limited.

Hydatid cysts may be asymptomatic (30-32%)[3,7] or may present with very severe symptoms.[8] Different symptoms may occur depending on the localization of the cyst, its size, adjacent organs, and complications due to rupture. The most common symptoms are cough, chest pain, dyspnea, and hemoptysis.[1,3,5,9] Also, membrane expectoration can be observed more specifically for this disease. Perforation of the cyst may cause serious morbidity and even mortality.[6] Rupture rate in the intrapleural area is reported to be between 1.5% and 2.3%.[8] The risk of rupture is expected to increase as the cyst size increases.[10] In a study examining the relationship between the size of cysts and complications, no difference was found between giant size and small size in terms of rupture into the bronchial area (36.7%-31.7% p=0.17), In contrast giant cysts were found to be riskier rupture into the intrapleural space (3.1%-22% p=0.002).[6] In the same study, although a numerical difference was found between the size groups in terms of size and preoperative and postoperative complications with a higher rate in giant cysts, no statistically significant difference was found (p=0.80, p=0.19, respectively).[6] In our study, 85.4% of the patients had at least one symptom at the time of admission, and the most common symptoms were similar to the literature. In our study, there were ruptures in 10 patients, including 6 bronchial and 4 intrapleural spaces. The rupture was

numerically higher on the left than on the right (16.7-28.6%), and 2 people with bilateral lesions had ruptured on at least one side. As the cyst size increased, a numerical increase was found in terms of rupture.

Lung hydatid cysts have been reported most frequently in the right lung and lower lobe.[2,11] It is 25-30% multiple[2,11] and a bilateral rate of 8.5-30% has been reported.[1,9] Due to the elastic structure of the lung, the dimensions of the cyst can reach large diameters rapidly.[6,12] Hydatid cysts of 10 cm and above are called giant hydatid cysts.[1,3,10] In our study, we detected the lesions most frequently in the right lung and lower lobes. In our study, the cysts were grouped according to their sizes, 24.4% of the cases were 9 cm and above, and 2 (4.9%) were giant cysts.

Radiologic methods and serologic tests are used to diagnose the disease. Radiological methods play the main role. In radiological imaging, the lesion may have a well-defined, homogeneous, round appearance, and it may even be confused with malignancy from time to time.[2,7] While there are specific radiological findings,[3] sometimes clinical correlation may be required for diagnosis. In our study, hydatid cyst was considered radiologically in 73% of the patients, while 27% had abscess-cyst formation and hydatid cyst was considered when clinically correlated. There may be hydropneumothorax appearance in ruptures to the intrapleural space, this appearance was present in 4 patients in our study. Due to the low diagnostic value,[2,7] no new diagnostic and follow-up tests were performed, apart from the existing serological tests at the time of admission.

Under appropriate conditions, surgery forms the basis of the treatment of pulmonary hydatid cysts.[9] The aim of surgery is to remove the cyst without contaminating the surrounding area while preserving the lung parenchyma as much as possible. Great parenchymal losses should be avoided.[13] Anthelmintic treatment is not recommended before surgery due to the risk of rupture.[5,6] The treatment approach is important in bilateral lesions, they can be operated with a two-stage approach. First of all, it can be started from the side that is not ruptured and is large and numerous, or the ruptured side that is complicated and presents symptoms.[3,5,9] Cystotomy+capitonage, enucleation, anatomical/non-anatomical resection can be applied as surgical procedures.[9,13] We approached all of our patients with posterolateral thoracotomy, we performed cystotomy+capitonage and enucleation in 40 of the patients, and we performed wedge resection in 1 patient, we did not perform anatomical resection. We approached 2 patients with bilateral lesions with consecutive thoracotomy. The symptomatic ruptured side in 1 patient was operated on first on the larger side in the other patient. The rate of simultaneous hydatid cysts in the lungs and liver has been reported to be 4-40%.[1,3] Masses in the liver dome or intra-abdominal organs such as the spleen can be accessed by opening the diaphragm. We performed this approach in 5 of our patients, including 4 liver domes and 1 spleen.

3.4-20% complications have been reported in the early postoperative period.[2,3,5] The most common postoperative complications are prolonged air leakage and infection processes.[5] Factors expected to increase postoperative complication; cyst size, number, simultaneous liver cyst, rupture and hemoptysis.[2] In our study, the postoperative complication rate was 22%. The most common early postoperative complications were expansion defect, dyspnea, atelectasis, prolonged air leak, arrhythmia, and hemoptysis. In our study, there was no statistically significant relationship between the number of lesions (p=0.367), rupture (p=1.00) and postoperative complications, but a numerical increase was observed with increasing lesion size. In addition, no statistically significant difference was found in terms of increase in lesion size and length of hospital stay (p=0.070).

It has been reported that tube thoracostomies are terminated in an average of 4 days[3] and the average postoperative hospital stay is 6-8 days.[3,5] It is reported that the length of hospital stay is not significantly affected in giant hydatid cysts.[10] In our study, the median drain termination time was 5 days, and the median discharge time was 7 days. No statistically significant correlation was found between size and rupture status and length of hospital stay (p=0.070, p=0.656, respectively).

The recurrence rate after surgical treatment is expected to be 0.6-1.7%.[3] To prevent recurrences after the operation, albendazole treatment is recommended for 3-6 months.[1,5] In some studies that had no long follow-up period and a small number of patients, it was reported that no recurrence was detected after surgery with albendazole treatment.[2,3,5] We applied albendazole treatment similarly to our patients in the postoperative period, and no recurrence was observed in the follow-ups.

In conclusion, lung hydatid cysts are a public health problem that can be seen in all age groups. It should be kept in mind in the differential diagnosis in cases where lung abscess-cyst is considered in radiological imaging. In these patients, the region and occupation should be questioned. Although different symptoms and complications related to the disease are encountered in lung hydatid cysts, surgery is an effective treatment method with low recurrence, morbidity and mortality.

Compliance with Ethical Standards

The study protocol was approved by the Kocaeli University Ethics Committee (Date: 09.05.2023, No: 2023-110).

Conflict of Interest

The author declares no conflicts of interest.

Author Contribution

All the authors equally contributed to this work.

Financial Disclosure

None

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Research Article | Araştırma Makalesi

EVALUATION OF CARDIAC AUTONOMIC DYSFUNCTION AND THE RISK OF ARRHYTHMIA IN CHILDREN WITH MITRAL VALVE PROLAPSE

MİTRAL KAPAK PROLAPSUSU OLAN ÇOCUKLARDA KARDİYAK OTONOMİK DİSFONKSİYONUN VE ARİTMİ RİSKİNİN DEĞERLENDİRİLMESİ

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Abstract

Objective: The occurrence of symptoms in patients with mitral valve prolapse (MVP) is linked to autonomic dysfunction and neuroendocrine causes rather than progressive mitral valve insufficiency. The goal was to assess the risk of autonomic dysfunction and arrhythmia in patients with MVP.

Methods: A cohort of 63 individuals with MVP was compared to a control group of 64 age- and gender-matched children. A comprehensive assessment was conducted, comprising physical examination, medical history taking, and various diagnostic tests, including 12-lead electrocardiography, autonomic function testing, echocardiography, and 24-hour Holter rhythm monitoring.

Results: In comparison to the control group, the MVP group had higher QTc dispersion, frontal QRS-T angle, Tp-e interval, and Tp-e/QTc ratio at rest. However, conventional measurements of heart rate variability in the Holter ECG or HRDC, a novel and understudied parameter in children, did not significantly differ between the two groups.

Conclusion: Although cases with pathological findings in the initial ECG were excluded from our study, the widened frontal QRS-T angle seen in MVP patients is a novel finding, and that when compared to the control group, these patients' HRDC doesn't seem to differ noticeably.

Keywords: Mitral valve prolapse; autonomic dysfunction; arrhythmia; child

Öz

Amaç: Mitral kapak prolapsusu (MKP) saptanan olgularda yakınmaların ortaya çıkışı ilerleyici mitral kapak yetersizliğinden çok otonomik işlev bozukluğu ve nöroendokrin nedenlere bağlıdır. Bu çalışmada MKP tanısı ile izlenen çocukların otonomik disfonksiyon ve aritmi riski açısından değerlendirilmesi amaçlanmıştır.

Yöntem: Çalışmaya primer MKP tanılı 63 hasta ve benzer yaş ve cinsiyetteki 64 çocuktan oluşan kontrol grubu dahil edildi. Tüm hastaların öyküleri alındı, fizik muayeneleri yapıldıktan sonra; 12 derivasyonlu EKG'leri, otonom işlev testleri, ekokardiyografi 24-saatlik ritim Holter incelemeleri gerçekleştirildi.

Bulgular: Ortalama dinlenme kalp hızı, hasta grubunda kontrol grubuna göre daha yüksek bulundu. Ortostatik hipotansiyon hasta grubunda 8 çocukta (%12,6), kontrol grubunda ise 4 çocukta (%6,2) saptandı. Yüzeyel EKG'de QTc dispersiyonu, frontal QRS-T açısı, Tp-e aralığı ve Tp-e/QTc oranı MKP'li hastalarda kontrol grubuna göre yüksek saptandı. Holter EKG'de kalp hızı değişkenliğini gösteren konvansiyonel ölçümler açısından iki grup arasında anlamlı fark saptanmadığı gibi HRDC açısından da iki grup arasında anlamlı fark saptanmadı.

Sonuç: Çalışmamıza başlangıç EKG'sinde patolojik bulgusu olan olgular dâhil edilmemesine rağmen MKP'li hastalarda yüksek frontal QRS-T açısının tespit edilmiş olmasının yeni ve önemli bir bulgu olduğunu düşünmekteyiz. Ayrıca yeni ve çocuklarda az çalışılmış bir parametre olan HRDC'nin MKP' li hastalarda anlamlı farklılık göstermediği ortaya çıkmış olup bununla ilgili daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Mitral kapak prolapsusu, otonom disfonksiyon, aritmi, çocuk

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Introduction

Mitral valve prolapse (MVP) is a cardiac condition that is often asymptomatic, but may present with a range of symptoms including atypical chest pain, irregular heartbeats, shortness of breath, presyncope, reduced exercise tolerance, migraine-like headaches, severe anxiety, and depression.[1] These symptoms are thought to be caused by autonomic dysfunction, which may be due to sympathetic system dominance, neurovascular and endocrine factors, and reduced vagal tone. Palpitation and chest pain are the most commonly reported symptoms in adult patients with MVP.[2] Palpitation and chest pain were reported to be the most common complaints in an adult study.[3] Additionally, MVP may be associated with various rhythm disorders, including ventricular tachyarrhythmias, bradyarrhythmias, atrioventricular blocks, and paroxysmal supraventricular tachycardia.[4]

In patients with primary MVP, particularly in the inferior leads, nonspecific ST-T-wave changes and T-wave inversion are frequently seen. Tests used to evaluate autonomic dysfunction of the heart are orthostatic hypotension (sympathetic) and resting heart rate (parasympathetic) measurements.[5] Decreased HRV, which reflects increased sympathetic and decreased vagal activity, has been linked to ventricular arrhythmia and sudden death in the general population, particularly in those with heart disease. This study's goal was to investigate the demographics, anthropometric measures, clinical manifestations, electrocardiographic findings, rhythm Holter results, and echocardiographic findings of children with MVP, and to evaluate their risk of autonomic dysfunction and arrhythmia.

Methods

Patients

In this study, we included children aged 6 to 18 who had been diagnosed with primary MVP and were followed up with every 6 to 12 months. We also included a control group of healthy children of similar age and gender who presented to the Pediatric Cardiology Outpatient Clinic with complaints such as murmur, chest pain, syncope, or palpitation and who did not have any cardiac abnormalities identified during their evaluation. We included patients who did not attend the control during the study by contacting them by phone for an interim visit, and we also included patients who were newly diagnosed with MVP during the course of the study.

The local ethics board approved the study (Date: 26 April 2021, Number: 10/04) and all participants were informed of the study's objectives during the initial interview. We inquired about complaints such as chest pain, palpitations, dizziness, fainting, blackouts, weakness, fatigue, shortness of breath, and sweating. Body mass index was calculated by measuring height and weight. The study began with a sample of 90 MVP patients who came to the outpatient clinic control during the study, as well as patients who did not come for the control but were contacted by phone. We excluded 27 patients from the study due to drug use, additional cardiac pathology, or additional pathology that could affect ECG and rhythm Holter measurements (Figure 1).

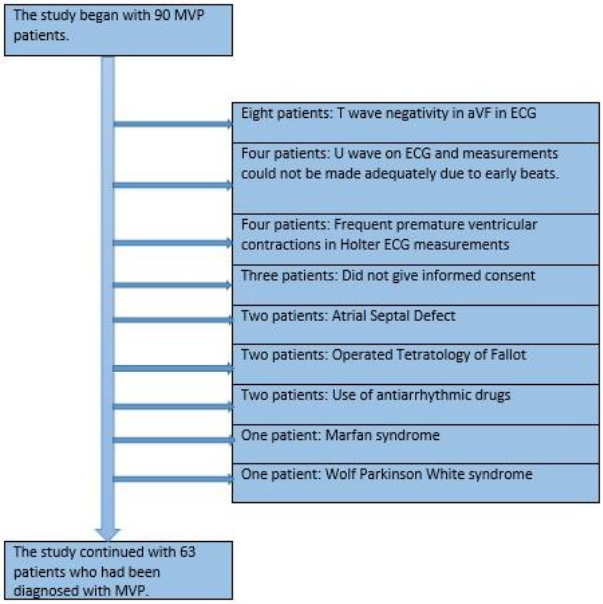

Figure 1. Flow chart of patient selection based on study inclusion criteria.

Electrocardiogram Examinations

The Cardioline ar2100view model ECG was used to record 12-lead electrocardiograms (ECGs) at a rate of 25 mm/s and an amplitude of 10 mm/mV in this study. The cases were positioned supine and given 10 minutes to rest before the ECGs were taken. The ECGs were then digitally scanned and analyzed for various parameters, including rate, rhythm, ventricular hypertrophy, atrial enlargement, QRS axis, and ST-T changes. These measurements were compared to age-appropriate normal values as reported in the literature.[6] Furthermore, QT, corrected QT (QTc), QTc dispersion, frontal QRS-T angle, Tp-e interval, and Tp-e/QTc values were investigated within the scope of the study. The study excluded leads with early beats or T waves whose end could not be determined precisely. Three QRS-T waves were assessed in each lead, and the study included cases where QT measurement could be made in at least nine leads by calculating the QT duration in milliseconds (ms).[7]

The Bazett formula was utilized to determine the corrected QT interval ($QTc = QT/\sqrt{RR}$).[8] QT dispersion was identified as the difference between the two QT intervals with the longest and shortest values recorded in the 12-lead ECG. The distance between the T wave's peak and its end in the precordial leads was identified as the Tp-e interval using the average of three different derivations. The Tp-e/QTc ratio was also calculated after Tp-e measurement. The frontal QRS-T angle was measured utilizing the difference between the QRS and T axes recorded in the ECG device's report section. For

measurements greater than 180 degrees, this angle was deducted from 360 degrees and recalculated (Figure 2).

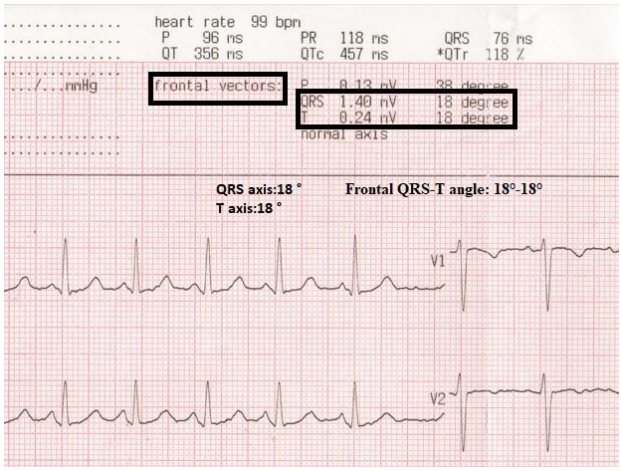

Figure2. Frontal QRS-T angle measurement on surface ECG.

Autonomic Function Tests

After a 10-minute period of rest in the supine position, the patients' ECGs, initial blood pressure measurements, and heartbeats were recorded. The participants were then instructed to stand still for 10 minutes with their arms and legs close to their bodies, and their heart rate and blood pressure were measured at the end of this time. A systolic blood pressure drop of more than 20 mmHg was considered abnormal and diagnosed as orthostatic hypotension. In this manner, orthostatic hypotension was used to assess sympathetic dysfunction and resting heart rate was utilized to assess parasympathetic dysfunction in the heart autonomic function tests.

Echocardiography

An expert cardiologist performed echocardiographic exams on study participants using a Philips Affiniti 30 model echocardiography device and an S4-2 sector probe. While the subjects were lying in the left lateral and supine positions, an echocardiographic examination was conducted using two-dimensional, M-mode, color Doppler, pulsewave Doppler, and continuous Doppler from all echocardiographic views. The diagnostic standard for MVP in the echocardiographic examination was acknowledged to be any partial or complete displacement of the anterior or posterior leaflets from the level of the mitral annulus to the left atrium greater than 2 mm.[9] The thicknesses of the anterior and posterior mitral valves were also measured. Non-classical MVP valves were defined as having a valve thickness of less than 5 mm, whereas classical MVP valves were defined as having a valve thickness of more than 5 mm.

Rhythm Holter Analysis

A 24-hour recording was taken from 38 patients with MVP and 34 subjects from the control group with a three-channel Biocare H-12 Plus model rhythm Holter device, based on the symptoms and findings (palpitation suggestive of arrhythmia, syncope, chest pain) among the subjects included in the study. Records were assessed for baseline rhythm, mean heart rate, lowest and highest heart rates, supraventricular tachycardia, premature ventricular contractions (PVC), ventricular tachycardia, supraventricular premature beat, presence of pause, and HRV. Ventricular arrhythmias detected in the patient and control groups were evaluated using the modified Lown criteria. Ventricular arrhythmias above Class 2 were considered complex ventricular arrhythmias.[10]

Time-based heart rate variability measurements are used to evaluate autonomic dysfunction, including the mean of all normal RR intervals (mean RR), standard deviation of all normal sinus RR intervals (SDNN), mean of RR intervals over all 5-minute segments in the recordings (SDANN), and consecutive normal RR intervals (mean RR). In a 24-hour rhythm Holter, automatic calculations were performed to determine the square root of the mean difference between the RR intervals (RMSSD), frequency-based heart rate variability measures such as low frequency (LF), high frequency (HF), and LF/HF ratios. Heart rate deceleration capacity (HRDC) data, which were automatically recorded on the Holter ECG device, were collected to quantitatively evaluate cardiac parasympathetic function (Figure 3).

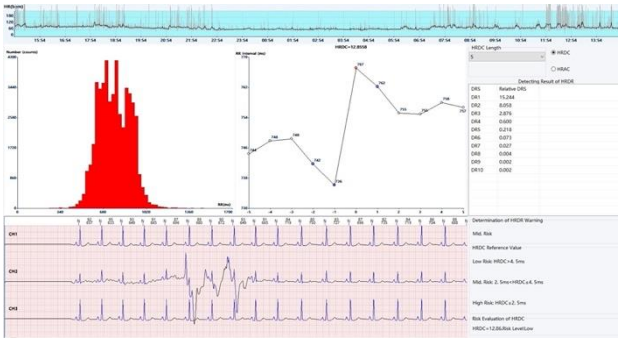

Figure3. HRDC (heart rate deceleration capacity) measurement in Rhythm Holter.

Statistical Analysis

In our study, we utilized SPSS version 26.0 as our statistical analysis program. The means and standard deviations of numerical variables were presented together. To ascertain whether the variable data were normally distributed, the Kolmogorov-Smirnov test with Lilliefors correction was used. The means were compared using the Student's t-test. The relationship between categorical data was examined using the Pearson Chi-square test. The correlation relationship was determined using the Pearson correlation coefficient. A p-value of 0.05 was considered statistically significant in each test.

Results

The study included 63 patients with primary MVP who met the inclusion criteria, as well as a control group of 64 children. Age and gender did not differ significantly between the two groups. The BMI of the patient group was discovered to be significantly lower than that of the control group ($p<0.05$) (Table 1). Nineteen (30.16%) of

the MVP patients had no symptoms. The most common symptom was chest pain, which was present in 20 (31.25%) of the children. Palpitation (20.63%), fatigue (17.46%), dispnea (12.5%), blackout (10.94%), dizziness (6.25%), syncope (6.25%), and sweating (3.13%) were the most common symptoms following chest pain. There was no discernible difference between the systolic blood pressure values at admission and control (p>0.05). The mean resting heart rate in the patient group was 97.56±16.37 beats per minute, compared to 91.61±13.56 beats per minute in the healthy group, and it was discovered to be statistically significantly higher in the patient group. (p<0.05). Orthostatic hypotension was found in 8 patients (12.6%) and 4 controls (6.2%), but the difference was not statistically significant (p=0.348).

Table 1. Demographic characteristics and body measurements of the patient and control groups

Demographic features		Patients (n=63)	Controls (n=64)	p
Sex	**Male**	43 (68.25%)	35 (54.69%)	0.165
	Female	20 (31.75%)	29 (45.31%)	
Age (years)		12.82±3.82	12.09±3.71	0.274
Body weight (kg)		41.07±13.41	44.02±14.53	0.238
Height (cm)		153.25±17.11	149.22±18.92	0.211
BMI (kg/m²)		17.03±3.07	19.12±2.76	**<0.001**

Student's t-test, BMI: Body mass index. Values were expressed as mean±standard deviation.

The ECGs of the patients with MVP and the control group were all in sinus rhythm, and the PR and QRS intervals and QRS axes were all within the normal range for their age. In either the patient or control groups, no signs of atrial or ventricular hypertrophy were detected on the ECG. While there was no significant difference in QT and QTc measurements between the patient and control groups, QTc dispersion, frontal QRS-T angle, Tp-e interval, and Tp-e/QTc ratio were significantly higher in MVP patients than in the control group (p<0.05). Furthermore, the frontal QRS-T angle was found to be greater than 90 degrees in 6 (9.3%) of the patients with MVP (Table 2).

Table 2. Electrocardiogram findings in the patient and control groups

ECG parameters	Patients (n=63)	Controls (n=64)	p
QT (ms)	353.33±23.28	352.81±22.92	0.899
QTc (ms)	391.75±26,04	396.97±21,11	0.217
QTc dispertion (ms)	25.11±10.21	21.61±8.42	**0.037**
Frontal QRS-T angle (degrees)	39.97±27.87	31.23±17.75	**0.038**
Tp-e interval (ms)	82.06±6.99	78.59±6.64	**0.005**
Tp-e/QTc ratio	0.21±0.02	0.2±0.02	**0.003**

Student's t-test. Values were expressed as mean±standard deviation.

The average amount of prolapse in MVP patients was 3.93±1.24 mm, and the average mitral valve thickness was 4.48±0.99 mm. While 4 patients (6.35%) had no mitral regurgitation (MR), 14 had trace MR, 32 had mild MR, 11 had moderate MR, and 2 had severe MR. In 47 (74.6%) patients with MVP, valve thickness was found to be less than 5 mm, and they were diagnosed with non-classical MVP. In 16 (25.3%) patients with MVP, valve thickness was found to be greater than 5 mm, and they were diagnosed with classical MVP. Though the difference between symptomatic and asymptomatic patients was not statistically significant, it was discovered that symptomatic patients had higher valve thickness and prolapse amounts. The severity of MR and the amount of MVP were found to have a strong correlation (p<0.001; r=0.76) in the correlation study, while the severity of MR and the mitral valve thickness had a positive correlation (p<0.001; r=0.48).

A 24-hour rhythm Holter monitoring was conducted in 38 (60.3%) of the MVP patients and 34 (53.1%) of the healthy peers. The mean RR, SDNN, SDANN, RMSSD, and PNN50 parameters from the time-dependent HRV measurements did not significantly differ between the patient and control groups. Furthermore, there was no discernible difference in the LF, HF, and LF/HF rates between the patient and control groups, which are frequency-based measures of heart rate variability. When HRDC measurements were compared between MVP cases and controls, no discernible difference was found (Table 3).

Table 3. Heart rate variability measurements of the patient and control groups

Heart Rate Variability	Patients (n=38)	Controls (n=34)	p
Mean RR (ms)	592.61±78.87	587.03±102.89	0.794
NN (ms)	79.02±36.72	75.48±28.44	0.648
SDANN (ms)	111±33.25	110.12±32.7	0.91
RMSSD (ms)	63.46±53.32	63.42±32.37	0.997
PNN50 (%)	16.29±14.89	13.01±12.19	0.309
HRDC	23.1±13.83	21.37±8.87	0.53
LF (ms²)	1183.91±902.53	1094.58±850.38	.665
HF (ms²)	953.91±1119.14	866.5±679.89	0.691
LF/HF ratio	1.83±1.02	1.71±1.3	0.651

Student's t-test. Values were expressed as mean±standard deviation.Mean RR: Mean of all normal RR intervals, SDNN: Standard deviation of all normal sinus RR intervals over a 24-hour period, SDANN: Standard deviation of the mean of RR intervals over all 5-minute segments, RMSSD: Root of the square of the difference between consecutive RR intervals, PNN50: 50 ms between percentage of the number of consecutive RR intervals with a difference of more than 50 ms, HRDC: Heart rate deceleration capacity, LF: Low frequency, HF: High frequency.

Discussion

There is evidence that suggests a female to male ratio of 2:1 in primary mitral valve prolapse (MVP).[11] When the demographic characteristics of the patient group were examined in our study, which included 63 patients with primary MVP and a control group of 64 healthy people, 43 (68.25%) of the patients with MVP were found to be girls and 20 (31.75%) were boys. The female/male ratio was 2.15, which was consistent with the literature. It is generally accepted that there is a relationship between asthenic body type and MVP, though this has yet to be established in children. Although this difference was not statistically meaningful, our study found that the average weight of the patient group was lower than that of the healthy controls. However, the patient group's BMI was statistically significantly lower than the healthy subjects,

which is consistent with other studies in the literature.[12,13]

Several studies have found that patients with primary MVP have a high resting heart rate due to decreased parasympathetic tone.[14,15] Catecholamine levels have also been found to be higher in patients with symptomatic MVP compared to the control group, and there is a link between autonomic dysfunction in most patients with primary MVP and regional differences in ventricular myocardium repolarization time.[16] In contrast, a study on school-age children found no significant difference in resting heart rate between MVP patients and healthy children.[17] Our study did find a statistically significant difference in mean resting heart rate between the MVP patient group (97.56±16.37/min) and the control group (91.61±13.56/min), suggesting that parasympathetic activity is suppressed in patients with MVP. Orthostatic hypotension, tachycardia, and rhythm problems are common in patients with MVP. While not statistically significant, our study found orthostatic hypotension to be more common in the MVP patient group, present in 8 children (12.6%) in the patient group and 4 children (6.2%) in the control group.

Arrhythmias are a common occurrence in individuals with mitral valve prolapse (MVP), but the majority of these arrhythmias do not pose a significant threat to the patient's well-being. In order to screen for arrhythmias, it is recommended that patients with MVP undergo routine electrocardiography (ECG), while those presenting with symptoms such as syncope and palpitations should undergo Holter ECG monitoring.[18] QT prolongation, which can be observed in MVP, has been linked to the development of ventricular arrhythmias, including ventricular fibrillation, which is a known cause of sudden death in individuals with MVP. A history of syncope with severe regurgitation, complex arrhythmias, and QT prolongation is considered a potential risk for sudden death.[13] In a study comparing healthy children to those with primary MVP, there was no significant difference in QTc intervals between the two groups. However, other research has found that the QTc intervals of patients with MVP are longer than those of healthy individuals.[7,18] In order to assess the risk of subclinical arrhythmias, our study excluded individuals with preexcitation, wide QRS complexes due to intraventricular or bundle branch block, and frequent premature atrial and/or ventricular contractions as detected by ECG or Holter monitoring. Only cases in which QT measurements were possible in at least nine leads were considered. We found that there was no significant difference in QTc measurements between the MVP and control groups. It is suggested that the differences in QTc interval results between studies may be due to variations in the methods for identifying the T wave's end.

QT dispersion, which is thought to reflect regional differences in ventricular repolarization and can serve as a marker of rhythm disturbances, has been found to be significantly higher in patients with MVP experiencing complex ventricular rhythm disorders compared to those with simple ventricular rhythm disorders in adult patients.[19,20] Similarly, pediatric patients with MVP have been found to have significantly higher QTc dispersion compared to healthy controls.[7,21] In our study, we excluded individuals with pathological findings such as frequent VEA, bundle branch block, and ST-T changes from the analysis and only evaluated subclinical cases. Despite this, we discovered that the MVP group's QTc dispersion was considerably higher than that of the healthy peers ($p<0.05$). This increase in QT dispersion in youngsters with primary MVP may be an early indicator of autonomic dysfunction of the heart, potentially preceding the detection of parasympathetic and sympathetic disorders through autonomic function testing. The QRS-T angle is a measure of myocardial repolarization that has been linked to various cardiac conditions, including ventricular hypertrophy, arrhythmias, conduction disturbances, and myocardial dysfunction. In a 2014 study, Oehler et al. found that an increased QRS-T angle was associated with left ventricular mass and a poor prognosis.[22] The frontal QRS-T angle, which has received less research attention, has been shown to triple the risk of sudden cardiac death in individuals with chronic heart disease, according to a study by Aro et al.[23] May et al. found that a widened QRS-T angle was a strong predictor of all-cause mortality and myocardial infarction in a sample of diabetic patients.[24] Our own study found that the frontal QRS-T angle was significantly higher in patients with MVP compared to controls, with 9.3% of MVP patients displaying an angle greater than 90 degrees. No study that examined the frontal QRS-T angle in a pediatric disease could be found in our literature search. The frontal QRS-T angle in children with MVP has not been studied in this manner. Patients with negative T waves in leads DI and aVF were excluded from our study because such changes could affect the T axis and result in abnormal QRS-T angles. Nonetheless, the elevated QRS-T angles observed in children with MVP suggest that it could be a useful marker for subclinical arrhythmias and sudden death.

The Tp-e interval, which represents the duration between the peak and end of the T wave on the electrocardiogram (ECG), can serve as a marker of transmural repolarization distribution. Additionally, the Tp-e/QT and Tp-e/QTc ratios can be utilized as an index of arrhythmia.[25] It has been established that prolongation of the Tp-e interval and an elevated Tp-e/QT ratio are associated with sudden cardiac death in various clinical circumstances.[26] Research has demonstrated that the Tp-e/QT ratio is a more reliable predictor of ventricular arrhythmogenesis and sudden cardiac death than the Tp-e interval.[27] In a study of adult patients with mitral valve prolapse (MVP), Yontar et al. found that the Tp-e interval, as well as the Tp-e/QT and Tp-e/QTc ratios, were significantly higher in the MVP group compared to controls.[28] Demirol et al. also observed significantly higher values for the Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios in MVP patients as compared to controls in a study involving 110 MVP patients and 107 controls in children.[21] Our study discovered that the Tp-e interval and Tp-e/QTc ratio were

significantly higher in MVP patients in comparison to the control group. This differs from other studies because patients with ST-T segment changes on the ECG were excluded. We speculate that this difference is due to an increase in ventricular repolarization parameters resulting from structural changes in the mitral valve, papillary muscle, and ventricular myocardium in MVP patients, as well as increased autonomic tone.

Heart rate variability (HRV) is a measure of the fluctuation in the time interval between heartbeats. It is believed to reflect the balance between sympathetic and vagal activity in the body. Reduced HRV has been linked to an increased risk of ventricular arrhythmias and sudden death, especially in people who have heart disease. In research studies, HRV is commonly measured using time-based indices such as SDNN (standard deviation of normal-to-normal intervals), SDANN (standard deviation of the average of normal-to-normal intervals), and RMSSD (root mean square of successive differences).[29] Studies on HRV in patients with mitral valve prolapse (MVP) have produced conflicting results. Some studies have found that children with MVP have lower HRV compared to healthy controls, suggesting that the suppression of parasympathetic activity in these individuals may disrupt the balance between sympathetic and vagal activity.[30,31] On the other hand, other studies have found no significant differences in HRV between MVP patients and healthy controls.[32] In the present study, 24-hour Holter monitoring was conducted on 38 MVP patients and 34 healthy controls. Between the two groups, there were no discernible differences in the time-dependent or frequency-based HRV measurements.

Heart rate deceleration capacity (HRDC) has recently been demonstrated as a more reliable predictor of vagal tone and cardiovascular outcomes than other traditional heart rate variability (HRV) measures.[33,34] A 2018 study by Lin et al. involving 281 adult patients with end-stage renal disease found that deceleration capacity is a superior index to root mean square of the successive differences (RMSSD) in predicting left ventricular hypertrophy, regardless of kidney failure.[35] In a 2020 study on patients with Kawasaki disease, Lu et al. compared 50 patients with coronary artery involvement to 130 patients without such involvement, and found that HRDC was significantly lower in the group with coronary artery involvement, potentially making it a cardiac electrophysiological index that could be used to predict coronary artery involvement in the acute phase in children with Kawasaki.[36] In our study, there was no significant difference in HRDC measurements between cases of mitral valve prolapse (MVP) and healthy participants, although the small study population and fewer patients undergoing rhythm Holter examination may have contributed to this finding.

Limitations

Our study has several limitations, including its small sample size of 63 MVP cases, of which Holter ECG analysis was only applicable to 38. In comparison to adult population studies, our sample size is modest. Additionally, as our study was cross-sectional, we were unable to assess the patients' follow-up results.

In conclusion, our study found that MVP cases had elevated resting heart rates and more instances of orthostatic hypotension, which are key indicators of autonomic dysfunction and consistent with prior literature. We also found significant differences between healthy subjects and MVP cases in terms of QTc dispersion, frontal QRS-T angle, Tp-e interval, and Tp-e/QTc ratio, similar to the few previous studies conducted in children. The wide frontal QRS-T angle observed in MVP patients is a novel and significant finding, especially given that cases with pathological findings on initial ECG were excluded from our study. Additionally, we found that HRDC, a parameter that has only recently been studied in children with Kawasaki disease, does not differ significantly in MVP patients.

Compliance with Ethical Standards

Ethical approval was obtained from the Local Ethics Committee of Trakya University (Nisan 2021; No: 10/4).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

Authors contributed equally to this work.

Financial Disclosure

Financial disclosure none.

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Araştırma Makalesi | Research Article

SEKONDER PROGRESİF MULTİPL SKLEROZDA KLİNİK, DEMOGRAFİK VE RADYOLOJİK ÖZELLİKLER: TEK MERKEZ DENEYİMİ

CLINICAL, DEMOGRAPHIC AND RADIOLOGICAL FEATURES IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS: A SINGLE CENTER EXPERIENCE

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ÖZ

Amaç: Multipl sklerozis (MS) inflamasyon, demiyelinizasyon ve akson hasarı ile karakterize ak madde ön planda olmak üzere, korteks ve derin gri maddeyi de etkileyebilen otoimmün bir santral sinir sistemi hastalığıdır. Relapsing remitting Multipl skleroz (RRMS) ve sekonder progresif Multipl skleroz (SPMS) dönemlerindeki hastaların demografik, klinik ve radyolojik özellikleri değerlendirilerek progresyonu ön gördürücü faktörlere katkı sağlamak amaçlanmıştır.

Yöntem: Kocaeli Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı Multipl Skleroz polikliniğinde takip edilen MS hastalarından RRMS ve SPMS grubundaki hastaların verileri veri tabanından kaydedilmiştir. İki grup klinik, demografik ve radyolojik bulgular açısından karşılaştırılarak değerlendirilmiştir.

Bulgular: Çalışmaya 121 SPMS ve 802 RRMS hastası dahil edildi. Her iki grup arasında yaş, cinsiyet, eğitim durumu gibi demografik özellikler ve MS tanısı aldıklarındaki yaşları arasında anlamlı farklılık bulunmadı. Hastalık süresi SPMS'lerde RRMS'lere göre daha uzun bulundu. Genişletilmiş özürlülük durum ölçeği skorları (EDSS), SPMS'lerde RRMS'lere göre daha yüksek bulundu. Son 12 aydaki klinik atak öyküsü ve radyolojik bulgulardaki aktivite RRMS'lerde SPMS'e göre daha yüksek bulundu. Spinal bulgularla başlayan hastaların oranı ise SPMS grubunda daha yüksekti.

Sonuç: SPMS'yi klinik olarak tanımlamak için genel olarak kabul gören standartlaştırılmış bir değerlendirme yoktur. Klinik ve radyolojik bulgular eşliğinde yapılan çalışmalar arttıkça progresyon tanısı ve ön gördürücü faktörler ile ilgili bilgiler netlik kazanacaktır.

Anahtar Kelimeler: Multipl sklerosis, progresyon, relaps

ABSTRACT

Objective: Multiple sclerosis (MS) is an autoimmune central nervous system disease that is characterized by inflammation, demyelination and axonal damage that can affect the cortex and deep gray matter, especially the white matter. It is aimed to contribute to the predictive factors of progression by evaluating the demographic, clinical and radiological characteristics of patients in relapsing remitting Multiple sclerosis (RRMS) and secondary progressive Multiple sclerosis (SPMS) periods.

Methods: The data of the patients in the RRMS and SPMS groups, among the MS patients followed in the Multiple Sclerosis outpatient clinic of Kocaeli University Faculty of Medicine, Department of Neurology were recorded from the database. The two groups were compared and evaluated in terms of clinical, demographic and radiological findings.

Results: 121 SPMS and 802 RRMS patients were included in the study. There was no significant difference between the two groups in terms of demographic characteristics such as age, gender, educational status, and the age at which they were diagnosed with MS. Disease duration was found to be longer in SPMS than in RRMS. EDSS was higher in SPMS than RRMS. The clinical attack history in the last 12 months and the activity in radiological findings were found to be higher in RRMS compared to SPMS. The rate of patients who started with spinal findings was higher in the SPMS group.

Conclusion: There is no definitively accepted standardized assessment to clinically define SPMS. As studies carried out with clinical and radiological findings increase, information about the diagnosis of progression and predictive factors will become clearer.

Keywords: Multiple sclerosis, progression, relapse

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Giriş

Multipl sklerozis (MS) inflamasyon, demiyelinizasyon ve akson hasarı ile karakterize ak madde ön planda olmak üzere, korteks ve derin gri maddeyi de etkileyebilen otoimmün bir santral sinir sistemi (SSS) hastalığıdır.[1] Miyelin kılıfı, oligondendrositler ve daha az oranda akson ve sinir hücresinin kendisi hasarlanır. Demiyelinizasyonun yanı sıra gelişen aksonal dejenerasyonun MS'de ortaya çıkan irreversible nörolojik disabilitenin temel nedeni olduğu artık bilinmektedir. Bu yönüyle MS; inflamatuar, demiyelinizan ve nörodejeneratif bir hastalık olarak tanımlanmaktadır.[2]

Klinik olarak MS homojen bir hastalık olmayıp her hastada farklı seyretmektedir. Bu çeşitlilik hastalığın başlangıç yaşı ve şeklinde, progresyonunda, atak sıklığı ve şiddetinde görülmektedir.[3] Çoğu durumda MS ataklarla ve iyileşmeler ile seyreden relapsing remitting Multipl skleroz (RRMS) klinik formda ilerlese de primer progresif Multipl skleroz olarak kabul edilen çok daha az sayıda hasta başlangıçtan itibaren ataktan bağımsız sinsi progresyonla seyredebilir. RRMS hastalarının bir kısmı hastalıklarının ilerleyen dönemlerinde ataktan bağımsız progresyonla ilerleyen, sinsi kötüleşmenin olduğu sekonder progresif Multipl skleroz (SPMS) olarak kabul edilen progresif döneme geçebilirler.[4] RRMS ve SPMS arasında, hastalığın patogenezi, klinik durum ve özellikle tedaviye verilen terapötik yanıt açısından büyük farklılıklar vardır. RRMS'den SPMS'ye geçişi gösteren net klinik, görüntüleme, immünolojik veya patolojik kriterler henüz oluşturulmamıştır.[5] Biz bu çalışmada SPMS tanısıyla takipli hastaların klinik, radyolojik, demografik özelliklerini RRMS hastaları ile karşılaştırarak sunmayı ve bu şekilde literatüre ışık tutmayı amaçladık.

Yöntem

Bu gözlemsel retrospektif kohort çalışması Kocaeli Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu onayı (2023/25) alınması sonrasında Kocaeli Üniversitesi Tıp Fakültesi Nöroloji Anabilim Dalı Multipl Skleroz polikliniğinde takip edilen MS hastaları ile yapıldı. Elektronik veri tabanımızda kayıtlı hastaların verileri incelenerek RRMS ve SPMS hastaları belirlendi. Hastalar geriye dönük olarak incelendiğinde 6 ay öncesine göre EDSS ≤5,5 olan hastalarda EDSS de 1 puan artış; EDSS ≥6 olduğunda, relaps olmaksızın 0,5 puan EDSS artışı varlığında SPMS olarak değerlendirildi. RRMS ve SPMS hastalarının yaşları, cinsiyetleri, eğitim düzeyleri, medeni durumları, hastalık süreleri, atak sayıları, kranial ve servikal manyetik rezonans incelemelerindeki T2 hiperintens yeni lezyonların varlığı, demiyelinizan plakların yerleşimleri, ilk klinik atak semptomları ve genişletilmiş özürlülük durum ölçeği skorları (EDSS) kaydedilerek karşılaştırıldı. Hastaların atak sayıları ve manyetik rezonans (MRG) incelemeleri için son 12 ay verileri değerlendirildi. Normal dağılım gösteren değişkenlerin karşılaştırılmasında bağımsız iki örnek T testi normal dağılım göstermeyen değişkenlerin karşılaştırılmasında Mann-Whitney U testi kullanıldı.

Bulgular

Çalışmaya 81'i kadın 40'ı erkek 121 SPMS hastası ve 579'u kadın 223'ü erkek 802 RRMS hastası dahil edildi. RRMS ve SPMS hastalarının klinik ve demografik özellikleri Tablo 1'de özetlenmiştir. Her iki grup yaşlarına göre değerlendirildiğinde RRMS hastalarının yaş ortalaması 43 (35-52) iken SPMS grubunun yaş ortalaması 57 (50-64,5) olarak bulundu (p<0,001). Kadın cinsiyet oranı hem RRMS hem de SPMS grubunda daha yüksekti. RRMS grubunda kadın cinsiyet oranı 72,1 olarak bulundu. SPMS grubunda bu oran %66,9'du. MS tanı tarihinden günümüze kadar geçen hastalık sürelerine bakıldığında SPMS'lerde ortalama hastalık süresi 12 yıl olarak bulundu. RRMS'lerde ise ortalama hastalık süresi 5 yıl idi. Hastaların eğitim yılları mezun oldukları sınıfa göre hesaplandı. RRMS'te ortalama eğitim yılı 11 (8-12) yıl olarak bulunmuşken SPMS'te ise 8 (5-10) yıl idi (p<0,001). Genişletilmiş özürlülük durum ölçeği skorları (EDSS) değerlendirildi. RRMS grubunda ortalama EDSS 2(1-3) olarak bulunurken SPMS grubunun ortalama EDSS 5,5 (4,5-6) idi. Her iki grup arasındaki EDSS farkı istatistiksel olarak anlamlıydı (p<0,001). Son 12 ayda klinik atak öyküsüne bakıldığında RRMS grubunda son 12 ayda atak geçiren hasta oranı %17 idi, SPMS grubunda ise %5 idi. Radyolojik bulgular göz önüne alındığında iki grup arasındaki en dikkati çeken farklılık optik nörit bulguları olan hastalar ile spinal bulguları olan hastalardaydı. Ayrıca SPMS'lerde RRMS'lere göre yeni lezyon sayısı anlamlı derecede daha düşüktü (p<0,05). RRMS hastalarının %41'inde son 12 ayda MRG de yeni lezyon gözlendi (p<0,05). SPMS hastalarının ise %16'sında yeni lezyon gözlendi. İlk klinik atağı optik nörit olarak başlayan hasta sayısı RRMS grubunda 185 (%23,1) iken SPMS grubunda ise 17 hasta (%14) olarak bulundu. İlk klinik atağı beyin sapı bulgusu ile başlayan hastaların oranı %37 (297 hasta) iken SPMS grubunda %31 (38 hasta) idi. İlk klinik atak bulgusu spinal tutulumla uyumlu hasta sayısı ise RRMS grubunda 143 (%17,8) iken SPMS grubunda 30 (%24,8) idi.

Tartışma

Bu çalışmada SPMS hastalarının klinik, demografik, radyolojik özellikleri RRMS'lerle kıyaslanarak her iki grup arasındaki farklılıklar ve benzerlikler değerlendirilmiştir. MS kadınlarda erkeklere oranla iki kat daha fazla görülen bir hastalıktır.[1] Bizim hastalarımızda da her iki gruptaki kadın cinsiyet oranı literatürle uyumlu olarak yüksek bulunmuştur. Her iki grup arasında kadın cinsiyet açısından istatistiksel anlamlı farklılık bulunmamıştır. RRMS ile takip edilen hastaların bir kısmı ilerleyen süreçte SPMS dönemine geçmektedir. Hangi hastaların progresif faza geçtiği ya da hastaların progresif faza geçiş sürelerindeki farklılıklar ile ilgili oldukça fazla yayın olsa da bu konuda kesinleşmiş kriterler mevcut değildir.[6] SPMS grubunun yaş ortalamasının RRMS'lerden yüksek olması ve hastalık süreleri arasında anlamlı farklılık olmasının sebebi klinik sürecin ve progresif faza geçişin neticesinde beklenen bir durumdur.[7] Yapılan çalışmalarda eğitim süresi ile özürlülük arasında negatif bir ilişki bulunmuş olsa da bu negatif

korelasyonun RRMS'lerde daha güçlü olduğu bildirilmiştir.[8] Bizim çalışmamızda her iki grup arasında eğitim düzeyleri arasında anlamlı farklılık saptanmış olup SPMS grubunun eğitim düzeyi daha düşüktür. MS hastalığının ataklarla seyrettiği RRMS döneminde inflamasyon hakimken progresyon fazında geçtikçe nörodejenerasyon artar.[8,9] Dolayısıyla hastalık aktivitesi, atak sıklığı , MRG aktivitesi RRMS döneminde daha yüksekken progresif faza geçtikçe özürlülük artışı gözlenir.[10] Literatürle uyumlu olarak bizim hastalarımızda da RRMS'lerde son 1 yıldaki atak geçiren hasta oranı ile MRG'de yeni lezyon ortaya çıkan hasta oranı SPMS'e göre anlamlı derecede daha yüksek bulunmuşken EDSS puanı ise SPMS'lerde daha yüksektir. Yapılan çalışmalarda klinik ve MRG bulguları değerlendirildiğine spinal kord lezyonlarının progresyon için ön gördürücü olduğu bildirilmiştir.[11,12] Bizim hastalarımızda da progresif olanlara baktığımızda spinal kord tutulumu ile başlayan hastaların oranı RRMS'lere göre anlamlı derecede yüksek bulunmuştur. İlk klinik atak fenotipin önemi ve progresyonla ilişkisi yapılan çalışmalar arttıkça daha da anlam kazanacaktır. SPMS'yi klinik olarak tanımlamak için birçok çalışma mevcuttur. Ancak, genel olarak kabul gören standartlaştırılmış bir değerlendirme yoktur. Progresyonu tanımlamak için çoklu prognostik faktörlerin bir arada incelenmesi önerilmiştir.[13,14] Klinik ve radyolojik bulgular eşliğinde yapılan çalışmalar arttıkça progresyon tanısı ve ön gördürücü faktörler ile ilgili bilgiler netlik kazanacaktır.

Tablo 1. RRMS ve SPMS klinik ve demografik özellikleri

	SP n (%)/Median (IQR)	RRMS n (%)/Median (IQR)	p
Cinsiyet			0,245*
Kadın	81 (66,9)	578 (72,1)	
Erkek	40 (33,1)	224 (27,9)	
Yaş	57 (50-64,5)	43 (35-52)	**<0,001****
Eğitim düzeyi	8 (5-10)	11 (8-12)	**<0,001****
EDSS puanı	5,5 (4,5-6)	2 (1-3)	**<0,001****
Hastalık süresi, ortalama yıl	5	12	**0,001****
Son 1 yıldaki MR aktivitesi			**<0,001***
Yok	102 (84,3)	475 (59,2)	
Var	19 (15,7)	327 (40,8)	
İlk atakta optik nörit varlığı			**0,02***
Yok	104 (86)	617 (76,9)	
Var	17 (14)	185 (23,1)	
İlk atakta spinal tutulum			0,06*
Yok	91 (75,2)	659 (82,2)	
Var	30 (24,8)	143 (17,8)	

*Pearson's chi-square test, **Mann-Whitney U test, IQR: Interquartile range

Açıklamalar
Çalışma 5-7 Kasım 2021 tarihinde İstanbul'da yapılan "MS TEDAVİLERİ İLE İLGİLİ BİLMEK İSTEYECEĞİNİZ HER ŞEY!" toplantısında sözlü bildiri olarak sunulmuştur.

Etik Standartlara Uygunluk
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Olgu Sunumu | Case report

AYNI KADAVRADA ARTERIA CIRCUMFLEXA FEMORIS MEDIALIS ve LATERALIS'LERİN ATİPİK VARYASYONU

COEXISTING TWO VARIATIONS OF THE LATERAL and MEDIAL CIRCUMFLEX FEMORAL ARTERIES

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ÖZ

Amaç: Bu olgunun hazırlanmasının amacı literatürde yer alan varyasyon çeşitliliğine katkı sağlamak ve invaziv işlemlerde öngörüyü artırmaktır.

Yöntem: 58 yaşında erkek bir kadavranın sol trigonum femorale'sinde yapılan disseksiyon esnasında iki farklı varyasyon görülmüştür.

Bulgular: Olgumuzda arteria circumflexa femoris medialis (ACFM), arteria femoralis (AF) veya arteria profunda femoris (APF)'den çıkan ayrı bir arter olarak mevcut değildi. ACFM 'nin yükselen dalı doğrudan AF'den, APF çıkış noktasının yakınından çıkmış ve ACFM'nin inen iki dalı farklı noktalardan APF'den çıkmıştı. Ayrıca ACFL APF'nin orijinine yakın AF'den çıkmıştı.

Sonuç: ACFL'nin bu varyasyonu literatürde bulunabilmesine rağmen, ACFM'nin bu varyasyonu ile ilgili yeterli bilgiye literatürde ulaşılamamıştır. ACFM ve ACFL'nin tüm varyasyonları hakkında yeterli bilgiye sahip olmak, radyolojik girişimsel işlem planlamasında yol gösterici olacaktır.

Anahtar Kelimeler: Arteria circumflexa femoris medialis, arteria circumflexa femoris lateralis, varyasyon

ABSTRACT

Objective: The purpose of the preparation of this case is to contribute to the diversity of variations in the literature and to increase the prediction in invasive procedures.

Methods: Two different variations were observed during dissection in the left femoral triangle of a 58-year-old male cadaver.

Results: In our case, the MCFA was not available as a separate artery from the femoral artery (FA) or deep femoral artery (DFA). Ascending branch of the MCFA originated directly from the FA just proximal to the origin of the DFA, and the two descending branches of the MCFA originated from the DFA separately. Also, the LCFA originated from the FA proximal to the origin of the DFA.

Conclusion: Although this variation of the LCFA can be found in the literature, there is not enough knowledge about this variation of MCFA in the literature. Having sufficient knowledge of all variations of MCFA and LCFA will guide radiological interventional procedure planning.

Keywords: Medial circumflex femoral artery, lateral circumflex femoral artery, variation

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Giriş

Arteria circumflexa femoris medialis (ACFM) genellikle arteria profunda femoris (APF)'in posteromedial yüzünden bazen de arteria femoralis'ten (AF) çıkan bir arterdir.[1] ACFM'nin iki terminal dalı vardır: ramus ascendens (ra) ve ramus descendens (rd). ACFM, hamstring kasları, uyluk adduktor kasları, m. obturatorius externus'u ve m. gracilis'i besler. Ayrıca caput femoris, collum femoris, fossa acetabuli'deki yağ dokusu ve n. ischiadicus'u (siyatik sinir) da besler.[1] AF, kolay erişilebilir bir arter olduğu için radyolojik girişimsel işlemlerde ve kateterizasyonda oldukça sık kullanılır.[1] ACFM bu bölge ile yakın ilişkisi nedeniyle travma sonrası veya total kalça artroplastisi gibi operasyonlar sırasında kesilmesi riski taşır.[2] ACFM greftlerin damar pedikülü olarak plastik cerrahi operasyonlarda da büyük öneme sahiptir.[3] Ayrıca femur başının idiyopatik iskemik nekrozunda selektif arteriyografide femur başının arteriyel beslenmesini belirlemek için de ACFM kullanılır.[2] APF'nin ACFM dışındaki diğer ana dalı arteria circumflexa femoris lateralis (ACFL)'tir. Normalde ACFL, APF'nin posterolateral yüzünden çıkan bir arterdir. ACFL caput femoris, collum femoris, trochanter major, m. vastus lateralis'i ve dizi besler. ACFL, aortopopliteal bypass, koroner arter bypass greftleme ve anterolateral uyluk fleplerinde kullanılır.[1]

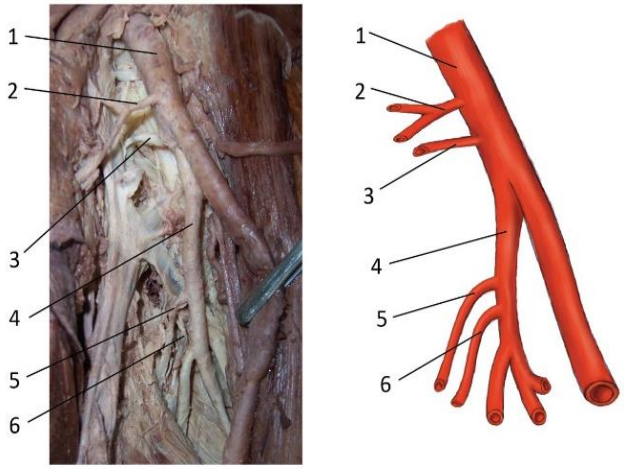
Kalça eklemi cerrahisi ve diğer girişimsel işlemler sırasında femur başı nekrozunu önlemek için bu arterlere (ACFM ve ACFL) zarar vermemek önemlidir.[1]

ACFM ve ACFL'nin varyant kökenlerini ve dallanmalarını bilmek, girişimsel işlemleri komplikasyonsuz gerçekleştirmek için çok önemlidir.

Bu yazının amacı, nadir bir MCFA dal varyasyonu ve LCFA varyasyonu sunarak genişleyen bilgi havuzuna katkıda bulunmaktır.

Olgu

İUC-Cerrahpaşa Tıp Fakültesi Anatomi Anabilim Dalı rutin eğitim diseksiyonları esnasında, 58 yaşında erkek bir kadavranın sol inguinal bölgesinde ACFM'nin ra ve rd dallarının çıkış yerlerinde ve ACFL'nin çıkış yerinde varyasyonlar görüldü (Şekil 1). ACFM'nin ra dalının, doğrudan AF'den, APF'nin çıkış noktasının proksimalinden köken aldığı ve rd'nin iki dal şeklinde, APF'den farklı iki noktadan çıktığı görüldü. Ayrıca, ACFL'nin de AF'den orijin aldığı görüldü (Şekil 1).



Şekil 1. Arteria femoralis (AF) çıkışlı arteria circumflexa femoris medialis'e (ACFM) ait ramus ascendens (ra) olgusu. ACFM'nin ra dalı, doğrudan AF'den, arteria profunda femoris'in (APF) çıkış noktasının proksimalinden köken alıyor ve ramus descendens iki dal şeklinde, APF'den farklı iki noktadan çıkıyor. Ayrıca, arteria circumflexa femoris lateralis, AF'den orijin alıyor.
**1. A. femoralis, 2. A. pudenda externa, 3. ACFM ramus ascendens, 4. A. profunda femoris, 5. ACFM ramus descendens I, 6. ACFM ramus descendens II*

Tartışma

Arteriyel varyasyonları anlamak için arteriyel embriyolojiyi bilmek önemlidir. Arteria iliaca interna (Aİİ)'nın bir dalı olan siyatik arter fetal yaşamda ilk olarak alt ekstremitenin damarlanmasından sorumludur.[4] Fetüs 10 mm uzunluğunda ve sekiz haftalık olduğunda siyatik arter geriler ve AF baskın olarak alt ekstremite kanlanmasını sağlar.[4] Daha sonra ventral AF ile dorsal siyatik arter arasında anastomozlar oluşur.[4] Bu sırada pelvis ve uyluğun önünde bulunan kılcal damarlar tarafından rete pelvicum ve rete femorale oluşur.[4] Bu ağlar kan akışını arttırır ve arter ağının olgunlaşmasını kolaylaştırır. Arteriyel varyasyonlar, kapiller basınçtaki artışla ilişkili olabilir. Bu nedenle bu kılcal ağlardaki akım değişimleri ve akım duruşları önemlidir.[4,6]

ACFM ve ACFL, bilinmeyen kanallardan bilinmeyen bölgelere akan kan sebebiyle rete femorale'den ayrı olarak gelişebilir. Bu varsayımlar henüz kanıtlanmamıştır ve bu konu tam olarak anlaşılamamıştır.[4]

ACFM, klasik olarak APF'nin bir dalıdır ve bazen doğrudan AF'den de dallanabilir.

Adachi yaptığı çalışmaların sonucuna göre ACFM'nin vakaların %67,2'sinde APF'den, %14'ünde AF'den dallandığını bildirmiştir.[5] Adachi (1928), bizim olgumuzda görülen direk AF'den ayrılan bir ra ve/veya rd'den bahsetmemiştir. Lippert ve Pabst (1985), ACFM'nin doğrudan AF'den dallanma oranını %18 ve APF'den dallanma oranını da %58 olarak bildirmiştir. Ancak Lippert ve Pabst ra ve/veya rd'nin bağımsız olarak AF'den çıkışından bahsetmemiştir.[5,6] Labetowich ve arkadaşları (ark.) ACFM'nin %62,5 oranında APF'den ve %18,75 oranında AF'den çıktığını bildirmişlerdir.[7] Bu sonuçlar Lippert ve Pabst'ın sonuçlarına çok benzerdir.

Prakash ve ark.[8] ACFM'nin orijini ile ilgili çalışmalarında benzer sonuçlara ulaşmışlardır. Bu sonucun aksine

Zlotorowicz ve ark.[9], ACFM'nin APF'den çok AF'den çıktığını bildirmiştir.

Tomaszewski ve ark.[10] ACFM'nin olguların %64,6'sında APF'den, %32,2'sinde AF'den ve %81,1'inde de bağımsız bir dal olarak çıktığını bildirmişlerdir.

ACFM'nin olmaması, önceki çalışmalarda oldukça nadir (%1,7 ve altı) bir varyasyondur. Bu sıklık Labetowicz ve ark. tarafından da %18,75 olarak bildirilmiştir.[7]

Literatür taramamıza da dayanarak bizim olgumuzda görülen ra ve rd'nin ayrı ayrı AF'den çıkışı varyasyonunun nadir görülen bir varyasyon olduğunu söyleyebiliriz.

Ayrıca, aynı olguda aynı taraf ACFL AF'den çıkmaktadır. Adachi, ACFL'nin en yaygın olarak APF'den (%78,2) kaynaklandığını, ikinci en yaygın kaynağın ise AF (%18,3) olduğunu bildirmiştir.[5] Lippert, ACFL'nin %76'sının APF'den ve %19'unun da AF'den çıktığını bildirmiştir.[6] Benzer gözlemler Prakash ve ark.[8] ve Zlotorowicz ve ark.[9] tarafından da yapılmıştır. Ayrıca Tomaszewski ve arkadaşlarının meta-analiz çalışmalarında ACFL'nin %76,61 oranında APF'den ve %19,1 oranında AF'den çıktığı sonucuna ulaşılmıştır.[10]

ACFM ve ACFL'nin her türlü varyasyonu hakkında yeterli bilgiye sahip olmak, girişimciye işlem planlamasında yardımcı olacaktır. Ayrıca bu bilgi caput femoris'te ACFM ve ACFL yaralanmasına bağlı avasküler nekroz oranını azaltacaktır. Makalemiz nadir bir ACFM varyasyonu ile ACFL varyasyonunun birlikte bulunması açısından değerlidir. Tek varyasyon dahi radyolojik girişimsel işlemlerde komplikasyona sebep olabilirken, birden fazla varyasyonun aynı kişi ve aynı taraf ekstremitede olabileceğini bilmenin girişimsel işlem başarısı ve dolayısıyla hasta sağlığı açısından oldukça önemli olduğu düşüncesindeyiz.

Etik Standartlara Uygunluk

Bu çalışma 2006-2007 rutin eğitim disseksiyonu esnasında çıkan bir olgudur. Etik onay gerekmemektedir.

Çıkar Çatışması

Yazarlar arasında çıkar çatışması bulunmamaktadır.

Yazar Katkısı

MÜ: Idea/Concept; ET: Design; AİS, MÜ, ET, BB: Data Collection/Processing; ADE: Analysis/Interpretation; ZAŞ: Literature Review; ZAŞ, ET: Drafting/Writing; ET, MÜ: Critical Review.

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