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EDITORIAL

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Hip and Knee Osteoarthritis: An Overview

Kalça ve Diz Osteoartriti: Genel Bir Bakış

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ABSTRACT

Osteoarthritis (OA) is currently the most common musculoskeletal disease causing significant pain, disability and socioeconomic costs worldwide. It primarily affects weight-bearing joints such as the knees and hips. It is the leading cause of disability in older adults causes pain, loss of function and impaired quality of life. The etiopathology of OA is complex and multifactorial with genetic, biological and biomechanical components. OA was previously thought to be simply a "wear and tear" disease predominantly associated with aging, and mechanically driven. However, it is now known that it is a much more complex process including mechanic, inflammatory and metabolic factors. Most clinical studies of hip and knee OA have focused primarily on improvement in pain and joint function. Current treatment methods do not seem to be sufficient to stop the course of OA, and functional outcomes may be poor in despite of all treatment modalities. The focus is so now on disease prevention and early OA treatment.

Key Words: Hip, Knee ,Osteoarthritis

ÖZ

Osteoartrit (OA) şu anda dünya çapında önemli bir ağrı, sakatlık ve sosyoekonomik maliyete neden olan en yaygın kas-iskelet hastalığıdır. Öncelikle dizler ve kalçalar gibi ağırlık taşıyan eklemleri etkiler. Yaşlı erişkinlerde önde gelen sakatlık nedenidir ve ağrıya, işlev kaybına ve yaşam kalitesinin düşmesine neden olur. OA etyopatolojisi, genetik, biyolojik ve biyomekanik bileşenlerle karmaşık ve çok faktörlüdür. OA önceleri ağırlıklı olarak yaşlanmayla ilişkili ve mekanik olarak yönlendirilen basitçe bir "aşınma ve yıpranma" hastalığı olduğu düşünülüyordu. Ancak inflamatuar ve metabolik faktörlerden oluşan çok daha karmaşık bir süreç olduğu artık bilinmektedir. Kalça ve Diz OA'sı ile ilgili çoğu klinik çalışma, esas olarak ağrı ve eklem fonksiyonundaki iyileşmeye odaklanmıştır. Mevcut tedavi yöntemleri OA gidişatını durdurmakta yeterli gözükmemektedir ve tedaviye rağmen fonksiyonel sonuçlar kötü olabilmektedir. Dolayısıyla artık, hastalığı önleme ve erken osteoartrit tedavisine odaklanılmaktadır.

Anahtar kelimeler: Kalça, Diz, Osteoartrit

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Osteoarthritis (OA) is currently the most common musculoskeletal disease causing significant pain, disability and socioeconomic costs worldwide. It primarily affects weight-bearing joints such as the knees and hips. It is the leading cause of disability in older adults causes pain, loss of function and impaired quality of life [1-3]. Pathologically; osteoarthritis (OA) is a progressive, degenerative disease characterized by focal deterioration of synovial and articular cartilage, cyst, sclerosis, osteophyte formation in subchondral bone, and alterations in all involved joint structures [4,5]. Chronic overload and impaired biomechanics of the joint lead to destructive modifications in synovial tissue, subchondral bone metabolism and articular cartilage. This causes clinical pain, stiffness, swelling, loss of motion, and functional disability in the affected joint [2,6]. <

The etiopathology of OA is complex and multifactorial with genetic, biological and biomechanical components. OA was previously thought to be simply a "wear and tear" disease predominantly associated with aging, and mechanically driven. However, it is now known that it is a much more complex process including mechanic, inflammatory and metabolic factors. More recent investigations have identified numerous other factors and pathogenesis that contribute to the onset of OA [1,2].

In the pathogenesis of OA; synovial fluid analyzes have shown that proteolytic enzymes, reactive oxygen radicals and lipid peroxidation have harmful potentials [4,7]. In addition, increases in proinflammatory cytokines, particularly IL-1, TNF, and IL-6, have been shown to play a significant

role in the synovial fluid and synovial membrane [8]. There are many modifiable and non-modifiable risk factors for OA like: genetic predisposition, age, obesity, metabolic syndrome, previous joint injuries, lifestyle factors, and female gender [2]. Injuries involving the joint, such as anterior cruciate ligament and meniscus injuries, may contribute to the development of OA [9,10].

The goal of the treatment of OA is to prevent damage to cartilage and other structures, to reduce pain, to preserve existing joint range of motion, and to reduce secondary functional failures [4,11]. For this purpose, lifestyle modifications, analgesics, nonsteroidal anti-inflammatory drugs, physical therapy agents and various intra-articular injections were defined, and surgical interventions were recommended for patients who did not benefit from these treatments. These treatment options can be applied alone or in combinations, and guidelines have been advanced in this regard [2,4,11]. Intra-articular injections are often glucocorticoids (GC) and hyaluronic acid (HA). Clinical experience has shown that GCs are very useful in the treatment of OA exacerbations, but they do not alter the underlying process and may have some side effects [4,5]. Intra-articular HA injection; by normalizing the elasticity and viscosity of the synovial fluid, it can contribute to tissue regeneration while improving its protection, lubrication and shock-absorbing effects. Therefore, it is effective in reducing pain and improving joint function [4,5,11]. Tenoxicam has been indicated as another cost-effective intra-articular injection treatment option [11].

Some treatments can be combined. It has been reported that arthroscopic debridement is beneficial in cases with knee OA in appropriate indications. Furthermore intra-articular HA applications can improve the effectiveness of treatment, and oral vitamin E combinations may be beneficial in relieving symptoms [4]. However, it is stated that low and high molecular weight HA preparations are not superior to each other in decreasing the symptoms of OA [12]. Total or unicondylar knee replacement surgeries are successful treatment methods for pain relief, especially for patients with severe knee pain and advanced joint degeneration and destruction who do not respond to conservative treatments [13]. On the other hand, many new treatments such as nerve blockage, mesenchymal stem cell injections and platelet-rich plasma injections are under investigation [2,5].

Most clinical studies of hip and knee OA have focused primarily on improvement in pain and joint function. Current treatment methods do not seem to be sufficient to stop the course of OA, and functional outcomes may be poor in despite of all treatment modalities. The focus is so now on disease prevention and early OA treatment. There is currently an unmet demand for further research into the pathogenesis of OA as well as its course and treatment. However, advances in both imaging and biochemical markers offer potential outcome measures for diagnosis and new treatments [1,3].

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RESEARCH ARTICLE

ARAŞTIRMA

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Assessment of femoral notch morphology in male patients with anterior cruciate ligament injury: an MRI study

Ön Çapraz Bağ Yaralanmalı Erkek Hastalarda Femoral Çentik Morfolojisinin Değerlendirilmesi: MRI Çalışması

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ABSTRACT

Aim: The objective of the present study was to evaluate the femoral notch type, notch width index (NWI), notch angle (NA) and α angle in patients with ACL injury and compare with nonathletic male population, using magnetic resonance imaging (MRI).
Methods: 79 patients with complete ACL tear and 80 patients as control group (aged 19-43 years) who had knee MRI were evaluated. NWI, NA measurements and notch shape were evaluated on axial fat-saturated proton-weighted sequences. Femoral notch shape was classified as A, U and W types.
Results: A statistically significant association was found between notch type, NWI, NA and ACL injury (p<0,001). Type A notch in the ACL-injured group (79.75 %) was significantly higher than the control group (24%). NWI was lower in patients with ACL-injured group than in control group (0.249 ± 0.020 vs 0.281 ± 0.022) Notch angle was lower in patients with ACL-injured group than in control group (47.15 ° ± 5.63 ° vs 50.73 ° ± 5.44°). A significant association between stenotic notch type A and NWI (p <0,001). The α angle was lower in patients with ACL-injured group than in control group but it was not statistically different (41.9 ° ±2.79 °vs 42.06 ° ±2.53 °; p= 0.978).
Conclusion: This study showed that however low NWI, NA values are a risk factor for ACL injury, the strongest predictive factor was stenotic femoral notch type A. α angle had no significant correlation in ACL injury.

Key Words: Anterior cruciate ligament, femoral notch type, intercondylar notch angle, magnetic resonance imaging

ÖZ

Amaç: Bu çalışmanın amacı, sporcu olmayan, erkek, ön çapraz bağ (ÖÇB) yaralanmalı hastalarda femoral çentik tipi, çentik genişlik indeksi (NWI), çentik açısı (NA) ve α açısını manyetik rezonans görüntüleme (MRI) kullanarak değerlendirmek ve karşılaştırmaktır.
Yöntemler: Komplet ÖÇB yırtığı olan 79 hastanın ve 80 hastalık kontrol grubunun (19-43 yaş arası) diz MRI görüntüleri değerlendirildi. NWI, NA ölçümleri ve çentik şekli, eksenel yağa doymuş proton ağırlıklı sekanslar üzerinden değerlendirildi. Femoral çentik şekli A, U ve W tipleri olarak sınıflandırıldı.
Bulgular: Çentik tipi, NWI, NA ve ACL yaralanması arasında istatistiksel olarak anlamlı bir ilişki bulundu (p<0,001). ÖÇB yaralanmalı grupta; A tipi çentik (%79.75), kontrol grubundan (%24) önemli ölçüde daha yüksekti. ÖÇB hasarlı grupta NWI kontrol grubuna göre daha düşüktü (0.249 ± 0.020 vs 0.281 ± 0.022). Çentik açısı ÖÇB hasarlı grupta kontrol grubuna göre daha düşüktü (47.15 ° ± 5.63 ° vs 50.73 ° ± 5.44°). Stenotik çentik tipi A ile NWI arasında anlamlı bir ilişki mevcut idi (p <0,001). ÖÇB yaralanmalı hastalarda α açısı kontrol grubuna göre daha düşüktü ancak istatistiksel olarak fark yoktu (41.9 ° ±2.79 °vs 42.06 ° ±2.53 °; p= 0.978).
Sonuç: Bu çalışma, düşük NWI, NA değerlerinin ÖÇB yaralanması için bir risk faktörü gibi görünse de, en güçlü prediktif faktörün stenotik femoral çentik tip A olduğunu göstermiştir. α açısı ÖÇB yaralanmasında anlamlı bir korelasyon göstermemiştir.

Anahtar Kelimeler: Ön çapraz bağ, femoral çentik tipi, interkondiler çentik açısı, manyetik rezonans görüntüleme

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INTRODUCTION

Anterior cruciate ligament (ACL) is an important stabilizer of the most common injured knee joint. Approximately 70% of ACL injuries are non-contact and occur during a sudden change of footsteps or when an athlete slows down [1]. Previous studies have shown that ACL injuries and ACL deficiency lead to articular cartilage damage, chronic knee instability and early secondary osteoarthritis [2].

Multiple intrinsic and extrinsic predisposing factors such as biomechanical abnormalities, neuromuscular deficits, hormonal change and environmental factors may be effective in ACL injury. In many studies, the association between the risk of increased ACL damage and anatomical features of the knee has been shown [3]. These anatomic risk factors are factors such as knee and general joint laxity, knee geometry (intercondylar notch, tibial slope), ACL volume and body mass index. Although intercondylar notch morphology has been investigated with different imaging modalities, their results are contradictory.

Although the number of ACL injuries is lower in women than in men, the prevalence of ACL injuries in women is significantly higher than in men. This difference can be explained by the anatomical differences between women and men. Therefore, studies on risks should be evaluated in separate groups [4].

In this study, non-athlete male patients with acute complete ACL injury were included to eliminate anatomical differences. The aim was to evaluate the femoral notch type, notch width index (NWI), notch angle (NA) and alpha 'α angle' components in these patients and to determine the most valuable risk factor among them.

MATERIALS AND METHODS

Ethical approval was obtained from the ethics committee of the health institution where the study was conducted (No:266/04.05.2018). Male nonathletic adult patients who were referred to our radiology department with clinical diagnosis of ACL injury between May 2016 and May 2018, were retrospectively evaluated. Patients whose history of swelling or pain started as a result of a trauma to the knee or sports injury within three weeks were included in the study. On physical examination, anterior drawer tests were positive in all patients. Inclusion criteria were defined as follows: (1) Male patients (2) Skeletal maturity > 18 years old (3) History of knee pain with sports injury or trauma in the last 3 weeks (4) no previous surgery (5) entire sequences are obtained and all images are clearly monitored. Exclusion criteria: 1- Female patients 2- Skeletal immaturity < 18 years old. 3- Any other ligament injury history 4- High energy trauma history 5- Fractures or tumors involving articular surfaces 6- Radiologic findings of osteoarthritis [5,6] (because of the effect on reducing NWI) 7- Partial ACL tear.

Physical examination and MR images of the control group patients were entirely normal. We selected 159 cases, 79 patients and 80 controls and our institutional review board approved the study.

All MR sequences were performed with a 1,5 Tesla scanner (MAGNETOM, Siemens, Erlangen, Germany) while the knee in the extension position. The regular knee MRI procedures in our hospital were includes: Axial proton density fat-saturated (PDFS): TR 4240 ms, TE 41ms, 160 mm FOV, slice thickness: 4 mm, sagittal T1-weighted: TR 606 ms, TE 9,4 ms, slice thickness: 4 mm and coronal T1-weighted: TR 471ms, TE 9.4 ms, slice thickness: 4 mm, Sagittal PDFS: TR 3540 ms, TE 31 ms, slice thickness:3 mm, Coronal PDFS: TR 3280 ms, TE 20 ms, slice thickness: 4 mm. The images were evaluated by a radiologist with 9 years of experience in musculoskeletal MRI, who had no knowledge of the patients' age, gender, type of trauma, medical history and physical examination findings, by using Picture Archiving and Communication System (PACS, General Electric, Chicago, IL, USA). Complete ACL tear was determined in sagittal fat-saturated MRI images. While the patients without ACL injury constituted the control group, those with complete ACL injuries constituted the study group. Complete tears of ACL were diagnosed based on the presence of non-visualization of normal intact fibers of the ACL.

Axial fat-saturated proton-weighted sequences were selected for femoral NWI measurement and

morphology evaluation. The femoral notch shape, described by Van Eck et al., was classified as type A, type U and type W [7]. Type A is the stenotic form that appears narrow from the middle to the apex. Type U also has a wider contour on the top than type A. In Type W, femoral notch has two apices of the notch roof and wider than type U (Figure 1) [7,8].

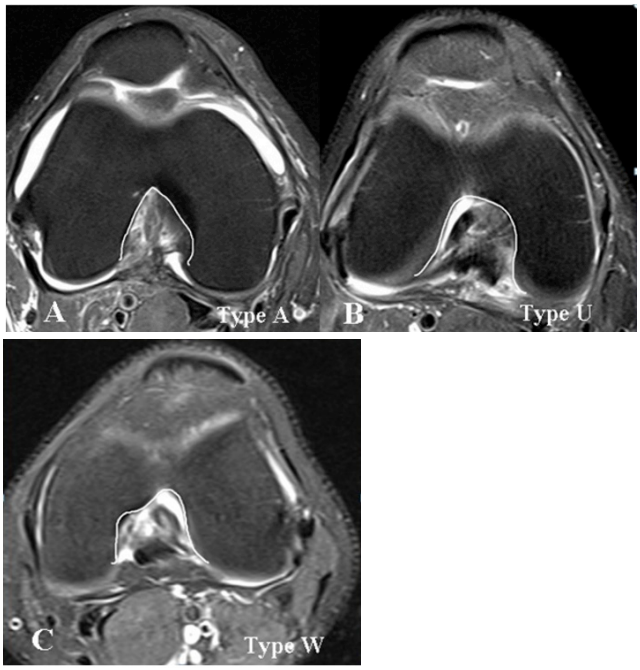

Fig.1. Axial PD (Fat Sat) MRI demonstrating femoral notch shapes; type A, type U and type W.

NWI was measured as described by Domzalski et al. [9]. NWI was determined by the ratio between central notch width and intercondylar width at the level of popliteal groove. The values above 0.270 or more were considered normal and less than 0.269 was stenotic (Figure 2A).

The angle of the notch was defined as the line from the top of the intercondylar notch to the most inferior edge of the notch at the medial and lateral condyles (Figure 2B). Last, α angle was the angle between the longitudinal femoral axis and the Blumensaat line (BL) measured as described Fernandez et al. [10] (Figure 3). The same radiologist evaluated all MRI examinations twice, at two different sittings spaced three weeks apart.

Statistical Analysis

The statistical analysis was done by using the SPSS® version 17 (IBM Corp., Armonk, USA). Mean, standard deviation, median and minimum-maximum values were used to present descriptive analyses. Independent samples t-test was used for comparisons between the two normally distributed independent groups. Non-normally distributed variables were analyzed using the Mann-Whitney U test. The measurement data was analyzed using the Spearman Correlation test. Risk factors for ACL rupture were evaluated by binary logistic regression analysis. Odds ratios (ORs) and their 95 % confidence intervals (CIs) were estimated. P-values < 0.05 were evaluated as statistically significant results.

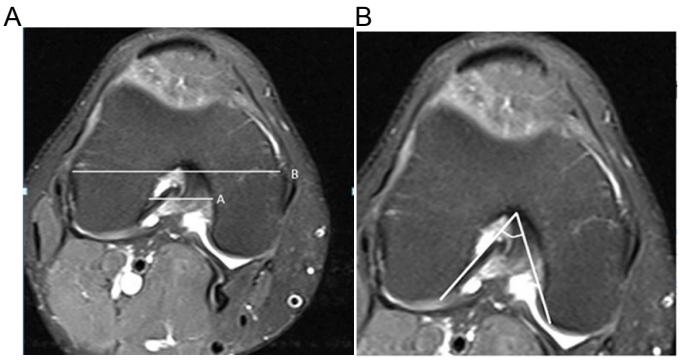

Fig. 2. A) Axial PD (Fat Sat) MRI demonstrating measurement of femoral NWI. A Femoral notch width B Intercondylar width. NWI= A/B, B) Axial PD (Fat Sat) MRI demonstrating notch angle measurement.

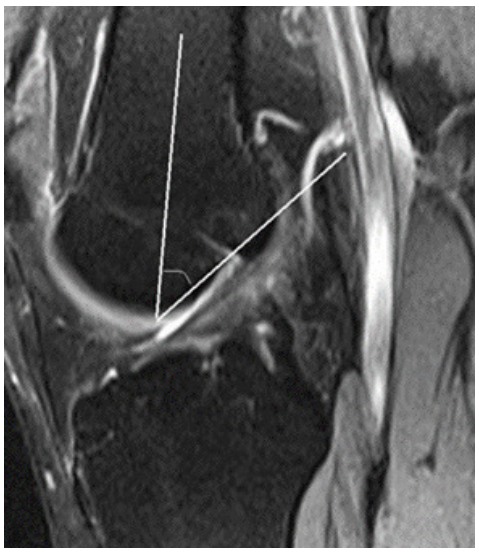

Fig. 3. Sagittal PD (Fat Sat) MRI image demonstrating α angle measurement.

RESULTS

The mean age of patients was 30.5 ±5.69 (range 19-43 years) and there was no statistical difference in age between groups. The comparison of notch

type, NWI, notch angle and α angle values among patients with ACL injured group and control group are summarized in Table 1. The coefficient of variation was < 10% for intraobserver analysis's.

Table 1. Comparison of NWI, NA, α angle and type of notches between the ACL-injured Group and Healthy Group

	ACL injury		Control		p
	Mean ± s.d.	Median	Mean ± s.d.	Median	
NWI	0.249 ± 0.02	0.251	0.281± 0.022	0.282	<0.001[1]
NA	47.15± 5.63	47.00	50.73± 5.44	51.00	<0.001[2]
α angle	41.97± 2.79	42.00	42.06± 2.53	42.00	0.978[2]
Type A	63	(79.75)	24	(30.00)	<0.001[3]
Type U	16	(20.25)	56	(70.00)	

[1]Independent t test [2]Mann-Whitney U Test [3]Chi-square Test (instead of mean ± s.d, n/% ratio is given)

In the control and patient groups, one patient each had notch shape type W. Type W and type U numbers are combined because type w is very small and close to type U. A statistically significant association was observed between notch type and ACL rupture (p<0,001). Type A notch rate was 79.75% in the ACL damaged group. It was significantly higher than the control group (24%). Type A ratio in the ACL-damaged group was 3.93 times higher than the type U ratio. NWI and NA values were statistically different between patients with ACL-damaged group and control group. NWI was lower in patients with ACL-damaged group than in control group (0.249 ± 0.020 vs 0.281 ± 0.022; p <0,001). NA was lower in patients with ACL-injured group than in control group (47.15 º ± 5.63 º vs 50.73 º ± 5.44º; p <0,001). Notch angle cut off value was determined as 49.5º (sensitivity %67.09 and specificity %61.25).

The stenotic notch type A and NWI had a significant cooperation. The NWI measurements of type A is lower than that of notch type U (0.254 ± 0.024 vs 0.278 ± 0.023; p <0,001). Notch stenosis was found in 90 patients (56.6 %). Stenotic type A notch was observed in sixty-six (73.33 %) of these patients (Table 2). This 66 people (73,33%) were type A and 24 people (26,67%) were type U with NWI less than 0,269. Similarly, there is a strong partnership between stenotic notch type A and NA. NA measurements of type A is lower than that of type U (47.55 º ± 5.43 º vs 50.64 º ± 5.82 º; p <0,001). The α angle was lower in patients with ACL-injured group than in control group but it was not statistically difference (41.9 º ±2.79 ºvs 42.06 º ±2.53 º; p= 0.978).

When the factors affecting ACL injury were examined by regression analysis, it was shown that the strongest connection was associated with the notch type and it was determined that the probability of rupture in A-type notches increased 8.13 times (% 95 G.A. = 3.84-17.301) (Table 3).

Table 2: Correlation between NWI and notch type (p<0,001)

	NWI<0.269		NWI≥0.270	
	n	%	n	%
Type A	66	(73,33)	21	(30,43)
Type U	24	(26,67)	48	(69,57)

Table 3. Binary logistic Regression Analysis to determine the factors affecting ACL injuries

Factor	Coefficient (B)	Std. Deviation	Odds Ratio	%95 CI		p
				Min.	Max.	
Type A	2.096	0.385	8.134	3.824	17.301	<0.001
Notch angle	0.095	0.035	1.099	1.026	1.178	0.007
α angle	-0.058	0.072	0.943	0.819	1.086	0.419
Constant	-3.0926	3.226	0.045			0.338

CI: Confidence interval

DISCUSSION

Our study showed that NWI was significantly smaller in patients with ACL injury, than in the healthy ACL group. Subjects with an ACL tear also showed to have stenotic form of notch and a smaller femoral notch angle. On the other hand, increased α angle was not associated with the risk of ACL tear. In our study, stenotic type A notch shape had the greatest risk of ACL injury.

Van Eck et al. and Sutton et al. reported that type A shape of femoral notch was easy to affect notch stenosis in ACL ruptured patient [7,11]. In addition, Sutton et al. showed that the A-type ratio in women was greater than in men. Al-Saeed et al. reported that type A patients had a higher risk than other types [8]. In the study of Basukala et al., 30% of the patients with U type notch had ACL rupture, on the other hand, 74% of the patients with A-type notch had rupture [12]. Shen et al. compared 125 patients who underwent ACL reconstruction and 125 patients without ACL rupture. They found that there is no significant difference in notch shape

[13]. Huang et al. compared 61 patients who underwent ACL reconstruction with a 78-patient control group. They found no significant difference about notch shape [14]. In our study, we found that type A in the ACL injured group was 3.93 times higher than type U, and type A was higher in the ACL injured group than the non-injured matched controls.

NWI has been measured on x-ray, CT, and MR images in several studies. Souryal et al. measured NWI using tunnel view radiographs and reported smaller NWI measurements in the ACL-ruptured group with male and female population [15]. Since MRI provides easier, faster and repeatable evaluation, many studies have used MRI to measure NWI but no clear NWI cut-off value could be found to detect notch stenosis. Uhorchak [16], LaPrade [17], Domzalski [9] and Souryal et al. [15] determined 0.18, 0.19, 0.27, 0.2, respectively. Basukala et al. NWI cut off value was taken as 0.27 in their study. While NWI decreased in 40% of the group with ACL injury, it was 13% in the group without ACL injury. This was statistically significant. On the other hand, 40.67% of the group with ACL injuries had narrow NWI while 59.32% had wide NWI [12]. Huang et al. found that the NWI was significantly smaller in both axial and coronal MR images in the ACL damaged group compared to the control group [14]. Furthermore, Shen et al. found smaller NWI in ACL injured group. The cut off value of NWI was determined as 0.252 [13]. In contrast, Van Diek et al. and Vrooijink et al. reported in their studies with both male and female population that NWI is unrelated to ACL rupture [18,19].

Bouras et al. showed a significant relationship between NWI and stenotic notch type A but no correlation was found between NWI and ACL rupture in female ACL-injured population [20]. In our study in ACL-injured group, NWI was statistically lower than the controls. In stenotic type A group, NWI values were lower than type U. In ACL-ruptured group patients the ratio of patients whose NWI values <0,269 were higher than healthy matched controls.

In the literature, the relationship between ACL injury and femoral notch angle has been rarely investigated [22-24]. Herzog et al. found femoral notch angle of 45.7 º ± 10.9 º in the patient group and 49.8 ° ± 7.2 º in the control group [21]. The most important reason for not finding a difference between the groups as Herzog et al. said that the study population consists of a limited number of individuals. Whereas Anderson AF et al. [22] with CT, Cha JH et al. [23] and Alentorn-Geli E. et al. [4] with MRI, reported that NA <50º would lead the risk of ACL injury, Stein et al. [6] showed no association between ACL injury and femoral notch angle <50º. Huang et al. and Shen et al. found that the NA was significantly smaller in the case group than that in the control group [13,14]. NA was determined as 50.36º ±5.70º by Huang et al. and it was significantly different with control group (p>0.018) [19]. In our study, femoral notch angle (47.15 º ± 5.63 º) was significantly lower in the ACL damaged group than in the control group (50.73 º ± 5.44º).

Fernandez-Jaen T et al. first described α angle and measured higher α angle values in ACL injured patients with male and female population with 57.5º ± 5.5º, compared than control group with 56.2 º ± 4.5 º [10]. Bouras et al. reported no significant difference in patients with ACL-injuries than controls in the female population (44 º ±3 º vs 43 º ±4) [20]. In these two studies, 13º of contradiction was found in the measurements of both the ACL-injuries and healthy groups. In contrast, Shen et al. found increased α angle (described as β angle) was the most crucial component for ACL injury. They indicated that more than 38.5 º α angle was associated with an increased risk of ACL injury (41.48 º ± 2.22 º vs. 38.30 º ± 3.16 º) [13]. On the other hand, Huang et al. observed that the risk of ACL injury increased with the decrease in α angle (described as INA). In the study, it is stated that decreased α angle creates a sharp edge on notch outlet, thus facilitating the ACL injury [14]. In our study there was no statistically significant difference between the two groups in terms of α angle (41.9 º ±2.79 º vs 42.06 º ±2.53 º).

Our study has several limitations. First, this was a retrospective study, therefore we could not achieve all the clinical information such as height, weight, physical examination findings and activity frequency. Second, while evaluating the femoral notch stenosis, we excluded the stenosis-associated ACL laxity and thinning and did not

measure ACL volume. Third, while evaluating the femoral notch morphology, we did not evaluate the notch volume and made measurements in only two dimensions. Finally, the risk factors for ACL injury are multifactorial, which aims to evaluate only femoral notch morphology.

CONCLUSION

In our study, there was a strong relationship between ACL injury and notch type, NWI and NA. The type A notch has been shown to be the most powerful factor in the prediction of anterior cruciate ligament rupture. Notch angle cut off value was determined as 49.5º in our study. Although there are studies reporting different results about alpha angle, it was not found as a risk factor in our study.

Description of risk factors can enable the implementation of preventive measures for people at risk. Many intrinsic factors such as NWI and femoral notch morphology were examined and it was observed that they cause variability according to gender, ligament laxity and race. We tried to evaluate these intrinsic factors in Turkish population and these results emphasize the importance of notch morphology and will also contribute to both prevention programs and knee surgery in ACL injuries. Therefore, more studies are required to explain different results about risk factors of ACL injuries.

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Ethics Committee Approval: This study was approved by the Medipol University Non-Interventional Clinical Research Ethics Committee. (Ethics Committee No:266).

ORCID and Author contribution: **A.S.A.(0000-0002-9610-2209):** Concept and Design, Literature search, Analysis and Interpretation, Manuscript Writing, Critical Review. **A.T. (0000-0003-3078-1285):** Concept and Design, Data Collection, Analysis and Interpretation, Manuscript Writing, Critical Review

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RESEARCH ARTICLE

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The effects of the COVID-19 pandemic on patient application to outpatient plastic surgery clinics and management of treatments: a retrospective comparative study

COVID-19 Pandemisinin Plastik Cerrahi Kliniklerine Hasta Başvurusu ve Tedavilerin Yönetimine Etkileri: Geriye Dönük Karşılaştırmalı Çalışma

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ABSTRACT

Aim: The aim of this study was to show the differences in patient profile and treatment selections in outpatient plastic surgery clinic, by comparing the pre-pandemic and the pandemic period for one-year processes.

Methods: The patients who applied to outpatient clinic of plastic surgery during the pre-pandemic and pandemic periods were included in the study. The data related to demographic characteristics, reasons for application of outpatient plastic surgery clinic, pre-diagnosis and treatment modalities outpatient or inpatient - were collected retrospectively.

Results: It was observed that there was a significant numerical difference in the number of applications of the patients between the pre-pandemic and the pandemic periods. The application rate of females decreased, while the rate of males increased during the pandemic period. When we examined the application rates in the age groups, the patient application rates in the 12-18, 18-25, and 25-40 age groups increased. In the other age groups, the patient application rates were decreased ($p<0,01$). When the reasons for patient application were examined one by one, the burn injury rate remains the same, while acute-chronic wounds, maxillofacial trauma and other reasons rates increased ($p<0,001$). When the outpatient and inpatient treatment rates were compared, the outpatient treatment rate increased, while the inpatient treatment rate decreased ($p<0,001$).

Conclusion: This study shows the changes in the applications of patients and preferences of treatments during the pandemic period compared to the pre-pandemic period.

Key Words: COVID-19 Pandemic, Outpatient plastic surgery clinic, the patient application

ÖZ

Amaç: Bu çalışmanın amacı, bir yıllık süreçlerde pandemi öncesi ve pandemi dönemini karşılaştırarak plastik cerrahi polikliniğinde hasta profili ve tedavi seçimlerindeki farklılıkları ortaya koymaktır.

Yöntemler: Alanya Alaaddin Keykubat Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu iznini takiben çalışmaya başlandı. Pandemi öncesi ve pandemi süreçleri için sırasıyla 11 Mart 2019 ve 11 Mart 2020 tarihinden itibaren birer yıllık iki dönem alındı. Belirlenen dönemlerde plastik cerrahi polikliniğine başvuran hastalar çalışmaya dahil edildi. Demografik özellikler, plastik cerrahi polikliniğine başvuru nedenleri, ön tanı ve yatarak veya ayaktan tedavi şekilleri ile ilgili veriler geriye dönük olarak toplandı.

Bulgular: Hastaların pandemi öncesi ve pandemi dönemleri arasında başvuru sayılarında anlamlı sayısal fark olduğu gözlendi. Pandemi döneminde COVID-19 vaka sayısı ile ters orantılı olarak hasta başvurularında düşüş gözlemlendi. Pandemi döneminde kadınların başvuru oranı azalırken erkeklerin oranı arttı. Başvuru oranlarına baktığımızda 12-18, 18-25 ve 25-40 yaş gruplarında oranların arttığı görüldü. Diğer yaş gruplarında ise hasta başvuru oranları azaldı ($p<0,01$). Başvuru nedenleri göz önüne alındığında pandemi döneminde tüm nedenlere bağlı olgu sayısında pandemi öncesine göre istatistiksel olarak anlamlı azalma görüldü ($p<0,001$). Hasta başvuru nedenleri tek tek incelendiğinde yanık oranları aynı kalırken, akut-kronik yaralar, maksillofasiyal travma ve diğer başvuru neden oranları arttı ($p<0,001$). Ayakta ve yatarak tedavi oranları karşılaştırıldığında, ayakta tedavi oranı artarken, yatarak tedavi oranı azaldı ($p<0,001$).

Sonuç: Bu çalışma, pandemi döneminde pandemi öncesi döneme göre hastaların uygulamalarındaki ve tedavi tercihlerindeki değişimleri göstermektedir.

Anahtar sözcükler: COVID-19 pandemisi, plastik cerrahi polikliniği, hasta başvurusu.

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INTRODUCTION

The novel coronavirus (2019-nCoV) disease (COVID-19), whose virus name had been changed by the International Committee on Taxonomy of Viruses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had many important effects on public health and human welfare, causing a global pandemic [1] and having had a significant impact on daily human life [2]. During the pandemic, it has become mandatory for patients to avoid non-essential visits to healthcare facilities, in order not to expose themselves or others to further illness [3]. In addition, the COVID-19 pandemic paved the way for the change in the appearance, activities and treatment attitudes of hospitals and clinics, in particular for branches such as plastic, reconstructive and aesthetic surgery, which are not directly related to COVID-19 infection, for the obligatory reshaping of treatment priorities and discovering new treatment methods [4]. However, coronaviruses are prone to genetic recombination that can lead to new genotypes and future outbreaks, therefore the need for constant preparation for ongoing and future outbreaks and changing standards are also non-negligible aspects for plastic surgery departments to consider [5]. This is responsible for the late effects of the COVID-19 pandemic. The fields of plastic surgery are trauma, burns and acute infections, as well as elective reconstruction surgery apart from cosmetic and aesthetic surgery [6]. There are studies in the literature on the modifications in the definition of elective surgery in plastic surgery clinics and the changes in the approach of plastic surgeons to the emergency patient [3-6]. There are several studies in the literature that have examined the effects of the early pandemic period, consisting of the initial six months. However, the number of studies on the later effects of the pandemic period is limited.

The goal of this study was to compare the pre-pandemic and pandemic periods, one year prior and one year after, in order to evaluate the demographic and clinical data of patients who applied to outpatient plastic surgery clinics, and to offer suggestions for relevant patient approach strategies of plastic and reconstructive surgery clinics, during pandemics and/or similar emergencies.

MATERIALS AND METHODS

COVID-19 was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020, on the very same day the first case was reported in Turkey [7]. A term of one year (March 11, 2019 to March 10, 2020) was determined as the pre-pandemic period. Similarly, a successive period (March 11, 2020 to - March 10, 2021) was determined as the pandemic period. The patients who applied to the outpatient clinic of the plastic surgery Training and Research Hospital, during the pre-pandemic and pandemic periods, were included in the study. The essential approval was obtained from the hospital to use its database. The study protocol was approved by the ethics committee of the Faculty of Medicine. Database related to demographic characteristics, reasons for the application of outpatient plastic surgery clinic, pre-diagnosis and treatment selection - outpatient and inpatient - were collected retrospectively. The pre-pandemic and the pandemic periods were evaluated separately.

Statistical

A standard software package (SPSS 20 for Windows; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Statistical significance was analyzed using the Chi-square test. The Chi-square statistical analysis method was used to assess whether there was a significant difference between the collected parameters belonging to those periods by. In these analyses, a p-value of equal or less than 5% was considered statistically significant. Data was presented as n (%).

RESULTS

During the pre-pandemic period of one year, the number of admissions of patients to the plastic surgery outpatient clinic was 2 645, and during the pandemic period, the number was 968 (Table 1). It was observed that there was a significant numerical difference in the number of applications of the patients between the pre-pandemic and the pandemic periods. It was also noted that there was a decrease in the application of patients, which was inversely related to the number of COVID-19 cases during the pandemic term (Figure 1).

When the pre-pandemic and pandemic periods

were compared, a significant difference was observed in terms of gender (p<0,01) (Table 1).When the rates of admitted female and male patients were considered, the application rates of female and male patients were 55.0% and 45.0%, respectively, over the pre-pandemic period. However, the application rate of females decreased to 49.1%, while the rate of males increased to 50.9% during the pandemic period.

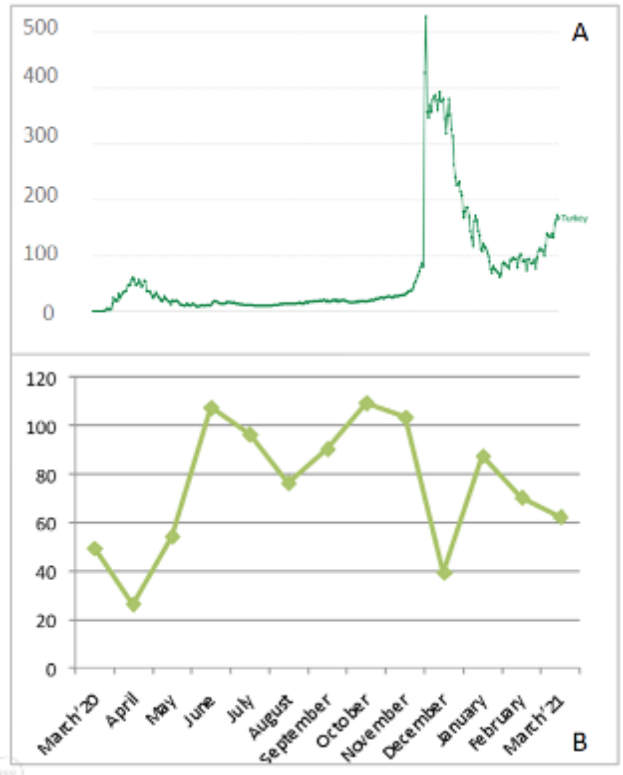

Figure 1: The monthly number of COVID-19 cases (A) and number of patient admission (B)

Based on the statistical analyses, a significant decrease was observed in each age group (p<0,001) during the pandemic period, when compared to the pre-pandemic period (Table 2). When we examined the application rates in the age groups, the patient application rates in the 12-18, 18-25, and 25-40 age groups increased from 4.9% to 5.8%, from 14.4% to 17.5%, and from 26.7% to 30.3%, respectively. In the other age groups, the patient admission rates were decreased (p<0,001).

Regarding the reasons for the application of patients to the outpatient plastic surgery clinic, a statistically significant reduction was observed in the number of all-cause cases during the pandemic period, compared to the pre-pandemic period (p<0,001) (Table 3). When the reasons for patient application were examined, the burn injury rate remained the same (0.2%), while acute wounds, chronic wounds, maxillofacial trauma and other reasons rates increased from 11.2% to 13.3%, from 4.3% to 7.2%, from 1.7% to 3.6%, and from 17.8 to 32.2%, respectively. However, aesthetic and skin tumors - the majority of which were benign skin lesions, such as nevus - were among the reasons for patient application. During the pandemic period, the application rates of these cause-cases decreased from 25.5% to 20.4% and from 39.3% to 3%, respectively.

A statistically significant decrease was observed in the number of outpatient treatments and inpatient treatments during the pandemic period, when compared to the pre-pandemic period (p<0,001) (Table 1). When the outpatient and inpatient treatment rates were compared, the outpatient treatment rate increased from 90.8% to 95.7%, while the inpatient treatment rate decreased from 9.2% to 4.3%.

DISCUSSION

The main results of this study show that the number of admitted patients decreased during the pandemic period. The graph of daily COVID-19 case numbers in Turkey and the graph of the number of admitted patients were evaluated together for a detailed examination. We can point out that the number of patient applications decreased as the number of COVID-19 cases increased. Overall, we suspect that this is due to strict social distancing rules, stay-at-home orders and quarantines. However, it was observed that these effects continued not only in the early period of the pandemic, but also in the late period (Figure 1).

The COVID-19 pandemic has changed the healthcare delivery system of the healthcare institutions. Strict social distancing was only the way to avoid the rapid spread of COVID-19 and the inevitable oversaturation of hospital resources [8]. Despite this fact, patients have been continuing to apply to the plastic surgery outpatient clinic, which has resulted in a marked change in the number of applications of the patients, the reasons for admission and preferences of treatments.

Table 1. Comparison of the gender distributions and treatment selections during the pre-pandemic and the pandemic periods

Variables	Gender		Total % (n)	P	Treatment Option		Total % (n)	p
	Female % (n)	Male % (n)			Outpatient % (n)	Inpatient % (n)		
Pre-pandemic	55.0 (1454)	45.0 (1190)	100 (2644)	0.002*	90.8 (2401)	9.2 (244)	100 (2645)	<0.001
Pandemic	49.1 (475)	50.9 (493)	100 (968)		95.7 (925)	4.3 (42)	100 (967)	
Total	53.4 (1929)	46.6 (1683)	100 (3612)		92.1 (3326)	7.9 (286)	100 (3612)	

Chi square test; *<0.01

Table 2. Distribution of the age groups during the pre-pandemic and the pandemic periods

Variables		Group of age							P
		0-12	12-18	18-25	25-40	40-60	>60	Total	
Pre-pandemic	Count	192	129	382	707	873	412	2645	0.005*
	%	7.3	4.9	14.4	26.7	31.1	15.6	100	
Pandemic	Count	67	56	169	293	258	125	968	
	%	6.9	5.8	17.5	30.3	26.7	12.9	100	
Total	Count	259	185	551	1000	1081	537	3613	
	%	7.2	5.1	15.3	27.7	29.9	14.9	100	

Chi square test; *<0.01

Table 3. Comparison of the reasons of patient application during the pre-pandemic and the pandemic periods

Variables		Reason of Patient Application								P
		Skin tumor	Burn injury	Maxillofacial trauma	Aesthetic	Chronic wound	Acute wound	Others	Total	
Pre-pandemic	Count	1040	4	44	674	114	297	472	2645	<0.001
	%	39.3	0.2	1.7	25.5	4.3	11.2	17.8	100	
Pandemic	Count	223	2	35	197	74	129	312	968	
	%	23.0	0.2	3.6	20.4	7.2	13.3	32.2	100	
Total	Count	1263	6	79	871	184	426	784	3613	
	%	35.0	0.2	2.2	24.7	5.1	11.8	21.7	100	

Chi square test

According to the study by Ozturk et al., asymptomatic American Society of Anesthesiologists (ASA) I-II risk group patients under the age of 69 were the leading choice groups for treatments, including cosmetic surgery, throughout the pandemic period. Patients in other age groups, as well as those in the ASA III-IV risk categories, should be postponed to the greatest extent possible [3]. In a study from Turkey published in 2022 by Tabakan et al., the mean age of the patients was not significantly different between the pre-pandemic and pandemic periods [9].

In our study, when patient applications were evaluated according to age groups, we observed that the rates of patient applications changed. We suspect that the main reason for this change was that the extreme age groups (the group with the age range of 0-12 years, and persons over 60 years of age) were required to remain confined at home, in order to protect themselves as the riskier groups.

However, there are only a few studies that specify whether there were gender variations in applications and treatments throughout the pandemic. In the study by Tabakan et al., no difference was found when the applications were evaluated in terms of gender [9]. When the gender distribution of patient applications was examined, it was observed that there was a decrease in the rate of female applications and an increase in the rate of male applications. The reason for this is that the applications of female patients are mostly for aesthetic reasons. The decrease in applications for aesthetic reasons and the decrease in rates of female application as well as the increase in rates of male application are interrelated.

There are studies in the literature stating that elective cases and aesthetic surgery have a negative effect on COVID-19 infection [3-8], in contrast, there are also studies stating that there is

no serious negative effect [9]. In our study, we also observed that the rate of aesthetic applications decreased because of the effective warning announcements for not applying unnecessarily to hospitals in Turkey. The most common reason for patient application is elective procedures such as cosmetic management of nevi, in cases with skin tumors. Therefore, the rate of general skin tumors among the reasons for patient admission has decreased.

Another important finding of our study was that when the pre-pandemic and pandemic periods were compared in terms of treatment methods, the observed result was a decreased outpatient and inpatient treatment. When the treatment options were examined one by one, however, the rate of inpatient treatment decreased while the rate of outpatient treatment increased. This shows that the treatment plan determined by the plastic surgeon with the patient is mostly outpatient treatment. Thus, the time of stay in the hospital is reduced, the hospital staff workforce, the hospital equipment and its resources can be duly directed to the pandemic [2].

The World Health Organization made many recommendations to confront the COVID-19 pandemic, the most important of which was to remain isolated at home [10]. This situation altered the patient admission behavior in many clinics. While research on COVID-19 was being carried out, many studies were initiated to determine how the pandemic would affect routine patient applications and treatments: researchers have succeeded in overcoming many challenges to this global health emergency [11]. Studies on this subject continue and the results of our study can contribute data on patients to ensure that better protection and treatment strategies are created in pandemic and/or emergency health situations.

The study's limitations are that it was a single-center study and did not include admission rates to private hospitals and clinics. It is, however, a predictor of plastic surgery patient applications in university and public hospitals.

Conclusions

Our research revealed the changes in the applications of patients and preferences of treatments during the pandemic period, compared to the pre-pandemic period. The outcomes of our study may contribute to the establishment of case management approaches and help to predict patient application distribution in future emergencies, in plastic surgery outpatient clinics.

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RESEARCH ARTICLE

ARAŞTIRMA

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The evaluation of vaccination status and the factors affecting vaccination in cancer patients

Kanser hastalarında aşılanma durumu ve aşılanmayı etkileyen faktörlerin değerlendirilmesi

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ABSTRACT

Aim: Coronavirus disease 2019 (COVID-19) pandemic increased the mortality of cancer patients by causing direct infection or collateral damage to the healthcare system. After the development of effective vaccines against COVID-19 infection, mortality rates declined. In this study, we try to investigate the vaccination among cancer patients.
Methods: A survey was applied to patients with cancer in order to investigate the attitudes towards vaccination and the factors effecting vaccination in two medical oncology centers in Turkey.
Results: 271 patients were included in the study. No difference was observed in the attitudes of patients towards vaccination according to cancer type. 83% of the patients were vaccinated against COVID-19. In 75% of the study population, vaccine was administered in the earliest available time. Receiving chemotherapy was the most significant reason to avoid vaccination among the study group (p=0,002). There was no significant difference in terms of treatment type for COVID-19 between patients with or without adequate vaccination. The most negative factor affecting vaccination was active chemotherapy treatment. Social relations and traditional media were the most positive factors for vaccination.
Discussion: Vaccination is of vital importance for patients who are treated or on remission. Even if patients are to receive chemotherapy, they should be informed about vaccination and should be encouraged for vaccination.

Keywords: COVID-19, vaccine, cancer

ÖZ

Amaç: COVID-19 pandemisi, doğrudan enfeksiyona yol açarak veya sağlık sisteminde aksamayla beraber sekonder olarak kanser hastalarının ölüm oranını artırdı. SARS-CoV-2'nin yol açtığı enfeksiyona karşı etkili aşıların geliştirilmesinden sonar ölüm oranları düştü. Bu çalışmada kanser hastalarının aşı olup olmadığını incelemeye çalıştık.
Yöntemler: Türkiye'de iki medikal onkoloji merkezindeki hastaların aşıya yönelik tutumları ve aşılamayı etkileyen faktörleri araştırmak amacıyla kanserli hastalara anket uygulandı.
Bulgular: Çalışmaya iki yüz yetmiş bir hasta dahil edildi. Hastaların aşıya yönelik tutumlarında kanser türüne göre farklılık gözlenmedi. Hastaların %83'ü COVID-19'a karşı aşılanmıştı. Çalışma popülasyonunun %75'ine mümkün olan en kısa sürede aşı uygulanmıştı. Çalışma grubunda aşıdan kaçınmanın en önemli nedeni kemoterapi almaktı (p=0,002). Yeterli dozda aşısı olan ve olmayan hastalar arasında COVID-19 tedavisinin türü açısından anlamlı bir fark yoktu. Aşılamayı etkileyen en olumsuz faktör aktif kemoterapi tedavisiydi. Sosyal ilişkiler ve geleneksel medya aşılama için en olumlu etkenlerdi.
Sonuç: Tedavi gören veya remisyonda olan hastalar için aşılanma hayati önem taşımaktadır. Hastalar kemoterapi alacak olsalar bile aşı konusunda bilgilendirilmeli ve aşı için teşvik edilmelidir.

Anahtar kelimeler: COVID-19, aşı, kanser

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INTRODUCTION

Infectious diseases have existed throughout human history and have remained one of the main causes of death for many years, along with wars. At the end of 2019, a new type of coronavirus was identified as the cause of numerous pneumonia cases in Wuhan, a city in China's Hubei Province. This virus spread rapidly and caused a global pandemic. The disease was named COVID-19, meaning ''coronavirus disease 2019''. Coronaviruses can cause infections in both humans and animals. Animal coronavirus diseases involve multiple body systems, such as gastrointestinal, respiratory, and central nervous systems. Clinical symptoms in animals are varying from encephalomyelitis, nephritis, and hepatitis to peritonitis [1]. Human coronavirus diseases' clinical symptoms can range from asymptomatic to severe pneumonia that can lead to multi-organ dysfunction [2].

The World Health Organization (WHO) has declared the new type of COVID-19 as a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, and subsequently announced COVID-19 disease as a pandemic on March 11, 2020. Cancer is the most common cause of death after cardiovascular diseases in developed and developing countries. According to the GLOBOCAN database, approximately 19.3 million new cancer cases were reported globally in 2020 [3]. More attention should be paid to cancer patients, because they are usually older and have multiple comorbidities.

The susceptibility of cancer patients to infection with the influenza virus was known before the SARS-CoV-2 virus emerged [4]. Influenza increases the risk of hospital admission about four-fold and the risk of death about ten-fold in cancer patients compared to healthy individuals [5].

When the data of COVID-19 disease in cancer patients from 14 different hospitals in China's Hubei province were evaluated, there was an almost three times higher death rate in COVID-19 patients with cancer disease than in non-cancer counterparts. The mortality rate was particularly high in patients with hematological malignancies, lung cancers, and stage IV malignancies, independent of cancer type [6]. The mortality in cancer patients is affected by direct and indirect effects of the COVID-19 pandemic, such as infection and treatment interruptions [7]. Although these patients were susceptible to infection, the factors effecting vaccination were not evaluated in detail. Every country has its own dynamics that might affect patient behavior; however, there are limited data regarding the potential reasons which can affect the vaccination status in Turkish cancer patients.

Most of the studies regarding COVID-19 vaccines have excluded patients who had cancer disease or those receiving systemic anti-cancer therapy, hence the data on safety and efficacy of vaccines in such patients are currently limited. However, based on the data from current studies and safety profiles of other vaccines, expert panels and national guidelines strongly recommend the vaccination in cancer patients, even if the data regarding safety and efficacy are limited. As of February 2022, SARS-CoV-2 infection has caused approximately 400 million infections and 5.8 million deaths worldwide. In Turkey, it caused 13 million cases and 90,000 deaths [8].

Based on the results from clinical trials, the FDA has approved three types of COVID-19 vaccines as follows; Pfizer-BioNTech/BNT162b2 (mRNA) [9], Moderna/mRNA 1273 (mRNA) [10], and Janssen/Ad26.COV-2 (viral vector) [11].

We developed a questionnaire consisting of 13 questions in order to analyze the 'perspectives of cancer patients' towards the vaccines that have been proven to be effective against the COVID-19 and are allowed to be used in our country, including the percentages of vaccination, the reasons for vaccination, the reasons for refusal, and the severity of patients who are infected with COVID-19.

In this study, we aimed to show the different attitudes on vaccination against COVID-19 in Turkish cancer patients, emphasizing the positive and negative factors affecting vaccination, with the goal of giving information to authorities, physicians, and patients to better control and manage future health crisis or pandemic.

MATERIAL AND METHODS

Study participants

Patients with cancer diagnosis receiving active treatment who applied to the department of medical oncology outpatient clinic of Eskişehir City Hospital and Afyonkarahisar Health Sciences University were enrolled if they had the following criteria; 18 years and over, having literacy and good cognitive functions, and those who wanted to fill the questionnaire. Patients who don't know reading and writing, who had died from COVID-19 infection or don't want to fill the questionnaire were excluded. The survey applied for two months between the 1st of October and the 1st of November 2021. We have prepared a questionnaire form for determining the vaccine status and clarifying the opinions about the vaccination of cancer patients. The questionnaire form is available in the appendix.

Statistical analyses

Statistical analysis of the study was performed using SPSS version 22.0. Descriptive data were calculated using median, frequency, and means. The Chi-square test was used for categorical data. The continuous data were evaluated with parametric or non-parametric tests according to whether they were equally distributed or not. P value of less than 0.05 was considered statistically significant

RESULTS

A total of 271 patients, 173 (63.8%) from Afyon Health Sciences University Hospital and 98 (36.2%) from Eskişehir City Hospital, were included. Of the patients, 57.2% were female and 42.8% were male. The percentages of the patients by cancer types with decreasing order were as follows; breast cancer 33.6%, lung cancer 15.5%, colon cancer 15.5%, gastric cancer 6.6%, ovarian cancer 5.2%, pancreas cancer 2%, and others (21.8%). Considering the type of cancer, there was no significant difference among patients in terms of vaccination rates (p=0.23).

Among 271 patients, 71.6% were receiving chemotherapy and 81.2% were infected with COVID-19. Of the patients with COVID-19 disease, 83.7% survived without hospitalization, 14.3% required hospitalization, and 2% were treated in the intensive care unit.

Of the patients participating in the survey, 83.8% were vaccinated against COVID-19. Of the patients who underwent vaccination, 74.4% were vaccinated right after the vaccine was developed, 13% were vaccinated within 3 months of the vaccine development, and 12.6% were vaccinated within 3 to 6 months after the vaccine was developed. The rate of not getting vaccinated was significantly higher in patients receiving active chemotherapy (p=0.002). There was no significant difference in the severity of COVID-19 infection between patients receiving chemotherapy and those not receiving treatment.

Of the patients getting vaccinated, the percentages of patients with the number and type of vaccination were as follows; 1 dose of Sinovac in 3.4%, 2 doses of Sinovac in 18.4%, 3 doses of Sinovac in 12%, 1 dose of BioNTech in 3.4%, 2 doses of BioNTech 22.2%, 2 doses of Sinovac+1 dose of BioNTech in 18%, 2 doses of Sinovac+2 doses of BioNTech in 3%, 1 dose of Sinovac+2 dose of BioNTech in 0.4%, and 3 doses of BioNTech in 3.4%. The rate of patients who received at least 2 doses of vaccine was 76%. When patients were compared according to the number of vaccinations as <2 vs. ≥2, there was no significant difference among groups in terms of having COVID-19 infection or its severity (p=0.61 and p=0.31, respectively).

Of the 44 patients who did not receive the vaccine, the reasons for refusal were as follows; 22.7% did not believe in its effect, 9.1% thought it would have side effects, 4.5% waited to see its long-term effects, 61.4% refused because of having received chemotherapy, and 1 patient did not state a reason as seen inTable-1.

Negative factors leading to not getting vaccinated were found as family and friends in 29.5%, television (TV) and radio in 4.5%, social media, and internet in 6.8%, chemotherapy in 50%, no reason in 4.5%, family and friends + TV and radio in 4.5% as seen in Table-2.

Among patients getting vaccinated, 79.9% believed in its effect, 8.7% thought it would not have any side effect, and 11.4% both believed in its effect and thought it would not have any side effect (Table-1).

Positive reasons leading to patients getting vaccinated were as follows; family and friends in 24.1%, TV and radio in 24.6%, social media, and internet in 2.7%, physician advice in 18.3%, family and friends+ TV and radio in 14.7%, family and friends + physician advice in 7.1%, TV and radio + physician advice in 3.1%, and all reasons in 5.4% (Table-2).

Table 1. The decision of patients for vaccination according to vaccinated and unvaccinated groups

Decision	Vaccinated N (%)	Decision	Unvaccinated N (%)
Believe in Effect	175 (79,9)	Disbelieve in Effect	10 (22,7)
Lack of Adverse Effect	19 (8,7)	Fear of Adverse Effect	4 (9,1)
None	-	Wait to see long term effect	2 (4,5)
All	25 (11,4)	Ongoing Chemotherapy	27 (61,4)
		None	1 (2,3)
		All	-
Total	219	Total	44

N: Number, (%): Percentage

Table 2. The source of influence for both negative and positive ways for vaccination

Source of influence	Positive for vaccination N (%)	Negative for vaccination N (%)
Family and Friends	54 (24,1)	13 (29,5)
TV and Radio	55 (24,6)	2 (4,5)
Social Media	6 (2,7)	3 (6,8)
Ongoing Chemotherapy	N/A	22 (50)
Physician Advice	41 (18,3)	N/A
None	N/A	2 (4,5)
Combined	56 (24,9)	2 (4,5)
All	12 (5,4)	0 (0)
Total	224	44

TV: Television, N/A: Not Available, N: Number, (%) Percentage

DISCUSSION

After the vaccination program started in our country, citizens were classified according to risk groups. The risk groups and the order of vaccination were published on the website of the Ministry of Health and updated periodically [12]. As in the rest of the world, the priority for vaccination was given to healthcare workers, elderly individuals, and those with chronic diseases.

Despite the devastating consequences of the COVID-19 pandemic, there is still a group of skeptical people who deny the existence of the disease, do not believe in vaccines, and refuse to adhere to preventive strategies [13-14]. Although it is an excellent method to prevent infectious diseases, vaccination has often aroused suspicion, giving rise to anti-vaccine ideology and anti-vaccine movements. Some negative attitudes towards the vaccine, possible side effects, and fear of needles can be counted among the reasons for refusing the vaccine [15]. The development of new vaccines within a relatively short time and with new techniques has raised some questions about the vaccine in a particular part of society. The main fears for cancer patients towards vaccines are the risk of side effects and safety [16].

Even before the SARS-CoV-2 pandemic, there were several barriers to vaccination programs among cancer patients as demonstrated in a study by Ariza-Heredia et al. [17]. Despite clear recommendations to vaccinate patients receiving chemotherapy against preventable infections such as influenza, vaccination rates in these groups always remained low [18-19].

With the start of vaccination, there have been a great deal of information flow in written, visual, and social media, some of which had no scientific basis about the vaccine. As in other vaccines that are in the vaccination calendar, some part of society has begun to hesitate about getting vaccinated. People's hesitance towards vaccines may block COVID-19 vaccines from reaching large masses, hence prolonging the pandemic. However, there is limited data on the rate of vaccination and patients' point of view towards COVID-19 vaccines. In a multicenter survey study on Korean cancer patients, 61.8% of the participants stated that they were willing to receive the COVID-19 vaccine [20].

Our aim in this study was to evaluate the vaccination rates and perspectives of cancer patients towards the vaccine. Various vaccines have been developed against SARS-CoV-2, and as of February 16, 2022, more than ten billion doses of COVID-19 vaccines have been administered worldwide.

Only 16.2% of our patients were not vaccinated, 3.4% received only 1 dose of Sinovac, and 3.4%

received 1 dose of BioNTech. The rate of patients who received at least 2 doses of vaccine was 76%. As of February 2022 in our country, 84.75% of individuals (over the age of 18) were reported to receive at least 2 doses of vaccine [21]. Although our survey could not provide clear information about the timing, almost 25% of our patients were vulnerable to COVID-19 infection. Considering the time elapsed after the 2 doses of vaccination in cancer patients, this rate is likely to be higher.

In general, our patients' perspective on the vaccine was positive. More than half of the unvaccinated patients, the reason for refusal was active chemotherapy treatment. The second most common cause of not getting vaccinated was that patients did not believe in the effect of the vaccine (22.7%). Contrary to expectations, in our study group, the negative effect of the close environment was more remarkable than that of social media. Of the patients who received the vaccine, the reason for undergoing vaccination in 79.9% was that they believed in its effect. Family-friends and media organs were the most effective factors in getting vaccinated. According to our study, we see that the encouragement of our surroundings and media organs is effective in vaccination. The future concept of vaccination encouragement can be organized through health authorities in these circumstances. In addition, some actions in social media can be taken against the disinformation about vaccines in special patient populations

In our study, the vaccination rate of cancer patients was lower than the normal population. The most important reason for not getting vaccinated in this group was that more than half of the patients were receiving active chemotherapy treatment. In addition, the rate of patients who had fears of having side effects or did not believe in its effect was also quite high. This study may have a mainstream effect on the prevention of cancer patients from misinformation in the time of social health crisis, such as pandemic or epidemic. The results of the study may demonstrate some solutions to health authorities, society leaders, and members of press or social media about how to cope with misinformative issues on cancer patients. Additionally, this study is important in terms of indicating the different social dynamics in Turkey comparing with other countries in terms of vaccination and pandemic.

Limitations: One of the main limitations was that it could not be known whether patients with COVID-19 infection were infected before or after the vaccination. Moreover, the requirement of reminder dose for patients who received two doses of vaccine could not be questioned.

Conclusion

In conclusion, patients with cancer tend to have more severe COVID-19 infections than normal individuals. In addition, the development of antibodies via vaccine is less common in cancer patients than in the normal population. The most important reason for being against the vaccination is receiving active chemotherapy in our study. For these reasons, vaccination is of vital importance for patients who are treated or on remission. Even if patients are to receive chemotherapy, they should be informed about vaccination and should be encouraged for vaccination.

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Effects of adenoid and nasal pathologies in pediatric epistaxis

Adenoid ve Nazal Patolojilerin Pediatrik Epistaksisteki Etkileri

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ABSTRACT

Aim: The aim of this study was to investigate the effects of adenoid and nasal pathologies in paediatric patients with recurrent epistaxis.
Methods: A total of 100 (61 boys, 39 girls) individuals aged 2–17 years (mean age: 8.9 ± 3.6 years) were included in this study. Anterior rhinoscopy and flexible nasal endoscopy were used to examine all the patients. The epistaxis duration, treatment in active epistaxis by parents, medical history, medical treatment and interventions were recorded. The location of the epistaxis site, nasal mucosa type, the presence of nasal vestibulitis, nasal septum deviation location and type, adenoid size and the degree of inferior turbinate hypertrophy were recorded.
Results: The deviation was present in 31 (62%) patients with recurrent epistaxis and in 14 (28%) patients without epistaxis. The presence of deviation was significantly higher in the epistaxis group than in the control group ($p < 0.05$). The nasal mucosa type was friable mucosa in 37 (74%) patients, vascularised mucosa in 11 (22%) patients and friable-vascularised mucosa in 2 (4%) patients in recurrent epistaxis group. A significant relationship was detected between nasal mucosa type and age, the presence of the deviation, deviation location, the Mladina type in epistaxis group ($p < 0.05$, $p < 0.05$, $p < 0.05$, $p < 0.05$).
Conclusion: Nasal septum deviation, inferior turbinate hypertrophy and nasal mucosa type are associated with paediatric recurrent epistaxis.

Keywords: Paediatric, Epistaxis, Nasal Septum Deviation, Treatment

ÖZ

Amaç: Bu çalışmanın amacı, tekrarlayan epistaksisi olan çocuk hastalarda adenoid ve nazal patolojilerin etkilerini araştırmaktır.
Yöntemler: Bu çalışmaya 2-17 yaşları arasında (ortalama yaş: 8.9 ± 3.6 yıl) 100 (61 erkek, 39 kız) birey dahil edildi. Tüm hastaların muayenesinde anterior rinoskopi ve fleksibl nazal endoskopi kullanıldı. Hastanın tıbbi öyküsü, epistaksis süresi, aktif epistaksiste ebeveynler tarafından uygulanan tedavi yöntemi, tıbbi tedavi ve müdahaleler kaydedildi. Epistaksisin yeri, nazal mukoza tipi, nazal vestibülit varlığı, nazal septum deviasyonu yeri ve tipi, adenoid dokunun boyutu ve alt konka hipertrofisi derecesi kaydedildi.
Bulgular: Tekrarlayan epistaksisi olan 31 (%62) hastada ve epistaksisi olmayan 14 (%28) hastada deviasyon mevcuttu. Epistaksis grubunda deviasyon varlığı kontrol grubuna göre anlamlı derecede yüksekti ($p < 0.05$). Epistaksis grubunda; 37 (%74) hastada nazal mukoza frajil mukoza, 11 (%22) hastada vaskülarize mukoza ve 2 (%4) hastada frajil – vaskülarize mukoza mevcuttu. Epistaksis grubunda burun mukozasının tipi ile yaş, deviasyon varlığı, deviasyon yeri, Mladina tipi arasında anlamlı bir ilişki saptandı ($p < 0.05$, $p < 0.05$, $p < 0.05$, $p < 0.05$).
Sonuç: Nazal septum deviasyonu, alt konka hipertrofisi ve nazal mukoza tipi pediatrik tekrarlayan epistaksis ile ilişkilidir.

Anahtar Kelimeler: Pediatrik, Epistaksis, Nazal Septum Deviasyonu, Tedavi

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INTRODUCTION

Paediatric epistaxis is a very common disease primarily encountered by the emergency department, paediatricians, family physicians and otorhinolaryngologists [1]. Recurrent epistaxis affects approximately 9% of children [2]. Until the age of 10, 60% of children will suffer from epistaxis at least once, although in childhood it rarely requires nasal packing or hospitalisation [3]. Paediatric epistaxis is more common in 3 to 8 years-old children. Epistaxis is rarely seen in children younger than 2 years. In this situation, severe diseases such as trauma and acute leukaemia must be suspected [3-4].

There are several risk factors for epistaxis such as viral and bacterial rhinosinusitis, allergic rhinitis, physical and chemical irritation, facial injury, temperature and humidity and nasal tumours [5-6]. Mild anterior epistaxis is more common in children [7-8]. Most of the epistaxis originates from the anterior septum [9-10] and this area is commonly susceptible to damage, such as nasal secretions and trauma-related injury [9].

Epistaxis usually originates from the anterior part of the septum and spontaneously bleeds and is generally self-limiting [3]. Moistening and antibiotic ointments are commonly prescribed in the treatment of paediatric epistaxis [9]. In the majority of children, nasal ointments and saline solution are sufficient for treatment, whereas some patients may require additional interventions such as cautery [10]. In addition to these risk factors, nasal septum deviations have often been blamed, although the cause or causes of recurrent epistaxis have not been identified yet [5]. The aim of this study was to investigate the effects of adenoid and nasal pathologies in paediatric patients with epistaxis.

MATERIALS AND METHODS

This study was conducted retrospectively. It received approval from the ethics committee of our hospital (Approval number: 2011-KAEK-25 2019/05-19) and was prepared in accordance with the Helsinki Declaration Principles. Informed consent was obtained from all of our patients' mothers to participate in this study.

Subjects

A total of fifty (29 boys, 21 girls) patients with recurrent epistaxis aged between 3 and 17 years (mean age: 9.0 ± 3.1 years) and fifty (32 boys, 18 girls) patients without epistaxis aged between 2 and 16 years (mean age 8.8 ± 4.0 year) were included in this study. A case form was designed to record the recurrent epistaxis history of all patients. Those with a history of more than one intermittent epistaxis were included in the recurrent epistaxis group. The patients included in the control group consisted of patients who applied to our clinic with other complaints.

Patients with post-operative epistaxis and those with intranasal mass, foreign body or major nasal trauma were excluded. Furthermore, patients who had a systemic disease (renal or hepatic insufficiency and hereditary haemorrhagic telangiectasia, a bleeding disorder) were also excluded from the study. The epistaxis duration, treatment in active epistaxis by parents, medical history, medical treatment and interventions were recorded. Treatment in active epistaxis by parents was classified as nothing was done, pressure was applied onto the nasal ala and anterior packing.

Rhinological Examination

The epistaxis side was classified as left or right epistaxis. In the anterior rhinoscopic examination, the location of the epistaxis site, nasal mucosa type and the presence of nasal vestibulitis were recorded.

The deviation location was classified into three classes as anterior, posterior or antero-posterior. The deviation side was classified as left or right. Nasal septum deviation was classified into seven types, according to the Mladina [11] classification. Posterior deviations and non-deviated nasal septums were noted as Mladina class 0. For each patient, the degree of inferior turbinate hypertrophy was classified into the following four classes: normal, mild, moderate and serious.

Adenoid sizes were classified as 0%–25% in the Group 1, 26%–50% in the Group 2, 51%–75% in the Group 3 and 76%–100% in the Group 4, according to the endoscopic nasopharynx examination [12 13].

The nasal mucosa type was classified as normal mucosa, friable mucosa, vascularised (visible vessel) mucosa or friable – vascularised mucosa. The interventions were classified as medication (antibiotherapy and antiseptic cream), silver nitrate cautery or anterior nasal packing.

Statistical Analysis

The Shapiro-Wilk test, Mann-Whitney U test and Student t-test were used. Categorical variables were compared using Fisher's exact test and Pearson's chi-squared test. In the multivariate analysis to determine the factors associated with the frequency and epistaxis duration, location of the epistaxis site, nasal mucosa type, treatment in active epistaxis by parents and treatment outcomes, logistic regression (backward logistic regression) was used. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the IBM SPSS ver. 23.0.

RESULTS

The deviation was present in 31 (62%) patients in recurrent epistaxis group and in 14 (28%) patients in control group. The anterior deviation was in 22 (44%) patients, the posterior deviation was in 1 (2%) patient and the antero-posterior deviation was in 8 (16%) patients in the recurrent epistaxis group. The anterior deviation was in 3 (6%) patients, the posterior deviation was in 9 (17%) patients and the antero-posterior deviation was in 2 (4%) patients in the control group.

In the Mladina classification, Type 0 was in 20 (40%) patients, Type 1 was in 7 (14%) patients, Type 2 was in 3 (6%) patients, Type 3 was in 5 (10%) patients, Type 4 was in 1 (2%) patient, Type 5 was in 12 (24%) patients and Type 6 was in 2 (4%) patients in the recurrent epistaxis group. In the Mladina classification, Type 0 was in 45 (90%) patients, Type 1 was in 1 (2%) patient, Type 2 was in 0 (0%) patients, Type 3 was in 2 (4%) patients, Type 4 was in no (0%) patients, Type 5 was in 2 (4%) patients and Type 6 was in 0 (0%) patients in the control group.

Recurrent epistaxis was present on the right side in 17 (34%) patients, on the left side in 17 (34%) patients and on both sides in 16 (32%) patients. Nothing was done in 32 (64%) patients, pressure was applied onto the nasal ala in 10 (20%) patients and nasal packing was applied in 8 (16%) patients with active bleeding.

The nasal mucosa type was friable mucosa in 37 (74%) patients, vascularised mucosa in 11 (22%) patients and friable – vascularised mucosa in 2 (4%) patients in the epistaxis group (Figure-1). Regarding the interventions, it was medical therapy in 44 (88%) patients, silver nitrate cautery in 6 (12%) patients and nasal packing in no (0%) patients in the recurrent epistaxis group.

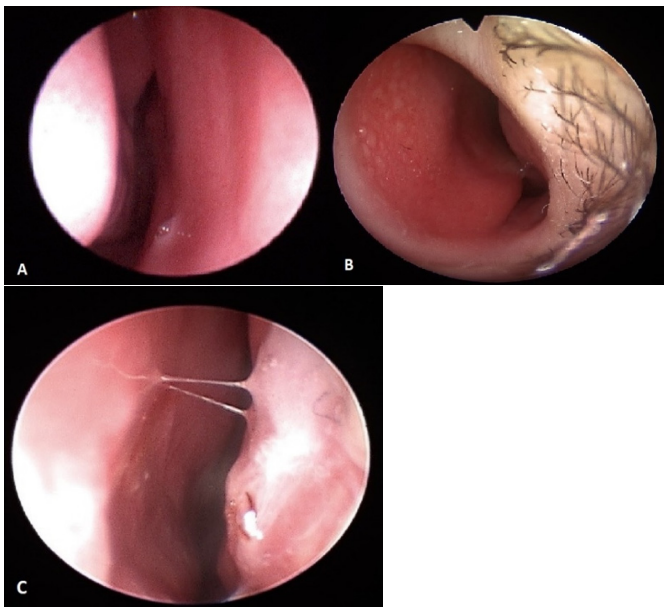

Figure 1 shows examples of friable-vascularized, friable and normal mucosa types (Figures are from our own archive.) 1A: Normal mucosa. 1B: Friable mucosa and septum deviation. 1C: Friable-vascularized mucosa.

The nasal mucosa type was friable mucosa in 4 (8%) patients, vascularised mucosa in no (0%) patients and friable – vascularised mucosa in no (0%) patients in the control group. Regarding the interventions, it was medical therapy in 4 (8%) patients, silver nitrate cautery in no (0%) patients and nasal packing in no (0%) patients in the control group.

The adenoid size classification results revealed Group 1 in 4 (8%) patients, Group 2 in 8 (16%) patients and Group 3 in 6 (12%) patients in recurrent epistaxis group. The adenoid size classification results revealed Group 1 in 6 (12%) patients, Group 2 in 10 (20%) patients, Group 3 in 3 (6%) patients and Group 4 in 2 (4%) patients in control group (Table 1).

Table 1. Ratio of Epistaxis duration, nasal mucosa type, treatment in active epistaxis by parents, gender, applied treatment, adenoid size, presence of nasal septum deviation, deviation location.

		Epistaxis Group		Control Group	
		n	%	n	%
Age (Mean ± Standard Deviation)		9.00±3.17	3-17	8.8±4.0	2-16
Epistaxis duration		4.74±4.70	0-20		
Epistaxis duration	Under 5 minutes	28	56.0%		
	Over 5 minutes	22	44.0%		
Nasal Mucosa Type	Friable Mucosa	37	74.0%	4	8.0%
	Vascularized Mucosa	11	22.0%	0	0%
	Friable -Vascularized Mucosa	2	4.0%	0	0%
Treatment in active epistaxis by parents	Nothing was done	32	64.0%		
	Pressure was applied on to nasal ala	10	20.0%		
	Anterior packing	8	16.0%		
Gender	Male	29	58.0%	32	64.0%
	Female	21	42.0%	18	36.0%
Applied treatment	Medication (antibiotherapy and antiseptic cream)	44	88.0%	4	8.0%
	Silver nitrate cautery	6	12.0%	0	0%
	Anterior nasal packing	0	0.0%	0	0%
Adenoid Size	0	32	64.0%	29	58.0%
	Group 1	4	8.0%	6	12.0%
	Group 2	8	16.0%	10	20.0%
	Group 3	6	12.0%	3	6.0%
	Group 4	0	0.0%	2	4.0%
Presence of nasal septum deviation	Absent	19	38.0%	36	72.0%
	Present	31	62.0%	14	28.0%
Deviation location	Absent	19	38.0%	36	72.0%
	Anterior	22	44.0%	3	6.0%
	Posterior	1	2.0%	9	18.0%
	Antero-posterior	8	16.0%	2	4.0%

Epistaxis Group

Logistic regression (backward logistic regression) was used in the multivariate analysis to determine the factors associated with the epistaxis duration, location of the epistaxis site, nasal mucosa type, treatment in active epistaxis by parents and treatment outcomes, however no relationship was found. There was a statistically significant relationship between the nasal mucosa type and age ($p < 0.05$). The age of patients who have vascularized epistaxis site (13 (7 - 17)) was higher than the age of patients who have friable epistaxis site (8 (3 - 13)). There was no statistically significant relationship between the ages of patients treated with medical therapy (8.5 (3-14)) and the ages of patients (13 (7 - 17)) applied silver nitrate cautery ($p > 0.05$).

There was a statistically significant relationship between nasal mucosa type and presence of deviation, deviation location and the Mladina classification (Table 2). There was a statistically significant relationship between nasal mucosa type and presence of deviation ($p < 0.05$). While nasal septum deviation was observed in all patients with vascularized nasal mucosa type, the rate of nasal septum deviation was lower in friable or friable-vascularized epistaxis site. In addition, the ratio of vascularized epistaxis site in patients with anterior nasal septum deviation was 72.7%. When the nasal mucosa type was evaluated according to the Mladina classification, it was seen that vascularized epistaxis site is not significantly observed in patients without nasal septum deviation. However, a vascularized epistaxis site was observed more frequently in Type 3 deviations.

There was no statistically significant relationship between epistaxis duration and deviation location, Mladina class, the degree of inferior turbinate

Table 2: Comparison of nasal mucosa type and presence of nasal septum deviation, deviation location, Mladina class in epistaxis group.

		Nasal Mucosa Type						P
		Friable		Vascularized		Friable Vascularized		
		n	%	n	%	n	%	
Presence of nasal septum deviation	Absent	18	48.6	0	0.0	1	50.0	0.004
	Present	19	51.4	11	100.0	1	50.0	
Deviation Location	Absent	18	48.6	0	0.0	1	50.0	0.008
	Anterior	13	35.1	8	72.7	1	50.0	
	Posterior	0	0.0	1	9.1	0	0.0	
	Antero-posterior	6	16.2	2	18.2	0	0.0	
Mladina Class	0	18	48.6	0	0.0	1	50.0	0.015
	1	6	16.2	1	9.1	0	0.0	
	2	2	5.4	1	9.1	0	0.0	
	3	2	5.4	4	36.4	0	0.0	
	4	1	2.7	0	0.0	0	0.0	
	5	7	18.9	4	36.4	1	50.0	
		1	2.7	1	9.1	0	0.0	

hypertrophy or adenoid size. There was no statistically significant relationship between treatment in active epistaxis by parents and the presence of deviation, deviation location, the Mladina class or nasal mucosa type. There was no statistically significant relationship between recurrent epistaxis and the presence of adenoid tissue and the degree of inferior turbinate hypertrophy ($p > 0.05$, $p > 0.05$).

Epistaxis and control group analysis

In the recurrent epistaxis group, the friable, vascularized and friable-vascularized types were seen statistically higher in the nasal mucosa compared to the control group ($p<0.001$). The presence of nasal vestibulitis was significantly higher in the recurrent epistaxis group than in the control group ($p<0.001$). There was no statistically significant difference about the presence of adenoid tissue between the recurrent epistaxis group and the control group ($p > 0.05$).

The presence of deviation was significantly higher in the recurrent epistaxis group than the control group ($p < 0.05$). Anterior and antero-posterior deviations were seen significantly higher in the epistaxis group then the control group ($p < 0.00$). The mild degree of inferior turbinate hypertrophy was significantly higher in the recurrent epistaxis group than the control group ($p < 0.05$) (Table 3).

Logistic regression was used in the univariate analysis to determine the factors associated with presence of deviation, deviation location, Mladina class, adenoid size, nasal mucosa type and the presence of vestibulitis. Multivariate regression analysis results were not significant.

There was a statistically significant relationship between epistaxis and presence of deviation ($p < 0.05$), presence of vestibulitis ($p < 0.001$), Mladina class 1 ($p < 0.05$), anterior deviation ($p < 0.001$), posterior deviation ($p < 0.05$) and antero-posterior deviation ($p < 0.05$). There was no statistically significant relationship between epistaxis and the presence of adenoid tissue, adenoid size ($p > 0.050$).

DISCUSSION

Spontaneous epistaxis is a significant complaint in the emergency department [8-14]. Paediatric epistaxis is a common condition in otorhinolaryngology practice. Recurrent epistaxis can be distressing and worrying for both parents and children [3]. In an earlier study, Shay et al. found that 57.4% of boys had epistaxis, which was slightly more frequent than that found in girls [1]. Similarly, we found 58% boys predominance in our study.

Paediatric epistaxis occurs as recurrent, non-life-threatening bleeding. The factors that induce bleeding include local inflammation, mucosal dryness and local trauma such as that caused

Table 3: Comparison of groups and deviation location, nasal mucosa type, Mladina class, adenoid size, the degree of inferior turbinate hypertrophy.

		Epistaxis		Control		P
		n	%	n	%	
Deviation Location	Absent	19	38.0	36	72.0	<0.001a
	Anterior	22	44.0	3	6.0	
	Posterior	1	2	9	18.0	
	Antero-posterior	8	16.0	2	4.0	
Nasal Mucosa Type	Normal	0	0.0	46	92.0	<0.001b
	Friable	37	74.0	4	8.0	
	Vascularized	11	22.0	0	0.0	
	Friable-Vascularized	2	4.0	0	0.0	
Mladina Class	0	20	40.0	45	90.0	0.004b
	1	7	14.0	1	2.0	
	2	3	6.0	0	0.0	
	3	5	10.0	2	4.0	
	4	1	2.0	0	0.0	
	5	12	24.0	2	4.0	
	6	2	4.0	0	0.0	
Adenoid Size	Absent	32	64.0	28	58.0	0.508b
	Group 1	4	8.0	6	12.0	
	Group 2	8	16.0	10	20.0	
	Group 3	6	12.0	3	6.0	
	Group 4	0	0.0	2	4.0	
The degree of inferior turbinate hypertrophy	Absent	14	28.0	19	38.0	0.001b
	Mild	28	56.0	10	20.0	
	Moderate	7	14.0	20	40.0	
		1	2.0	1	2.0	

[a] Pearson Chi-Square tests [b] Fisher-Freeman-Halton test

by nose picking. In rare cases, epistaxis can be originated from systemic factors, such as bleeding disorders or from local factors such as tumours. Epistaxis is rare in children below 2 years of age. If there is a clinical suspicion, it should be investigated for bleeding disorders or local tumours [6-15]. Bleeding may also be originated from the lateral nasal wall. Posterior bleeding may result from the posterior branches of the sphenopalatine artery [16]. However, posterior nosebleeds are extremely rare in children [2]. Posterior bleeding was not observed in our study groups.

It is recommended that the clinician perform a careful evaluation of the patient's age, symptoms and findings of the anterior rhinoscopic examination, for determining the cause of the epistaxis. Furthermore, nasal endoscopy should be included in the examination for a child with continuous bleeding with no obvious source of bleeding on anterior rhinoscopy [10]. As the majority of nosebleeds originate from the anterior part of the septum, significant vascularisation in the anterior nasal septum or dry raw crusty areas or a bent nasal septum requires careful inspection during examination. Nasal vestibulitis is also common secondary to infection [2]. Bleeding may occur when this area is exposed to dryness or minor trauma [10]. In addition, approximately half of the children with epistaxis experience significant vascularisation of the nasal septum [17].

Montague et al. [17] described the occurrence of paediatric epistaxis. First, they indicated that Staphylococcus aureus colonised the nose of children. S. aureus colonisation causes nasal crusting and irritation and low-grade inflammation. At this stage, inflammation and trauma increase nasal vascularisation. Nosebleeds occur due to the damage caused by the separation of the crusts from their places by digital trauma. With prolonged inflammation, inflammatory mediators are released that can lead to the growth of visible, prominent new vessels. Continuous inflammation due to digital trauma can ultimately lead to squamous metaplasia [17].

In the majority of cases, nasal bleeding stops spontaneously after a few minutes, or short-term pressure applied on the nostrils is generally sufficient to stop it [2]. For the treatment of significant or recurrent epistaxis, vasoconstrictor drops, cauterisation with silver nitrate in office conditions and topical creams should be applied. Nasal packing is rarely required in children [3]. Histological examination reveals inflammatory infiltrate findings surrounding the vessels. This provides evidence that nasal staphylococci can be aggressively eliminated using antiseptic creams [17]. Cauterisation is applied in the operating room conditions in cases of persistent epistaxis [9]. In this study, nasal vestibulitis was seen in the majority of patients in epistaxis group in anterior rhinoscopic examination. In addition, with increasing age, there was an increase in vascularisation in the epistaxis site and consequently an increase in the severity of bleeding. This situation increases the necessity of medical interventions such as cauterisation and nasal packing for bleeding control. The presence of vestibulitis in the nose is a factor that determines the severity of the effect of bleeding in the site. In paediatric epistaxis, posterior haemorrhage is less common and less severe. However, we observed that anterior bleeding may be more serious and may require more serious medical interventions such as cauterisation and nasal packing in extreme cases.

Other causes of epistaxis include infections, allergic rhinitis, bleeding disorders and trauma [3]. Besides these risk factors, several factors have been identified, but the relationship with epistaxis has not been clarified. Nasal septum anomalies have often been reported to be the cause, but the relationship remains to be clarified [5-6]. Epistaxis tends to be present on the deviation side in patients with nasal septum deviation [18]. Fuller et al. reported that functional septorhinoplasty can perform safely in select paediatric patients with significant nasal obstruction [19].

In paediatric patients with nasal septum deviation, vascularisation in the epistaxis site was increased when the Mladina Class 3 in our study. As a result, the requirement for cauterisation was increased in these patients, rather than medical treatment in paediatric patients with nasal septum deviation. Vascularization in the epistaxis site increases due to chronic vestibulitis and nasal septum deviation with age. In addition, it was observed that inferior turbinate hypertrophy was effective in the presence of recurrent epistaxis. Nasal septum deviation and inferior turbinate hypertrophy narrow the nasal airflow passage. This may lead to vascular increase in the deviated part by thinning the nasal mucosa with nasal vestibulitis. This situation may result to the need for further epistaxis treatments. In the Mladina Class 1 deviations, nasal septal deviation and nasal vestibulitis cause thinning of the nasal mucosa. Since there is no vascularization in such epistaxis, it can be intervened more easily.

The nasal septum deviation and inferior turbinate hypertrophy, which are closely associated with recurrent epistaxis and epistaxis treatment, are not well known by the emergency department doctors, paediatricians, family physicians, especially in paediatric patients. Therefore, patients are treated temporarily and inappropriately, on an outpatient basis. Patients with paediatric epistaxis must be referred to the otorhinolaryngologist by the emergency department for the evaluation of possible nasal pathologies. Recurrent epistaxis will thus be prevented, with adequate treatment.

Our study had some limitations. In the etiology of epistaxis development, many risk factors such as viral and bacterial rhinosinusitis, allergic rhinitis, physical and chemical irritation, facial injury, temperature and humidity, nasal tumours are important. A well designed study should include large numbers of cases to eliminate the relative the risks associated with these factors.

CONCLUSION

The nasal septum deviation, inferior turbinate hypertrophy and vascularisation are related to each other in paediatric recurrent epistaxis. With increasing age, there is an increase in vascularisation in the epistaxis site and consequently, an increase in the severity of bleeding. In epistaxis patients, the presence of deviation, inferior turbinate hypertrophy and/or vestibulitis, vascularisation can be identified correctly through nasal examination by an ENT specialist and a permanent treatment can be provided.

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Expression Profiles Of PTEN And POGZ Genes In Patients With Autism

Otizmli Hastalarda PTEN Ve POGZ Genlerinin Ekspresyon Profilleri

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ABSTRACT

Aim: Autism spectrum disorder (ASD), a group of heterogeneous neurodevelopmental disorders, is characterized by complex behavioral phenotypes. Despite extensive studies over many years, the causes of ASD are still unknown. PTEN and POGZ genes are studied as candidate genes that may be responsible for the ASD phenotype. We aimed to investigate the expression levels of PTEN and POGZ genes in autistic patients.
Methods: Gene expressions of PTEN and POGZ were investigated in 50 ASD patients and 50 age and gender matched healthy controls. This study was conducted in the Erciyes University Genome and Stem Cell Center (GENKOK).
Results: POGZ gene expression was increased in patients compared to controls. According to gender, the expression results of the autistic male patients were significant. PTEN mRNA expression was not statistically significant but found to be lower in patients than in controls. The relationship between the expression of these genes and cognitive deficits was not significant.
Conclusion: We recommend investigating other possible candidate genes in larger cohorts and comparing the results with different additional cilinical findings in ASD.

Key Words: Autism, Autism Spectrum Disorders, PTEN, POGZ, Expression

ÖZ

Amaç: Otizm spektrum bozukluğu (OSB), karmaşık davranışsal fenotiplerle karakterize, heterojen bir grup nörogelişimsel bozukluktur. Uzun yıllar boyunca yapılan kapsamlı çalışmalara rağmen, OSB'nin nedenleri hala bilinmemektedir. PTEN ve POGZ genleri, OSB fenotipinden sorumlu olabilecek aday genler olarak gösterilmiştir. Otistik hastalarda PTEN ve POGZ genlerinin ekspresyon düzeylerini araştırmayı amaçladık.
Yöntem: OSB tanılı 50 hastada ve yaş-cinsiyet uyumlu 50 sağlıklı kontrolde PTEN ve POGZ gen ekspresyonları araştırıldı. Bu çalışma Erciyes Üniversitesi Genom ve Kök Hücre Merkezi'nde (GENKÖK) yapılmıştır.
Bulgular: POGZ geninin hastalarda kontrollere göre daha fazla eksprese olduğu ve otistik erkek hastalarda bu genin ekspresyonunun anlamlı olduğu bulundu. PTEN gen ekspresyonu istatistiksel olarak anlamlı değildi ancak hastalarda kontrollere göre daha düşük bulundu. Bu genlerin ekspresyonu ile bilişsel gerilik arasındaki ilişki ise anlamlı değildi.
Sonuç: Daha büyük hasta grupları ile diğer olası aday genlerin araştırılmasını ve sonuçların farklı ek klinik belirtilerle hastalarda karşılaştırılmasını önermekteyiz.

Anahtar Kelimeler: Otizm, Otizm Spektrum Bozuklukları, PTEN, POGZ, Ekspresyon

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by repetitive and restricted behaviors and interests, as well as social communication impairments [1-3]. Autism is a common subtype of ASD [4]. It is a chronic disease that starts in early childhood and lasts for life. There has been a significant increase in the autism incidence worldwide: according to recent reports, 1 in every 54 children has the condition [5]. The complex etiology of the disease causes different phenotypes to occur, even in the same family. Despite extensive studies over many years, the causes of ASD are still unknown. It is known that it is not a single gene which is responsible for the pathogenesis of ASD [6-12]. To date, more than 800 ASD candidate genes have been identified and they are involved in various biological pathways [13].

Both of PTEN and POGZ genes are shown as candidate genes that may be responsible for the ASD phenotype [13]. PTEN is a gene on chromosome 10 and it has an epigenetically different function: its gene function is namely important in neurodevelopment [14]. Deletion of the PTEN gene results in death during the embryonic period [15]. It may contribute to the diversity of the ASD phenotype as an important regulator of the PI3K/AKT mTOR pathway [15,16]. Several roles of the PTEN gene in autism have been shown in various studies [17-19].

POGZ is a gene that encodes pogo transposable element-derived protein with zinc finger domain affecting ASD [20]. POGZ has a major role in chromatin regulation, cellular function and gene expression. Disorders in chromatin-related mechanisms may cause pathological effects [21]. POGZ is highly expressed in the human fetal brain [21,22]. POGZ deficiency may affect mitosis, brain development and dysfunction [23]. A recent study demonstrated that Pogz deficient mice had been mimicking several of the ASD symptoms including learning and motor deficits, growth impairment, microcephaly and increased sociability [24].

Studies have shown that there is a relationship between PTEN and POGZ genes and ID accompanying some autism cases. Thus we used these genes, which are more associated with clinical findings of autism [15,17-19,25-27]. This is the first report investigating the expression of target genes (PTEN, POGZ) in 50 ASD patients and 50 age-gender matched healthy controls in Turkey. We also investigated whether these gene expressions were related to cognitive impairment in ASD patients.

MATERIAL AND METHODS

Ethical Compliance

This study was approved by the institutional ethical board of Erciyes University (No:2016/491). Informed consents were obtained from the parents of the children who participated in the study.

Selection of patients

Fifty patients aged 2 to 10 were enrolled from Erciyes University Faculty of Medicine Department of Child Psychiatry, after undergoing psychiatric, physical and neurologic examinations. All children with ASD were newly diagnosed by a childhood and adolescence psychiatrist, based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V). The Childhood Autism Rating Scale (CARS) scale was used to assess the severity of ASD from mild to moderate to severe [28]. Fifty healthy controls aged 1 to 10 without a chronic, medical and psychiatric medication or genetic disease, were included in the study. Whole blood samples of patients and healthy controls were taken into sterile 2 ml vacuum tubes containing EDTA (ethylenediamine-tetraacetic acid) for further analysis. All of the blood samples from patients were taken before starting the medications to avoid the possible effects for gene expression.

RNA isolation and gene expression studies

We performed the analysis in the Erciyes University Genome and Stem Cell Center (GENKOK). Total RNA was isolated from peripheral blood samples (TRIzol, Roche, Germany). The RNA quality and quantity were measured with BioSpec-Nano Spectrometer. Complementary DNA (cDNA) was synthesized from the RNA obtained using the Transcriptor High Fidelity cDNA synthesis kit (Roche, Germany). Expressions of POGZ and PTEN genes were investigated with Quantitave Real-Time PCR (LightCycler 480, Roche,

Germany) using SYBR green. The experiment comprised the steps of the reaction mixture for 1 cycle of 10 min at 95˚C for deactivation and subsequently, 45 cycles of 10 sec each at 95˚C, 30 sec at 60˚C, 1 sec at 72˚C for denaturation and 30 sec at 40˚C for cooling. Each sample was double studied and beta-actin (ACTB) was selected as housekeeping gene. Results of the target gene expression levels were determined by delta Ct method.

Statistical analysis

The statistical results of this study were calculated using GraphPad Prism (Version 6.01) program and the graphs of the results were prepared again with this program. Comparisons between the groups were evaluated by nonparametric t-test. $p<0.05$ was considered significant.

RESULTS

Study groups

The study group consisted of 50 individuals with 39 males and 11 females with the age range of 2 to 10 years, whereas the control group consisted of 39 males and 11 females, with the age range of 1 to 10 years. The characteristics of the patients included in the study are shown in Table 1. Seven of the patients identified for this study had consanguineous marriage, 23 had congenital anomalies and 19 had an intellectual disability (ID). Table 2 shows the patients with ASD included in the study and their clinical findings.

Table 1. Demographics of patients and controls included in the study

Demography	Autism (n=50)	Control (n=50)
Gender	39 Males and 11 Females	39 Males and 11 Females
Average of age	4.08	3.85
Range of age	2-10	1-10

Gene expression results of POGZ and PTEN genes in patients with ASD and controls

The expression levels of POGZ and PTEN genes in the blood of autistic patients were determined. The expression results of POGZ gene was statistically significant ($p< 0.0001$), although those for the PTEN gene was not significant ($p=0.7884$). Figure 1 shows gene expression profiles of the groups. Figure 1A depicts the comparison of expression of POGZ and PTEN genes in 50 ASD patients and 50 controls. While the POGZ gene was expressed more in patients with autism than controls, the PTEN gene was found to be less expressed in patients with ASD than in the controls.

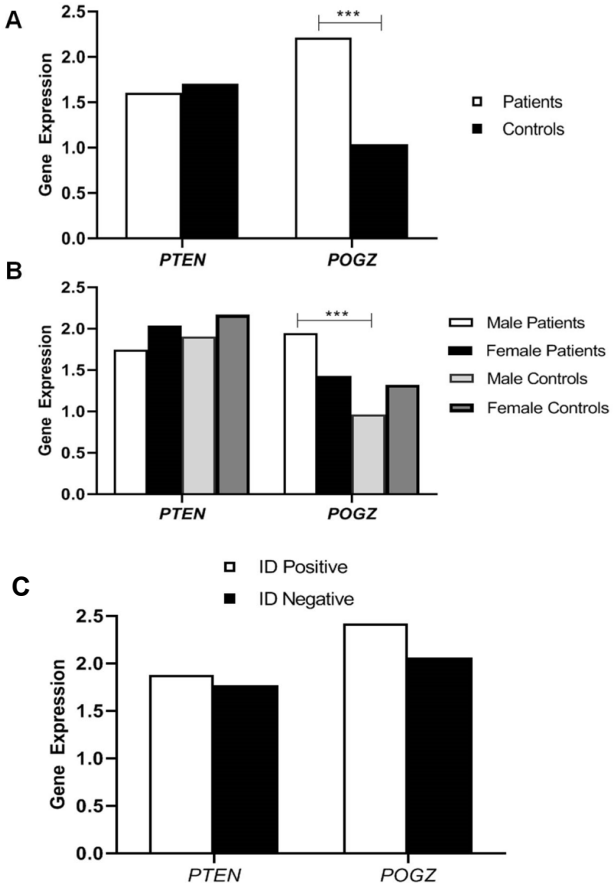

Figure 1. Gene expression profiles of the groups. (A) Expression profiles of PTEN and POGZ genes in 50 ASD patients and 50 controls. (B) Expressions of PTEN and POGZ genes according to gender. (C) The comparison of expressions of PTEN and POGZ genes with ID Positive and ID Negative patients

When compared according to gender, the expressions results of these genes were not statistically significant in male and female patients (for POGZ $p=0.2380$, for PTEN $p=0.6556$, respectively) (Figure 1B). While the expression of POGZ gene was statistically significant by comparing male patients and male controls ($p<0.0001$), PTEN gene expression was not significant in male patients and male controls ($p=0.7513$). The expression results of genes were not statistically significant in female patients and female controls (for POGZ $p=0.8236$, for PTEN $p=0.8862$, respectively).

It was also investigated whether the expression

Table 2. Clinical findings in patients with autism

No	Disease Group	Gender (Male, Female)	Age (Year)	Consanguinity	Congenital Anomaly	Intellectual Disability
1	ASD	M	2	Negative	Negative	Negative
2	ASD	M	6	Negative	Positive	Positive
3	ASD	M	3	Negative	Positive	Negative
4	ASD	F	3	Negative	Positive	Positive
5	ASD	M	6	Positive	Positive	Negative
6	ASD	M	6	Negative	Negative	Negative
7	ASD	M	5	Negative	Negative	Negative
8	ASD	M	4	Negative	Negative	Negative
9	ASD	M	6	Negative	Positive	Positive
10	ASD	F	4	Positive	Positive	Positive
11	ASD	M	4	Positive	Negative	Positive
12	ASD	M	3	Negative	Positive	Negative
13	ASD	M	3	Negative	Negative	Positive
14	ASD	M	3	Negative	Negative	Negative
15	ASD	F	3	Negative	Negative	Negative
16	ASD	M	9	Negative	Negative	Negative
17	ASD	F	9	Negative	Negative	Negative
18	ASD	F	4	Negative	Negative	Negative
19	ASD	M	9	Positive	Negative	Negative
20	ASD	M	4	Negative	Positive	Positive
21	ASD	M	4	Negative	Positive	Negative
22	ASD	M	2	Negative	Positive	Negative
23	ASD	M	2	Negative	Positive	Negative
24	ASD	M	4	Negative	Negative	Positive
25	ASD	M	5	Negative	Negative	Positive
26	ASD	F	3	Negative	Negative	Negative
27	ASD	M	4	Negative	Positive	Negative
28	ASD	M	3	Negative	Negative	Positive
29	ASD	M	3	Negative	Negative	Positive
30	ASD	M	2	Negative	Negative	Positive
31	ASD	F	3	Negative	Negative	Negative
32	ASD	M	4	Positive	Positive	Negative
33	ASD	M	5	Negative	Positive	Negative
34	ASD	M	3	Negative	Positive	Negative
35	ASD	M	4	Negative	Positive	Negative
36	ASD	M	5	Negative	Positive	Negative
37	ASD	F	3	Negative	Positive	Negative
38	ASD	M	3	Negative	Negative	Negative
39	ASD	M	3	Negative	Negative	Negative
40	ASD	M	4	Negative	Negative	Positive
41	ASD	F	3	Negative	Negative	Positive
42	ASD	F	4	Positive	Negative	Positive
43	ASD	M	4	Negative	Positive	Positive
44	ASD	M	3	Negative	Positive	Positive
45	ASD	M	3	Negative	Positive	Negative
46	ASD	M	4	Negative	Positive	Negative
47	ASD	M	2	Negative	Negative	Negative
48	ASD	F	4	Negative	Negative	Positive
49	ASD	F	9	Negative	Negative	Positive
50	ASD	M	3	Positive	Positive	Negative

levels of PTEN and POGZ genes are associated with the finding of ID and this finding was shown in Figure 1C. There were no significant differences for PTEN and POGZ gene expressions with/without ID (p=0.8519; p=0.5063).

DISCUSSION

Genetics plays a key role in the etiology of ASD [8,29]. PTEN and POGZ genes are shown as candidate genes that may be responsible for the ASD phenotype [13]. Since the role of these genes in autism is not well known, the expressions of PTEN and POGZ genes were investigated in this study, through the blood samples of Turkish patients with autism and corresponding controls.

The PTEN gene can contribute to the diversity of the ASD phenotype as an important regulator of the PI3K/AKT/mTOR pathway [15]. This signaling pathway activity is required for cell growth, survival and proliferation. Therefore, abnormalities in this pathway cause psychiatric and neurological disorders such as schizophrenia, autism and brain tumors [19]. A study with Pten knock-out mice was reported to result in long-term changes in autistic-like behavior (social behavior, repetitive behavior and anxiety, memory and learning deficits) [15]. The most common clinical finding in humans with mutated PTEN is macrocephaly [14,30]. Butler et al. investigated the PTEN gene mutation in 18 patients (13 males and 5 females aged 3-18 years) who were diagnosed with ASD and macrocephaly. As a result of the study, it was determined that three male patients were carriers of germline PTEN mutation [27]. Kaymakcalan et al. also identified three pathogenic/likely pathogenic mutations by PTEN gene sequence analyses in Turkish ASD and macrocephaly children [31].

Some of the PTEN and POGZ mutations have been related to ASD [15,21,27]. PTEN mutation carriers are strongly affected by genetic and environmental factors. Individual mutations lead to very different phenotypes, even within the same family [32,33]. Recent case reports have suggested that 25% to 50% of ASD children with PTEN mutations were identified [33,34]. Individuals with autism who have mutations in the PTEN gene have a distinct profile of cognitive impairments and structural abnormalities in the brain [35-37]. In our study, it was found that there was less PTEN gene expression in the patient group as opposed to the controls, however this finding was statistically insignificant (p=0.7884). Expression changes of this gene were also

investigated on gender basis and it was found that there was a decrease in PTEN expression of autistic male patients, compared to the controls. In female patients, PTEN was found to be less expressed than in the controls. Research on both the number of patients and the basis of gender may provide more detailed information about how this decrease in PTEN expression is reflected in the etiology of autism.

POGZ encodes pogo transposable element-derived protein with zinc finger domain affecting ASD [20]. Previous studies have shown that POGZ is involved in chromatin remodeling, neurite outgrowth, neuronal proliferation and gene transcription regulation [21,38-40]. In fetal brain tissues, the POGZ expression pattern may well play an essential role in early embryonic development [26]. POGZ deficiency may affect mitosis, brain development and dysfunction [23]. A recent study demonstrated that Pogz deficient mouse mimicked several of the ASD symptoms, including learning and motor deficits, growth impairment, microcephaly and increased sociability [24].

Pathogenic POGZ mutation causes impaired cortical development and reversible autism-like phenotypes. De novo mutations were likely gene-disrupting variants that cause ID and ASD [25]. Matsumura et al. showed that POGZ regulates neuronal development, and POGZ de novo mutations impaired neuronal development in the developing mouse brain and induced pluripotent cell lines from an ASD patient [41]. Our expression results of POGZ gene was statistically significant. POGZ gene was expressed more in patients with autism. Also we were investigated expression changes of the POGZ gene in terms of gender. Autistic males had more POGZ expression than the controls and this result was found to be significant. In female patients, POGZ was found to be more expressive than the controls but this finding was not significant. With the small number of female patients included in this study, the increase in gene expression may not be found to be significant. Genotype–phenotype correlation analysis has revealed that there is a relationship between and PTEN and POGZ genes with ID accompanying some autism cases [15,26]. In our study, POGZ and PTEN expressions were examined in terms of ID associated with autism. The results of both genes were not statistically significant.

CONCLUSION

In future studies, by investigating the expression of PTEN and POGZ genes in larger cohorts and comparing the obtained results with the other clinical findings determined in Turkish ASD patients, the unknowns regarding these genes in the etiology of autism can be eliminated. They may be used as a potential biomarker in the clinic and may contribute to the development of clinical phenotype-specific treatment options among patients. It will also be useful to investigate and find other genes, which may be new candidate genes for autism. We only used blood samples from the patients because the difficulty and inaccessibility in taking and analyzing brain tissue, and this remains one of the biggest obstacles in autism neuropathology [42]. Also, the expression of the genes may be studied in specific brain regions and other biological samples from autism patients. Therefore, the real effect of the expression of these genes on the autism phenotype may be determined by further analysis.

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ORCID and Author's contributions: **T.T. (0000-0003-2216-4084):** Data collection, processing, practice, analysis, literature search, writing. **E.F.S. (0000-0002-5644-5442):** Design, Data Collection, processing, analysis, writing, critical review. **E.D. (0000-0002-8424-4947):** Patients' selection, writing, critical review. **N.S. (0000-0001-7120-1561):** Patients' selection, Data Collection. **Z.H. (0000-0002-0711-4014):** Analysis and writing. **D.B.O. (0000-0003-3189-2112):** Design and

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RESEARCH ARTICLE

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Effect of miRs-17/20 on vasospasm in subarachnoid hemorrhage model of rats

miR-17/20'nin Sıçanların Subaraknoid Kanama Modelinde Gelişen Vazospazm Üzerine Etkisi

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ABSTRACT

Aim: To investigate the effects of melatonin and miRNA-17/20 administration on vasospasm and vascular damage on the bacillary artery in the Subarachnoid hemorrhage (SAH) model of rats.
Methods: Rats were divided into 6 groups: Sham, SAH, SAH+NegmiRNA, SAH+MEL, SAH-miRs-17/20 group, SAH+MEL+miRs-17/20. For creating the SAH model the skin was cut with a vertical incision in the anterior region of the head.120 µL of fresh non-heparinized autologous arterial blood collected from the tail artery was injected into the prechiasmatic cistern under aseptic conditions. All steps in the Sham were the same as in the SAH group, except for blood injection. In the SAH+NegmiRs-17/20, miRs-17/20 miRNA Mimic-Negative Control#1 was administered 1 hour after SAH operation. In the SAH+MEL,10 mg/kg melatonin was administered intraperitoneally 1 hour after the SAH operation. In the SAH-miRs-17/20, mimic-miR-17 and mimic-miR-20 were given intranasally 1 hour after the SAH operation. In the SAH+MEL+miRs-17/20,intranasal mimic-miR-17 and intraperitoneal melatonin were administered 1 hour after the SAH operation. Brain samples, including the bacillary artery, were taken and subjected to routine tissue processing procedures. Vessel samples were evaluated and graded in histological sections stained with the H-E method in terms of vasospasm, edema in the tunica media, and folding of the lamina elastica interna.
Results: The co-administration of melatonin and miRs-17/20 reduced the vasospasm and edema formation in the vessel wall. It has also been demonstrated that the application of miRs-17/20 after SAH alone reduces the development of edema in the vessel wall and folding of the internasal lamina elastica due to vasospasm.
Conclusion: It has been shown that miRs-17/20 can reduce vasospasm in the vessel wall and prevent vessel damage by reducing edema.

Keywords: Subarachnoid Hemorrhage, microRNAs, melatonin, rat

ÖZ

Amaç: Mevcut çalışmamızın amacı, ratlarda oluşturulan subaraknoid kanama (SAH) modelinde melatonin ve miRNA-17/20 uygulamasının basiller arterde gelişen vazospazm ve damar hasarı üzerine etkisinin araştırılmasıdır.
Yöntemler: Çalışmada kullanılan 36 adet sıçan 6 gruba ayrılmıştır; Sham, SAH, SAH+NegmiRNA, SAH+MEL, SAH-miRs-17/20 group, SAH+MEL+miRs-17/20. Sıçanlara anestezi altında SAH modeli uygulandı. Kafanın ön bölgesinden dikey bir kesi ile cilt açılarak kemiğe ulaşıldı. İnsizyondan sonra, kuyruk arterinden toplanan 120 µL heparinize olmayan taze otolog arteriyel kan aseptik koşullar altında 10 saniyede yavaşça prekiazmatik sisternaya enjekte edildi. Sham grubunda kan enjeksiyonu dışında tüm basamaklar SAH grubuyla aynıydı. SAH+NegmiRs-17/20 grubunda, miRs-17/20 miRNA Mimic Negative Control#1 SAH operasyonundan 1 saat sonra uygulandı. SAH+MEL grubunda, SAH operasyonundan 1 saat sonra 10 mg/kg melatonin intraperitoneal olarak verildi. SAH-miRs-17/20 grubundaysa SAH operasyonundan 1 saat sonra intranazal olarak mimic-miR-17 ve mimic-miR-20 verildi. SAH+MEL+miRs-17/20 grubunda, SAH operasyonundan 1 saat sonra intranazal mimic-miR-17 ile intraperitoneal melatonin (10 mg/kg) uygulandı. Deney sonunda sıçanlardan basiller arteri de içeren beyin örnekleri alınıp rutin doku takip işlemlerine tabi tutuldu. Sonrasında H-E yöntemi ile boyanan histolojik kesitlerde damar örnekleri vazospazm, tunica mediada ödem ve lamina elastica internada kıvrımlanma kriterleri açısından değerlendirilip derecelendirildi.
Bulgular: SAH modeli oluşturulan sıçanlarda, SAH modeli sonrası melatonin ve miRs-17/20'nin birlikte uygulanmasının damar duvarında oluşan vazospazm ve ödem oluşmasını anlamlı şekilde azalttığı gösterilmiştir. SAH sonrası miRs-17/20 uygulamasının da tek başına damar duvarında ödem gelişmesini ve vazospazma bağlı lamina elastica internada kıvrımlanmayı azalttığı ortaya konmuştur.
Sonuç: Çalışmamızda, miRs-17/20'nin damar duvarında vazospazmı azaltabileceği, ödemi de azaltarak damar hasarını önleyebileceği gösterilmiştir.

Anahtar kelimeler: Subaraknoid kanama, microRNA, melatonin, sıçan

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INTRODUCTION

Subarachnoid hemorrhage (SAH) is a neurological emergency caused by the extravasation of blood into the subarachnoid space [1]. It accounts for 5% of all stroke cases and a headache is the most common symptom in patients with SAH. In addition, these patients may have at least one more symptom or finding, such as nausea, vomiting, neck stiffness, photophobia, short-term loss of consciousness, or focal neurological deficit. 74% of patients with SAH have a headache, 77% have nausea and vomiting, 53% have a short-term loss of consciousness and 35% have neck stiffness [2]. While 10 to 15% of patients die before reaching the hospital, 30% of SAH patients who are able to apply to any health institution die within the following year [3].

The most significant complication after SAH is vasospasm [4]. The blood accumulating in the subarachnoid space after SAH causes some chemical changes, which result in smooth muscle contraction in the tunica media layer of the vessel wall and ultimately, pathological narrowing. This is called vasospasm and it develops within a few weeks after bleeding [5]. While vasospasm is concentrated near the bleeding site, it is seen in varying degrees in adjacent vascular structures [4]. Vasospasm is thought to be one of the most important causes of mortality and morbidity in SAH and while it is seen in 30 or 70% of patients after SAH, it can increase the risk of ischemia and infarction up to 36%. Vasospasm due to SAH also worsens the impaired blood flow, leading to ischemia [6].

Although the cause of vasospasm developing after SAH has not been fully understood yet, complex and multifactorial factors such as inflammation, altered vascular resistance, impaired autoregulation, micro thromboembolism and undeveloped collateral anatomy as well as genetic effects, are blamed in the etiology [7]. It is thought that spasmogens that occur with the destruction of thrombocytes and especially erythrocytes leaking out of the vein after SAH, cause vasospasm. These spasmogens include oxyhemoglobin, reactive oxygen species (ROS), thromboxane-A2 (TxA2), endothelin-1 (ET-1), angiotensin and catecholamines [7, 8].

MicroRNAs (miRNAs) are a family of small non-coding RNAs that are important regulators of gene expression [9]. These molecules are composed of 21 to 22 nucleotides that regulate the stability or translational efficiency of targeted mRNAs [10]. Studies have shown its effects in many pathological conditions [11-12-13-14]. miRNA-17 and miRNA-20 are miRNAs belonging to the miRNAs-17-92 group [13]. miRNA-17 and miRNA-20 appear to play a role in many aspects of the central nervous system (CNS) [14].

Melatonin is a hormone produced by the pineal gland and its production occurs in the dark phase and is acutely suppressed by light [15]. Melatonin is known to have an antioxidant effect that reduces ROS production in cells. Many studies have benefited from this therapeutic effect of melatonin in many pathological conditions, including neurodegenerative diseases [16]. In addition, studies are showing that melatonin has antiapoptotic, anti-inflammatory and antioxidant effects in the treatment of SAH [17, 18].

Our study aimed to investigate the effects of melatonin and miRNA-17/20 administration on vasospasm and vascular damage on the bacillary artery, in the SAH model created in rats.

MATERIALS AND METHODS

Trial design

The tissues used in this study are the tissues obtained from the study titled “Examination of the protective effects of melatonin and miR17/20 administration on acute brain damage in rats with experimental subarachnoid hemorrhage model”, which was approved by the Animal Experiments Local Ethics Committee of Çanakkale Onsekiz Mart University, with the decision number 2019/03-05. Before the study started, an application was made to the Animal Experiments Local Ethics Committee of Çanakkale Onsekiz Mart University and approval was obtained with the number 38285931-604.02.04-E.2000074137 dated 12/06/2020. Animal procedures were performed according to the “Guide for the Care and Use of Laboratory Animals” principles [19].

All steps of the study were conducted at the Çanakkale Onsekiz Mart University Experimental

Animals Research Center, open for supervision. In this study, 36 Wistar albino male rats (aged 3-4 months, weight 250-350 grams) were used. The rats were obtained from the Çanakkale Onsekiz Mart University Experimental Research Center. All rats were housed in pairs in appropriate cages in an animal room maintained at a standard humidity (35%-50%) and temperature of 24±1 °C, with 12 hours of light and 12 hours of darkness, and were fed with standard food and water ad libitum.

Experimental Groups and Surgical Procedure

The thirty-six (36) rats used in the study were randomly divided into 6 groups.

Group 1: Sham (n=6)

Group 2: SAH (n=6)

Group 3: SAH+Negative control miRNA group (SAH+NegmiRNA) (n=6)

Group 4: SAH+Melatonin (SAH+MEL) group(n=6)

Group 5: SAH-miRs-17/20 group (n=6)

Group 6: SAH+MEL+miRs-17/20 group (n=6)

SAH Operation

In our study, the pre-chiasmatic SAH model was used as previously described in the literature [20]. In animals administered general anesthesia with intramuscular Ketamine hydrochloride (60 mg/kg) and xylazine hydrochloride (5 mg/kg), the skin was opened with a vertical incision in the anterior region of the head, and the bone was reached. A 1.5-mm diameter hole was drilled 7.5 mm forward from the bregma and 2 mm to the right of the sagittal line. By using a 30-degree posterior sagittal angle, the anterior bone base was reached 2-3 mm in front of the chiasm. After the incision, 120 µL of fresh non-heparinized autologous arterial blood collected from the tail artery was slowly injected into the pre-chiasmatic cistern for 10 seconds under aseptic conditions. Unlike the original model, arterial blood collected through an open incision from the tail artery was used instead of tail venous blood. A 30G injector is used for arterial blood injection: 0,5 mL of blood was injected. After the surgical procedure was completed, the hole was closed with bone wax. In the sham group, the pre-chiasmatic cistern was entered using a 30G needle tip and after waiting 10 seconds (sec), the injector was removed without giving any fluid. The process was carried out at 37°C ± 0.5°C using a heating pad. In conclusion, all steps in the Sham group were the same as in the SAH group, except for blood injection.

In the SAH+NegmiRs-17/20 group, miRs-17/20 miRNA Mimic Negative Control#1 (200 pmol) was divided equally into both nostrils 1 hour after the SAH operation. During this application, the rats were anesthetized with 3% isoflurane. In the SAH+MEL group, 10 mg/kg melatonin was administered intraperitoneally 1 hour after the SAH operation. Mimic-miR-17 (200 pmol) and mimic-miR-20 (200 pmol) were administered intranasally to rats in the SAH-miRs-17/20 group 1 hour after the SAH operation. In the SAH+MEL+miRs-17/20 group, intranasal mimic-miR-17 (200 pmol) and mimic-miR-20 (200 pmol) and intraperitoneal melatonin (10 mg/kg) were administered 1 hour after the SAH operation.

Intranasal miRNA Administration

rno-miR-20b-5p mimic (miR-20) (miRBase Accession: MIMAT0003211/5 ' C A A A G U G C U C A U A G U G C A G G U A G / miRVana® miRNA mimic, Thermo Fisher Scientific, USA), rno-miR-17-1-3p mimic (miR-17) (miRBase Accession: MIMAT0004710/5 'ACUGCAGUGAAGGCACUUGUGG/miRVana® miRNA mimic, Thermo Fisher Scientific), and miRs-17/20 miRNA Mimic Negative Control #1 (Thermo Fisher Scientific) were dissolved in nuclease-free water and 200 pmol doses were prepared. A 10-µL liquid solution prepared for each miRNA was applied to the nostril via a soft pipette tip attached to a micropipette. The solution containing miR-17 was administered to the left nostril, and the solution containing miR-20 was administered to the right nostril. Both miRNAs were obtained and stored under cold chain conditions throughout the entire experimental procedure. To prevent nasal irritation and to obtain sufficient time for the given fluid to reach the brain, miRNA application was performed under 3% isoflurane anesthesia. The rats were kept in the supine position for 3 minutes after the application.

Melatonin Preparation and Application

Melatonin (N-acetyl-5-methoxy tryptamine; product code: M5250-1G; Sigma-Aldrich, St. Louis, MO, USA) was dissolved in absolute ethanol (Absolute GR for analysis, MERCK, Germany) and further diluted in saline to achieve a final concentration of 2.4% (v/v) ethanol. The final solution was injected IP (10 mg/kg) in rats 1 h after SAH.

Histological Examination

Brain samples, including the bacillary artery, taken from the animals in the experimental groups were immediately placed in 10% neutral buffered formalin for fixation. At the end of the 48-hour fixation period, the tissues were embedded in paraffin blocks after routine dehydration and clearing procedures. Sections of 4 microns taken from the blocks were subjected to routine hematoxylin and eosin (H-E) staining. Afterward, H-E-stained sections were evaluated under a camera-attached light microscope (Olympus CX43) and photographs were taken. The evaluation of the sections was made according to the criteria of vasospasm, edema in the tunica media and folding of the lamina elastica interna, as previously described [21]. Post-assessment grading was also done as previously stated in the literature [22]:

no visible change=1,

minimal change=2,

moderate change=3, and

severe change=4 points.

Statistical analysis

The data obtained from the evaluations were compared using the IBM SPSS Statistics package program version 25 and the values with $p<0.05$ were considered significant. The t-test was used for the independent variables in the comparison of the groups.

RESULTS

Vessel sections taken from the rats were stained with H-E and light microscopic evaluation was performed on the criteria of vasospasm, edema in the tunica media, and folding of the lamina elastica interna. According to the evaluation made for vasospasm criteria: a significant increase was observed in all groups compared to the Sham group (The p values for groups 2, 3, 4, 5, and 6 are 0.00, 0.001, 0.008, 0.016, 0.022, respectively). When the SAH group was compared with the SAH+NegmiRs group, vasospasm values were found to be similar (p=0.11). Although the mean of the SAH+Mel and SAH+miRs-17/20 groups were lower than the SAH group, no statistically significant difference was found (p values of 0.111 and 0.065, respectively). A significant decrease in vasospasm values was observed in the SAH+Mel+miRs-17/20 group compared to the SAH group (p=0.001). No significant difference was found in other group comparisons.

In the evaluation made for assessment of edema in the tunica media, which is the middle layer of the vessel wall: significant increases were observed in the SAH, SAH+NegmiRs, SAH+MEL, SAH-miRs-17/20 groups compared to the Sham group (p values were 0.00, 0.00, 0.00, 0.004, respectively). However, when the Sham group and the SAH+Mel+miRs-17/20 group were compared, these two groups were found to be similar (p=0.111). Significant reductions were observed in the SAH+miRs-17/20 and SAH+Mel+miRs-17/20 groups compared to the SAH group (p values 0.002 and 0.006, respectively). It was observed that the amount of edema in the tunica media was significantly decreased in the SAH+miRs-17/20 and SAH+Mel+miRs-17/20 groups compared to the SAH+Mel group (p values 0.044 and 0.041, respectively). No significant difference was found in other group comparisons.

In the evaluation made according to the folding of lamina elastica interna (LEI) criteria in the vessel wall: LEI values were significantly increased in the SAH group (p=0.00) and SAH+NegmiRs group (p=0.001) compared to the Sham group. Results for the Sham group and the SAH+Mel and SAH+miRs-17/20 groups were similar (p values 0.296 and 0.096, respectively). A significant increase was found in the SAH+Mel+miRs-17/20 group compared to the Sham group (p=0.007). LEI was significantly decreased in the SAH+Mel, SAH+miRs-17/20, and SAH+Mel+miRs-17/20 groups compared to the SAH group (p values 0.017, 0.049, and 0.03, respectively). When the

SAH+NegmiRs group was compared with the SAH+Mel and SAH+Mel+miRs-17/20 groups, a significant decrease was observed in these groups compared to the SAH+NegmiRs group (p values 0.025 and 0.049, respectively). No significant difference was observed in other group comparisons.

The light microscopic micrographs belong to experimental groups can be seen in Figure 1. Folding of lamina elastica interna of vessel section from SAH group can be seen in Figure 2. The mean and the standard deviations of the groups can be seen in Table 1.

Table 1: The mean values and the standard deviations of the groups

Groups	Vasospasm (Mean±SD)	Edema in the Tunica Media (Mean±SD)	Folding of the Lamina Elastica Interna (Mean±SD)
Sham (n=6)	0.16±0.40	0.00±0.00	0.33±0.51
SAH (n=6)	2.5±0.54	2.66±0.51	2.33±0.81
SAH+NegmiRNA (n=6)	1.83±0.71	1.83±0.75	2.16±0.75
SAH+MEL (n=6)	1.66±1.03	2.16±0.75	0.83±0.98
SAH-miRs-17/20 (n=6)	1.50±1.04	1.16±0.75	1.16±0.98
SAH+MEL+ miRs-17/20 (n=6)	1.00±0.63	0.83±1.16	1.33±0.51

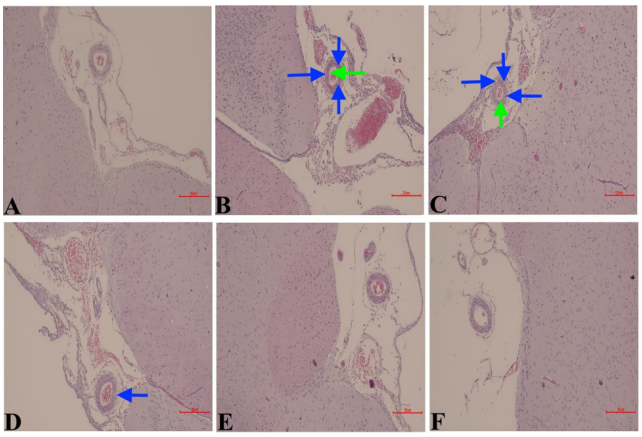

Figure 1. Light microscopic micrographs of H-E-stained sections of experimental groups. A, B, C, D, E, and F belong to Sham, SAH, SAH+ NegmiRNA, SAH+MEL, SAH+miRs-17/20, and SAK+MEL+ miRs-17/20 groups, respectively. Green arrows mark the vasospasm areas and blue arrows mark the edema areas in tunica media (Magnification, x100).

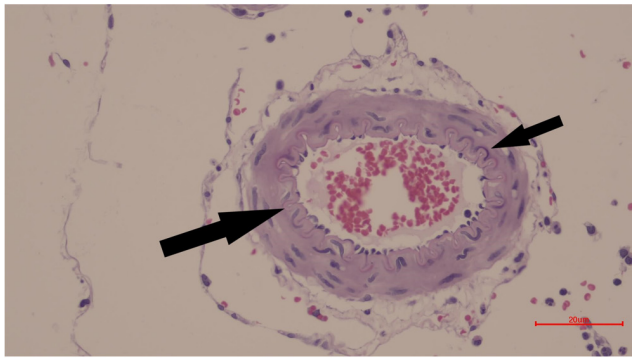

Figure 2: Light microscopic micrograph of H-E-stained section of SAH group. Black arrows mark the folding of lamina elastica interna of the vessel (Magnification, x400)

DISCUSSION

In our study, histopathological evaluations were made in rats for which the SAH model was created, and it was shown that the co-administration of melatonin and miRs-17/20 after the SAH model, significantly reduced the vasospasm and related edema formation in the vessel wall. It was also demonstrated that the application of miRs-17/20 after SAH alone reduces the development of edema in the vessel wall and folding of the internasal lamina elastica, due to vasospasm.

SAH is a neurological emergency caused by the extravasation of blood into the subarachnoid space [1]. Although mortality has decreased in recent years, its morbidity is still high [23]. Patients often face permanent disability, cognitive impairment and mental problems, such as depression and anxiety [24]. For these reasons, the correct planning of SAH treatment without delay may be a factor that increases the patients' quality of life.

The most important complication after SAH is vasospasm [4]. The blood accumulating in the subarachnoid space after SAH causes some chemical changes in this region. These changes result in smooth muscle contraction in the vessel wall and ultimately pathological narrowing. This is called vasospasm [6] and it develops within a few weeks after bleeding. While vasospasm is concentrated near the bleeding site, it is seen in varying degrees in adjacent vascular structures [4]. Vasospasm is thought to be one of the most important causes of mortality and morbidity in SAH. While it is encountered in 30 to 70% of patients after SAH, it can increase the risk of ischemia and infarction up to 36%. This vasospasm, which

develops because of SAH, worsens the impaired blood flow and leads to ischemia [6]. As a result, neuron damage and loss occurs and accordingly, various complications develop. For these reasons, the treatment of vasospasm after SAH may be important in improving the quality of life of patients with SAH.

Melatonin is a hormone produced by the pineal gland, its production occurs in the dark phase and it is acutely suppressed by light [15]. Positive effects have been shown in the treatment of many diseases, and studies are showing that melatonin has antiapoptotic, anti-inflammatory and antioxidant effects, especially in the treatment of SAH [25]. Melatonin, which is effective in the treatment of SAH in previous studies, was used alone and together with miR-17/20 in our current study. Accordingly, it was shown that while melatonin alone causes a decrease in the histopathological findings seen in SAH, its effect increases when used together with miR-17/20.

miRNAs are a family of small non-coding RNAs that are important regulators of gene expression [9]. 21 to 22 nucleotide molecules that regulate the stability or translational efficiency of targeted mRNAs [10]. Studies have shown their effects in many pathological conditions [11-12-13-14]. miRNA-17 and miRNA-20 are miRNAs belonging to the miRNAs-17-92 group [13]. miRNA-17 and miRNA-20 appear to play a role in many conditions involving the CNS, such as brain and spinal cord injury [14]. In this study, we investigated the effect of SAH treatment on reducing vasospasm in the bacillary artery. It was observed that the mean vasospasm in the miR-17/20 group was decreased, compared to the SAH group. When melatonin was administered in addition to miRs-17/20, significant improvement was observed compared to the SAH group. Decreased vasospasm values may cause a decrease in ischemic brain damage and ultimately an increase in quality of life after SAH.

Edema in the tunica media, which contains the muscle layer in the vessel wall after SAH, is an indicator of vessel damage. In our study, it was shown that the application of miRs-17/20 reduces edema developing after SAH. This decrease was also found to be more significant than the decrease obtained with melatonin. This result reveals that miRs-17/20 may have a protective effect against vascular damage after SAH. If the edema decreases, the blood flow will increase as the vessel diameter will be wider, and ischemia can be prevented.

The lamina elastica interna (LEI) is a thin elastic membrane located in the vessel wall between the tunica intima and the tunica media. In vasospasm, contraction occurs in the tunica media, the muscle layer in the vessel wall and as a result, folds are seen in the LEI. In our study, the LEI values in the group given miRs-17/20 after SAH were found to be similar to the Sham group. It was shown that miRs-17/20 can reduce the contraction of the vessel wall after SAH.

Limitations

In this study, we could only perform the histopathological evaluation but not so other methods, such as immunohistochemical and biochemical ones. In addition, if radiological evaluations, such as cerebral arterial angiography, could be performed, the study's results may be sturdier for demonstrating the protective effect of miR-17/20 on vasospasm. These are our study's limitations.

CONCLUSION

miR-17 and miR-20 are miRNAs whose therapeutic effect is focused on in brain injury models. In this study, the effects of miRs-17/20 and melatonin against vasospasm and vascular damage in the basilar artery in rats with the SAH model, were investigated. In conclusion, it was shown that miRs-17/20 can reduce vasospasm in the vessel wall and prevent vessel damage by reducing edema.

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Influenza and pneumonia knowledge level and vaccination status of pneumoconiosis patients

Pnömokonyoz Hastalarının İnfluenza ve Pnömoni Konusunda Bilgi Düzeyi ve Aşılı Olma Durumları

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ABSTRACT

Aims: In pneumoconiosis, which is a chronic lung disease, frequent seasonal flu and pneumonia worsen the course of the disease. Therefore, it is important that patients have seasonal flu and pneumococcal vaccines. The study aims to measure the knowledge level of patients with pneumoconiosis about influenza and pneumonia and to determine their vaccination status.
Methods: We reached 73 patients with pneumoconiosis and had them fill out a 26-question questionnaire that evaluated their information about influenza and pneumonia and their vaccination status. The study was designed as descriptive, cross-sectional. We also examined the sociodemographic, socio-economic characteristics and working conditions of the patients.
Results: The mean age of 73 patients, one of whom was female, was 46.4±7.8 years. They started working life in middle adolescence. Most of them are primary school graduates and they estimated their income was not sufficient. One-third of the patients were hesitant about vaccination in general. Some had not heard of the seasonal flu and pneumonia vaccine. Thirty-four patients (46.6%) said that they heard about the vaccines from the TV or the internet, not from the healthcare professionals. After the diagnosis of pneumoconiosis, influenza and pneumonia vaccination rates were very low (14 patients/19.2% and 16 patients/21.9%, respectively). One-third of the patients were unaware that pneumonia was a lung disease. When we asked, "Why haven't you been vaccinated against pneumonia?" the answer "I just got this information" came to the fore (39 patients/53.5%). Most patients (42/57 patients) who were not vaccinated against pneumonia after being diagnosed with pneumoconiosis were not aware that pneumonia could be prevented by vaccination (p<0.001). However, most of those who have been vaccinated said that they had this knowledge before (15/16 patients).
Conclusion: Patients with pneumoconiosis need regular information and advice about influenza and pneumococcal vaccines.

Key-words: Pneumoconiosis, influenza, pneumonia, vaccine, pneumococcal vaccine.

ÖZ

Amaç: Kronik bir akciğer hastalığı olan pnömokonyozda sık sık influenza ve pnömoniye yakalanmak hastalığın seyrini kötüleştirir. Bu sebepten hastaların influenza ve pnömokok aşılarını olması önem arz eder. Çalışmanın amacı pnömokonyozlu hastaların influenza ve pnömoni hakkında bilgi düzeylerini ölçmek ve aşılı olma durumlarını belirlemektir.
Yöntem: Yetmiş üç pnömokonyoz tanılı hastaya ulaşarak mevsimsel grip ve pnömoni hakkında bilgileri ve aşılı olma durumlarını değerlendiren 26 soruluk anket bilgi formu doldurmalarını sağladık. Çalışma tanımlayıcı, kesitsel olarak tasarlandı. Hastaların sosyodemografik, sosyoekonomik özelliklerini, çalışma şartlarını da inceledik.
Bulgular: Biri kadın 73 hastanın yaş ortalaması 46,4±7,8 yıl idi. Hastalar çalışmaya orta ergenlik döneminden itibaren başlamış. Çoğu ilkokul mezunu ve gelir durumlarının yeterli olmadığını düşünüyorlardı. Hastaların üçte biri genel olarak aşı konusunda tereddütte idi. Grip ve zatürre aşısını duymayanlar vardı. Otuz dört hasta (%46,6) aşıları bizzat sağlıkçılardan değil, TV veya internetten duyduğunu söyledi. Pnömokonyoz teşhisi sonrası grip ve zatürre aşısı olma oranları çok düşüktü (sırasıyla, 14 hasta/%19,2 ve 16 hasta/%21,9). Hastaların üçte biri zatürrenin akciğer hastalığı olduğu, 41 hasta (%56,2) ise pnömokonyozun zatürre riskini artırdığı bilgisine sahip değildi. "Neden zatürre aşısı olmadınız?" diye sorduğumuzda ise "Bu bilgiye henüz yeni ulaştım" cevabı ön plana çıktı (39 hasta/%53,5). Pnömokonyoz teşhisi aldıktan sonra zatürre aşısı olmayan hastaların büyük çoğunluğu (42/57 hasta) zatürrenin aşıyla önlenebileceği bilgisine sahip değildi. Diğer taraftan aşıyı olanların çoğu önceden bu bilgiye sahip olduklarını söyledi (15/16 hasta) (p<0.001).
Sonuç: Pnömokonyozlu hastaların influenza ve pnömokok aşıları hakkında düzenli bilgi ve tavsiyeye ihtiyacı vardır.

Anahtar Kelimeler: Pnömokonyoz, influenza, pnömoni, aşı, pnömokok aşısı.

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INTRODUCTION

Pneumoconiosis is defined as an irreversible chronic interstitial lung disease characterized by accumulating inorganic dust in the lungs and the fibrotic tissue response in the lungs, to the accumulated dust. This disease, which is widespread globally, is a public health problem. Respiratory and heart failure resulting from chronic inflammation and fibrosis in the lung tissue is the main cause of mortality. Concomitant infections (upper and lower respiratory tract infections, tuberculosis) contribute to the acceleration of this process. Pneumoconiosis is in the class of occupational chronic interstitial lung diseases, but these patients may develop concomitant emphysema or chronic obstructive pulmonary disease (COPD) [1,2]. Coal workers' pneumoconiosis is also associated with an increased risk of COPD. In a study conducted in China, they showed that the prevalence of COPD in pneumoconiosis increased up to 40% [3]. Unfortunately, there is no effective treatment for pneumoconiosis. Some measures are critical to slow down the course of the disease: quitting smoking, avoiding dust in the work and home environment, screening and treatment of latent tuberculosis, pulmonary rehabilitation, as well as getting influenza and pneumococcal vaccines, as in every chronic lung disease, are the most important of these measures [4].

Influenza is an acute viral respiratory infection that causes significant morbidity and mortality worldwide. Three types of influenza (A, B, and C), a seasonal RNA virus, cause illness in humans. Influenza A is the type most responsible for causing pandemics due to its high susceptibility to antigenic variation [5]. The influenza virus is highly contagious and infects 5% to 15% of the world's population each year. It causes significant morbidity and mortality, especially in immunocompromised and at-risk individuals, and invites the development of bacterial superinfections. It evolves constantly, mutating rapidly and unpredictably, producing new viruses that can evade the humoral immunity produced by current influenza virus vaccines [6]. Pneumonia, a lower respiratory tract infection, is responsible for high morbidity and mortality, and is the cause of approximately 75% of antibiotic use worldwide. Pneumococci are the most common bacteria in lower respiratory tract infections. Risk factors for invasive pneumococcal infections (pneumonia, meningitis) are well defined. Sickle-cell anemia, diabetes mellitus, chronic heart, kidney, lung and liver diseases, alcohol abuse, cancers and immunosuppressive diseases, are associated with an increased frequency of pneumococcal infections [7]. Infectious exacerbations and pneumonia occur frequently in the follow-up of chronic lung diseases (such as COPD, asthma, bronchiectasis, interstitial lung diseases), which are among the priority public health problems. Depending on these, physician/emergency applications, hospitalization or intensive care support are required. In various studies, the risk of developing pneumonia was 7 to 10 times higher, the risk of developing pneumococcal pneumonia 3 times, and the risk of hospitalization was 3 to 9 times higher in patients with chronic lung disease, compared to healthy individuals [8].

Vaccination continues to be the most effective and economical way to prevent many infections and their complications, especially influenza and pneumonia. There are currently three types of seasonal flu vaccines licensed for use in humans: inactivated, live attenuated and recombinant hemagglutinin influenza vaccines [9]. Since 2012, an additional B strain has been added to the traditionally used trivalent (two A and one B strains) inactivated influenza vaccine, and a quadrivalent inactivated vaccine has been developed. This vaccine is recommended for all individuals at risk of influenza, such as those under the age of two, over the age of 65, organ transplant recipients, pregnant women, as well as those suffering from chronic heart, neurological, kidney and lung diseases [10]. The pneumococcal vaccine, which has been in use since 1983, has significantly reduced the burden of pneumonia in both pediatric and elderly populations. The pneumococcal vaccine is divided into two, as whole cell vaccine and subunit vaccine. The whole cell vaccine includes live attenuated vaccine and inactivated vaccine, while the subunit vaccine includes the polysaccharide vaccine, conjugate vaccine and protein-based vaccine. Commercially available pneumococcal vaccines are subunit vaccines. Among them, the most commonly used vaccines are pneumococcal polysaccharide 23 (PPV23) and

pneumococcal conjugate 13 (PCV13) vaccines. Considering that not every vaccine provides full protection, it is worth mentioning that studies are being conducted on new vaccines [11].

We know that influenza and pneumonia affect the quality of life of pneumoconiosis patients. There are many ways to encourage patients to get vaccinated and one of these is education. With this study, we aimed to measure the knowledge level of patients with pneumoconiosis about influenza and pneumonia, and to determine their vaccination status.

MATERIAL AND METHODS

Data source and study population

The study was conducted through the data obtained from the electronic health records of the patients with pneumoconiosis, who applied to the Ege University Medical Faculty Hospital Occupational Diseases polyclinic, between November, 2015-December, 2021, and the information questionnaire filled by the patients. Sociodemographic and socioeconomic characteristics of the patients, information on working conditions and ILO (International Labour Organization) Pneumoconiosis Radiograph results, were obtained from the outpatient clinic records. The opacities observed in the PA chest X-ray were evaluated by two B readers by comparing them with the standard ILO radiographs in terms of size, shape, and extent, if any, in terms of pleural plaques and additional pathologies. With the Information Questionnaire, the knowledge level of the patients about influenza, pneumonia and their vaccination status, was evaluated using various questions, numbering a total of twenty-six questions. The study complied with the Declaration of Helsinki, and was approved by Ege University Rectorate Faculty of Medicine Dean's Medical Research Ethics Committee (Approval Decision: 21-12.1T/18; Date: 20.12.2021).

Statistical Analysis

The IBM SPSS Statistics 24 program was used in the analysis of the data. Categorical variables were expressed in cross-tables and numerical variables in mean, median, standard deviation, minimum and maximum. In the comparison of independent categorical variables, the Chi-square test was used. P value of <0.05 was considered statistically significant.

RESULTS

Only one of the 73 patients included in the study was female and the mean age was 46.4±7.8 years. The patients started working in mid-adolescence and experienced dust exposure for a long period, on average 18.7±8.1 years. The mean duration of follow-up for pneumoconiosis was 4.1±3.2 years, and cigarette consumption was calculated as 13.3±11.6 pack-years (Table 1).

Table 1. Numerical sociodemographic characteristics of the patients.

Variables	Mean	Standard deviation	Min.	Max.
Age (year)	46.4	7.8	26	72
Pneumoconiosis disease duration (years)	4.1	3.2	1	28
Exposure time (years)	18.7	8.1	3	42
Age of employment (years)	17.4	4.2	10	25
Smoking (packyear)	13.3	11.6	1	60

When we look at the other sociodemographic characteristics, we observed that almost half of the patients (48%) did not attend school beyond secondary school. More than 90% of the patients were married and living with their family. When pneumoconiosis was diagnosed, most of them were working in the glass-earth-ceramic and mining industry (87.7%). Another remarkable point was that more than half of the patients had income at or below the minimum wage (52%). Considering that smoking is an important additional risk factor for the progression of pneumoconiosis (in the presence of silica dust), it was satisfying to note that 13 patients (17.8%) had never smoked and 25 patients (34.2%) had quit smoking. Active alcohol consumption was 13.7% (10 patients). We obtained the ILO (International Labour Organization) pneumoconiosis classification from the electronic health records and found that most patients were in category I (42 patients/57.5%). while eleven patients (15.1%) were in category III. Among the accompanying chronic diseases, hypertension, diabetes mellitus and cardiopulmonary diseases were the most common. Occupational hearing loss and musculoskeletal system diseases were more prominent among occupational diseases (Table 2).

Table 2. Other sociodemographic and socioeconomic characteristics of the patients.

Features	Number (N)	Percent (%)
Gender		
Female	1	1.4
Male	72	98.6
Education		
No	1	1.4
Primary	34	46.6
Secondary	15	20.5
High	21	28.8
University	2	2.7
Marital status		
Married	70	95.9
Single or widower	3	4.1
Industry		
Glass, earth, ceramic	37	50.7
Mining	27	37
Metallurgy	5	6.8
Petrochemistry	2	2.7
Construction	2	2.7
Income status		
Less than minimum wage	25	34.2
Minimum wage	13	17.8
More than minimum wage	35	47.9
Smoking status		
Never smoked	13	17.8
Still smoking	35	47.9
Quitted smoking	25	34.2
Alcohol		
Never drank	62	84.9
Still drinking	10	13.7
Quit drinking	1	1.4
*ILO Pneumoconiosis Category		
I	42	57.5
II	20	27.4
III	11	15.1
Comorbid diseases		
No	33	45.2
Hypertension	11	15.1
Diabetes Mellitus	6	8.2
Respiratory system diseases	6	8.2
Cardiovascular diseases	5	6.8
Others	12	16.5
Co-occupational illness		
No	36	49.3
Hearing loss	23	31.5
Musculoskeletal diseases	10	13.7
Asthma, COPD	4	5.5

*ILO: International Labour Organization

All 73 patients answered the questionnaire questions entirely, which revealed that although most of the patients with pneumoconiosis (48 patients / 65.8%) believed in the effect of vaccines in general, a substantial number were unconvinced (24 patients / 32.8%). There were still patients who had not heard of seasonal flu and pneumonia vaccines (6 patients/8.2% and 19 patients/26%, respectively). Another interesting point was that almost half of the patients heard about these vaccines via television or the internet (34 patients/46.6%). More than one-third of the patients said they often had the seasonal flu (28 patients/38.4%). After the diagnosis of pneumoconiosis, influenza and pneumonia vaccination rates were very low (14 patients/19.2% and 16 patients/21.9%, respectively). Some of the vaccinated patients may have received these vaccines due to other chronic diseases. The number of patients who had pneumonia even once in their lifetime was six (8.2%). We learned that a significant part of the patients did not know that influenza and pneumonia were transmitted by respiratory tract, and moreover, they did not know that pneumonia was a lung disease (27 patients/37% and 25 patients/34.2%, respectively). More than half of the patients did not know that pneumoconiosis increases the risk of pneumonia and may cause severe pneumonia (41 patients/56.2%). Most patients said that they did not know that pneumonia could cause sepsis and meningitis (57 patients/78.1%), and almost half did not realize that pneumonia could be fatal (32 patients/43.8%). It was observed that 43 patients (58.9%) did not have the information that pneumonia could be prevented with vaccines, and that 86.3% (63 patients) did not have the information that these vaccines are free for chronic lung diseases such as pneumoconiosis. Thirty-four patients (46.6%) said that they did not know that the seasonal flu vaccine should be repeated every year, and 55 patients (75.3%) did not know that the conjugate vaccine (PCV13) should be given only once in a lifetime. When we asked, “Why didn't you get a seasonal flu shot?”, the majority of the patients said they didn't care or they just got this information (83.5%). When asked, “Why haven't you been vaccinated against pneumonia?”, the answer “I just got this information” was the majority of the responses (39 patients/53.5%) (Table 3).

Table 3. Responses of the patients to the Questionnaire Information Form questions.

Questions	Number (N)	Percent (%)
Your general attitude towards vaccines?		
I believe in its effects	48	65.8
Don't believe its effects	1	1.4
I'm undecided	24	32.8
Have you heard of the seasonal flu (influenza) vaccine?		
Yes	67	91.8
No	6	8.2
Have you heard of the pneumonia (pneumococcal) vaccine?		
Yes	54	74
No	19	26
What channel did you hear about these vaccines?		
Occupational physician	4	5.5
Family doctor	12	16.4
Occupational diseases specialist	7	9.6
TV or internet	34	46.6
I researched myself	10	13.7
I did not hear	6	8.2
Do you often get influenza (every year)?		
Yes	28	38.4
No	45	61.6
Have you had the flu vaccine after the diagnosis of pneumoconiosis?		
Yes	14	19.2
No	59	80.8
Have you had pneumonia?		
Yes	6	8.2
No	67	91.8
Have you been vaccinated for pneumonia after the diagnosis of pneumoconiosis?		
Yes	16	21.9
No	57	78.1
Did you know that seasonal flu and pneumonia are transmitted through the respiratory tract?		
Yes	46	63
No	27	37
Did you know that pneumonia is a lung disease?		
Yes	48	65.8
No	25	34.2
Do you know that pneumoconiosis increases the risk of pneumonia and pneumonia is severe in pneumoconiosis?		
Yes	32	43.8
No	41	56.2
Did you know that pneumonia causes sepsis or meningitis?		
Yes	16	21.9
No	57	78.1
Did you know that pneumonia can be deadly?		
Yes	41	56.2
No	32	43.8
Did you know that pneumonia can be prevented with a vaccine?		
Yes	30	41.1
No	43	58.9
Do you know that these vaccines are free to you?		
Yes	10	13.7
No	63	86.3

Table 3 Continued...		
Did you know that the influenza vaccine should be given every year?		
Yes	39	53.4
No	34	46.6
*Did you know that the pneumonia vaccine should be given once in a lifetime?		
Yes	18	24.7
No	55	75.3
Why didn't you get the seasonal flu shot?		
I didn't care	32	43.8
I'm vaccinated	11	15.1
I just got this information	29	39.7
I feel healthy	1	1.4
Why didn't you get the pneumonia vaccine?		
I didn't care	16	21.9
I'm vaccinated	16	21.9
I just got this information	39	53.5
I feel health	2	2.7

*The most common vaccine in Türkiye is the conjugate vaccine (PCV13).

Most patients (42/57 patients) who were not vaccinated against pneumonia after being diagnosed with pneumoconiosis, were not aware that pneumonia could be prevented by vaccination ($p<0.001$). However, most of those who have been vaccinated said that they had this knowledge before (15/16 patients) (Table 4).

Table 4. The relationship between the knowledge that pneumonia can be prevented by vaccination and the status of being vaccinated.

		Did you know that pneumonia can be prevented with a vaccine?		
		No	Yes	Total
Have you been vaccinated for pneumonia after the diagnosis of pneumoconiosis?	No	42	15	57
	Yes	*1	15	16
	Total	43	30	73

Pearson's chi square, $p<0.001$, *Expected count > 5

DISCUSSION

We studied 73 patients with pneumoconiosis who were followed up by our department for six years. These patients had relatively low education, income and other socioeconomic status. They did not have sufficient information regarding influenza, pneumonia and their vaccines. Most of the patients did not know that these diseases are transmitted by respiratory tract, that pneumonia is a vaccine-preventable lung disease, that the vaccine is given free of charge in chronic diseases. The most important outcome was that only 19.2% of patients received influenza vaccine and 21.9% received pneumococcal vaccine after the diagnosis of pneumoconiosis. Clearly in this regard, both patients and health professionals have a great responsibility.

Pneumoconiosis is an incurable dust disease in the group of interstitial lung diseases with known cause. Silicon dioxide in exposed dust causes alveolar macrophage dysfunction. The disease is not limited to the involvement of the interstitial space, thanks to many risks such as the duration of exposure, the density of the dust and accompanying cigarette consumption. Functionally, obstructive airway disease, radiologically emphysema, bronchiectasis areas, dead spaces accompany the event. All this predisposes patients to influenza and pneumonia. Conversely, these diseases also contribute to the progression of pneumoconiosis [12,13].

There is evidence suggesting that infectious microbial agents such as viral (parainfluenza, adenovirus, cytomegalovirus), bacterial (Streptococcus pneumoniae, Haemophilus influenzae, mycobacterium) and fungi may play a role in pulmonary fibrosis. Although there are few studies detecting the presence of infectious agents in the induction and exacerbation of pulmonary fibrosis using animal models, there is insufficient data in the literature regarding the microbial induction of fibrosis in patients. Studies involving antimicrobials such as antivirals, antibiotics and antifungals show great promise for treating

pulmonary fibrosis and strengthen the relationship between microbial agents and fibrosis [14]. Known as the 2009 pandemic influenza A virus, H1N1 rapidly causes acute respiratory distress syndrome (ARDS) and bronchoalveolar pneumonia. Later, it causes pulmonary fibrosis by showing histological features including interstitial septal thickening, type II pneumonocyte hyperplasia, fibrosis and squamous metaplasia [15]. From this perspective, conclude that vaccines may be effective in preventing fibrosis and reducing the progression of pneumoconiosis.

Although regular influenza and pneumococcal vaccination is recommended for those with chronic diseases in high-risk groups to reduce mortality and morbidity, adequate vaccination has been achieved in only few high-risk individuals worldwide. The World Health Organization (WHO) reported that the influenza vaccination rate should be at least 75% in high-risk groups. While available data shows that the influenza vaccination rate in European countries is approximately 50.3%, this rate is lower in many Asian countries [16]. Influenza virus causes pneumonia and ARDS in the lung, both by itself and along with bacteria such as Staphylococcus aureus, Streptococcus pneumoniae, in active smokers with chronic lung disease [17]. Evidence suggests that co-administration of pneumococcal and influenza vaccines in chronic lung disease may prevent community-acquired pneumonia and acute exacerbations and even that administration of pneumococcal vaccine in the early stages of COPD, may help maintain stable health status of patients. Despite the need to prevent lung infections in those with chronic lung disease and the evidence for pneumococcal vaccine efficacy, vaccine coverage and awareness remains low [18]. In a study of 2 131 patients with chronic lung disease where most had asthma and COPD, the rate of active vaccination was 46.5% for influenza and 14.6% for pneumococcus. The main reason for the low influenza and pneumococcal vaccination rates of the patients was lack of information (53.5% and 87.6%, respectively) [19]. In a retrospective cohort study by Fekete et al., vaccination rates were 23.6% for influenza and 10.8% for pneumococci, with only 6% of patients receiving both vaccines. The vaccination rate was higher for severe forms of COPD in both vaccines. Only 28.4% of the patients were informed by their physicians about the necessity of vaccination due to their chronic disease. While 36% of the patients thought that vaccination against influenza was beneficial, 26% thought that the pneumococcal vaccine was beneficial. According to 31.2% of patients, influenza virus causes only mild illness and 54% have never heard of pneumococcal bacteria [20].

We could not find many sources in the literature related to pneumonia-related mortality rates in patients with pneumoconiosis, which was the reason we mostly referred to other chronic lung diseases. Studies related to pneumonia mortality are generally all-cause epidemiological studies. Generally, decreased pulmonary function, radiographically high-grade profusion or large opacities, tuberculosis and smoking are risk factors leading to death in patients with pneumoconiosis. In the study by Jo et al., 82 pneumoconiosis patients were divided into two groups, as deceased and survivor, and they found that the deceased group had more previous pneumonia history, higher interstitial fibrosis status and longer hospital stay [21].

Study Limitation: The main limitation of our study was that it was cross-sectional. It would be useful to follow-up on patients after a period, perhaps three or six months, to see how many have been vaccinated and see how much their knowledge level has changed.

Conclusion:

In conclusion, pneumoconiosis is an incurable, irreversible chronic lung disease with interstitial involvement. As the disease progresses, massive pulmonary fibrosis occurs. The main treatment for the disease is to stay away from dust, smoking and comply with the pulmonary rehabilitation program. It is imperative to protect patients against tuberculosis and infectious pneumonia. Therefore, screening for latent tuberculosis and vaccinations such as influenza and pneumococcus should be performed. Unfortunately, pneumoconiosis, like other comorbid conditions (asthma, COPD, diabetes mellitus, patients greater than 65), does not receive enough attention in terms of vaccination. When we searched the literature, we did not find many studies directly related to

this subject. With the coronavirus (COVID-19) pandemic, we have once again witnessed how dangerous infections targeting the lungs are. As a result of this study, we observed that patients with pneumoconiosis need regular education about influenza and pneumonia. At the same time, it is necessary to constantly encourage patients to be vaccinated.

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Ethics Committee Approval: This study was approved by the Ege University Rectorate Faculty of Medicine Dean's Medical Research Ethics Committee (Approval Decision: 21-12.1T/18; Date: 20.12.2021).

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Evaluation Of Morbid Obese Patients In Terms Of Sexual Dysfunctions: A Cross-Sectional Study

Morbid Obez Hastaların Cinsel İşlev Bozuklukları Açısından Değerlendirilmesi: Kesitsel Bir Çalışma

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ABSTRACT

Aim: Obesity is a risk factor for sexual dysfunction. The aim of this study was to determine the frequency of sexual dysfunction in patients diagnosed with morbid obesity.

Methods: The patient group included in the study consisted of 78 morbidly obese patients with BMI≥40 kg/m2 and 68 healthy individuals with normal BMI. The data were obtained by using the sociodemographic information form filled by the participants, Beck anxiety scale, Beck depression scale and Golombok Rust Sexual Satisfaction Inventory.

Results: Obese individuals were found to have sexual dysfunction compared to individuals with normal body BMI ($p<0.05$). When the Golombok Rust subscale scores of obese men were compared to those of normal-weight individuals, a significant deterioration was found in all subscale scores, including frequency, communication, satisfaction, avoidance, touch, impotence and premature ejaculation. In addition, the anxiety and depression scores of obese individuals were shown to be higher than those of normal-weight individuals ($p<0.05$).

Conclusion: Morbidly obese individuals should be evaluated in terms of sexual functions. We believe that regulating obesity treatment, including possible treatment for sexual dysfunction, will increase the success rate and enhance the quality of life for patients.

Key Words: Sexual dysfunction, Depression, Morbid obesity, Anxiety, Stress

ÖZ

Amaç: Obezite cinsel işlev bozukluğu için bir risk faktörüdür. Bu çalışmanın amacı morbid obezite tanısı almış hastalarda cinsel işlev bozukluğu sıklığını saptamak amaçlanmıştır.

Yöntemler: Çalışmaya dahil edilen hasta grubu için BKI≥40 kg/m2 olan 78 morbid obez hasta birey ve normal BKI değerine sahip 68 sağlıklı birey oluşturmuştur. Veriler, katılımcılar tarafından doldurulan sosyodemografik bilgi formu, Beck kaygı ölçeği, Beck depresyon ölçeği ve Golombok Rust Cinsel Doyum Envanteri kullanılarak elde edilmiştir.

Bulgular: Obez bireylerin normal vücut BKI'sına sahip bireylere göre cinsel işlev bozukluğu yaşadığı saptanmıştır ($p<0.05$). Obez erkeklerin Golombok Rust alt ölçek puanları normal kilolu bireylerinkilerle karşılaştırıldığında, frekans, iletişim, memnuniyet, kaçınma, dokunma, iktidarsızlık ve erken boşalma gibi tüm alt ölçek puanlarında anlamlı bir bozulma bulundu. Ayrıca obez bireylerin anksiyete ve depresyon puanlarının normal kilolu bireylere göre daha yüksek olduğu gösterilmiştir ($p<0.05$).

Sonuç: Morbid obez bireyler cinsel işlevler açısından değerlendirilmelidir. Olası cinsel işlev bozukluğu tedavisi de dahil olmak üzere obezite tedavisinin düzenlenmesinin hastaların başarı oranını artıracağına ve hastaların yaşam kalitesini artıracağına inanıyoruz.

Anahtar Kelimeler: Cinsel işlev bozukluğu, Depresyon, Morbid obezite, Anksiyete, Stres

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INTRODUCTION

Obesity is a chronic condition characterized by a rise in body fat tissue. Although the high amount of calories consumed daily and the low amount of energy consumed are regarded as the primary reasons for obesity, it is well known that obesity is caused by a mix of genetic and environmental factors(1, 2). The body mass index is used to determine the degree of obesity (BMI). BMI is calculated by dividing body weight in kilograms by height in centimeters squared. Obesity is described as a BMI more than 30, while morbid obesity is classified as a BMI greater than 40.Obesity, the frequency of which has been increasing in recent years, has now gone beyond being a cosmetic problem and has begun to be seen as a disease. In recent years, the number of studies addressing the relationship between obesity and psychopathology has increased. According to these studies, obesity is a complicated condition that affects an individual's anxiety, depression, health status, and quality of life, and has a significant comorbidity rate with sexual dysfunction (3). The mechanism of occurrence of sexual dysfunction secondary to obesity is multifactorial (4, 5).

As BMI is associated with sexual dysfunction, it has been proposed that sexual health deteriorates as well; however, the reasons for this association are not thoroughly explored. Obesity-related hormonal and inflammatory problems have also been identified as contributing factors. In obese women, a decrease in sex hormone-binding globulin (SHBG) may result in a decrease in free sex steroids, creating a compensatory hyperandrogenemic environment and affecting sexual functions in women. Again, the inflammatory environment and oxidative stress caused by excess adipose tissue also impair vascular and endothelial functioning, which has negative effects on sexual functions. In addition to these physiopathological reasons, concerns about physical appearance and body image in obese individuals, and physical restrictions caused by obesity are also listed as psychological causes of sexual dysfunction (6). The purpose of this study was to look into the sexual dysfunction, anxiety, and depression levels of morbidly obese and non-obese persons.

MATERIALS AND METHODS

This research included male and female participants aged 18 to 65 years old with a BMI over 40, no Diabetes Mellitus, and significant mental problems (Mental illness, Bipolar Disorder, Mental Retardation, Alcohol-Substance Addiction) who have been followed up on and treatment at the endocrinology outpatient department. Patients who came to the outpatient clinic or were referred from other outpatient clinics were questioned face to face and given a consent forms if they wished to participate in the trial; only those who supplied written consent were included in the study. The researcher performed every one of the interviews at the outpatient clinic over the course of 45-60 minutes, utilizing the face-to-face interview approach. The study's ethics committee decision was made by the Inonu University clinical research ethics committee. All. All steps of the study were carried out according to the Helsinki Declaration (2015-165).

Control Group: It consists of men and women who applied to the Endocrinology outpatient clinic and did not have any disease, between the ages of 18 and 65 with BMI<35, and did not have a major psychological disorder (Schizophrenia, Bipolar Disorder, Mental Retardation, Alcohol-Substance Addiction). In the selection of these patients, patients with endocrinological problems leading to sexual dysfunction were not included in the study.

Exclusion Criteria

Cognitive impairment, dementia, schizophrenia, schizoaffective disorder, bipolar disorder, alcohol and substance use disorders are serious medical conditions that may prevent participation in the study.

Data Collection Tools

The patients were initially given a sociodemographic data form, an interview form concerning beck anxiety, beck depression, and psychiatric information. The Golombok Rust Inventory of Sexual Satisfaction was then administered to the patients in order to assess sexual satisfaction.

Personal Information Form

In the Personal Information Form, questions

about the demographic characteristics of morbidly obese individuals with BMI ≥40 kg/m2 and the control group with BMI<35, who applied to our endocrinology outpatient clinic, were included in the research group. There are 15 items in the form. These items are gender, marital status, occupation, education level, number of children in the family, whether they received any physical or psychiatric diagnosis, treatment, whether they received any psychological counseling assistance, use of alcohol and smoking habits. In addition to these, there are also items related to the variables, such as whether the participants used any substance or not.

Golombok Rust Inventory of Sexual Satisfaction

The Golombok Rust Inventory of Sexual Satisfaction (GRISS) was created by Rust and Golombok (1983) to assess the quality of sexual intercourse and sexual dysfunctions. Items are graded on a five-point Likert scale: "never-0 points," "rarely-1 point," "sometimes-2 points," "mostly-3 points," and "always-4 points." Negative questions were coded in reverse to ensure uniformity in scale interpretation. Both the scale's overall score and the scores generated from the subdimensions can be used to evaluate the scale. High scores indicate deterioration in sexual functions and the quality of the relationship. The received raw scores can then be converted into standard scores ranging from 1 to 9 (5 is the cut-off point). Since scores of 5 points and above are defined as the deterioration of sexual relations or functions, the participants with a score of 5 or higher were called the "problematic group", and those with a score below 5 points were called the "group with no problems". A separate profile can be created for men and women, or couples can share a common profile. The scale's standardization study was conducted by Tuğrul et al. (1993). The Golombok Rust Inventory of Sexual Satisfaction's Cronbach alpha internal consistency coefficient was calculated to be 0.83 for men and 0.94 for women, respectively. According to the data obtained from this sample, Cronbach's alpha values for all sub-dimensions in the female form ranged from 0.059 to 0.88 and in the male form from 0.42 to 0.85 (7).

Beck Depression Inventory

The Beck Depression Inventory examines somatic, emotional, cognitive, and motivational depression symptoms. The scale's purpose is not to establish a precise diagnosis, but rather to measure the intensity of depression symptoms in a consistent manner. The Beck Depression Inventory is a self-assessment tool that may be used in groups. It is suitable for both teenagers and adults over the age of fifteen. A deadline for submitting an application does not exist. The response time is between 10 and 15 minutes. The Beck Depression Inventory has 21 symptom categories, which are as follows: mood, pessimism, dissatisfaction, sensation of failure, sense of guilt, sense of punishment, self-hatred, self-blame, want to punish oneself, weeping episodes, irritability, socially introversion, lack of direction, body image inhibition of workability, sleep disorders, fatigue-fatigue, appetite decreased, weight loss, somatic complaints, loss of sex drive. It is an easy-to-apply scale that individuals can answer on their own. There are four options for each of the 21 symptom categories on the form. In the last week, including the day of the application, the individual is asked to select the sentence that best reflects his or her feelings. Each item's score ranges from 0 to 3. The depression score is generated by summing all these scores. The maximum score possible is 63. A high total score indicates a high level or severity of depression (8).

Beck Anxiety Inventory

In the Beck Anxiety Inventory reliability study conducted by Ulusoy, Şahin, and Erkmen (1996), 177 psychiatric patients were examined, and the scale's Cronbach Alpha internal consistency coefficient was found to be 0.93. In the study, it was also determined that the item-total score correlation coefficients ranged from 0.45 to 0.72. The test-retest reliability coefficient of the scale was calculated as r=0.57. In the study conducted for the validity study of the Beck Anxiety Inventory, the correlation of the scale (criterion-related validity) with the Automatic Thoughts Scale was found as 0.41, the correlation with the Beck Hopelessness Scale as 0.34, the correlation with the Beck Depression Inventory as 0.46, the correlation with the State Anxiety Inventory

(STAI-S) as 0.45 and the correlation with the State-Trait Anxiety Scale (STAI-T) as 0.53, respectively. In the construct validity study of the Beck Anxiety Inventory, it is also noted that the scale can considerably differentiate the anxious group from other diagnostic groups (depression, mixed and control groups). As a result of the factor analysis applied, it was determined that the scale consisted of two factors: "subjective anxiety" (1st, 4th, 5th, 7th, 8th, 9th, 10th, 11th, 14th, 15th, 16th, 17th and 19th items) and "somatic symptoms" (2nd, 3rd, 6th, 12th, 13th, 18th, 20th and 21st items) (9).

Statistical Analysis

For statistical analysis of our research data, we used SPSS 17.0 program. For quantitative data, arithmetic mean standard deviation was employed, whereas number (n) and percentage (%) were used for qualitative information. The Shapiro Wilk normality test was used to assess variables for quantitative data. The unpaired t test, Mann Whitney U test, and Pearson Chi-Square Analysis were used to compare the groups based on the normality test outcomes. A $p<0.05$ value was considered statistically significant.

RESULTS

The study comprised 98 morbidly obese individuals with a BMI of 40 kg/m2 or more who were married or had a permanent sexual partner. The research eliminated 10 individuals owing to diabetes (DM), 5 patients due to diabetes plus hypertension (DM+HT), and 5 patients due to other systemic disorders and medication usage. 57.7% (n=45) of the remaining 78 patients were female, while 42.3% (n=33) were male. The patients' mean BMI was 45.25±5.33 kg/m2, and their mean age was 37.80±8.53 years years. In order to compare with the patient, 68 healthy volunteers (28 girls (41.2%) and 40 men (58.8%)) with a BMI of 35kg/m2 or less were recruited in the study. There was no statistically significant difference in age between the patient and control groups (p=0.070). It was observed that the rate of participants in the control group (29.4%) with a university degree was higher compared to the patient group (28.2%). It was observed that the individuals participating in the study were generally "Working Individuals" in both groups. The mean Beck Depression Scale score of the patient group was 12.65±8.77, and the mean Beck Anxiety Scale score was 13.56±10.84, respectively. The mean Beck depression scale score of the control group was 6.26±3.88, and the mean Beck anxiety scale score was 8.91±7.75. A statistically significant difference was found between the two groups in terms of Beck depression and Beck anxiety scale scores (p=0.00, p=0.012, respectively) (Table 1).

Table 1. Comparison of sociodemographic data between patient and control groups

	Patient (n=78)	Control (n=68)	p
Sex (Female/Male)	(33/45)	(35/33)	0.046*
Age(Years)	37.80±8.53	35.60±5.93	0.076**
Education			
Primary School	%34.6	%1.5	0.001
Middle School	%12.8	%11.8	
High School	%24.4	%57.4	
University	%28.2	%29.4	
WorkWorking/	%57.7	%76.5/	0.017
Not Working	%42.3	%23.5	
Beck Depression Scale	12.65±8.77	6.26±3.88	0.001**
Beck Anxiety Scale	13.56±10.84	8.91±7.75	0.012**

*Pearson chi square test. **Mann Whitney U test.

The rates of patients who had problems in the sub-dimensions of frequency of sexual intercourse, communication, satisfaction, avoidance, and touching were calculated by converting the raw scores obtained from the Golombok Rust Inventory of Sexual Satisfaction (GRISS) to standard scores. Furthermore, the rates of premature ejaculation and erectile dysfunction in the male group, and vaginismus and anorgasmia in females were evaluated separately. In the analyzes comparing the mean GRISS subscale and total raw score in the patient and control groups, it was found that there was a statistically significantly higher deterioration in the scores of the other subscales of sexual functions, excluding vaginismus, in the patients (Table 2). There was no statistically significant difference between the vaginismus scores of patient and control groups (p=0.77). Scores of 5 and above in subscale raw scores indicate deterioration in that area. In this regard, it was determined that the deterioration in the "satisfaction" area (subscale score=6.08±3.15) was 26/33=78.7% in the patient group. It was observed that apart from "satisfaction", there was a significant problem in "premature ejaculation"

(subscale score=6.69±3.26) with a rate of 23/33=69.6% in men. It was also observed that the women in the patient group had problems in the area of "anorgasmia" other than the "satisfaction" area (subscale score=5.84±3.08) (Table 2).

Table 2. Comparison of GRISS subscale and total raw score averages between the patient and control groups

Golombok Rust Inventory of Sexual Satisfaction	Patient Group (Mean±S.D.)	Control Group (Mean±S.D.)	p**
Frequency	3.93±1.95	2.20±1.88	0.001
Communication	3.75±2.21	2.36±2.19	0.001
Satisfaction	6.08±3.15	3.52±2.97	0.001
Avoidance	3.56±3.13	1.51±2.20	0.001
Touching	3.79±3.31	2.35±2.73	0.001
GRISS total	36.92±15.12	21.86±16.73	0.001
Female-specific parameters			
Vaginismus	4.68±2.26	4.89±3.63	0.770
Anorgasmia	5.84±3.08	3.82±3.49	0.004
Male-specific parameters			
Premature ejaculation	6.69±3.26	2.77±2.00	0.001
Erectile dysfunction	4.66±2.23	2.17±1.87	0.001

**Mann Whitney U test, p<0.05.

According to the Golombok Rust Inventory of Sexual Satisfaction subscales of female morbidly obese patients, a deterioration rate of 35.5% was detected in frequency, 37.7% in communication, 68% in satisfaction, 44.4% in avoidance, 44.4% in touching, 48.8% in vaginismus and 64.4% in orgasm disorder, respectively. According to the Golombok Rust Inventory of Sexual Satisfaction subscales of male morbidly obese patients, a deterioration rate of 36.3% was detected in frequency, 27.2% in communication, 78.7% in satisfaction, 24.2% in avoidance, 27.2% in touching, 54.5% in impotence and 69.6% in premature ejaculation, respectively (Table 3).

DISCUSSION

The aim of this study was to investigate the hypothesis that morbidly obese individuals may experience worse sexual dysfunction than non-obese individuals. The main finding of the study is that morbidly obese individuals have more deterioration in all sub-scores other than GRISS total score and vaginismus in comparison to the healthy control group. In addition, anxiety and depression scores on the Beck Depression Inventory and the Beck Anxiety Inventory were found to be statistically significantly higher in morbidly obese individuals compared to the control group.

Table 3. Comparison of GRISS between patient and control groups in men and women

Women	Scale	Patient		Control		p
		n	%	n	%	
Frequency	<5	29	(64.4)	22	(78.5)	0.201
	5≤	16	(35.6)	6	(21.5)	
Satisfaction	<5	14	(31.1)	16	(57.1)	0.028
	5≤	31	(68.9)	12	(42.9)	
Communication	<5	28	(62.2)	18	(64.2)	0.859
	5≤	17	(37.8)	10	(35.8)	
Avoidance	<5	25	(35.5)	21	(75.0)	0.094
	5≤	20	(44.5)	7	(25.0)	
Touching	<5	25	(55.5)	18	(64.2)	0.461
	5≤	20	(44.5)	10	(35.8)	
Vaginismus	<5	23	(51.1)	11	(39.2)	0.325
	5≤	22	(48.9)	17	(60.8)	
Orgasmic disorder	<5	16	(35.5)	18	(64.2)	0.017
	5≤	29	(64.5)	10	(35.8)	
Men						
Frequency	<5	21	(63.6)	40	(100)	0.001
	5≤	12	(36.4)	0	(0)	
Satisfaction	<5	7	(21.2)	21	(52.5)	0.006
	5≤	26	(78.8)	19	(47.5)	
Communication	<5	24	(72.7)	38	(95)	0.008
	5≤	9	(26.3)	2	(5)	
Avoidance	<5	25	(75.7)	40	(100)	0.001
	5≤	8	(24.3)	0	(0)	
Touching	<5	24	(72.7)	39	(97.5)	0.002
	5≤	9	(26.3)	1	(2.5)	
Impotence	<5	15	(45.4)	37	(92.5)	0.001
	5≤	18	(54.6)	3	(7.5)	
Premature Ejaculation	<5	10	(30.3)	34	(85)	0.001
	5≤	23	(69.7)	6	(15)	

*Pearson chi square test.

According to data from the World Health Organization, overweight and obesity are a significant global public health issue, with more adults being overweight or obese than underweight. In 2016, 39% of males aged 18 and older and 40% of women, about 2 billion adults globally, were overweight, while 11% of men and 15% of women, more than 500 million, were obese. Over the past four decades, the prevalence of both overweight and obese individuals has risen substantially (10-12) .

Obesity causes many mental and physical health issues. It is evident that the lives of obese people are restricted by both health problems and many social obstacles. In addition to sexual dysfunction, it is a complex condition that affects the individual's health status and quality of life, as well as psychological stress, and depression (13, 14).

Sexual dysfunction resulting from obesity is caused by multiple factors. Morbid obesity has high comorbidity rates that are clearly associated with sexual dysfunction. It is known that metabolic diseases such as DM and HT, which are common in morbidly obese individuals (15); mental diseases such as depression and anxiety, and drugs used have an effect on sexual functions (16, 17). In addition, factors such as self-esteem and body image influence both the initiation of sexual activity and the avoidance behavior (17, 18). The exclusion of metabolic diseases, drug use and the presence of psychiatric disease in our study constitutes the strength of our study. The fact that the patient group identified in the study results had higher rates of Beck Anxiety and Beck Depression than the control group is an expected finding in morbidly obese individuals. In their study, Nimbi et al. concluded that obesity causes deterioration in mental status and increases anxiety and depression scores (19). Although this increase also found in our study indicates that the patient group experienced more depressive symptoms and anxiety, it was not significant enough to be diagnosed. Because the participants to be included in the patient group in our study were interviewed by a psychiatrist according to DSM-5, and those diagnosed with psychiatric diseases were excluded from the study.

The significance of sexuality in human life cannot be denied. It has major effects on the quality of life for both men and women. The effect of erectile dysfunction on men's quality of life has been demonstrated in many publications (20). Few studies have examined the effect of sexuality on women's quality of life. In a study including 2095 patients aged between 30-69 years, sexual dysfunction rates were determined, and it was shown that sexual dysfunction negatively affects quality of life (21). It has also been reported that the effect of sexual life on quality of life decreases as the age of the woman increases (13, 22).

In their study, Botlani et al. found that high BMI values are associated with sexual dysfunction and many other chronic diseases. They found that individuals with a high BMI were more likely to report a decline in sexual quality (23). In addition, in another study examining the relationship between sexual dysfunction and obesity, bariatric surgery improved sexual dysfunction in morbidly obese women. It was found that individuals with high sexual dysfunction scores had lower scores and improved sexual life quality after weight loss after bariatric surgery (24).

In terms of the components of the applied sexual life scale, it was revealed that obese women had more deterioration in sexual desire, ease of orgasm, and orgasmic satisfaction subgroups than the control group. Sexual complaints were more common among sick women (63.6%) than among women in the control group (50.0%). In the study of Goitein et al., it was found that sexual parameters reduced in obese men, including sexual desire, erection, ejaculation and sexual satisfaction. Compared to the control group, there was a significant decrease in sexual desire, arousal, lubrication, orgasm, and sexual satisfaction in obese women (25). Regarding sexual dysfunction, there was no significant age-related difference between the patient and control groups. The difference in sexual dysfunction scores between patients and controls cannot be explained by sociodemographic data. In our study, it was important that the patient and control groups had comparable sociodemographic characteristics. In our study, the rates of sexual intercourse frequency, communication, satisfaction, avoidance and touching problems were calculated in the Golombok Rust Inventory of Sexual Satisfaction (GRISS). In addition, the rates of precocious ejaculation and erectile dysfunction in males and vaginismus and anorgasmia in females were evaluated separately. In the analyses comparing the GRISS in the patient and control groups, it was discovered that other than vaginismus, there was statistically significantly more deterioration in sexual function total and subscale scores. There was no statistically significant difference between the vaginismus scores between the women in the patient and control groups (p=0.77). In the patient

group, it is noticeable that the deterioration in the "satisfaction" area is particularly evident. Furthermore, there are significant problems with "premature ejaculation" in addition to "satisfaction" in men. It is observed that the women in the patient group have problems in the area of "anorgasmia" apart from the area of "satisfaction". As can be seen, there are differences between the results of our study and the results of the studies in literature, as well as when the results of the studies in the literature are compared between each other. These differences may be due to the scales used, differences in sociodemographic data, and not exclusion of comorbid diseases. Considering that comorbid diseases and sociodemographic characteristics are two key factors affecting sexual life, the most important aspect of our study is the exclusion of comorbid diseases and the sociodemographic comparison between the patient and control group. Our findings indicate that the sexual dysfunction seen in morbid obesity does not only occur secondary to comorbid diseases. Obesity alone causes sexual dysfunction independent of comorbidity. Further studies are required to elucidate the causes of this situation.

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Frequency and predictors of hyperkalemia in the heart failure outpatient clinic

Kalp yetmezliği polikliniğinde hiperkaleminin sıklığı ve öngördürücüleri

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ABSTRACT

Aim: Hyperkalemia is a common and potentially life-threatening problem in heart failure (HF). In this study, we aimed to show the frequency of hyperkalemia and related factors in the HF outpatient clinic with real-life data.
Methods: 1 146 patients monitored in the HF outpatient clinic with left ventricular ejection fraction ≤ 40% and potassium level ≥ 3.5 mmol/L were included.
Results: The potassium value of the patients was median 4.6 mmol/L [IQR, 4.3-5]. It was evaluated in three groups as 3.5-5 mmol/L (normokalemia), 5.1-5.5 mmol/L (mild hyperkalemia) and ≥ 5.5 mmol/L (moderate to severe hyperkalemia), according to baseline potassium levels. Mild hyperkalemia was present in 14.5% and moderate to severe hyperkalemia was present in 7.1%. The potassium value was > 5 mmol/L in 21.6% of the patients. The estimated glomerular filtration rate (eGFR) (OR: 0.969, 95% CI: 0.961-0.976, p<0.001), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) (OR: 1.697, 95% CI: 1.124-2.562, p=0.012), and mineralocorticoid receptor antagonists (MRA) (OR: 1.511, 95% CI: 1.066-2.142, p=0.02) were considered as independent factors for hyperkalemia.
Conclusion: eGFR level, ACE-I/ARB, and MRA were associated with hyperkalemia in chronic HF in real-life data.

Key Words: Heart Failure; Hyperkalemia; Potassium; Renin-Angiotensin System.

ÖZ

Amaç: Hiperkalemi, kalp yetmezliğinde (KY) yaygın ve potansiyel olarak yaşamı tehdit eden bir sorundur. Bu çalışmada KY polikliniğinde hiperkalemi sıklığı ve ilişkili faktörlerin gerçek yaşam verileriyle gösterilmesi amaçlanmıştır.
Yöntemler: KY polikliniğinde izlenen sol ventrikül ejeksiyon fraksiyonu ≤ %40 ve potasyum düzeyi ≥ 3.5 mmol/L olan 1146 hasta çalışmaya dahil edildi.
Bulgular: Hastaların medyan potasyum değeri 4.6 mmol/L [IQR, 4.3-5] idi. Başlangıç potasyum düzeylerine göre 3.5-5 mmol/L (normokalemi), 5.1-5.5 mmol/L (hafif hiperkalemi) ve ≥ 5.5 mmol/L (orta-ciddi hiperkalemi) olmak üzere üç grupta değerlendirildi. %14.5'inde hafif hiperkalemi ve %7.1'inde orta ila şiddetli hiperkalemi mevcuttu. Hastaların %21.6'sında potasyum değeri > 5 mmol/L idi. Tahmini glomerüler filtrasyon hızı (eGFR) (OR: 0.969, 95% CI: 0.961-0.976, p<0.001), anjiyotensin dönüştürücü enzim inhibitörü/anjiyotensin reseptör blokeri (ACE-I/ARB) (OR: 1.697, 95% CI: 1.124-2.562, p=0.012) ve mineralokortikoid reseptör antagonistleri (MRA) (OR: 1.511, 95% CI: 1.066-2.142, p=0.02) hiperkalemi için bağımsız faktörler olarak saptandı.
Sonuç: eGFR düzeyi, ACE-I/ARB ve MRA gerçek yaşam verilerinde kronik KY'de hiperkalemi ile ilişkili saptandı.

Anahtar Kelimeler: Hiperkalemi, Kalp yetmezliği, Potasyum, Renin-Anjiyotensin Sistemi.

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INTRODUCTION

Hyperkalemia is a condition characterized by a blood potassium level of > 5.0 mmol/L (mEq/L). This is a critical and problematic situation that is often seen in the clinical follow-up of heart failure (HF) patients [1,2]. The severity of hyperkalemia is defined as mild, with potassium levels >5.0 to <5.5 mmol/L, moderate, between 5.5 and 6.0 mmol/L and severe, > 6.0 mmol/L [1]. Renin-angiotensin-aldosterone system modulators (RAAS-M), known to reduce mortality and recommended by guidelines, are the cornerstone of HF treatment. However, the widespread use of these agents has resulted in an increased incidence of life-threatening hyperkalemia [1,3].

The frequency of hyperkalemia varies according to the reference value. In acute HF, the proportion of potassium levels > 5 mmol/L has been reported to be 35% [4]. In one study, the rate of patients with > 5 mmol/L in the angiotensin-converting enzyme inhibitor (ACE-I) group was reported at 13.5%, and 12.3% in the angiotensin receptor/neprilysin inhibitor (ARNI) group, with the frequency of hyperkalemia at > 5.5 mmol/ L reported as 2.5% vs. 2.2%, respectively [5]. When mineralocorticoid receptor antagonists (MRAs) were added in addition to ACE-I, the incidence of hyperkalemia (> 5.5 mmol/L) has been reported at 11.8% with eplerenone and 13% with spironolactone [6,7].

Many studies have observed the association of potassium levels with mortality in chronic HF [8-10]. Reducing the dose or completely discontinuing RAAS-M due to increased potassium may result in symptoms of withdrawal from this therapy, which has been shown to improve clinical outcomes [11,12].

We aimed to show the frequency of hyperkalemia and related variables, in patients followed up in a specialized HF outpatient clinic.

MATERIALS AND METHODS

1 239 patients with left ventricular ejection fraction (LVEF) ≤ 40%, followed in a tertiary hospital HF clinic between 2015 and 2020, were retrospectively analyzed. 1 156 patients, who were followed up for at least one year and whose potassium level was known at admission, were evaluated for the study. The patients were evaluated according to the basal potassium level at the first HF outpatient clinic admission. Since hyperkalemic and normokalemic patients were to be compared, 10 patients were excluded because their potassium level was < 3.5 mmol/L. Thus, 1 146 patients diagnosed with HF according to the HF Guidelines [2], with LVEF ≤40%, potassium level ≥ 3.5 mmol/L and ≥ 18 years of age, were included in the study. Demographic and biochemical parameters and drugs used by patients were collected from hospital records. In our hospital, potassium levels are measured from serum and other biochemical measurements are standard. The patients were compared in three groups according to their baseline serum potassium levels as 3.5-5 mmol/L, 5.1- < 5.5 mmol/L, and ≥ 5.5 mmol/L [1]. Approval was obtained for the study by the local ethics committee.

Statistical analysis

Statistical analyses were evaluated with the Statistical Package for the Social Sciences software v. 22.0 (IBM Corp.; Armonk, NY, USA). Using the Kolmogorov-Smirnov test, data with normal distribution was presented as standard deviation, and mean and non-normally distributed data was presented as interquartile ranges (IQR) [25-75] as the median. Groups were compared according to normality using the Kruskal-Wallis test or Student's t-test. Categorical variables were provided as numbers and percentages and compared with the Chi-square test. Parameters associated with hyperkalemia were presented as 95% confidence intervals (CI) and odds ratios (OR) by logistic regression analysis. A statistically significant P value was accepted at 0.05.

RESULTS

1 146 eligible HF patients (822 males, 324 females) were included in the study. The median age of the patients was 64 [IQR, 54-73]. 55.8% (n:639) had an ischemic etiology and an LVEF of 30% [IQR, 25-35%]. 53.6% (n:614) had hypertension and 40.1% (n:459) had diabetes. 43% of patients were NYHA II and 24% were NYHA III or IV.

The median potassium value was 4.6 mmol/L [IQR, 4.3-5]. The potassium level of the majority of patients (78.4%) was normal (3.5-5 mmol/L),

while those with mild hyperkalemia (5.1-<5.5 mmol/L) made up 14.5% and moderate to severe hyperkalemia (≥ 5.5 mmol/L) was 7.1%. Only 1% (n:12) of patients had potassium > 6 mmol/L. When the cut-off value of potassium was evaluated as > 5 mmol/L, the frequency of hyperkalemia was 21.6% (n:247). The comparison of variables according to the patient's potassium levels is shown in Table 1. Patients with hyperkalemia were significantly older than patients with normal potassium levels (p<0.001). Most of those with potassium ≥ 5.5 mmol/L were men (p=0.03). In this group, 51.9% of the patients had diabetes (p=0.03) and other comorbidities were similar. Among the laboratory findings, hemoglobin A1c, creatinine, and N-terminal pro-brain natriuretic peptide were higher in the hyperkalemia group (p<0.001, p<0.001, p=0.03, respectively) while estimated glomerular filtration rate (eGFR) and sodium were lower (p<0.001, p<0.001, respectively). The eGFR was < 60 mL/min/1.73m² in 476 (41.5%) of all patients. The rate of GFR < 60 mL/min/1.73m² was higher in patients with moderate to severe hyperkalemia and mild hyperkalemia, than in those with normokalemia (69.1% vs. 54.8% vs 36.6%, p<0.001).

When medical treatments were evaluated, 80.9% (n:927) of the patients were using ACE-I/ARB, 71.1% (n:815) were taking ACE-I and only 9.8% (n:112) were taking ARB. Additionally, only 2.5% (n:29) of patients were using ARNI with, 70% (n:802) using MRA and 92.8% (n:1064) using beta-blockers. While the rate of using any RAAS-M was 89.3% (n:1023), the rate of using MRA together with ACE-I/ARB was 62% (n:710). Of those with hyperkalemia (potassium > 5 mmol/L), 82.2% (n:203) were using ACE-I/ARB, while 64.8% (n:160) were taking both ACE-I/ARB and MRA. The comparison of medical treatments and groups according to potassium levels is given in Table 2. Those who received ACE-I/ARB, MRA and those who take 50% or more of the target dose, were similar between the normokalemia and hyperkalemia groups. In addition, all groups had similar rates of using beta-blockers, ARNI, any RAAS-M and dual RAAS-M (ACE-I/ARB and MRA).

Factors associated with hyperkalemia were examined by logistic regression analysis, which included eGFR, diabetes, hypertension, ACE-I/ARB, MRA and beta-blockers use (Table 3). eGFR (OR: 0.969, 95% CI: 0.961-0.976, p<0.001), ACE-I/ARB (OR: 1.697, 95% CI: 1.124-2.562, p=0.012) and MRA (OR:1.511, %95 CI: 1.066-2.142, p=0.02) were independent variable for hyperkalemia.

DISCUSSION

We analyzed real-life data of patients followed in the HF outpatient clinic. We showed the following: (i) hyperkalemia affected 21.6% of the patients, mild hyperkalemia frequency was at 14.5%, with moderate to severe hyperkalemia frequency at 7.1%; (ii) factors associated with hyperkalemia were eGFR level, ACE-I/ARB and MRA use.

Hyperkalemia is not exceptionally rare in the general population, but its true incidence is unknown; it is estimated to occur in the range of 2 to 3% [13]. The reason for the variation in frequency is that different potassium thresholds are used to define hyperkalemia. In the SOLVD study, hyperkalemia (≥ 5.5 mmol/L) was 6% and severe hyperkalemia (≥ 6.0 mmol/L) was 1.1% during the 2.7-year follow-up [14]. In the PARADIGM-HF study, the ARNI group comprised 16.1% of patients with potassium > 5.5 mmol/L and 4.3% of patients with potassium > 6 mmol/L [15]. In EMPHASIS-HF, the rate of hyperkalemia (>5.5 mmol/L) in patients taking eplerenone was 11.8%, while the rate of severe hyperkalemia (>6 mmol/L) was 2.5% [6]. In the RALES study, in which ACE-I was used in combination with spironolactone, 13% of patients had hyperkalemia (>5.5 mmol/L) and only 2% had severe hyperkalemia (>6 mmol/L) [7]. Similarly, mild hyperkalemia was found at 14.5%, moderate to severe hyperkalemia was found at 7.1% and only 1% of patients had potassium > 6 mmol/L in our study.

Current guidelines support patients with low ejection fraction HF receiving triple therapy, ACE-I/ARB or ARNI, beta-blocker, and MRA. All these drugs are known to be at their greatest effectiveness in recommended target doses tested in clinical trials or tolerated by the patients [2]. RAAS-M used in the treatment of HF are common, with causes of hyperkalemia, and patients with hyperkalemia are more likely to be taking these drugs. However, it has been

Table 1. Baseline characteristics of the patients according to potassium levels.

Variables	K^+ 3.5-5 mmol/L (n =899, 78.4%)	K^+ 5.1-5.5 mmol/L (n=166, 14.5%)	K^+ ≥5.5 mmol/L (n=81, 7.1%)	P-value
Potassium (mmol/L)	4.5 (4.3-4.8)	5.2 (5.1-5.3)	5.7 (5.5-5.9)	<0.001
Age (years)	63 (53-72)	66 (57-73)	68 (60-77)	<0.001
Male, n (%)	647 (72)	109 (65.7)	81.5 (66)	0.03
Female, n (%)	252 (28)	57 (34.3)	15 (18,5)	
BMI (kg/m^2)	26 (24-30)	27 (23-30)	25 (23-28)	0.20
HF duration (months)	12 (3-48)	12 (2-60)	12 (2.5-54)	0.84
LVEF, %	30 (25-35)	30 (24-35)	30 (25-35)	0.29
Causes of HF				
Ischemic, n (%)	495 (55.1)	101 (60.8)	43 (53.1)	0.34
Non Ischemic, n (%)	404 (44.9)	65 (39.2)	38(46.9)	
Medical history				
Diabetes, n (%)	345 (38.4)	72 (43.4)	42 (51.9)	0.03
Hypertension, n (%)	472 (52.5)	93 (56)	49 (60.5)	0.31
Hyperlipidemia, n (%)	346 (38.5)	69 (41.6)	28 (34.6)	0.55
Coronary artery disease, n (%)	461 (51.3)	84 (50.6)	37 (45.7)	0.63
Physical findings				
Systolic BP (mmHg)	110 (100-130)	120 (100-130)	110 (100-130)	0.58
Diastolic BP (mmHg)	60 (60-80)	62 (60-80)	70 (60-80)	0.64
Heart rate (b.p.m)	76 (67-87)	76 (68-86)	75 (65-88)	0.83
Atrial fibrillation, %	170 (18.9)	27 (16.3)	19 (23.5)	0.70
NYHA I, n (%)	297 (33)	52 (31.3)	29 (35.8)	0.66
NYHA II, n (%)	394 (43.8)	68 (41)	31 (38.3)	
NYHA III or IV, n (%)	208 (23.1)	46(27.7)	21 (25.9)	
ICD, n (%)	108 (12)	12 (7.2)	7 (8.6)	0.16
CRT, n (%)	26 (2.9)	4 (2.4)	2 (2.5)	
Laboratory data				
Plasma glucose (mg/dl)	105 (91-139)	109 (91-137)	108 (91-157)	0.87
HbA1c, %	6.3(5,8-7.2)	6.5 (6-7.3)	6.9 (6.1-8.2)	<0.001
Creatinine (mg/dL)	1.08 (0.93-1.3)	1.19 (1-1.48)	1.4 (1.11-1.65)	<0.001
eGFR (mL/min/1.73m^2)	67.5 (52.5-82.5)	56 (42.3-72.7)	50.1 (37.3-66.9)	<0.001
eGFR ≥60, %	570 (63.4)	75 (45.2)	25 (30.9)	<0.001
eGFR <60, %	329 (36.6)	91 (54.8)	56 (69.1)	
Sodium (mmol/L)	139 (137-140)	138 (135-140)	137 (134-139)	<0.001
Albumin (g/dL)	4.2 (3.9-4.5)	4.2 (3.8-4.4)	4.2 (3.7-4.3)	0.11
Calcium (mg/dL)	9.4 (9-9.8)	9.4 (8.9-9.8)	9.5 (9.2-9.9)	0.25
Total cholesterol (mg/dL)	167 (136-204)	167 (129-215)	165 (131-192)	0.74
Haemoglobin (g/dL)	13.2 (11.8-14.5)	12.9 (11.4-14.3)	12.4 (11.2-14.4)	0.05
NT-proBNP (ng/L)	1774 (623-4422)	1930 (720-4238)	2489 (908-8087)	0.03
CRP (mg/dL)	5 (2-11)	5 (2-11)	5.5 (3-11.2)	0.65

K^+, potassium; BMI, body mass index; HF, heart failure; LVEF, left ventricular ejection fraction; BP, blood pressure; b.p.m., beats per minute; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein. eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The p values, between the groups were determined using the Kruskal–Wallis test or the α^2 test. All numerical data are expressed as the median (25-75% interquartile range).

shown that the mortality benefits of these drugs continue, even in hyperkalemia [11,12,16-18]. HF guidelines recommend discontinuing RAAS-M as needed, albeit briefly, and carefully restarting it as soon as possible by monitoring potassium levels [2]. However, because of these concerns, most clinicians choose to cut or reduce dose ACE-I/ARB or MRA when potassium is > 5.5 mmol/L [19]. One of the main reasons for reducing or discontinuing RAAS-M titration is hyperkalemia. Discontinuation

Table 2. Baseline medication of the patients according to potassium levels.

Medication	K^+ 3.5-5 mmol/L (n =899)	K^+ 5.1-5.5 mmol/L (n=166)	K^+ ≥5.5 mmol/L (n=81)	p
ACE-I/ARB, %	724 (80.5)	138 (83.1)	65 (80.2)	0.72
ACE-I, %	643 (71.5)	119 (71.7)	53 (65.4)	0.40
ARB, %	81 (9)	19 (11.4)	12 (14.8)	
ACE-I/ARB, ≥%50 target doses, %	474 (54.4)	96 (58.9)	56 (50)	0.18
MRA, %	624 (69.4)	120 (72.3)	58 (71.6)	0.71
≥%50 target doses,%	470 (61)	89 (63.6)	43 (63.2)	0.31
ARNI, %	23 (2.6)	3 (1.8)	3(3.7)	0.66
Any RAAS-M	802 (89.2)	151(91)	70 (86.4)	0.55
ACE-I/ARB + MRA	550 (61.2)	107 (64.5)	53 (65.4)	0.58
Loop diuretics, %	606 (67.4)	105 (63.3)	56 (69.1)	0.52
Thiazide diuretics, %	208 (23.1)	40 (24.1)	20(24.7)	0.92
Beta-blockers, %	833 (92.7)	157 (94.6)	74(91.4)	0.58
Statin, %	393 (43.8)	66 (39.8)	29 (35.8)	0.27
Acetylsalicylic acid, %	525 (58.4)	96 (58.2)	44 (54.3)	0.77
Digoxin, %	83 (9.2)	11 (6.6)	7 (8.6)	0.55

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonists; ARNI, angiotensin receptor/neprilysin inhibitor; RAAS-M, renin-angiotensin-aldosterone system inhibitors. The p values, between the groups were determined using the χ^2 test

Table 3. Logistic regression analysis for hyperkalemia.

Variables	Odds ratio (95% Confidence Interval)	P-value
eGFR	0.969 (0.961-0.976)	<0.001
Diabetes	1.217 (0.896-1.651)	0.208
Hypertension	0.914 (0.671-1.246)	0.571
ACE-I/ARB	1.697 (1.124-2.562)	0.012
MRA	1.511 (1.066-2.142)	0.02
Beta-blockers	1.075 (0.594-1.945)	0.811

eGFR, estimated glomerular filtration rate; ACE-I/ARB, angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonists.

or dose reduction of these life-saving drugs due to hyperkalemia may play a role in increasing long-term mortality in high-risk HF patients [20-22].

Independent predictors of hyperkalemia were reported as baseline serum creatinine, serum potassium, atrial fibrillation, history of diabetes and NYHA class III or IV [14]. In the CHARM program, male gender, advanced age, baseline hyperkalemia (≥ 5.0 mmol/L), diabetes, creatinine ≥ 2.0 mg/dl and use of ACE-I or spironolactone were defined as risk factors for hyperkalemia [23]. Similarly, in our study, we found eGFR, ACE-I/ARB and MRA to be strong independent predictors for hyperkalemia. Although the diabetes rate and hemoglobin A1c level were higher in those with hyperkalemia, it was not related to diabetes in the regression model. However, we think that it may be indirectly related to low eGFR caused by uncontrolled diabetes.

The use of RAAS-M was common in the PROTECT study, with 75.6% of patients using ACE-I and 45.7% using MRA. Hyperkalemia (potassium > 5 mmol/L) was present in 35% and there was no increase in mortality with hyperkalemia at day 180. However, in this study, reduction and discontinuation of RAAS-M, especially MRAs, were reported as a leading cause of increased mortality [4]. In our study, ACE-I/ARB use was 80.9%, MRA use was 70%, and ACE-I/ARB use together with MRA was 62%. Although the number of patients with potassium > 5 mmol/L was lower (n:247, 21.6%), the rate of MRA use was higher than in the PROTECT study. In addition, in our study, we did not find a significant increase in hyperkalemia in those using ACE-I/ARB, MRA, and those taking at least 50% of the target dose.

Limitations

Our study population was retrospectively obtained

from data belonging to a single center that follows up in the HF outpatient clinic, so the results cannot be generalized to other regions or to our country. However, we think that it can be a catalyst that generates ideas for future studies. We didn't know how long patients took these medications before the potassium assessment, and we did not analyze whether the patients used potassium-binding drugs. Therefore, the effect of potassium binders on outcomes is unknown. Also, medications such as antibiotics, heparins or non-steroidal anti-inflammatory drugs can contribute to hyperkalemia [24]. Since our study was retrospective, information on whether the patients received treatment other than HF treatment at that time is limited. Only the initial potassium values of the patients at the time of their outpatient application and the drugs they were taking were evaluated. Potassium changes or drug changes were not evaluated during follow-up. Another limitation is that in our hospital, serum potassium levels are measured, not plasma. Serum levels can be measured as 0.5 mEq/L higher than plasma levels [1].

CONCLUSION

Hyperkalemia is frequently seen in patients receiving RAAS-M in chronic HF with the recommendation of current guidelines. We found that low eGFR, ACE-I/ARB and MRA were more closely associated with hyperkalemia. Close monitoring and awareness in terms of hyperkalemia in these patients may be important in increasing adherence to treatment.

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Gender differences in patients undergoing transcatheter aortic valve replacement: a cross-sectional study

Transkateter Aort Kapak Replasmanı Uygulanan Hastalarda Cinsiyet Farklılıkları: Kesitsel Bir Çalışma

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ABSTRACT

Aim: Transcatheter aortic valve replacement (TAVR) is an effective treatment modality for patients with high-risk symptomatic severe aortic stenosis (AS) who are not suitable for surgery. Gender-related differences in TAVR are still deliberated, thus in this study we aimed to investigate the effect of gender on clinical outcomes in patients who underwent TAVR in our clinic.
Methods: 270 consecutive patients who underwent TAVR between January 2015 and January 2022 were included in the study. In addition to the patient's medical history, transthoracic or transesophageal echocardiography and computed tomography findings were examined to evaluate AS. Patients with symptomatic, high-risk severe aortic stenosis were treated with self-expanding Evolute-R devices. The patients were followed up for the first year after discharge. Follow-up was done by clinical visits and phone calls.
Results: In-hospital mortality (5.4% vs. 7.4%; p=0.507), death at one-year follow-up (14.9% vs. 13.1%, p=0.681), and major adverse cardiovascular and cerebrovascular events (MACCE) at one-year follow-up (26.4% versus 23.8%, p =0.627) rates, there was no statistically significant difference between male and female genders. Kaplan Meier curves were used for survival analysis, including one-year mortality and MACCE rates. Accordingly, no statistically significant difference was found between the two genders in terms of mortality and MACCE (respectively; p= 0.910; p=0.889).
Conclusion: In our patient group who underwent TAVR, we could not detect a significant difference in clinical outcomes between both genders. In recent years, the effect of gender on clinical outcomes may decrease with device and procedural developments.

Key words: Aortic stenosis, gender, mortality, transcatheter aortic valve replacement

ÖZ

Amaç: Transkateter aort kapak replasmanının (TAVR) cerrahiye uygun olmayan, yüksek riskli semptomatik şiddetli aort darlığı (AS) olan hastalar için etkili bir tedavi yöntemidir. TAVR'da cinsiyete bağlı farklılıklar hala tartışılmaktadır. Bu çalışma ile kliniğimizde TAVR uygulanan hastalarda cinsiyetin klinik sonuçlar üzerine etkisini araştırmayı amaçladık.
Yöntemler: Ocak 2015 ile Ocak 2022 tarihleri arasında TAVR yapılan ardışık 270 hasta çalışmaya dahil edildi. AS'yi değerlendirmek için hastanın tıbbi öyküsünün yanı sıra transtorasik veya transözofageal ekokardiyografi ve bilgisayarlı toraks tomografisi bulguları incelendi. Semptomatik, yüksek riskli şiddetli aort darlığı tespit edilen hastalara kendiliğinden genişleyebilen Evolute-R cihazlarıyla işlem yapıldı. Hastalar taburculuk sonrası ilk bir yıl takip edildi. Takipler klinik ziyaretler ve telefon görüşmeleriyle gerçekleşti.
Bulgular: Hastane içi mortalite (%5.4'e karşı %7.4 ; p=0.507), bir yıllık takipte ölüm (%14.9'e karşı %.13.1, p=0.681) ve bir yıllık takipte majör advers kardiyovasküler ve serebrovasküler olaylar (MACCE) (%26.4'e karşı %23.8, p=0.627) oranları açısından kadın ve erkek cinsiyetleri arasında istatistiksel olarak anlamlı farklılık saptanmadı. Bir yıllık mortalite ve MACCE oranlarını içeren sağkalım analizi Kaplan-Meier eğrileri kullanıldı. Buna göre her iki cinsiyet arasında mortalite ve MACCE açısından istatistiksel olarak anlamlı farklılık saptanmadı (sırasıyla; p= 0.910; p =0.889).
Sonuç: TAVR yapılan hasta grubumuzda her iki cinsiyet arasında klinik sonlanımlar açısından önemli bir farklılık saptayamadık. Son yıllarda cihaz ve prosedürle ilişkili gelişmelerle cinsiyetin klinik sonuçlar üzerine etkisi azaltılmıştır.

Anahtar Kelimeler: Aort darlığı, cinsiyet, mortalite, transkateter aort kapak replasmanı

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INTRODUCTION

Degenerative aortic stenosis (AS) is the most common heart valve disease in developed countries [1]. The incidence is similar in men and women, and it constitutes nearly half of the valve diseases [2]. The effect of gender differences on clinical outcomes has recently become the focus of attention in cardiology. In that context, the effect of gender differences on clinical outcomes was investigated in cardiac procedures, such as percutaneous coronary intervention (PCI), coronary artery bypass operations (CABGO), catheter ablation in atrial fibrillation and cardiac implantable electronic devices [3 6].

Transcatheter aortic valve replacement (TAVR) has proven to be an effective treatment for patients with high-risk symptomatic severe AS who are not suitable for surgery [7-9]. Degenerative diseases are more common in women than in men, compared to atherosclerotic diseases, therefore the rate of female patients is relatively high in studies of aortic valve diseases in which degeneration is prominent and related to TAVR [10]. Studies have shown that female patients with severe AS undergo fewer aortic valve replacement (AVR) and their prognosis is worse than men [11]. Women do not favour surgery because of their small body structure, co-morbidities, greater avoidance of aggressive treatment and worse AVR results, compared to men [11]. Based on these studies, female gender has been included in The Society of Thoracic Surgeons (STS) risk score used for postoperative mortality, and has become an independent risk factor for surgery [12].

Although many studies have been reported on complications and mortality by gender after TAVR, the results are quite inconsistent [13]. Studies have shown that there is no clear consensus on the differences according to gender before and after TAVR and the situations related to protection from cardiovascular events that may develop as a result [14]. In this retrospective observational study, we aimed to investigate the effect of gender on clinical outcomes, in patients who underwent TAVR in our clinic.

MATERIALS AND METHODS

Study design

This was a retrospective study conducted with patients who underwent TAVR between January 2015 and January 2022. Some 270 consecutive patients who underwent elective or emergency transfemoral TAVR were included in the study. Patients undergoing TAVR were evaluated with a multidisciplinary approach before the procedure. A team of experienced interventional cardiologists performed the procedure. The study was conducted in accordance with the Declaration of Helsinki.

Eligibility Criteria

Inclusion criteria for the study were determined as follows: a) The patients with symptomatic severe AS who were considered as high-risk for valve surgery b) Patients evaluated as suitable for TAVR by a multidisciplinary team (a special cardiac team consisting of invasive and non-invasive cardiologists, cardiac surgeons and anesthesiologists), c) Criteria for severe AS: determined by echocardiography AV Doppler mean gradient was accepted as >40 mm Hg or peak jet velocity >4.0 m/s, and aortic valve area <1 cm2 or aortic valve index <0.5 cm2/m2.

Patients with a previous history of pacemaker implantation, TAVR or surgical AVR or bicuspid aortic valve, were excluded from the study. Furthermore, patients with a prior of infective endocarditis within the last six months, cardiogenic shock, life expectancy lower than one-year due to malignancy, were also excluded.

TAVR procedure and clinical follow-up

In addition to the patient's medical history, transthoracic or transesophageal echocardiography and computed tomography of the thorax were used to evaluate AS. Patients with symptomatic, high-risk severe AS were treated with self-expanding Evolute-R devices. TAVR procedures were performed by experienced invasive cardiologists, in a single center. Device selection and procedure was left to the discretion of the operator. The patients were followed up for the first year after discharge, which was ensure through clinical visits and phone calls.

Endpoints and definitions

In our study, the gender differences were compared in a heterogeneous patient population undergoing TAVR. The clinical endpoint was accepted as one-year rates of all-cause mortality and major adverse cardiovascular and cerebrovascular events (MACCE).

Statistical analysis

The SPSS (IBM, USA, version 25) was used for statistical analysis. Categorical variables were presented as percentages (%) and statistical analysis was done with the Chi-square test or Fisher's exact test. The distribution of continuous variables was evaluated by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed continuous variables were expressed as mean [standard deviation (SD)] or as median (interquartile range) in case of skewed distribution. Continuous variables between two independent groups were analyzed by the Student's t-test or Mann-Whitney U test, as appropriate. Log rank test and the Kaplan-Meier curve were used to determine the difference in event-free survival rates between the two groups. A p value of < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 270 patients were included in the study: 148 patients (54.8%) were in the female gender group and 122 patients (45.2%) were in the male gender group. Key characteristics of the study population are summarized in Table 1. The mean age of women was 80.1 (6.2) years, and the mean age of men was 77.8 (6.3) years. There was a significant difference between the groups (p=0.003). The New York Heart Association (NYHA) was used to measure the functional capacity of the patients before the procedure, and most of the patients were in the NYHA 3-4 (96.3%) group: there was no significant difference between the two groups (98% vs. 94.3%, p=0.108).

The most common comorbid disease in the study population was hypertension (55.9%), followed by anemia (53%), heart failure (38.5%), chronic renal failure (28.5%), dyslipidemia (25.2%), diabetes mellitus (24.4%) and atrial fibrillation (23.3%). There was no significant difference between the two groups in terms of body mass index, hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease (COPD), history of cerebrovascular disease (CVD), chronic renal failure, anemia or atrial fibrillation. Other demographic and clinical characteristics of the patients are summarized in Table 1.

The proportion of men was higher in patients with prior PCI (28.4% vs. 35.2%, p=0.227) or a history of CABGO (6.1% vs. 20.5%, p<0.001). Likewise, heart failure was significantly higher in males across groups (25.7% vs. 54.1%, p<0.001, respectively). Smoking was significantly higher in males (14.9% vs. 37.7%, respectively, p<0.001). Although the rate of peripheral arterial disease was low in both populations, it was more common in males (1.4% vs. 4.9%, respectively, p=0.146). The size of the implanted valve was significantly higher in males (27.32(2.86) mm vs. 30.45(3.27) mm, p<0.001) (Table 1). There was no significant difference between the groups in terms of balloon predilatation and postdilatation rates (predilatation p=0.982, postdilatation p=0.774). Left ventricular ejection fraction (LVEF) was significantly lower in males [54.38(9.61) vs 46.81(12.62), p<0.001, respectively]. From left ventricular parameters: LVEDD (p<0.001), LVESD (p<0.001), LAD (p=0.012) were found to be low in women, while IVSD (p<0.001) was found to be high in men. The ascending aortic diameter was lower in women than in men (3.59(0.54) vs. 3.77(0.53), p=0.025, respectively). The rate of moderate-to-severe aortic regurgitation (AR) was significantly higher in women (16.8% vs. 7%, p=0.014). Moderate-severe mitral regurgitation (MR) (p=0.961) and tricuspid regurgitation (TR) (p=0.314) were not statistically significant between the two groups. Systolic pulmonary artery pressure (SPAP) values were not significant between the groups [42 (20) vs 40 (20), respectively, p=0.801] (Table 2). Echocardiographic and multislice computed tomography data of the patients before and after TAVR are summarized in Table 2.

Study outcomes and clinical endpoints

Although a permanent pacemaker, arrhythmia, acute renal failure, major bleeding and major vascular complications were more common in

Table-1. Baseline characteristics and procedural demographics

Characteristics	Overall n=270 (100%)	Female n=148 (54.8%)	Male n=122 (45.2%)	p value
Age, years	79.08(6.37)	80.13(6.25)	77.80(6.33)	0.003
Body mass index, kg/m²	23.0(2.52)	23.23(3.04)	22.73(1.66)	0.112
STS risk score, %	8.55(2.70)	8.83(3.02)	8.36(2.42)	0.161
NYHA III-IV, n%	260(96.3)	145(98.0)	115(94.3)	0.108
Hypertension, n%	151(55.9)	89(60.1)	62(50.8)	0.125
Diabetes mellitus, n%	66(24.4)	42(28.4)	24(19.7)	0.098
Dyslipidemia, n%	68(25.2)	41(27.7)	27(22.1)	0.294
Previous PCI, n%	85(31.5)	42(28.4)	43(35.2)	0.227
Previous CABGO, n%	34(12.6)	9(6.1)	25(20.5)	<0.001
Prosthesis valve, n%	3(1.1)	2(1.4)	1(0.8)	N/A*
Peripheral artery disease, n%	8(3.0)	2(1.4)	6(4.9)	0.146*
COPD, n%	29(10.7)	11(7.4)	18(14.8)	0.053
Atrium Fibrillation, n%	63(23.3)	40(27.0)	23(18.9)	0.114
Previous CVD, n%	4(1.5)	2(1.4)	2(1.6)	N/A*
Chronic renal failure, n%	77(28.5)	38(25.7)	39(32.0)	0.254
Heart failure, n%	104(38.5)	38(25.7)	66(54.1)	<0.001
Anemia, n%	143(53.0)	82(55.4)	61(50.0)	0.375
Smoking, n%	68(25.2)	22(14.9)	46(37.7)	<0.001
Implanted valve size, mm	28.74(3.42)	27.32(2.86)	30.45(3.27)	<0.001
Balloon Predilatation, n%	73(27.3)	40(27.4)	33(27.3)	0.982
Balloon Postdilatation, n%	64(24.0)	34(23.3)	30(24.8)	0.774

*Data are expressed as mean [standard deviation(SD)] or frequencies (percentages) as appropriate. STS; society of thoracic surgeons, NYHA; New York heart association, PCI; percutaneous coronary intervention, CABGO; coronary artery bypass graft operation, COPD; chronic obstructive pulmonary disease, CVD; cerebrovascular disease. N/A; not applicable. *Fisher Exact test was used

women in terms of procedural complications, no statistically significant difference was found. There was no significant difference between the two groups in terms of the frequency of early hospital readmission after TAVR (4.7% vs. 9.0%, respectively; p=0.160). Additionally, in-hospital mortality (5.4% vs. 7.4%; p=0.507), death at one-year follow-up (14.9% versus 13.1%, p=0.681), and MACCE at one-year follow-up (26.4% versus 23.8%), p=0.627), no statistically significant difference was found between male and female genders (Table 3). Other procedural complications and clinical endpoints are summarized in Table 3.

Accordingly, no statistically significant difference was found between both genders in terms of mortality and MACCE (p= 0.910, Log-rank: 0.013; p=0.889, Log-rank: 0.019, respectively) (Figure 1).

DISCUSSION

In our study, we examined the effects of pre- and post-procedure gender differences on clinical outcomes in patients who underwent the TAVR procedure. When we look at the results of TAVR, we found similar rates of successful implantation of the valve, peri-procedural complications, mortality and MACCE, although men and women have similar demographic characteristics.

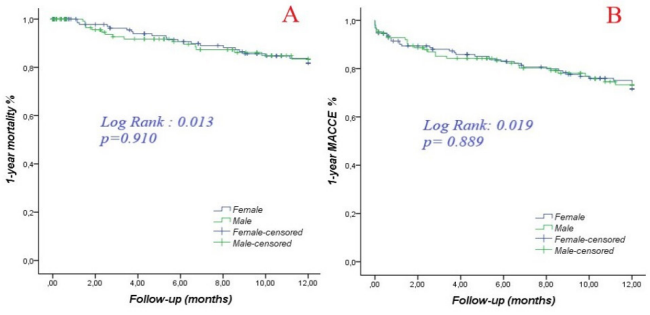

Figure 1. Comparison of men and women with Kaplan-Meier analysis for one-year mortality and one-year composite endpoint (MACCE)

The mean age and functional capacities of the patients participating in our study were higher in women than in women, and women presented with more advanced age and more severe symptoms compared to men. This result is consistent with previously reported study results [11]. In the PARTNER A study, it has been reported that mortality rates in patients who underwent TAVR

Table-2. Baseline Echocardiographic and Multislice Computed Tomography Parameters

Echocardiographic parameters		Overall n=270 (100%)	Female n=148 (54.8%)	Male n=122 (45.2%)	p value
AV doppler mean gradient, mmHg		48.64(9.50)	49.13(10.31)	48.05(8.42)	0.351
AV doppler max gradient, mmHg		79.10(15.01)	79.32(16.12)	78.83(13.60)	0.787
AV opening area, cm2		0.67(0.18)	0.67(0.17)	0.68(0.19)	0.925
LVEF, %		50.95(11.68)	54.38(9.61)	46.81(12.62)	<0.001
LVEDD, mm		4.87(0.61)	4.69(0.57)	5.10(0.60)	<0.001
LVESD, mm		3.52(0.81)	3.29(0.70)	3.90(0.84)	<0.001
LAD, mm		4.46(0.57)	4.38(0.56)	4.55(0.57)	0.012
IVSD, mm		1.39(0.17)	1.41(0.18)	1.35(0.20)	<0.001
Ascending aorta diameter, mm		3.67(0.54)	3.59(0.54)	3.77(0.53)	0.025
Moderate-severe MR, n%		81(30.7)	44(30.6)	37(30.8)	0.961
Moderate-severe AR, n%		30(11.5)	10(7.0)	20(16.8)	0.014
Moderate-severe TR, n%		63(23.8)	31(21.4)	32(26.7)	0.314
SPAP, IQR, mmHg		41(20)	42(20)	40(20)	0.801
Baseline Multislice Computed Tomography Measurements					
Aort-RCA distance, mm		16.88(3.79)	15.70(3.04)	18.05(4.10)	<0.001
Aort-LMCA distance, mm		13.27(3.77)	12.32(2.88)	14.26(4.31)	0.001
Ascending aorta, mm		34.60(4.10)	33.92(4.0)	35.31(4.11)	0.036
Aortic anulus diameter, mm		24.08(2.81)	22.65(2.07)	25.44(2.75)	<0.001
NCC-sinus valsalva diameter, mm		30.20(5.69)	27.97(5.34)	32.56(5.10)	<0.001
RCC-sinus valsalva diameter, mm		28.33(4.89)	26.58(4.23)	30.13(4.89)	<0.001
LCC-sinus valsalva diameter, mm		29.65(6.82)	27.24(6.37)	32.12(6.40)	<0.001
Aortic annulus perimeter, mm		77.59(8.21)	73.39(6.38)	81.74(7.72)	<0.001
Aortic annular area, mm2		457.02(99.36)	406.5(73.3)	505.7(97.1)	<0.001
Angular angle, IQR		48.21(8.93)	48.14(8.06)	48.28(9.77)	0.923
Echocardiographic parameters after TAVR					
LVEF, (%)		52.71(10.33)	54.73(10.24)	50.29 (9.96)	0.003
AV doppler mean gradient, mmHg		8.91(4.85)	9.34(4.88)	8.39(4.79)	0.216
SPAP, IQR, mmHg		35.98(14.22)	34.85(13.44)	37.38(15.12)	0.294
Paravalvular leak, n%	Mild	107(39.6)	53(35.8)	54(44.3)	0.158
	Moderate-severe	7(3.1)	4(3.1)	3(3.0)	N/A*

*Data are expressed as mean(SD), frequencies (percentages) or as median (interquartile range) as appropriate. AV; aortic valve, LVEF; left ventricle ejection fraction, LVEDD; left ventricle end diastolic diameter, LVESD; left ventricle end systolic diameter, LAD; left atrium diameter, IVSDD; interventricular septum diastolic diameter, MR; mitral regurgitation, AR; aortic regurgitation, TR; tricuspid regurgitation, SPAP; systolic pulmonary artery pressure, IQR; interquartile range, RCA; right coronary artery, LMCA; left mean coronary artery, NCC; non-coronary cusp, RCC; right-coronary cusp, LCC-left coronary cusp. N/A; not applicable. *Fisher Exact test was used.

were similar in men in the two-year follow-up compared to those who underwent AVR, while mortality rates were lower in women [15]. This causes TAVR rates to be higher in women than in men and similarly, the rate for women was higher in our study.

In a study conducted by O'Connor et al., it was reported that there were significant differences between the genders when the clinical and demographic characteristics of patients who underwent TAVR were compared [16]. Diabetes mellitus, high body mass index (BMI), previous myocardial infarction, prior percutaneous coronary intervention and low ejection fraction (EF), have been shown to be more common in male patients [17]. It has been shown that female patients have more advanced age, higher transvalvular gradient, higher pulmonary artery pressure, higher EF and smaller annulus values. Thus, although female patients are initially healthier in terms of baseline comorbidities compared to men, they become older and fragile. The findings of our study were also compatible with this, and we found the comorbidity rates to be similar for both genders.

In another study, pre-procedure multislice computed tomography was found to have smaller body surface areas, aortic annulus diameters, shorter coronary exit-annulus distances and less

Table-3.Procedural Complications and Clinical Endpoints of the Patients

Complications	Overall n=270 (100%)	Female n=148 (54.8%)	Male n=122 (45.2%)	p value
Technical success, n%	264(97.8)	144(97.3)	120(98.4)	0.555
Permanent pacemaker, n%	23(8.5)	14(9.5)	9(7.4)	0.542
New-onset stroke, n%	9(3.3)	5(3.4)	4(3.3)	N/A*
Pericardial tamponade, n%	7(2.6)	6(4.1)	1(0.8)	0.132*
Arrhythmia, n%	50(18.5)	30(20.3)	20(16.4)	0.414
Acute renal insufficiency, n%	14(5.2)	11(7.4)	3(2.5)	0.067
Major bleedings, n%	15(5.6)	10(6.8)	5(4.1)	0.343
Major vascular complications, n%	18(6.7)	10(6.8)	8(6.6)	0.948
Coronary obstruction, n%	1(0.4)	1(0.7)	0	N/A*
New-onset LBBB, n%	95(35.4)	51(34.5)	44(36.7)	0.707
Peri-procedural MI, n%	3(1.1)	1(0.7)	2(1.6)	0.593
Hospitalization day, IQR	3(4)	3(4)	3(5)	0.439
Early hospitalization postoperative, n%	18(6.7)	7(4.7)	11(9.0)	0.160
In-hospital mortality, n%	17(6.3)	8(5.4)	9(7.4)	0.507
First month death, n%	24(8.9)	13(8.8)	11(9.0)	0.947
First year death, n%	38(14.1)	22(14.9)	16(13.1)	0.681
In-hospital MACCE, n%	27(10)	14(9.5)	13(10.7)	0.744
First month MACCE, n%	34(12.6)	19(12.8)	15(12.3)	0.894
1-year MACCE, n%	68(25.2)	39(26.4)	29(23.8)	0.627

*Data are expressed as mean(SD), frequencies (percentages) or as median (interquartile range) as appropriate. LBBB; left bundle branch block, MI; myocardial infarction, IQR; interquartile range, MACCE; major adverse cardiac and cerebrovascular events. N/A; not applicable. *Fisher Exact test was used.

amount of valve calcification in women [16,18]. This situation is quite similar to the results of our study, and by considering these parameters in valve preference in women, smaller volumes of valves were preferred. Myocardial response to left ventricular pressure overload due to AS is different in men and women. While more concentric hypertrophy develops in female patients, inappropriate remodelling and related left ventricular dilatation are more prominent in males [18]. Therefore, myocardial fibrosis is lower in women and irreversible myocardial damage is less common, while systolic functions are more impaired in men. Similarly, in our study, while changes in diastolic parameters were observed less in women in echocardiographic examination, left ventricular hypertrophy was more often observed.

In previous studies, vascular complications after TAVR were found to be significantly higher in women, but this is thought to be due to more advanced age, smaller body surface area and smaller diameter vessels. In addition, vascular complications increase as a result of smaller mean diameters of the common femoral artery and greater vascular tortuosity [16]. However, in our study, although peripheral arterial disease was lower in women at the beginning, vascular complications increased significantly after TAVR, but no statistically significant difference was found between the two groups. When we look at the results of another study in which subgroup analyses of randomized studies were performed, it was observed that women were indeed older, had less comorbidity, and had higher rates of procedure-related vascular complications and bleeding. On the other hand, it has been shown that early and long-term survival rates in women are better than in men [19]. Similarly, in a meta-analysis including 47 188 patients, it was found that although periprocedural complication rates were higher in women, their one-year all-cause mortality rates were lower than those of men [20]. In the recent PARTNER-2 study, it was reported that women were more fragile, had higher STS scores and higher rates of vascular complications [21]. Accordingly, gender differences were not shown in terms of 30-day mortality, one-year mortality, stroke and other clinical outcomes [21]. Previous studies have shown that female gender is a risk factor for coronary obstruction after TAVR [22], however coronary obstruction was observed in only one patient in our study, but it was statistically insignificant. Likewise, we did not find a significant difference between the two genders in terms of permanent pacemaker implantation. Data

on the effect of gender in terms of periprocedural stroke rate are unclear. It is thought that the risk of stroke is higher in women due to the effect of the materials used during TAVR on atheroma plaques in the ascending aorta, due to the smaller aortic diameter [23]. In some studies, stroke rates were higher in women, while in others they were similar [16].

In the WIN-TAVR study conducted with 1 019 patients, it was shown that survival in women was better than in men [24]. On the other hand, the fact that fragility, osteoporosis and vertebral fractures are more common in women may cause intrathoracic rotation of the heart, making device implantation difficult [24]. Contrary to previous studies, this situation was thought to increase complications, but in our study, complication rates were not different between the two genders.

In another study, the rates of moderate and severe paravalvular AR were found to be similar between both genders [21]. Researchers attributed these results to increased experience, use of larger valves, and less paravalvular AR as a result of advances in valve technology [21]. In addition, some studies have found that the rates of paravalvular aortic failure and permanent pacemaker after TAVR are higher in men. The reason for this is thought to be larger valves, more osteoarthritis in men and complications related to the use of older technology valves, especially in the older studies [25]. Long-term rates of paravalvular AR may be lower in women and it is suggested that the reason for this may be patient valve incompatibility and left ventricular remodelling. Consistent with these findings, we did not find a significant difference between the two groups in our study, although the rate of mild paravalvular leak was less in women. In addition, there was no difference between the two groups in terms of moderate and severe paravalvular leak.

Limitations

There are some limitations of our study. One-to-one operator experience could not be evaluated and basic characteristics and comorbid conditions may have affected the results, as they were not homogeneously distributed between the genders. In addition, complications such as minor bleeding that did not require intervention, mild pleural effusion, wound infections and treatable arrhythmias were not considered.

Conclusion

We could not find a significant difference in clinical outcomes between both genders in our patient group who underwent TAVR. In recent years, with device and procedural developments, the effect of gender on clinical outcomes has decreased. In order to generalize the results of the study, multicenter studies with larger participation are needed.

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Risk factors associated with mortality in patients with methanol poisoning: a retrospective study

Metanol zehirlenmesi olan hastalarda mortalite ile ilişkili risk faktörleri: retrospektif bir çalışma

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ABSTRACT

Aim: Methanol poisoning (MP) is an significant medical problem worldwide, and despite advances in diagnosis and treatment, the mortality rate in these cases remains high. This study aimed to evaluate the clinical and laboratory factors to determine in-hospital mortality in patients with MP.

Methods: This single-center, retrospective, observational study was conducted with 65 adult MP cases visiting the emergency department (ED) of a tertiary training and research hospital, between January 01, 2017 and February 01, 2022. Data was statistically compared between survivors and non-survivors.

Results: The in-hospital mortality rate was 41.5%. The rate of cases with respiratory distress, low Glasgow coma scale (GCS) (≤8), and delayed arrival to the hospital (>24 hours) was higher in the group of non-survivors compared to the group of survivors. Non-survivors had a higher anion gap (30.5 mEq/L vs. 25.5mEq/L), base excess (-25.0 mmol/L vs. -18.6 mmol/L), lactate (10.2 mmol/L vs. 2.2 mmol/L) levels, and lower pH (6.76 vs. 7.14) and bicarbonate (6.3 mmol/L vs. 10.3 mmol/L) levels than survivors (p<0.001). In ROC analysis, pH (AUC= 0.916) and base excess (AUC=0.915) were blood gas parameters with the highest AUC values in predicting mortality in MP cases. Folate use in the treatment had a statistically significant effect on mortality (P=0.015).

Conclusion: In MP cases, delay in a hospital visit, severe metabolic acidosis, high lactate levels, low GCS on arrival to the ED and no folate therapy, were associated with increased in-hospital mortality rates. Our data will contribute to the clinical management of MP patients and the development of treatment protocols.

Keywords: Methanol, Folic Acid, Acidosis, Anion gap, Alcoholic Intoxication

ÖZ

Amaç: Metanol zehirlenmesi (MZ) dünya çapında önemli bir tıbbi sorundur, tanı ve tedavideki gelişmelere rağmen bu vakalarda ölüm oranı yüksektir. Bu çalışmada MZ olan hastalarda hastane içi mortaliteyi öngörmek için klinik ve laboratuvar faktörlerinin değerlendirilmesi amaçlandı.

Yöntemler: Bu tek merkezli, retrospektif, gözlemsel çalışma, 01 Ocak 2017 ve 01 Şubat 2022 tarihleri arasında üçüncü basamak bir eğitim ve araştırma hastanesinin acil servisini (AS) ziyaret eden yetişkin 65 MZ vakası ile yürütülmüştür. Veriler hayatta olanlar ve hayatta olmayanlar arasında istatistiksel olarak karşılaştırıldı.

Bulgular: Hastane içi ölüm oranı %41,5 idi. Hayatta kalmayanlar grubunda solunum sıkıntısı, düşük GKS (≤8), ve hastaneye geç başvuran (24 saaten sonra) vakalarının oranı, hayatta kalanlar grubuna göre daha yüksekti. Ölen hastaların grubunda yaşayanlara kıyasla daha yüksek anyon açığı (30,5 mEq/L vs. 25,5mEq/L), baz fazlalığı (-25,0 mmol/L vs. -18,6 mmol/L), laktat seviyeleri (10,2 mmol/L vs. 2,2 mmol/L) ve daha düşük pH (6,76 vs. 7,14) ve bikarbonat (6,3 mmol/L vs. 10,3 mmol/L) seviyeleri vardı (p<0.001). ROC analizinde pH (AUC= 0,916) ve baz fazlalığı (AUC=0,915), MZ olgularında mortaliteyi öngörmede en yüksek AUC değerlerine sahip kan gazı parametreleriydi. Tedavide folat kullanımının mortalite üzerinde istatistiksel olarak anlamlı bir etkisi oldu (p=0.015).

Sonuç: MZ olgularında hastaneye başvuruda geçikme, şiddetli metabolik asidoz, yüksek laktat düzeyleri, acil servise gelişte düşük GKS ve folat tedavisi verilmemesi, artan hastane içi mortalite oranları ile ilişkiliydi. Verilerimiz MZ hastalarının klinik yönetimine ve tedavi protokollerinin geliştirilmesine katkıda bulunacaktır.

Anahtar Kelimeler: Methanol, Folik asid, Asidoz, Anyon açığı, Alkol zehirlenmesi

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INTRODUCTION

Methanol, obtained by tree fermentation, is a colorless, volatile, toxic type of alcohol found in a variety of household and industrial products [1]. Although methanol is not very toxic, formaldehyde and formic acid, two of its metabolites, cause most of the toxic effects in methanol poisoning (MP) [2,3]. Acute MP is characterized by a latent period of several hours in which patients are asymptomatic or show mild central nervous system (CNS) depression, followed by nausea, vomiting, abdominal pain, respiratory distress, progressively decreasing vision, progressive encephalopathy, and severe metabolic acidosis [2,3]. MP therapy includes standard supportive care, antidote therapy (ethanol or fomepizole), renal replacement therapy (RRT), folic acid (folate) and buffer (sodium bicarbonate) treatments [2,4].

However, despite improved treatments, high mortality rates are still reported in MP cases [2,5]. The main reason for this is the delayed visit to the hospital and the delayed diagnosis due to difficulties. The main difficulties in diagnosis are the inability in many centers to measure methanol, the lack of specificity of early symptoms and other laboratory data for MP, and the difficulty in obtaining an accurate anamnesis in case of attempted self-harm or substance abuse [2,4,5]. There is often a diagnostic dilemma and it is up to the clinician to consider MP as the etiology of many nonspecific findings, particularly metabolic acidosis. However, among MP cases that we can encounter in the form of outbreaks, it is vital to recognize the critically ill, triage these patients, transfer them to poisoning centers and start their treatment early [5].

This study aims to evaluate demographic, clinical and laboratory data to predict the prognosis of MP cases visiting the emergency department (ED) in the form of isolated episodes or outbreaks, at different times over five years.

MATERIALS AND METHODS

Study design and setting: This single-center, retrospective, observational study was conducted with consecutive MP cases visiting the ED of a tertiary training and research hospital, between January 2017 and February 2022. This hospital is a toxicology center, a level 1 trauma center, a STEMI center and a stroke center with multiple medical and surgical specialties, including an emergency medicine residency. There are 612 beds in the hospital, the annual number of ambulance visits to the ED is approximately 20 000 and the total of ED visits number approximately 300 000 per year.

Approval for this study was obtained from the ethics committee of the research institution. (Date: 07.02.2022, Protocol Number: 2022/42) and was conducted in accordance with the Declaration of Helsinki. The study was retrospective and the requirement for informed assent was waived as a result. Additionally, all personal data has been securely safeguarded (by detaching identifying data from the primary dataset) and made only accessible to academics. An anonymous analysis was done on all the data.

Criteria for inclusion and exclusion: The study included patients admitted to the ED with a diagnosis of MP and at least 18 years old. In addition to a strong history or clinical suspicion, the diagnosis of MP was made when the serum methanol content was more than 20 mg per deciliter or when at least two of the following three symptoms were present:

1. An arteria pH below 7.3.

2. Serum bicarbonate less than 20 mEq/L, and/or

3. Serum osmolar gap of more than 10 mOsm/kg.

Methanol levels cannot be measured in our hospital. However, the methanol level of four patients could be measured with blood samples sent to external centers. Patients younger than 18 years of age, who started their treatment elsewhere and were referred to our hospital, and whose data could not be reached, were excluded from the study.

Data: All patients who visited the ED during the study were scanned from the hospital's electronic medical record system, with their defined diagnoses (preliminary, differential, consultation and definitive diagnosis) during their hospital stay. Physician and nurse notes, consultations, daily follow-ups and laboratory data of patients whose diagnoses included the words "alcohol", "ethanol", "methanol" or "poisoning" were

examined. The data of the patients included in the study were recorded in a pre-designed form. The form included demographic data (age, gender, comorbidities), complaints, vital parameters, consciousness status, alcohol or substance abuse, alcohol administration method and time, laboratory results, radiological imaging reports, patient management and prognosis. Analysis of laboratory data included plasma bicarbonate levels, serum electrolyte levels, liver and kidney function test results, pancreatic enzyme levels, arterial blood gas analysis, cardiac markers and glucose and coagulation parameters. In our study, all vital parameters, laboratory and imaging results, were based on the initial data obtained at the time of arrival of the cases to the ED.

The following equation was used to determine the anion gap (AG) in serum:

AG = (Na+ + K+) – (Cl- + HCO3-) (6)

Treatment Protocol: Patients were given the necessary airway, respiratory and circulatory support, following a rapid initial screening assessment, that included mental state and vital signs to establish the urgent steps required to stabilize the patient. Standard supportive care, antidote therapy, elimination therapy, buffer (sodium bicarbonate) and folate are all used in the management of MP [2].

Intravenous (IV) ethanol (10%) was administered as an antidote. Only one patient could get fomepizole, due to a shortage of supply. When arterial pH was below 7.25 or serum bicarbonate was consistently below 20 mEq/L, patients received ethanol treatment intravenously as a 10% solution in 5% glucose (loading dose: 4–8 mL/kg, followed by a maintenance dose of 1-2 mL/kg/h). If necessary, the ethanol infusion rate was increased during hemodialysis (HD) to 2.5–3.0 ml/kg/h. A serial blood gas analysis was carried out roughly every two hours to assess the acidity level and track the medication's effectiveness. HD was performed on cases that met any of the following criteria: abnormality of vision, an initial arterial pH of less than 7.1, an arterial pH that could not be maintained at or above 7.3 or, a decrease in the arterial pH of more than 0.05 unit despite bicarbonate supplementation, worsening of vital signs despite intensive supportive care or renal failure. HD was performed on the patients as quickly as feasible. Since formate or methanol levels cannot be detected, HD was carried out at a high blood flow rate until pH levels returned to normal. Hemodynamically unstable patients (MAP 70 mmHg, GCS ≤8, intubated) or receiving positive inotropic treatment underwent hemodiafiltration (HDF) in the intensive care unit. To treat acidosis in all patients with a pH under 7.3, isotonic saline was given together with an IV bolus of 1 mEq/kg sodium bicarbonate. The infusion rate was customized based on fluid status, baseline pH and serum sodium level. When the arterial pH reached 7.35, the therapy was considered successful and the infusion was halted. As a cofactor treatment, folinic acid was administered. Additionally, thiamine hydrochloride, pyridoxine hydrochloride and cyanocobalamin were given. No patient received any form of gastrointestinal decontamination, such as gastric lavage or Ipecac syrup, or activated charcoal.

Statistical analysis: The statistical analysis of the study's data was conducted using the SPSS for Windows Inc. Version 22 (SPSS Inc.; Illinois, USA) and the MedCalc Statistical Software version 19.0.6. (MedCalc Software bvba, Belgium). Whether the continuous variables were normally distributed or not was calculated using the Shapiro-Wilk test. Non-normally distributed data was compared with the Mann-Whitney U test, and normally distributed data was compared with Student's t-test. Pearson chi-square test was used to compare the categorical results of the patients. Data was provided with means and standard deviations when parametric tests were employed to compare continuous variables. Median (25th and 75th percentiles) values for nonparametric tests were presented. Numbers and percentages (%) values for categorical data were presented. Receiver operating characteristic (ROC) curves were used to compare blood gas parameters to predict in-hospital mortality. The statistical significance level was consented as $p < 0.05$.

RESULTS

The study included 65 MP cases meeting the inclusion and exclusion criteria. Most of the patients were middle-aged (mean: 46.7±13.1 years), male (93.8%) and persistent alcohol drinkers (76.9%).

None of the patients had purchased their drinks from a monopoly dealer. The rate of those who buy drinks containing methanol is 76.9%, while the rate of those who prepare their drinks with the alcohol they buy is 23.1%. All of the patients had been poisoned by the methanol-containing beverages they drank assuming it was alcohol. Three (4.6%) patients had hypertension and one (1.5%) patient had diabetes mellitus. All patients were symptomatic and visual symptoms were the most common clinical feature with 90.8%. The proportion of patients with GCS <15 at the time of ED visit was 55.4% (n=36), and five more patients developed altered consciousness during ED follow-up. Most of the patients were treated with ethanol antidote (84.6%), RRT (IHD [61.5%], HDF [32.3%]), folic acid (58.5%) and bicarbonate (67.7%). A 42-year-old male patient, who was administered fomepizole on the 4th hour of his admission to the ED, died on the 4th day of his hospitalization. The in-hospital mortality rate was 41.5%. In our analysis, there was no statistically significant difference in gender (p=0.636) or mean age (p=0.061) between survivors and non-survivors. In terms of vital parameters, non-survivors had a lower mean arterial pressure (MAP) (86.6 ± 16.6 vs. 97.2 ± 12.0; p=0.042) and higher respiratory rate (23.9 ± 4.3 vs. 17.3 ± 1.7; p <0.001) than survivors. In-hospital mortality rates were 25.0% (n=4) for those visiting the ED within the first 24 hours after oral administration, while 69.2% (n=9) for those visiting after 48 hours. The median hospital stay of non-survivors was 4 (IQR:2-6) days. In addition, the in-hospital mortality rate was 20% (n=8) in patients treated with IHD and 71.4% in patients treated with HDF (P<0.001). However, patients who received folic acid therapy had a lower in-hospital mortality rate than those who did not (28.9% [n=11] vs. 59.3% [n=16]; respectively, p=0.015). Demographic data, vital parameters, clinical findings and treatments of patients grouped in terms of in-hospital mortality, are summarized in Table 1.

Brain CT imaging was performed in 78.4% (n=51) and diffusion-weighted magnetic resonance (DW-MRI) imaging was performed in 27.6% (n=18) of the patients, when they presented to the ED. No pathological finding was detected in this imaging. However, intracranial hemorrhage was seen in five cases in the radiological imaging performed between the 3rd and the 5th day following the arrival at the ED. Four patients had pre-dialysis brain CT scans and no pathological findings. Hematoma areas were reported in the bilateral basal cisterns in four patients and in the white matter adjacent to the lateral ventricular in one patient. INR, PT and aPTT values in the blood taken on the same day, as the hemorrhage-detected brain CT of these five patients were within the reference range.

Non-survivors had a greater anion gap (30.5 mEq/L [25.3-38.3] vs. 25.5 mEq/L [22.3-28.0]; p<0.001), higher PCO2 (43.6 [23.4-51.3] vs 29.8 [21.2-36.1]; p=0.015) and lactate (10.2 mmol/L [2.5-12.3] vs. 2.2 mmol/L [1.8-2.9]; p<0.001) levels, and lower pH (6.76 [6.69-7.15] vs. 7.14 [7.10-7.27]; p<0.001), bicarbonate (6.3 mmol/L [5.2-8.8] vs. 10.3 mmol/L [7.0-17.9]; p<0.001) and base excess (-25.0 mmol/L [-34.4 to -21.2] vs -18.6 mmol/L [-22.9 to – -6.5]; p<0.001) than survivors. The ethanol level measured in the blood taken at the time of admission of 47 patients (72.3%) was analysed. Nine patients had ethanol levels above the reference range (0-15 mg/dl). There was no statistically significant difference in mortality between those with and without high initial blood sample ethyl alcohol levels (22.2% [n=2], 39.5% [n=15]; respectively, p=0.455). Only eight cases had diagnoses supported by laboratories, and only one of these patients died. The methanol level in the blood of the deceased patient was 436 mg/dl, and the ethanol level was 131 mg/dl. Analysis of initial laboratory samples of MP cases is summarized in Table 2.

In ROC analysis, pH (AUC= 0.916 [%95 CI: 0.820-0.970]) and base excess (AUC=0.915 [%95 CI: 0.819-0.970) were blood gas parameters with the highest AUC values in predicting mortality in MP cases. The graph of the ROC analysis of blood gas parameters is shown in Figure 1. From the cut-off values determined according to Younden index J, pH ≤6.8 had the highest specificity (%100 [%95 CI:90.7-100]), HCO3 ≤6.7 mmol/L (%85.2 [%95 CI: 66.3-95.8]) and Base excess ≤ -25 mmol/L (85.2 [%95 CI: 66.3-95.8]) were the values with the highest sensitivity (Table 3).

Table 1. Comparison of demographic characteristics, vital parameters, clinical findings, and treatments of survivors and non-survivors.

		All patients	Survivor	Non-survivor	p
Male, n (%)		61 (93.8)	35 (92.1)	26 (96.3)	0.636
Age, years, mean ± SD		46.7 ± 13.1	44.1 ± 13.4	50.3 ± 11.8	0.061
Vital parameters, mean ± SD					
MAP, mmHg		92.8 ± 14.9	97.2 ± 12.0	86.6 ± 16.6	0.042
Pulse, n/min		85.5 ± 12.4	85.1 ±11.0	86.2 ± 14.3	0.706
Tempatura, oC		36.5 ± 0.23	36.5 ± 0.22	36.4 ± 0.23	0.437
SpO2, %		94.0 ± 4.7	96.4 ± 2.5	90.5 ± 5.0	<0.001
Glasgow coma score, n (%)					
≤8		19 (29.2)	3 (7.9)	16 (59.3)	<0.001
9-14		17 (26.2)	10 (26.3)	7 (25.9)	
15		29 (44.6)	25 (65.8)	4 (14.8)	
Complaints, n (%)					
Visual disturbances		59 (90.8)	32 (84.2)	27 (100)	0.037
Gastrointestinal symptoms		42 (64.6)	26 (68.4)	16 (59.3)	0.447
Dyspnea		20 (30.8)	5 (13.2)	15 (55.6)	<0.001
Alcohol consumption habit, n (%)		50 (76.9)	27 (71.1)	23 (85.2)	0.183
Drug misuse and addiction, n (%)		11 (16.9)	5 (13.2)	6 (22.2)	0.337
Time from exposure to hospital arrival, hours, n (%)					
<24		16 (24.6)	12 (31.6)	4 (14.8)	0.044
24-48		36 (55.4)	22 (57.9)	14 (51.9)	
>48		13 (20.0)	4 (10.5)	9 (33.3)	
Door-to-diagnosis time, h, median (IQR)		1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.672
Mechanical ventilation		34 (52.3)	7 (18.4)	27 (100)	<0.001
Treatment, n (%)		Treatment, n (%)	Treatment, n (%)	Treatment, n (%)	
RRT	IHD	40 (61.5)	32 (84.2)	8 (29.6)	<0.001*
	HDF	21 (32.3)	6 (15.8)	15 (55.6)	
Folate		38 (58.5)	27 (71.1)	11 (40.7)	0.015
Ethanol antidote		55 (84.6)	33 (86.8)	22 (81.5)	0.555
Bicarbonate		44 (67.7)	17 (44.7)	27 (100)	<0.001
Door-to-treatment time, h, Median (IQR)					
IHD or HDF		5.0 (3.0-8.0)	5.5 (3.8-9.0)	4.5 (3.0-7.0)	0.221
Folate		13.0 (6.0-16.8)	14.0 (6.0-18.0)	6.0 (6.0-9.5)	0.124
Ethanol		4.0 (2.0-5.0)	4.0 (2.0-4.0)	3.5 (1.0-6.5)	0.905
Bicarbonate		1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	0.564

HDF: Hemodiafiltration, h: hours, IHD: Intermittent hemodialysis, RRT: Renal replacement treatment, SD: Standart division, MAP: Mean Arterial Pressure, SpO2: Oxygen saturation by pulse oximetry, Door-to-diagnosis time: Time from admission to the emergency department to diagnosis of methanol poisoning, Door-to-treatment time: Time from arrival in the emergency department to the start of treatment.*Statistical comparison was made between patients who performed IHD and HDF

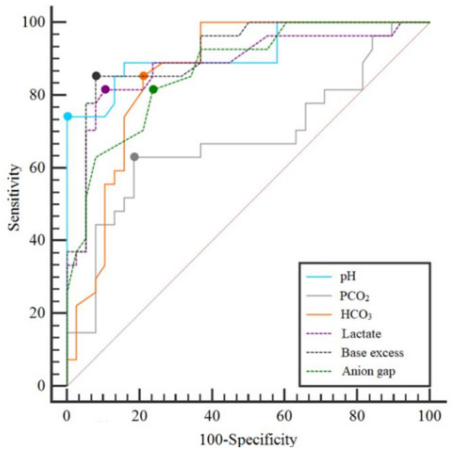

Figure 1: The receiver operating characteristic curve of arterial blood gas analysis parameter

Table 2. Comparison of laboratory parameters of survivors and non-survivors.

Laboratory parameters	Survivor, Median (IQR)	Non-survivor, Median (IQR)	P
pH	7.14 (7.10-7.27)	6.76 (6.69-7.15)	<0.001
PCO2 (mmHg)	29.8 (21.2-36.1)	43.6 (23.4-51.3)	0.015
HCO3 (%)	10.3 (7.0-17.9)	6.3 (5.2-8.8)	<0.001
Lactate (mmol/L)	2.2 (1.8-2.9)	10.2 (2.5-12.3)	<0.001
Base Excess (mmol/L)	-18.6 (-22.9 to -6.5)	-25.0 (-34.4 to -21.2)	<0.001
Anion gap (mEq/L)	25.5 (22.3-28.0)	30.5 (25.3-38.3)	<0.001
HS-Trop T (ng/l)	4.6 (2.0-9.8)	18.6 (14.0-25.1)	0.096
CK (U/L)	155 (97-430)	167 (128-379)	0.984
INR	1.18 (1.04-1.22)	1.38 (1.08-1.63)	<0.001
PTZ (sn)	15.2 (13.6-15.8)	17.9 (14.1-21.8)	<0.001
aPTT (sn)	30.1 (27.8-32.9)	32.4 (29.9-36.6)	<0.001
Glucose (mg/dl))	117 (98-145)	159 (156-215)	<0.001
Creatinine (mg/dl)	0.91 (0.74-1.09)	1.79 (1.37-2.55)	<0.001
AST (U/L)	35.5 (29.8-76.1)	34.1 (25.1-39.7)	0.001
ALT (U/L)	31.1 (24.8-48.7)	18.1 (12.0-29.0)	0.627
Amilaz (U/L)	75 (56-120)	119 (64-211)	0.032
Lipase (U/L)	43 (26-76)	73 (42-105)	0.042
Potassium (mmol/L)	4.6 (3.9-5.7)	5.1 (5.1-5.6)	0.001
Sodium (mmol/L)	140 (136-144)	145 (142-147)	0.001
Calcium (mg/dl)	8.51 (7.95-9.47)	8.62 (7.61-10.18)	0.139
Chloride (mmol/L)	109 (105-112)	111 (108-116)	0.108
Ethanol (mg/dl)	8.0 (2.25-25.8)	5.0 (0.0-7.5)	0.097

aPTT: Activated partial thromboplastin time, CK-MB: Creatinine kinase, HCO3: Bicarbonate, HS-Trop T: High Sensitivity Troponin T, INR: International normalized ratio, PTZ: Prothrombin time, PCO2: Partial Pressure of Carbon Dioxide.

Table 3. Cut-off values for the maximum sensitivity, specificity, PLR, NLR, PPV, and NPV of the arterial blood gas parameters.

	AUC (%95 CI)	Cut-off	Sens. (%95 CI)	Spec. (%95 CI)	PLR (%95 CI)	NLR (%95 CI)	PPV (%95 CI)	NPV (%95 CI)
pH	0.916 (0.820-0.970)	≤6.8	74.1 (53.7-88.9)	100 (90.7-100.0)		0.26 (0.1-0.5)	100 (83.2-100)	84.4 (70.5-93.5)
PCO2	0.678 (0.550-0.788)	>37.4	62.9 (42.4-80.6)	81.6 (65.7-92.3)	3.42 (1.6-7.1)	0.45 (0.3-0.8)	70.8 (48.9-87.4)	75.6 (59.7-87.6)
HCO3	0.865 (0.757-0.937)	≤6.7	85.2 (66.3-95.8)	78.9 (62.7-90.4)	4.05 (2.1-7.6)	0.19 (0.07-0.5)	74.2 (55.4-88.1)	88.2 (72.5-96.7)
Lactate	0.855 (0.781-0.950)	>5.9	81.5 (61.9-93.7)	89.5 (75.2-97.1)	7.74 (3.0-19.9)	0.21 (0.09-0.5)	84.6 (65.1-95.6)	87.2 (72.6-95.7)
Base Excess	0.915 (0.819-0.970)	≤-25	85.2 (66.3-95.8)	92.1 (78.6-98.3)	10.79 (3.6-32.3)	0.16 (0.06-0.4)	88.5 (69.8-97.6)	89.7 (75.8-97.1)
Anion Gap	0.868 (0.762-0.939)	>28	81.5 (61.9-93.7)	76.3 (59.8-88.6)	3.44 (1.9-6.3)	0.24 (0.1-0.5)	71.0 (52.0-85.0)	85.3 (68.9-95.0)

HCO_3: Bicarbonate, NPV: Negative likelihood ratio, NPV: Negative predictive values, PLR: Positive likelihood ratio, PPV: Positive predictive values.

DISCUSSION

In this study, 65 MP cases who visited the ED of a toxicology center over a 5-year period were analyzed. The in-hospital mortality rate was statistically higher in those who visited the ED late and had low GCS and respiratory distress at the time of arrival to the ED. In terms of laboratory, high anion gap metabolic acidosis and high lactate levels were associated with mortality in MP cases. Folate treatment had a statistically significant positive effect on mortality.

The incidence of MP is likely to be underestimated, given the difficulty of making an accurate diagnosis and the lack of diagnostic equipment such as format or methanol level. The mortality rate in MP cases remains high despite medical interventions such as ethanol, bicarbonate and hemodialysis, so clinicians continue to seek appropriate methods

to identify patients at high risk of poor outcomes and develop treatment modalities that will give the best prognosis [7,8].

Methanol poisoning cases occur as isolated episodes or epidemics in different geographies and periods [1,5,9]. In this study, a significant portion of MP cases (78.5%) consisted of patients in three different outbreaks (March 2017, March 2020, and December 2020). The last two MP outbreaks coincided with the COVID-19 pandemic as of the date of their outbreak [10].

After oral administration, methanol reaches peak concentration within 30 to 60 minutes [11]. In contrast, methanol metabolism is slow (8 mg·dl·h) and long latent periods of up to 96 hours can occur, especially if the antidote is ingested with ethanol [12,13]. In our study, the mortality rate in patients who were treated by visiting the ED within the first 24 hours following oral administration was considerably lower than in those who visited later.

Consistent with the literature, a high anion gap metabolic acidosis during the predialysis period was found in our study to be an important prognostic factor in MP cases [5]. Metabolic acidosis in MP has been associated with formic acid accumulation in the early stage [3,14]. In the next period, increased lactic acid production in tissues as a result of inhibition of mitochondrial cytochrome-c oxidase by formic acid, contributes to both anion gap and acidosis [2,15]. In our study, the group of non-survivors had higher median serum lactate values compared to the survivors. Decreased pH due to increased lactate production results in decreased renal excretion of formic acid and increased diffusion of formic acid across the blood-brain barrier [13]. This causes CNS depression [16]. In our study, the presence of low GCS and coma at the time of arrival to the ED was associated with increased mortality, consistent with the literature [8,17]. In our study, 19 (29.2%) of 65 patients were in a coma (GCS<8) when they arrived at the ED, and 16 of these patients died. Besides, as pH decreases, inhibition of cytochrome oxidase becomes stronger and cellular damage accelerates [18]. The putamen is highly susceptible to the resulting cytotoxic hypoxemia [19]. However, brain CT imaging is often normal when performed within the first 24 hours after methanol ingestion [20]. In our study, no pathology was detected in the brain CT and DW-MRI imaging performed at the time of arrival to the ED, however, intracranial hemorrhage was detected in five patients in the imaging performed in the later period. Although it is not routinely recommended in MP cases, neuroradiological imaging of patients who visit the ED with the complaint of changing consciousness is important.

Low Ph levels, low GCS and high formate levels have been reported among poor prognostic indicators. Our hospital cannot measure formate levels, however our study's relationship between folate treatment and mortality was statistically significant. This may be due to the effect of folate on formate metabolism in the early stages of poisoning. In addition, the anion gap can be used in centers where the formate level cannot be measured. Hovda et al. reported that anion gaps and serum formate concentrations were well correlated at admission [21]. Our study observed a higher anion gap in the non-survival group compared to the survivors. Anion and osmolar gaps (OG) can be used in diagnosing and triaging MP cases [21]. However, when calculating the osmolar gap in MP cases, the effect of ethanol, which is likely to be swallowed together with methanol and used in the treatment as an antidote, should not be overlooked. It has also been reported that OG decreases and AG increases as time progresses in MP [21]. The time factor must be taken into account when interpreting these examinations.

The primary purpose of RRT in MP cases is to rapidly remove both main alcohols and toxic acid metabolites. IHD is a preferred treatment modality over HDF because of its faster toxin clearance [22]. As in our study, HDF is generally preferred in hemodynamically unstable patients [23]. The mortality rate in patients who underwent HDF was higher in our study, than in patients who underwent IHD. The reason for this may be that HDF is preferred in patients for unstable before predialysis. Antidote treatment was administered to 86.1% of the patients in our study. Intravenous ethanol was administered to all patients who received antidote treatment except one, because ethanol is an antidote that we can easily access in our hospital compared to fomepizole. However, ethanol has some side effects such as sedation

and respiratory depression. In our study, a statistically significant relationship between the use of ethanol in treatment and mortality could not be established. Dialysis was performed on the patients who visit our ED shortly after starting ethanol treatment. Although ethanol treatment was continued during dialysis, the desired therapeutic level may not have been reached because the ethanol level could not be monitored [12, 24].

Study Limitations: First, this study was designed retrospectively and some patients for whom methanol poisoning was not suspected may have been overlooked. Second, there was a relatively limited number of MP patients and a limited number of cases had a laboratory-confirmed (methanol level >20 mg/deciliter) diagnosis of MP. Diagnosis of a significant group of patients is based on clinical features, other laboratory tests and blood gas analysis. Furthermore, the timing and quality of their interventions may differ.

CONCLUSION

According to the study, low GCS on arrival at the ED, delay in hospital visits, high anion gap metabolic acidosis and elevated lactate levels, were all associated with higher in-hospital mortality rates for MP patients. The use of folate can be considered in treating all MP patients due to its advantages on mortality.

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Different metabolic and clinical profiles between patients with pure Alzheimer dementia and epileptic Alzheimer dementia: a metabolic study

Saf Alzheimer Demansı ile Epileptik Alzheimer Demansı Hastaları Arasındaki Faklı Metabolik ve Klinik Profiller: Metabolik bir çalışma

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ABSTRACT

Aim: To investigate the clinical characteristics and cerebral FDG PET metabolisms of dementia patients who were also diagnosed with epilepsy and compare the differences with pure Alzheimer dementia patients.
Methods: In this case-control study, a total of 14 patients, 7 patients with pure Alzheimer disease as a control group and 7 age and gender-matched patients with Alzheimer disease and concomitant epilepsy as a study group, were included. Detailed neurocognitive battery and brain fludeoxyglucose positron emission tomography (FDG PET-CT) were performed for all subjects.
Results: In comparison of neurocognitive test scores, there was no significant difference between the study and control groups. However, geriatric depression scale scores were significantly lower in study group than the controls (p= 0.026). In cerebral FDG-PET CT profiles of subjects we detected significantly lower metabolism in left and right cerebellum, left lentiform nucleus, right thalamus and vermis in the study group (p=0.008, p=0.023, p=0.003, p=0.002, p=0.002, respectively). In the right parietotemporal cortex and right and left associative visual cortex, we found higher metabolism in the study group than controls (p=0.023, p=0.012, p=0.003, respectively).
Conclusion: Epileptic patients with Alzheimer's dementia may have distinct clinical and metabolic profiles, than pure Alzheimer's disease patients. Even if there is no difference in the neurocognitive clinical scores of the patients, depression and related functional abnormalities may be a biomarker of epileptic AD.

Key words: Alzheimer disease, epilepsy, FDG-PET CT, metabolism, depression

ÖZ

Amaç: Epileptik Alzheimer hastalarının klinik özelliklerini ve serebral FDG PET metabolizmalarını araştırmak ve saf Alzheimer demansı hastaları ile arasındaki farkları karşılaştırmaktır.
Yöntemler: Bu vaka-kontrol çalışmasına Alzheimer hastalığı olan 7 hastadan oluşan control grubu ve Alzheimer hastalığına eşlik eden epilepsisi olan 7 hastadan oluşan çalışma grubu olmak üzere toplam 14 hasta dahil edildi. Tüm katılımcılara ayrıntılı nörobilişsel bateri ve beyin florodeoksiglukoz pozitron emisyon tomografisi (FDG PET-CT) uygulandı.
Bulgular: Nörobilişsel test puanları karşılaştırıldığında, çalışma ve kontrol grupları arasında anlamlı bir fark yoktu. Ancak geriatrik depresyon ölçeği puanları çalışma grubunda kontrollere göre anlamlı derecede düşüktü (p= 0.026). Çalışma grubundaki olguların serebral FDG-PET BT profillerinde sol ve sağ serebellum, sol lentiform nükleus, sağ talamus ve vermiste anlamlı düzeyde daha düşük metabolizma saptadık (p=0,008, p=0,023, p=0,003, p=0,002, p =0,002, sırasıyla). Sağ parietotemporal korteks ve sağ ve sol birleştirici görsel kortekste, çalışma grubunda kontrollere göre daha yüksek metabolizma bulduk (sırasıyla p=0.023, p=0.012, p=0.003).
Sonuç: Alzheimer demansı olan epileptik hastalar, saf Alzheimer hastalarından farklı klinik ve metabolik profile sahip olabilir. Hastaların nörokognitif klinik skorlarında fark olmasa bile depresyon ve ilişkili fonksiyonel anormallikler epileptik AD hastaları için bir biyobelirteç olabilir.

Anahtar Kelimeler: Alzheimer hastalığı, epilepsi, FDG-PET BT, metabolizma, depresyon

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INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by extensive brain network alterations, implicated in several other neurological disorders. Epilepsy and depression are two of these conditions that may also be accompanied by a degree of cognitive impairment [1].

Some research suggests that elderly epilepsy patients are more likely to acquire cognitive impairment and eventually dementia [2,3]. This raises the issue of whether dementia causes seizures, or if both are caused by the same pathophysiological processes. This could be related to the fact that the neuropathological underpinning of seizures in Alzheimer's disease is a disproportional neuronal degeneration in distinct brain regions involving several changes at the cellular and molecular level, such as toxic accumulation of proteins, synaptic degeneration, circuit remodelling, and abnormal synchronization. This bidirectional relationship between epilepsy and dementia has been suggested by the observation that dementia patients appear to be at a higher risk of experiencing seizures [4].

Depression or major depressive disorder (MDD), the most common neuropsychiatric condition in AD, is also a risk factor for the development of AD, through the neurodegeneration in the brain [5-7]. It is likely that depression influences the risk of AD by diminishing the neuroprotective capability of the brain, hence accelerating the course of the disease. Nonetheless, it is also plausible that depression is an early sign of AD (8). However, compared to either AD or MDD alone, hospitalization rates are much greater when AD and MDD coexist. The exact process that causes depression in people with dementia is still not well understood.

Despite this, fundamental molecular abnormalities, such as an increase in plasma brain amyloid beta protein and neurofibrillary tangles of MDD patients have been observed [9-13]. In addition, an overactivation of the HPA axis, as well as neuroinflammation could be responsible for the occurrence of both disorders [14].

In spite of these encouraging findings, it has been found that there are no case reports or longitudinal studies that indicate a common pathophysiology between epilepsy, depression and dementia. In this study, our objective was to evaluate and contrast the clinical characteristics, cerebral FDG PET metabolism and clinical features of dementia patients, who also presented with epilepsy. To the best of our knowledge, no previous research has investigated the role of functional features, as well as the neurobehavioral outcomes associated with those pathologies, in dementia patients who have also been diagnosed with epilepsy and depression.

MATERIAL AND METHODS

Patient Selection: For this case-control study, a total of fourteen patients were included: seven patients with pure Alzheimer's disease and seven patients with Alzheimer's disease and concomitant epilepsy. Detailed neurocognitive batteries and brain fludeoxyglucose positron emission computerized tomographies (FDG PET-CT) were performed for all participants.

The study was approved by the Local Ethics Committee of Istanbul Medipol University (with the number E-10840098-772.02-2712, date 05.05.22) and followed the Helsinki Declaration principles. The participants were informed about the study and written consent was provided from all participants. The potential participants with a history of cranial trauma, intracranial operation, tumor or any lesion that may affect the metabolism of the central nervous system, those with drug or alcohol use, younger than fifty and older than eighty, were all excluded from the study.

Cognitive evaluation: Neuropsychological assessment of the participants was consisted of mainly attention and executive functions, memory, visuospatial functions, language and mood. Digit span and Stroop Test for attention and executive functions assessment, Verbal Memory Processes Test (VMPT) for memory assessment, Verbal Fluency and Boston Naming Test (BNT) for language assessment, Benton Face Recognition Test (BFRT) for evaluation of visuospatial functions, as well as the Geriatric Depression Scale for mood assessment and Mini Mental State Evaluation (MMSE) for global assessment, were applied to all participants.

Neuroimaging: Brain fludeoxyglucose positron emission tomography computerized tomography (FDG PET-CT) images were taken using a Philips Gemini TF PET/CT equipped with 16 slice computerized tomography. Patients with a glucose level lower than 160 mg/dl, and 18F FDG were administered intravenously at a dose of 0.1 mCi (3.7 MBq) / kg. After the injection, the patient had a rest quietly in a dimly lit room for minimum 30 minutes during the uptake phase. At 60 minutes after the injection, data was acquired and PET images were reconstructed with CT data for PET attenuation correction. The raw FDG-PET data was processed by the NeuroQ software (Version 3,5. Syntermed Inc., Atlanta, USA). Brain 18F-FDG PET images in axial, coronal, and sagittal slices and the quantitative results of NeuroQ analysis were visually evaluated by two blinded nuclear medicine physicians. The NeuroQ programme calculated the average pixel values in standardized regions of interest (ROI) and compared these counts with the control database. Finally, hypometabolic brain regions were significantly defined as a decrease of more than two standard degrees of regional brain metabolism.

Statistical Analyses: Behaviours of quantitative variables were expressed with centralization and measures of variance: Mean ± standard deviation (SD). The Fisher Exact Test was used to determine the differences in ratios or relationships between categorical variables. To show the behavioral differences of the group averages, the Mann-Whitney U-Test method was used where they did not meet the assumptions of normality and homogeneity. Statistical significance was determined as p = 0.05 for all cases. Statistical analyses were provided with the IBM SPSS (Statistics Package for Social Sciences for Windows, Version 21.0, Armonk, NY, IBM Corp.) package programme.

RESULTS

In this study, we evaluated the data of fourteen subjects consisting of seven (2 male/5 female) patients with Alzheimer Disease and Epilepsy as a study group and seven (5 male/ 2 female) patients with pure Alzheimer Disease as a control group. The mean age of the study group was 67.14 ± 9.08 years and similarly, the mean age of the control group was 61.71 ± 5.65 years; there was no statistically significant difference between the groups in terms of age and gender (p > 0.05, Table 1).

Table 1. Demographic Features of Subjects

Subjects		Study Group (AD + E)	Controls (AD)	p
Sex n (%)	F	5 (71.4%)	5 (71.4%)	1
	M	2 (28.6%)	2 (28.6%)	
Age		67.14 ± 9.08	61.71 ± 5.65	0.336
(Mean ± SD, Median Min–Max)		73 (54 - 75)	62 (53 - 72)	

p> 0.05 is significance

In comparison of neurocognitive test scores including MMSE, Digit Span, Stroop test, VMPT, Verbal Fluency, BFRT, BNT there was no significant difference between the study and control groups. However, geriatric depression scale scores were significantly lower in the study group than in the controls (p= 0.026, shown in Table 2).

Table 2. Comparison of Cognitive Test Scores Between Two Groups

Neurocognitive Battery	Study Group	Controls	P
Benton Facial Recognition Test	37.86 ± 5.15	43.4 ± 7.5	0.085(m)
	40 (30 - 44)	47 (30 - 47)	
Boston Naming Test	16.86 ± 3.08	18.14 ± 7.49	0.367(m)
	18 (12 - 20)	19 (7 - 27)	
Digit Span	5.0 ± 2.52	5.57 ± 2.7	0.795(m)
	5 (2 - 8)	5 (2 - 10)	
Geriatric Depression Scale	12.14 ± 4.15	5.33 ± 4.37	0.026(m)
	12.5 (7 - 18)	4 (0 - 12)	
MMSE	20.25 ± 1.5	15.0 ± 5.39	0.105(m)
	20 (19 - 22)	15 (7 - 23)	
Stroop Interference	106.5 ± 31.82	172.5 ± 95.08	0.8(m)
	106.5 (84 - 129)	160.5 (83 - 286)	
Verbal Fluence	8.29 ± 5.02	12.57 ± 11.39	0.949(m)
	9 (0 - 17)	7 (0 - 28)	
Verbal Memory Task Learning	43.43 ± 25.84	39.29 ± 20.34	0.902(m)
	33 (6 - 84)	42 (2 - 61)	
Verbal Memory Task Total Recall	9.57 ± 4.08	6.71 ± 5.53	0.326(m)
	10 (2 - 13)	6 (0 - 13)	

Stats: Mean ± SD/Median (Min–Max), (m) Mann Whitney U Test

In cerebral FDG-PET CT profiles of subjects, we detected significantly lower metabolism in left and right cerebellum, left lentiform nucleus, right thalamus and vermis in the study group

Table 3. Comparison of FDG-PET Profiles of Groups

Localisation	Study Group	Controls	P
Left Associative Visual Cortex	-0.25 ± 2.17	-5.55 ± 3.62	0.003(m)
	0.27 (-4.21 - 2.3)	-5.62 (-11.74 - 0.11)	
Left Caudate Nucleus	-0.17 ± 0.62	0.9 ± 1.52	0.252(m)
	-0.24 (-0.91 - 0.82)	0.49 (-1.02 - 3.16)	
Left Cerebellum	1.76 ± 1.23	3.93 ± 1.19	0.008(m)
	1.8 (0.04 - 3.56)	3.85 (2.34 - 5.99)	
Left Inferofrontal Cortex	-1.93 ± 1.58	-0.65 ± 1.61	0.142(m)
	-1.61 (-4.09 - -0.34)	-0.43 (-3.98 - 1.17)	
Left Inferolateroposterior Temporal cortex	-1.6 ± 1.53	-3.27 ± 1.88	0.091(m)
	-1.02 (-3.99 - -0.11)	-3.29 (-6.24 - -0.77)	
Left Inferior Parietal Cortex	-1.31 ± 2.05	-0.31 ± 2.72	0.47(m)
	-1.09 (-4.79 - 1.93)	-0.44 (-4 - 4.83)	
Left Lentiform Nucleus	0.04 ± 0.74	1.71 ± 0.96	0.003(m)
	-0.41 (-0.49 - 1.49)	1.76 (0.37 - 2.96)	
Left Medial Frontal Cortex	-0.59 ± 1.76	-1.86 ± 1.72	0.114(m)
	-0.2 (-4.34 - 0.69)	-1.45 (-4.8 - 0.7)	
Left Parietotemporal Cortex	-3.23 ± 2.07	-5.64 ± 2.21	0.071(m)
	-2.69 (-6.46 - -1.16)	-4.97 (-8.86 - -3.08)	
Right Associative Visual Cortex	0.83 ± 1.59	-3.87 ± 3.63	0.012(m)
	1.2 (-1.34 - 3.54)	-4.71 (-7.75 - 2.63)	
Right Cerebellum	1.4 ± 0.98	2.72 ± 1.14	0.023(m)
	1.81 (-0.01 - 2.49)	2.61 (1.13 - 4.67)	
Right Inferofrontal Cortex	-0.53 ± 2.57	0.69 ± 1.58	0.252(m)
	-1.91 (-2.74 - 4.2)	0.66 (-1.92 - 2.82)	
Right Inferoparietal Cortex	-0.2 ± 1.63	-1.46 ± 3.72	0.408(m)
	-0.21 (-2.42 - 1.96)	-1.46 (-6.65 - 3.94)	
Right Parietotemporal Cortex	-0.47 ± 1.75	-3.73 ± 2.95	0.023(m)
	-0.05 (-3.71 - 1.4)	-4.71 (-6.63 - 2.32)	
Right Posterior Cingulate Cortex	-2.34 ± 1.86	-3.62 ± 1.42	0.114(m)
	-2.07 (-5.87 - -0.45)	-3.8 (-6.42 - -1.87)	
Right Thalamus	0.44 ± 0.54	1.85 ± 0.82	0.002(m)
	0.49 (-0.27 - 1.38)	1.84 (0.62 - 2.89)	
Vermis	0.72 ± 1.83	3.21 ± 0.52	0.002(m)
	-0.12 (-1.6 - 3.23)	3.32 (2.53 - 4.09)	

Stats: Mean ± SD/Median (Min–Max), (m) Mann Whitney U Test

(p=0.008, p=0.023, p=0.003, p=0.002, p=0.002, respectively). In the right parietotemporal cortex and right and left associative visual cortex, we found higher metabolism in the study group than controls (p=0.023, p=0.012, p=0.003, respectively) (Table 3).

DISCUSSION

According to our findings, AD patients with epilepsy and high depressive scores showed relatively

increased metabolism in the parieto-temporal cortex, and right associative visual cortex, but a decreased metabolism in the cerebellum, vermis, left lentiform nucleus and right thalamus. Our findings contradict previous human data that indicated a significant overlap in areas associated with Alzheimer's disease and temporal lobe epilepsy pathophysiology, characterized by critical hippocampal metabolic and structural changes that are also connected to memory loss or dementia symptoms, even in the absence of seizures [15]. However, while histological diagnosis in humans is challenging and can only be done post-mortem,

detecting dynamic brain alterations in AD patients with concurrent epilepsy problems is conceivable [3]. Based on this, the clinical, neuropsychometric assessment and neuroimaging techniques, have astounding importance and continue to be exciting ways to determine whether shared and unshared alterations among these disorders are related to clinical presentation and prognosis.

Various functional and structural abnormalities might also play a part in depression in the AD. For instance, data from magnetic resonance imaging (MRI) has demonstrated that older people who suffer from depression symptoms have degeneration in both the frontocortical and limbic circuits, which are similar networks that are compromised when AD starts in its earliest stages [16-19]. It is possible that the high incidence of major depressive disorder in Alzheimer's disease can be explained by the role of corticolimbic dysfunction in the development of affective disorders [20]. Notable is the discovery that a disturbance of corticolimbic networks is essential for fundamental facets of cognitive and emotional functions. Despite this, there is not yet sufficient evidence to demonstrate a causal association between atrophy in these brain regions and the co-occurrence of these two disorders [21]. Our research found that Alzheimer's patients with epilepsy showed specific regions linked to depression and epilepsy pathogenesis, in addition to an Alzheimer's disease-specific metabolic pattern consistent with the literature [22]. Common regions included crucial areas (the left parietotemporal, left Broca, left post cingulate, left post temporal, left sup lateral and right temporal right sensorimotor cortical regions), all of which have been attributed to Alzheimer's disease. Our findings of overlapping regions in AD and AD+Epilepsy groups are consistent with recent clinical data showing reduced resting-state activity and functional connectivity within the default mode network in patients with epilepsy or Alzheimer's disease [23]. Within this framework, we found substantial parallel changes in both groups that are pertinent to the research on Alzheimer's disease. For example, Alzheimer's disease patients who also had epilepsy, were discovered to exhibit patterns of lower cortical and crucial regional hypometabolism, which are not common in pure Alzheimer's disease patients but observed more commonly in patients with epilepsy and depression. In accordance with this, the prevalence of geriatric depression in the AD and epilepsy groups was significantly higher than in the pure AD group. Hence, decreased metabolism in the left lentiform nucleus and increased metabolism in the post temporal regions, may indicate a common cortico-limbic axis impairment in MDD, and the existence of some hypermetabolic areas, which are uncommon in Alzheimer's disease, may be a signal of epilepsy-associated elevated brain metabolism. In a comparable manner, significant hypometabolism in the cerebellum, as well as increased activity in the visual association and parietotemporal cortices, are consistent with prior research on epilepsy, AD and depression [24].

To the best of our knowledge, AD patients who present with both seizures and depression are extremely rare, and no previous research has employed FDG PET to detect shared and unshared regions across these comorbid illnesses.

Limitations: Our study had offered valuable metabolic and clinic information for alternative treatment options in AD and epilepsy [25]. Nevertheless, the sample size was quite limited. The inability to pinpoint the precise epileptic origin of patients may be seen as another limitation of our work.

CONCLUSION

Our findings show that AD and epilepsy patients have a more distinct clinical and metabolic profile than pure AD patients, and that depression and associated functional abnormalities may be a biomarker of AD patients with concomitant epilepsy.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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RESEARCH ARTICLE

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Comparison of Clinical Outcomes on Different Treatment Methods for Patients with Lateral Epicondylitis

Lateral Epikondilitli Hastalarda Farklı Tedavi Yöntemlerinin Klinik Sonuçlarının Karşılaştırılması

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ABSTRACT

Aim: In our study, the effectiveness of steroid injection therapy, extracorporeal shock wave therapy (ESWT) and splint use in the treatment of lateral epicondylitis, were compared.
Methods: A total of 97 patients (28 males, 57 females, mean age: 47 years) with a clinical diagnosis of lateral epicondylitis were included in the study. The patients were divided into three treatment groups. Steroid injection was applied to 30 patients, ESWT treatment to 28 patients, and bandage treatment to 29 patients. Patients were evaluated with Visual analog scale (VAS) and Disabilities of the Arm, Shoulder and Hand (DASH) scores before and after treatment.
Results: A decrease in VAS and DASH scores and clinical improvement compared to pre-treatment were observed in all three groups. Although positive results were obtained with all three treatment methods, we found that the most statistically significant treatment method was steroid injection. Better results were obtained in the group that received steroid injection with the peppering technique. ($p<0.05$).
Conclusion: The results of this study showed that local steroid injection, ESWT application and bandage treatment may be beneficial in the short term in the treatment of patients with lateral epicondylitis. However, it was evaluated that the best improvement in scores was obtained with local steroid injection with the peppering technique, whereas the least improvement was obtained with bandage treatment.

Keywords: Lateral epicondylitis, Elbow, Tendinitis, Tennis elbow

ÖZ

Amaç: Çalışmamızda lateral epikondilit tedavisinde steroid enjeksiyon tedavisi, ekstrakorporeal şok dalga tedavisi (ESWT) ve splint kullanımının etkinliği karşılaştırıldı.
Yöntemler: Klinik olarak lateral epikondilit tanısı alan toplam 97 hasta (28 erkek, 57 kadın, ortalama yaş: 47) çalışmaya dahil edildi. Hastalar üç tedavi grubuna ayrıldı. 30 hastaya steroid enjeksiyonu, 28 hastaya ESWT tedavisi, 29 hastaya bandaj tedavisi uygulandı. Hastalar tedavi öncesi ve sonrası Visual analog scale (VAS) ve Disabilities of the Arm, Shoulder and Hand (DASH) skorları ile değerlendirildi.
Bulgular: Her üç grupta da tedavi öncesine göre VAS ve DASH skorlarında azalma ve klinik düzelme gözlendi. Her üç tedavi yönteminde de olumlu sonuçlar elde edilmesine rağmen istatistiksel olarak en anlamlı tedavi yönteminin steroid enjeksiyonu olduğunu saptadık. Biberleme (peppering) tekniği ile steroid enjeksiyonu yapılan grupta daha iyi sonuçlar alındı. ($p<0.05$).
Sonuç: Bu çalışmanın sonuçları lateral epikondilitli hastaların tedavisinde lokal steroid enjeksiyonu, ESWT uygulaması ve bandaj tedavisinin kısa dönemde faydalı olabileceğini göstermiştir. Ancak skorlarda en iyi iyileşmenin biberleme tekniği ile lokal steroid enjeksiyonu, en az iyileşmenin ise bandaj tedavisi ile elde edildiği değerlendirildi.

Anahtar kelimeler: Lateral epikondilit, Dirsek, Tendinit, Tenisçi dirseği

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INTRODUCTION

Lateral epicondylitis (LE) is known as tennis elbow. It is characterized by pain and tenderness around the lateral epicondyle at the elbow and it usually occurs as a result of repetitive use of the wrist extensor group muscles [1]. The diagnosis of LE is often made by anamnesis and physical examination. These patients often describe pain when lifting objects and using the forearm. The incidence of LE is 1 to 3% and it is more common among women. Although etiological factors, such as microtear of the musculotendinous part of the extensor carpi radialis brevis or non-inflammatory tendinosis of the lateral epicondylitis are blamed, microscopically, it is evaluated as tendinosis with widespread fibrosis in the lateral epicondyle region, vascular hyperplasia and irregular collagen alignment [2,3]. Non-operative treatment is recommended as initial therapy for LE and is considered successful in the majority of patients [2].

There are many various options available in the treatment of lateral epicondylitis. Among these, rest, orthosis use, physical therapy modalities, nonsteroidal anti-inflammatory drugs (NSAID) and injections (corticosteroid, autologous blood, platelet-rich plasma, prolotherapy), are the commonly used treatments [4]. Extracorporeal shock wave therapy (ESWT) is a method that is also frequently used in treatment, despite varying results in the current literature [5]. Corticosteroid injection is currently among the most widely used treatments and provides significant short-term relief of symptoms [6,7]. There are also studies on the effectiveness of various splints in the treatment of lateral epicondylitis [4,8].

There are many studies on the efficacy and/or comparative results of treatment modalities [2-8]. However, there is insufficient objective evidence and little consensus on which treatment is more effective [4,7]. Moreover, to the best of our knowledge, there are no studies which have evaluated and compared cortisone, ESWT and splint treatments together.

In this study, we aimed to compare the efficacy of treatment in patients who received ESWT, corticosteroid or a forearm band retrospectively.

PATIENTS AND METHODS

Patients who applied to our clinic with the complaint of lateral elbow pain and diagnosed with lateral epicondylitis by anamnesis and physical examination, were evaluated. Patients with complaints of increased pain with palpation of the lateral epicondyle, grip or resistant extension of the wrist for at least six weeks were included in the study. After providing information about the risks of the treatment methods based on the study, their effect on the quality of life and the average treatment process, the choice of treatment was left to the patient. Patients who did not receive any treatment despite having pain in the previous six weeks were included in the study, but the following exclusion criteria were applied: patients with cervical radiculopathy, traumatic elbow joint pathology, arthritis, peripheral nerve compression neuropathy, previous elbow surgery and systemic or neurological disorders in the affected side upper extremity. In addition, patients who had been treated for an elbow pain or had a corticosteroid injection for elbow pain in the previous three months were also excluded from the study. Ethics committee approval required for this study was obtained from the Local Ethical Committee. (Number: 10354421-2022/04-02).

All patients were informed about the procedures to be applied and their consent was obtained. Our study was carried out in accordance with the Declaration of Helsinki.

The patients included in the study were divided into three groups as steroid injection, physical therapy (ESWT) and splint group. All patients were evaluated with VAS and DASH scores before and after the application. No additional treatment method was applied to the patients in all three groups except the treatment applied in their own group.

Treatment protocol

For patients in the corticosteroid group (group 1), a single dose of 0.5 mL of corticosteroid (betamethasone dipropianate 6.43 mg, betamethasone sodium phosphate 2.63 mg) and 0.5 mL of local anesthetic (2% lidocaine, epinephrine) was applied in the painful epicondyle area under sterile conditions; the most painful

point was determined and the tissue with multiple stretches (peppering technique) was applied (Figure 1).

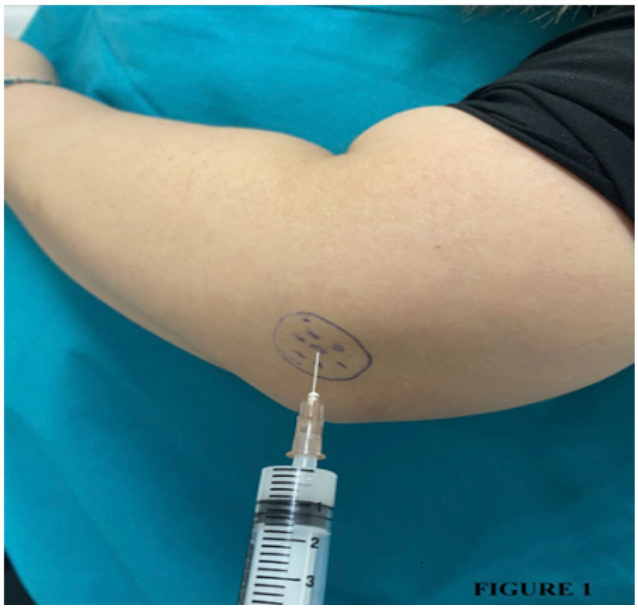

Figure 1: İnjection with peppering technique

The same protocol was applied to the patients in the ESWT group (group 2) as 1.6 bar, 15.0 Hz, 2000 beats, one day/week, for a total of three weeks (Figure 2). ESWT procedure was performed with Vibrolith Ortho brand device.

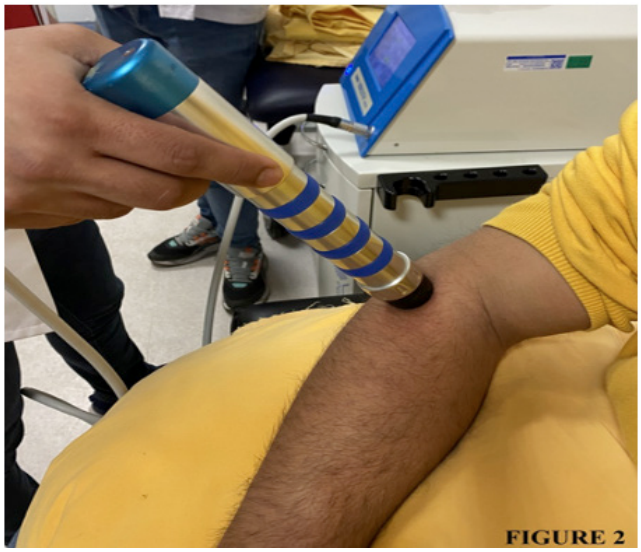

Figure 2: ESWT therapy in physiotherapy laboratory

Lateral epicondylitis bandage was applied to the patients in the splint group (group 3). The epicondylitis bandage was applied to the forearm 4-5 cm distal to the epicondyle. Bandages were used for 6 weeks. They were told to put on the bandage when they woke up and only remove it at night in the process (Figure 3). Scoring was done by providing controls to the patients once before the treatment and once every two weeks after the treatment.

Figure 3: Patient with lateral epicondylitis bandage

Statistical method

Data was evaluated with the SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)). Continuous variables were given as mean ± standard deviation, median (25th to 75th percentiles (IQR), mimum and maximum values, and categorical variables were given as numbers and percentages. The Shapiro Wilk test was used to examine the conformity of the data to the normal distribution. When the parametric test assumptions were not met, the Kruskal-Wallis's analysis of variance was used to compare independent group differences. The Dunn Test was used for pairwise analyses in studies with statistically significant differences. Calculation of delta values was made using the difference values obtained between measurements. Examination of the normal distribution in dependent group examinations was done by using delta values. In dependent group comparisons, when parametric test assumptions were provided, paired samples t test was used; when parametric test assumptions were not met, the Wilcoxon signed rank test was used. In addition, delta values and Cohen d effect size values were used in the comparison of the changes between the three groups. Differences between categorical variables were analyzed with the Chi-square test. In all studies, $p<0.05$ was considered statistically significant.

RESULTS

Results of 97 patients, 29 (29.89%) male and 58 (59.79%) female, were evaluated. The mean age of the patients was 47 years. The right side was affected in 55 (56.70%) of the patients, and the left side was affected in 42 (43.29). There was no statistically significant difference between the groups in terms of age and gender. However, in the examination made according to the parties, it was seen that there was a statistically significant difference between the three groups. The rate of occurrence on the right side in the steroid group was statistically significantly higher than in the Splint group (Table 1).

Table 1.

group		1(steroid)	2(ESWT)	3(Bandage)	p
side	Right	23 (%76,7)	19 (%67,9)	13 (%44,8)	0.033* (cs=6.811)b
	Left	7 (%23,3)	9 (%32,1)	16 (%55,2)	
gender	Woman	19 (%63,3)	17 (%60,7)	22 (%75,9)	0.427 (cs=1.7)
	Male	11 (%36,7)	11 (%39,3)	7 (%24,1)	
age	A.M ± S.D	48,2 ± 7,64	46,21 ± 7,34	46,76 ± 8,28	0.758 (kw=0.555)
	Med (IQR)	46 (43 - 54)	47 (40,25 - 50)	49 (40 - 53,5)	
	min - max	37 - 75	34 - 64	30 - 61	

*p<0.05 statistically significant difference; A.M: Arithmetic mean; S.D: standard deviation; Med (IQR): Median (25th-75th percentiles); min – max: Minimum – maximum; b: Significant difference between 1st and 3rd groups, cs: Chi-Square test; kw: Kruskal Wallis Variance Analysis;

In the DASH1 examination, there was a statistically significant difference between the three groups. The values of the Splint Group were found to be significantly lower than the values of the Steroid and ESWT groups. No statistically significant difference was found between the three groups in the DASH2 examination (Table 2). It was observed that the difference (delta) values obtained from DASH1 and DASH2 measurements showed statistically significant differences between the three groups. The values of the Splint Group were found to be significantly lower than the values of the Steroid and ESWT groups. The change in the splint group was significantly less than in the other groups (Table 2).

When the within-group changes of DASH examinations were examined, it was seen that the changes before and after the three groups were statistically significant. It is seen that the 2nd measurement values in all three groups showed a significant decrease compared to the 1st measurement. When the changes in each group were examined with the Cohen effect size, it was seen that Cohen d=7.18 in the steroid group, Cohen d=0.87 in the ESWT group and Cohen d=4.36 in the Splint group. It was seen that the most effective change was in the Steroid group and the lowest change was in the ESWT group (Table 2).

In the DASHD examination, there was a statistically significant difference between the 3 groups. The values of the Splint Group were found to be significantly lower than the values of the Steroid and ESWT groups (Table 2).

In the VAS1 examination, there was a statistically significant difference between the three groups. The values of the Splint Group were found to be significantly lower than the values of the Steroid and ESWT groups. No statistically significant difference was found between the three groups in the VAS2 examination (Table 2).

It was observed that the difference (delta) values obtained from VAS1 and VAS2 measurements showed statistically significant differences between the three groups. The values of the Splint Group were found to be significantly lower than the values of the Steroid and ESWT groups. The change in the splint group was significantly less than in the other groups (Table 2).

When the intra-group changes of VAS examinations were examined, it was seen that the changes before and after were statistically significant in all three groups. It is seen that the 2nd measurement values in all three groups showed a significant decrease compared to the 1st measurement. When the changes in each group were analyzed with the Cohen effect size, it was seen that it was Cohen d=0.880 in the steroid group, Cohen d=0.879 in the ESWT group and Cohen d=0.887 in the Splint group. It was seen that the most effective change was in the Splint group and the lowest change was in the ESWT group. Considering the effect sizes, it can be said that the changes in the groups do not show a significant clinical difference (Table 2).

In the VASD examination, it was observed that

Table 2.

group		Steroid	ESWT	Splint	p
DASH1	A.M ± S.D	74,25 ± 7,26	77,59 ± 5,39	61,03 ± 10,77	0.0001* (kw=32.810)bc
	Med (IQR)	73,75 (68,78 - 81,7)	77,9 (74,6 - 81,48)	60 (54,59 - 67,92)	
	min - max	62,5 - 85,8	62,5 - 88,3	43,33 - 82,5	
DASH2	A.M ± S.D	9,21 ± 8,8	14,83 ± 13,4	10,42 ± 5,24	0.147 (kw=3.839)
	Med (IQR)	7,9 (0 - 15,2)	14,2 (4,4 - 22,3)	10 (6,67 - 12,5)	
	min - max	0 - 31,7	0 - 63,3	2,5 - 26,23	
In-group p		0.0001* (t=39.309)	0.0001* (z=-4.623)	0.0001* (t=23.482)	
Delta DASH	A.M ± S.D	65.03 ± 9.06	62.76 ± 15.25	50.62 ± 11.61	0.0001* (kw=23.834)bc
	Med (IQR)	65.85 (57.9 - 72.5)	64.95 (53.13 - 73.9)	50.83 (45.84 - 55.84)	
	min - max	43.3 - 85.8	5.9 - 88.3	17.1 - 73.33	
DASHD	A.M ± S.D	65,03 ± 9,06	62,76 ± 15,25	50,62 ± 11,61	0.0001* (kw=23.834)bc
	Med (IQR)	65,85 (57,9 - 72,5)	64,95 (53,13 - 73,9)	50,83 (45,84 - 55,84)	
	min - max	43,3 - 85,8	5,9 - 88,3	17,1 - 73,33	
VAS1	A.M ± S.D	9,3 ± 0,79	8,61 ± 1,13	6,07 ± 1,25	0.0001* (kw=53.086)bc
	Med (IQR)	9 (9 - 10)	9 (8 - 9,75)	6 (5 - 7)	
	min - max	7 - 10	6 - 10	3 - 8	
VAS2	A.M ± S.D	1,27 ± 1,6	0,96 ± 0,92	0,76 ± 0,91	0.358 (kw=2.057)
	Med (IQR)	1 (0 - 2)	1 (0 - 2)	1 (0 - 1)	
	min - max	0 - 8	0 - 2	0 - 4	
In-group p		0.0001* (z=-4.822)	0.0001* (z=-4.656)	0.0001* (z=-4.775)	
Delta VAS	A.M ± S.D	8.03 ± 1.52	7.64 ± 1.25	5.31 ± 0.97	0.0001* (kw=48.623)bc
	Med (IQR)	8 (7 - 9)	8 (7 - 8)	5 (5 - 6)	
		2 - 10	6 - 10	3 - 7	
VASD	A.M ± S.D	8,03 ± 1,52	7,64 ± 1,25	5,31 ± 0,97	0.0001* (kw=48.623)bc
	Med (IQR)	8 (7 - 9)	8 (7 - 8)	5 (5 - 6)	
	min - max	2 - 10	6 - 10	3 - 7	

*p<0.05 statistically significant difference; A.M: Arithmetic mean; S.D: standard deviation; Med (IQR): Median (25th-75th percentiles); min – max: Minimum – maximum; b: Significant difference between 1st and 3rd groups c: Significant difference between the 2nd and 3rd groups, kw: Kruskal Wallis Variance Analysis; t: Paired samples t test; z: Wilcoxon Signed Rank test

there was a statistically significant difference between the three groups. The values of the Splint Group were found to be significantly lower than the values of the Steroid and ESWT groups (Table 2).

DISCUSSION

The main results of this study show that LE patients benefit from all three treatments. However, considering the average recovery scores, it was found that the least effective method was the epicondylitis bandage treatment.

There are many studies on the efficacy and/or comparative results of treatment modalities [2-8]. Although there are a number of methods for the conservative treatment of lateral epicondylitis, the evidence on the effectiveness of treatment methods is insufficient due to methodological differences between studies [9]. Also, there is insufficient objective evidence and consensus on which treatment is more effective [4,7].

In the literature, there are mostly reports on the results of steroid injection, and it is reported that the results of short-term treatment are particularly successful [6,7]. Tonks JH et al. [10], based on the results of their prospective randomized controlled trial, advocate steroid injection alone as the first treatment option in patients presenting with tennis elbow and demanding a rapid return to daily activities [9]. However, the method of administration of steroid injection in the lateral epicondylitis also seems important. Many studies have reported that injection with the peppering technique (multiple injections into the sensitive area after the needle insertion, injection without leaving the skin, withdrawal, redirection and repositioning),

is more effective than a single point injection [11,12,13]. Altay at al. reported that injection with the peppering technique was a reliable method in one-year follow-up in their study in which they compared local anesthetic (lidocaine) alone with the combination of lidocaine and triamcinolone, and applied the peppering technique [11]. Okçu et al. evaluated the clinical results of single injection and peppering injection in patients who applied betamethasone and 1 ml prilocaine combination with DASH Turkish score [12]. As a result, they stated that the late treatment success in lateral epicondylitis depends on the injection technique rather than the local effect of the corticosteroid, and the peppering technique gives long-term and more effective results. Doğramacı et al. evaluated the results with VAS and satisfaction score at the 3rd week and 6th month in their prospective randomized studies in which they applied 1 mL triamcinolone and 1 mL lidocaine combination as a single injection, the same combination with the peppering technique and lidocaine alone with the peppering technique [13]. The authors reported that the peppering technique of corticosteroid injection was associated with the best results. In our study, the most significant improvement was observed in the DASH and VAS scores after the application, compared to the pre-application in the steroid group made with the peppering technique.

In addition to many treatment methods, non-operative measures such as extracorporeal shock wave therapy, have been extensively evaluated in recent years. Various studies have reported that ESWT is successful in the treatment of lateral epicondylitis. [5,9,14,15]. Guler et al. evaluated the results in ESWT and placebo patients according to VAS and clinical results. They reported that the VAS results were significantly better in the ESWT group, but the clinical results did not differ significantly [5]. Yuruk et al. divided the patients with lateral epicondylitis into two groups as exercise and ESWT, placebo and exercise, and then applied 2000 beats per week to the ESWT group for a total of three sessions. Patients were evaluated at six and twelve weeks at the end of treatment. The authors reported that although VAS scores were similar in both groups, the ESWT group was significantly better in terms of comprehension and functionality [9]. Erdem et al. reported that patients diagnosed with lateral epicondylitis had better VAS and clinical scores compared to the control group, in which they applied three sessions of ESWT treatment, once every 2000 beats a week [15].

In our study, the protocol was applied to the patients in the ESWT group for a total of three weeks, with 2000 beats, once a week. It was observed that the post-application scores of the patients improved significantly compared to the pre-application scores.

Although some studies have presented results regarding the short-term benefits of splinting, there is insufficient evidence of long-term benefit compared to other treatment modalities [16]. Moreover, it is stated that long-term splint applications may cause negative consequences such as forearm muscle weakness and atrophy [14]. They stated that corticosteroid, autologous blood and prolotherapy injections may be beneficial in the treatment of LE. However, the authors reported that the use of wrist splints did not provide an increase in grip strength and functional improvement, although it reduced pain [4]. Bisset LM et al., in their study where they compared the effectiveness of two different splints, applied a counterforce brace applied to the forearm and forearm-elbow. They stated that both bandage applications had a positive effect in the short term. However, the authors stated that the forearm bandage was sufficient [17]. Belhan and Karakurt, in their study comparing lateral epicondyle bandage and steroid injection in patients with LE, reported that steroid injection was more effective than lateral epicondyle bandage [18].

In our study, epicondylitis bandage was applied to the forearm from 4-5 cm distal to the epicondyle in patients in the splint group. Although there was an improvement in the scores after the application compared to prior, the least significant improvement was observed in the bandage group compared to the other treatment groups.

LE usually occurs between the ages of 35-50 and affects men and women equally [9]. However, it has been stated that female gender, dominant side and manual labour are important risk factors for lateral epicondylitis [19]. In our study, there was no significant difference between the genders. There was, however, a statistically significant

difference in terms of sides in our study. We did not investigate whether the affected side of the patients was dominant and the statistical difference in terms of parties may be related to this fact.

Although many treatment methods have been described in the treatment of lateral epicondylitis, the most important problem regarding the frequently used treatments such as steroid, ESWT and splint is that there does not exist a complete consensus in the literature on the dosage, namely steroid applications in different doses and active ingredients, and application method of these treatments [2-9,12-17]. Similarly, we could not find any application concensus on issues such as ESWT frequency, dose, number of strokes and duration. Similarly, when studies on the results of splint treatment are carefully examined in the literature, it is seen that different splints, bandages, etc. are used. Different corticosteroids and different doses of administration [20], betamethasone [12], triamcinolone [13] or methylprednisolone [21] have been reported in the literature. There are different splint applications [4,17] and finally ESWT applications at different durations and doses [5,9,15]. It is therefore very challenging to make comparisons due to methodological differences between studies in the literature.

Limitations: The limitations of this study are that we only researched the short-term results and did not perform a dominant-side research in the study. The fact that the study was not randomized prospective may also be a limitation.

Conclusion: The results of this study show that local steroid injection, ESWT application and bandage treatment may be beneficial in the short term, in the treatment of patients with lateral epicondylitis. However, it was evaluated that the best improvement in scores was obtained with local steroid injection with the peppering technique, whereas the least improvement was obtained with bandage treatment.

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Ethics Committee Approval: The study was approved by the Alanya Alaaddin Keykubat University Faculty of Medicine Clinical Research Ethics Committee, (Document date and number: 10354421-2022/04-02).

ORCID and Author contribution: **A.A. (0000-0002-9507-3178):** Data collection, Analysis and Interpretation, Literature search. **A.G. (0000-0002-9012-8053):** Statistical Analysis, Manuscript Writing, Critical Review. **A.A. (0000-0001-5797-1287):** Concept and design, Critical Review, Supervision.

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RESEARCH ARTICLE

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Orbital and Ocular Adnexal Lymphomas: A Retrospective Single Center Study

Orbital ve Oküler Adneksiyal Lenfomalar: Retrospektif Tek Merkezli Çalışma

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ABSTRACT

Aim: To evaluate and present the clinical and histopathologic features of patients with orbital and adnexal lymphoma.
Methods: Eight patients who had histologically proven orbital and adnexal lymphoma between 2011 and 2021 were evaluated retrospectively. The clinical appearance, age, sex, imaging, tumor location, treatment methods, pathologic diagnosis, and systemic features of the patients were obtained from patient files.
Results: The mean age of the patients was 59.1 (range, 42-79) years. Six of the patients were male and two were female. Painless mass and orbital swelling were the most common first signs and symptoms in the patients. The magnetic resonance imaging findings demonstrated unilateral involvement in six patients and bilateral involvement in two patients. Intraorbital location in three patients (behind the orbital septum), lid location in two patients (eyelids in front of the orbital septum), conjunctival involvement in one patient, and lacrimal gland involvement in two patients were detected. All cases were reported as non-Hodgkin B-cell lymphoma [primary extranodal marginal lymphoma of the mucosa-associated lymphoid tissue (n=5), diffuse large B-cell lymphoma (n=2), follicular lymphoma (n=1)].
Conclusion: Orbital lymphomas can be seen more frequently among orbital tumors and clinical findings vary according to the location in the orbit. Ophthalmologists should be attentive to orbital swellings and consider orbital and ocular adnexal lymphomas among differential diagnoses.

Keywords: lymphoma; orbital diseases; non-Hodgkin lymphoma

ÖZ

Amaç: Orbital ve adneksiyal lenfomalı hastaların klinik ve histopatolojik özelliklerini değerlendirmek ve sunmak.
Yöntemler: 2011-2021 yılları arasında histolojik olarak orbital ve adneksiyal lenfoma saptanan sekiz hasta retrospektif olarak değerlendirildi. Hastaların klinik görünümü, yaşı, cinsiyeti, görüntülemesi, tümör lokalizasyonu, tedavi yöntemleri, patolojik tanıları ve sistemik özellikleri dosyalardan elde edildi
Bulgular: Hastaların yaş ortalaması 59.1 (dağılım 42-79) idi. Hastaların 6'sı erkek, 2'si kadındı. Hastalarda ağrısız kitle ve orbital şişlik en sık görülen ilk belirti ve bulguydu. Manyetik rezonans görüntüleme bulgularında 6 hastada unilateral, 2 hastada bilateral tutulum gösterdi. 3 hastada intraorbital yerleşim (orbital septum arkası), 2 hastada göz kapağı yerleşimi (göz kapakları orbital septum önünde), 1 hastada konjonktival, 2 hastada gözyaşı bezi tutulumu tespit edildi. Tüm vakalar patolojik incelemede Non-Hodgkin B hücreli lenfoma [Mukoza ile ilişkili lenfoid dokunun primer ekstranodal marjinal lenfoması (5 hasta), diffüz büyük B hücreli lenfoma (2 hasta), foliküler lenfoma (1 hasta)] olarak rapor edildi.
Sonuç: Orbita tümörleri nadir olmakla birlikte bunlar arasında orbital lenfoma daha sık görülebilmekte ve orbitadaki lokalizasyona göre klinik bulgular değişmektedir. Göz hekimleri orbital şişliklere karşı dikkatli olmalı ve ayırıcı tanılar arasında orbital ve oküler adneksiyal lenfomaları düşünmelidir.

Anahtar kelimeler: Lenfoma, orbita hastalıkları, Non-Hodgkin lenfoma.

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Introduction

Orbital and ocular adnexal lymphomas are malignant lymphoid neoplasms that develop as primary or secondary tumors in the orbit, conjunctiva, lacrimal gland, lacrimal sac, and eyelid [1,2]. It is the most common adult orbital malignancy, accounting for approximately 10% of all orbital tumors and 2% of all nodal and extranodal lymphomas [3,4]. Although most orbital lymphomas are B-cell non-Hodgkin lymphomas; T-cell lymphomas, Burkitt lymphoma, and Hodgkin lymphoma have also been reported in the literature [5-8]. Differential diagnoses include inflammatory lesions, vascular tumors, lacrimal gland tumors, neurogenic tumors, myogenic tumors, and metastatic tumors [3-9].

Due to the increasing incidence of lymphomas of the orbit and adnexia and their progression, if not treated appropriately, it is important to investigate the frequency of distribution according to age, diagnosis, and treatment methods. Our study aimed to evaluate and report the clinical and histopathologic findings of patients with orbital and adnexal lymphoma.

Materials and Methods

This retrospective study received approval from the Ethics Committee of Cukurova University and was adherent to the tenets of the Declaration of Helsinki. All cases diagnosed as orbital or adnexal lymphoma in Cukurova University Faculty of Medicine between January 2011 and May 2021 were analyzed retrospectively. The demographic characteristics and clinical and histopathologic findings of eight patients with orbital or ocular adnexal lymphoma were evaluated. Incisional biopsy was performed in all patients after routine eye examinations. Tissue samples were fixed in 4% formalin solution and sent for histopathologic examination. Patients diagnosed as having lymphoma as a result of the biopsy were included in the study.

Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans were evaluated for systemic involvement to determine the location of the tumor. Systemic investigation of the patients was performed by the Internal Medicine-Oncology clinic. In the follow-up of the patients, the clinical appearance, age, sex, imaging, tumor location, treatment methods, pathologic diagnosis, and systemic features were examined, retrospectively.

Results:

The mean age of the patients was 59.1 (range, 42-79) years. Six patients were male and two were female. Painless mass and swelling in the eye were the most common first signs and symptoms in the patients (Figures 1 and 2). In the ophthalmologic examination findings of the patients, proptosis, eyelid lesions, chemosis, salmon patch appearance in the conjunctiva, decreased visual acuity, epiphora, limited eye movements, ptosis, pain, strabismus, and optic nerve compression were observed. The MRI findings demonstrated unilateral involvement in six patients and bilateral involvement in two patients (Figure 3).

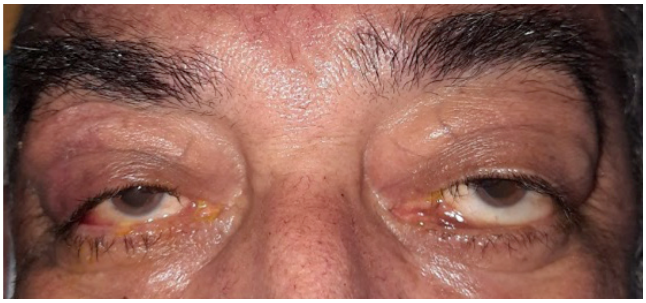

Figure 1. The patient had complaints of mass and swelling in both eyes.

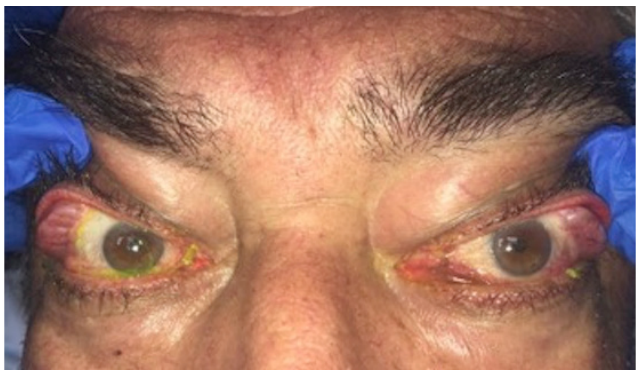

Figure 2. Bilateral lacrimal gland involvement was observed.

The diagnosis was made through incisional biopsies in all patients and evaluating their histopathologic features (Figure 4). All cases were reported as non-Hodgkin B-cell lymphoma; primary extranodal marginal lymphoma of the mucosa-associated lymphoid tissue was observed in five patients, diffuse large B-cell lymphoma in two patients, and follicular lymphoma in one patient. Intraorbital location in three of the eight

patients (behind the orbital septum), lid location in two patients (eyelids in front of the orbital septum), conjunctival involvement in one patient, and lacrimal gland involvement in two patients were detected (Table 1). Orbital disease was primarily observed in eight patients. One patient with conjunctival involvement had a salmon patch appearance (Figures 5 and 6). The mean follow-up period of the patients was 15.8 (range, 6-48) months. Complete regression was observed in all patients with chemotherapy and/or radiotherapy, and no recurrence was observed in the follow-up. The treatment protocol was arranged by the Oncology Department according to the subtype and location of the disease (Table 1).

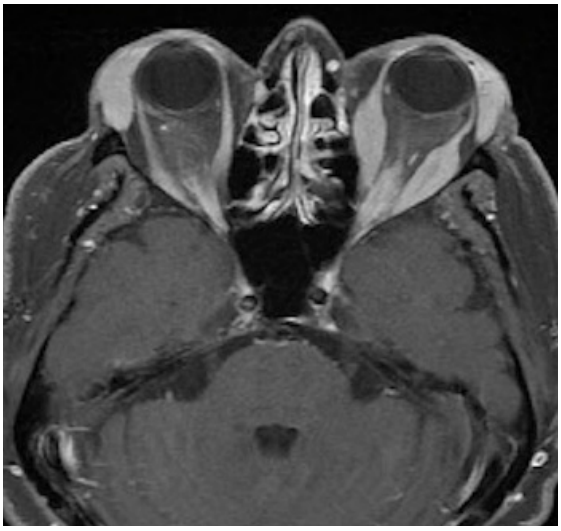

Figure 3. Bilateral symmetrical exophthalmos, hypertrophy in the periorbital muscles, and hypertrophy in the lacrimal glands were observed in magnetic resonance imaging.

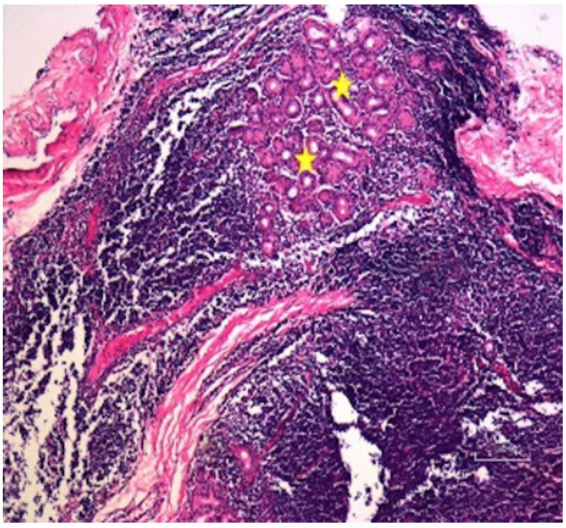

Figure 4. Areas of dense lymphoid infiltration and lacrimal gland ducts with asterisks were visible (hematoxylin-eosin, x100) in the pathological evaluation of the biopsy.

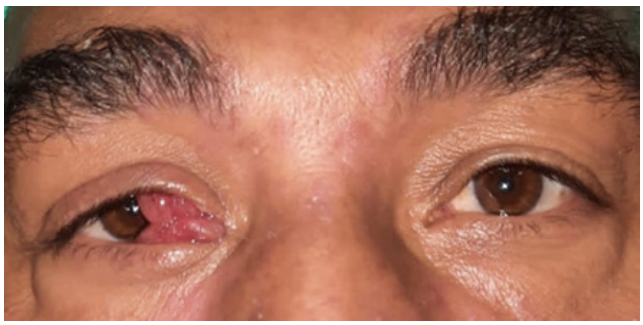

Figure 5. This patient had conjunctival involvement in right eye.

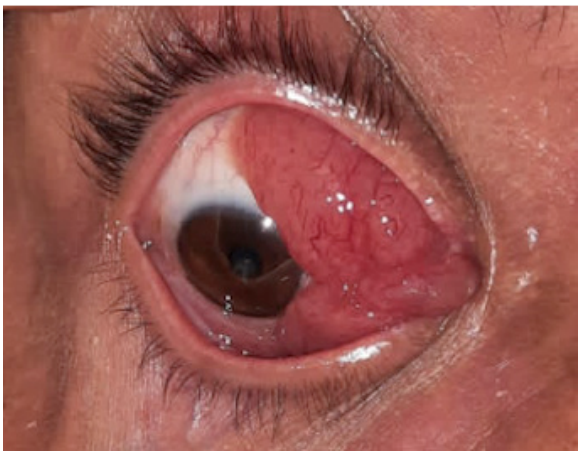

Figure 6. Conjunctival involvement with salmon patch appearance was seen in biomicroscopic evaluation.

Discussion:

Despite the small area of the orbit, follow-ups and treatments are different from one another due to the variations in tumor types [1,2]. Due to the different tissue types involved, many different tumor types can be seen in the orbit. In the approach to orbital tumors, the age of the patient, the location of the tumor, and radiologic findings should be considered [1]. Orbital and ocular adnexal lymphoma is the most common adult orbital malignancy [1-4]. Most orbital and ocular lymphomas are B-cell non-Hodgkin lymphomas; T-cell lymphomas, Burkitt lymphoma, and Hodgkin lymphoma have also been seen [1,2]. According to the Revised European American Lymphoma (REAL) classification, the most common lymphoma subtypes in the ocular adnexia are extranodal marginal zone B-cell lymphoma, diffuse large-cell B-cell lymphoma, and follicular lymphoma, respectively [2,9]. Less common B-cell lymphoma subtypes include lymphoplasmocytic lymphoma/immunocytoma, mantle cell lymphoma, plasmacytoma, and immunoblastic lymphoma

Table 1. Patients and characteristics of orbital lymphoma.

Patient	Sex	Age	Location	Diagnosis	Initial complaint	Unilateral/ bilateral	Chemotherapy	Radiotherapy
1	F	70	Intraorbital location (behind the orbital septum)	NHL; Primary extranodal marginal lymphoma of the mucosa-associated lymphoid tissue	Swelling in the left eye, painless mass	Unilateral	Rituximab	(-)
2	M	64	Intraorbital location (behind the orbital septum)	NHL; Primary extranodal marginal lymphoma of the mucosa-associated lymphoid tissue	Swelling in the right eye	Unilateral	Rituximab	(+)
3	M	79	Right eyelid (in front of orbital septum)	NHL; Primary extranodal marginal lymphoma of the mucosa-associated lymphoid tissue	Painless mass and swelling in the right eyelid	Unilateral	Rituximab	(-)
4	F	58	Left eyelid (in front of orbital septum)	NHL; Follicular lymphoma	Swelling in the left eyelid, ptosis, pain	Unilateral	(-)	(+)
5	M	56	Lacrimal gland involvement	NHL; Primary extranodal marginal lymphoma of the mucosa-associated lymphoid tissue	Ptosis, epiphora, proptosis	Bilateral	Rituximab	(-)
6	M	42	Intraorbital location (behind the orbital septum)	NHL; Diffuse large B-cell lymphoma	Bilateral eyelid swellibg and ptosis	Bilateral	Rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	(-)
7	M	46	Right eye conjunctival involvement	NHL; Primary extranodal marginal lymphoma of the mucosa-associated lymphoid tissue	Chemosis, salmon patch appearance in conjunctiva	Unilateral	Rituximab	(-)
8	M	58	Lacrimal gland involvement	NHL; Diffuse large B-cell lymphoma	Pain, limited eye movements,ptosis, epiphora	Unilateral	Rituximab-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	(-)

[9,10]. In the histopathologic evaluation of orbital lymphomas, marginal zone lymphoma is seen most commonly, followed by diffuse large B-cell lymphoma [1,2,9,10]. In our study, the most common marginal zone lymphoma diagnosis was in line with the literature.

Lymphomas in the orbital region can be detected at all ages but are generally seen in 50–70-year-olds [1,2,8-10]. The mean age of 59.1 years of the patients in our study is concordant with the literature. Orbital lymphomas are generally unilaterally observed in the literature, bilateral involvement is rarely witnessed [9-12]. Our study detected unilateral involvement in six patients and bilateral involvement in two patients.

In orbital tumors, the age of the patient, the location of the tumor, and radiologic findings should be considered in the approach [1,13]. A radiologic examination is recommended in terms of localization, spread, and differential diagnosis of the disease before biopsy [11,13]. The definitive diagnosis of the disease is made by histopathologists [13,14]. In the literature, the most common location of lymphomas is stated as the intraorbital region (orbital septum posterior), followed by the eyelids, lacrimal gland involvement, and conjunctival region involvement [8-14]. In our study, the most common involvement was the intraorbital region (behind the orbital septum), followed by the eyelids and lacrimal glands. Depending on the location of the tumor, various findings such as diplopia, vision loss, proptosis, watering, chemosis, decreased visual acuity, and eyelid edema can be seen in the patients [1-3,8,10-14]. Orbital painless mass and

swelling were the most common ophthalmologic signs in our patients.

The differential diagnosis of orbital lymphoma includes the following: pseudotumor, orbital metastases, diffuse lymphangioma, lacrimal adenoma, and cavernous hemangioma [11-14]. Some clinical conditions may guide the suspicion of lymphoma. The clinical presentation is nonspecific and depends on the location of the lymphoma. Patients typically demonstrate pink or red salmon patches of swollen conjunctiva. Orbital presentation is most commonly observed as a painless palpable mass. Eyelid swelling and enlarged gland prolapse may occur in lymphoma. These findings should make physicians suspect lymphoma [9-14].

Limitations

There are several limitations in this single-institution retrospective analysis of orbital and ocular adnexal lymphoma. Our small sample size may have affected the statistics. The other inherent limitation is the retrospective nature of the study and associated selection biases. Despite inherent limitations, there is a lack of studies about orbital and ocular adnexal lymphoma in the literature. This study is important because it is the first to report from the south of Turkey in the literature about orbital and ocular adnexal lymphoma.

Conclusion

Lymphomas are common among orbital tumors and clinical findings change depending on the place in orbit. When patients present with ophthalmologic findings such as painless orbital mass, chemosis, or epiphora, ophthalmologists should be careful to include lymphoma in their differential diagnosis

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REVIEW ARTICLE

DERLEME

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Basic medical sciences should be mainly taught by clinicians for a tight integration of basic and clinical sciences in medical education.

Tıp eğitiminde temel ve klinik bilimlerin sıkı entegrasyonu için temel bilimler esas olarak klinisyenler tarafından öğretilmelidir.

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ABSTRACT

Today, medical education faces many problems. However, the most serious problem is the inability to integrate basic and clinical sciences. For this reason, students alienate from basic sciences, and clinicians are leaving sciences to basic scientists every day. Basic medical sciences learned in the preclinical term are remembered less by students and cannot be sufficiently associated with clinical reality. This is because basic scientific knowledge learned without a clinical framework is low-value data that the student does not know how to use. Therefore, all reform initiatives in the medical education curriculum stick to the obstacle of basic sciences. Now is the time to take bold steps. The first step should be to remove the preclinical term from medical education. Medical education should only consist of clinical education terms. This will gain the student and clinician a lot more time for clinical training. The second step should be to take basic sciences education from basic scientists and place it under the responsibility of clinicians. Clinicians can decide much better how much of basic science knowledge is clinically relevant. As a component of clinical education, it is best for students to internalize the basic sciences during classes, at the bedside, and in other clinical practices under the clinician's authority. Thus, students may be graduated as academic clinicians who have internalized the basic sciences and integrated the basic sciences with clinical reality.

Keywords: medical education, curriculum, clinical apprenticeship, integration, basic medical sciences

ÖZ

Bugün tıp eğitimi birçok sorunla karşı karşıyadır. Fakat en ağır sorun temel ve klinik bilimlerin entegre edilememesidir. Bu nedenle öğrenciler temel bilimlerden soğumuş, klinisyenler ise bilimi temel bilimcilere bırakmıştır. Klinik öncesi dönemde öğrenilen temel bilimler öğrenciler tarafından unutulmakta, klinik bilgiyle bağdaştırılamamaktadır. Çünkü klinik bilgi olmadan öğrenilen bir temel bilim bilgisi öğrenci için nasıl kullanacağını bilmediği düşük değerli bir bilgidir. Bu yüzden tıp eğitimi müfredatındaki her reform temel bilimlere takılıp kalmaktadır. Artık cesur adımlar atmanın zamanı gelmiştir. Birinci adım tıp eğitiminden klinik öncesi dönemin çıkarılması olmalıdır. Tıp eğitimi tamamen klinik eğitim döneminden oluşmalıdır. Bu durum klinik eğitim için öğrenciye ve klinisyen öğreticiye çok daha fazla zaman kazandıracaktır. İkinci adım temel bilim eğitiminin temel bilimcilerden alınıp klinisyenlerin sorumluluğuna verilmesi olmalıdır. Bir temel bilim bilgisinin ne kadarının hangi şekilde klinikle ilişkili olduğuna bir temel bilimci değil ancak klinisyen karar verebilir. Temel bilimlerin klinik eğitimin bir bileşeni olarak klinisyen tarafından derslik, hasta başı ve diğer klinik uygulamalar sırasında öğrenciye özümsetilmesi en doğrusudur. Böylece öğrenciler temel bilimleri özümsemiş ve temel bilimleri klinik durumla entegre etmiş akademik klinisyenler olarak yetişecektir.

Anahtar Kelimeler: tıp eğitimi, müfredat, klinik stajlar, entegrasyon, temel bilimler

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Introduction

Today, medical education faces serious challenges [1]. Contrary to popular belief, this difficulty is not caused by new developments. The main reason for the problem is that medical education has been divided into basic and clinical sciences since the Flexner report. The inclusion of basic sciences in medical education originally integrated research into teaching and patient care. A clinician could be an equally good researcher, doctor, and teacher. However, over time, as the basic sciences became molecular, clinicians could not cope with this situation and had to leave the basic sciences to the scientists [2].

Many innovations such as problem-based learning, team-based learning, and the use of simulation have occurred in medical education. However, the impact of all these developments on clinician training has been quite limited [3]. Therefore, reforming the medical education curriculum is an ongoing issue. However, interventions remain at the level of curricular tampering rather than producing a fundamental change [4]. The main focus of the reform is on the preclinical years of the curriculum, while the internship structure of the undergraduate clinical years has remained largely unchanged [5]. In other words, despite many interventions, basic and clinical sciences still could not be integrated [4].

While students receive basic sciences education, they cannot establish an adequate relationship with clinical reality. Therefore, basic sciences begin to be forgotten in the early days of clinical education [3]. To solve this problem, there are suggestions such as a revision of basic sciences at the end of clinical education. More precisely, it is recommended that students review basic sciences after acquiring clinical knowledge and in this way integrate basic and clinical sciences [6].

The biggest obstacle to reforming the medical curriculum is the separation of education into basic and clinical sciences [4]. In the author's opinion, there are two main problems arising from this separation. The first problem is the perception that basic sciences should be taught before clinical sciences. This situation ossifies the curriculum and hampers any serious reform. The second problem is that basic sciences are taught separately from and before clinical education, leading to the perception that this education should be mainly given by basic scientists. As a result, today, physicians who do not remember the knowledge they learned in the preclinical years and who cannot integrate basic sciences with clinical knowledge can still become good clinicians [7].

It is an important problem that clinicians do not grow well in the field of basic sciences and leave basic sciences to scientists [8]. In medical education, it does not seem right to teach basic sciences first and then clinical sciences. The author proposes that basic sciences be taught as a component of clinical sciences- not first and foremost. More importantly, as a basic scientist, the author recommend that basic sciences be taught mainly by clinicians.

The involvement of basic sciences in the medical education curriculum

Abraham Flexner convinced the medical authority of his time that basic sciences should be a critical component of the medical education curriculum, thus creating the "preclinical curriculum" [6]. Today, more than 100 years after the Flexner Report initiated major reforms in American and Canadian medical schools, the overall format of medical education is still more or less the same. The preclinical education period is followed by a series of clinical education experiences. Since the time basic medical sciences education entered the curriculum, it has been taught mainly in a didactic format [3]. However, it is seen that didactic education is not effective even in the professional period [9].

The medical education system today follows a similar path all over the world. The medical school curriculum, which accepts high school graduates, consists of premedical sciences, basic medical sciences, and clinical medicine (usually 5 to 7 years). The curriculum of medical faculties that accept bachelor’s graduates consists of basic medicine and clinical medicine (usually 4 years) [10]. Preclinical and basic sciences are taught before clinical sciences. In some medical schools, clinical courses are started to be given from the beginning of medical education in order to introduce the student to the clinical environment

at an early stage.

The aim of basic sciences education is for the clinician to establish a relationship between the disease and its biological basis when making clinical decisions [7]. Basic medical sciences include mainly anatomy, physiology, biochemistry, microbiology, pharmacology, and pathology. The student receives basic sciences education for 1.5 to 2 years in a 4-year curriculum and 2 to 3 years in a longer curriculum. The education is given by basic scientists who are not clinicians but have a doctorate in the relevant field. Thus, it is aimed that medical doctors will be educated as academic clinicians.

The decline of basic sciences in medical education

Unfortunately, medical students' interest in basic sciences has decreased considerably in recent years. Today, in many places of the world, medical school students do not actually attend preclinical classes unless attendance is compulsory. Instead, they prefer self-learning the lessons from video recordings or other sources [11]. Many students question the necessity of basic sciences in medical education. Many clinical students state that they do not understand why they are taught preclinical subjects that do not seem relevant to clinical sciences [12]. An important reason for the decrease in students' interest is that basic sciences are taught independently from the clinical sciences. Conversations with medical students about the first-year medical curriculum reveal that about half of the lessons progress without even a simple case of a patient [13]. As a result, it has been observed that senior medical students do not remember much from their first-year basic sciences subjects [12].

The fact that preclinical courses are not remembered in the following years and are not associated with clinical reality has discredited basic sciences. Today, the interest in basic sciences has decreased considerably, and it is seen as a burden by students. Some scholars propose a basic medical sciences recovery plan and recommend that basic sciences be given in clinical years [5]. They claim that revising the basic sciences in the senior year will both increase the extent to which students recall basic sciences and improve their understanding of clinical medicine [6]. Some researchers, on the other hand, suggest that preclinical courses should be taught with a video system outside the lecture hall, or even teaching preclinical courses in the classroom should be abolished altogether [11-13]. Emanuel boldly emphasizes that from 2025, all basic sciences courses should be offered online only [11].

Integration of basic sciences into clinical medicine

A major challenge to reform in medical education is the historical separation of basic and clinical sciences. It is necessary to integrate basic and clinical medical sciences throughout medical education. In this way, students should be able to think about clinical practices while learning basic sciences and scientific principles while learning clinical practice [4]. However, today, the separated curriculum structure has largely left to the student's own efforts the integration of discipline-based knowledge with disease-oriented knowledge [14]. One of the problems is that basic sciences are taught independently and before clinical sciences. As a result of this situation, it is not possible for students to associate the concepts of basic sciences with clinical practice without adequate clinical training [6]. Basic sciences are the language of medicine and the basis of clinical knowledge, so the integration problem should be solved by ensuring harmony between basic and clinical sciences in the curriculum [15]. According to medical professionals, an understanding of the content of basic sciences is essential for competent clinical practice. They suggest that basic sciences education should be integrated with clinical practice throughout all undergraduate medical education [5].

While clinicians are in favor of the integration of basic sciences, basic scientists are reluctant. It is reported that in general, basic scientists have a negative attitude toward integration and change [4]. The idea of integration often assumes that the basic scientist and clinician come together to teach students in a hall or sometimes at the bedside. Imagine a discussion in a classroom involving students, a child with a metabolic disease, their parents, the treating clinician, and a biochemistry

professor [13]. Or imagine basic scientists included in departmental visits of clinicians [8]. It is difficult to even imagine people in such different positions coming together. Also, what kind of a scientific hierarchical relationship will be established between a basic scientist and a clinician in the same hall or at the bedside? Where the clinician is, a basic scientist will always feel compelled to withdraw. This is because the students in the hall or at the bedside are medical students, and their role models are primarily clinicians. The clinician will naturally be in a dominant position. Moreover, while the clinician is familiar with all clinical and partially all basic sciences related to the patient's disease, the basic scientist is only an expert in their field. In this case, a basic scientist cannot be expected to want to come together to lecture with the clinician for integration purposes. The main problem here is the point of view of clinicians and basic scientists. While clinicians have patient and disease-focused assessments, basic scientists often have a molecular-based scientific perspective, far from the clinic. In the end, students will not be able to integrate two differently originated types of knowledge, so the knowledge emphasized by the clinician will be dominant.

It is clear that the idea of bringing basic scientists together with clinicians is not a solution for integration. If students are desired to gain scientific curiosity and the research spirit, it should be ensured that each student participates in at least a few basic scientific studies throughout their study period. Make sure basic scientists are very enthusiastic about it.

Teaching basic medical sciences to medical students by clinicians

Preclinical sciences are taught, often didactically, by basic scientists. Basic scientists are not physicians or clinicians; they are trained in non-medical fields. They have little or no knowledge of clinical medicine. They know little about the relevance of the knowledge they teach to both other branches in the basic sciences and clinical reality. If radical reform and integration in medical education are desired, it must start with the teaching staff first. Researchers interested in educational transformation largely agree that any attempt to significantly change the curriculum must begin with the teaching staff and continue to keep them at the center of change [4].

This article's suggestion is that basic medical sciences education should be given mainly by clinicians. Clinical education should begin at the beginning of medical education. Basic sciences should be given by clinicians during classroom and bedside practices of clinical medical education. The reality is that much of the knowledge learned in the preclinical term is lost during the clinical years. Much of the knowledge of basic sciences given is unrelated to clinical reality and leads the student to waste their time. What needs to be done is a review of all basic sciences by relevant clinicians; thus, the revised knowledge is transferred to the student by the clinician in the clinical context.

In fact, there is also a decline in clinical sciences today. For example, bedside learning is seen as one of the most important methods of teaching various skills important to the medical profession, but its use is decreasing [16]. Clinicians have left the science to basic scientists, and the bedside teaching and apprenticeship model has also declined [8-17]. What needs to be done is a student-centered education in a more professional climate where basic and clinical sciences are integrated with the clinician's identity by revising the classical apprenticeship model [17]. At this point, two important inadequacies of clinicians emerge. The first is the issue of developing teaching skills because clinician teachers acquire their teaching skills without any formal training [18]. Secondly, clinicians should achieve competency in the basic sciences of their field since they do not feel knowledgeable enough about teaching basic sciences [5].

What basic sciences courses should be taught by a clinician? Take epilepsy, for example. Neurosurgeons can teach the anatomy of the brain, and pathologists can introduce the histology of the brain cells as much as the student needs in the clinical context. A neurologist can easily teach the physiology, biochemistry, and pathophysiology of the brain. In fact, a neurologist, not a pharmacologist, can explain in detail antiepileptic drugs in the clinical context. As a pharmacologist

and medical doctor but not a neurologist, the author is of this opinion, because students express often their discomfort which they learn this information away from the clinical context.

The student should learn about a drug from the clinician who made the decision to administer it to the patient. The student should learn the anatomy of the brain from a neurosurgeon performing brain surgery. This is because knowledge detached from clinical context is of low value, dry, and unlovable for a medical student.

In fact, a clinician, for example, a cardiologist, should already know the anatomy, histology, physiology, biochemistry, pathology, and pharmacology of the heart. Medical doctors already learn all this during their medical training but forget most of it because too much information is loaded, and the clinical context is not established. For example, a cardiologist can teach the essence of all basic sciences of the heart to their students by spending 5 to 10 minutes in each lesson during the clinical term. A clinician can teach basic subjects at the right times during clinical applications and in other clinical education practices, so the internalization and absorption of basic sciences can be enabled.

How will the clinician learn basic medical sciences? All clinicians have already taken all courses related to basic sciences during their school years. However, they remember less of a lot of knowledge of basic sciences as time passes. By watching short videos (5 to 10 minutes), they can overcome their inadequacy in basic sciences [3]. Basic scientists will have more time when basic sciences education is placed under the responsibility of clinicians. As an alternative option, basic scientists can provide brief lectures for clinicians. Thus, the relationship between the clinician and the basic scientist continues in a different dimension. The clinician learns the most up-to-date knowledge from the basic scientist and internalizes it by relating it to clinical reality. Then, the clinician transfers the internalized knowledge to students little by little and continuously throughout the clinical education term. Thus, both students may be trained to become academic clinicians and the clinician may gain new academic and scientific skills.

Clinicians are responsible for conveying basic medical knowledge to students, providing clinical skills, and instilling the values of the profession into students [2]. Today, apprenticeship experience with clinical instructors is becoming more and more important in medical education. Exposure to physician-educator-scientist role models that demonstrate the integration of sciences and clinical practice during education is important to motivate clinical students into investing in research education [7]. It is necessary to increase the contact between faculty members and clinical students [19]. The involvement of basic sciences in clinical education will lead to the abolition of the preclinical period in medical education. Thus, medical education will consist of only clinical education terms from the beginning. This will prolong the clinical education term, and the clinician and apprentice relationship will continue for a much longer time. One of the things that medical students need most is to establish more communication and relationship with their scholars, both professionally and humanely [19].

Conclusion

The uniqueness of medical school is not classroom-based preclinical education. The most important aspect of medical education emerges in the apprenticeship model, where an experienced physician and student share clinical situations, and the transfer of knowledge and learning is inextricably intertwined with patient care. The main task of medical schools is to focus their students on clinical education and redesign medical education [11]. The challenge in fundamentally redesigning the content of medical education is to find and prepare faculty members to teach the revised curriculum [2]. Putting new courses in the medical education curriculum and putting a new burden on the student is not the solution. As a matter of fact, studies show that one in two students suffer from burnout even before they start residency [20]. For students, graduating from medical school as soon as possible and entering the physician workforce is critical and should be supported [3].

In conclusion, the main problem in medical education is that basic and clinical sciences are learned in isolation from each other, and basic sciences are taught by non-clinician professors. The primary solution to this problem is to remove

all preclinical terms from the curriculum and to continue medical education completely in the clinical context. Then, clinicians should teach basic sciences and enable students to internalize them as part of clinical knowledge. Thus, the new generation of medical doctors can graduate as academic clinicians who have internalized the basic sciences and integrated the basic sciences with clinical reality.

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