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Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

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Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

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Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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Mucormycosis in Hematologic Malignancies: Clinical Follow-Up and Treatment Results

Hematolojik Malignitelerde Mukormikozis: Klinik Takip ve Tedavi Sonuçları

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ABSTRACT

Introduction: Mucormycosis is an aggressive-progressive invasive fungal infection caused by mold fungi in the division of mucorales of the zygomycetes class with high mortality, and is the most common fungal infection in patients with hematologic malignancies.

Methods: This study retrospectively evaluated patients with mucormycosis diagnosis between January 2015 and December 2019, including demographic features, hematologic diseases and comorbidities, radiological evaluations, symptoms and signs, treatments, and outcomes.

Results: Maxillofacial 9/19 (47.37%) of patients and 10/19 (59.9%) rhinoorbital mucor. Hematologic malignancy was observed in 15 (78.95%) patients, whereas others had additional pre-disposing factors, such as diabetes mellitus and chronic renal failure. The most common find-ings were persistent fever, mucopurulent nasal flux, and periorbital edema. Endoscopic sinus surgery + medication was administered in 12/19 (62.2%) patients and antifungal therapy in 7/19 (37.8%). In addition, 15/19 (79.95%) patients died and 4/19 recovered with sequela.

Conclusion: The first large-scale mucormycosis study from our country will guide in determining the treatment algorithm. Effective and early surgery and antifungal application reduce mortality in mucormycosis by early diagnosis and multidisciplinary approach, without bone destruction in the paranasal sinus computed tomography with recurrent fever and earlystage sinusitis finding by performing a biopsy.

Keywords: Fungal infection, mucormycosis, hematology

ÖZ

Amaç: Mukormikoz, yüksek mortaliteye sahip zigomiset sınıfının mucorales bölümünde yer alan, küf mantarlarının neden olduğu agresif ilerleyen invaziv bir mantar enfeksiyonudur. Hematolojik maligniteli hastalarda en sık görülen mantar enfeksiyonu olarak karşımıza çıkmaktadır.

Yöntemler: Çalışmamızda Ocak 2015-Aralık 2019 tarihleri arasında mukormikoz tanısı alan hastalar retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, hematolojik hastalıkları ve komorbiditeleri, radyolojik değerlendirmeleri, semptom ve bulguları, tedavileri ve sonuçları değerlendirildi.

Bulgular: Olgularımız 9/19 (%47,37) maksillofasiyal ve 10/19 (%59,9) rinoorbital mukor hastalarıydı. Hastaların 15'inde (%78,95) sadece hematolojik malignite varken, diğerlerinde diabetes mellitus ve kronik böbrek yetmezliği gibi ek predispozan faktörler vardı. En sık görülen bulgular inatçı ateş, mukopürülan burun akısı ve periorbital ödemdi. Hastaların 12/19'u (%62,2) endoskopik sinüs cerrahisi + antifungal tedavi ve 7/19'u (%37,8) sadece antifungal tedavi gördü. Hastaların 15/19'u (%79,95) öldü ve bunların 4/19'u sekel ile iyileşti.

Sonuç: Ülkemizden ilk büyük ölçekli mukormikoz çalışması, tedavi algoritmasının belirlenmesi açısından yol gösterici olacaktır. Erken tanı ve multidisipliner yaklaşımla, etkili ve erken cerrahi ve antifungal uygulama ve biyopsi ile, mukormikozda mortalitenin, tekrarlayan ateş ile paranazal sinüs bilgisayarlı tomografide kemik destrüksiyonu olmaksızın, azaltılabileceğini düşünmekteyiz.

Keywords: Fungal enfeksiyon, mukormikoz, hematoloji

Introduction

Mucormycosis is an aggressive-progressive invasive fungal infection caused by mold fungi in the division of mucorales of the zygomycetes class (1,2), which is the most common fungal infection after Aspergillus spp. in patients with stem cell and solid organ transplantation (3,4). The true incidence of the disease is unknown; however, its incidence in the United States is 1.7/1000000 per year with approximately 500 cases per year (5). The incidence of autopsies performed in the risky patient

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group was 8-13%, as it is responsible for 10% of the invasive mold-fungal infections in the high-risk patient group (6,7).

Disease prevalence is high in patients with uncontrolled diabetes mellitus (DM), especially in undeveloped countries; however, it was reported in patients with hematologic malignancy and organ transplantation (8,9). In recent years, mucormycosis cases were reported under posaconazole prophylaxis, and was published that voriconazole prophylaxis causes a mucormycosis predisposition (10-13).

Turkey has very few numbers of reported mucormycosis incidences and publications with hematologic malignancy at the level of case reports, without case series. This study aimed to retrospectively evaluate patients with hematologic malignancies and mucormycosis, who were followed and treated in our hospital.

Methods

Our single-center retrospective study examined mucormycosis cases over the age of 18 years with hematologic malignancy between January 2015 and December 2019 with the approval of the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethical Committee (approval number: 2204, date: 21.02.2020). Informed consent was obtained from all participants. The diagnosis was made based on the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) (14) diagnostic criteria. Demographic features, additional comorbidities, laboratory, clinical, and treatment results of the cases were evaluated through the hospital registration system.

Statistical Analysis

This study contains descriptive data of the patient group. STATA software version 12.0 was used to analyze patient data. Data results were given as mean, standard deviation, or median and interquartile range according to their suitability. Informed consent was obtained from patients for clinical information and result utilization.

Results

Out of 19 patients who met the study criteria, 12 were female and 7 were male, and the median age was 58 years (range: 23-84). Apart from hematologic malignancy, predisposing conditions were determined as DM, chelation therapy (using deferoxamine), and additional immunosuppressive therapy. According to the EORTC/MSG criteria, 12/19 (63.16%) were evaluated as definite and 7/19 (36.84%) were possible mucormycosis. The cases had hematologic malignancy in 12/19 (63.16%) and multiple predisposing factors in 7/19 (36.85%). Case diagnoses were evaluated as follows: Acute myeloid leukemia (AML) (n=6), myelodysplastic syndrome (MDS) (n=6), acute lymphocytic leukemia (n=4), and lymphoma (n=3).

Paranasal sinus computed tomography (CT), which was the first choice in radiological imaging, was evaluated as rhinosinusal (RS) with isolated sinus involvement and rhinoorbital (RO) with orbital involvement. RO was classified in 9/19 (42.1%) of cases and RS in 10/19 (57.9%). In addition to the cases evaluated as RO (n=10), orbital magnetic resonance imaging (MRI) was performed. Of these cases, 62.2% were operated on and histopathologically confirmed. The demographic and clinical characteristics of the cases were evaluated in the study as presented in Table 1. The most common symptoms and signs was high fever in 17 patients (89.47%), mucopurulent nasal discharge in 15 patients (78.95%), percent sensitivity in 12 (63.16%), periorbital edema in 11 (57.90%), redness in 9 (47.37%), paralysis in 8 (42.11%), palate necrosis in 5 (26.32%), proptosis (21.05%) in 4, and exophthalmos (15.79%) in 3.

Our study calculated the annual disease incidence over 10000 applications/year and is 0.02-0.3/10000 between 2015 and 2019, as shared in Figure 1.

Mycological cultures were made in 7 cases, but in 2 Mucor spp. reproduction was detected, without possible typing. However, histopathological confirmation was provided in all patients who are operated on.

Considering the most common symptoms and signs, 17 patients (89.47%) had a high fever, 15 (78.95%) had mucopurulent nasal discharge, 12 (63.16%) had face sensitivity, 11 (57.90%) had periorbital edema, 9

Table 1. Demographic characteristics, clinical forms, hematologic diseases, and therapeutic outcomes of patients

	n (%)
Age, median (range)	58 (23-84)
Genter (male/female)	7/12
Hemotologic diseases/comorbidities	
AML	5 (26.32)
ALL	4 (33.33)
Lymphoma	2 (10.53)
AA	2 (10.53)
MDS	2 (10.53)
MM + DM* + CRF*	1 (5.26)
AML + DM*	1 (5.26)
MDS + DM* + CRF*	2 (10.53)
Antifungal use	**11 (57.89)**
Fluconazole	4 (33.33)
Posaconazole	3 (15.79)
Voriconazole	4 (33.33)
Anatomical localization	
Maxillofacial	9 (42.1)
Rhinoorbital	10 (57.9)
Treatment	
Endoscopic sinus surgery + medication	12 (62.2)
Only medication	7 (37.8)
Outcome	
Death	15 (79.95)
Mucor	12 (63.15)
Myocardial infarction	2 (10.53)
Hemorrhage	1 (5.26)
Recovery	4 (33.33)

AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, AA: Aplastic anemia, MDS: Myelodysplastic syndrome, MM: Multiple myeloma, DM*: Diabetes mellitus, CRF*: Chronic renal failure

(47.37%) had redness, 8 (42.11%) had paralysis, 5 (26.32%) had palate necrosis, 4 (21.05%) had proptosis, and 3 (15.79%) had exophthalmos. Symptoms and findings of patients are demonstrated in Table 2.

Posaconazole prophylaxis was given to 3/19 (15.79%) cases, whereas 4/19 (21.05%) were taking voriconazole 2x4 mg/kg/day with high-possible invasive fungal infection. Liposomal amphotericin B (L-AMB) 1x5-6 mg/kg/day was administered to all patients diagnosed with mucor and 2 patients, without previously posaconazole prophylaxis treatment, received posaconazole and L-AMB combination therapy. The mean anti-fungal application time was 55.63 (3-260) days, 102.5 (20-260) days for survivors, 49.27 (3-100) for non-survivors. Posaconazole and L-AMB combination was administered in 2 of the surviving cases. The overall mortality rate was 79.95% and mortality attributed to mucor was 63.15% (3 patients died due to different reasons).

Discussion

Mucormycosis is an angioinvasive fungal infection with hematologic malignancy, especially in patients receiving chemotherapy and/or immunosuppressive therapy, causing sudden onset and high mortality. The causative spores of fungi are found mostly in soil, rotten fruits and vegetables, and moldy foods. Spores settle on the sinuses through inhalation or on the mucous membrane by contact cause invasion, vascular occlusion, and diffuse tissue necrosis in the vascular endothelium in cases with dysfunctional phagocytosis and neutrophil functions. Host defense determines the disease spread; therefore, in addition to hematologic malignancy, they are at high risk situations due to the following: diabetic ketoacidosis, intense and long-term corticosteroid use, premature birth, human immune deficiency virus, and patients who underwent solid organ transplantation. Therefore, despite the systemic antifungal usage and aggressive surgical debridement, mortality is very high (15-17), which was rarely reported in healthy people after iatrogenic injuries and after natural disasters such as volcano eruption and proboscis (18-21).

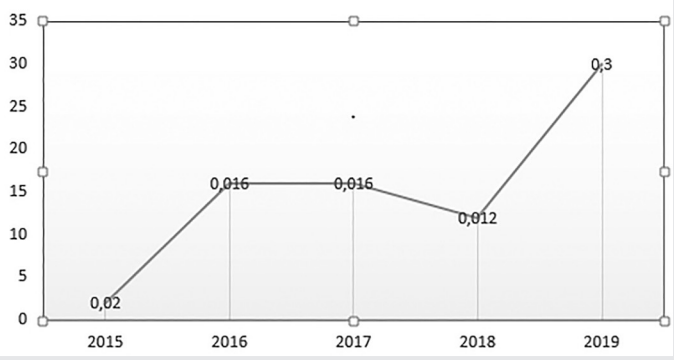

Figure 1. 10000 applications/year incidence between 2015 and 2019

*Demonstrates the change in the incidence of mucormycosis in patients diagnosed with hematological malignancies in our center between 2015 and 2019

Table 2. Symptoms and findings of patients

Symptoms/findings n (%)
Fever 17 (89.47)
Mucopurulent discharge 15 (78.95)
Facial sensitivity 12 (63.16)
Periorbital edema 11 (57.90)
Redness 9 (47.37)
Paralysis 8 (42.11)
Palate necrosis 5 (26.32)
Propitozis 4 (21.05)
Exophthalmos 3 (15.79)

Its clinical course was known for a long time; however, its epidemiology remains undetermined. Patients with hematological malignancy and organ transplantation are at the forefront in developed countries; however, uncontrolled DM ranks first in developing countries, such as Iran and India (8,22-25). A study from Turkey by Kursun et al. (26) determined DM as 50% and hematologic malignancy as 18% in series of 28 cases. The study of Arda et al. (27) reported hematologic malignancies as 50% and DM as 25%. A meta-analysis that included 851 cases by Jeong et al. (28) revealed that DM was 40%, hematological malignancy was 33%, and organ transplantation was 14% as predisposing.

The annual incidence was 0.47/10000 in the study from Lebanon; however, another study for DM was reported as 10.31/10000 (29,30), whereas Our study calculated the annual incidence as 0.073/10000 years for patients with hematological malignancies (Figure 1).

The annual incidence was 0.47/10000 in the study from Lebanon, with DM as 10.31/10000, whereas our study calculated it as 0.073/10000 per year for patients with DM.

The definitive diagnosis is made by histopathological examination; however, imaging methods help determine the invasion and complications rather than the disease diagnosis. CT demonstrated bone destruction and MRI provides more information in the intracranial and orbital structure invasion evaluation (31). McDonogh et al. (32) emphasize the need to suspect mucormycosis when symptoms of sinusitis are seen clinically and radiologically in patients with immune deficiency or DM. Mucosal sinus CT should be taken in all our patients to detect mucosal thickening in the early stages. Bone destruction is an early sign for mucor (n=10), thus an orbital and facial MRI was taken to determine the orbital spread. RO was observed in 9/19 (42.1%) cases and RS in 10/19 (57.9%).

Mucormycosis begins with necrosis in the palate or sinuses reaching the orbital and brain tissues (33). Patients usually present with facial paralysis and headache, fever, and signs related to soft tissue inflammations. Depending on the necrosis, black creams on the palate and nose are observed. Symptoms and findings detected in our study were resistant fever (89.47%), mucopurulent nasal discharge (78.95%), and facial area pain (67.2%) in both groups. Palate necrosis was seen in 26.32% in RS localization, neurological symptoms were seen in RO localization; paralysis in 47.37%, proptosis in 21.05%, and exophthalmos in 15.79%.

For a definitive diagnosis, a deep biopsy sample is taken from the suspicious nasal and/or oral mucosal lesions and fresh tissue samples are examined by histopathological and microbiological methods; septum-free, randomly-branching hyphae should be seen and macroscopic and

microscopic examination of colonies that were grown in Sabouraud dextrose agar media should be done (34). The review of Jeong et al. (28) achieved a histopathological diagnosis of 88%.

The underlying disease must be corrected to use systemic antifungal therapy in mucormycosis treatment, removal of necrotic tissues due to invasion and thrombosis, and host defense recovery. Operation decision in patients with hematologic malignancy becomes difficult due to factors, such as thrombocytopenia, anemia, and coagulation pathologies. Therefore, earlier antifungal therapy initiation is vital. A study by Chamilos et al. (35) retrospectively evaluated 70 patients with hematologic malignancies, which revealed a two-fold increase in mortality 12 weeks after diagnosis in patients in which anti-fungal therapy was started after the 6th day following the mucor diagnosis. In our study, all patients received L-AMB after a paranasal sinus CT. The average time of operation of patients was 4.4 (1-15) days after CT.

Statistical comparison was not made due to a small case group. Our overall mortality rate was 15/19 (79.95%); however, three of our cases died due to non-mucormycosis reasons. Mortality attributed to mucor was calculated as 63.15%. According to published studies, the mortality rate varies between 30% and 69%. The survivor evaluation revealed that most of them were RS located, with the time of operation at 2.2 (1-18) days after the paranasal sinus CT, and the average duration of antifungal therapy was 102.5 (90-120) days. Survivors used 62.8% (35-92) L-AMB and were cured with a posaconazole (800 mg PO/day) tablet within 172.6 (75-354) days.

Posaconazole is an azole with anti-mucor activity. Suspension form absorption is directly related to food and its consumption is recommended with a fatty or high-calorie meal. In our country, the first approved suspension form for invasive fungal infection prophylaxis during MDS and AML induction therapy was firstly used in our cases. In our series (n=5), patients who developed mucor under prophylaxis (15.79%) were using posaconazole (3x200 mg/day), but three of these cases were used for <10 days.

This retrospectively planned study was unable to evaluate the effective dose at a blood concentration level of the drug. Different studies reported that breakthrough infections develop under posaconazole prophylaxis and inappropriate usage of the recommended prophylactic medication (36-38). Posaconazole tablet was used after discharge in patients using L-AMB at the hospital. Posaconazole tablets were preferred due to their high efficacy, good tolerability, and low drug interaction.

Study Limitations

The most important limitation of the study was the small patient group. The difference in the time to surgery was an important obstacle to make a comparison between patients.

Conclusion

In our country, published case-based reports are limited and we believe that it is the first large-scale mucormycosis study conducted in a group of patients with hematologic malignancies, which will shed light on the future treatment algorithm determination. In this study, effective surgery and antifungal application reduce mucormycosis mortality by performing an early diagnosis with a multidisciplinary approach and biopsy sampling with persistent fever before bone destruction in the paranasal sinus CT and before further development.

Acknowledgments: We respectfully remember all the colleagues we lost in the COVID-19 fight.

Ethics Committee Approval: This study was approved by the Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2204, date: 21.02.2020).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

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Comparison of Humeral Intramedullary Nail Internal Locking System and Standard External Locking System

Humerus İntramedüller Çivi İçten Kilitleme Sistemi ile Standart Eksternal Kilitleme Sisteminin Karşılaştırılması

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ABSTRACT

Introduction: This study aimed to compare the "Freehand Distal Locking (FHDL)" method, which is a standard in the distal locking stage of the humerus intramedullary nails, and the "Inside-to-Out Distal Locking (IODL)" Method, which was developed as a new nailing model.

Methods: A total of 51 patients who underwent intramedullary nailing surgery due to humeral shaft fractures in our clinic were included in the study. Trigen Humeral nail (Smith and Nephew, Memphis, USA) with FHDL was used in 24 patients, and InSafeLock Humeral nail (TST, İstanbul, Turkey) with IODL in 27 patients. The effects of these two different nailing and locking techniques used in humeral shaft fractures in terms of surgical duration, radiation exposure duration, and functional/radiological results were evaluated.

Results: The mean follow-up period of the 51 patients (28 males and 23 females; mean age: 41.8 years) was 34.6 months (range: 9-76). According to the AO classification, 24 fractures were evaluated as type A, 17 were type B, and 10 were type C. The general evaluation of all cases revealed positive correlations between the surgical and radiation exposure durations ($r=0.855$; $p<0.01$). As the surgery duration prolonged, the ionizing radiation exposure increased. The comparison of the two groups determined a decreased surgical duration by 24.9 minute (81.6 min vs 106.5 min) and a decreased radiation exposure duration by 28.8 sec (17.7 sec vs 41.5 sec) in the IODL case group compared to the FHDL case group ($p<0.05$). The functional result evaluation revealed constant scorings that were satisfactory and close to each other in both groups (94.3 vs 93.3) ($p>0.05$). The full union was obtained in all patients except one case in the FHDL group. Symptomatic biceps tendinopathy findings were detected in four cases in the IODL group and five in the FHDL group. Local pain and sensitivity were detected in two cases in the IODL group in the form of impingement in the triceps olecranon insertion, where the distal end of the endopin is located.

Conclusion: Distal locking is the most problematic stage of humerus nailing surgeries. Adjustable external guides solve

ÖZ

Amaç: Bu çalışmada humerus intramedüller çivilerinin distal kilitleme aşamasında standart kullanılan "Serbest El Distal Kilitleme" (SEDK) yöntemi ile yeni bir çivi modelinde geliştirilen "İçten Dışa Distal Kilitleme" (İDDK) yönteminin karşılaştırılması amaçlanmıştır.

Yöntemler: Kliniğimizde humerus diafiz kırığı nedeniyle intramedüller çivi ameliyatı yapılan 51 hasta çalışmaya dahil edildi. Bu hastaların 24'ünde SEDK yapılan Trigen Humerus çivisi (Smith ve Nephew, Memphis, ABD), 27'sinde ise İDDK yapılan InSafeLock Humerus çivisi (TST, İstanbul, Türkiye) kullanıldı. Humerus kırıklarında kullanılan bu iki farklı çivi ve kilitleme tekniğinin; ameliyat süresi, radyasyon maruziyeti süresi ve fonksiyonel/radyolojik sonuçlar üzerine etkisi incelendi.

Bulgular: Çalışmaya dahil edilen 51 hastanın (28 erkek ve 23 kadın; ortalama yaş: 41,8 yıl) takip süresi ortalama 34,6 ay (dağılım: 9-76) idi. AO sınıflamasına göre kırıkların 24'ü tip A, 17'si tip B ve 10'u tip C olarak değerlendirildi. Tüm olgular genel olarak değerlendirildiğinde ameliyat süresi ve radyasyona maruziyet süreleri arasında pozitif yönde korelasyon olduğu saptandı ($r=0,855$; $p<0,01$). Ameliyat süresi uzadıkça ionize radyasyona maruziyetinin arttığı görüldü. İki grup karşılaştırıldığında; IODL olgu grubunda SEDK olgu grubuna kıyasla ameliyat süresinin 24,9 dakika (81,6 min vs 106,5 min), radyasyona maruziyet süresinin 28,8 saniye (17,7 sn vs. 41,5 sn) kısaldığı tespit edildi ($p<0,05$). Fonksiyonel sonuçlar değerlendirildiğine; her iki grupta birbirine yakın ve tatminkar Constant skorlamaları (94,3 vs 93,3) elde edildi ($p>0,05$). SEDK grubundaki bir olgu hariç tüm hastalarda tam kaynama elde edildi. İDDK grubundan dört olguda, SEDK grubunda ise beş olguda semptomatik biceps tendinopati bulguları görüldü. İDDK grubunda iki olguda endopinin distal uçunun bulunduğu triceps olekranon insersiosunda impingement tarzında lokal ağrı ve hassasiyet tespit edildi.

Sonuç: Distal kilitleme, humerus çivi ameliyatlarının en sorunlu aşamalarındandır. Dış kılavuzlar proksimal kilitleme sorununu çözebilirken, distal kilitlemede yetersiz kalmaktadır.

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the proximal locking problem; however, they are insufficient in distal locking. Therefore, the FHDL method is more preferred in distal locking, which causes problems like prolonged surgical durations and excessive ionizing radiation exposure.

The surgical duration shortened and ionizing radiation exposure decreased at significant levels in the IODL humerus nailing with endopin. In addition, the lack of additional incisions for distal locking will avoid possible neurovascular injuries and incision-related wound complications.

Keywords: Humerus diaphysis fractures, humerus intramedullary nailing, distal locking

Bundan dolayı distal kilitlemede freehand tekniği daha çok tercih edilmektedir. Bu da ameliyat süresinin uzaması ve aşırı ionize radyasyona maruziyet gibi problemlere neden olmaktadır. Endopin ile İDDK yapılan humerus çivisinde ameliyat süresinin kısaldığı ve iyoize radyasyona maruziyetin önemli ölçüde azaldığı görülmektedir. Ayrıca distal kilitleme için ek bir insizyonun gerektirmemesi, olası nörovasküler yaralanmaların ve insizyona bağlı yara komplikasyolarının önlenmesinde fayda sağlayacaktır.

Anahtar Kelimeler: Humerus diafiz kırıkları, humerus intrameduller çivileme, distal kilitleme

Introduction

Humerus diaphysis fractures account for 3-5% of all fractures in the body, and approximately 20% of the humerus fractures (1,2). Consensus on the best treatment approach for these fractures is unavailable (3). Surgical methods, such as intramedullary nailing, plaquing, or external fixation are often used in this respect in addition to non-surgical procedures like functional bracing (4). Open reduction and internal fixation with plaque/screw traditionally preferred surgical treatment methods for humerus shaft fractures. However, this method causes complications, such as radial nerve damage, fracture hematoma discharge, increased blood loss, periosteal blood flow deterioration, and postoperative infection, due to a direct fracture area exposure in open reduction (2,4,5). Therefore, intramedullary nailing gained popularity as a surgical method for humerus diaphysis fractures. Many authors argued that intramedullary nailing should be the standard approach in humerus diaphysis fracture surgery (2,6,7). Intramedullary nailing is a less invasive procedure that contributes more union by increasing fracture fixation stability, minimizes the risk of iatrogenic radial nerve damage, and reduces other complications based on open reduction (6,8,9). The most important disadvantage of intramedullary nailing is the difficulty in placing the nail and distal locking screws. Different distal locking systems were developed; however, the "Freehand Distal Locking (FHDL")" is still the most commonly used method. This method, which is based on blinded soft tissue dissection to minimize iatrogenic neurovascular injury, requires surgical expertise. In addition, it prolongs the general surgical duration and increases the ionized radiation exposure duration in the patient and the surgical team (10-12). Novel implant designs were developed to make the distal locking technique safer and overcome these problems (10).

This study aimed to clinically compare the humerus intramedullary nails in which two different distal locking techniques were used.

Methods

Necessary permissions for this retrospective study were obtained. The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 1863, date: 14.06.2019). Informed consent was obtained from all study participants. Patients who applied to our emergency department with humeral shaft fractures, who underwent antegrade intramedullary nailing surgery between January 2012 and December 2019, were included in this study. Patients with pathological fractures, vascular nerve injuries, open fractures, revision surgery cases, and are polytraumatized were excluded from the study. The gender, age, fracture type, intra- and postoperative complications, radiation exposure during surgery, and surgical duration of patients were recorded and examined. Graphics in routine clinical follow-ups were evaluated. Functional scoring of patients was made according to the latest clinical follow-ups. Patients were divided into two groups according to the nail model used in fracture fixation. A total of 24 cases using the Trigen Humeral nail (Smith and Nephew, Memphis, USA) had FHDL technique and 27 cases using the "Inside-to-out Distal Locking (IODL)" technique had an endopin sent through InSafeLock Humeral nail (TST, İstanbul, Turkey) were included in the study.

Surgical Technique

A similar surgical technique was used in both groups until the distal locking stage of the nail. Patients in lounge-chair position under general anesthesia first underwent prophylactic antibiotherapy with 1 gr of intravenous cefazolin. Preparations were made for necessary sterilization. Approximately 3 cm anterolateral incision was made toward the distal from the acromion to reach the top of the humerus. The entry point of the nail was between the tuberculum majus and sulcus intertubercularis medial, and on the posterior lateral biceps tendon. From this point, a guide K-wire and C-arm were sent to the metaphysis medulla. The nail entry point was expanded by carving as large as the diameter of the nail over the K-wire. The fracture was reduced under the C-arm control. The guide was passed through the fracture line, and the distal fracture part was advanced toward the end of its medulla. The nail size used for fixation was determined with another guidewire of the same size. Starting with the smallest reamer over the guidewire in the medulla, a carving was made to send the thickest nail possible. For proximal screw locking, the nail in an appropriate size and thickness attached to the external guide was inserted into the medulla. Then the surgery team moved on to the intramedullary locking stage of the nail. After which, proximal screw locking was made in the FHDL group, firstly over the external guide. Then, the distal screws were inserted with the FHDL technique under the scope control with mini-incision. In this technique, the distal locking hole of the nail was found with the perfect circle technique in lateral imaging and then drilled. Before leaving the

drill from the locking hole, the procedure was checked with anterior-posterior and lateral imaging. After the screw insertion, the screw position is rechecked with lateral imaging. If the image of the circle in the monitor was closed with the screw head, the locking was considered successful. In the IODL group, the humerus distal posterior cortex in the distal end of the nail was drilled inside-out with the K-wire sent through the nail channel. Distal locking was performed with the endopin sent from the nail channel (Figure 1A). The InSafeLock humerus nail is designed to keep the proximal end of the endopin below the proximal locking screws of the nail. In this way, it allows proximal locking over the external guide (Figure 1B). After the proximal locking, the incision was closed and the surgery was terminated (Figure 1C). Patients who started exercises on the postoperative second day in both groups were discharged and called for routine follow-ups.

Statistical Analysis

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program was used for statistical analyses. The descriptive statistical methods (mean, standard deviation, median, frequency, ratios, minimum, and maximum) were used in analyzing the study data, as well as the Mann-Whitney U test to compare the variables without normal distribution in quantitative data. The Spearman Correlation Analysis was used to evaluate the relationship among the quantitative variables. The significance level was evaluated at $p<0.05$ levels.

Results

The study included 51 patients (28 males and 23 females; mean age 41.8 years) who underwent intramedullary humerus nails. The follow-up time was 34.6 months on average (distribution: 9-76). According to the AO classification, 24 fractures were evaluated as type A, 17 as type B, and 10 as type C. The nail selection used in the fracture detection did not depend on any rule but was made according to the nail model supplied by our hospital purchasing unit.

The general evaluation of all cases revealed a positive correlation between the surgical and radiation exposure duration ($r=0.855$; $p<0.01$) (Table 1). The comparison of both groups revealed a decreased surgical and radiation exposure duration at significant levels in the IODL group compared to that of the FHDL group ($p<0.05$). The functional result evaluation revealed satisfactory and close to each other constant scores in both groups ($p>0.05$) (Table 2).

Union was achieved in all cases in the IODL group (Figure 2). Only one case had non-union in the FHDL group. The case revision surgery includes the intramedullary nails extirpation, open reduction, grafting, and plaque for fixation. The case with the union in the follow-ups was excluded from the study. In addition, symptomatic biceps tendinopathy findings were detected in four cases in the IODL group and five in the FHDL group. Soft tissue problems were not encountered in favor of impingement in the distal locking area of the FHDL group; however, local pain and sensitivity were described in two cases in the IODL group in the form of impingement in the triceps olecranon insertion, where the distal end of the endopin was located. Three patients in the IODL group and two in the FHDL group had a local infection in the shoulder incision area in the early postoperative period. In addition, local redness and mild discharge in the distal locking zone were observed in three patients in the FHDL group. All local infection findings were conservatively followed, provided with full cure.

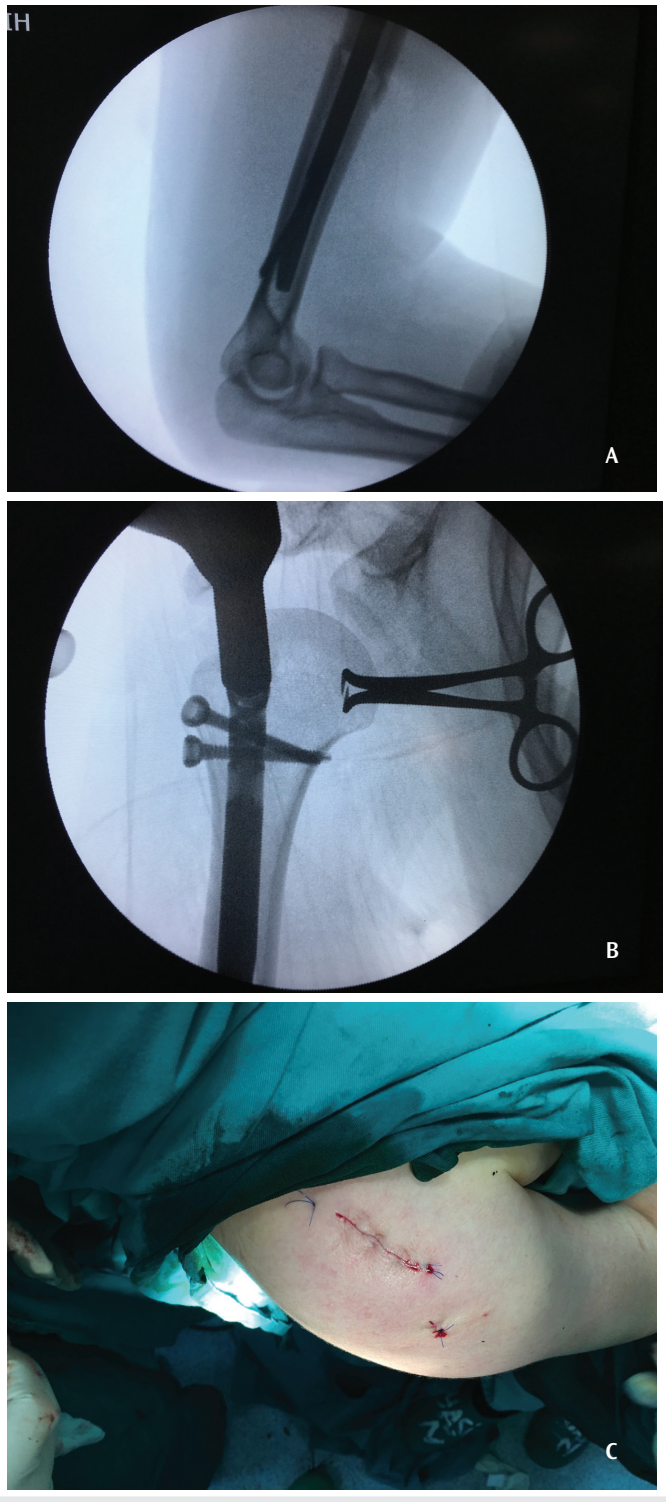

Figure 1. (A) A 22-year-old female lateral scope image after a distal lock with endopin, (B) scope image of the same case after proximal lock, (C) surgery incision image of the same case

Table 1. Relationship between surgical and radiation exposure durations

	Surgery duration-duration to radiation exposure	
	r	p
Total	0.855	0.001**
FHDL group	0.858	0.001**
IODL group	0.875	0.001**

r: Spearman's correlation coefficient, **p<0.01

Table 2. Evaluation of surgery duration, radiation exposure duration, and functional scoring according to groups

		Total	FHDL group	IODL group	p
Surgery duration (min)	Min-max (median)	52-184 (84)	68-184 (98)	52-158 (74)	0.018*
	Mean ± SD	92.91±32.52	106.47±34.58	81.61±26.61	
Duration to radiation exposure (s)	Min-max (median)	8-64 (22)	18-64 (38)	8-52 (13)	0.001**
	Mean ± SD	28.52±17.87	41.47±14.79	17.72±12.22	
Constant score	Min-max (median)	80-100 (96)	81-100 (96)	80-100 (96)	0.754
	Mean ± SD	93.82±6.25	93.27±6.88	94.28±5.84	

Mann-Whitney U test, *p<0.05, **p<0.01, Min: Minimum, max: Maximum, FHDL: Freehand Distal Locking, IODL: Inside-to-Out Distal Locking

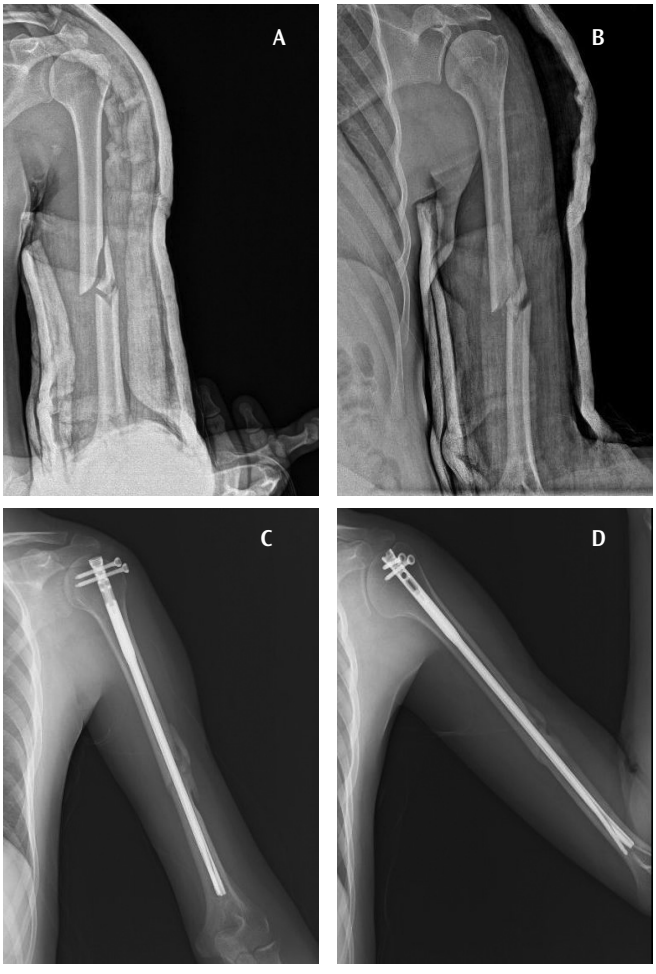

Figure 2. (A, B) Humerus diaphysis fracture preoperative bilateral X-ray image of a 32-year-old male, (C, D) bilateral X-ray image of the same case in postoperative 12th month

Discussion

Distal screw locking is one of the most problematic stages of humerus intramedullary nail surgeries. Standard external guides attached to the intramedullary nail proximally aiming to lock the extremities outside have greatly solved the problem of locking proximal holes. However, these guides cannot bring the targeted success in locking distal holes due to the deterioration of the compliance between the nail and the external guide as proceeded toward the distal area from the proximal bone area. The nail pushed to the medullary canal is forced to bend and twist, thus, the specific tilt design changes. Therefore, the adjustment between the rigid external guide and the nail, which is forced to take the bone medulla shape, is disrupted. As a result, the drilling to find the nail holes through the external guide goes off the intended track (2,13). In addition, the curved and narrowing anatomic structure of the distal humerus makes it difficult to drill the lateral cortex and frequently causes the drilling to shift from the targeted area. Moreover, the lack of the upper extremity fixation during surgery increases the probability of missing the distal nail hole by causing small rotational movements in the nail and the distal humerus fracture segment (2), causing the humerus nail to be abandoned during distal locking (2,14,15). Some researchers conducted studies on whether distal locking is required or not (14,15). A clinical trial compared the bipolar locking (proximal + distal) and unipolar locking (only proximal) application in the humerus nails and detected no significant differences between the two groups in terms of bone union and clinical outcomes (14). Another similar study reported radiological and functional positive results when the nail proceeded as much as possible toward the distal medulla area instead of a fixed distal locking area. The study emphasized that ideal nail size selection is important in surgery. Short nail selection would not end up with shoulder impaction, whereas long nails cause impingement in the shoulder. In addition, in the case of excessive nail impaction, iatrogenic fracture occurs, thus requiring technical skills and experience. In addition, the need for long-term immobilization was a weakness of

this method (15). Unlike these studies, mechanical studies have proven that distal locking was required for rotational and axial stability (16,17). The humerus intramedullary nailing, which is based on the principle of intramedullary area fixation without distal locking, is weaker against twisting and torsional forces compared to nailing the distal locking and emphasized that distal locking is necessary for proper fracture union and positive outcomes in functional terms (17). A mechanical study showed that this requirement is provided with the novel IODL technique by comparing the standard distal locking screw models (16). The biomechanical evaluation was not carried out in our study; however, the rotational and axial stability was provided clinically with both distal locking methods. The controls were confirmed to preserve the stability during surgeries and with the radiological/functional results in the follow-ups.

Electromagnetic-Guided Targeting (EMGT) system is often used in overcoming the distal locking problem in intramedullary nails (2,18-20). The EMGT system is effective in intramedullary nail surgeries in lower extremity fractures (2,18). A meta-analysis study showed that the EMGT system shortened the surgical duration and reduced ionizing radiation exposure in the femur and tibia intramedullary nail surgeries. The study determined that the EMGT system decreased the locking time in distal screws by 4.1 min (7.0 vs 11.1), the radiation exposure duration by 25.3 sec (5.4 vs 30.7), and surgical duration by 10 min (69.0 vs 79.0) compared to that of the FHDL technique. In addition, the success of the EMGT system in achieving the target was similar to that of the FHDL technique (18). The EMGT system is successful in intramedullary nailing of the lower extremity; however, its efficiency in humerus intramedullary nailing is controversial (2,11). The EMGT system did not have any success superiority to FHDL system in distal locking in humerus intramedullary nails and did not make a significant difference in total surgical duration (70.0 vs 71.9) (2). However, our study observed that the surgical duration (106.5 min vs 81.6 min); therefore, the radiation exposure duration (41.5 sec vs 17.7 sec) was prolonged when the FHDL technique was used. The IODL technique was applied in a newly-developed humerus nail, thus no published studies comparing it with EMGT were found in the literature review. A separate apparatus and fluoroscopic imaging are required to detect the appropriate screw size for the screw delivery in the EMGT system. However, the IODL technique uses predetermined endopin sizes according to the nail size. No fluoroscopic imaging is required to determine the endopin size. Therefore, the IODL technique is advantageous compared to the EMGT system.

These different locking methods used in humerus intramedullary nails bring with them some iatrogenic injuries. However, with the evolving nailing technologies, injuries were minimized especially in the proximal locking area (10,21). The different techniques applied for the distal locking area change the rate of injury. A previous study compared two different nail models in an anatomical cadaver in terms of nerve injuries, wherein the IODL technique (InSafeLock Nail) was applied to the right humerus of seven cadavers for distal locking and the FHDL technique (Trigen nail) was applied to the left humerus. Then, the distal and proximal locking areas were dissected and examined. The proximal locking areas of the nails were similar and safe in terms of nerve injuries. In the distal region, the neurovascular structures in the nails that underwent the IODL technique were in the safe zone; however, the screws were close to the radial nerve (9 mm on average) in the nails with the FHDL technique. The lack of an extra incision in the IODL technique contributed to the neurovascular structure protection. The study reported that the surgical duration decreased in the IODL technique when surgical durations of both techniques were compared (10). Our study, parallel to this study, revealed that the IODL technique was more advantageous in terms of surgery than the FHDL technique. The clinical outcome evaluation determined that neurovascular complications were not seen in any of our patients and both nails were similarly safe.

Another possible complication of intramedullary nail surgeries of humerus fractures is iatrogenic tendon injuries. These injuries were related to the nail model, the nail entry point, and the locking method. This problem is minimized parallel to the developing nail designs.

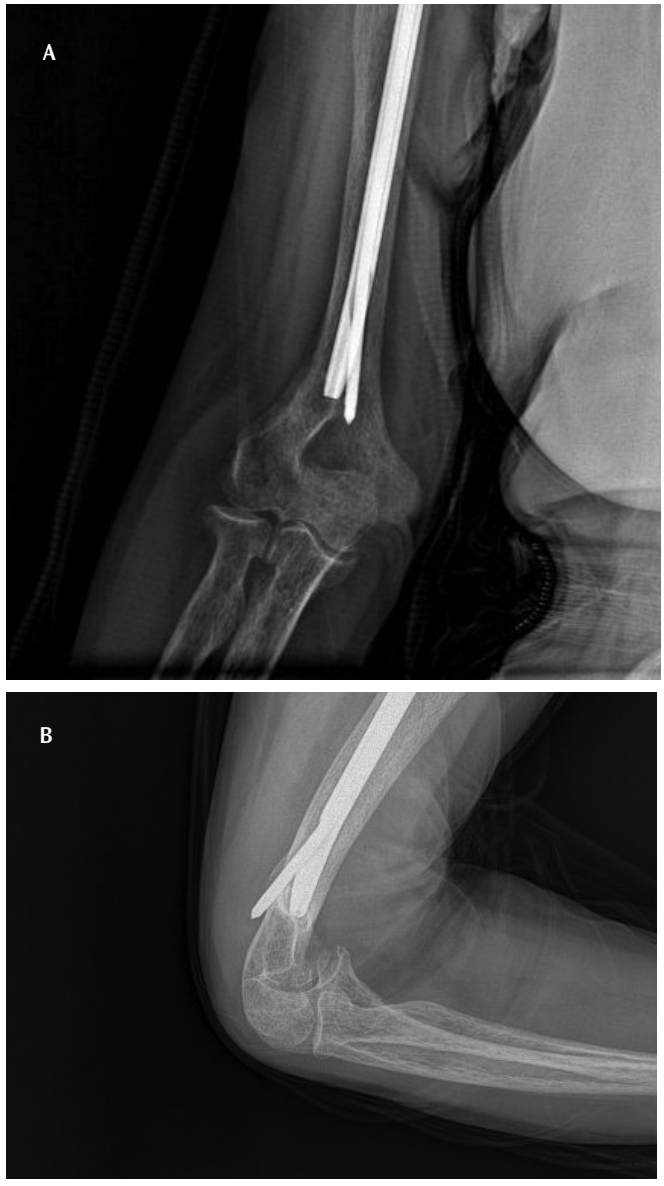

Figure 3. (A, B) bilateral X-ray image of a 54-year-old male patient describing pain in the postoperative posterior elbow

Especially the flat, small-diameter, and lock design of the third-generation intramedullary humerus nails ensures that the integrity of the rotator cuff is maintained (21,22). A previous study reported that the rotator cuff tendon lesions in these nails were rare and asymptomatic, with prevalence close to the general population. The same study showed that biceps long-head tendinopathy is more frequent (20% of the total cases) and symptomatic. Technical problems were emphasized to cause this (21). Our study not detected soft tissue problems in the distal locking area in the FHDL group; however, two cases experienced pain and sensitivity in the distal end of the endopin located in the posterior elbow area in the IODL group, which is believed to be caused by using an endopin, which is incompatible with nail length because of a technical mistake (Figure 3A, B). The proximal area examination detected symptomatic biceps tendinopathy in the nails of five cases in the FHDL group and four cases in the IODL group. The complaints regressed with conservative treatment in all patients who had symptomatic soft tissue problems. No complications were detected that require nail extirpation in any of our patients who use InSafeLock nails. The Trigen nail was extirpated in a patient who developed non-union; after removing the locking screws from the same incision areas, it was extirpated as standard other long bone nails. Any literature data on the extirpation of InSafeLock nails, which are a new design, were unavailable.

Study Limitations

The retrospective nature and the small number of cases are the main limitations of our study. In addition, the time of radiation exposure during the distal locking stage was not calculated because the duration was recorded as total time in surgical documents. Mechanical and anatomical studies are found in the literature regarding nail application by using IODL technique. However, any clinical trials on this nail in the literature review are unavailable. This present study is one of the leading clinical trials comparing the IODL technique and traditional FHDL technique.

Conclusion

The distal locking stage is the main determinant of future intramedullary nail designs. Electromagnetic locking apparatus developed in recent years, such as computer-assisted navigation systems, different nail designs, etc, show this situation. The IODL technique in the novel InSafeLock nail design is a practical solution to the distal screw locking stage of humerus intramedullary nail surgeries, which are difficult and time-consuming.

Ethics Committee Approval: The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 1863, date: 14.06.2019).

Informed Consent: Informed consent was obtained from all study participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.B., Y.Ö.; Concept - A.B.; Design - A.B., Y.Ö.; Data Collection or Processing - A.B.; Analysis or Interpretation - A.B.; Literature Search - A.B., Y.Ö.; Writing - A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Renal Arterial and Venous System Variations in 1,073 Kidney Donors in Turkey

1.073 Türk Böbrek Donöründe Renal Arterial ve Venöz Sistem Varyasyonları

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ABSTRACT

Introduction: Renal vasculature variations are seen in both arterial and venous systems. In Turkey, 80% of kidney transplantations are performed by living donors. Therefore, this study aimed to identify the incidence and morphologic variations of renal vessels in a group of Turkish kidney donors.

Methods: The computed tomography angiography of 1,073 kidney donors were retrospectively evaluated for vascular variations, such as multiple renal arteries (MRA), polar or accessory renal arteries (ARA), early division of renal artery, multiple renal veins (MRV), retro-aortic renal vein (RARV), and inferior vena cava duplication.

Results: One vascular variation in the renal vascular system was found in 637 of 1,073 (59.4%) kidney donors. The MRA was observed in 380 (35.4%) donors. The ARA were reported in 180 (16.8%) and 227 (20.2%) donors, respectively. Renal arteries were divided earlier than expected in 230 (21.4%) donors. The MRV and RARVS were seen in 205 (19.1%) and 77 (7.2%) patients, respectively. Only 2 cases of inferior vena cava duplication were determined.

Conclusion: Renal arterial and venous system variations are very common, and detailed preoperative evaluation provides an opportunity to choose the best surgical modality and minimize intra- and post-operative complications.

Keywords: Renal arterial variations, renal venous variations, multiple renal artery, multiple renal vein

ÖZ

Amaç: Renal vaskülatür varyasyonları hem arteriyel hem de venöz sistemlerde görülür. Türkiye'de böbrek nakillerinin %80'i canlı vericiler tarafından yapılmaktadır. Bu yüzden, bu çalışma, bir grup Türk böbrek donöründe böbrek damarlarının insidansını ve morfolojik varyasyonlarını belirlemeyi amaçladı.

Yöntemler: Bin yetmiş üç böbrek vericisinin bilgisayarlı tomografi anjiyografisi; çoklu renal arterler (MRA), polar veya aksesuar renal arterler (ARA), renal arterin erken bölünmesi, çoklu renal venler (MRV), retro-aortik renal ven (RARV) ve inferior vena kava duplikasyonu gibi vasküler varyasyonlar açısından retrospektif olarak değerlendirildi.

Bulgular: Renal vasküler sistemde bir vasküler varyasyon 1.073 böbrek vericisinin 637'sinde (%59,4) bulundu. MRA, böbrek donörünün 380'inde (%35,4) saptanmıştır. ARA varlığı sırasıyla 180 (%16,8) ve 227 (%20,2) donörde tespit edilmiştir. 230 (%21,4) canlı böbrek donöründe renal arter beklenenden erken dallanmıştır. MRV ve RARV sırasıyla; 205 (%19,1) ve 77 (%7,2) hastada görülmüştür. Sadece 2 olguda vena cava inferior duplikasyonu saptandı.

Sonuç: Renal arteriyel ve venöz sistem varyasyonları çok yaygındır, ve detaylı preoperatif değerlendirme, en iyi cerrahi tekniği seçme, intra-operatif ve post-operatif komplikasyonları en aza indirme fırsatı sağlar.

Anahtar Kelimeler: Renal arteriyel varyasyonlar, renal venöz varyasyonlar, multipl renal arter, multipl renal ven

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Introduction

Kidney transplantation is the most desired and cost-effective renal replacement therapy modality for patients with end-stage renal disease (ESRD). Living kidney donation has gained importance in ESRD treatment in response to increasing organ need and shortage.

Renal vascular variations are common in the general population and essential for preoperative surgical evaluation. A wide range of variations is observed in both renal arterial and venous systems, with unequal prevalence in different populations (1). Ethnic and racial differences cause a wide range of variation frequencies worldwide (1,2).

This study aimed to define and detect the rate of renal vascular variations in living kidney donors from our transplant center in Turkey.

Methods

A total of 1,073 patients underwent living kidney donation from October 2010 to September 2020 in our center. Informed consent was obtained preoperatively from all donors and recipients. Computed tomography (CT) angiography (Siemens SOMATOM definition AS CT scanner, Siemens AS, Berlin and Munchen) was performed preoperatively on every living donor candidate to determine renal vascular anatomy and surgical modality. A volume of 70-90 mL of non-ionic contrast medium was injected at 3.5-4 mL/s through an antecubital vein with an automatic power injector. Images were obtained from the level of the diaphragm to the end of the pelvis. Axial, sagittal, coronal, and three-dimensional reconstruction images were assessed by a radiologist.

Reports of CT angiograms were retrospectively investigated to confirm renal vessel number and morphology. Renal arterial blood supply variations were grouped under three titles: Accessory renal artery (ARA), polar renal artery (PRA), and early division (ED) (Figure 1, 2). An additional renal artery, which arises from the abdominal aorta and enters the renal hilum other than the main renal artery, was named ARA (1,3,4). Renal arteries that directly enter into the kidney poles were called PRA (1,5). The presence of ARA or PRA was categorized as multiple renal arteries (MRA). ED of the renal artery was defined as branching within the proximal 1.5 cm of the main renal artery (6,7).

Variations in renal venous vasculature occurred in three different types: Multiple renal veins (MRV) (Figure 3), retro-aortic renal vein (RARV) (Figure 4), and inferior vena cava duplication (Figure 5). An additional renal vein that arises from the renal hilum and separately drains into the inferior vena cava from the main renal vein was named MRV (6). RARV means the abnormal passage of renal vein posterior to the aorta and drains into the inferior vena cava (8,9). A couple of infra-renal inferior vena cava was defined as inferior vena cava duplication (10). This study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Ethical Committee (approval number: 2021-06/22, date: 24.03.2021).

Statistical Analysis

Statistical analysis was done by Statistical Package for the Social Sciences software, version 24 (SPSS, Chicago, IL). Demographic data were expressed as mean ± standard deviation of ages and gender frequencies. A chi-square test was used to search the correlation between the gender and renal arterial and venous system variations. A p-value of <0.05 was considered statistically significant.

Results

The study group included 481 (44.8%) males and 592 (55.2%) females with a mean age of 49±12.4 years. Frequencies and percentages of renal

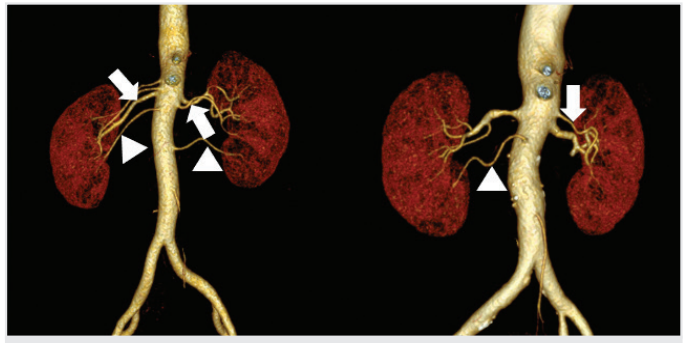

Figure 1. Three-dimensional computed tomography reconstruction of the abdominal arteries; accessory renal artery (arrow), polar renal artery (arrowhead)

Table 1. Frequencies and percentages of renal vascular variations

Type of vascular variations	Male (%)	Female (%)	Total (%)
Renal arterial variations			
Multiple renal artery	181 (16.9%)	199 (18.5%)	380 (35.4%)
Accessory renal artery	119 (11.1%)*	108 (10.1%)*	227 (20.2%)
Polar renal artery	78 (7.3%)	102 (9.5%)	180 (16.8%)
Early division	97 (9%)	133 (12.4%)	230 (21.4%)
Renal venous variations			
Multiple renal vein	93 (8.7%)	112(10.4%)	205 (19.1%)
Retro-aortic renal vein	33 (3.1%)	44 (4.1%)	77 (7.2%)
Vena cava inferior duplication	1 (0.1%)	1 (0.1%)	2 (0.2%)
Any vascular variation	293 (27.3%)	344 (32.1%)	637 (59.4%)

Statistically significant association was found between the male gender and ARA in this study, *$p<0.05$

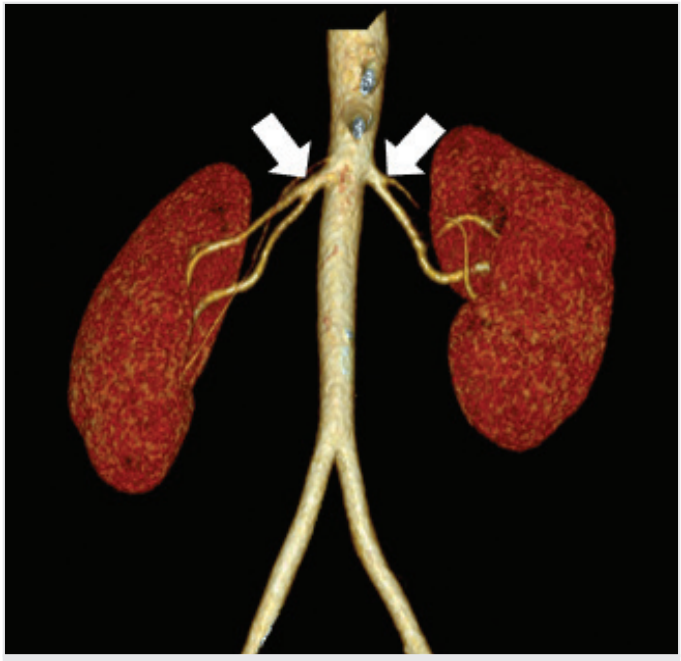

Figure 2. Three-dimensional computed tomography reconstruction of the renal arteries; early division point of the renal artery (arrow)

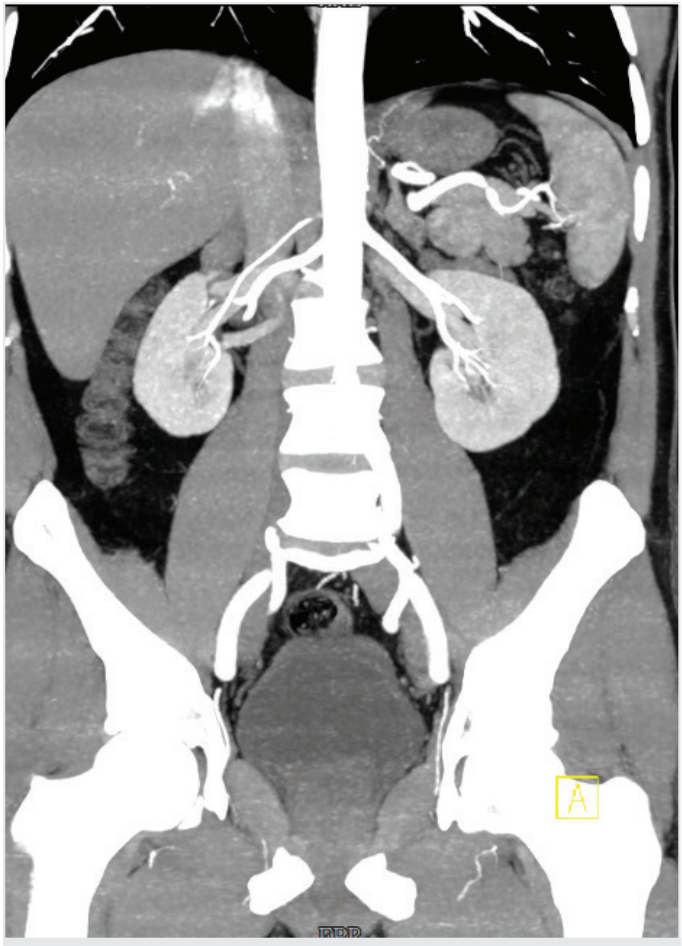

Figure 3. Coronal section of abdominal computed tomography angiography; multiple renal veins (arrow), polar renal artery (arrowhead)

vascular variations are demonstrated in Table 1. MRA was found as the most common variation in the renal arterial system and MRV in the renal venous system.

A correlation was found between MRA and MRV in our study (p=0.001). MRA and MRV were seen concurrently in 93 (8.7%) kidney donors. ARA had simultaneous PRA in 26 (2.4%) donors (p=0.016). MRV appeared with ARA in 63 (5.9%) donor candidates (p=0.001).

ARA was more commonly seen in male patients (p=0.01). No statistical significance was found between the existence of any other renal arterial or venous system variations and gender (p>0.05).

Discussion

Variations of renal vasculature are seen in a wide range, with a critical role in many invasive procedures, especially in renal transplantation (11,12). Different rates of renal vascular variations were found in

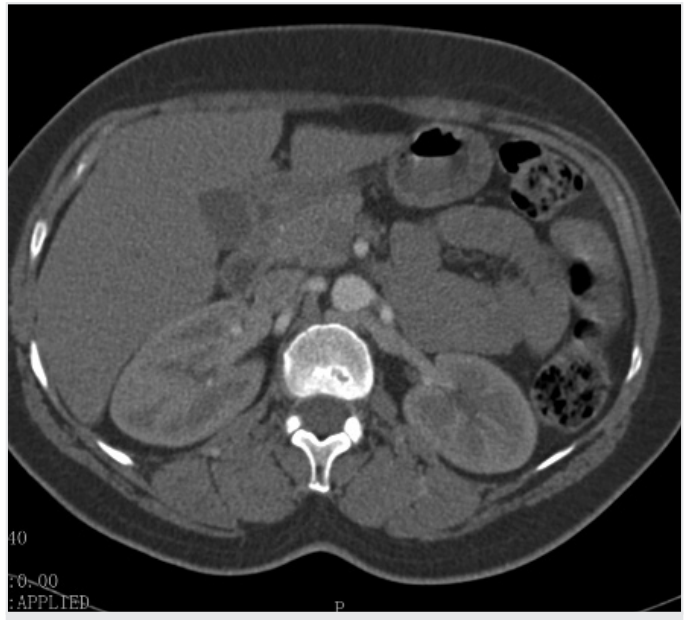

Figure 4. Transverse scan of abdominal computed tomography angiography; retro-aortic renal vein (arrow), aorta (arrowhead)

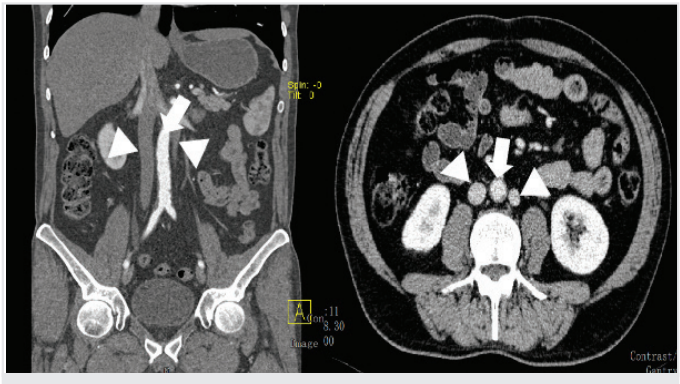

Figure 5. Coronal and transverse imaging of abdominal computed tomography angiography; vena cava ınferior duplication (arrowhead), aorta (arrow)

ethnically different populations (2,13). Complex renal embryogenesis, the sensitivity of visualizing technique, and the type of population are the causative factor for different MRA frequencies (14).

The MRA incidence fluctuates from 4% to 61.5% in literature (14). In the Turkish population, MRA frequency was established in 24-42% (1,7,9,12). This study revealed the MRA percentage (35.4%) was compatible with the Turkish population-based studies. Remarkable different percentages of ED were found by Çınar and Türkvatan (9), Ozkan et al. (1), and Gümüş et al. (7) in the Turkish population; 6%, 5%, 8%, and 26,7%, respectively. The prevalence of ED was found in 21.4% in our study.

The MRV incidence was established in 10.4-29% in literature (5,15,16). The MRV incidence is manifested in 21.6% and 18.8% in the Turkish population as reported by Çınar and Türkvatan (9) and Koc et al. (10), respectively. RARV occurs in a lower number compared to renal vein multiplication in the Turkish population between 3.1-4.7% in different studies (2,9,13,17). A comparatively higher prevalence (7.2%) was detected in the present study. The incidence of inferior vena cava duplication was determined in 0.1% and 0.2% in Turkey-based studies and the compatible result (0.2%) was obtained from our study (2,10,18).

In 2016, Çınar and Türkvatan (9) declared no association between the renal arterial and venous system variations. However, in our study, an association was found between MRA and MRV, ARA and MRV, PRA and ARA ($p=0.001$; $p=0.001$; $p=0.016$, respectively).

Gümüş et al. (7) found a higher prevalence of MRA and ED in males [($p=0.043$) and ($p=0.006$), respectively]. In 2012, Dilli et al. (2) revealed that RARV was two times more common in females than in males ($p=0.036$). However, this study found a statistically significant association between the male gender and ARA ($p=0.01$).

Study Limitations

The limitations of this study are the lack of the circumaortic renal vein and the comparison of radiological and intraoperative findings of vascular variations.

Conclusion

Therefore, 59.4% of living kidney donors have at least one anatomic variation in renal vasculature. MRA and MRV are the most common variations in the renal vascular system. Since 80% of kidney transplantation is performed from living donors in our country, renal vasculature variations must be evaluated before the operation to prevent possible intraoperative complications.

Ethics Committee Approval: This study was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Ethical Committee (approval number: 2021-06/22, date: 24.03.2021).

Informed Consent: Informed consent was obtained preoperatively from all donors and recipients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - A.H.K., Ü.Ç., İ.B.; Design - T.E., G.Y., Ü.Ç., İ.B.; Data Collection or Processing - U.C., E.Ö.; Analysis or Interpretation - U.C., G.Y., Ü.Ç., İ.B.; Literature Search - A.H.K., S.A.V.P.; Writing - A.H.K.

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The Comparison of the Long-Term Efficiency of Short Columellar Strut Graft and Suture Techniques on Maintaining Nasal Tip Projection and Nasolabial Angle Following Primary Open Rhinoplasty

Primer Açık Yaklaşım Rinoplastide Burun Ucu Projeksiyonu ve Nazolabiyal Açının Uzun Dönem Korunmasında Sütür Teknikleriyle Greft Tekniklerinin Etkinliğinin Karşılaştırılması

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ABSTRACT

Introduction: We aimed at comparing nasal tip projection and nasolabial angle changes following primary open rhinoplasty with short-floating columellar strut graft and suture techniques.

Methods: Participants were divided into two groups depending on the type of technique employed. In the first group, short-floating columellar strut grafts were employed. The second group involved those who underwent suture techniques only.

Results: We included 119 patients who underwent primary rhinoplasty in the study. The mean value of preoperative nasolabial angle measurement was 92.77±8.5 degrees and 92.14±6.7 degrees in groups 1 and 2, respectively. Postoperative nasolabial angle measurement in group 1 was 107.2, 104.3 and 101.3 degrees in the 1st, 3rd, and 5th postoperative year, respectively. Postoperative nasolabial angle measurement in group 2 was 107.4, 104, and 102.2 degrees in the 1st, 3rd, and 5th postoperative year respectively. The mean value of preoperative nasal tip projection was 0.605±0.07 and 0.653±0.08 in groups 1 and 2, respectively. Postoperative nasal tip projection measurement in group 1 was 0.636, 0.632 and 0.627 in the 1st, 3rd, and 5th postoperative year, respectively. Postoperative nasal tip projection measurement in group 2 was 0.656, 0.634 and 0.632 in the 1st, 3rd, and 5th postoperative year, respectively.

Conclusion: Suture techniques were efficient than columellar strut grafts in maintaining the nasolabial angle but not the nasal tip projection when.

Keywords: Rhinoplasty, nasolabial angle, nasal tip projection

ÖZ

Amaç: Bu çalışmanın amacı, primer açık yaklaşım rinoplasti sonrası burun ucu projeksiyonunu ve nazolabiyal açı değişikliklerini short-floating kolumellar grefti ve sütür teknikleriyle karşılaştırmaktır.

Yöntemler: Hastalar burun ucu modifikasyonu için kullanılan tekniğin türüne göre iki gruba ayrıldı. Birinci grupta short-floating kolumellar greftler kullanıldı. İkinci grupta sadece dikiş teknikleri kullanıldı.

Bulgular: Çalışmaya 119 primer rinoplasti hastası dahil edildi. Preoperatif nazolabiyal açı ölçümünün ortalama değeri grup 1 ve grup 2'de sırasıyla; 92,77±8,5 ve 92,14±6,7 derece idi. Grup 1'de postoperatif nazolabiyal açı ölçümü postoperatif 1., 3. ve 5. yılda sırasıyla 107,2, 104,3 ve 101,3 derece idi. Grup 2'de postoperatif nazolabiyal açı ölçümü postoperatif 1., 3. ve 5. yılda sırasıyla; 107,4, 104 ve 102,2 derece idi. Preoperatif burun ucu projeksiyon ölçümü ortalama değeri grup 1 ve grup 2'de sırasıyla; 0,605±0,07 ve 0,653±0,08 idi. Grup 1'de ameliyat sonrası burun ucu projeksiyon ölçümü ameliyat sonrası 1., 3. ve 5. yılda sırasıyla; 0,636, 0,632 ve 0,627 idi. İkinci grupta postoperatif burun ucu projeksiyon ölçümü ameliyat sonrası 1., 3. ve 5. yılda sırasıyla 0,656, 0,634 ve 0,632 olarak hesaplandı.

Sonuç: Sütür tekniklerinin nazolabiyal açıyı korumak açısından etkili olduğunu, ancak kolumellar greftlerine kıyasla burun ucu projeksiyonunu sürdürmede etkisinin daha az olduğu anlaşılmaktadır.

Anahtar Kelimeler: Rinoplasti, nazolabial açı, burun ucu projeksiyonu

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Introduction

Rhinoplasty is one of the most common procedures performed by plastic surgeons, otolaryngology specialists, and maxillofacial specialists (1). These procedures are performed for reconstructive and esthetic purposes. Various nasal deformities may develop in patients as a result of posttraumatic injuries, congenital anomalies, and previous failed operations. These deformities cause possible difficulties in breathing in such patients. Functional problems can occur either alone or combined with disfigurement noticeable in external view. Rhinoplasty procedures have been under constant change and improvement throughout history.

One of the most difficult surgical stages is the part related to tip shaping, projection, and rotation (2). In previous studies, the measurements of nose dorsal length, columellar length, lobular length, nasocolumellar, and nasolabial angles were evaluated to enable the proper analysis of changes in nasal rotation and projection (3). In some of the procedures for tip shaping, rotation, and projection, supportive grafts were employed, and in some, combined techniques were employed (4-7).

The main goal of rhinoplasty is to improve the functionality of the nose as well as the structure (8). In other words, keeping the nasal airway passage is mainstay aims of this procedure. The surgery can either be approached through a closed or open technique. In general, open technique is more often employed. Although closed technique cannot be employed to any nose, it is beneficial for surgeons to know and apply both techniques (8). Prior to rhinoplasty, planning is made according to the face tip of the person, and the nose cartilage, bone, soft tissue, and skin are reshaped (9).

Preparation for rhinoplasty starts with the evaluation of the detailed patient history, detailed examination of the nasal airway, and nasofacial analysis of the patient. It is also important for the surgeon to understand the patient's expectations as well as determine the patient's compliance with this procedure. Eating habits should be checked, in order to predict conditions such as post-operatory ecchymosis bleeding can be more easily predicted (10). External valve, internal valve, conchae, and septum should be carefully examined for the evaluation of nasal airway. The presence of collapse was analyzed with the help of a speculum and by performing a deep inspiration (9). Deviation, tilt, spur formation, perforation, polyp, and tumoral masses should be noted (10). Paranasal computed tomography or other imaging methods should be taken in patients who are deemed necessary.

In rhinoplasty, alterations and corrections of the bone-cartilage roof, nasal dorsum, septal deviation, nasal tip shape, nasal floor, alar wings, tip rotation, alar flaring, columella, nostril, nasal projection are performed (1,4,8,10,11). It is performed under general anesthesia mostly except for some limited tip plasties. During the procedure, local solutions with adrenaline are injected to reduce the risk of bleeding in the surgical field. If we are careful during the local injection, unwanted consequences such as trigeminal cardiac reflex are prevented (12).

Tip shaping, which is one of the most important parts in rhinoplasty, should be to obtain a nose tip suitable for the patient's face and general nose shape. Nose tip has unique skin and cartilage structure, contours and curved shape (alar wing, and columella). Various types of suture techniques and graft types are used in tip shaping to obtain an appropriate stability and angle of the nose tip. Columellar strut grafts are frequently employed among other tip grafts such as lateral crural strut grafts, alar rim grafts, alar batten on-lay grafts, shield grafts, tip-on-lay grafts, floating grafts, caudal septal extension grafts (11,13). As revealed in the anatomical studies, a number of ligamentous structures are important for the structure nasal tip (14-16). Nasal tip skeletal cartilage structure is mainly formed of the caudal part of the septum and the alar cartilage structure. It should also be noted that nasal tip has its own tripod structure. Nasal tip changes can be made with surgical maneuvers in these structures. Tip defining points can be rearranged with resection or extension maneuvers performed medially, laterally, intermediate crus or septal distally. In addition, the projection can be reduced and increased (16-18). In primary rhinoplasty cases, the underlying anatomical causes of tip asymmetries are frequently the deformities in caudal septum, lower lateral cartilage, and anterior nasal spine (19,20). The excessive resection of the support cartilage tissue can also produce asymmetrical results (21,22).

Methods

This was a retrospective study. The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Local Ethics Committee (approval number: 2802, date: 16.04.2021). Informed consents granted by all patients. Patients operated for primary rhinoplasty with mild and moderate deformities between the years 2011 and 2015 were included in the study. Those with severe columellar and alar deformities, severely weak and asymmetric lower lateral cartilages and severely under projected nasal tips, where techniques such as tip grafting or septal extension might be required, were excluded from the study. All the patients were operated upon by the first author. The surgeon used short-floating columellar strut graft on all of his patients between the years 2011 and 2013. After 2013, the surgeon used suture techniques only. Moreover, the open approach was employed in all participants by performing transcolumellar and marginal incisions and dorsal hump reduction, septoplasty, septal graft harvesting, cephalic trimming, and lateral osteotomies. Spreader grafts were performed as required. The patients were divided into two groups depending on the techniques employed. In the first group, columellar short-floating strut grafts were placed for tip modification. The strut grafts were harvested from septal cartilage. In the second group, only sutures were used to modify the tip without any kind of graft. Transdomal, interdomal and septocrural sutures were used in all the patients in this group (group 1: Graft group, group 2: Suture group). Photoshop software CC 2015 (Adobe Systems, San Jose, California, USA) software was used to measure parameters with the Ruler tool for each patient. Nasal projection and nasolabial angle measurements were performed from preoperative, postoperative 1st year, postoperative 3rd year, and postoperative 5th year photos. Goode's method was used to measure nasal projection. Three fixed points including the most projected point of the nose tip, nasion, and and the alar point. In this method, the nose tip protrusion is calculated from the ratio of the distance from the alar point to the most reflected point of the nose tip and the distance from nasion to the most predicted point of the nose tip (Figure 1a). To assess nasal tip rotation, the nasolabial angle (the angle between the two lines drawn from

the subnasal point to the columella and the upper lip) was measured (Figure 1b).

Statistical Analysis

Descriptive analysis was performed using GraphPad Prism 7.0 software (GraphPad Software, Inc., La Jolla, CA, USA).

Results

We included 119 patients in the study. The mean age of participants was 29.2±7 (range: 21-54). Sixty-two were males while fifty-seven were females. In addition, 67 patients were in the suture group and 52 patients were in the graft group (Table 1). No major complications were encountered in any of the patients (Figure 2, 3).

The mean value of preoperative nasal tip projection measurement was 0.605±0.07 and 0.653±0.08 in groups 1 and 2, respectively. Postoperative nasal tip projection measurement in group 1 was 0.636, 0.632 and 0.627 in the 1st, 3rd, and 5th postoperative year, respectively. Postoperative nasal tip projection measurement in group 2 was 0.656, 0.634 and 0.632 in the 1st, 3rd, and 5th postoperative year, respectively (Figure 4, Table 2).

The mean value of preoperative nasolabial angle measurement was 92.77±8.5 and 92.14±6.7 degrees in groups 1 and 2, respectively. Postoperative nasolabial angle measurement in group 1 was 107.2, 104.3 and 101.3 degrees in the 1st, 3rd, and 5th postoperative year, respectively. Postoperative nasolabial angle measurement in group 2 was 107.4, 104, and 102.2 degrees in the 1st, 3rd, and 5th postoperative year respectively (Figure 5, Table 3).

There was a significant increase in nasal projection of the patients between preoperative and postoperative 1st year measurements in the graft group. There was no significant difference between preoperative and postoperative 5th year nasal projection measurement across patients in the graft group. Similarly, there was no significant difference between preoperative and postoperative 1th year nasal projection measurements

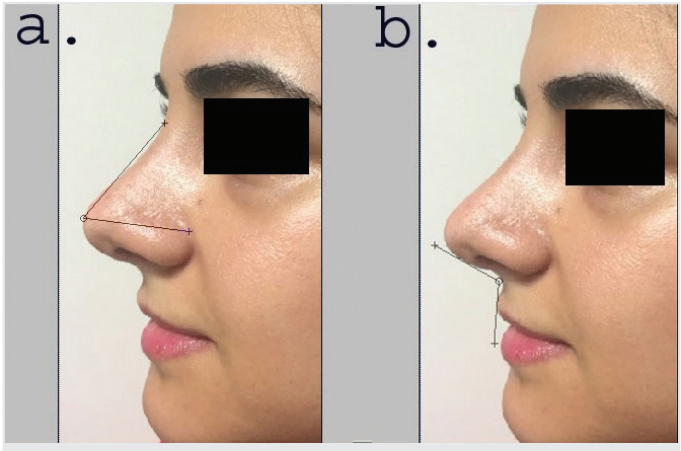

Figure 1. (a) Nasal tip projection calculation from photoshop software. (b) Nasolabial angle calculation from photoshop software

Table 1. Number of patients and sex distribution in each group

	Group 1 graft	Group 2 suture	Total
Male	25	37	62
Female	27	30	57
Total	52	67	119

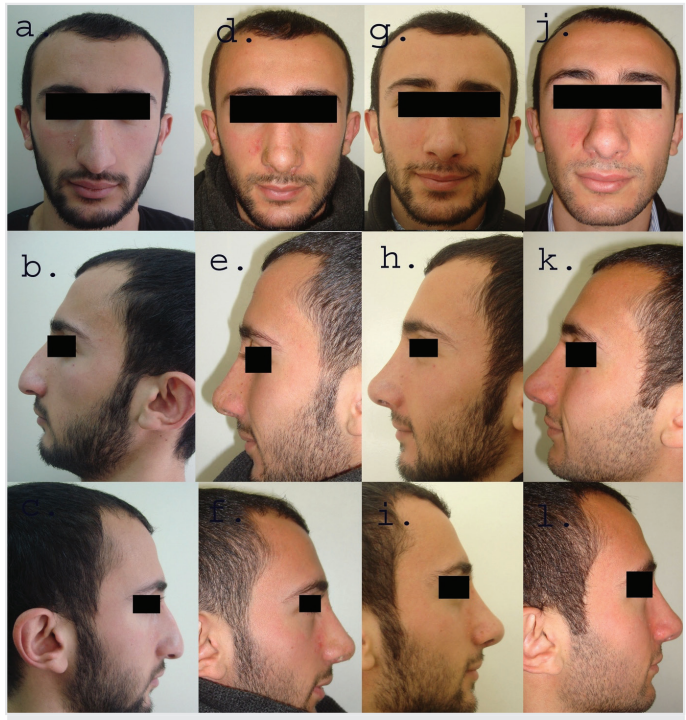

Figure 2. Preoperative (a, b, c), postoperative 1st month (d, e, f), postoperative 3rd year (g, h, i) and postoperative 5th year (j, k, l) photos of patient from the graft group

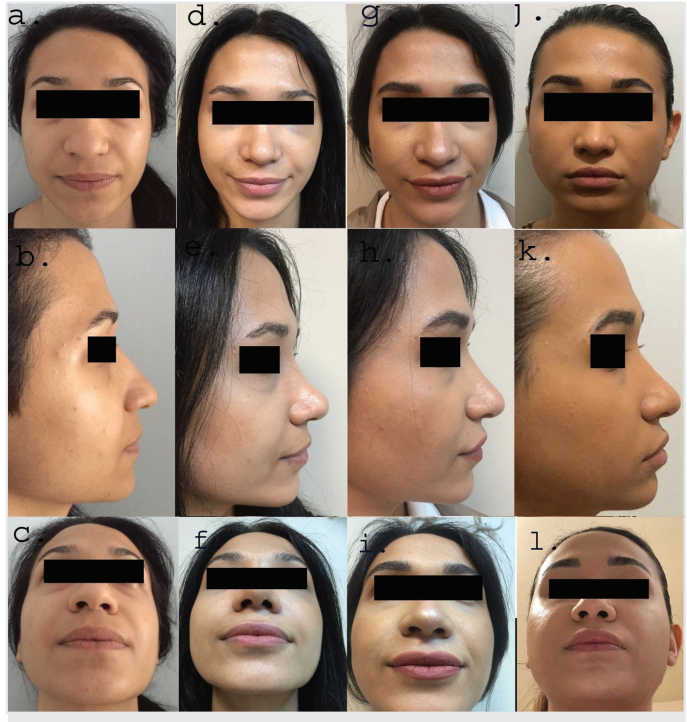

Figure 3. Preoperative (a, b, c), postoperative 1st month (d, e, f), postoperative 3rd year (g, h, i) and postoperative 5th year (j, k, l) photos of patient from the suture group

of the patients in the suture group. Moreover, there was a significant decrease in the nasal projection of the patients between preoperative and postoperative 5th year measurements in the suture group (Table 4).

There was significant increase in the nasolabial angle of the patients between preoperative and postoperative 1st, 3rd and 5th year measurements in the graft group as well as the nasolabial angle of patients between preoperative and postoperative 1st, 3rd, and 5th year measurements in the suture group (Table 5).

Discussion

In tip revision surgery, one of the main goals is to provide the projection appropriate for the facial expression and sex of the patient. Achieving a stable but also mobile nasal tip should be the ultimate goal. If possible, photographs of patients from their youth should be provided. These can provide a healthy planning strategy to the surgical team in the restructuring of the nose tip, especially in patients with a history of trauma or unsuccessful surgical intervention.

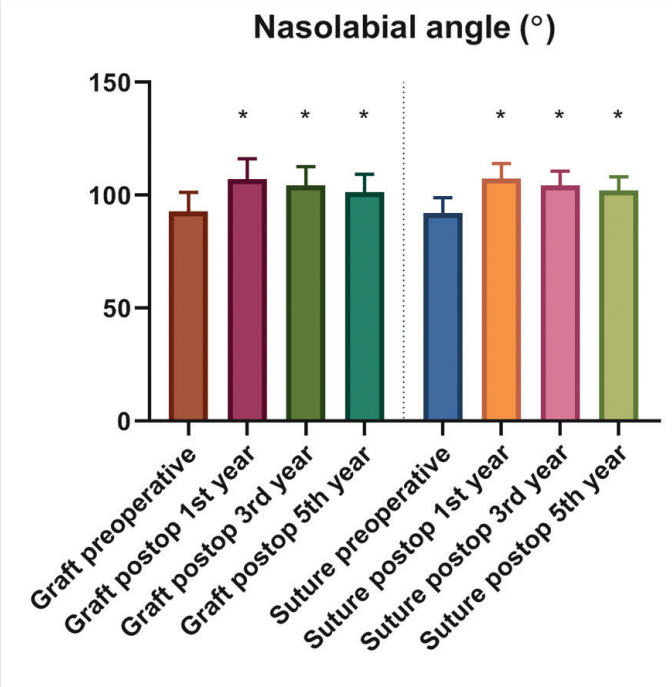

Figure 4. Nasal tip projection measurements
*: p<0.05 when compared to preoperative measurements

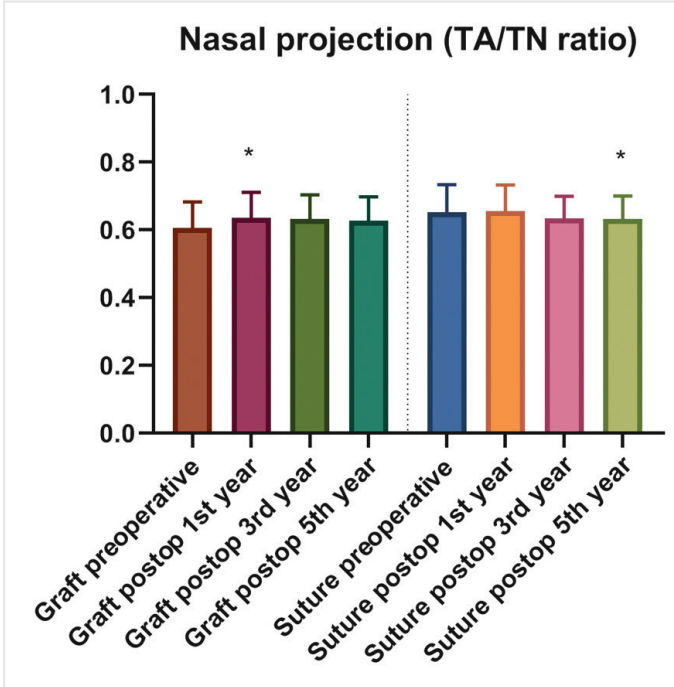

Figure 5. Nasolabial angle measurements
*: p<0.05 when compared to preoperative measurements

Table 2. The mean value of nasal projection measurements

	Preoperative	Postoperative 1st year	Postoperative 3rd year	Postoperative 5th year
Group 1: Graft group (n=52)	0.605±0.07	0.636	0.632	0.627
Group 2: Suture group (n=67)	0.653±0.08	0.656	0.634	0.632

Table 3. The mean value of nasolabial angle measurements

	Preoperative	Postoperative 1st year	Postoperative 3rd year	Postoperative 5th year
Group 1: Graft group (n=52)	92.77±8.5	107.2	104.3	101.3
Group 2: Suture group (n=67)	92.14±6.7	107.4	104	102.2

Table 4. Nasal tip projection measurements

Groups	Mean rank diff.	Significant?	Summary	Adjusted p-value
Graft pre vs Graft 1	-56.29	Yes	*	**0.0369**
Graft pre vs Graft 3	-52.61	No	ns	0.0512
Graft pre vs Graft 5	-44.01	No	ns	0.1028
Suture pre vs Suture 1	10.49	No	ns	0.6591
Suture pre vs Suture 3	46.4	No	ns	0.0509
Suture pre vs Suture 5	52.14	Yes	*	**0.0282**

Table 5. Nasolabial angle measurements

Groups	Mean rank diff.	Significant?	Summary	Adjusted p-value
*Graft pre vs Graft 1	-206	Yes	****	**<0.0001**
*Graft pre vs Graft 3	-167.7	Yes	****	**<0.0001**
*Graft pre vs Graft 5	-121.3	Yes	****	**<0.0001**
*Suture pre vs Suture 1	-230	Yes	****	**<0.0001**
*Suture pre vs Suture 3	-181.9	Yes	****	**<0.0001**
*Suture pre vs Suture 5	-146.8	Yes	****	**<0.0001**

In tip shaping, transdomal sutures, interdomal sutures, lateral crus cephalic trimming are applied as the standard surgical technique in most cases. Strut graft is frequently used to provide tip projection. This graft can be prepared as short and long form. The prepared strut graft can be placed free-floating between the medial crus or fixed to the anterior nasal spina.

Septocrural/septocolumellar suturing technique is frequently used in providing projection as well. Permanent monofilament prolene suture materials or monofilament pds-derived suture materials can be used in the septocrural suture technique. Since prolene suture material is permanent, they can cause exposure and foreign body reactions in the medium, especially in patients with thin skin. The polydioxanone suture maintains the proper nose tip position and stability until wound healing and adequate soft tissue support is achieved. Although there is no certainty about the number of septocrural sutures to be placed, at least two sutures are generally accepted. It is obvious that the fineness of the suture material used and the patient's cartilage tissue support are important to decide on this. In addition to graft and suture techniques, a combination of these or a number of other cartilage-like flap or suspension techniques are also used in projection and rotation improvement.

In our study, columellar strut grafts (short and floating) were used in the first group, while septocrural sutures without grafts were used in the second group. We have seen that projection loss was evident at five years following the surgery in the suture group when compared to the graft group. In a previous study by Şirinoğlu (4), no significant difference in the decrease of projection and nasolabial angle was found in the first month and first year after surgery between the short-floating strut grafts and the two septocolumellar sutures. We predict that this follow-up duration was not sufficient to observe the loss of the projection with the suture group (4). In the study of Rohrich et al. (5), 1,734 patients were evaluated retrospectively for 15 years. Effective results were observed with the use of columella strut grafts in long-term follow-up in cases with inadequate tip support and asymmetry (2,5). In another study, Cerkes (23) described problems related to the insufficient support of nasal tip, and explained the importance of the tripod structure of the nasal tip. The importance of this structure enables us to obtain desired results and aim for the adaptation of the collumellar and lateral crural grafts to be used in reconstruction so as to ensure symmetry and keep the nose tip support at the desired level (23). Cerkes (23) that deals with low dorsum, inadequate projection, and short nose features, short and weak alar cartilage structure is mentioned and racially based differences are mentioned. It is aimed to support the cartilage structure with the grafts which is weak to increase the tip projection (24).

Kuran et al. (3) analyzed postoperative 1st year dorsal length, columellar length, tip projection, tip projection/dorsal length ratios, columellar length/dorsal length ratios and a few more values in a 2-group 18-patient randomized study using cartilaginous graft and tip binding sutures. They found statistically significant values in both groups compared to preoperative measurements in most parameters (3). In another study by Kuran et al. (11), 11 patients were followed for 18 months. Cartilageinous flaps prepared from the lateral crus cephalic sections based on medial crus which minimized the rotational disorders and positively affected the symmetry of the dorsal aesthetic lines. The flaps used had a positive effect on projection depending on the dorsal adaptation points of pedicled cartilageinous grafts (11). Yeşiloğlu et al. (13) evaluated rotation, projection, and supratip deformities of 32 patients on average 2-year follow-up using the lateral cartilage-based cartilage suspension technique. The reversible technique is considered to be the most remarkable feature. The desired results were obtained in asymmetric patient rotations and therefore projection. Patient satisfaction was observed at a high rate (13).

Stephan and Wang (20) used the columellar strut graft effectively in asymmetrical nasal tip repair. Especially they achieved successful results with suture techniques that they combined in deviated noses. The importance of finding the underlying structural disorder before the tip asymmetry correction was emphasized in this study (20).

Cingi et al. (25) have done a comprehensive study on nasal tip sutures. They have detailed the positive effects of various suture techniques on projection and other structural problems. In our study, objective results were found to support these analyzes in patients using both strut grafts and suturing techniques (25). In a previous study the use of columellar strut grafts with the correct indication in patients with inadequate projection was emphasized. The importance of preoperative patient analysis was emphasized (26). Schinkel and Nayak (15) states that nasal tip surgery should be addressed at the initial stages of rhinoplasty surgery. It is necessary to have a good command of the tip anatomy for successful tip modification.

The values we obtained at the end of our 5-year follow-up period of mild and moderate deformed noses operated with the same technique showed that there was a decrease trend in projection and nasolabial angle in both the collumellar strut graft and suture group. The decrease between the first year and third year in the nasolabial angle in suture group was significant in only in suture group. The decrease between the

first year and fifth year in the nasolabial angle in both suture group and strut group was significant. But despite this decrease when compared with the preoperative nasolabial angle values, positive gain was observed at 5 years in both groups. If we interpret the results from here, it seems that the nasolabial angle values were maintained in the first 5 years follow-up in patients with mild and moderate deformed noses.

Study Limitations

This study had several limitations. This was a retrospective study and the patients were collected from a single-center. Patient standardization was not perfect and future prospective randomized studies can be beneficial to overcome these limitations and support our findings.

Conclusion

There was a significant difference in projection with the suture group when compared to the strut group in the postoperative fifth year measurements. This probably depends on the strength of the cartilage and in patients with weak cartilages, the projection was lost without a strut graft at the fifth postoperative year. The projection loss can also be attributed to the presence of deep tissue contraction which the sutures cannot withstand. In cases with strut grafts, the graft support provides a more resistant nose tip support, thus less projection loss is found. The preoperative projection values of the strut group patients we operated were less. Despite this, the long-term projection support was better provided, and the nasolabial angle sufficiently increased despite the decrease in both groups. In projection-related problems, using supporters such as strut grafts is more beneficial in cases where maintaining the projection is critical.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Local Ethics Committee (approval number: 2802, date: 16.04.2021).

Informed Consent: Informed consents granted by all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - D.A.; Concept - D.A., M.S.; Design - D.A., G.T., M.S.; Data Collection or Processing - D.A., G.T., M.S.; Analysis or Interpretation - D.A., G.T., M.S.; Literature Search - G.T., M.S.; Writing - D.A., M.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Prevalence and Associated Risk Factors of COVID-19 Infection Among Healthcare Workers in a Pandemic Hospital

Pandemi Hastanesinde Çalışan Sağlık Çalışanlarında COVID-19 Enfeksiyonunun Yaygınlığı ve İlişkili Risk Faktörleri

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ABSTRACT

Introduction: This study aimed to investigate the prevalence of Coronavirus disease-2019 (COVID-19) infection among healthcare workers in our hospital with the risk factors affecting the transmission and course of the disease and to determine the control measures.

Methods: Medical records of healthcare workers diagnosed with COVID-19, confirmed by polymerase chain reaction (PCR) between 11 March and 30 April 2020, were retrospectively analyzed in our hospital in the center of İstanbul, the city with the highest number of cases in our country. Real-time PCR detection was used to verify the diagnosis of the healthcare workers. A rapid diagnostic test kit for COVID-19 immunoglobulin M (IgM) and IgG antibodies was used in seroconversion analysis.

Results: In our hospital, 4,177 COVID-19 cases confirmed by the laboratory between March 11 and April 30 2020 were followed. Of the 4177 cases, 165 (3.95%) were healthcare workers. The majority of healthcare workers with positive test results were nurses (36.3%), and 118 (71.5%) of the healthcare workers worked 40 h or more per week. Thoracic tomography examinations were performed in all infected healthcare workers, and 69 (41.8%) were diagnosed with pneumonia by the detection of ground patchy lesions.

Conclusion: During the epidemic, early training of healthcare workers on the disease, use of personal protective equipment, and infection control are extremely important to reduce the risk of infection among healthcare workers. Periodic screening of asymptomatic healthcare workers can also help protect patients and hospital staff and prevent loss of workforce.

Keywords: Healthcare workers, risk factors, COVID-19

ÖZ

Amaç: Bu çalışmada, hastanemizde görev yapan sağlık çalışanlarının Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu prevalansı ile hastalığın bulaşını ve seyrini etkileyen risk faktörlerinin araştırılması ve kontrol önlemlerinin belirlenmesi amaçlanmıştır.

Yöntemler: Ülkemizde olguların en fazla olduğu şehir olan İstanbul'un merkezinde olan hastanemizde 11 Mart-30 Nisan 2020 tarihleri arasında polimeraz zincir reaksiyon (PCR) ile konfirme edilmiş COVID-19 tanısı alan sağlık çalışanlarının tıbbi kayıtları retrospektif olarak incelenmiştir. Sağlık çalışanlarının tanıları gerçek zamanlı PCR tespit yöntemi ile konulmuştur. Serokonversiyon incelemesi için hızlı test tanı kiti COVID-19 immünoglobulin M (IgM) ve IgG kullanılmıştır.

Bulgular: Hastanemizde 11 Mart-30 Nisan 2020 tarihleri arasında laboratuvar tarafından konfirme edilmiş 4.177 COVID-19 olgusu takip edilmiştir. Toplam 165'i (%3,95) sağlık çalışanıydı. Pozitif olanların çoğunluğunu hemşireler (%36,3) oluşturmakta ve sağlık çalışanların 118'i (%71,5) haftada 40 saat ve üzerinde çalışmaktadır. Enfekte sağlık çalışanın tümüne toraks tomografisi çekilmiş olup 69'unda (%41,8) yamasal lezyonlar saptanarak pnömoni tanısı konulmuştur.

Sonuç: Salgın sırasında sağlık çalışanlarının hastalıkla ilgili bilgilendirilme, kişisel koruyucu ekipman kullanımı ve enfeksiyon kontrolü ile ilgili eğitimlerinin erken dönemde yapılması sağlık çalışmalarında enfeksiyon riskini azaltma açısından son derece önemlidir. Asemptomatik sağlık çalışanlarının da düzenli aralıklarla taranmasının hastaların ve hastane personelinin korunması açısından faydalı olacağı ayrıca iş gücü kaybının da önüne geçileceği açıktır.

Anahtar Kelimeler: Sağlık çalışanları, risk faktörleri, COVID-19

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Introduction

The new Coronavirus disease-2019 (COVID-19) appeared in late December 2019 in Wuhan, the first epicenter in Hubei Province of the People's Republic of China (1). COVID-19 has a high mortality rate and progresses with severe pneumonia and acute respiratory distress syndrome (2). The responsible virus, named "Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)" by the Coronavirus Working Group of the International Committee on Taxonomy of Viruses because of its close resemblance to SARS-CoVs, is an enveloped RNA virus with a single chain and positive polarity and belongs to the Betacoronavirus family (3). Within 3 months of the first reporting of this new coronavirus, the number of cases exceeded 100,000 worldwide; on March 11, 2020, the World Health Organization (WHO) announced that COVID-19 became a pandemic (4). As of April 30, 2020, the number of cases was 3,090,445 in the world; the first case in Turkey was reported on March 11, 2020, with a total of 117,589 confirmed cases (5,6). The first case of COVID-19 in our hospital was confirmed on March 14, 2020.

SARS-CoV-2 is highly contagious and may have a long incubation period before symptoms such as fever, cough, shortness of breath, and diarrhea appear. SARS-CoV-2 infection may be asymptomatic in some patients, but it may also cause multiple organ failure with lung, heart, and liver involvement in some patients (7). While the fatality rate of the disease in the world is 6.89%, this value is 2.72% in Turkey (8).

COVID-19 is transmitted through contact and droplets and continues to spread rapidly, and the rate of virus spread (R0) is 2.55-5.7 (9,10). With the surge of COVID-19 cases, infection prevention and control practices in healthcare environments have become necessary. The personal protection of healthcare workers (HCWs) is highly important. The type and amount of personal protective equipment (PPE) that should be used when treating a patient with COVID-19 varies depending on clinical work and environment. Providing direct inpatient treatment to patients with COVID-19, HCWs should wear a medical mask, apron, gloves, and eye protection in the form of goggles or face shield. HCWs performing aerosol-producing procedures should wear an apron/overalls and use an N95 mask instead of a surgical mask (11). During a pandemic, the probability of transmission is very high. Given their significantly long work hours and aerosol-generating procedures, HCWs are highly at risk of contracting the disease and spreading it to inpatients and hospital staff.

WHO-China joint mission reported 3,387 COVID-19 cases among healthcare professionals at 476 medical institutions in China on February 25, 2020 (12). As of April 8, 2020, 22,073 COVID-19 infection cases among HCWs from 52 countries were reported to WHO (13). As of April 30, 2020, the Ministry of Health of our country reported that 7,428 workers were infected among 1 million 100 thousand HCWs (14).

Taking measures to prevent contamination among HCWs and continuous update of their knowledge of specific infections are crucial in the development and implementation of prevention programs. Determining the individual, operational, and institutional characteristics of contamination and preventive measures will be effective in developing the targeted part of prevention programs.

This study aimed to investigate the prevalence of COVID-19 infection among HCWs working in our hospital with the risk factors affecting the transmission and course of the disease and to determine the control measures.

Methods

Medical records of HCWs diagnosed in our hospital with COVID-19, confirmed by the laboratory between March 11 and April 30, 2020 were retrospectively analyzed. Our hospital, which was appointed as a pandemic hospital at the beginning of the outbreak, is a tertiary healthcare institution with 612 beds, 2737 HCWs (724 physicians, 864 nurses, 10 pharmacists, 978 allied health personnel, and 161 paramedics and technicians) located in the center of İstanbul, the city with the highest number of COVID-19 cases in Turkey.

This research protocol was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (approval number: 2020-10, date: 04.05.2020). All participants consisted of clinicians, nurses, and allied health personnel.

HCWs in different departments were divided into two groups according to risk exposure. Those working in departments where interventional medical or surgical procedures that produce respiratory aerosols are performed, including the COVID-19 clinic and intensive care unit, were identified as high-risk groups. Those working in other low-risk clinics and outpatient clinics were considered as the general group. All participants were given an informed consent form.

Clinical signs and symptoms and radiological examination results of the cases were recorded in the hospital system, and data were retrieved from the system retrospectively. Spectrum of illness severity was divided into four groups as defined by WHO (15). Diagnostic criteria for mild COVID-19 include mild clinical symptoms without evidence of viral pneumonia or hypoxia. Moderate COVID-19 symptoms incude pneumonia (fever, cough, dyspnea, fast breathing) and SpO_2 ≥90% on room air. Severe COVID-19 symptoms include pneumonia (fever, cough, dyspnea, fast breathing) plus respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 <90% in room air. Critical COVID-19 symptoms include respiratory failure, shock, or multiorgan dysfunction. These symptoms have been observed among HCWs. Real-time polymerase chain reaction (RT-PCR; Rotor gene Q, QIAGEN, Germany) was used for the diagnosis of HCWs. A rapid diagnostic test kit for COVID-19 immunoglobulin M (IgM) and IgG antibodies (Weimi Bio-Tech) was used in seroconversion analysis. The sociodemographic characteristics of the patients, time to symptomatic progression, history of contact, use of protective equipment, clinical findings, laboratory examinations, imaging data, treatment methods, and results were retrospectively analyzed by the workplace health unit.

Statistical Analysis

Numerical, percentage, and mean distributions of the patients' sociodemographic characteristics were analyzed, and Pearson chi square analysis was performed to compare pneumonia and risk groups and sociodemographic data. Logisitic regression analysis was applied in the multivariate analysis. Statistical significance was considered at $p<0.05$.

Results

A total of 165 (11.5%) of 1425 HCWs who had nasopharyngeal and oropharyngeal combined SARS-CoV-2 PCR tests between March 14 and April 30 were positive among HCWs with suspected contact or symptoms. The number of SARS-CoV-2 PCR-positive cases followed in the outpatient clinic and/or hospitalized in our hospital was 4177, and 79 (3.62%) HCWs were infected during the follow-up of the highest number of cases (2261) between April 1 and 15 (Graph 1). The average age of the HCWs who tested positive was 34.4±9.41; 46.1% of them were aged 18-30 years, and 66.7% were women. The majority of HCWs with positive test results were nurses (36.3%), and 118 (71.5%) of the HCWs worked 40 h or more per week. In terms of contact, 20 (12.1%) stated that they had contact with patients diagnosed with COVID-19 from outside the hospital in the last 14 days. In addition, 56 (33.9%) of them had a family member diagnosed with COVID-19 after the diagnosis. In terms of comorbidity, 127 (77%) did not have additional diseases, and 83 (50.3%) were not smokers. The number of staff working in the high-risk department was 108 (65.5%). Six of the HCWs had biological injuries, and 48 were in the same room when an aerosol treatment was administered to the patient. Sociodemographic data of the cases are listed in Table 1.

Approximately 47.9% of the patients were diagnosed between April 1 and 15. Considering the time of diagnosis, 24.2% were diagnosed 6-10 days after complaints. Twenty-nine of the cases (17.6%) were hospitalized and followed up. Depending on the disease severity, 158 (95.7%) cases were mild-moderate, 6 cases were severe, and only 1 case was critically ill, which was followed up in the intensive care unit. No case of death was reported. Findings related to the disease are shown in Table 2. Twenty-seven (16.4%) of the infected HCWs were asymptomatic, the most common clinical symptom was fever in 32.1%, and the most common complaint was myalgia with 46.1%. Computed tomography (CT) was performed in all infected HCWs, and 69 (41.8%) were diagnosed with pneumonia by the detection of ground patchy lesions. The significant variables in the univariate analysis according to clinical findings and pneumonia status are shown in Table 3. In univariate analysis, a statistically significant difference was found between pneumonia status and the variables of age, gender, fever, myalgia, and lack of symptoms ($p<0.05$). No significant difference was found between other variables and pneumonia ($p>0.05$). Important variables in univariate analysis were included in the multivariate analysis. The effects of age, gender, fever, and myalgia on pneumonia were evaluated using Enter Logistic Regression analysis. Results showed that the model was significant (Table 4). An increase of one unit in age increased the effect on pneumonia with an odds ratio of 1.043-fold (95% confidence interval: 1.006-1.082, $p<0.05$). Among the clinical findings, fever was found to be significant in patients with pneumonia ($p<0.05$).

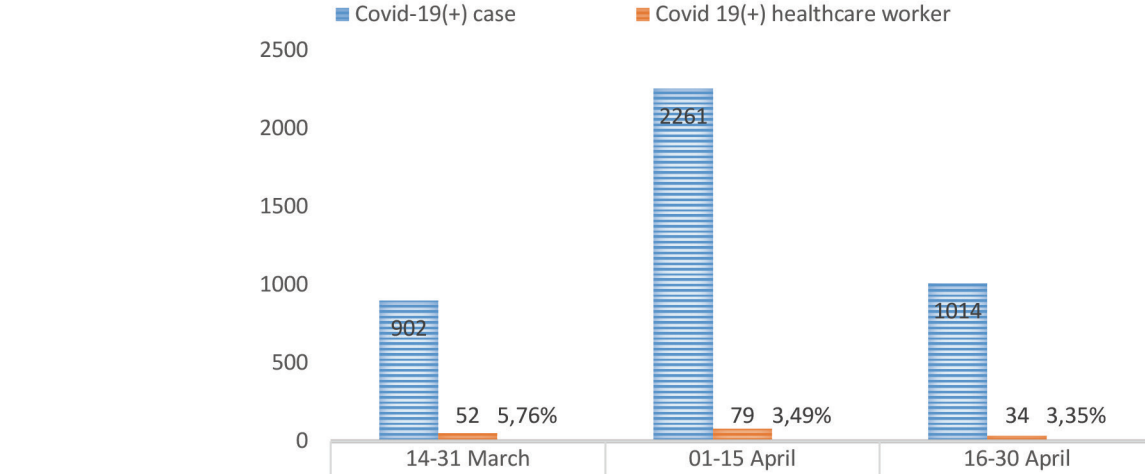
On the basis of the results of the rapid antibody test performed in the first month of their diagnosis, 61.9% had IgM and 64.3% had IgG. Antibodies were tested in 35 patients with pneumonia, of whom 30 (85.7%) developed antibodies, and this rate was significantly higher than those without pneumonia ($p<0.05$).

The examination of clinical findings of HCWs in risky departments entering the patient room and exposed to aerosol procedures revealed a statistically significant difference between the patients' risk status and additional disease and pneumonia status ($p<0.05$).

No statistically significant difference was found between the risk group and other variables ($p>0.05$). Findings of some variables with risk group are shown in Table 5.

Discussion

HCWs worldwide have been the vulnerable and most affected risk group because of their frequent and close contact with COVID-19 patients.



	14-31 March	01-15 April	16-30 April
Covid-19(+) case	902	2261	1014
Covid 19(+) healthcare worker	52	79	34
%	5,76%	3,49%	3,35%

Graphic 1. Number of infected patients and HCWs

HCW: Healthcare workers, COVID-19: Coronavirus disease-2019

Table 1. Sociodemographic variables

		n (165)	%
Age	18-30	76	46.1
	31-44	66	40
	≥45	23	13.9
Average		**34.4±9.41**	
Gender	Male	55	33.3
	Female	110	66.7
Occupation	Doctor	34	20.6
	Nurse	60	36.4
	Cleaning services	31	18.8
	Patient help desk	31	18.8
	Other personnel	9	5.4
Weekly working time	<40	47	28.5
	≥40	118	71.5
Risk group	General department	57	34.5
	High-risk department	108	65.5
Person diagnosed with COVID at home	Yes	56	33.9
	No	109	66.1
Contact outside hospital	Yes	20	12.1
	No	145	87.9
Additional disease	No	127	77
	DM	7	4.2
	HT	4	2.4
	COPD	4	2.4
	Cancer	2	1.2
	CVD	1	0.6
	Other	20	12.1
Smoking	Non-smoker	83	50.3
	Smoker	33	20
	Used to smoke	11	6.6
	Not known	38	23
Aerosol procedure		**48**	**29**
Biological injuries		**6**	**3.6**

DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CVD: Cardiovascular disease, COVID: Coronavirus disease

Table 2. Findings related to the disease

		n (165)	
Time of diagnosis following complaint (day)	1-5 days	125	75.8%
	6-10 days	40	24.2%
Treatment continued	In the hospital	29	17.6%
	At home	136	82.4%
	No	96	58.2%
Pneumonia finding	Mild	57	34.5%
	Moderate	9	5.5%
	Severe	3	1.8%
Severity of disease	Mild	71	43%
	Moderate	62	37.5%
	Severe	6	3.6%
	Critically ill	1	0.6%

Table 3. Univariate analysis of risk factors with pneumonia status

Risk factor		All cases (165)	Pneumonia (+) n (69)	Pneumonia (-) n (96)	p
Age	18-30	76 (46.1%)	26 (37.7%)	50 (52.1%)	0.030*
	31-44	66 (40%)	28 (40.6%)	38 (39.6%)	
	≥45	23 (13.9%)	15 (21.7%)	8 (8.3%)	
Sex	Male	55 (33.3%)	29 (42%)	26 (27.1%)	0.033*
	Female	110 (66.7%)	40 (58%)	70 (72.9%)	
Weekly working time (hour)	<40	47 (28.5%)	21 (30.4%)	26 (27.1%)	0.638
	≥40	118 (71.5%)	48 (69.6%)	70 (72.9%)	
Underlying health condition	No	127 (77%)	49 (71%)	78 (81.3%)	0.315
	Diabetes	5 (3%)	3 (4.3%)	2 (2.1%)	
	Hypertension	6 (3.63%)	5 (7.2%)	1 (1%)	
	COPD	4 (2.4%)	2 (2.9%)	2 (2.1%)	
	Malignancy	2 (1.2%)	1 (1.4%)	1 (1%)	
	Cerebrovascular disease	1 (0.6%)	1 (1.4%)	0	
	Other	20 (12.1%)	8 (11.6%)	12 (12.5%)	
Baseline symptoms	Fever	53 (32.1%)	32 (46.4%)	21 (21.9%)	0.001*
	Sore throat	48 (29.1%)	17 (24.6%)	31 (32.3%)	0.286
	Cough	48 (29.1%)	38 (55.1%)	39 (40.6%)	0.67
	Shortness of breath	50 (30.3%)	24 (34.8%)	26 (27.1%)	0.288
	Headache	70 (42.4%)	35 (50.7%)	35 (36.5%)	0.067
	Smell and taste loss	53 (32.1%)	25 (36.2%)	28 (29.2%)	0.338
	Diarrhea	34 (20.6%)	15 (21.7%)	19 (19.8%)	0.76
	Myalgia	76 (46.1%)	39 (56.5%)	37 (38.5%)	0.022*
	No symptom	27 (16.4%)	2 (2.9%)	25 (26%)	0.001*
Time of diagnosis following complaint (day)	1-5 days	125 (75.8%)	54 (78.3%)	71 (74%)	0.525
	6-10 days	40 (24.2%)	15 (21.7%)	25 (26%)	
Rapid antibody test		n (84)	n (35)	n (49)	
	IgM	52 (61.9%)	28 (80%)	24 (49%)	0.003*
	IgG	54 (64.3%)	30 (85.7%)	24 (49%)	0.001*

COPD: Chronic obstructive pulmonary disease, IgM: Immunoglobulin M, *Pearson chi-square test

Table 4. Multivariate analysis results of the factors with an effect on pneumonia

	p	ODDS	95% CI OR	
			Lower	Upper
Age	0.023*	1.043	1.006	1.082
Sex (male)	0.096	1.831	0.899	3.731
Fever	0.018*	0.420	0.205	0.862
Myalgia	0.063	0.523	0.264	1.037

CI: Confidence interval, OR: Odds ratio

HCWs that had risky contact and infection can also infect other staff and patients. Early identification of asymptomatic and symptomatic HCWs is crucial to prevent virus infection from staff and maximize current workforce.

In the study conducted in the Netherlands, in the PCR testing performed between March 7 and 12 on 1353 HCWs experiencing symptoms in the last 10 days, 86 HCWs (6.4%) were SARS-CoV-2 positive (16). In a study conducted by Keeley et al. (17) in the UK, an even higher infection rate was observed among HCWs, and 282 (18%) of 1533 HCWs were PCR-positive; however, the contact status of the personnel has not been investigated. In our hospital, PCR was performed on 1425 HCWs who applied with COVID-19-related symptoms or who had a history of risky contact with COVID-19 cases, and 165 (11.5%) of them were positive. Rates of SARS-CoV-2-infected HCWs vary by country, region, or even hospitals. This result may be related to many factors, such as different test procedures, infection control precaution protocols of hospitals, working conditions of HCWs, individual characteristics, number of infected cases followed, and COVID-19 prevalence of the community in the region.

At the press conference, the Minister of Health of our country stated that as of April 29, 7428 HCWs (6.5%) were infected with SARS-CoV-2 (14). According to the world reports, this rate was 8.3% in Italy, 3.8% in China and 3% in the USA (18-20). İstanbul is the city with the highest number of cases in our country, and our hospital is one of centers with

Table 5. Findings of some variables with risk group

Risk factors		High-risk department, n (108)	General department, n (57)	p
Age	18-30	54 (50%)	22 (38.6%)	0.327
	31-44	39 (36.1%)	27 (47.4%)	
	≥45	15 (13.9%)	8 (14%)	
Sex	Male	34 (31.5%)	21 (36.8%)	0.487
	Female	74 (68.5%)	36 (63.2%)	
Weekly working time (hour)	<40	26 (24.1%)	21 (36.8%)	0.084
	≥40	82 (75.9%)	36 (63.2%)	
Underlying health condition	No	89 (82.4%)	38 (66.7%)	0.033*
	Diabetes	2 (1.9%)	3 (5.3%)	
	Hypertension	1 (0.9%)	5 (8.8%)	
	COPD	3 (2.8%)	1 (0.9%)	
	Malignancy	0	2 (3.5%)	
	Cerebrovascular disease	1 (0.9%)	0	
	Other	12 (11.1%)	8 (14%)	
Baseline symptoms	Fever	39 (36.1%)	14 (24.6%)	0.131
	Sore throat	29 (26.9%)	19 (33.3%)	0.383
	Cough	53 (49.1%)	24 (42.1%)	0.394
	Shortness of breath	34 (31.5%)	16 (28.1%)	0.65
	Headache	47 (43.5%)	23 (40.4%)	0.695
	Smell and taste loss	38 (35.2%)	15 (26.3%)	0.246
	Diarrhea	25 (23.1%)	9 (15.8%)	0.266
	Myalgia (muscle pain)	53 (49.1%)	23 (40.4%)	0.285
	No symptom	14 (13%)	13 (22.8%)	0.10
Pneumonia finding		55 (50.9%)	14 (24.6%)	0.001*

COPD: Chronic obstructive pulmonary disease, *Pearson chi-square test

the most cases in İstanbul. Between March 14 and April 30, 2020, 4177 COVID-19 cases confirmed by the laboratory were followed, and all units participated in the follow-up of COVID-19. In all COVID-19 cases followed in our hospital, the HCW rate was 3.9%, which was lower than the rate across the country. This result could be associated with the fact that following the announcement of WHO stating that "international public health emergency" was declared on January 30 for the COVID-19 outbreak in China, the training of all staff was urgently completed before the case was reported in our country.

The total number of confirmed COVID-19 cases followed at our hospital between March 14 and 31 was 902, 5.76% of which were HCWs. Meanwhile, HCWs constituted only 3,49% of the 2261 patients who were followed up between April 1 and 15, when the cases were most intense. The high number of infected staff when the number of cases was low may be associated with the poor personal protection of HCWs, the poor knowledge about the pathogen, and the poor awareness of personal protection at the beginning of the pandemic.

Infected 20 HCWs reported contact with COVID-19 patients confirmed by the laboratory outside the hospital. Although 145 HCWs have reported that they were infected in the hospital, they may also be infected by contact with presymptomatic or asymptomatic people in households or multiple environments. Countries significantly differ in the PCR testing of HCWs, and their current programs focus on symptomatic screening rather than asymptomatic staff (17). Although 27 (16.4%) of the infected HCWs were asymptomatic, 2 cases had ground-glass appearance in thoracic CT, and cough complaints started after the diagnosis. In the UK, PCR performed on 1032 asymptomatic HCWs showed positivity in 30 cases, and detailed examination showed that 17 cases were truly asymptomatic (21). PCR test is an important part of the diagnostic strategy, and its capacity to detect asymptomatic infection indicates the need for regular screening of all staff in the COVID unit.

Nurses were the most infected (36.3%) among the total infected HCWs possibly becasue they are more in close contact and spend more time while giving care to patients. In addition, although the HCWs in the patient help desk (Data entry, security) had no contact with the patient rooms, they were infected at the same rate as the HCWs in cleaning services possibly because of their contact with all patients during the first admission to the hospital and insufficient use of PPE.

While long working hours increase the risk of respiratory infection, moderate working hours may benefit the health and safety of HCWs (22).

In our hospital, 71.5% of the infected HCWs worked 40 h or more per week. Depending on the special role of the healthcare staff, limitations of working hours should be considered in terms of viral load during the pandemic period.

During the pandemic, HCWs can often infect the people they live with. In our study, 33.9% of the infected HCWs also had infected family members, which increased the loss of workforce because the HCWs should take care of themsevelves and their family members. Concerns about transmitting the disease emerged with the requirement for HCWs to leave the house and the need for accommodation. Meeting the accommodation needs of HCWs during the pandemic is extremely important in preventing the spread of the disease and in reducing the loss of labor.

Among the additional measures that can reduce the risk of transmitting viruses to colleagues and patients of the infected HCWs, the Centers for Disease Control and Prevention recommends scanning all HCWs for fever and respiratory symptoms before starting their shift (20). Among the symptoms of infected HCWs in our hospital, the occurrence rate of myalgia was 46.1%, headache 42.4%, fever 32.1%, and cough 29.1%. A study conducted in a center in the Netherlands observed that the two most common symptoms among HCWs were myalgia (62%) and headache (57%) (16). Although these findings are subjective, screening of HCWs by questioning all findings, including headache and myalgia, at the beginning of their shift may be recommended.

Severe disease may occur in healthy individuals of any age, but predominantly advanced age or underlying medical comorbidity causes changes in the severity of the disease (23). In the general population, the rate of severe disease is 14-24.9%, and the rate of critical disease is 5% (18,24).

Among the infected HCWs, 6 had severe disease (3.6%) and 1 critical (0.6%), and 5 of these patients were over 45 years old. The reason for the low disease severity among the infected HCWs compared with the general population is associated with the average age of the employees being 34 and the incidence of comorbidities being 23%. CT examinations were performed in all infected HCWs, and 69 (41.8%) were diagnosed with pneumonia by the detection of ground patchy lesions. The presence of pneumonia in SARS-CoV-2-infected HCWs has been detected more frequently in men over 45 years of age and is similar to the general population (25). Of the infected HCWs, 65.5% were employed in the high-risk department, and the incidence of pneumonia was 50.9% in this group, whereas 24.6% among those working in the general department was found statistically significant (p=0.001). The frequency of pneumonia among those working in the high-risk department may be associated with high exposure to respiratory aerosol procedures. Thus, not employing HCWs with comorbidities in high-risk departments is suggested.

In patients, seroconversion usually occurs 2-4 weeks after the initial symptoms following infection with SARS-CoV-2 (26,27). In our study, seroconversion was 64.3% in the rapid-format card test for antibodies performed 4 weeks after diagnosis in infected HCWs. In asymptomatic and oligosymptomatic HCWs, this rate was 49%; in HCWs with pneumonia, seroconversion was significantly higher with 85.7% (p=0.001). Perera et al. (28) investigated seroconversion by using ELISA in PCR-positive patients, and a significant correlation was reported between disease severity and IgG formation.

Study Limitations

The limitation of our study is that long-term results are not yet available, and their follow-up continues. Not using ELISA for seroconversion can also be stated as a limitation.

Conclusion

During the epidemic, early training of HCWs on the disease, use of PPE, and infection control is extremely important to reduce the risk of infection among HCWs. Periodic screening of asymptomatic HCWs will also be beneficial to protect patients and hospital staff and prevent loss of workforce.

Ethics Committee Approval: This research protocol was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (approval number: 2020-10, date: 04.05.2020).

Informed Consent: All participants consisted of clinicians, nurses, and allied health personnel.

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The Importance of Cryopreserved Parathyroid Tissue Autotransplantation in the Hypoparathyroidism Treatment after Secondary Hyperparathyroidism Surgery

Sekonder Hiperparatiroidi Cerrahisi Sonrasında Gelişen Hipoparatiroidinin Tedavisinde Dondurularak Saklanan Paratiroid Dokularının Ototransplantasyonunun Önemi

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ABSTRACT

Introduction: Severe hypocalcemia is a rare but serious complication of secondary hyperparathyroidism (SH) surgery. Continuous intravenous calcium replacement is required and patients are not discharged. Cryopreserved parathyroid autotransplantation (CPA) is the most effective and lasting treatment option for severe hypocalcemia. However, a cryopreservation laboratory is necessary for this procedure.

Methods: Subtotal parathyroidectomy performed 150 SH cases (age range: 26-69 years, mean age: 39.5 years, men/women: 2/1) were retrospectively evaluated. Severe hypocalcemia (serum calcium level of <6.5 mg/dL) was developed in 7 (4.6%) cases. CPA was performed and cases were observed in a minimum of 18 months.

Results: After transplantation in five cases, intravenous and oral calcium replacement was ceased and cases were discharged. Transplantation failed in two cases, thus second time CPA. After the second CPA, intravenous calcium is ceased and cases were discharged. Any side effects or complications were not seen during the observation period.

Conclusion: CPA is the most effective and lasting treatment option for severe hypocalcemia. CPA is not difficult to perform but a cryopreservation laboratory and experienced laboratory team are necessary for this procedure. The presence of this laboratory in SH surgery performed centers reduces the risk of mortality and morbidity.

Keywords: Cryopreservation, parathyroid, severe hypoparathyroidism, autotransplantation

ÖZ

Amaç: Şiddetli hipokalsemi, sekonder hiperparatiroidizm (SH) cerrahisinin nadir fakat ciddi bir komplikasyonudur. Sürekli intravenöz kalsiyum replasmanı gerekebilir ve hastalar hastaneden taburcu edilemez hale gelebilir. Dondurularak saklanmış paratiroid dokusunun ototransplantasyonu, şiddetli hipokalsemi için en etkili ve kalıcı tedavi seçeneğidir. Ancak bu işlem için kriyoprezervasyon laboratuvarı gerekebilir.

Yöntemler: Subtotal paratiroidektomi yapılan 150 SH olgusu (yaş aralığı: 26-69, ortalama yaş: 39,5, erkek/kadın: 2/1) retrospektif olarak değerlendirildi. Yedi (%4,6) olguda şiddetli hipokalsemi (serum kalsiyum düzeyi <6,5 mg/dL) gelişti. Bu olgulara dondurularak saklanmış paratiroid dokusunun ototransplantasyonu yapılmış ve olgular en az 18 ay gözlemlenmiştir.

Bulgular: Beş hasta transplantasyon sonrası intravenöz ve oral kalsiyum replasmanı kesilerek taburcu edildi. İki olguda ise transplantasyon başarısız oldu ve onlara ikinci kez paratiroid ototransplantasyonu uygulandı. İkinci transplantasyon sonrası intravenöz kalsiyum kesilerek hastalar taburcu edildi. Hiçbir olguda 18 aylık gözlem süresinde herhangi bir yan etki veya komplikasyon görülmedi.

Sonuç: Dondurularak saklanmış paratiroid dokusunun ototransplantasyonu, şiddetli hipokalsemi için en etkili ve kalıcı tedavi seçeneğidir. Bu transplantasyonu yapmak zor değildir ancak bu işlem için kriyoprezervasyon laboratuvarı ve deneyimli laboratuvar ekibi gereklidir. SH cerrahisi yapılan merkezlerde bu laboratuvarın bulunması mortalite ve morbidite riskini azaltmaktadır.

Anahtar Kelimeler: Krioprezervasyon, paratiroid, şiddetli hipoparatiroidizm, ototransplantasyon

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Introduction

Secondary hyperparathyroidism (SH) is usually associated with chronic renal failure (1-3). Parathyroidectomy is required in 15% of patients undergoing dialysis within the first 10 years and 38% during the first 20 years (4-6). Total parathyroidectomy or subtotal parathyroidectomy with intraoperative parathyroid autotransplantation is the most common surgical procedure (1-3). One of the major complications observed after any thyroidectomy and SH surgery is hypoparathyroidism. Transient hypoparathyroidism after SH surgery occurs in up to 90% of patients, whereas permanent hypoparathyroidism in up to 20% (3).

Parathyroid autotransplantation was first described by Halsted (7) in dogs. This procedure was later extensively used in thyroid surgeries (in cases of accidentally removed parathyroid tissues) and SH surgeries (8-10). The parathyroid autotransplantation was traditionally performed as an intraoperative procedure with fresh tissues. According to subsequent scientific and technological developments, excised fresh tissues transferred from operating rooms to the laboratories were frozen to preserve their viability. Thus, many tissues such as the ovum, sperm, pancreas islet cells, meniscus, trachea, teeth, and parathyroid are safely cryopreserved and de-froze for auto or allotransplantation when necessary (11).

Cryopreserved parathyroid autotransplantation (CPA) was first performed by Wells and Christiansen (12) in 1974. Later, this process was used with different techniques in many scientific studies (13,14).

SH operations are performed in many centers; however, the CPA was not a widespread procedure due to the high cost in setting up the cryopreservation laboratory and qualified personnel requirements.

Cryopreservation laboratory is necessary for SH surgery performing centers because severe hypocalcemia causes a cardiac arrhythmia, fibrillation, and cardiac arrest. Serious risks severe hypocalcemia cases need continuous intravenous calcium replacement and intensive hospital care (15).

In this study, we presented our results of CPA in cases of severe hypocalcemia after SH surgery.

Methods

A retrospective clinical research was designed and applied to the local human ethics committee. After research protocol approval by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2879, date: 18.06.2021), informed consent was obtained from all participants. A total of 150 patients (age range: 26-69 years, mean age: 39.5 years, men/women: 2/1) underwent SP between June 2013 and December 2017 in the department of endocrine surgery. All patients underwent standard subtotal parathyroidectomy, which removed all three parathyroid tissues and half of the fourth parathyroid tissue. Excised parathyroid tissues were cut into two pieces. One piece was sent to the pathology laboratory for histopathological examination and the other piece was prepared to be sent to the cryopreservation laboratory.

The parathyroid capsule and other surrounding tissues were carefully dissected from the parathyroid tissues to be sent to the cryopreservation laboratory. After washing the tissues several times with physiological saline, they were transferred to the laboratory by placing them in Falcon tubes of 15 mL volume containing phosphate buffer solution (PBS). Cell isolation was performed according to the protocol described below.

Parathyroid Cell Isolation and Cryopreservation

Tissues were received in the laboratory by an experienced biologist. In a negative pressure sterile cabinet, tissues are taken into a sterile vial shredded mechanically with a scalpel and filtered with a cell strainer (70 µm, BD Biosciences®, USA). Filtered cells are collected in 5 mL PBS and centrifuged at 270 g for 5 min at room temperature. The supernatant was removed, and cells were re-suspended in 1 mL PBS. Cell viability was assessed with a Muse™ Cell Analyzer (Merck Millipore®, Germany). Cells were cryogenically stored in PBS containing 10% of dimethyl sulfoxide (AppliChem®, Germany) using an isopropanol-based freezing container and then stored in a liquid nitrogen tank.

The cells are prepared for transplantation according to the protocol described below when CPA is decided in patients whose cells were previously cryopreserved.

Preparation of Cells for Transplantation

The cells in the liquid nitrogen tank were removed and placed in an incubator (ESCO, Singapore) at 37 °C with a 5% carbon dioxide-humidified atmosphere. After cultivation for approximately 72 hours, cells were collected and centrifuged at 270 g for 7 min at room temperature. The supernatant was removed and cells were re-suspended in 2 mL PBS. Cells were counted with cell counters, and an average of $70x10^6$ cells was injected into the deltoid muscle of the non-dominant arm of patients.

After the transplantation, patients were observed in the endocrine surgery clinic. Intravenous calcium supplementation was gradually reduced. The patient was discharged when he became asymptomatic without taking any intravenous calcium and his serum calcium and parathormone (PTH) levels were elevated. Discharged patients were followed up weekly during the first month; then at 2, 4, and 6 months; and finally, at 6-month intervals at the outpatient clinic.

Statistical Analysis

Data of patients were entered into the Statistical Package for the Social Sciences 21 (IBM, Armonk, NY, USA) program, and the desired parameters were given by specifying the mean ± standard deviation, as well as the minimum and maximum values.

Results

Severe hypocalcemia was accepted as a serum calcium level of 6.5 mg/dL or less in the postoperative period. Symptomatic severe hypocalcemia at postoperative day one was observed in 23 (15.3%) of 150 patients. Mean serum calcium level was 5.61±3.05 mg/dL (range: 4.0-6.5 mg/dL) and the mean serum PTH level was 62.63±125.68 pg/mL (range: 0-285 pg/mL). These patients were followed for 1 week with intravenous and oral calcium plus vitamin D supplementation, which is a routine practice in our clinic. Up to the seventh postoperative day, 16 (10.7%) patients

did not require intravenous calcium supplements; their symptoms almost disappeared, and were discharged. Intravenous and oral calcium plus vitamin D supplementations were administered; however, the serum calcium levels remained below 6.5 mg/dL in 7 (4.6%) patients and continued to be symptomatic. All patients were evaluated in the endocrine council and CPA was decided.

The mean age of the seven patients who underwent CPA was 44.5±8.5 (range: 22-56) years, and the female to male ratio was 1.33. The serum PTH and calcium changes of patients are shown in Table 1, 2.

After CPA, except for two cases, serum PTH and calcium levels increased, symptoms decreased, intravenous calcium supplementation ceased, and patients were discharged. However, serum PTH and calcium levels were decreased at very low levels in cases 1 and 2. In case 1 serum PTH levels were 3 pg/mL and 1.3 pg/mL, serum calcium level at 6 mg/dL and 5.5 mg/dL in postoperative week 1 and month 1, respectively. In case 2, serum PTH levels were 2.5 pg/mL and 2.5 pg/mL and serum calcium level were 5.5 mg/dL and 5.6 mg/dL in postoperative week 1 and month 1, respectively (Table 1, 2). Occasional intravenous calcium infusion is required and symptoms persisted. In these cases, the second CPA was performed 3 months after the first transplantation. Serum PTH and calcium levels increased, symptoms disappeared, and intravenous calcium supplementations were ceased.

Serum PTH and calcium values were observed in all cases, which underwent CPA, at least 18 months (range: 18-25 months). None of the patients required intravenous or oral calcium supplementation. Only cases 1 and 2 were continued to take oral calcium effervescent tablets daily. None of the patients had local or systemic side effects or complications.

Discussion

Severe hypoparathyroidism is a rare complication of thyroid and SH surgery (3,16). When hypoparathyroidism is not severe, patients are discharged from the hospital with oral calcium and vitamin D preparations. In severe hypocalcemia, patients are impossible to be discharged due to continuous intravenous calcium infusion.

Falls due to muscle spasms or weakness and fall-related bone fractures are the main morbidity mechanisms, and cardiac arrest due to hypocalcemic myocardial fibrillation is the main mechanism of mortality of these cases (15). Four options for severe hypoparathyroidism management are as follows: a continuous intravenous calcium infusion, subcutaneous recombinant PTH injection, parathyroid allotransplantation, and CPA (13,17-19).

Continuous intravenous calcium infusion is an easy and inexpensive option; however, this approach requires appropriate hospital conditions and follow-up by an experienced clinician. Rapid and high-dose infusions increase the risk of myocardial fibrillation. The clinical effect of intravenous calcium infusion occurs rapidly (within minutes), but with short-term effectiveness (within hours) (17,20).

A recombinant PTH injection is a fast-acting option like an intravenous calcium infusion and does not require follow-up in hospital settings (21). However, it is very expensive and, in many countries, is not covered by the social insurance system.

Parathyroid allotransplantation is a process that requires a specific laboratory, experienced multidisciplinary staff from the clinical (internal medicine, endocrinology, endocrine surgery, etc), and biological sciences (22,23). In the literature, some case reports and very limited clinical series are available about parathyroid allotransplantation (19,23).

Table 1. PTH (pg/mL) value changes of the autotransplantation cases

	Preop	Postop day 7	Post Tx week 1	Post Tx month 1	Post Tx month 3	Post Tx month 6	Post Tx month 12	Post Tx month 18
Case 1	2308	1.9	3	1.3	12.9*	14	14	14
Case 2	>3500	0	2.5	2.5	7.5*	11	12	12
Case 3	>3500	18	19	19	19	21	19	19
Case 4	3235	67	70	75	74	87	85	85
Case 5	2764	28	32	34	38	38	38	38
Case 6	>3500	22	21	19	26	22	17	20
Case 7	2700	15	19	21	20	21	19	21

*: Second Tx performed, PTH: Parathormone, Preop: Preoperative, Postop: Postoperative

Table 2. Calcium (mg/dL) value changes of the autotransplantation cases

	Preop	Postop day 1	Post Tx week 1	Post Tx month 1	Post Tx month 3	Post Tx month 6	Post Tx month 12	Post Tx month 18
Case 1	9.7	6.1	6	5.5	6.4*	6.9	6.8	6.8
Case 2	11.9	5.7	5.5	5.6	6.1*	6.9	6.8	7
Case 3	10.4	4	4.8	5.1	7.6	8	7.8	8
Case 4	9.7	6.1	7.7	8	8.3	8.1	8.7	8.5
Case 5	10	5.3	6.8	6.9	7	8.1	7.5	8.1
Case 6	9.3	4.9	6.1	7	8.1	7.8	7.2	7.8
Case 7	9.4	5.7	6.2	6.4	6.4	6.8	6.9	6.9

*: Second Tx performed, Preop: Preoperative, Postop: Postoperative

Our center is the unique parathyroid allotransplantation center in Turkey approved by the Turkey Ministry of Health. In our center, tissues obtained from SH surgery as donors in parathyroid allotransplantations are used. Therefore, many patients who underwent SH are referring to our center, thus many SH surgeries are performed (24).

CPA is one of the most effective and also natural treatment options if excised parathyroid tissues are cryopreserved during SH surgery (25). Since the patient's tissues are used, an immunological reaction is not a risk, thus no immunosuppression is required (14,26). The most important limitation of this treatment option is the need for a specific cryopreservation laboratory and experienced biologist staff.

Different results were reported in the literature regarding the success of autotransplantation after cryopreservation of parathyroid tissue (14,26,27). Shepet et al. (27) reported that four patients who developed severe hypoparathyroidism after SH surgery underwent a CPA, of which only 1 was successful. Agarwal et al. (14) reported a success rate of 100% as a result of CPA in nine patients.

Schneider et al. (26) reported a 100% success rate in a series of 606 patients who underwent SH surgery and 13 patients who received CPA due to severe hypoparathyroidism. Another study reported that CPA was performed in a total of 25 patients with severe hypoparathyroidism following surgical interventions (secondary, persistent, and recurrent hyperparathyroidism) with different indications. Complete success was reported in 16 patients and partial success in 9 (28).

The significant differences in CPA success rates in the literature are mainly due to the laboratory process, as well as the donor cell quality and quantity (14,26,27). The laboratory process has two main stages: freezing and de-freezing (14,29). Freezing is start when the tissues are removed from the patient. This stage consists of multiple steps, including fast transportation from the operating room to the laboratory at a body temperature, cell isolation into the sterile cabin, centrifugation, cell storage in proper medium, -80 °C freezing in one night, and transfer to the liquid nitrogen tank. The de-freezing stage consists of taking cells out of the liquid nitrogen tank and heating them to 36 °C, culture medium incubation, cell counting, transportation to the patient room in a sterile tube at body temperature, and transplant to the patient via intramuscular injection (14,30). Incorrect and inadequate implementation of any of these steps will affect all subsequent steps and will therefore determine the CPA's success.

In 150 cases, the incidence of hypoparathyroidism was 4.6% (7 cases) in our series, who underwent SH surgery, which is consistent with other series in the literature (3,6). Our CPAs were performed with three experienced laboratory staff (two postdocs and one medical biologist) in our parathyroid transplant laboratory with specific devices for parathyroid tissue. Our relatively high success rate is related to our experienced surgical team, laboratory team, and laboratory infrastructure.

In two cases, second transplantation was performed because symptoms persisted and serum calcium and PTH levels were not elevated. After the second transplantation, symptoms disappeared, and serum calcium and PTH levels were elevated, thus intravenous calcium infusion was ceased and cases were discharged from the hospital.

Conclusion

Therefore, severe hypocalcemia is a rare but life-threatening complication of SH surgery. In addition to oral supplementation, these cases require continuous intravenous calcium infusion in hospital conditions. CPA is the most effective and lasting treatment option for these cases. CPA is not difficult to perform but it necessitates a cryopreservation laboratory and experienced laboratory team. The presence of this laboratory in SH surgery performing centers reduces the risk of mortality and morbidity.

Ethics Committee Approval: This study approval by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2879, date: 18.06.2021).

Informed Consent: Informed consent was obtained from all participants.

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Validity of Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratio in the Diagnosis of Pulmonary Embolism in Patients with Renal Disorder

Renal Fonksiyon Bozukluğu Olan Hastalarda Nötrofil/Lenfosit ve Platelet/Lenfosit Oranlarının Pulmoner Emboli Tanısında Kullanılabilirliği

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ABSTRACT

Introduction: Acute pulmonary embolism (APE) is a common and sometimes fatal form of venous thromboembolism. The fact that patients do not consult with a specific clinical picture and accompanying comorbid conditions make the diagnosis difficult. Chronic renal failure is one of the comorbid conditions with increased susceptibility to thrombosis. Due to clinical presentation variabilities, the limited use of the d-dimer test in patients with renal dysfunction, and the limitation of use of computed tomography (CT) angiography due to potential renal side effects, an easily accessible, inexpensive, sensitive and specific guide laboratory parameter within acceptable limits is needed in the diagnosis of patients with impaired renal function. In this study, neutrophil/lymphocyte ratios (NLR) and platelet/lymphocyte ratios (PLR) will be compared between two patient groups with and without renal dysfunction and APE attack. It is aimed to demonstrate the usability of these rates together with clinical, laboratory and radiological evaluations in the diagnosis of pulmonary embolism.

Methods: In the selection of patient groups, the retrospective files of patients with chronic renal failure who applied to the emergency service of our hospital between January 2015 and 2019 and then were diagnosed with APE were examined. The control group consist of the patients with chronic renal failure who applied to the nephrology and internal medicine outpatient clinic without any additional pathology. Information such as gender, age, existing diseases, laboratory tests such as hemogram, D-dimer, troponin, creatinine glomerular filtration rate, lower extremity venous Doppler ultrasonography and thorax CT angiography results of the patients were recorded. NLR and PLR ratios were calculated in all groups. The results were evaluated with SPSS.

Results: NLR and PLR values were found to be significantly higher in the case group diagnosed with pulmonary embolism (p=0.000). At NLR 3.50 cut-off value, sensitivity was 70.6%, positive prediction was 84.6%, specificity was 86.8%, and

ÖZ

Amaç: Akut pulmoner emboli (APE); yaygın ve bazen ölümcül olan bir venöz tromboemboli şeklidir. Hastaların spesifik bir klinik tabloyla başvurmamaları ve eşlik eden komorbid durumlar tanıyı güçleştirir. Kronik böbrek yetmezliği de tromboza yatkınlığın arttığı komorbid durumlardandır. Klinik prezantasyon değişkenlikleri, D-dimer testinin renal disfonksiyonlu hastalarda kullanım kısıtlılığı, bilgisayarlı tomografi (BT) anjiyografinin olası renal yan etkilerinden dolayı kullanım kısıtı nedeniyle renal fonksiyonları bozuk hastaların tanısında, kolay ulaşılabilir, ucuz, kabul edilebilir sınırlarda sensitif ve spesifik bir kılavuz laboratuvar parametresine ihtiyaç duyulmaktadır. Bu çalışmada renal fonksiyon bozukluğu mevcut ve APE atağı geçiren ve geçirmeyen iki hasta grubu arasında nötrofil/lenfosit oranları (NLR) ve platelet/lenfosit oranları (PLR) karşılaştırılacaktır. Bu oranların pulmoner emboli tanısındaki klinik, laboratuvar ve radyolojik değerlendirmelerle birlikte kullanılabilirliğinin gösterilmesi amaçlanmıştır.

Yöntemler: Hasta gruplarının seçiminde Ocak 2015-2019 tarihleri arasında hastanemiz acil servisine başvurarak APE tanısı almış, kronik böbrek yetmezliği olan hastaların geriye dönük dosyaları incelenmiştir. Kontrol grubu olarak ise ek patolojisi olmayan, nefroloji ve dahiliye polikliniğine başvurmuş, kronik renal yetmezliği bulunan hastalar alınmıştır. Hastaların cinsiyet, yaş, mevcut hastalıkları, laboratuvar tetkiklerinden hemogram, D-dimer, troponin, kreatinin glomerüler filtrasyon hızı, alt ekstremite venöz Doppler ultrasonografi ve toraks BT anjiyografi sonuçları kaydedilmiştir. Tüm gruplarda NLR ve PLR oranları hesaplanmıştır. Sonuçlar SPSS ile değerlendirilmiştir.

Bulgular: Pulmoner emboli tanılı olgu grubunda NLR ve PLR değerleri anlamlı olarak daha yüksek bulunmuştur (p=0,000). NLR 3,50 cut-off değerinde duyarlık %70,6, pozitif kestirim %84,6, özgüllük %86,8, negatif kestirim %74,2 olarak bulunmuştur. PLR 125 cut-off değerinde duyarlık %68,8, pozitif

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negative prediction was 74.2%. Sensitivity was 68.8%, positive prediction was 67.0%, specificity was 65.1%, negative prediction was 67% at PLR 125 cut-off value.

Conclusion: NLR and PLR values can be used in addition to clinical, laboratory and imaging methods in the diagnosis of APE in patients with chronic renal failure and can give results that may help the clinician. However, more comprehensive studies should be conducted with larger case groups.

Keywords: Acute pulmonary embolism, chronic renal failure, NLR, PLR

kestirim %67,0, özgüllük %65,1, negatif kestirim %67 olarak saptanmıştır.

Sonuç: Kronik böbrek yetmezlikli hastalarda, APE tanısında NLR ve PLR değerleri klinik, laboratuvar ve görüntüleme yöntemlerinin yanında kullanılabilir ve klinisyene yardımcı olabilecek sonuçlar verebilir. Fakat daha geniş olgu gruplarıyla daha kapsamlı çalışmalar yapılmalıdır.

Anahtar Kelimeler: Akut pulmoner emboli, kronik renal yetmezlik, NLR, PLR

Introduction

Acute pulmonary embolism (APE) is a common and sometimes fatal form of venous thromboembolism (VTE). Despite all the improvements in diagnosis and treatment, it can be mortal. D-dimer test, lower extremity Doppler ultrasonography, thorax computed tomography (CT) angiography and ventilation perfusion (V/Q) scintigraphy can be used for diagnosis. Geneva and Wells scoring and D-dimer are used together in the diagnosis of possible pulmonary embolism. These scores and the D-dimer test were found to be safe, especially in young patients who do not have any additional disease (1).

Tendency to thrombosis seen in chronic renal failure is increased due to decreased fibrinolytic activity, endothelial damage, decreased pro-coagulant factors and increased anticoagulant factors (2). In this patient group, the diagnostic value of the D-dimer test in the diagnosis of pulmonary embolism is lower than in patients without renal dysfunction. D-dimer level increases in cases of decreased renal function due to decreased elimination and increased coagulation activation, and its specificity decreases significantly in these patients (3).

Pulmonary CT angiography is the gold standard diagnostic test in the diagnosis of APE, but the contrast agent used during the process worsens renal functions. In the diagnosis of patients with impaired renal function, due to clinical presentation variability, limitation of use of the d-dimer test in patients with renal dysfunction, and reservations due to possible renal side effects of a standard diagnostic tool such as CT angiography, there is a need for an easily applicable, low cost, sensitive and specific guide laboratory parameter within acceptable limits. Inflammation has been shown to play an important role in cases of VTE. This study was designed to predict the utility of neutrophil/lymphocyte (NLR) and platelet/lymphocyte ratios (PLR), which are markers of inflammation, in the diagnosis of pulmonary embolism in patients with chronic renal failure.

Methods

The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 1825, date: 10.05.2019).

This is planned as a retrospective, randomized and controlled study. Patients with chronic renal failure who applied to the emergency outpatient clinic of our hospital between January 2015 and 2019 and were diagnosed with APE were included in the study.

Inclusion criteria: Age, glomerular filtration rate (eGFR) <60-90 mL/min/1.73, and structural abnormalities detected by renal damage markers or radiologically (structural abnormalities or urinary sediment abnormalities or albuminuria albumin-to-creatinine ratio >30 mg/gr detected with imaging methods more than 3 months) and APE confirmed and specified by computed tomographic angiography, both patients receiving hemodialysis were included in the study.

Exclusion criteria: Patients with solid organ malignancies, patients with acute and/or chronic infections, and patients with drug use that would affect the parameters in the hemogram were excluded from the study.

Patients who were followed up with the diagnosis of chronic renal failure in the nephrology and internal diseases outpatient clinics of our age-gender matched hospital, who had not had an embolism before, were included in the study as the control group.

The patients' age, gender, current diseases, hemogram, D-dimer, troponin, creatinine and eGFR values, lower extremity venous Doppler USG and pulmonary CT angiography results were recorded.

Results were grouped according to their eGFR values: below 30 mL/min/1.73 m^2, between 30-60 mL/min/1.73 m^2 and between 60-90 mL/min/1.73 m^2. Patients with pulmonary embolism were divided into groups according to severity and anatomical localization as massive and submassive, segmental and subsegmental, unilateral and bilateral. In the case group consisting of patients with pulmonary embolism, those with diabetes mellitus (DM), hypertension and heart failure were recorded and they were also examined for the presence of deep vein thrombosis and were grouped as present or absent deep venous thrombosis (DVT).

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median minimum and maximum, frequency and ratio values were used. The distribution of variables was measured with the Kolmogorov-Smirnov test. Independent sample t-test and Mann-Whitney U test were used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fischer's test was used when the chi-square test conditions were not met. The effect level was investigated with the receiver operating characteristic curve. SPSS 22.0 program was used in the analysis.

Results

A total of 215 patients, aged between 18-75 years, who met the inclusion criteria, were included in the study, 109 as the case group and 106 as the control group.

41.3% (n=45) of the case group were male and 58.7% (n=64) were female. Of the control group, 39.6% (n=42) were male and 60.4% (n=64) was female. There was no significant difference between the groups in terms of gender frequencies (p=0.804).

In the case group, 28.4% (n=31) of the subjects had type 2 DM, 47.7% (n=52) had hypertension and 27.5% (n=30) had heart failure.

While the mean hemoglobin value in the case group was 11.9±1.9 g/dL, it was 12.6±1.7 g/dL in the control group. The hemoglobin value in the case group was significantly lower than the in the control group (p=0.021).

In the case group, 16.5% (n=18) of the subjects had eGFR below 30, 33% (n=37) had an eGFR between 30-60, 49.5% (n=54) had an eGFR value between 60-90. In the control group, 16% (n=17) of the subjects had an eGFR value below 30, 34.9% (n=37) had an eGFR value between 30-60, 49.1% (n=52) had an eGFR value between 60-90. GFR value did not differ significantly between groups with and without APE diagnosis (p=0.988).

The mean NLR in the case group was 6.5±6.8, the median value was 4.4. Mean NLR in the control group was 2.4±2.2; the median value was 2.1. In the case group, the mean PLR was 197.5±174.2; the median value was 162.8. The mean PLR in the control group was 116.0±42.1, and the median value was 110.1 (Table 1). NLR and PLR values in the case group were significantly higher than the control group (p=0.000) (Table 2).

At the NLR cut-off value of 3.50, the sensitivity was 70.6%, the positive prediction was 84.6%, the specificity was 86.8%, and the negative prediction was 74.2%. At the PLR 125 cut-off value, the sensitivity was 68.8%, the positive prediction was 67.0%, the specificity was 65.1%, and the negative prediction was 67% (Table 3).

The mean NLR of patients with massive pulmonary embolism was 6.8±6.4. The mean NLR of patients with submassive pulmonary embolism was found to be 6.3±7.1. There was no significant difference in NLR values between massive and submassive pulmonary embolism groups (p=0.372) (Figure 1).

The mean NLR value of patients with segmental pulmonary embolism was 6.6±6.6. The mean NLR value of patients with subsegmental pulmonary embolism was 6.3±7.8. There was no significant difference in NLR values between cases with segmental and subsegmental pulmonary embolism (p=0.349).

The mean NLR of cases with unilateral pulmonary embolism was found to be 6.5±5.8, and cases with bilateral pulmonary embolism were found as 6.5±7.5. NLR values did not differ significantly between cases with unilateral pulmonary embolism and bilateral pulmonary embolism (p=0.360) (Figure 2).

The mean PLR of patients with massive pulmonary embolism was 193.9±116.0. The mean PLR of patients with submassive pulmonary embolism was 199.8±204.2. There was no significant difference in PLR values between massive and submassive pulmonary embolism groups (p=0.660).

The mean PLR value of patients with segmental pulmonary embolism was 203.6±190.0. The mean PLR value of patients with subsegmental

Table 1. Comparison of leukocyte, neutrophil, lymphocyte and platelet values of case and control groups

Variable	Case (n=109)*	Control (n=106)*	p**
Leukocytes (count/mm^3)	10372±5492	7775±2065	0.001
Neutrophil (count/mm^3)	7801±5244	5431±8850	0.001
Lymphocyte (count/mm^3)	1665±1029	2360±1059	0.001
Platelet (1000*) (count/mm^3)	244±96	247±68	0.319

*The mean ± standard deviation is given, **p<0.05 was taken as the cut-off value of significance

Table 2. NLR and PLR values in case and control groups

ROC curve			
	Area	Area under curve	p
NLR	0.808	0.747-0.868	**0.001**
PLR	0.714	0.645-0.783	**0.001**

ROC: Receiver operating characteristic, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio

Table 3. Diagnostic value of NLR and PLR in detecting APE in patients with CKD

		Control group	Case group	Sensitivity	Positive prediction	Specificity	Negative prediction
NLR	≤3.5	92	32	70.6%	84.6%	86.8%	74.2%
	>3.5	14	77				
PLR	≤125	69	34	68.8%	67.0%	65.1%	67.0%
	>125	37	75				

NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, APE: Acute pulmonary embolism, CKD: Chronic kidney disease

pulmonary embolism was 171.9±77.2. There was no significant difference in PLR values between cases with segmental and subsegmental pulmonary embolism (p=0.957).

The mean PLR of cases with unilateral pulmonary embolism was 201.3±219.1, and the mean of cases with bilateral pulmonary embolism was 194.4±130.3, and there was no significant difference in PLR values between cases with unilateral and bilateral pulmonary embolism (p=0.951).

NLR value did not differ significantly in the groups with and without DM, hypertension, DVT, and heart failure (p=0.577, p=0.505, p=0.822, p=0.266).

When the relationship between GFR levels and NLR values of the patients in the case group was examined, the NLR value in the group with eGFR <30 mL/min/1.73 m^2 was found to be significantly lower than the group with eGFR between 60-90 mL/min/1.73 m^2 (p=0.010) (Table 4).

The PLR value did not differ significantly in the groups with and without DM, hypertension, heart failure, and DVT (p=0.904, p=0.051, p=0.745, p=0.529) (Table 5). The PLR value did not differ significantly in the GFR groups (p=0.594) (Table 6).

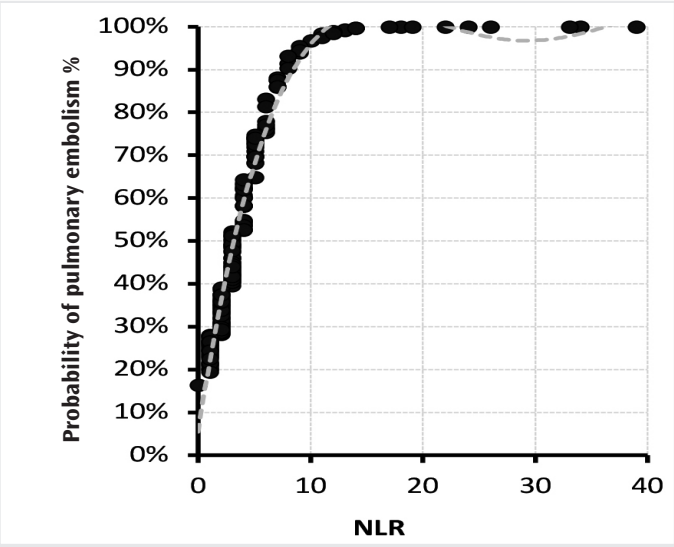

Figure 1. Probability of pulmonary embolism by NLR values
NLR: Neutrophil lymphocyte ratio

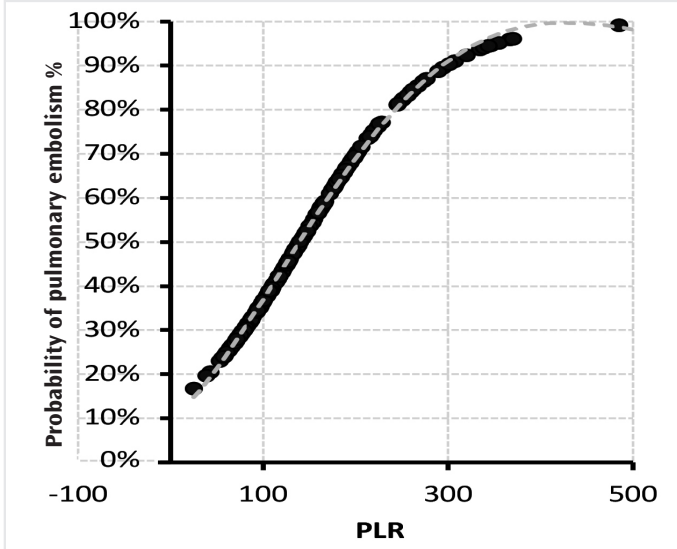

Figure 2. Probability of pulmonary embolism by PLR values
PLR: Platelet lymphocyte ratio

Table 4. Relationship between pulmonary embolism severity and anatomical localization and NLR values

		NLR (min-max)	NLR (median)	NLR (mean ± SD) (n%)	p*
Severity	Massive submassive	1.17-33.21	4.9	6.8±6.4	0.372**
		0.57-39.23	4.1	6.3±7.1	
Anatomical	Segmental subsegmental	0.57-39.23	4.3	6.6±6.6	0.349**
		1.13-34.32	4.5	6.3±7.8	
Unilateral/bilateral	Unilateral bilateral	0.81-34.32	5.1	6.5±5.8	0.360**
		0.57-39.23	4.1	6.5±7.5	

NLR: Neutrophil lymphocyte ratio, *p<0.05 was taken as the cut-off value of significance, **Calculated by Mann-Whitney U test, min: Minimum, max: Maximum, SD: Standard deviation

Table 5. Relationship between pulmonary embolism severity and anatomical localization and PLR values

		PLR (min-max)	PLR (median)	PLR (mean ± SD) (n%)	p*
Severity	Massive	42.60-587.80	152.6	193.9±116.0	0.660**
	submassive	38.66-1573.91	162.9	199.8±204.2	
Anatomical	Segmental	38.66-1573.91	161.1	203.6±190.0	0.957**
	subsegmental	68.98-333.69	163.4	171.9±77.2	
Unilateral/bilateral	Unilateral bilateral	38.66-1573.91	168.7	201.3±219.1	0.951**
		42.60-681.82	152.6	194.4±130.3	

PLR: Platelet lymphocyte ratio, *p<0.05 was taken as the cut-off value of significance, **Calculated by Mann-Whitney U test, min: Minimum, max: Maximum, SD: Standard deviation

Table 6. Relationship between clinical conditions associated with pulmonary embolism and GFR level and PLR values

		PLR (min-max)	PLR (median)	PLR (mean ± SD) (n%)	p*
DM	(-)	60.91-587.80	165.6	7.3±7.6	0.904**
	(+)	38.66-1573.91	156.0	6.2±6.5	
HT	(-)	38.66-587.80	185.0	6.9±6.8	0.051**
	(+)	56.62-1573.91	136.1	6.1±6.8	
CHF	(-)	42.60-587.80	164.5	7.0±5.7	0.745**
	(+)	38.66-681.82	159.4	6.3±7.2	
DVT	(-)	38.66-681.82	136.1	7.1±9.2	0.529**
	(+)	74.14-1573.91	146.5	5.8±6.4	
GFR	<30	42.60-1573.91	170.3	10.3±10.7	0.594***
	30-60	56.62-587.80	163.4	6.8±5.5	
	60-90	38.66-484.91	148.1	5.0±5.4	

DM: Diabetes mellitus, DVT: Deep vein thrombosis, GFR: Glomerular filtration rate, HT: Hypertension, CHF: Congestive heart failure, PLR: Platelet lymphocyte ratio, *p<0.05 was taken as the cut-off value of significance, **Calculated by Mann-Whitney u test, ***Calculated by Kruskal-Wallis test, min: Minimum, max: Maximum, SD: Standard deviation

Discussion

APE is a cardiovascular disease with high morbidity and mortality. It has been determined to be the most common cause of in-hospital sudden deaths and its annual incidence is 60-70/100,000 (4).

APE causes reperfusion injury, leading to an increase in oxidative stress, myeloperoxidase enzyme and reactive oxygen radicals in the lung. In addition, severe hypoxia caused by pulmonary artery vasoconstriction increases adrenergic and neurohormonal system activity. As a result, inflammatory cytokines are released and all these developments exacerbate the thrombosis (5). As in all atherothrombotic patients, inflammation has an important role in the pathophysiology of pulmonary embolism. The place of some inflammatory parameters has been demonstrated in studies. Among these parameters, B-type natriuretic peptide (BNP), N-terminal-proBNP, interleukin-6 (IL-6), IL-8, troponin and myoglobin can be counted (6,7).

Afzal et al. (8) showed for the first time the increase in leukocytes in pulmonary embolism. In this study, it was revealed that neutrophils play an important role in the inflammatory response in atherosclerotic background (8). Leukocytes are associated with both thrombogenesis and an increase in fibrinogen, factor VII, and factor VIII levels (9).

In acute stress, lymphopenia is a frequent occurrence in the inflammatory response process (10). The increase in corticosteroid levels in stressful situations may be the reason for this. Pulmonary embolism is also an acute stress picture.

The key role of platelets in inflammation and thrombosis is known. Thus, the three hematological parameters -neutrophils, lymphocytes and platelets- are also used as inflammation parameters. PLR and neutrophil/lymphocyte ratio (NLR) levels can indicate the severity of inflammation and correlate with the severe form of the disease. This situation has also been shown in cardiovascular diseases (11-13). Various studies have shown that PLR and NLR levels are associated with poor prognosis of many inflammatory diseases and malignancies (14). Relationships between cardiovascular diseases and prognosis have been studied in aortic valve replacement (15), coronary artery disease (16), non-valvular atrial fibrillation (17), and heart failure cases (18).

It has been shown in the studies of Yang and Liu (19) and Ferroni et al. (20) that PLR and NLR levels may be a marker of VTE. Again, in a study by Farah et al. (21), white blood cell, PLR, NLR values in the acute VTE group were found to be statistically significant and higher than the control group, and it was argued that NLR could be a useful marker for early detection of potential acute VTE.

Karataş et al. (22), in their retrospective study in our country, performed a mortality study of up to 20 months with 241 cases of APE. In this study, they found NLR >5.93 and PLR >191 cut-off values to be significant (22). Soylu et al. (23), on the other hand, studied only the level of NLR in in-hospital mortality. NLR was determined as >5.7 cut-off value (23). Ozcan Cetin et al. (24) followed 459 cases for 28.8 months and found PLR >147.8 to be significant (145). Ma et al. (25), on the other hand, found statistical significance at the level of NLR >5.99 and PLR >325, which they studied as markers in a 30-day mortality study. In our study, the mean NLR of patients with massive pulmonary embolism was 6.8±6.4, and the mean PLR was 193.9±116.0, which is in line with the literature.

In these studies, it has been shown that high NLR value increases short-term mortality approximately 9 times and overall mortality approximately 10 times. Again, high PLR value increases short-term mortality 7 times, long-term mortality 6 times and overall mortality 6 times (25).

In our study, a relationship was found between low hemoglobin level and the diagnosis of pulmonary embolism. When the hemogram values of the patients diagnosed with pulmonary embolism with chronic kidney disease (CKD) and those who did not have any additional disease other than CKD were compared, it was found to be significantly lower in the pulmonary embolism group. Anemia is an expected result in chronic renal failure, but cases with similar CKD stages were obtained in the case and control groups, thus eliminating the effect of CKD on anemia. There is no study in the literature showing the relationship

between hemoglobin level and pulmonary embolism, but there are studies showing the negative effects of anemia on mortality in cases with pulmonary embolism (26). Again, age is an independent risk factor in Geneva criteria. The age factor can be associated with anemia, and it is known that the incidence of anemia increases with increasing age (27). In addition, tachycardia, which is included in the Wells pulmonary embolism clinical prediction scoring, may also be associated with anemia.

Contrast nephropathy is a concern for the clinician, especially in patients with impaired renal function. Our concerns on this issue are mostly shaped by data obtained from cardiac patients who have undergone radiological intervention. There is a study in the literature on the effect of CT pulmonary angiography on contrast nephropathy. Kwok detected contrast nephropathy cases in 41% and dialysis need in 26% after CT pulmonary angiography in APE cases with risk factors. They developed a contrast nephropathy risk score at the end of the study and do not recommend the application of CT pulmonary angiography if the risk score they determined exceeds 16 (28).

Pulmonary CT angiography, which is the gold standard test for pulmonary embolism, should be applied in patients with renal dysfunction considering the benefit-harm balance, and in this case, alternative diagnostic methods such as transthoracic echocardiography, lower extremity venous Doppler ultrasonography and V/Q scintigraphy gain importance. Due to the increase in procoagulant factors and decrease in renal elimination, the d-dimer level also increases in these patients and its clinical usefulness in the diagnosis of VTE decreases.

Study Limitations

The limitations of the study are that it is single-centered and retrospective, and the number of patients is small.

Conclusion

NLR and PLR values, which are simple indicators of the inflammatory response and inexpensive, easily calculated parameters, can be used in the diagnosis of suspected pulmonary embolism in patients with renal dysfunction, but should be supported by larger studies on the subject.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 1825, date: 10.05.2019).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - E.T.; Concept - M.E.P.; Design - M.E.P.; Data Collection or Processing - E.T.; Analysis or Interpretation - E.T.; Literature Search - E.T., M.E.P.; Writing - E.T., M.E.P.

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Evaluation of the Predictive Value of Left Anterior Fascicular Block on Determination of Left Main and/or Proximal Left Anterior Descending Coronary Artery Disease in Patients with Stable Angina: A Propensity Score Matching Analysis

Sol Anterior Fasiküler Bloğun Stabil Anginalı Hastalarda Sol Ana ve/veya Proksimal Sol Ön İnen Koroner Arter Hastalığının Belirlenmesinde Öngördürücü Değerinin Araştırılması: Bir Eğilim Skoru Eşleştirme Analizi

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ABSTRACT

Introduction: Successful revascularization of lesions located in the left main and/or proximal left anterior descending (LM and/or pLAD) coronary artery improves survival than medical therapy only. Therefore, accurate identification of high-risk patients with suspected stable angina pectoris is critical for outpatient clinics. Since the septal perforators of the left anterior descending coronary artery are the main source of blood supply of the left anterior fascicle, we hypothesized that the presence of left anterior fascicular block (LAFB) can predict obstructive stenoses of LM and/or pLAD coronary arteries in patients with suspected stable angina pectoris.

Methods: We consecutively enrolled 790 patients referred for invasive coronary angiography due to suspected stable angina pectoris.

Results: The number of patients with LAFBs was 68 (8.6%). Furthermore, 218 patients (27.6%) had obstructive coronary artery disease (CAD). The prevalence of obstructive CAD, revascularization with coronary artery bypass graft surgery, and obstructive LM and/or pLAD coronary artery lesions was higher in patients with LAFB. From univariate analysis, the presence of LAFB was significantly associated with predicting obstructive LM and/or pLAD lesions (odds ratio: 3,587; 95% confidence interval: 1,465-5,785; p=0.005). However, this association disappeared after adjustment for other cardiovascular risk factors.

Conclusion: In patients with suspected stable angina pectoris, LAFB is not frequently a "normal variant" and is associated with known cardiovascular risk factors. It acts as a marker rather than a determinant of obstructive LM and/or pLAD coronary artery lesions.

Keywords: Left anterior fascicular block, obstructive left main coronary artery lesion, obstructive proximal left anterior descending coronary artery lesion, stable angina pectoris

ÖZ

Amaç: Sol ana ve/veya proksimal sol ön inen (LM ve/veya pLAD) koroner arterde yer alan lezyonların başarılı revaskülarizasyonu, yalnızca medikal tedaviye kıyasla sağkalımı artırmaktadır. Bu nedenle, stabil angina pektoris şüphesi olan hastalarda bu bölgelerdeki kritik darlıklar için yüksek riskli hastaların saptanması önemlidir. Sol ön inen koroner arterin septal perforatörleri, sol anterior fasikülün ana kan besleme kaynağı olduğundan, stabil angina pektoris şüphesi olan hastalarda sol anterior fasiküler blok (LAFB) varlığının, LM ve/veya pLAD koroner arterlerinin obstrüktif stenozlarını öngörebileceği hipotez olarak düşünüldü.

Yöntemler: Stabil anjina pektoris şüphesi nedeniyle invaziv koroner anjiyografi için sevk edilen ardışık 790 hasta çalışmaya alındı.

Bulgular: LAFB'li hasta sayısı 68 (%8,6) idi. Ayrıca 218 hastada (%27,6) obstrüktif koroner arter hastalığı saptandı. LAFB'li hastalarda; obstrüktif koroner arter hastalığı, koroner arter by pass greft cerrahisi ile revaskülarizasyon tedavisi ve obstrüktif LM ve/veya pLAD koroner arter lezyonu prevalansı daha yüksekti. LAFB'nin varlığı, tek değişkenli analizde obstrüktif LM ve/veya pLAD lezyonlarını öngörmede istatiksel olarak önemli bir değişkendi (odds ratio: 3.587; %95 güven aralığı: 1.465-5.785; p=0,005). Ancak bu ilişki, diğer kardiyovasküler risk faktörleri için düzeltme yapıldıktan sonra ortadan kalktı.

Sonuç: Stabil anjina pektoris şüphesi olan hastalarda LAFB "normal bir variant" değildir ve bilinen kardiyovasküler risk faktörleri ile ilişkilidir, ancak obstrüktif LM ve/veya pLAD koroner arter lezyonunun bağımsız bir yordayıcısı olmaktan çok bir belirteç görevi görmektedir.

Anahtar Kelimeler: Sol anterior fasiküler blok, obstrüktif sol ana koroner arter lezyonu, obstrüktif proksimal sol ön inen koroner arter lezyonu, stabil angina pektoris

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Introduction

Coronary artery disease (CAD) is the primary source of disability and even death worldwide (1). The World Health Organization estimates that CAD mortality will reach 23.4 million in 2030 (2). The most frequent presentation of ischemic heart disease is chronic stable angina (3). Diagnostic algorithms based on history, physical examinations, and electrocardiograms are well established. While invasive coronary angiography (ICA) has been considered the "gold standard" test for the detection of CAD, it is invasive and has also potential disadvantages such as predisposure to cerebrovascular events, bleeding, and even death (4). In patients without unstable conditions, current guidelines stipulate the first-line use of non-invasive tests to define the need for invasive tests such as coronary angiography, especially in patients with intermediate pre-test probability (5). Depending on patient selection, the predictive values of current pre-test probability models are still not optimal. In addition, obstructive coronary lesions are found in 41% of patients with positive results from non-invasive tests (6). Since successful revascularization of lesions in the left main and/or proximal left anterior descending (LM and/or pLAD) coronary artery improves survival when compared with medical therapy only, the accurate identification of high-risk patients with stable angina pectoris is crucial. Using cost-effective, easy obtainable, and non-invasive methods that can detect an obstructive LM and/or pLAD coronary arteries may be beneficial in clinical practice. Electrocardiography (ECG) is still an important part of the initial evaluation of patients presenting with cardiac complaints, despite its existence that spans out more than a century. Left anterior fascicular block (LAFB), an ECG pattern representing failure or delay of conduction in the left anterior fascicle, was initially defined as left anterior hemiblock by Rosenbaum et al. (7,8). Although there are conflicting results in different study populations regarding the clinical importance of LAFB (9-14), CAD remains one of the most common causes of LAFB (15). The His bundle splits into the two bundle branches at the fibrous and muscular boundaries joint of the interventricular septum. Then, the left bundle branch gives an anterior, posterior, and, in some cases, septal fascicles. The left anterior fascicle is nourished by the septal perforators from the LAD coronary artery mainly and therefore, is more sensitive to ischemia. Since the septal perforators of the LAD coronary artery are the main source of blood supply for the left anterior fascicle, we hypothesized that the presence of LAFB can predict obstructive stenoses of the LM and/or pLAD coronary arteries in patients with stable angina pectoris.

Methods

Study Population

We included 790 consecutively enrolled patients with stable angina pectoris and referred to ICA between September 2016 and January 2020. Each patient was included doing a coronary angiography. Those with angina pectoris and complaints equivalent to angina were considered eligible for the study. Afterward, a detailed medical history and at least one non-invasive diagnostic test was performed by an experienced cardiologist to determine CAD. Patients with acute coronary syndrome, history of CAD and cardiovascular consequence, malignancy, congenital heart disease, moderate-to-severe liver and/or renal diseases, acute or chronic inflammatory diseases, moderate-to-severe valvular heart disease, and cardiomyopathies were excluded from the study as well as those with preexisting right bundle branch block (RBBB), left bundle branch block (LBBB), pace rhythm, pre-excitation syndromes, and associated ischemic ST-T abnormalities. Sociodemographic and medical history parameters were recorded. Included patients were separated into two groups depending on the occurrence of LAFB. Patients were also grouped according to the presence of obstructive LM and/or pLAD lesions.

Informed consent was granted by all patients before enrollment. The approval form the Clinical Research Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital was obtained (approval number: 2020/62, date: 12.11.2020).

Electrocardiographic Evaluation

A standard surface 12-lead electrocardiogram ECG, with a paper speed of 25 mm/s and a voltage of 10 mm/mV was employed for investigations (Nihon Kohden, cardiofax GEM, ECG-9020K, Japan). All ECGs were recorded and analyzed by one experienced cardiologist blinded to the clinical data of the participants. LAFB was defined according to specified criteria: 1) QRS axis on frontal plan between -45 and -90 degrees, 2) qR pattern in lead aVL 3) R-peak time in lead aVL of 45 ms or more 4) QRS duration less than 120 ms (16).

Coronary Angiography and Echocardiography

Trans-radial or trans-femoral Judkins techniques were used to explore the coronary arteries in all patients. Obtained fluoroscopic images were judged by an experienced interventional cardiologist. Patients were categorized as individuals without CAD, with mild CAD, with significant CAD, and with obstructive CAD. Mild CAD was considered if lumen-diameter narrowing was less than 50% within any epicardial coronaries. In addition, significant CAD was accepted as lumen-diameter narrowing of more than 50% within any epicardial coronaries. Lastly, obstructive CAD was described as a lumen-diameter narrowing of more than 50% of the LM coronary artery or narrowing ≥70% within any epicardial coronaries. SYNTAX scores (version 2.28) were calculated in arteries with ≥1.5 mm diameter and have luminal obstruction ≥50%. Decisions related to revascularization strategies were made based on the preference of the attending physicians.

Transthoracic echocardiography (Philips Epiq 7 systems, Andover, MA) was performed on all participants at the time of their first examination. The left ventricular ejection fraction (LVEF) was obtained using the modified Simpson's method (17). Left ventricular hypertrophy (LVH) was equally detected by calculating the left ventricular mass (LVM) according to the Devereux formula (18). The LVM index (LVMI) was then derived by correcting the LVM for body surface area.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc. Chicago, Illinois, USA). Continuous variables were evaluated for normality distribution using the Kolmogorov-Smirnov test. If variables were normally distributed, they were expressed as the means ± standard deviation. Whereas, if the distribution was not normal, variables were expressed as median and inter-quartile ranges. However, categorical variables were expressed as numbers and percentages and

were compared using the chi-square test. An Independent sample t-test was employed for parametric variables, whiel the Mann-Whitney U test was employed for non-parametric variables. Propensity scores for all individuals were estimated using a logistic regression model including age, sex, occurrence of diabetes mellitus (DM), hypertension and dyslipidemia, current smoking, and family history of CAD. A 1:1 nearest neighbor matching was performed with a caliper width of 0.2. The score-matched pairs were reanalyzed. A logistic regression analysis was performed to predict the presence of obstructive LM and/or pLAD lesions. First, we separately analyzed the relationships between the dependent variable and risk factors for CAD and LAFB. The variables that have p-value of <0.1 in a univariate regression analysis were included in the multivariate logistic regression analysis (forced entry method). A p-value <0.05 (2-tailed) was considered statistically significant.

Results

We observed that 750 patients (94.9%) undertook at least one non-invasive test, and 40 patients (5.1%) were referredfor ICA directly (Table 1). The median age was 58 years old and 532 (67.3%) of them were males. The number of patients with LAFB was 68 (8.6%). Furthermore, 218 patients (27.6%) had obstructive CAD and had been treated with PCI, coronary artery bypass graft, or optimal medical therapy alone (18.5%, 7.6%, and 1.5%, respectively). The prevalence of obstructive CAD and CABG use was significantly different across LAFB and non-LAFB. Also, the prevalence of obstructive LM and/or pLAD lesions was higher in patients with LAFB. Patients with LAFB had a significantly higher LVMI. The prevalence of LAFB increased with increasing LVH grades (19) (Figure 1). Patients with obstructive LM and/or pLAD lesions were older and had a higher prevalence of hypertension, DM, dyslipidemia, family history of CAD, and LAFB (Table 2).

After propensity score matching (68 vs 68 patients), the age, sex, DM, smoking status, hypertension, dyslipidemia, family history of CAD were similar between groups (Table 3). The obstructive LM and/or pLAD lesion rate remained significantly higher in patients with LAFB [8 (11.8%) vs 22 (32.2%), p=0.004].

In univariate analyses, the presence of LAFB was a significant predictor of obstructive LM and/or pLAD lesions (odds ratio: 3,587; 95% confidence interval: 1,465-5,785; p=0.005). Multivariate logistic regression analysis, using significant parameters obtained from univariate analysis, was conducted to reveal independent predictors of obstructive LM and/or pLAD lesions. A history of hypertension and DM were found to be independent predictors of obstructive LM and/or pLAD lesions. Although there was a significant relationship between the presence of LAFB and dependent variable in univariate logistic regression models, only known cardiovascular risk factors showed a direct significant association after adjusting for confounders. Thus, the presence of LAFB was not an independent predictor of obstructive LM and/or pLAD lesions (Table 4).

Discussion

We aimed at assessing the relationship between LAFB and obstructive LM and/or pLAD lesions in patients referred to ICA with stable angina pectoris. The cross-sectional analysis of our study revealed an association between the presence of LAFB and obstructive LM and/or pLAD lesions, advanced age, prevalence of dyslipidemia, and LVMI. Even though LAFB had a significant predictive value from univariate analysis, this

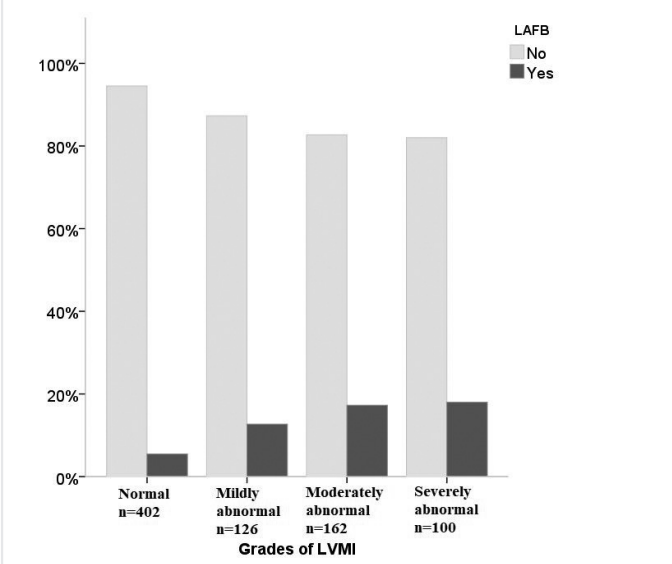

Figure 1. The plots show an upward trend in LAFB presence in line with increasing LVMI grades

LAFB: Left anterior fascicular block, LVMI: Left ventricular mass index

Table 1. Characteristics of symptoms and diagnostic tests of study population

	All patients (n=790)	Female (n=258)	Male (n=532)
Initial diagnostic test			
Exercise ECG	206 (26.1%)	52 (20.2%)	154 (28.9%)
CCTA	378 (47.8%)	128 (49.6%)	250 (47%)
MPI	166 (21%)	66 (25.6%)	100 (18.8%)
ICA	40 (5.1%)	12 (4.6%)	28 (5.3%)
Result of non-invasive testing			
Positive	258 (32.7%)	66 (25.6%)	192 (36.1%)
Negative	466 (59%)	174 (67.4%)	292 (54.9%)
Inconclusive	66 (8.4%)	18 (7%)	48 (9%)
Obstructive CAD	218 (27.6%)	54 (20.9%)	164 (31%)

CAD: Coronary artery disesae; CCTA: Coronary computed tomography angiography; ECG: Electrocardiogram; ICA: Invasive coronary angiography; MPI: Myocardial perfusion imaging

Table 2. Baseline characteristics and laboratory findings of study population according to the presence of obstructive LM and/or pLAD lesion

Baseline characteristics	All patients (n=790)	Obstructive LM and/or pLAD lesion – (n=652)	Obstructive LM and/or pLAD lesion + (n=138)	p
Age (years)	58 (50-65)	58 (48-64)	63 (57-65)	<0.001
Male gender, (n, %)	532 (67.3)	219 (67.2)	47 (68.1)	0.831
Diabetes mellitus, (n, %)	256 (32.4)	102 (31.3)	29 (42)	<0.001
Current smoking, (n, %)	310 (39.2)	132 (40.5)	27 (39.1)	0.680
Hypertension, (n, %)	240 (30.4)	164 (50.3)	55 (79.7)	0.001
Dyslipidemia, (n, %)*	452 (57.2)	91 (27.9)	29 (42)	<0.001
Family history of CAD, (n, %)	240 (30.4)	87 (26.7)	34 (49.3)	<0.001
BMI (kg/m^2)	29.4 (27-33.7)	29.4 (26.6-34.2)	30.4 (27.7-31.6)	0.306
BSA (m^2)†	1.96 (1.85-2.07)	1.96 (1.86-2.07)	1.92 (1.84-2.06)	0.118
LAFB, (n, %)	68 (8.6)	46 (7.1)	22 (15.9)	0.001
Laboratory parameters and echocardiography				
Hemoglobin (g/dL)	14.8 (13.5-15.8)	14.9 (13.5-16)	14.7 (13.2-15.3)	0.079
WBC (10^3/µL)	7.7 (6.4-9.2)	7.6 (6.4-9.1)	8.9 (6.5-10.1)	<0.001
Neutrophil, (10^3/µL)	4.2 (3.5-5.1)	4.1 (3.4-4.8)	5.1 (3.8-5.2)	<0.001
Lymphocyte, (10^3/µL)	2.1 (1.9-2.7)	2.2 (2.0-2.7)	2.1 (1.9-2.2)	0.025
Platelets, (10^3/µL)	240 (200-286)	241 (203-287)	232 (195-273)	0.065
Total cholesterol (mg/dL)	205 (182-240)	205 (179-235)	216 (187-252)	0.084
LDL-C (mg/dL)	149 (125-174)	144 (121-172)	157 (131-193)	<0.001
HDL-C (mg/dL)	40 (34-44)	40 (35-44)	35 (32-40)	<0.001
Triglyceride (mg/dL)	167 (128-202)	165 (127-206)	170 (151-199)	0.051
Serum creatinine (mg/dL)	0.81 (0.71-0.94)	0.80 (0.67-0.91)	0.9 (0.8-1.0)	<0.001
Urea (mg/dL)	32 (28-36)	32 (28-36)	36 (34-39)	<0.001
Sodium (mEq/L)	137 (133-142)	137 (133-142)	137 (135-141)	0.678
Potassium (mEq/L)	4.4 (3.8-5.0)	4.4 (3.9-5.0)	4.4 (3.8-4.9)	0.225
LVEF (%)	63 (60-65)	63 (60-65)	64 (60-65)	0.528
LV mass (g)	192 (169-227)	192 (169-220)	220 (175-241)	<0.001
LVMI (g/m^2)	97 (85-116)	95 (83-113)	112 (97-120)	<0.001

BMI: Body mass index, BSA: Body surface area, CAD: Coronary artery disease, HDL-C: High-density lipoprotein cholesterol, LAFB: Left anterior fascicular block, LDL-C: Low-density lipoprotein cholesterol, LM and/or pLAD: Left main coronary artery and/or proximal left anterior descending coronary artery, LVEF: Left ventricular ejection fraction, LVMI: Left ventricular mass index, WBC: White blood cell, *: The presence of dyslipidemia was defined according to age- and gender-adjusted percentiles from National Health and Nutrition Examination Survey III data, †: Calculated according to the DuBois method

association disappeared after adjustment for other cardiovascular risk factors. We found that the presence of LAFB has no independent role in predicting obstructive LM and/or pLAD lesions. Therefore, it should be considered a marker rather than a determinant of LM and/or pLAD lesions in patients with suspected stable angina pectoris.

In previous studies, the presence of LAFB differed when evaluated in different groups. In the general population, the prognostic implications of LAFB have been examined in studies with inconsistent results. Miller et al. (14) demonstrated that patients with LAFB had the poorest outcome among patients with uncomplicated ventricular conduction blocks, and emphasized that LAFB is a significant predictor of mortality. Conversely, other epidemiological studies suggested that isolated LAFB may not have adverse prognostic implications (12,20,21). Biagini et al. (13) concluded that LAFB is associated with an increased risk of cardiac death in patients with suspected CAD referred for dobutamine stress echocardiography. Similarly, as a recent study revealed that the presence of LAFB is related to an increased risk of all-cause death when compared with isolated RBBB in patients without apparent ischemic heart disease (22). In another study conducted in patients with no evidence of cardiac disease, investigators found a significant association between LAFB, and hypertension orcardiac disease (11).

Although LAFB has many etiologies, one of the most important causes is CAD (15). Previous studies have shown that high-grade narrowing of the LAD coronary artery can induce the development of LAFB (23-26). Assali et al. (23) reported that patients in whom LAFB develops during inferior wall acute myocardial infarction have a higher prevalence of stenosis in the LAD coronary artery. Lévy et al. (24) found that LAFB is associated with significant stenosis of the LAD coronary artery in patients with significant CAD at ICA. In another study, the same clinicians also showed that transient LAFB during an attack of angina pectoris may be indicative of a severe obstruction of the LAD coronary artery in the vicinity of the first perforator (25). It has been shown that selective opacification of the left coronary artery can cause transient left anterior hemiblock (26).

Table 3. Demographic, clinical, laboratory, and angiographic characteristics of study patients according to the presence of LAFB

		Before matching			After matching		
Baseline characteristics	**All patients (n=790)**	**LAFB – (n=722)**	**LAFB + (n=68)**	**p**	**LAFB – (n=68)**	**LAFB + (n=68)**	**p**
Age (years)	58 (50-65)	58 (50-64)	62 (56-69)	0.002	61 (51-68)	62 (56-69)	0.433
Male gender, n (%)	532 (67.3)	480 (66.5)	52 (76.5)	0.093	54 (79.4)	52 (76.5)	0.679
Diabetes mellitus, n (%)	256 (32.4)	228 (31.6)	30 (44.1)	0.076	21 (30.9)	30 (44.1)	0.111
Current smoking, n (%)	310 (39.2)	278 (38.5)	32 (47.1)	0.167	38 (55.9)	32 (47.1)	0.303
Hypertension, n (%)	240 (30.4)	214 (29.6)	24 (35.3)	0.141	19 (27.9)	24 (35.3)	0.356
Dyslipidemia, n (%)*	452 (57.2)	404 (56)	48 (70.6)	0.020	43 (63.2)	48 (70.6)	0.380
Family history of CAD, n (%)	240 (30.4)	212 (29.4)	28 (41.2)	0.043	18 (26.5)	28 (41.2)	0.120
BMI (kg/m^2)	29.4 (27-33.7)	29.4 (26.6-33.8)	29.8 (27.8-33.2)	0.244	28.7 (25.4-30.4)	29.8 (27.8-33.2)	0.002
BSA (m^2)†	1.96 (1.85-2.07)	1.95±0.15	1.96 (1.87-2.10)	0.500	1.97 (1.83-2.07)	1.96 (1.87-2.10)	0.449
Laboratory parameters and echocardiography							
Hemoglobin (g/dL)	14.8 (13.5-15.8)	14.8 (13.5-16)	14.7 (13.8-15.4)	0.435	15.1 (13.5-16.1)	14.7 (13.8-15.4)	0.146
WBC (10^3/µL)	7.7 (6.4-9.2)	7.8 (6.5-9.2)	7.65 (6-9)	0.762	8.1 (7.6-10.4)	7.65 (6-9)	0.052
Neutrophil, (10^3/µL)	4.2 (3.5-5.1)	4.2 (3.5-5.1)	4.3 (3.4-5.2)	0.715	4.95 (3.7-6.0)	4.3 (3.4-5.2)	0.008
Lymphocyte, (10^3/µL)	2.1 (1.9-2.7)	2.1 (1.9-2.7)	2.0 (1.7-2.5)	0.021	2.2 (2.1-3.0)	2.0 (1.7-2.5)	0.055
Platelets, (10^3/µL)	240 (200-286)	240 (200-286)	251 (198-294)	0.636	271 (232-299)	251 (198-294)	0.011
Total cholesterol (mg/dL)	205 (182-240)	205 (184-236)	217 (166-249)	0.080	212 (182-240)	217 (166-249)	0.670
LDL-C (mg/dL)	149 (125-174)	149 (125-174)	156 (133-183)	0.110	133 (128-167)	156 (133-183)	0.356
HDL-C (mg/dL)	40 (34-44)	40 (34-44)	37 (33-40)	0.056	36 (32-44)	37 (33-40)	0.807
Triglyseride (mg/dL)	167 (128-202)	167 (131-202)	171±76	0.557	154 (138-203)	171±76	0.848
Serum creatinine (mg/dL)	0.81 (0.71-0.94)	0.81 (0.70-0.94)	0.84 (0.72-0.95)	0.249	0.9 (0.7-1.0)	0.84 (0.72-0.95)	0.454
Urea (mg/dL)	32 (28-36)	32 (28-36)	32 (28-37)	0.541	32 (28-35)	32 (28-37)	0.190
Sodium (mEq/L)	137 (133-142)	137 (133-142)	137 (132-141)	0.101	136 (132-140)	137 (132-141)	0.958
Potassium (mEq/L)	4.4 (3.8-5.0)	4.4 (3.8-5.0)	4.4 (3.9-4.9)	0.657	4.4 (3.9-4.9)	4.4 (3.9-4.9)	0.944
LVEF (%)	63 (60-65)	63 (60-65)	65 (62-66)	0.070	65 (60-68)	65 (62-66)	0.840
LV mass (g)	192 (169-227)	187 (166-227)	227 (210-248)	<0.001	192 (170-241)	227 (210-248)	0.001
LVMI (g/m^2)	97 (85-116)	95 (83-113)	112 (104-129)	<0.001	97 (85-114)	112 (104-129)	<0.001
Angiographic characteristics							
Normal, n (%)	184 (23.3)	168 (23.3)	16 (23.5)	0.961	4 (5.9)	16 (23.5)	0.110
Mild CAD, n (%)	288 (36.5)	268 (37.1)	20 (29.4)	0.207	40 (58.8)	20 (29.4)	0.001
Significant CAD, n (%)	318 (40.3)	286 (39.6)	32 (47.1)	0.231	24 (35.3)	32 (47.1)	0.163
- LAD, n (%)	216 (27.3)	186 (25.8)	30 (44.1)	0.001	16 (23.5)	30 (44.1)	0.011
- CX, n (%)	130 (16.5)	114 (15.8)	16 (23.5)	0.100	18 (26.5)	16 (23.5)	0.692
- RCA, n (%)	190 (24.1)	168 (23.3)	22 (32.4)	0.094	16 (23.5)	22 (32.4)	0.252
- Single vessel disease, n (%)	136 (17.2)	126 (17.5)	10 (14.7)	0.566	6 (8.8)	10 (14.7)	0.287
- Three-vessel disease, n (%)	70 (8.9)	60 (8.3)	10 (14.7)	0.076	8 (11.8)	10 (14.7)	0.613
Obstructive CAD, n (%)	218 (27.6)	188 (26)	30 (44.1)	0.001	20 (29.4)	30 (44.1)	0.075
- PCI, n (%)	146 (18.5)	130 (18)	16 (23.5)	0.262	16 (23.5)	16 (23.5)	1.000
- CABG, n (%)	60 (7.6)	46 (6.4)	14 (20.6)	<0.001	4 (5.9)	14 (20.6)	0.011
- OMT alone, n (%)	12 (1.5)	12 (1.7)	0	0.284	2 (2.9)	0	0.154
Obstructive LM and/or pLAD lesion, n (%)	138 (17.5)	116 (16.1)	22 (32.2)	0.001	8 (11.8)	22 (32.2)	0.004
SYNTAX score	0 (0-8)	0 (0-7)	3 (0-21)	0.053	0 (0-4)	3 (0-21)	0.073
- Low (0-22), n (%)	682 (86.3)	630 (87.3)	52 (85.3)	0.013	60 (88.2)	52 (85.3)	0.072
- Intermediate (23-32), n (%)	66 (8.4)	56 (7.8)	6 (8.8)	0.048	4 (5.9)	6 (8.8)	0.090
- High (>32), n (%)	42 (5.3)	36 (5)	8 (9.5)	0.178	4 (5.9)	8 (9.5)	0.511

BMI: Body mass index, BSA: Body surface area, CABG: Coronary artery bypass graft, CAD: Coronary artery disesae, CX; Circumflex coronary artery, HDL-C: High-density lipoprotein cholesterol, LAD: Left anterior descending coronary artery, LAFB: Left anterior fascicular block, LDCC: Left dominant coronary circulation, LDL-C: Low-density lipoprotein cholesterol, LM and/or pLAD: Left main coronary artery and/or proximal left anterior descending coronary artery, LVEF: Left ventricular ejection fraction, LVMI: Left ventricular mass index, OMT: Optimal medical therapy, PCI: Percutaneous coronary intervention, WBC: White blood cell, *: The presence of dyslipidemia was defined according to age- and gender-adjusted percentiles from National Health and Nutrition Examination Survey III data, †: Calculated according to the DuBois method

Table 4. Predictors of patients with obstructive coronary artery disease and LM and/or pLAD lesion

	Predictors of patients with obstructive LM and/or pLAD lesion			
	Univariate analysis		Multivariate analysis †	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.037 (0.993-1.083)	0.094	-	-
Male gender	0.465 (0.189-1.046)	0.096	-	-
Hypertension	5.902 (2.470-8.098)	<0.001	4.907 (2.064-7.192)	<0.001
Diabetes mellitus	4.839 (2.034-7.513)	<0.001	4.154 (1.225-6.210)	0.022
Dyslipidemia	1.061 (0.677-1.662)	0.796	-	-
Current smoking	0.552 (0.242-1.258)	0.157	-	-
Family history of CAD	1.412 (0.612-3.259)	0.419	-	-
LAFB	3.587 (1.465-5.785)	0.005	2.554 (0.894-3.298)	0.160
LVMI	1.997 (0.981-1.014)	0.763	-	-

CAD: Coronary artery disease, LAFB: Left anterior fascicular block, LM and/or pLAD: Left main coronary artery and/or proximal left anterior descending coronary artery, LVMI: Left ventricular mass index, OR: Odds ratio, CI: Confidence interval, †: The variables included in multivariable analysis were age, male gender, hypertension, diabetes mellitus, and LAFB

It is difficult to distinguish between a left axis deviation caused by LAFB and that caused by LVH. In general, LVH does not shift the axis more leftward than -30 degrees. However, these two situations may overlap. Our results indicate that LVMI was higher in the LAFB group. In addition, LAFB prevalence was highest in patients with severely abnormal LVMI. LVH is associated with coronary heart disease mortality and hypertension (27). Moreover, as LVH advances, the deterioration in coronary microvascular circulation (28) can cause conduction abnormality in the left anterior fascicle, which is very sensitive to ischemia. Hypertension is an important cause of increased LVMI and the presence of LAFB. These two clinical parameters, which have a significant but not an independent predictive value in our study, are indirect markers that reflect the role of hypertension in CAD. However, the left conduction system structure is more complex and variable than the simplified trifascicular structure. This may be why an obstructive LM and/or pLAD lesions were not directly and independently associated to LAFB.

DM is a major risk factor for CAD with increasing prevalence. It is also associated with increased LVM and interstitial and perivascular fibrosis (29). Therefore, cardiomyopathy and LVH are two other DM-associated abnormalities in cardiovascular function. There is paucity of data on the relationship between DM and cardiac conduction system disorders. Jeong et al. studied 14,540 patients and found that DM is independently associated with RBBB, but not LBBB (30). In another study, García Rubí and Baduí Dergal (31). detected a high prevalence of bifascicular block among patients with diabetes. Although the increased prevalence of LBBB in patients with DM was not reported, the presence of LBBB in DM indicates advanced cardiovascular involvement and CAD complexity (32,33). In our study, DM was more prevalent in the group with LAFB. This could reveal the direct effect of diabetes on atherosclerosis or LVH. Another possible theory suggests that autonomic neuropathy is another complication in patients with diabetes associated with the emergence of LAFB in this group. However, the evidence for such an association is lacking; therefore, more research is necessary to ascertain this relationship.

Study Limitations

Our study has several limitations. The study was conducted with a relatively small sample. In addition, CAD was only evaluated through visual interpretation.

Conclusion

LAFB is associated with known cardiovascular risk factors, but it acts as a marker rather than a determinant of obstructive LM and/or pLAD lesions in patients with stable angina pectoris. The significantly increased prevalence of obstructive LM and/or pLAD lesions in patients with LAFB might be due to an increased prevalence in hypertension and DM, but there is a need larger studies to ascertain this finding. Nevertheless, LAFB is not frequently a "normal variant," and the presence of LAFB might help to identify obstructive LM and/or pLAD lesions in patients with suspected stable angina pectoris. Thus, physicians should have a low threshold for further cardiac evaluation if symptoms suggesting CAD are present.

Ethics Committee Approval: The approval form the the Clinical Research Ethics Committee of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital was obtained (approval number: 2020/62, date: 12.11.2020).

Informed Consent: Informed consent was granted by all patients before enrollment.

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Radiological Breast Evaluation Following Breast Reduction Surgery

Meme Küçültme Cerrahisi Sonrasında Memenin Radyolojik Değerlendirmesi

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ABSTRACT

Introduction: We aimed at evaluating the results of radiological [ultrasonography (US), mammography and magnetic resonance (MR)] exams in the follow-up of patients undergoing reduction mammaplasty.

Methods: We evaluated the postoperative bilateral breast US and mammography of 21 patients who underwent breast reduction surgery. Breast MR results of 9 patients with suspicious lesions were included in the examination.

Results: Postoperative radiological findings from all three imaging modalities were parenchymal distortion, rough calcification, fat cyst, focal fibrosis, fat necrosis, nipple retraction, malignant-like peripheral contrast, nodular lesion, malignant-like distortion and fluid collection with skin thickening. One patient eventually underwent a cyst excision and a tru-cut biopsy presented no malignant lesion was found.

Conclusion: Few studies demonstrate the radiological findings in the follow-up of patients following a mammaplasty, thereby prompting this study. After surgery, changes can occur in the breast of the patients that radiologically mimic malignancy. This can lead to unnecessary invasive procedures to rule out malignant changes. Thus, our study comes in to avoid these excess and unnecessary procedures.

Keywords: Breast, breast cancer, mammaplasty

ÖZ

Amaç: Çalışmamız redüksiyon mamoplasti ameliyatı geçiren hastaların takibinde radyolojik [ultrasonografi (US), mamografi ve manyetik rezonans (MR)] görüntüleme sonuçlarını değerlendirmeyi amaçlamaktadır.

Yöntemler: Ameliyat sonrası bilateral meme US'nin retrospektif değerlendirmesi ve meme küçültme ameliyatı geçiren 21 hastanın mamografisi yapıldı. Lezyon şüphesi olan 9 hastanın meme MR sonuçları muayeneye dahil edildi.

Bulgular: Parankimal distorsiyon, kaba kalsifikasyon, yağ kisti, fokal fibrozis, yağ nekrozu, meme başı retraksiyonu, malign benzeri periferik kontrast, nodüler lezyon, malign benzeri distorsiyon ve deri kalınlaşması ile sıvı toplanması üç görüntüleme yöntemini de içeren postoperatif radyolojik bulgulardı. Sonunda 1 hastaya kist eksizyonu ve tru-cut biyopsi yapıldı. Malign lezyon bulunmadı.

Sonuç: Meme küçültme ameliyatı sonrası hastaların takibinde saptanan radyolojik bulguları ve önemini gösteren az sayıda çalışma vardır. Ameliyat sonrasında hastaların meme dokularında radyolojik olarak maligniteyi taklit eden değişiklikler meydana gelebilir. Bu, kötü huylu değişiklikleri ekarte etmek için gereksiz invaziv prosedürlere yol açabilir. Cerrahların, radyologların ve onkologların bu konuda daha dikkatli olmaları gerekir.

Anahtar Kelimeler: Meme, meme kanseri, mammoplasti

Introduction

Breast-reduction surgery is among the most applied plastic surgeries in the world (1). Such patients are subjected to some changes in their breast that mimic malignancy-related findings in radiologic examinations, thereby prompting invasive or surgical procedures. Mammography in itself is usually not sufficient in the diagnosis, as well as ultrasound. However, magnetic resonance imaging (MRI) are usually requested for confirmation and occasionally lesions should be confirmed histopathologically with a biopsy (2,3). Fat necrosis in breast can occur as a result of previous breast surgery (lumpectomy, reduction, augmentation), radiotherapy, anticoagulant therapy, trauma, Weber-Christian disease, granulomatous angiopanniculitis and polyarteritis nodosa (4-6). Fat necrosis in breast can sometimes be difficult to distinguish from a malignant lesion.

Breast fat necrosis is a common benign condition that can cause a wide variety of mammographic findings such as tissue lumps, calcifications, fatty cysts and localized skin thickening (7). There are various clinical and

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imaging features where fat necrosis is sometimes not easy to distinguish from malignancy and can even be asymptomatic (8). In addition, the doctor can sometimes detect pathological condition by mammography only (9,10). To prevent biopsy, the mammographic spectrum of fat necrosis appearances must be recognized.

There are only limited number of studies in the literature that evaluate the clinical and radiological findings in long-term patient follow-up after breast reduction surgery. Therefore, we aimed to emphasizing the importance of radiological imaging in the long-term follow-up of patients who have undergone breast reduction surgery.

Methods

We examined the preoperative and postoperative findings (breast examinations and radiological imaging) in 21 patient files who underwent mammaplasty between January 2014 and January 2019. The study approval was obtained by University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethical Committee (approval number: 2660, date: 08.01.2021). Informed consents were equally received from all the patients.

The superomedial pedicle technique was performed in 19 patients, inferior pedicle in 1 patient and free nipple technique in 1 patient. Prior to the surgery, mammographies and ultrasounds were performed for screening purposes and no pathological findings were found.

Detailed breast examination, bilateral breast ultrasonography (US) and mammography were requested for preoperative follow-up as well as for long-term annual follow-up of 21 patients in the study. Breast MR was requested in 9 patients with suspicious lesions. One patient eventually underwent a cyst excision and tru-cut biopsy, which revealed no malignant lesions.

In ultrasonographic examinations, both breasts and axilla were examined on different planes using a broadband linear probe of 10-14 MHz (Toshiba Aplio 500, Minato, Tokyo, Japan). MRI examinations of cases with 1.5 Tesla MRI devices (GE Healthcare Signa HDi 1.5T, General Electric Medical Systems, Boston, MA, USA) were performed in the prone position with the breast coil. In all examinations, axial T1AG, fat-pressed axial and sagittal T2AG, diffusion-weighted and axial-plan fat-saturated T1-weighted dynamic contrast images were taken. Before the patient was taken into the MRI device, a catheter was inserted into the antecubital vein for the injection of the contrast agent.

Statistical Analysis

Descriptive analysis was performed using GraphPad Prism 7.0 software (GraphPad Software, Inc., La Jolla, CA, USA).

Results

The average age of the participants was 42.9±12 years (range: 20-58). Table 1, 2 reveal amongst others: The surgical technique, amount of breast resection, and the sternal notch-nipple areolar complex distance. Table 3 reveals clinical characteristics such as current diseases of participants, use of drugs and smoking. Histopathological examination of resected materials of all patients revealed no abnormalities. Scar revision surgery was performed in 2 patients (9.52%). In another patient, a suspicious tender mass was found during physical examination two years after surgery. Tru-cut biopsy accompanied by ultrasonography was then performed and was compatible with fat necrosis. Fat cyst excision was performed in this patient and a malignancy was ruled (Table 4).

Postoperative radiological findings from all three imaging modalities included parenchymal distortion (n=11; 52.3%), rough calcifications (n=8; 38.0%), fat cyst (n=7; 33.3%), focal fibrosis (n=6; 28.5%), fat necrosis (n=5; 23.8%), nipple retraction (n=5; 23.8%), malignant-like peripheral contrast (n=3; 14.2%), nodular lesions (n=1; 4.7%), malignant-like distortion (n=1; 4.7%) and fluid collection with skin thickening (n=1; 4.7%) (Table 5, Figure 1-8). The most common MRI findings were parenchymal distortion and asymmetry, malignant-like contrast, nipple retraction, focal fibrosis, postoperative fluid collection and fat necrosis.

In mammography, fat necrosis was generally seen as coarse dystrophic calcifications. In some cases, calcifications were heterogeneous and

Table 1. Summary of patient information

	Mean ± SD	Range
Mean age (years)	42.9±12	20-58
Mean follow-up time (months)	44±10	12-60
Left breast reduction (mg)	1190±410	537-2100
Right breast reduction (mg)	1121±334	630-1950
Left SN-NAC distance (cm)	32±4	27-40
Right SN-NAC distance (cm)	32±4	27-40
Planned SN-NAC distance (cm)	20±1	18-22

SN-NAC: Sternal notch-nipple areolar complex, SD: Standard deviation

Table 2. Summary of surgical techniques

	Frequency	Percentage
Superomedial pedicle	19	90.48%
Inferior pedicle	1	4.76%
Free nipple graft	1	4.76%
Bilateral	20	95.24%
Unilateral	1	4.76%

Table 3. Summary of patients' history

	Number	Percentage
Diabetes mellitus	2	9.52%
High blood pressure	5	23.81%
Drug use (progesterone)	1	4.76%
Insulin resistance	1	4.76%
Hypothyroidy	1	4.76%
Smoking	4	19.05%
Sleep apnea	1	4.76%

Table 4. Summary of surgery types

	Frequency	Percentage
Scar revision surgery	2	9.52%
Tru-cut biopsy	1	4.76%
Fat cyst excision	1	4.76%

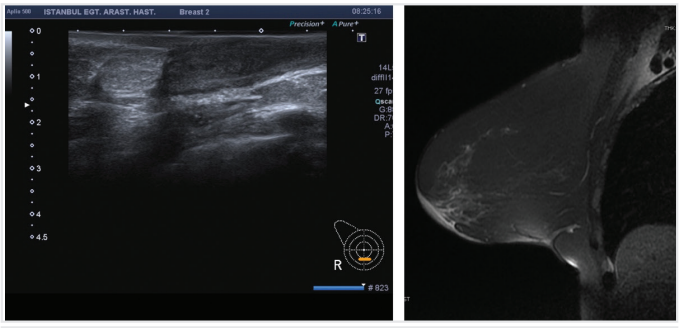

Figure 1. A 54-year-old patient, one year after breast reduction surgery, ultrasonography imaging (left) shows right breast periareolar skin thickening and skin edema, superficial fatty fluid collection. On magnetic resonance image (right; T2 fat-saturated sagittal image), there is skin edema, thickening in the periareolar area and inferior distortion in the incision line at the breast border in the periphery

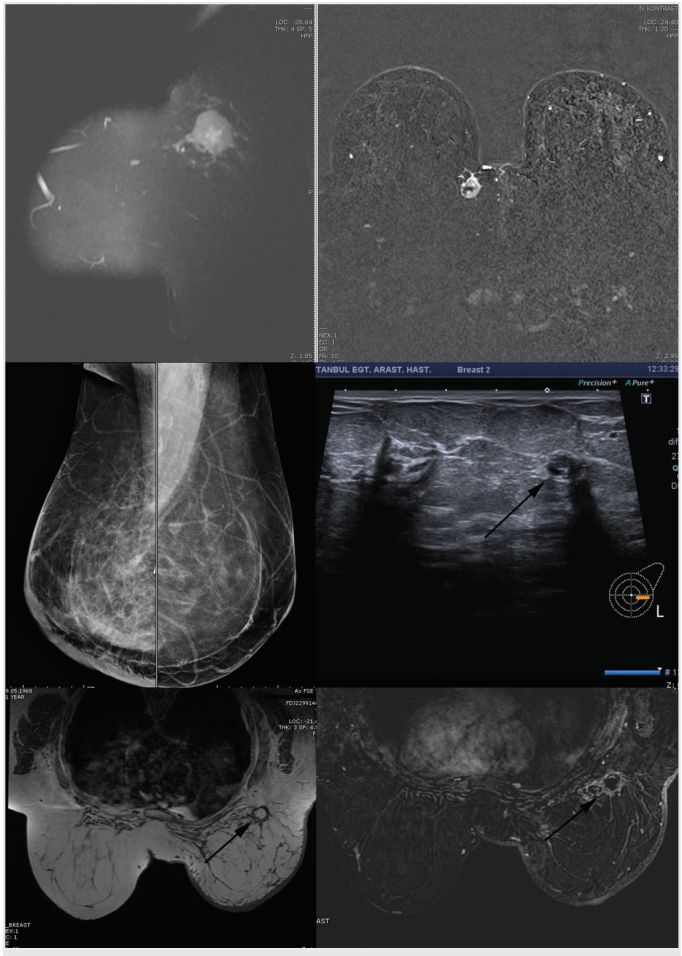

Figure 2. A 50-year-old patient with a right-sided skin-sparing mastectomy and left-sided reduction mammoplasty. Preoperative sagittal (upper left) and axial (upper right) T2, and dynamic contrasted magnetic resonance image (MRI) of the right breast showing high-grade malignant lesion with peripheral contrast uptake in the inner quadrant. Bilateral mammogram images of the patient ten months after surgery (middle left). Right breast showing radiotherapy-related skin thickness and general trabecular edema. Left breast image showing anterior contour lobulation and light distortion. Postoperative breast ultrasound images of the same patient. (middle right), millimetric fat cyst (black arrow) in the left breast outer quadrant are seen. Right breast T1 weighted image and dynamic MRIs showing fat necrosis with peripheral fat necrosis and inflammation (lower left, lower right)

biopsy was required for definitive diagnosis. In MRI, a fat necrosis could be perceived as a malignant-like distortion and mass-like appearance. MR contrast enhancement was seen in the periphery, especially in the early period following surgery and in cases of inflammation.

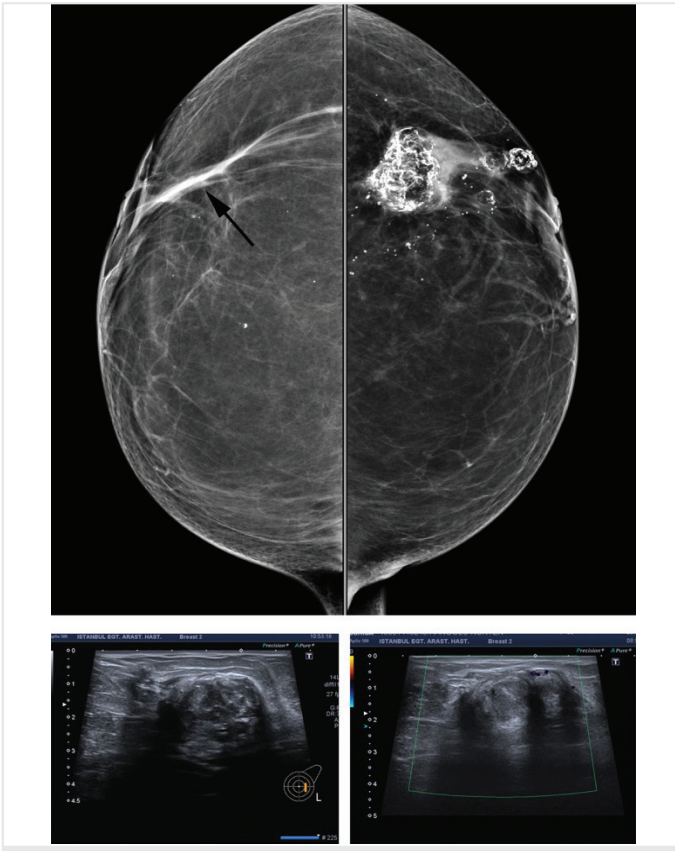

Figure 3. A 53-year-old woman postoperative 4th year following breast reduction surgery. Bilateral mammography images revealing a band like thin distortion (black arrow) in the right breast left outer quadrant (upper left) and calcification and fat necrosis in the left breast (upper right). Left breast ultrasound images showing rough calcifications (lower right) and hyperechoic fatty cysts (lower left)

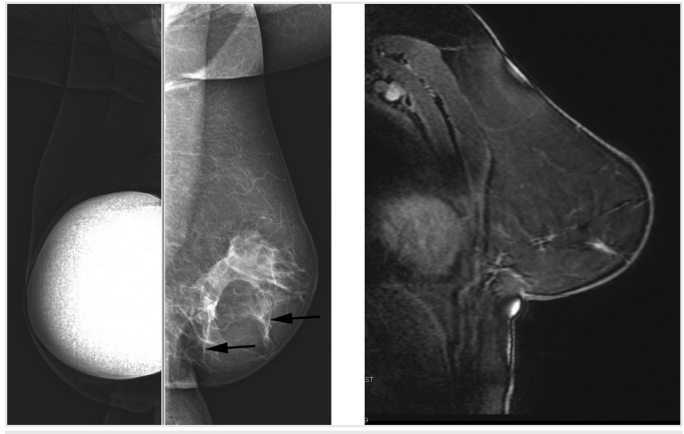

Figure 4. A 52-year-old patient three years following right breast implant reconstruction after a mastectomy, and a left reduction mammoplasty. Left breast reduction mammoplasty mammography image showing parenchymal distortion and fibrotic bands in the lower quadrant (left). Sagittal contrasted magnetic resonance image showing thin fibrotic band in the subareolar region of the lower quadrant (right)

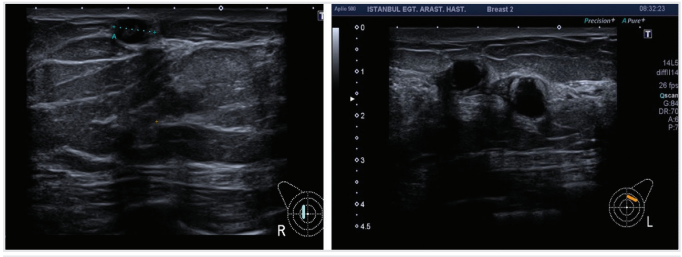

Figure 5. A 39-year-old patient's postoperative 4th year radiological ultrasonography images following breast reduction. Right breast shows hypoechoic subcutaneous cysts in the outer peri areolar area (left). Left breast image reveals outer quadrant parenchymal superficial hypoechoic and hyperechoic cysts (right)

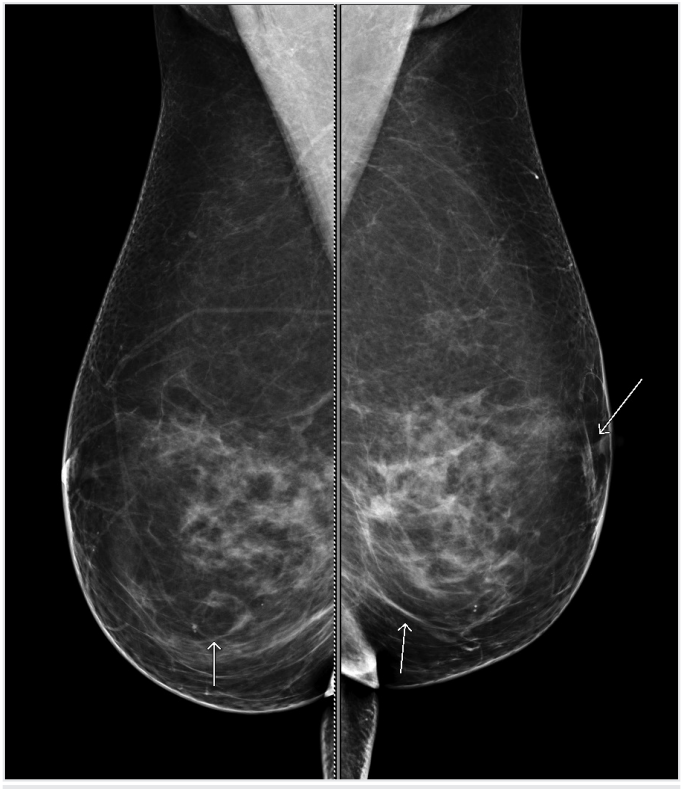

Figure 6. A 49-year-old patient bilateral mammograms postoperative 3rd year following breast reduction shows right breast lower quadrant radiolucent fat cysts with thin wall (left). Left breast image show nipple elevation and lower quadrant fibrotic tractions (right)

Table 5. Summary of radiological findings

	Frequency	Percentage
Parenchymal distortion	11	52.3%
Calcification	8	38.0%
Fat cyst	7	33.3%
Focal fibrosis	6	28.5%
Fat necrosis	5	23.8%
Nipple retraction	5	23.8%
Malignant like peripheral contrast	3	14.2%
Nodular lesion	1	4.7%
Malignant like distortion	1	4.7%
Fluid collection with skin thickening	1	4.7%

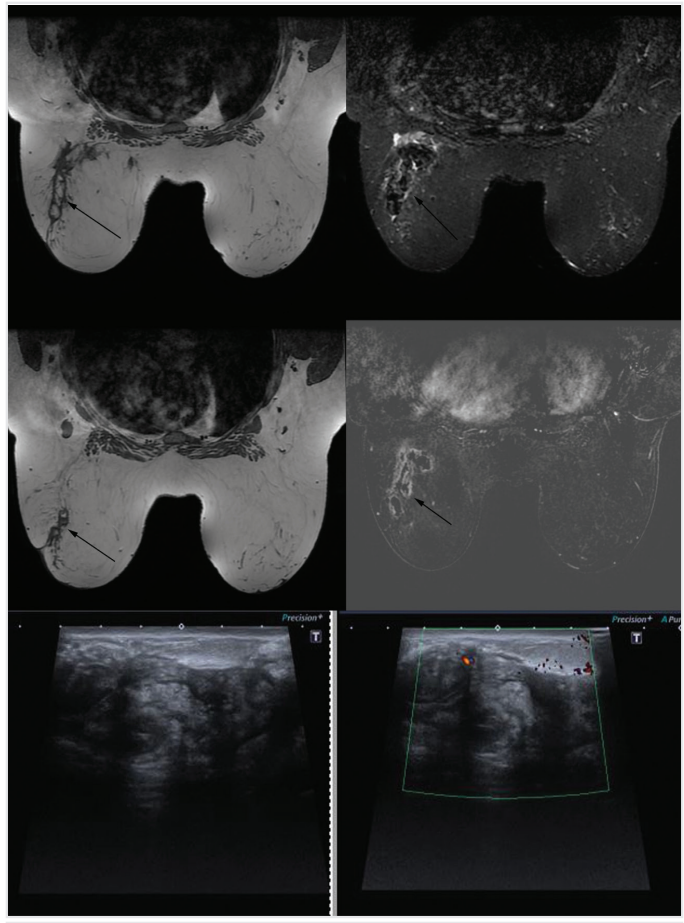

Figure 7. A 39-year-old patient three years following reduction mammoplasty. T1 weighted image (upper left), short inversion time inversion-recovery (upper right), and dynamic contrasted magnetic resonance images show inflamed fat necrosis with high-contrast uptake in the left outer quadrant. Axillary reactive lymph nodes are visible in the left axilla. Ultrasonography images (lower left, lower right) show heterogenic and hyperechogenic images of fat necrosis with hypervascularity in the doppler images

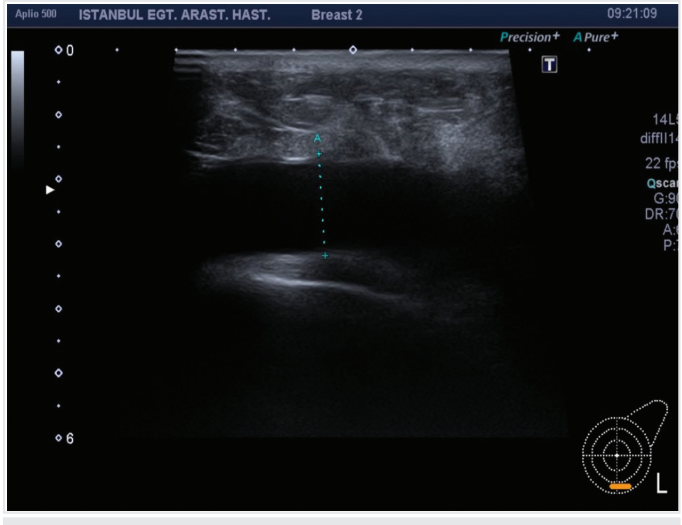

Figure 8. A 53-year-old patient one year after surgery with ultrasonography image showing an anechoic seroma formation in the lower quadrant

This enhancement pattern is also observed in malignant tumors, especially in the presence of necrosis. In fat necrosis, suppression of central areas in T1WI in hyperinstense and fat saturated series is typical and important in differential diagnosis (Figure 7) (11-17).

Discussion

Parenchymal tissue changes such as fat necrosis, fibrosis, scaring, which occur in imaging after a mammaplasty can mimic malignancies. If mammography or ultrasonography is not sufficient to differentiate these lesions from malignancy, MRI or histopathological verification with the biopsy is critical (2). The accurate recognition of the radiologic findings related to surgery in the postoperative period after a mammaplasty is key in distinguishing benign and malignant lesions.

The most common radiological findings in this period include asymmetric reposition of the remaining parenchyma tissue, nipple elevation, common parenchymal calcifications, fat necrosis and cysts, retroareolar fibrotic bands, thickening of the skin and postoperative local fluid collections. In these patients, fat necrosis is the finding with the most similar properties as malignant tumors. Kim et al. (11) revealed that the most frequent mammographic finding of the reduction mammoplasty was nipple elevation (84.3%). Other findings included retraction of the lower breast (80%), thickening of the skin (78.6%), downward shifting of the glandular tissue (47.1%), retro-areolar fibrotic band (42.9%), and areolar skin calcification or lipid cyst (35.7 %) (11).

Fat necrosis is often iatrogenic. It is seen in breasts that have undergone surgery and radiotherapy. The most common locations are subareoalar and periareolar regions, but they can also develop in other areas. In our patients, we found that fat necrosis was most commonly located in close proximity to the pedicle. This is due to limited vascularization in this area. Irregularly bounded lesions caused by fat necrosis can mimic breast cancer by causing thickening, withdrawal and parenchymal distortion on the skin. This is an issue especially in patients undergoing surgery or radiotherapy (18,19). Signs of fat necrosis in ultrasonography; solid, semisolid, oval, lobular mass with irregular edges or subcutaneous irregular hyperechoic lesions can be seen. Parenchymal distortion due to fibrotic, inflammatory, and calcified lesions can also be observed. Apart from that, it could be in the form of an anechoic mass with a simple cyst or posterior acoustic shading (18-21).

Long-term MRI findings due to fat necrosis can be fat cysts that hold round contrast. Fat necrosis can also be seen as heterogeneous hyperintense lesions in T1A views, and as heterogeneous hypointense lesion and an irregular or round mass after intravenous gadolinium injection in T2A views (2,22). Isointense parenchymal contrast pattern can be seen as a peripheral ring or nodule. In kinetic studies, the pattern of contrast specific to fat necrosis is unclear (22).

Another finding that can mimic malignancy is focal fibrosis from the proliferation of fibrous connective tissue surrounding ducts and acinus. Radiologically, we observe parenchymal distortion, irregularly-bounded oval and spicule-shaped lesions can be seen. Since these findings are similar to malignancy, it is necessary to perform biopsy for definitive diagnosis if there is no history of surgery, trauma, radiotherapy (19,21,23).

To avoid biopsy, it is necessary to properly define the spectrum of fat necrosis. There are no comprehensive studies to classify the postoperative changes of patients who have undergone a reduction mammaplasty. The role of ultrasonographic evaluation is evolving with technical developments. With high resolution ultrasonography, malignancies can often be discriminated (2). MRI is not a routine diagnostic method in the diagnosis of breast lesions but can be used in the presence of lesions that cannot be diagnosed by other radiological methods (19). Fat necrosis can still be difficult to diagnose, and in some cases, diagnosis is done with a tru-cut biopsy.

Study Limitations

This study has several limitations. First, it was a retrospective study and the patients were recruited from a single-center. Standardization of participants was not optimal and future prospective randomized studies could overcome these limitations.

Conclusion

Physicians need to adequately inform patients about the need for future ultrasound and biopsy after surgery. Moreover, the characteristics of palpable nodules and radiological findings after a mammaplasty require exploration in order to differentiate other lesions from malignant ones. Furthermore, patient check-up should be carried out systematically with a team consisting of a radiologist, plastic surgeon, and an oncologist, and they should be advised to continue their routine breast cancer screening.

Ethics Committee Approval: The study approval was obtained by University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethical Committee (approval number: 2660, date: 08.01.2021).

Informed Consent: Informed consents were equally received from all the patients.

Peer-review: Internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - G.T., D.A., M.S.; Concept - G.T., D.A., M.A.N., M.S.; Design - G.T., D.A., M.A.N., M.S.; Data Collection or Processing - G.T., D.A., M.S.; Analysis or Interpretation - D.A., M.A.N.; Literature Search - D.A., M.A.N.; Writing - G.T., M.S.

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Assessment of Left Ventricular Function using a Two-Dimensional Speckle Tracking Echocardiography in Asymptomatic Survivors of Hodgkin's Lymphoma in Long-Term Follow-Up

Kür Sağlanan Hodgkin Lenfoma Hastalarının Uzun Dönem Takibinde Sol Ventrikül Fonksiyonlarının İki Boyutlu Strain Ekokardiyografi ile Değerlendirilmesi

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ABSTRACT

Introduction: Two-dimensional speckle tracking echocardiography (2D-STE) is sensitive in the assessment of left ventricular (LV) systolic function and may aid in diagnosis of late cardiac effects in asymptomatic Hodgkin's lymphoma (HL) survivors in long-term follow-up.

Methods: This is a cross-sectional study of 21 HL survivors previously treated with anthracyclines, with (8/21) or without-mediastinal (8/21) radiotherapy and no recurrence at least 3 years after treatment compared to age-matched 43 healthy volunteers. To assess long-term cardiac complications, we performed 12-lead electrocardiography and 2D transthoracic echocardiography. In addition to conventional echocardiographic parameters, we used tissue Doppler echocardiography for LV diastolic functions and 2D-STE for evaluating the global longitudinal strain (GLS) of the LV myocardium.

Results: The mean age of the HL survivors was 40±15 years and the female sex was predominant (11/21). The average PR interval of the HL survivors was significantly longer (154.7±19.6 ms vs 133.8±13.9 ms, p<0.001) while the QTc interval was significantly shorter (383.8±18.7 ms vs 402.4±11.7 ms, p<0.001) than the control group. HL survivors had significantly impaired GLS compared to the control group (-19.3±2.6 vs -22.6±1.6, p<0.001). Thirteen of the HL survivors (61%) with normal LV ejection fraction had impaired GLS. The frequency of left ventricular diastolic dysfunction (LVDD) in the HL survivors group was significantly higher than that of the control group (52% vs 26%, p=0.015). Therefore, LVDD was detected in 61.5% of patients with a GLS <-20%.

Conclusion: 2D-STE could be used in predicting late-onset subclinical cardiac side effects following treatment in asymptomatic HL survivors for long-term follow-up.

Keywords: Cardiomyopathy, cardiotoxicity, cardio-oncology, diastolic dysfunction, Hodgkin's disease, strain echocardiography

ÖZ

Amaç: İki boyutlu strain ekokardiyografi (2D-STE) sol ventrikül (SV) sistolik fonksiyonlarının ölçümünde hassas bir ölçüm yöntemidir. Hodgkin lenfoma (HL) hastalarının takibinde ortaya çıkabilecek geç kardiyak yan etkilerin değerlendirilmesinde kullanılabilir.

Yöntemler: Bu çalışma antrasiklin (n=21) ± mediasten (8/21)/mediasten dışı (8/21) ışın tedavisi alan, en az 3 yıl takipte nüks saptanmamış 21 HL hastası ve yaşları eşleştirilmiş 43 sağlıklı bireyin karşılaştırıldığı kesitsel çalışmadır. Bireylerin kardiyak komplikasyonları 12 derivasyonlu elektrokardiyografi ve konvansiyonel ekokardiyografi ile değerlendirildi. SV diyastolik fonksiyonu için doku Doppler ekokardiyografi, SV miyokardiyumun global longitudinal strain (GLS) değerlendirmesi için 2D-STE kullanıldı.

Bulgular: HL hastalarının ortalama yaşı 40±15 saptandı ve çoğunlukla kadındı (11/21). HL hastalarında kontrol grubuna göre ortalama PR mesafesi anlamlı derecede artmış (154,7±19,6 ms vs 133,8±13,9 ms, p<0,001), QTc mesafesi azalmış (383,8±18,7 ms vs 402,4±11,7 ms, p<0,001) saptandı. HL hastalarında GLS değerleri kontrol grubuna göre anlamlı derece azalmış (-19,3±2,6 vs -22,6±1,6, p<0,001) saptandı. SV sistolik fonksiyonları normal olan 13 hastanın (%61,9) strain değerleri azalmış saptandı. Sol ventrikül diyastolik disfonksiyon (SVDD) sıklığı HL hastalarında kontrol grubuna göre anlamlı derecede yüksek saptandı (%52 vs %26, p=0,015). GLS'si azalmış saptanan 13 hastanın 8'inde (%61,5) SVDD saptandı.

Sonuç: HL hastalarında geç başlangıçlı kardiyak yan etkilerin saptanmasında 2D-STE kullanılması önerilir.

Anahtar Kelimeler: Kardiyomiyopati, kardiyotoksisite, kardiyo-onkoloji, diyastolik disfonksiyon, Hodgkin lenfoma, strain ekokardiyografi

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Introduction

Approximately 8,000 new Hodgkin's lymphoma (HL) patients are diagnosed in the United States annually (1). Cardiac complications constitute the most important non-malignant cause of mortality in HL survivors. Increased mortality rates due to cardiac related-events point to an inadequate screening of cardiac toxicity following treatment.

Patients with cardiotoxicity often have left ventricular diastolic dysfunction (LVDD) with preserved left ventricular systolic function (2). Left ventricle ejection fraction (LV-EF) measurements may not be sufficient for the evaluation of subclinical LV systolic dysfunction. Meanwhile, a two-dimensional speckle tracking echocardiography (2D-STE) enables a more detailed assessment of the LV myocardium with longitudinal strain measurements (3). However, its role in detecting late cardiotoxicity is unclear (4).

Thus, we aimed at examining long-term cardiac functions in asymptomatic HL survivors following treatment with adriablastin, bleomycin, vinblastine, dacarbazine (ABVD) protocol [with/without radiotherapy (RT)] and had no relapse for at least 3 years of follow-up.

Methods

Between 1999 and 2013, 21 HL survivors were evaluated in our study, which was conducted in the İstanbul University, İstanbul Faculty of Medicine, Department of Hematology. We included 43 healthy volunteers as controls and treated 213 HL patients in our clinic; however, patients without a follow-up file (n=140), those with relapsed Hodgkin's disease (n=5), those receiving non-ABVD chemotherapy (CT) or RT alone (n=34), and those who refused to participate in the study (n=13) were excluded (Figure 1).

The study included patients treated using the ABVD protocol (with or without RT) and had complete remission with no recurrence at follow-up for at least three years after remission.

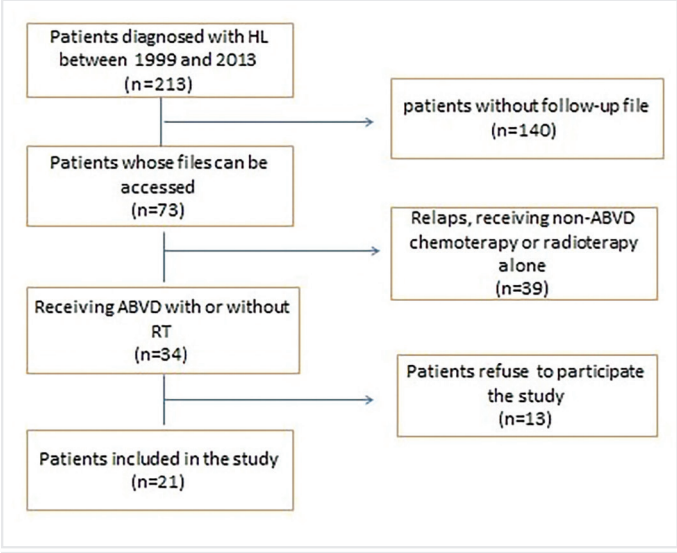

Figure 1. Distribution of patients with Hodgkin's lymphoma

ABVD: Adriablastin, bleomycin, vinblastine, dacarbazine protocol, HL: Hodgkin's lymphoma, RT: Radiotherapy

All patients were interrogated about complaints of shortness of breath, angina pectoris, syncope, or palpitation. Moreover, attending physicians conducted a thorough investigation of any history of heart failure or cardiomyopathy, ischemic heart disease, coronary angiography or angioplasty, pacemaker implantation or electrophysiologic study/ablation, pericardial disease, valvular heart disease, cardiac surgery, stroke or cerebrovascular disease.

The Eastern Cooperative Oncology Group (ECOG) performance scores of all participants were recorded. Levels of glucose (mg/dL), triglyceride (mg/dL), and low-density lipoprotein (LDL) cholesterol (mg/dL) were measured using blood samples.

Participants underwent 12-lead electrocardiography (ECG) after a 30-minute rest. All ECGs were taken at a rate of 25 mm/s and an amplitude of 10 mm/mV. QT, QTc, and PR intervals of all subjects were evaluated (5). All patients underwent two-dimensional transthoracic echocardiography (2D-TTE) using an iE33 echocardiography system (Philips Medical Systems, Andover, Massachusetts) through an X5-1 (1–5 MHz) transducer. All views were recorded and analyzed. A modified Simpson's method was used to calculate the LV-EF. Moreover, the apical 4-chamber view was used to document the mitral in-flow velocity pattern. The E/A ratio was equally evaluated. E' velocity and a' velocity were assessed using tissue Doppler image analysis. LVDD was defined as having an abnormal result in more than half of the four main parameters (>50% positive): Left atrial volume index >34 mL/m^2, septal e' <7 cm/sec or lateral e' <10 cm/sec, peak TR velocity >2.8 m/sec, average E/e' >14 (6).

In all patients, the global longitudinal strain (GLS) of the LV was assessed using 2D-STE. For deformation analysis, the CMQ mode of the Philips IE33, QLAB 10.8.5 software was used. At 42-56 times per second, 3 consecutive cardiac periods were videotaped from the apical 4-, 3- (long axis), and 2-chamber views. For each view, three points were placed at the end of diastole (two at the base of the LV and one at the apex). The software finally traced the endocardial and epicardial borders automatically. The operator adjusted measurements where necessary. Each LV wall was divided into 3 equal parts (base, mid, and apical), and 17 segmental strain curves were collected. Peak systolic strain was designed to compare the values of all segments at the time of aortic valve closure. Decreased GLS was described as GLS-20% (7).

The ECG recordings, 2D-TTE examinations, and laboratory tests of HL patients before ABVD treatment were extracted from patient files and recorded.

Before the study, all patients provided written informed consent in accordance with the Helsinki Declaration. The İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee approved the study (approval number: 343, date: 10.02.2015).

Statistical Analysis

The descriptive statistics were computed using the NCSS 2007 Statistical Software (Utah, USA). Continuous data were expressed as the mean ± standard deviations, and categorical data as percentages. When the distribution was normal, Pearson correlation analysis was used to assess the relationships between parameters; when the distribution

was not normal, the Spearman correlation analysis was used. The chi-squared test (when the variables were categorical) or the Independent samples t-test (when variables were continuous) were used to determine significant differences between groups. To compare differences in median values between patient groups, the Mann-Whitney U test was used. A p-value of <0.05 was considered statistically significant.

Results

Patient Group

The mean age of the HL survivors was 40±15 years, and at the time of diagnosis was 35±19 years. The female gender was predominant (52.3%). The average time after HL diagnosis was 7±2.4 years. The most common HL subtype detected was nodular sclerosis (47.6%).

ECOG performance scores of all patients were "0". No significant changes in plasma glucose (p=0.711), serum LDL cholesterol (p=0.084), serum triglyceride levels (p=0.622), systolic (p=0.964) and diastolic (p=0.563) blood pressures, and heart rate (p=0.611) were detected in patients before treatment.

The patients were treated with an average of 6.3 cycles (4-12 cycles) of ABVD protocol. Average doses of chemotherapeutic drugs administered were 319.7 mg/m^2 (200-600 mg/m^2) for adriamycin, 112.4 mg/m^2 (60-180 mg/m^2) for bleomycin, 72.5 mg/m^2 (40-120 mg/m^2) for vinblastine, 4721 mg/m^2 (2800-8400 mg/m^2) for dacarbazine. Eight patients received only non-mediastinal RT, five patients received only mediastinal RT, and three received both with a median dose of 25 Gy (18-36 Gy). Eight of twenty-one patients received mediastinal RT in our study.

Comparison of Patient Group and Control Group

In HL survivors and the control group, the mean age and sex ratio were similar (p=0.874, p=0.927, respectively). There were no significant differences in plasma glucose, LDL, and triglyceride levels between the two groups (p=0.126, p=0.08, p=0.165, respectively). The heart rates of the HL survivors were significantly higher than those in the control group (82±18 vs 73±10, p=0.049). The systolic and diastolic blood pressures were similar between the two groups (p=0.348, p=0.760, respectively).

Demographic characteristics and laboratory analysis of HL survivors and the control group are shown in Table 1.

Electrocardiogram

The PR interval in patient groups was significantly longer than those in control group (154.7±19.6 ms vs 133.8±13.9 ms, p<0.001). Nevertheless, the PR interval was not >200 ms (first degree AV block) in any patient. The patient group QTc interval was significantly shorter than that of the control group (383.8±18.7 ms vs 402.4±11.7 ms, p<0.001).

Echocardiography

There were no critical differences in LV volumes, diameters, wall thickness, and EF between the groups.

LVDD was significantly higher in the HL group than in the control group (52% vs 26%, p=0.015). Additionally, GLS was impaired considerably in HL patient group than in the control group (-19.3±2.6 vs -22.6±1.6, p<0.001).

Table 2 presents the conventional echocardiographic parameters of LV systolic and diastolic functions and ECG parameters for both patient and control groups.

Among the HL patient group, 52% (n=11) had LVDD, and 61% (n=13) had impaired GLS (<-20%). Eight patients with GLS <-20%, eight patients

Table 1. The demographic characteristics and laboratory parameter of HL survivors and control group

	Study group (n=21)	Control group (n=43)	p
Age	40.2±15	40.8±14.5	0.874
Sex			
Male	10 (47.6%)	21 (48.8%)	
Female	11 (52.4%)	22 (51.2%)	0.927
Glucose (mg/dL)	87±23	79±19	0.126
Lipid profile			
LDL (mg/dL)	127±52	103±53.5	0.088
Triglyceride (mg/dL)	127±65	104±58	0.165
Heart rate (bpm)	82±18	73±10	0.049
Systolic blood pressure (mmHg)	117±12	113±14	0.348
Diastolic blood pressure (mmHg)	77±8	76±7	0.760

P: Independent sample t-test, HL: Hodgkin's lymphoma, LDL: Low-density lipoprotein

Table 2. ECG and echocardiographic parameters of HL survivors and control group

	HL (n=21)	Control group (n=43)	p
LV-EF (%)	66±5	68±5	0.091
SV (mL)	67±17	62±18	0.360
ESV (mL)	33±11	36±14	0.475
EDV (mL)	101±26	99±22	0.781
LVEDD (cm)	4±0.52	4.6±0.44	0.822
LVESD (cm)	2.87±0.43	2.89±0.38	0.875
LAD (cm)	3.31±0.41	3.32±0.15	0.926
E (m/s)	73±22	86±17	0.017*
A (m/s)	68±18	67±16	0.793
e' (m/s)	9±4	9±2	0.295
a' (m/s)	8±2	7±2	0.064
E/A	1.14±0.44	1.36±0.49	0.089
e'/a'	1.2±0.72	1.49±0.72	0.134
LVDD	52 (%)	26 (%)	0,015*
GLS (%)	-19.3±2.6	-22.6±1.6	<0.001*
Electrocardiogram			
PR (ms)	154.7±19.6	133.8±13.9	<0.001*
QTc (ms)	383.8±18.7	402.4±11.7	<0.001*

E/A: Early diastolic transmitral flow/late diastolic transmitral flow, a': Late diastolic tissue velocity, e': Early diastolic tissue velocity, ESV: End systolic volume, EDV: End diastolic volume, GLS: Global longitudinal strain, LV-EF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, LAD: Left atrium diameter, LVDD: Left ventricular diastolic dysfunction, SV: Stroke volume, *: Significant p-value (<0.05), HL: Hodgkin's lymphoma, ECG: Electrocardiography

with LVDD, and five patients with both, were categorized in the mild-risk group for adriamycin toxicity dose (Table 3).

In both groups, only a mild valve regurgitation (mitral, aortic, tricuspid, or pulmonary) was detected.

Discussion

In general, half of the patients receiving anthracycline therapy developed cardiac toxicity (8). Cardiac side effects increase with the addition of RT to anthracycline-based CT in these patients. The risk of cardiac complications considerably increases 8-10 years after treatment (9,10). This suggests that screening for cardiac toxicity should be underwent many years for this population, especially in asymptomatic HL survivors. The National Comprehensive Cancer Network suggests the annual evaluation of cardiac complications in patients who received more than 300 mg of anthracycline-based therapy (11). Most (76.2%) patients received >300 mg anthracycline-based treatment in the current study.

ECG and TTE are the preferred screening tools for cardiac toxicity in asymptomatic patients (11,12). ECG abnormalities may be seen in early and late periods of CT treatment (12). QTc prolongation is a side effect of anthracycline therapy, with case reports of patients presenting with acute cardiotoxicity and heart failure (13). However, these were always in the setting of other co-existing conditions and concomitant use of other QTc-prolonging drugs. There is no increased incidence of torsade de pointes in patients using anthracyclines (14). In our study, QTc prolongation was not detected in any patient. On the contrary, QTc intervals were shorter in HL survivors than in those of the control group.

Several studies have found an increase in deaths due to myocardial infarction among patients treated for HL with mediastinal RT (15). In a retrospective study conducted in Florida, 10.4% (42/415) of survivors developed CAD at averagely 9 years after treatment. Notably, the only treatment-related factor associated with CAD development was the use of a radiation technique that targets a part of the heart (16). CAD was not detected in HL survivors of our study, perhaps due to the small number of patients treated with mediastinal RT (8 of 21 patients).

Table 3. Adriamycin doses and risk classification in patients with LVDD and GLS impairment

	Average dose (mg/m^2)	Risk group	(n=21)	%
GLS <-20%	333.7	Mild	8	38
		Moderate	4	19
		Severe	1	4
LVDD	303.5	Mild	8	38
		Moderate	3	14
		Severe	0	0
		Severe	1	4
GLS <-20%+ LVDD	317.3	Mild	5	23
		Moderate	3	14
		Severe	0	0

GLS: Global longitudinal strain, mild-risk: 300-450 mg/m^2, moderate risk: 450-550 mg/m^2, high (severe) risk: Cumulative dose limit >550 mg/m^2, LVDD: Left ventricular diastolic dysfunction

Thus, we concluded that LV-EF is not sensitive enough for the early diagnosis of cardiomyopathies caused by chemotherapeutics (17). When EF was normal, it was useful in detecting LVDD as an indicator of early cardiomyopathy (18). LVDD contributes to the onset of heart failure and precedes the development of systolic dysfunction (19). Some studies have examined the usefulness of diastolic parameters in detecting anthracycline-related cardiac injury (20). Moreover, LVDD prevalence was higher in HL survivors who received at least 35 Gy mediastinal RT (21). Consistent with these studies, the amplitude of the E-wave in HL patients was significantly lower than that of the control group (73±22 vs 86±17 p=0.017) as the onset of LVDD and 52% of patients had LVDD while LV-EF was normal. Two of 11 patients with LVDD received mediastinal RT.

Great developments in non-invasive myocardial mechanics and cardiac function evaluation have been made possible by 2D-STE. Current studies suggest that the detection of subclinical systolic dysfunction using 2D-STE could be the first sign of LV systolic dysfunction (22). GLS is regarded as the most promising 2D-STE parameter for estimating cardiotoxicity (23). A 10-15% relative decline in GLS throughout cancer treatment assigns patients at risk of subsequent LV-EF decrease or progression of congestive heart failure. It is thought to be an indicator of cardiotoxicity (24,25). The ASE/EACVI Expert Consensus recommends GLS-based follow-up of adults during and after cancer treatment (26). In many studies, subclinical systolic dysfunction was detected by 2D-STE after anthracycline therapy despite normal LV-EF (27,28). Also, GLS decline was associated with long-term survival and LV-EF long-term reduction (24,25). Otherwise, impaired GLS was associated with exposure to mediastinal RT and high doses of anthracyclines (29). In our study, GLS impairment was detected in 62% of patients (n=13) despite normal LV-EF. Four of them received mediastinal RT in our study. Furthermore, 25% of patients with both GLS <-20% and LVDD received mediastinal RT in our study. Adriamycin doses and risk classification for cardiac toxicity were accepted as mild-risk (300-450 mg/m^2), moderate risk (450-550 mg/m^2), and high risk (>550 mg/m^2) (30). Eight of thirteen patients with GLS <-20%; Eight of eleven patients with LVDD, and five of eight patients with both GLS <-20% and LVDD, were detected in the mild-risk group in terms of toxicity dose of Adriamycin (Table 3). According to our study, patients in the mild-risk group could be evaluated for cardiac toxicity as well.

RT regions and doses were different, and the number of participants was not sufficient for comparison; therefore, no comparison was made between patients receiving only CT and those receiving both CT and RT.

Study Limitations

There were some limitations in our study. The number of patients enrolled in the study was relatively small. Also, the predictive effect of impaired GLS on symptomatic heart failure or decreased LV-EF was not evaluated. Our study was a retrospective cross-sectional study, and we assessed LV functions only once after the evaluation before CT ± RT. Performing echocardiogram periodically in patients with HL may explain how GLS and LV-EF impairment progressed over time. Our recommendation is to conduct further studies on late-onset cardiac toxicity in HL survivors and determine the predictive role of STE in larger samples and over more extended follow-up periods.

Conclusion

Despite normal LV-EF, patients may have subtle late-onset changes of LV systolic function measured by STE. STE may detect subclinical LV systolic dysfunction and simplify long-term monitoring of asymptomatic HL survivors. Whether such subtle changes of LV systolic functions can predict the risk of developing heart failure should be investigated in further prospective studies.

Ethics Committee Approval: The İstanbul University, İstanbul Faculty of Medicine Local Ethics Committee approved the study (approval number: 343, date: 10.02.2015).

Informed Consent: Before the study, all patients provided written informed consent in accordance with the Helsinki Declaration.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.A., A.A.; Concept - M.A., A.A., N.Ö., B.U., M.N.; Design - M.A., B.U., M.N.; Data Collection or Processing - M.A., P.K.Ö., A.A., R.B.; Analysis or Interpretation - M.A., P.K.Ö., A.A., R.B., N.Ö., B.U., M.N.; Literature Search - M.A., P.K.Ö., A.A., R.B., N.Ö.; Writing - M.A., P.K.Ö., R.B., N.Ö., B.U., M.N.

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The Contribution of Sonoelastography to the Diagnosis and Correlation of Strain Index Values with Pathological Subgroups in Fibroepithelial Breast Lesions

Fibroepitelyal Meme Lezyonlarında Sonoelastografinin Tanıya Katkısı ve Patolojik Alt Gruplar ile Strain İndeks Değerlerinin Korelasyonu

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ABSTRACT

Introduction: Fibroepithelial lesions are the most common benign lesions of the breast. When detected by mammography and ultrasonography (USG), the limitations of these examinations and the goal of diagnosing malignant lesions at an early stage may lead to off-label biopsies. Unnecessary biopsy procedures can be avoided by developing additional reliable methods to complement existing diagnostic procedures. For more accurate characterization of breast lesions, US elastography is used, which gives information about elasticity and deformability of the tissue. In our study, we aimed to determine the contribution of elastography to the diagnosis in the evaluation of fibroepithelial lesions of the breast with USG and to determine the relationship between strain index (SI) values and pathological subgroups.

Methods: Our study included 160 lesions in 105 patients who were diagnosed with pathologically proven fibroepithelial lesion in the Radiology Clinic of İstanbul Training and Research Hospital between September 2013 and November 2014, or who were followed up for at least two years with no pathology and whose radiological appearance was interpreted in favor of fibroadenoma (FA). Voluntary consent form and ethics committee approval for the study were obtained from the patients. USG examinations were performed with a 13-18 MHz linear high resolution volumetric probe. Considering the color map obtained in the elastography evaluation, different measurements were made from the hardest areas in the mass.

Results: In the sonoelastographic evaluation of fibroepithelial lesions, the median mean SI value was calculated as 3.30 (between: 0.35 and 28.80). The SI value was found to be higher in complex FAs than in other subgroups. It was observed that the mean size decreased as the age group got older. A statistically significant positive correlation was found between elastography stiffness index and size ($p<0.0001$, Pearson correlation index 0.643).

ÖZ

Amaç: Fibroepitelyal lezyonlar memenin en sık görülen benign lezyonlarıdır. Mamografi ve ultrasonografi (USG) ile saptandığında, bu tetkiklerin sınırlamaları ve malign lezyonlara erken evrede tanı koyma hedefi endikasyon dışı biyopsilere yol açabilmektedir. Mevcut tanı prosedürlerini tamamlayacak ek güvenilir yöntemlerin geliştirilmesiyle gereksiz biyopsi işlemleri önlenebilir. Meme lezyonlarının daha doğru karakterize edilebilmesi için, elastisite ve dokunun deformabilitesi hakkında bilgi veren US elastografi kullanılmaktadır. Çalışmamızda memenin fibroepitelyal lezyonlarının USG ile değerlendirilmesinde elastografinin tanıya katkısını ve strain indeks (Sİ) değerlerinin patolojik alt gruplarla ilişkisini belirlemeyi amaçladık.

Yöntemler: Çalışmamıza İstanbul Eğitim ve Araştırma Hastanesi, Radyoloji Kliniği'nde Eylül 2013-Kasım 2014 tarihleri arasında patolojik olarak kanıtlanmış fibroepitelyal lezyon tanılı veya patolojisi olmamakla birlikte en az iki yıl takipli, radyolojik görünümü fibroadenom (FA) lehine yorumlanmış 105 hastada 160 lezyon dahil edildi. Hastalardan gönüllü onam formu ve çalışma için etik kurulu onayı alındı. USG incelemeler 13-18 MHz lineer yüksek rezolüsyonlu volümetrik prob ile gerçekleştirildi. Elastografi değerlendirmede elde edilen renkli harita göz önünde bulundurularak, kitle içerisinde en sert alanlardan farklı ölçümler yapılmıştır.

Bulgular: Fibroepitelial lezyonların sonoelastografik değerlendirmesinde medyan ortalama Sİ değeri 3,30 (arasında: 0,35 ve 28,80) olarak hesaplanmıştır. Kompleks FA'larda Sİ değeri diğer alt gruplardan yüksek bulunmuştur. Yaş grubu büyüdükçe boyut ortalamasının azaldığı görülmüştür. Elastografi sertlik indeksi ile boyut arasında istatistiksel olarak anlamlı pozitif yönde bir korelasyon saptanmıştır ($p<0,0001$, Pearson korelasyon indeksi 0,643).

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Conclusion: We think that US elastography contributes to morphological USG findings in the evaluation of fibroepithelial lesions of the breast and can guide the biopsy decision correctly.

Keywords: Ultrasonography, US elastography, fibroepithelial lesion, fibroadenoma

Sonuç: Memenin fibroepitelial lezyonlarının değerlendirilmesinde US elastografinin morfolojik USG bulgularına katkı sağladığı, biyopsi kararında doğru yönlendirme yapabileceğini düşünmekteyiz.

Anahtar Kelimeler: Ultrasonografi, US elastografi, fibroepitelyal lezyon, fibroadenom

Introduction

Fibroepithelial lesions of the breast describe a biphasic and heterogeneous group of neoplasms that range from benign to malignant, characterized by varying degrees of stromal proliferation associated with the epithelial compartment. We frequently see these lesions in the clinic (1).

Fibroadenomas (FA) are the most common solid benign lesions consisting of balanced biphasic proliferation of glandular and stromal elements. FAs accompanied by epithelial component changes are called complex FAs (1,2). FAs can be safely followed without further research (3).

Phyllodes tumor is similar to FA, but has more cellularity in its stroma, and its typical feature is the presence of malignant potential, despite its benign character. Phyllodes tumors can be classified as benign lesions or borderline and high-grade malignancies according to pathological findings (1). Fibroadenolipoma, on the other hand, is a rare benign tumor consisting of well-limited, encapsulated, fatty, fibrous and adenomatous elements (4). Phyllodes tumors can be benign or malignant. Clinically, it is usually a hard round tumor. The fact that the tumor is very large or its rapid growth also indicates a phyllodes tumor, rather than FA. In patients with very large phyllodes tumors, ulceration of the skin or invasion of the chest wall may occur (3).

The limitations of mammography (MG) and ultrasonography (USG) and the goal of diagnosing malignant lesions at an early stage may lead to off-label biopsies. The cancer detection rate of biopsies is between 10-30%. Unnecessary biopsy procedures increase the cost, disrupt patient comfort and cause anxiety. Unnecessary biopsy procedures can be avoided by developing additional reliable methods to complement existing diagnostic procedures (5).

In order to characterize breast lesions more accurately, the US elastography technique, which provides information about elasticity and deformability of the tissue, has been put into use. In this technique, the basic principles of USG technology and elastography are combined (6). Malignant tissues are generally found to be tougher than benign tissues due to the common desmoplastic reactions they contain, therefore they are observed as less elastic in sonoelastographic examinations (7).

Currently, the most preferred method in the clinical setting is real-time elastography (RTE), which provides "strain imaging" by means of compression. RTE can be performed with conventional USG equipment with related software, and in this method, an elastogram is created on the USG image and updated in real time at a frequency of 10-15 Hz to evaluate the relative elasticity of tissues in a specific target region.

The elastogram, which reflects the relative elasticity of the tissues, is displayed by color coding (high stiffness areas in blue, more deformable areas in red, and moderately elastic areas in green). The lighter shades of the base color represent different degrees of tissue deformability and correlate with the dynamic range of the analytical system.

Some researchers have suggested the use of "strain ratio" or "strain index (SI)" in order to minimize the differences between operators in the differentiation of malignant and benign lesions. Calculation of the strain ratio is based on determining the mean strain value measured in the lesion and comparing it with the mean strain value of a similar adipose tissue in the adjacent breast tissue. The strain ratio reflects the relative hardness of the lesion.

In some studies, it has been found that the mean SI of malignant lesions is higher than that of benign lesions (6).

In this retrospective study, we aimed to determine the contribution of elastography and SI values to the diagnosis in the evaluation of fibroepithelial lesions of the breast with USG and their correlation with histopathological subtypes.

Methods

Our study included 105 patients with a diagnosis of pathologically proven fibroepithelial lesion, 88 (55%) with at least two years of follow-up, and their radiological appearance interpreted in favor of FA, between September 2013 and November 2014 at the İstanbul Training and Research Hospital, Clinic of Radiology. One hundred and sixty lesions were included in the patient. Voluntary consent form were obtained from the patients. The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 550, date: 28.11.2014).

Patient Selection

According to the morphology, echo structure, size, long-short axis relationship, lesion borders, and orientation to the chest wall of the lesion in the axial and sagittal planes in the USG evaluation, it was interpreted in favor of FA; female patients over the age of 18 with lesions that resulted as fibroepithelial lesion as a result of pathology and were followed up for at least two years were included in the study.

Ultrasonographic B-mode and Elastography Evaluation

Ultrasonographic examinations were performed with a 13-18 MHz linear high resolution volumetric probe (Toshiba Aplio 400, Japan, 2014). Imaging and measurements were made by a single practitioner with 10 years of experience in breast radiology.

USG Technique

In the examination, all quadrants of the breast were scanned in different planes. Parameters such as the largest diameters of the fibroepithelial

lesions, shape and contour features, and internal echo structures were included in the study.

Elastography Technique

Following conventional USG, US elastography assessment was performed by applying repetitive compressions at one-second intervals, at constant power, on the mass. Images with the same morphology and wave spectrum at least 5 times were analyzed. Considering the color map obtained, different measurements were made from the hardest areas in the mass. Care was taken to ensure that the measurements did not include cystic and calcified areas. SI measurements were made with post processing elastography during the examination and real time elastography in those performed after June 2014. SI was calculated by placing the first region-of-interest (ROI) on the target lesion and the second ROI on the lateral subcutaneous adipose tissue at the same size and depth as the target lesion.

Statistical Analysis

Descriptive statistics were presented as mean, standard deviation, and percentage. The mean of the two groups was compared with the t-test for independent groups. The mean of more than two groups was compared with One-Way ANOVA comparison methods. The distribution of categorical features relative to each other and the comparison of sonographic and elastographic parameters of Fibroepithelial lesions according to histopathological diagnosis were made using the chi-square test. The significance level was accepted as 0.05 in all tests.

Results

One hundred and sixty lesions in 105 female patients were included in the study. The ages of the patients were between 18-75 and the mean age was calculated as 40,13. 23,1% of the patients were under 30 years old, 58.1% were between 30-48 years old and 18.8% were over 50 years old.

The side distribution of the lesions is given in Table 1, and the localization distribution is given in Chart 1. The mean lesion size of 160 cases was 15.98±9.47 mm (3.50-84.0 mm) and the mean SI of 159 cases was calculated as 5.30±4.97 (0.35-28.80).

In the sonoelastographic evaluation of the lesions; SI values obtained were between 0.35 and 28.80 (mean SI: 4.97). The median SI value was found to be 3.30. SI value could not be measured in the patient with borderline phyllodes tumor because the mass almost completely filled the breast.

When SI values were considered to be 5 for the malignant-benign distinction, 75.5% (n=120) were found to be below 5 and 24.5% (n=39) were found to be above 5 when an immeasurable lesion was ruled out in our cases.

Table 1. Side distribution of lesions

Side distribution	Number of lesions
Right breast	84 (52.5%)
Left breast	76 (47.5%)
Total	160

The distribution of the lesions according to their shape characteristics is given in Table 2. When Pearson chi-square test was used to evaluate the correlation between lesion shape features and SI values, the p-value was found to be 0.046, and the SI of lobular lesions was significantly lower than lesions with other morphology (Figure 1). When the lesions are classified according to their shapes, the lobular lesion with an SI below 5 is the most common (79.8%), and the least group with an SI below 5 is the spherical group.

When the lesions are evaluated according to their internal echoes, they are mostly homogeneous (80%) lesions with an SI below 5. When the Pearson chi-square test was used, the p-value was found to be 0.745, and there was no significant relationship between internal echo and SI. The distribution of internal echo characteristics according to USG is shown in Chart 2.

Using the One-Way anova test, a significant inverse relationship was found between the age groups of the patients and the size of the lesion (p=0.001). It was observed that the mean size decreased as the age group got older (Table 3). However, no significant correlation was found between SI and patient age (p=0.185).

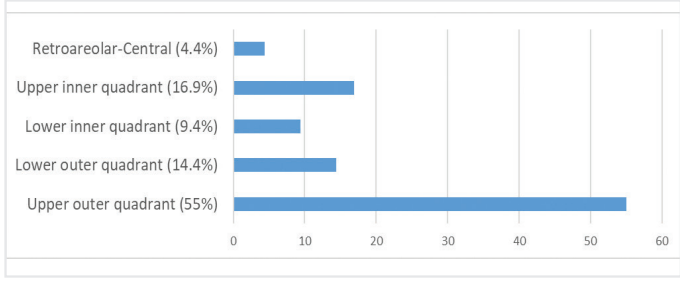

Chart 1. Distribution of lesion localizations

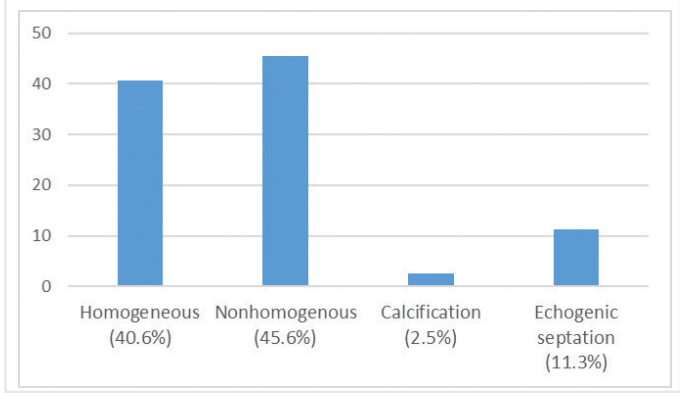

Chart 2. Distribution of internal echo characteristics according to ultrasonography

Table 2. The distribution of lesions according to their shape characteristics

Round (5%)	8
Oval (41.9%)	67
Lobule (52.5%)	84
Irregular (0.6%)	1

A statistically significant positive correlation was found between elastography stiffness index and size (p<0.0001, Pearson correlation index 0.643).

Percentage distribution of pathological subgroups is shown in Chart 3. When the mean SI values of the pathological subgroups were examined, the highest SI value and the largest dimension were found in complex FA (Figure 2). The highest mean age in lesions diagnosed with FA was found in degenerated FA (Table 4).

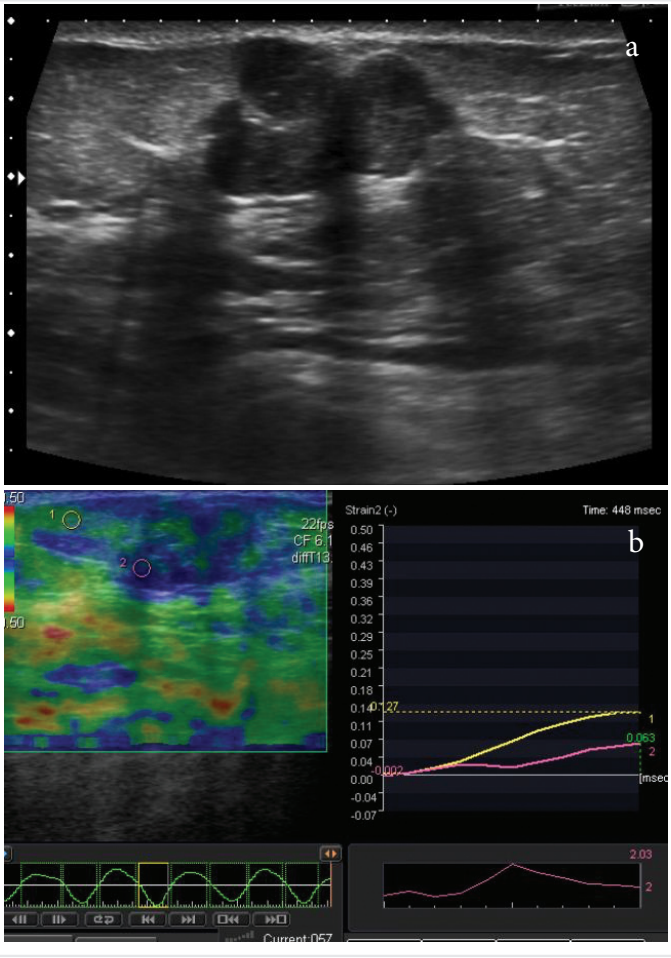

Figure 1. A 32-year-old patient with histopathological diagnosis of FA; a) hypoechoic solid lesion with lobulated contour and echogenic internal septation on B mode US image; b) It is seen that the SI value (2.03) is low in US elastography

FA: Fibroadenomas, US: Ultrasound, SI: Strain index

Table 3. Distribution of strain index values and sizes of lesions by age groups

Age groups		n	Mean ± SD
Size	<30 age	37	20.7±14.3
	30-49 age	93	15.1±7.0
	>=50 age	30	12.7±6.1
Strain index	<30 age	36	4.0±5.3
	30-49 age	93	4.8±4.9
	>=50 age	30	6.4±6.2

SD: Standard deviation

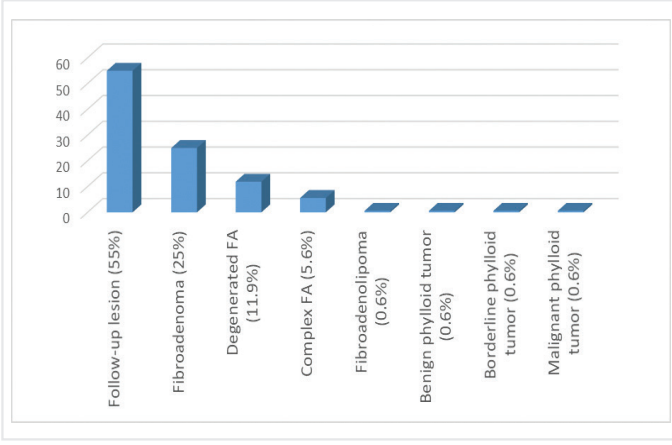

Chart 3. Distribution of pathological subgroups

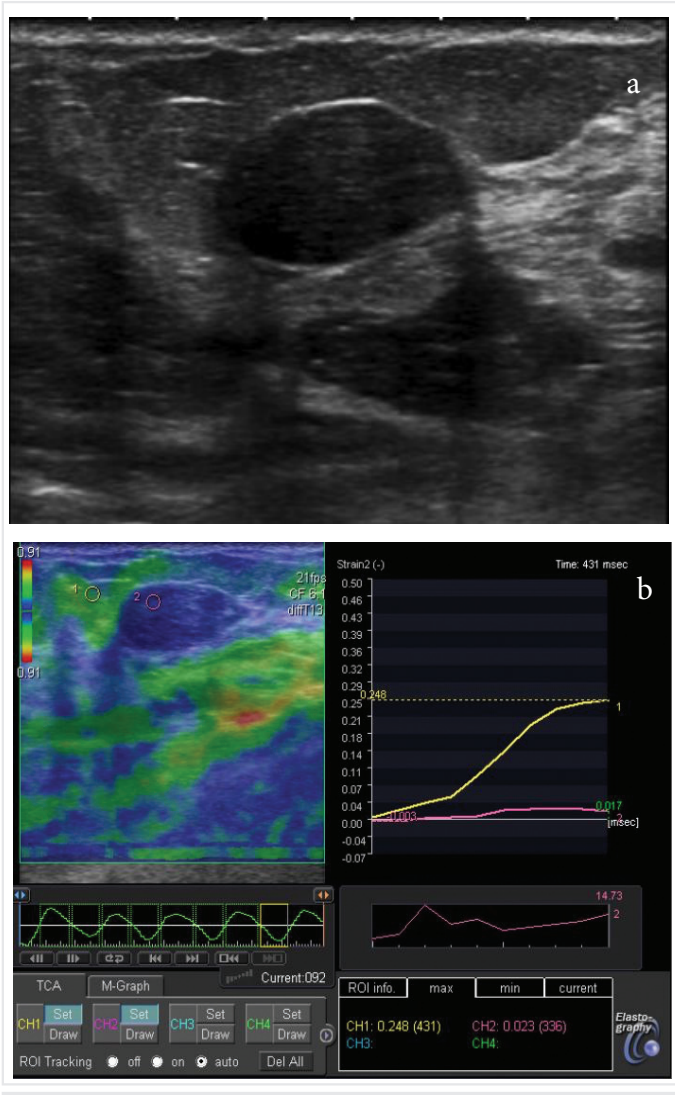

Figure 2. A 37-year-old patient with histopathological diagnosis of complex FA; a) oval shaped, hypoechoic-homogeneous lesion on B mode US image; b) the SI value (14.73) was found to be significantly higher in US elastography

FA: Fibroadenomas, US: Ultrasound, SI: Strain index

Table 4. Age, strain index and size characteristics of pathological subgroups

Pathological subgroup		Age	Strain index	Size (mm)
1. Basic FA	Number	40	40	40
	Mean ± SD	37.03±10.8	5.94±5.64	18.95±7.95
2. Complex FA	Number	9	9	9
	Mean ± SD	36.78±8.96	7.56±6.91	22.78±14.57
3. Degenerated FA	Number	19	19	19
	Mean ± SD	46.53±8.75	6.95±8.41	14.89±8.01
4. Benign phyllodes tumor	Number	1	1	1
	Mean ± SD	39	4.55	3.5
5. Borderline phyllodes tumor	Number	1	-	1
	Mean ± SD	27	-	84
6. Malignant phyllodes tumor	Number	1	1	1
	Mean ± SD	21	2.04	18
7. Follow-up lesion	Number	88	88	88
	Mean ± SD	39.38±13.76	4.07±3.64	13.26±5.05
8. Fibroadenolipoma	Number	1	1	1
	Mean ± SD	51	4.87	38

FA: Fibroadenomas, SD: Standard deviation

Discussion

FA are common benign lesions of the breast and are usually detected as a solitary breast mass in young women (1,2,8). FAs are benign fibroepithelial tumors and consist of epithelial and stromal layers. Multiple FAs are present in 15% of the cases (1). In the literature, FAs were detected most frequently in the upper outer quadrant, and in our study, 55% of the lesions were in this localization (9,10).

Phyllodes tumor of the breast is a rare fibroepithelial breast tumor that accounts for less than 1% of all primary breast neoplasms and 2-3% of all fibroepithelial tumors. Phyllodes tumors are usually seen in women between the ages of 35-55. Although similar to benign FAs, they are distinguished from FAs by histologically increased cellularity and clinically by local recurrence and metastatic spread. According to the classification of the World Health Organization, there are 3 types of phyllodes tumors: benign, borderline and malignant. High-grade malignant phyllodes constitute approximately 25% of all phyllodes (11).

The entire spectrum of benign and malignant epithelial changes can be seen in complex FAs. While benign processes such as lactational changes, simple cysts, apocrine metaplasia, and sclerosing adenosis may occur, atypia ductal or lobular hyperplasia, ductal or lobular *in situ* carcinomas and even invasive carcinomas may develop within FA or may develop in the adjacent parenchyma and invade the FA tissue secondarily (1).

In a study where they compared complex FAs with simple FAs, Sklair-Levy et al. (2) reported that complex FAs were more common in elderly patients and were smaller in size. In our study, the highest SI value and the highest mean size were observed in complex FAs in lesions diagnosed with FA. The highest mean age was obtained in degenerated FAs.

Our study showed that increasing lesion diameter of fibroepithelial lesions caused an increase in SI values indicating the degree of tissue stiffness, and this finding is consistent with the study of Elseedawy et al. (12) evaluated 151 fibroadenoma cases with shear wave elastography and showed that the main determinant of fibroadenoma stiffness was the size of the lesion. The reason for these findings was accepted as more compression of the adjacent normal tissue (12). In addition, in parallel with our findings, in a multicenter study conducted with 1,562 cases, it was shown that the stiffness of FA and malignant tumors was correlated with increasing lesion size, but there was no correlation between size and stiffness in other solid and cystic lesions of the breast (13).

In the study of Chao et al. (14) with 110 patients with phyllodes tumors and 2204 with FA, the most common morphology of FAs was reported to be round and oval, while phyllodes tumors were reported to be lobulated (14). However, in our study, the most common form of mass in both FA and phyllodes tumors was lobulated. The same study classified the lesions as homogeneous and heterogeneous according to their internal echoes. 1907 (86.5%) of FAs were homogeneous, 298 (13.5%) were heterogeneous; 39 (35.4%) of phyllodes tumors were reported as homogeneous and 71 (64.6%) as heterogeneous (14). Similar to the study of Chao et al. (14), the most common internal echo pattern was homogeneous in our study.

In recent years, elastography has been increasingly used in the evaluation of soft tissue lesions. In studies conducted in recent years, the sensitivity of elastography in the differentiation of benign and malignant breast lesions was 78-100%; and its specificity is reported as 21-99% (15).

Zhi et al. (16), in their study including 559 solid lesions, found the mean SI value of benign lesions as 1.8 and the mean SI value of malignant lesions as 8.42. FA, fibrocystic mastopathy and invasive ductal cancer constitute the majority of lesions in this study. The mean SI value of FAs was found to be 1.79 (16). In our study, this value was obtained as a mean SI value of 4.97 and a median SI value of 3.30 for fibroepithelial lesions, the majority of which consisted of FA (16).

Similarly, Burnside et al. (17) found that strain US elastography increases the sensitivity and specificity rate in diagnosis, but US elastography experience among radiologists significantly affects these rates.

The SI values of 79 benign lesions included in the study of Cho et al. (18) ranged from 0.54 to 38.76, with a mean SI value of 2.63. In this study, it was shown that sonoelastography and SI are useful in distinguishing between benign and malignant lesions, and it has been reported that they are beneficial in reducing the number of unnecessary biopsies (18).

In the study of Kim et al. (19), it was reported that sonoelastographic evaluation is most useful in the differentiation of benign-malignant breast lesions with complex echogenicity.

In recent studies, the efficiency of shear wave elastography and strain elastography has been compared with simultaneous applications. In these studies, it was shown that adding strain or shear wave elastography to B mode US findings improves diagnostic performance and these elastography techniques have similar diagnostic performance (20,21). In the study of Fujioka et al. (20), it was reported that the use of elastography in combination with B-mode US may be helpful in avoiding unnecessary biopsies in patients with BI-RADS category 4a masses.

Study Limitations

Lesions with radiological imaging findings suggestive of typical FA, followed for more than two years, and did not increase in size during follow-up did not have a histopathological diagnosis. In addition, since the data were evaluated retrospectively, the patients could not be differentiated as pre-peri-postmenopausal period, instead they were evaluated in different groups in terms of age. Since the number of our patients with phyllodes tumor is significantly low, the predictive value of the values obtained in this regard is limited.

Conclusion

Fibroepithelial lesions are breast lesions mostly consisting of FAs, which are common benign masses of the breast, and are frequently seen in young age. In the diagnosis, the diagnosis can usually be made correctly with the findings defined by classical B mode USG and follow-up is applied.

In the premenopausal period, biopsy is not required except for those who are larger than 2 cm in size and increase in size. After the age of 30, there are difficulties in diagnosis, especially in the perimenopausal period, unnecessary biopsies are performed, and more importantly, malignant lesions are interpreted as FA and malignancies can be missed, and delays in diagnosis and treatment may occur.

We think that US Elastography will contribute to the morphological USG findings in the evaluation of FAs and can guide the biopsy decision correctly. However, biopsy indications of newly developed solid lesions, especially in the postmenopausal period, cannot be eliminated by US elastography.

Ethics Committee Approval: The approval form the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee was obtained (approval number: 550, date: 28.11.2014).

Informed Consent: Voluntary consent form were obtained from the patients.

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Effect of Walking Exercise on Blood Parameters in Patients with Type 2 Diabetes Mellitus

Tip 2 Diabetes Mellituslu Hastalarda Yürüme Egzersizinin Kan Parametrelerine Etkisi

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ABSTRACT

Introduction: Lifestyle modification is the first-line treatment for the management of patients with type 2 diabetes mellitus (T2DM). Patient education and the use of technological tools that will increase compliance with the exercise program may increase physical activity in these patients. In this study, we aimed to examine the effect of pedometer-based walking intervention on clinical, diabetes-related cognitive and social factors, and quality of life outcomes in patients with T2DM.

Methods: Forty patients (17 male and 23 female) were randomly divided into the intervention (n=20; 13 male and 7 female) and control (n=20; 4 male and 16 female) groups. Both groups received diabetes education program, and instant messaging and calling application were used to facilitate and increase the communication between patients and researchers. The intervention group underwent the brisk walking program (40 minute/day and 3 times/week) for 12 weeks. The outcomes included the plasma glucose, hemoglobin A1c (HbA1c), blood lipids, body mass index, International Physical Activity Questionnaire-Short Form (IPAQ-SF), Multidimensional Diabetes Questionnaire, SF-36, and daily number of steps.

Results: The HbA1c level decreased significantly in the intervention group (p=0.020). No statistically significant difference was observed within and between groups in terms of the plasma glucose and lipid levels (p≥0.05). The IPAQ-SF walking and total physical activity scores increased in the intervention group (p<0.001) and had better results in diabetes-related cognitive and social factors and the quality of life (p<0.001).

Conclusion: Diabetes education, mobile phone application, and motivational strategies can increase the level of physical activity in patients with T2DM. Increased physical activity may have positive effects on glycemic control, diabetes-related self-efficacy, and the quality of life.

Keywords: Smartphone, pedometer applications, brisk walking, glycemic index, quality of life

ÖZ

Amaç: Tip 2 diabetes mellituslu (T2DM) hastalarda yaşam tarzı değişikliği, ilk basamak tedavi seçeneğidir. Hasta eğitimi ve egzersiz programına uyumu artıracak teknolojik araçların kullanımı bu hastaların fiziksel aktivite düzeyini artırabilir. Bu çalışmada, T2DM'li hastalarda pedometre ile takip edilen yürüme müdahalesinin klinik sonuçlara, diyabetle ilişkili bilişsel ve sosyal faktörlere ve yaşam kalitesine etkisini incelemeyi amaçladık.

Yöntemler: Kırk hasta (17 erkek, 23 kadın) müdahale (n=20, 13 erkek, 7 kadın) ve kontrol (n=20, 4 erkek, 16 kadın) olmak üzere rastgele iki gruba ayrıldı. Her iki gruba da başlangıçta diyabet eğitim programı verildi ve iletişimi kolaylaştırmak ve artırmak için anlık mesajlaşma ve arama uygulaması kullanıldı. Müdahale grubuna 12 hafta boyunca tempolu yürüyüş programı (40 dakika/gün ve 3 kez/hafta) uygulandı. Sonuç ölçümlerini plazma glukozu, hemoglobin A1c (HbA1c), kan lipidleri, vücut kitle indeksi, Uluslararası Fiziksel Aktivite Anketi-Kısa Form (IPAQ-SF), Çok Boyutlu Diyabet Anketi, SF-36 ve günlük adım sayısı oluşturdu.

Bulgular: Müdahale grubunda HbA1c düzeyi anlamlı olarak azaldı (p=0,020). Plazma glukoz ve lipid düzeylerinde grup içinde ve gruplar arasında istatistiksel olarak anlamlı fark yoktu (p≥0,05). Müdahale grubunun IPAQ-SF yürüme ve toplam fiziksel aktivite puanında artış saptandı (p<0,001) ve diyabetle ilişkili bilişsel ve sosyal faktörler ile yaşam kalitesi açısından da müdahale grubunda daha iyi sonuçlar elde edildi (p<0,001).

Sonuç: T2DM'li hastalarda diyabet eğitimi, cep telefonu uygulaması ve motivasyon stratejileri fiziksel aktivite düzeyini artırabilir. Artan fiziksel aktivite, glisemik kontrol, diyabetle ilişkili öz yeterlilik ve yaşam kalitesi üzerinde olumlu etkilere sahip olabilir.

Anahtar Kelimeler: Akıllı telefon, pedometre uygulamaları, tempolu yürüyüş, glisemik indeks, yaşam kalitesi

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Introduction

Diabetes mellitus (DM) is a chronic, non-communicable, metabolic disorders characterized by high blood glucose levels. International Diabetes Federation reported that 463 million people have diabetes in 2019, and this number is projected to reach 578 million by 2030 and 700 million by 2045. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes (around 90%) of diabetes worldwide (1). T2DM is the result of a complex combination of genetic, epigenetic, and environmental/lifestyle factors. Environmental/lifestyle risk factors include energy-dense Western-style diets, decreased physical activity, increased sitting and monitor viewing time, exposure to noise or fine dust, short or disturbed sleep, smoking, stress, depression, and low socioeconomic status (2).

Obesity and physical inactivity as a result of global urbanization may be the main reason for the increased burden of diabetes (3). A total of 28.2% of diabetic patients in the ultrasound reported achieving the recommended level of physical activity (4). However, exercise or physical activity is one of the most important treatment methods used in the clinical management of individuals with T2DM and has been included in numerous guidelines (5). Sedentary lifestyles are greatly influenced by increasing technological (such as elevator use, motor vehicle use, etc.) developments. In addition, the facilitation of communication by mobile phones and the loss of mobility required for face-to-face interviews negatively affects patients with T2DM and everyone else. However, with the well-integrated use of technology, changes in lifestyle can be supported, and adaptation to exercise training can be increased, thus ensuring the effective management of diabetes (6).

The use of smartphones to support physical activity offers unique, feasible, and cost-effective opportunities for clinicians and patients to improve rehabilitation (7). Therefore, using a pedometer increase physical activity and improve several health outcomes, at least in the short term (8). In our study, we downloaded a free pedometer application to the smartphone and aimed to examine the effect of the pedometer-based walking intervention on clinical, diabetes-related cognitive, and social factors and the health-related quality of life outcomes in patients with T2DM.

Methods

Participants

Patients diagnosed with T2DM and who applied to the Endocrinology and Metabolic Diseases Department in Pamukkale University were enrolled in the study. The study was approved by the Pamukkale University Non-Interventional Clinical Research and Ethics Committee to which the authors are affiliated (approval number: 60116787-020/47020, date: 11/07/2018). Informed consent was obtained from all patients.

The inclusion criteria were as follows: ages between 18-65 years old, a diagnosis of T2DM for at least 6 months in accordance with the American Diabetic Association's Standards of Medical Care in Diabetes, a hemoglobin A1c (HbA1c) level higher than 7%, capability to use a smartphone and communicate orally and in writing with a phone and message application. The exclusion criteria were as follows: engagement in regular exercise or physical activity program within the last 3 months, and concurrent pathologies that affect the ability to perform physical activity or everyday tasks (e.g., cardiac autonomic neuropathy, severe peripheral neuropathy, decompensated heart failure, myocardial infarction or stroke history, cancer, and extremity amputation).

A total of sixty eight patients were assessed for eligibility. Twenty-eight patients who did not meet the inclusion criteria were excluded from the study due to the lack of a smartphone (n=4), presence of concurrent pathologies (n=15), and engagement in regular exercises (n=9). Finally, forty patients (17 male and 23 female) were randomly divided into the intervention (n=20; 13 male and 7 female) and control (n=20; 4 male and 16 female) groups using computer-generated random numbers.

Interventions

All patients were given an education program about the definition of DM, symptoms, risk factors, types, treatment and complications, main aspects of self-care of the disease (foot care, eye care, and blood glucose monitoring), main aspects of dietary management, weight reduction, physical activity, blood pressure, smoking cessation, periodic investigations, and home monitoring (9). Booklets concerning all these issues were also handed out to all patients. Patients' pharmacological treatment were unaltered during the study, and no recommendations were given concerning changes in dietary habits.

All the patients were asked to install a free pedometer application (Runtastic Pedometer), which is compatible with all smartphones to record their number of steps. Presset et al. (10) recommended strapping the smartphone on the arm as tightly as possible for an accurate step count. Therefore, the patients were instructed to strap their phones on their arm from the moment they woke up until just before bedtime. The daily step count of both groups for 12 weeks was monitored with this application.

The intervention group walked outdoors (on a promenade) for 40 minute at a self-selected brisk speed three times a week for 12 weeks as a guideline for selecting a "brisk" walking pace (as per the current physical activity recommendations); they were told to imagine that they were walking as if they were in a hurry to catch a bus. This instruction was used successfully in other studies (11,12) to ensure that the participants walk with moderate intensity. The control group was not given a walking intervention and instructed not to change their diet and activity levels during the study.

In the first week, patients were called twice at an interval of 3 days to ensure that they were using the smartphone pedometer application appropriately. In addition, WhatsApp Messenger (WhatsApp Inc.) groups were created for both groups to facilitate and increase the communication between patients and researchers. During the study, reminder text messages were sent to the patients from WhatsApp groups 3 days a week. The intervention group was called, "Take the steps and beat diabetes!" The messages sent to this group were as follows: "Today is Monday! Your exercise day. Do not forget to check your blood sugar and walk for 40 minutes," and "Having a busy day does not prevent you from exercising; let's go for a walk!" The control group was called "We follow your daily steps!" The messages sent to this group were as follows:

"Today is Monday! Have a good day!"; "Good Morning! Do not forget to check your pedometer application."

Measurements

The demographic data of the patients [age, gender, body mass index (BMI), occupation, etc] and medical history (years with T2DM, comorbidity, the number of drugs taken per day, medication, etc) were recorded. Evaluations were performed at baseline and after 12 weeks.

Blood samples obtained during fasting and postprandial [fasting plasma glucose, postprandial glucose, HbA1c, and lipid levels (total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, and triglycerides] were measured.

Anthropometric data were collected by a blinded trained investigator. The patients dressed lightly and stood barefoot during measurement. The patients' height and weight were assessed using a Charder MS3400 device. BMI was calculated by dividing the weight in kilograms by the height in meters squared.

International Physical Activity Questionnaire-Short Form (IPAQ-SF, self-administered version) was used to assess the types of intensity of physical activity (vigorous- and moderate- intensity activity; walking) and sitting time that patients perform as part of their daily activities for the last 7 days. The combined total physical activity score was calculated and expressed in metabolic equivalent minutes per week (13).

The Multidimensional Diabetes Questionnaire (MDQ) was designed by Talbot to provide a comprehensive assessment of diabetes-related cognitive and social factors (14). The Turkish version of the MDQ is reliable and valid and is divided into three sections and six sub-dimensions. Section I includes the general perceptions of diabetes and related social support consisting of three dimensions: interference (9 items), severity (3 items), and social support (11 items). A high score indicates a high interference, severity, and social support. Section II comprises the social incentives related to self-care activities and consists of one dimension, that is, misguided support behaviors (4 items). High scores indicate misguided support behaviors. Section III represents the self-efficacy and outcome expectancies consisting of two dimensions: self-efficacy (7 items) and outcome expectancies (6 items). A high score indicates improved self-efficacy and outcome expectations (15).

SF-36 was used to determine the patients' health-related quality of life. The questionnaire consists of 36 items and provides scores on eight subscales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, mental health, role limitations due to emotional problems, social functioning, and vitality. The total score of the questionnaire ranges from 0 to 100, with a high score indicating a good quality of life (16).

Statistical Analysis

The data were analyzed using SPSS 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) package program. Continuous variables were given as mean ± standard deviation and median (minimum and maximum), and categorical variable values are presented as absolute numbers (n) and percentages (%). The conformity of continuous variables with normal distribution was evaluated using the Kolmogorov-Smirnov test. For comparison of the data between baseline and after 12 weeks measurements, paired-sample t-test for parametric test assumptions and Wilcoxon paired signed test for non-parametric test assumptions were used. The difference in changes between groups during the intervention was calculated based on their baseline levels, and Independent sample t-test for parametric test assumptions and Mann-Whitney U test for non-parametric test assumptions were used for comparison of the groups. The chi-square test was used for categorical variables. Statistical significance was set at $p \leq 0.05$.

Results

The patients in the intervention group (mean age: 53.90 years; 7 women and 13 men) have been diagnosed with T2DM for 8.45±6.57 years, whereas those in the control group (mean age: 48.85 years; 16 women and 4 men) have been diagnosed for 9.95±6.42 years. Table 1 provides the descriptive characteristics of the patients.

The intervention group attained an average of 6251.70±2722.15 steps per day, whereas the control group made 661.05±501.52 steps.

The HbA1c level decreased significantly in the intervention group after 12 weeks ($p=0.02$). No statistically significant difference was observed within and between groups in terms of their plasma glucose, HbA1c, and lipid levels ($p \geq 0.05$) (Table 2).

IPAQ-SF walking ($p=0.00$) and total physical activity ($p=0.00$) scores increased significantly in the intervention group after pedometer-based walking intervention. However, no change was noticed in the IPAQ-SF score of the control group. A significant difference was observed in favor of the intervention group in terms of the difference in between-group changes ($p=0.00$) (Table 2).

According to MDQ part I scores, no change in the intervention and control groups occurred during the 12-week period. However, a significant difference in favor of the intervention group was observed in terms of the difference in between-group changes regarding Section I-interference score ($p=0.01$). Section II-misguided support behaviors and Section III-self-efficacy scores of the intervention group improved at the end of 12 weeks ($p=0.001$), but no difference was observed in the control group ($p \geq 0.05$). However, a significant difference in favor of the intervention group was recorded in terms of the difference in between-group changes ($p=0.001$, $p=0.03$). For the intervention ($p=0.001$) and control groups ($p=0.02$), a significant increase in Section III-outcome expectancies scores was observed after 12 weeks (Table 2).

No statistically significant change was observed in SF-36 physical functioning, social functioning, role physical, role emotional, and pain subscales in within- and between-group comparisons ($p \geq 0.05$). General health perceptions ($p=0.001$), mental health ($p=0.01$), and energy/vitality ($p=0.01$) scores increased significantly in the intervention group after 12 weeks. A significant difference in favor of the intervention group was noticed in terms of the between-group differences in these scores (general health perceptions: $p=0.001$, mental health: $p=0.001$, energy/vitality: $p=0.01$) (Table 2).

Table 1. Descriptive characteristics of patients

Variables	Intervention group (n=20)		Control group (n=20)		p
	Min-max	Mean ± SD	Min-max	Mean ± SD	
Age (year)	37-65	53.60±7.84	34-61	48.85±6.63	**0.046**
Height (cm)	144-175	164.05±7.53	143-184	159.05±10.53	0.092
Weight (kg)	70-117	93.95±13.43	54.50-133.00	83.32±19.20	0.051
BMI (kg/m^2)	26.50-43.00	34.53±4.61	24.24-47.60	32.52±5.07	0.198
Years with diabetes	1-23	8.45±6.57	1-20	9.95±6.42	0.470
Charlson Comorbidity index	1-6	2.45±1.46	1-5	2.45±1.10	1.000
The number of drugs taken daily	1-11	4.55±2.62	2-14	4.25±2.59	0.751*
	n	%	n	%	p
Sex					
Female	7	35.0	16	80.0	0.343
Male	13	65.0	4	20.0	
Medication					
Insulin	13	65	8	60	0.752
Tablet	7	35	12	40	
Marital status					
Married	17	85.0	20	100.0	-
Single	3	15.0	-	-	
Occupation					
White-collar worker	5	25.0	1	5.0	-
Self-employment	1	5.0	-	-	
Blue-collar worker	-	-	2	10.0	
Retired	10	50.0	3	15.0	
Housewife	4	20.0	14	70.0	
Current smokers	6	30	2	10	**0.001**

*: Not normally distributed data. Statistically significant p-values are marked as bold text. Min: Minimum, max: Maximum, SD: Standard deviation, BMI: Body mass index

Discussion

The main goal of this study was to examine the effect of pedometer-based walking intervention on clinical, diabetes-related cognitive, and social factors and the health-related quality of life outcomes in patients with T2DM. Our results indicated that pedometer-based walking intervention has beneficial effects on physical activity, HbA1c level, social incentives related to self-care activities, diabetes-related self-efficacy, outcome expectancies, and general health perceptions, mental health, and vitality.

Counselling and effective and culturally oriented education intervention play an important role in achieving the patients' quality of life, mobility, self-care, and daily living activities (17). Diabetes education also enhances patients' and families' self-care knowledge, health skills, and confidence, allowing them to take increasing control of their lives. In addition, a significant decrease was observed in fasting blood glucose after educational intervention in patients with T2DM (9). Our study aimed to raise awareness about diabetes care, self-care, and daily vital activities by providing versatile diabetes training to type 2 diabetic patients and their relatives, and the results showed that diabetes education had useful effects on patients with T2DM.

Smartphone-based pedometer applications and connected wristbands are becoming widespread, and new technologies must be considered as a complementary tool to help populations reach physical activity recommendations to promote physical health (10,18). New communication and control methods provided by smartphones also have the potential to provide patients with reinforcement, measure intervention impact, and improve patient care on a large scale (18). A cognitive-behavioral approach and smartphone-assisted pedometer application promise to increase physical activity in patients with T2DM and is a good method to provide health counseling (19). For this purpose, a smartphone-based application was installed on each patient's phone, and the patients were instructed to strap their phones on their arm from the moment they got up until just before bedtime. Our results showed that the smartphone-based application has a beneficial effect on increasing physical activity in patients with T2DM.

Lifestyle modifications, such as a caloric restricted diet, reduced sedentary behavior, and increases in exercise, are the first-line treatment for the management of T2DM. Physical inactivity is a strong predictor for all-cause mortality (20), and an increase in physical activity can prevent or delay T2DM. However, different results have been reported regarding the effects of walking training on glycemic control in patients with

Table 2. Comparison of clinical- and patient-reported outcome scores of the groups

Variables	Intervention group (n=20)			Control group (n=20)			Δp
	Baseline (mean ± SD)	12-weeks (mean ± SD)	p	Baseline (mean ± SD)	12-weeks (mean ± SD)	p	
BMI (kg/m^2)	34.53±4.61	34.50±4.10	0.91	32±52±5.07	33.06±5.56	0.21	0.46
Weight (kg)	93.95±13.43	92.92±13.48	0.13	83.32±19.20	83.87±19.31	0.22	0.05
IPAQ-SF							
Walking score (MET-min/wk)	357.22±404.92	1419±740.38	**0.00***	350.62±393.71	358.05±372.28	0.68*	**0.00***
Total activity score (MET-min/wk)	405.22±440.40	2025±1577.12	**0.00***	502.02±588.18	538.05±598.16	0.47*	**0.00***
Glycemic control							
Fasting plasma glucose	142.25±28.70	139.890±22.49	0.46	141.58±52.99	135.25±33.67	0.39	0.88*
Postprandial glucose	195.50±86.58	203.55±63.04	0.60	193.25±90.04	201.95±62.23	0.79	0.85
HbA1c (%)	7.76±0.74	7.32±1.08	**0.02***	7.64±0.79	7.45±1.35	0.26*	0.41*
Lipids							
Total cholesterol (mmol/L)	173.90±34.23	173.35±31.67	0.95	171.10±40.89	167.95±43.85	0.74	0.84
HDL cholesterol (mmol/L)	43.85±14.25	46.85±17.24	0.28*	48.60±12.36	49.65±12.53	0.66*	0.64*
LDL cholesterol (mmol/L)	96.75±25.85	90.05±29.95	0.42	99.55±42.58	93.45±30.11	0.48	0.96
Triglycerides (mmol/L)	153.12±54.47	154.47±56.10	0.65	148.70±65.98	141.90±54.69	0.59	0.50*
MDQ							
Section I-interference	1.78±1.17	1.41±1.01	0.08	2.15±1.86	2.35±2.12	0.11	**0.01***
Section I-severity	4.02±1.87	4.29±1.82	0.42	4.78±1.64	4.98±1.71	0.59*	0.56*
Section I-social support	3.77±1.91	3.72±1.92	0.91*	3.50±2.20	3.59±2.16	0.09*	0.51*
Section II-misguided support behaviors	0.58±0.64	0.29±0.46	**0.00***	0.39±0.89	0.66±0.98	0.07*	**0.00***
Section III-self-efficacy	48.88±19.73	68.89±20.19	**0.00***	54.32±22.51	61.21±24.96	0.07	**0.03**
Section III-outcome expectancies	88.89±11.04	96.66±5.19	**0.00***	91.74±11.85	97.00±9.23	**0.02***	0.07*
SF-36							
General health perceptions	53.25±18.80	67.00±19.49	**0.00**	59.75±20.42	58.88±16.11	0.66	**0.00***
Physical functioning	83.25±16.96	87.75±15.52	0.07*	77.75±26.08	77.75±24.25	0.93*	0.11*
Mental health	58.20±22.76	65.80±22.83	**0.01***	61.60±10.65	60.15±12.43	0.25	**0.00***
Social functioning	76.88±19.98	83.13±18.26	0.14*	70.25±21.85	72.38±18.04	0.29*	0.25*
Role physical	81.25±30.21	76.25±32.92	0.51*	72.50±42.07	75.00±34.41	0.91*	0.60*
Role emotional	56.67±39.15	65.01±42.54	0.36*	48.33±46.49	47.50±40.93	0.89*	0.32*
Pain	77.13±22.19	84.50±15.76	0.12*	65.88±26.05	64.25±28.51	0.44	0.10*
Energy/vitality	52.25±26.03	62.00±26.33	**0.01***	57.25±20.29	56.09±21.11	0.56	**0.01***
Daily number of steps	-	6251.70±2722.15	-	-	661.05±501.52	0.00*	-

*: Not normally distributed data. Delta p (Δp) refers to difference in change between the groups during intervention in relation to baseline levels. Statistically significant p-values are marked as bold text. BMI: Body mass index, IPAQ-SF: International Physical Activity Questionnaire-Short Form, MET: Metabolic equivalent, HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MDQ: Multidimensional Diabetes Questionnaire, SF-36: Short Form-36, SD: Standard deviation

T2DM (21,22). Studies indicated that walking training can be applied in patients with T2DM but has little or no beneficial effect on glycemic control (HbA1c, fasting glucose, and postprandial glucose) (22); on the contrary, gait training improves glycemic control (21-23). Although not statistically significant, gait training improved glycemic controls in both groups. This finding may be due to the participation of both groups in diabetes education. In addition, a significant decrease in HbA1c level was observed in those who participated in the12-week pedometer-based walking program. Web and mobile health interventions used for behavioral interventions provide trends for benefits in diabetes self-efficacy, adherence, and glycemic control (6). We think that utilizing technological tools, which will increase compliance with the exercise program in addition to patient education, provides extra benefits for patients with T2DM.

Smartphone applications and computer-led health coaching can increase the physical activity level and exercise adherence in type 2 diabetic patients (18). Pedometer applications are frequently used in health promotion because they are easy to use, low cost, motivational, and self-monitoring (24). Pedometers are also effective tools to increase the level of physical activity among type 2 diabetic patients in the short term (25,26). The increase in physical activity level does not reflect the lipid level in these patients at the same rate. The overwhelming majority of studies have shown the absence of effect of any exercise training on lipids, such as high-density lipoprotein, low-density

lipoprotein, cholesterol profile and triglycerides, in relation to T2DM (23). In agreement with other studies, although the pedometer-based walking intervention increased physical activity level, it did not cause a statistically significant difference in the lipid profile.

Given the complex nature of T2DM, which is affected by cognitive and social factors, diabetes management includes multi-component self-care activities and lifestyle changes. In addition to clinical evaluation, psychosocial evaluations should be conducted and considered the following: such as the level of the diabetic's daily activities affected by diabetes (interference), the degree to which diabetics perceive the severity of diabetes (severity), social support provided by important people and healthcare professionals in the life of the diabetic (social support), supportive and misguided support behaviors of diabetic relatives (misguided support behaviors), the diabetic's self-confidence in performing self-care activities (self-efficacy), perceived importance of self-care behaviors, and the effectiveness of treatment in the metabolic control and prevention of complications (outcome expectancies) (15). In our study, outcome expectations increased in both intervention and control groups. With diabetes education and the messages we have sent, the patients' perception levels of the importance of self-care behavior and the treatment effectiveness may have increased. In addition, the intervention group had a decrease in misguided support behavior and an increase in self-efficacy. Regular walking may have increased the encouragement of family members about disease management, and increased physical activity may have led to the development of self-efficacy (27,28). In addition, the intervention group had better results in terms of interference, misguided support behaviors, and self-efficacy. A relationship exists between perceived interference, support, and positive outcome expectations with self-efficacy in patients with T2DM (29). With education, daily reminder messages, and walking intervention, the patients' self-management can be improved.

Quality of life measures is used in healthcare field to evaluate the healthcare outcomes in chronic conditions in which major health problems may persist (23). Understanding the dimensions of quality of life associated with diabetes and its comorbidities is important for the clinical management of the disease (30). Physical activity improves the quality of life of patients with T2DM (23,31) Our study yielded results similar to those of previous research. Encouraging sedentary patients with T2DM to increase their physical activity may improve their quality of life.

Study Limitations

The current study presented several limitations. When the Runtastic Pedometer was improperly connected, whether the phone can distinguish steps and movements or count steps when the patient was using the phone was unclear. In our study, the status of patients holding the phone to their arms throughout the day could not be controlled. The patients and their families were educated on diabetes and were told to continue their recommended diet. However, dietary compliance could not be tracked. Therefore, the statements of the patients about their dietary compliance were relied on. However, dietary habits could also be followed by smartphone applications.

Conclusion

In this study, we aimed to examine the effect of the pedometer-based walking intervention, which was performed three times a week for 12 weeks, on the clinical, diabetes-related cognitive, and social factors and the quality of life outcomes in patients with T2DM. We observed that walking had beneficial effects on the patients' physical activity, HbA1c level, social incentives related to self-care activities, diabetes-related self-efficacy, outcome expectancies, general health perceptions, mental health, and vitality. The findings of the current study indicated that diabetes education, smartphone-based pedometer application, and motivational strategies can increase the level of physical activity in patients with T2DM. Increased physical activity can have positive effects on glycemic control, diabetes-related self-efficacy, and the quality of life.

Ethics Committee Approval: The study was approved by the Pamukkale University Non-Interventional Clinical Research and Ethics Committee to which the authors are affiliated (approval number: 60116787-020/47020, date: 11/07/2018).

Informed Consent: Informed consent was obtained from all patients.

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Prognostic Role of Interleukin-23 in Prostate Adenocarcinoma: Comparison with Gallium-68 Prostate-Specific Membrane Antigen-11 Positron Emission Tomography/Computed Tomography Findings

İnterlökin-23'ün Prostat Adenokarsinomundaki Prognostik Rolü: Galyum-68 Prostat Spesfik Membran Antijeni-11 Pozitron Emisyon Tomografi/Bilgisayarlı Bulguları ile Karşılaştırma

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ABSTRACT

Introduction: Androgen deprivation therapy is the first line of treatment for advanced prostate cancer (PC). However, PC progressed in most patients when it becomes resistant to castration. This study aimed to investigate the possible role of interleukin-23 (IL-23), a cytokine expressed in various cancers, in the development of resistance to castration and prognosis in PC.

Methods: Twenty-three patients with PC were consecutively enrolled in the study to undergo gallium-68 (Ga-68) prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT). Among those patients, 13 were newly diagnosed as treatment-naive (ND), while 10 were evaluated for disease progression under hormonotheraphy. Before PET/CT, 5 mL of venous blood samples was obtained from the study participants. Serum levels of IL-23 were determined by enzyme-linked immunosorbent assay using an IL-23 receptor kit. The relationship of ND and castration-resistant (CR) groups with serum IL-23 level and the correlation of the rate of lymph node involvement, skeletal and distant metastasis Gleason scores, prostate-specific antigen (PSA) levels, and maximum standardized uptake value (SUV_{max}) of the prostate gland with IL-23 levels were analyzed.

Results: Ga-68 PSMA PET/CT revealed that 13 (56.5%) patients had skeletal metastases, 10 (43.5%) had non-pelvic nodal metastasis, and 3 (13%) had distant-organ metastasis. The difference between the serum IL-23 levels of the ND group and the CR group was not significant (p=0.664). The IL-23 levels were not significantly different between patients with and

ÖZ

Amaç: Androjen yoksunluğu tedavisi, ileri evre prostat kanseri (PK) için ilk tedavi seçeneğidir. Ancak çoğu hastada tedavi süresince hastalık kastrasyona dirençli hale geldiğinde progresyon görülür. Çeşitli kanser türlerinde eksprese edilen bir sitokin olan interlökin-23'ün (IL-23) PK'de kastrasyona direnç gelişimi ve prognozdaki olası rolünü araştırmayı amaçladık.

Yöntemler: Galyum-68 (Ga-68) prostat spesfik membran antijeni (PSMA) pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) görüntülemesi için çalışmaya 23 PK hastası alındı. Bunlardan 13'ü yeni tanılı-tedavi görmemiş (YT) hastalarken, 10'u hormonoterapi altında hastalık ilerlemesi açısından değerlendiriliyordu. PET/BT görüntülemeden önce çalışma katılımcılarından beş mililitre venöz kan örneği alındı. IL-23'ün serum seviyeleri, bir IL-23 reseptör kiti kullanılarak ELISA testi ile belirlendi. YT olgular ve kastrasyon dirençli olguların ilişkisi serum IL-23 seviyesi ile analiz edildi ve ayrıca lenf nodu, iskelet ve uzak metastaz tespit oranı, Gleason skorları, prostat spesifik antijen (PSA) seviyeleri ve IL-23 seviyeleri ile prostat bezinin SUV_{max} ile arasındaki ilişki seviyeleri araştırıldı.

Bulgular: Ga-68 PSMA PET/BT'de 13 (%56,5) hastada iskelet metastazı, 10'unda (%43,5) pelvik olmayan nodal metastaz ve 3'ünde (%13) metastatik uzak organ yayılımı saptandı. YT hastalar ile kastrasyon dirençli hastaların serum IL-23 düzeyleri arasındaki fark istatistiksel olarak anlamlı değildi (p=0,664). IL-23 düzeyleri metastatik hastalığı olan ve olmayan hastalar arasında anlamlı farklılık göstermedi. Ayrıca yaş, IL-23 seviyeleri ve total PSA seviyelerinin yanı sıra primer tümör

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without metastatic disease. Further, no significant association was found among age, IL-23 levels, and total PSA levels as well as primary tumor SUV_{max} and serum IL-23 levels.

Conclusion: Although a significant correlation was found between serum IL-23 levels and the development of castration resistance, the metastatic stage and SUV_{max} were not proven decisively. Thus, it can be assumed that IL-23 has no major role in the development of castration resistance and prognosis in PC.

Keywords: Interleukin-23, prostate adenocarcinoma, Ga-68 PSMA-11 PET/CT

SUV_{max} değerleri ve serum IL-23 seviyeleri arasında istatistiksel olarak anlamlı bir ilişki yoktu.

Sonuç: Serum IL-23 seviyeleri ile kastrasyona direnç gelişimi, metastatik hastalık ve SUV_{max} değerlerinin arasında anlamlı bir ilişki olmadığı için, IL-23'ün PK'nin prognozunda yeri olmadığı söylenebilir.

Anahtar Kelimeler: İnterlökin-23, prostat adenokarsinomu, Ga-68 PSMA-11 PET/BT

Introduction

Prostate cancer (PC) is the second leading cause of cancer-related death in men. Androgen deprivation therapy (ADT) is the first line of treatment for advanced PC. The androgen blockade at the castration level, where the serum testosterone level is <50 ng/mL, regresses the disease by causing both apoptosis and a pause in the division of cancer cells. Treatment response is evaluated based on a decrease in tumor size and reduced serum prostate-specific antigen (PSA) levels. An increase in PSA levels during the disease course indicates resistance to androgen blockade. Although various mechanisms have been proposed in the pathophysiology of castration resistance, many factors are still unclarified (1,2). Oncogene activation, inactivation of tumor-suppressor genes, intratumoral androgen production, and aberrant androgen receptor activation are known mechanisms in the development of this resistance (3).

Calcinotto et al. (4) proposed that interleukin-23 (IL-23), which is released from myeloid-derived suppressor cells, a group of immune cells consisting of monocytes and neutrophils, may cause castration resistance by interacting with the IL-23 receptor in PC cells. They reported that the serum and tissue levels of IL-23 were significantly higher in patients who developed castration resistance than in those sensitive to castration. Moreover, they showed that when an antibody blocking IL-23, i.e., enzalutamid, an androgen receptor blocker, was administered to castration-resistant (CR) mice, the castration resistance was reversed, and the tumor size shrunk (4,5).

Prostate-specific membrane antigen (PSMA) is a transmembrane receptor protein widely expressed in PC cells. Molecules labeled with radioisotopes targeting this receptor are used in both PC diagnosis and treatment. Various studies have shown that gallium-68 (Ga-68) PSMA positron emission tomography/computed tomography (PET/CT) aids in determining the response to treatment in patients receiving ADT and in the detection of tumor focus in patients with biochemical recurrence (6,7). In this prospective study, we investigated the role of serum IL-23 levels, a cytokine expressed in many cancers, and its correlation with Ga-68 PSMA PET/CT findings in the development of castration resistance and the prediction of PC prognosis.

Methods

Patients

This study included 23 patients with PC (median age: 72 years; range: 55-89 years), who were referred to our clinic for Ga-68 PSMA PET/CT for either staging or restaging purposes. The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Institutional Review Board (approval number: 1668, date: 01/02/2019). Written consent was obtained from all included patients for the use of their clinical findings for research purposes.

Among those 23 patients, 13 were newly diagnosed as treatment-naive (ND), while 10 were evaluated for disease progression under hormonotherapy (HT) and classified as having CRPC.

Patients whose PC progressed while under chemotherapy or those who had received chemotherapy before HT were excluded from the study. On the day of PET/CT, 5 mL of venous blood was obtained from all patients before the administration of the radiopharmaceutical agent. The plasma was separated and stored at 80 °C for later analysis.

Measurement of IL-23 Concentration

The IL-23 concentration in the plasma was measured using a human IL-35 enzyme-linked immunosorbent assay kit (Catalog No. E2164Hu, Bioassay Technology Laboratory, China) according to the manufacturer's protocol. Each sample was assayed three times.

Imaging

A whole-body PET scan (from vertex to upper thighs) was acquired using a Biograph mCT 20 PET/CT scanner (Siemens Molecular Imaging; Hoffman Estates, IL, USA) 60 min after intravenous injection of Ga-68 PSMA-11 (median: 175 MBq; range: 77-350 MBq). The maximum standardized uptake values (SUV_{max}) of the primary tumors were acquired from the area of the prostate gland with the highest uptake. Areas in the whole body with uptake above the background activity were defined as metastatic. Metastatic disease was defined according to the current guidelines, i.e., lymph nodes in the true pelvis as pelvic lymph node metastasis (PLNM; N1), extrapelvic lymph node metastasis (EPLNM; M1a), bone metastasis (BM; M1b), and metastasis in other sites with or without bone metastasis (MOS; M1c).

The IL-23 levels were compared between the CRPC group and ND group. The IL-23 levels were also compared between patients according to prognostic factors including Gleason score (7 and >7) and presence of metastatic disease. The correlation between age, IL-23 levels, and total PSA levels were investigated. The correlation of IL-23 and prostate SUV_{max} levels was also analyzed in the ND group.

Statistical Analysis

Data are presented as mean, median, standard deviation, and percentages. All analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp. Armonk, NY, USA). Normality was evaluated using Kolmogorov-Smirnov test. Comparisons between groups of quantitative variables were performed using the Mann-Whitney U test for two independent subgroups. Spearman correlation coefficient was evaluated for correlations. All tests were two-tailed, and $p<0.05$ was considered significant.

Results

Ga-68 PSMA PET/CT revealed that 17 of 23 (73.9%) patients (7 CRPC, 10 ND) had PLNM, 10 of 23 (43.4%) patients (8 CRPC, 2 ND) had EPLNM, 13 (56.5%) patients (9 CRPC, 4 ND) had BM, and 3 (13.0%) patients (2 CRPC, 1 ND) had MOS (Figure 1, 2).

In the CRPC group, 4 of 10 patients had increased PSA levels while under HT. Although all four had M1b disease, they did not undergo PSMA PET/CT previously and the progression in PET could not be evaluated. Four patients with elevated PSA levels also demonstrated progression based on Ga-68 PSMA-11 PET/CT findings. Two patients had stable or decreased PSA levels, despite progression noted in Ga-68 PSMA-11 PET/CT: one patient had M1b and one had M1c disease (Figure 3).

No significant difference was observed in serum IL-23 levels between the ND group and CRPC group (p=0.664). Similarly, no significant difference was found between IL-23 levels of patients with Gleason score 7 or ≥7 (p=0.295), with or without PLNM (p=0.529), with or without EPLNM (p=0.951), with or without BM (p=0.901), and with or without MOS (p=0.784; Table 1).

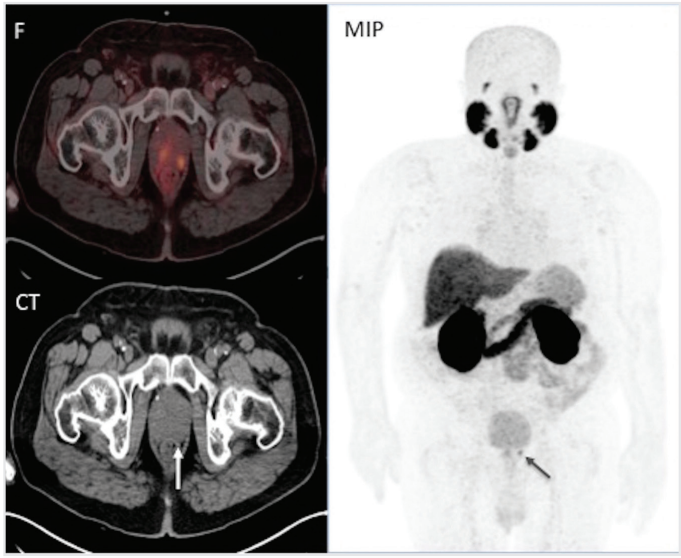

Figure 1. A 69-year-old man with newly diagnosed PC, Gleason score of 4+3, tPSA of 6.25 ng/mL, and IL-23 of 303.6 pg/mL. On Ga-68 PSMA PET/CT, only the primary lesion in the prostate gland (SUV_{max}: 7.2) was observed with no lymph node or distant metastasis

PC: Prostate cancer, tPSA: Total prostate-specific antigen, F: Fusion, CT: Computed tomography, MIP: Maximum intensity projection image, Ga-68: Gallium-68, PSMA: Prostate-specific membrane antigen, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value, IL: Interleukin

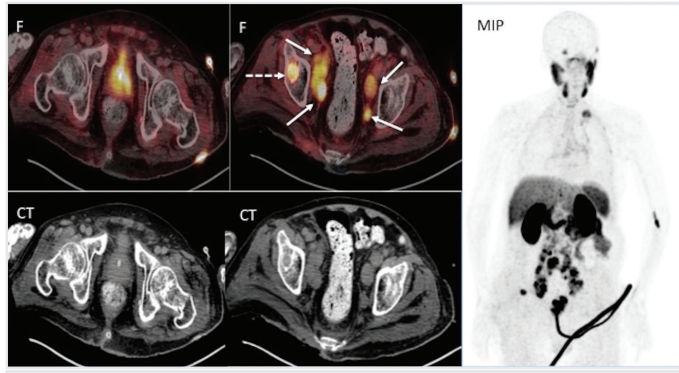

Figure 2. A 63-year-old man with newly diagnosed PC, Gleason score of 4+3, tPSA of 185 ng/mL, and IL-23 of 339.6 pg/mL. On Ga-68 PSMA PET/CT, the primary lesion in prostate gland involving both seminal vesicles (SUV_{max}: 49.1), multiple metastatic lymph nodes in the abdominopelvic (arrows) and left supraclavicular regions and pelvic bone metastasis (dashed arrow) were observed

PC: Prostate cancer, tPSA: Total prostate-specific antigen, F: Fusion, CT: Computed tomography, MIP: Maximum intensity projection image, Ga-68: Gallium-68, PSMA: Prostate-specific membrane antigen, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value, IL: Interleukin

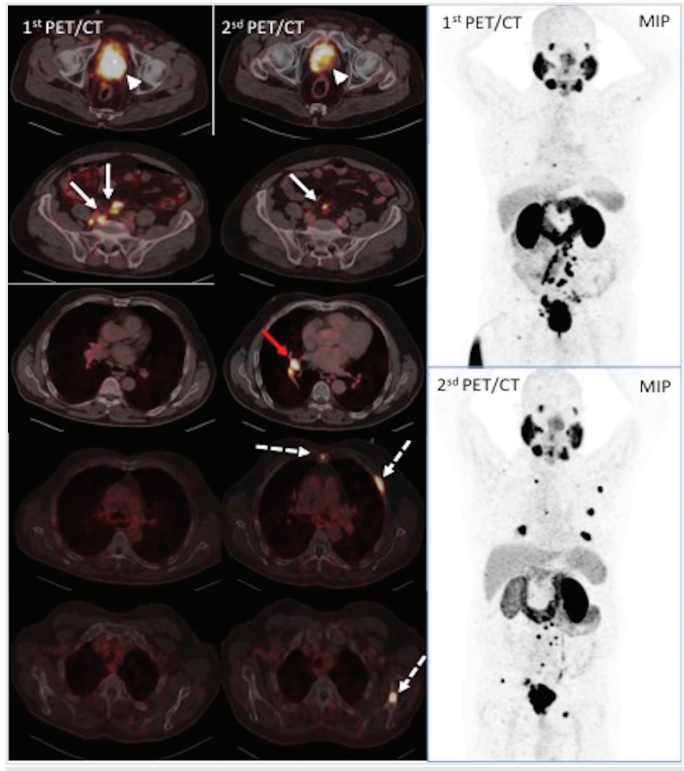

Figure 3. A 72-year-old man with PC and Gleason score of 3+5. He had been receiving hormonotherapy for 3 years. The tPSA level decreased from 54.3 ng/mL to 3.1 ng/mL between Ga-68 PSMA PET/CT scans at 6 months interval. However, in follow-up scan, while the primary lesion in the prostate gland and pelvic lymph nodes partially regressed, there were newly developed mediastinal metastatic lymph nodes and multiple bone metastases (fusion and maximum intensity projection images). The IL-23 level at the second PET/CT scan was 110.2 pg/mL (below the mean value of newly diagnosed cases with 316.02±85.94 pg/mL)

PC: Prostate cancer, tPSA: Total prostate-specific antigen, F: Fusion, CT: Computed tomography, MIP: Maximum intensity projection image, Ga-68: Gallium-68, PSMA: Prostate-specific membrane antigen, PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standardized uptake value, IL: Interleukin

No significant correlation was observed among patients' age, total PSA levels, and IL-23 levels (Table 2). The ND group showed no significant correlation between IL-23 levels and prostate gland SUV_{max} levels (Table 3).

Discussion

Many studies have investigated the prognostic effects of cytokines in PC. A very recent study found that IL-8 expression in the tumor microenvironment was associated with aggressive PC and androgen receptor loss in metastatic disease (8). Plasma IL-35 levels in patients with PC were reported to be significantly higher than those in patients with benign prostatic hyperplasia and healthy controls. Another study reported that increased IL-35 expression was associated with progression of disease stage and shorter survival (9). In another study, transforming growth factor-β1 was higher in prostate hyperplasia tissue samples than in PC samples, while IL-6 expression was significantly higher in PC samples than in hyperplasia samples (10). In PC, IL-15 was shown to stimulate the expansion of natural killer cells and was considered for intra-tumor therapy (11).

Table 1. Differences between IL-23 levels of patient groups according to disease status and prognostic factors

		IL-23 (pg/mL)		
Variables	**Number of cases**	**Mean ± SD**	**Median (min-max)**	**p**
Disease status				
CRPC	10	403.11±389.65	287.85 (110.2-1474.8)	0.664
ND	13	316.02±85.94	333.9 (178.4-512.7)	
Gleason score				
7	11	425.89±359.87	337 (208.2-1474.8)	0.295
>7	12	287.88±92.2	307.85 (110.2-457.5)	
PLNM				
Yes	17	357.56±300.7	319 (110.2-1474.8)	0.529
No	6	343.48±100.34	308.45 (251.4-512.7)	
EPLNM				
Yes	10	409.95±387.64	310.7 (110.2-1474.8)	0.951
No	13	310.76±86.58	313.3 (178.4-512.7)	
BM				
Yes	13	385.47±339.09	313.3 (110.2-1474.8)	0.901
No	10	312.83±99.07	320.3 (178.4-512.7)	
MOS				
Yes	3	310.73±129.55	262.4 (212.3-457.5)	0.784
No	20	360.36±277.01	316.15 (110.2-1474.8)	

CRCP: Castration-resistant prostate cancer, ND: Newly diagnosed, PLNM: Pelvic lymph node metastasis, EPLNM: Extrapelvic lymph node metastasis, BM: Bone metastasis, MOS: Metastasis of other sites, SD: Standard deviation, IL: Interleukin, min: Minimum, max: Maximum

Table 2. Relationship among age, IL-23 levels, and tPSA levels

All patients (n=23)	**Mean ± SD**	**Median (min-max)**
Age	710.4±8.42	72 (55-89)
IL-23 (pg/mL)	353.89±260.93	313.3 (110.2-1474.8)
Total PSA	60.23±121.6	13 (2.77-562)
	Correlation (Spearman)	
Age/IL-23	rs=-0.195, p=0.373	
Age/tPSA	rs=0.245, p=0.259	
tPSA/IL-23	rs=-0.053, p=0.809	

IL: Interleukin, SD: Standard deviation, min: Minimum, max: Maximum, tPSA: Total prostate-specific antigen

Table 3. Relationship between IL-23 levels and prostate SUVmax levels of newly diagnosed cases

Newly diagnosed cases (n=13)	**Mean ± SD**	**Median (min-max)**
IL-23 (pg/mL)	316.02±85.94	333.9 (178.4-512.7)
Prostate SUV_{max}	22.91±20.73	13.4 (6.7-74.3)
Prostate SUV_{max}/IL-23	rs=-0.258, p=0.394	

IL: Interleukin, SUV_{max}: Standardized uptake value, SD: Standard deviation, min: Minimum, max: Maximum

The effects of IL-12, IL-23, IL-27, and IL-35, which are members of the IL-12 cytokine families, on immune response in many diseases have been assessed in numerous studies. While the antitumor effects of IL-12 on various cancers are known, IL-23 was found to promote tumor growth by upregulating proangiogenic factors and increasing the mobility of tumor cells. Preclinical experiments showed that approaches that change the IL-12 and IL-23 levels in the tumor microenvironment can provide synergistic effects with other anticancer treatments. Moreover, IL-23, which is expressed in many cancers, could be an important therapeutic target (12). IL-23 is also proposed as a possible factor in the pathogenesis and disease progression of colorectal cancer (13,14). Another study showed that patients with breast cancer having higher IL-23 levels had poorer overall survival, suggesting a negative prognostic correlation (15).

In locally advanced and metastatic PC, ADT is the first and main disease management. For determining the therapy options in the ND group, Ga-68 PSMA PET/CT was showed to be effective in staging and revealing regional and distant metastases (16). However, most patients develop resistance to ADT after a short time, and the disease progresses. An increase in PSA level is the most commonly used marker of disease progression. However, in some patients with stable or slightly elevated PSA levels, Ga-68 PSMA PET/CT can accurately reveal disease progression as in two of our patients with CRPC. The available chemotherapy regimens containing docetaxel and cabazitaxel have moderate survival benefits (3). Unraveling the mechanisms that cause the development of resistance to androgen blockade will lead to significant improvements in guiding treatment.

Calcinotto et al. (4) revealed the possible association of IL-23 with castration resistance. They proposed that, under androgen-deprived conditions, IL-23 could activate the androgen receptor pathway in prostate tumor cells, promoting cell survival and proliferation. Moreover, they found that elevated IL-23 concentration in the blood and tumor samples from patients with CRPC and that antibody-mediated inactivation of IL-23 restored sensitivity to ADT in mice (5). These results are important for creating possible future treatments that block IL-23 and reverse the castration resistance. However, our results did not show any significant relationship between blood levels of IL-23 and castration resistance or poor prognostic factors in patients with PC.

Study Limitations

This study has several limitations including its limited sample size and that lack of comparison with a healthy control group. The lack of IL-23 measurement in prostate tissue samples is another limitation since correlation analysis with blood IL-23 levels was not performed.

Conclusion

Our findings failed to demonstrate a possible benefit of blocking the IL-23 pathway in patients with PC to reverse the castration resistance or avoid disease metastasis. In advanced metastatic disease, Ga-68 PSMA PET/CT can reveal the progression and resistance to ADT more accurately than PSA measurements, and radionuclide therapies targeting the PSMA receptor should be considered earlier than other possible therapy options.

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Institutional Review Board (approval number: 1668, date: 01/02/2019).

Informed Consent: Written consent was obtained from all included patients for the use of their clinical findings for research purposes.

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Comparison of Definitive Radiotherapy in the Young-Elderly and Elderly with Clinical Localized Prostate Cancer

Klinik Lokalize Prostat Kanserli Genç Yaşlı ve Yaşlı Hastalarda Küratif Radyoterapinin Karşılaştırılması

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ABSTRACT

Introduction: This study aimed to investigate the survival, treatment-related toxicities, and prognostic factors in the elderly (≥65) with prostate cancer treated with definitive radiotherapy (RT). Patients divided into two groups as young-old (65-74 years) and old (over 75 years) were examined.

Methods: A total of 178 patients with prostate cancer treated with definitive RT were retrospectively reviewed. The prognostic factors for survival, metastasis-free survival (MFS), biochemical recurrence-free survival (BFS), and treatment-related toxicities were analyzed.

Results: Pretreatment prostate-specific antigen (PSA), last PSA value, and Charlson comorbidity score (5-6) were significantly different between the two groups (p=0.001, p=0.004, and p=0.012, respectively). The elderly showed high pretreatment PSA, last PSA value, and Charlson comorbidity score (5-6). None of the other treatment or patient characteristics differed significantly between the groups. The median follow-up time was 68 months (range: 12-116 months) for the young-elderly. The 5-year overall survival (OS), BFS, and MFS were 86.4%, 91.5%, and 92.8%, respectively, in the young-elderly. Median follow-up time in the elderly patients was 60 months (range: 7-118 months) and 5-year OS, MFS, and BFS rates were 79.6%, 93.1%, and 93.4%, respectively. No statistical difference was found when the OS, BFS, and MFS were evaluated in 5 years in both groups. The multivariate analysis revealed that high radiation doses (76 Gy and ≥78 Gy) and high T-stage (T3-4) was a significant prognostic factor for the BFS in all patients (p=0.013, p=0.007, and p=0.026, respectively). The presence of high-risk patients in the risk stratification was borderline significant for the BFS (p=0.051). Acute hematological toxicity, such as leucopenia (38%), and late toxicity, such as rectal bleeding (10%), were frequently observed in the elderly.

Conclusion: No differences were found in the OS, BFS, and MFS between the two groups. High radiation doses and high T-stage was found as a prognostic factor for the BFS in all patients.

Keywords: Radiotherapy, aged, survival

ÖZ

Amaç: Bu çalışmada, küratif radyoterapi ile tedavi edilen yaşlı (65 yaş ve üzeri) prostat kanserli hastaların sağkalımları, tedaviye bağlı toksisiteleri ve prognostik faktörlerini araştırmayı amaçladık. Hastaları, genç yaşlı (65-74 yaş) ve yaşlı (75 yaş üstü) olarak iki grupta inceledik.

Yöntemler: Toplam 178 prostat kanseri hastası retrospektif olarak inceledik. Genel sağkalım, metastazsız sağkalım, biyokimyasal rekürrenssiz sağkalım (BFS), tedaviye bağlı toksisiteler ve bu sonuçlara etki eden prognostik faktörler analiz edildi.

Bulgular: Tedavi öncesi PSA, son PSA değeri ve Charlson comorbidite skoru yaşlı ve genç yaşlı hastalar arasında istatistiksel farklı bulundu (p=0,001, p=0,004 ve p=0,012). Yaşlı grupta, tedavi öncesi PSA değeri, son PSA değeri ve Charlson comorbidite skoru (5-6) yüksekti. Her iki grup arasında, diğer tedavi ve hasta özelliklerinden hiçbiri istatiksel olarak anlamlı bulunmadı. Ortanca takip süresi genç yaşlılar için 68 aydı (aralık: 12-116 ay). Genç yaşlı hastalarda 5 yıllık genel sağkalım (OS), BFS ve metastazsız sağkalım (MFS) %86,4, %91,5 ve %92,8 idi. Yaşlı hastalarda ortanca takip süresi 60 ay (aralık: 7-118 ay) ve 5 yıllık OS, MFS ve BFS oranları sırasıyla %79,6, %93,1 ve %93,4 idi. Her iki grupta da 5 yıllık OS, BFS ve MFS arasında fark bulunmadı. Çok değişkenli analizde, yüksek radyasyon dozları (76 Gy ve ≥78 Gy), ileri T-evresi (T3-4) tüm hastalarda BFS için anlamlı bir prognostik olarak bulundu (sırasıyla; p=0,013, p=0,007 ve p=0,026). Ayrıca risk sınıflandırmasında yüksek riskli hastalık BFS için sınırda anlamlı bulundu (p=0,051). Yaşlı hastalarda, akut hematolojik toksisite olarak lökopeni (%38) ve geç toksisite olarak rektal kanama (%10) daha sık izlendi.

Sonuç: Genç yaşlı ve yaşlı hastalarda genel sağkalım, BFS ve metastazsız sağkalım açısından bir fark bulunmadı. Tüm hastalarda BFS için yüksek radyasyon dozları ve yüksek T-evresi prognostik faktördü.

Anahtar Kelimeler: Radyoterapi, yaşlı, sağkalım

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Introduction

Prostate cancer has become one of the most frequently diagnosed cancers today as a result of prolonged life expectancy (1). The majority of patients with prostate cancer are over 75 years old at the time of diagnosis and this rate increases even more in developed countries due to their life expectancy prolongation (2). Older patients are more likely to have a more aggressive form of the disease at the time of diagnosis. Moreover, it is a heterogeneous group in terms of treatment response rates. Prostate cancer in the elderly that is mostly treated with active surveillance, watchful waiting, androgen deprivation therapy (ADT) and/or radiotherapy (RT), and prostatectomy is rarely recommended (3). Patients may have one or more of these treatments together.

The elderly is unclearly defined, and the minimum age for classifying the elderly ranges from 65 to 70 years. Some studies subdivided the older patients into "younger old" (65-74 years old) and "older" (75-84 years) (4), whereas our study categorized 65-74 years old as younger old and 75 years old and over as an elderly group and compared both groups. Therefore, this study aimed to investigate prognostic factors, treatment outcomes, survival, and toxicity in both groups of patients with prostate cancer treated with RT. In addition, the prognostic risk factors affecting the overall survival (OS), metastasis-free survival (MFS), and biochemical recurrence-free survival (BFS) were investigated in these patients.

Methods

Eligibility Criteria

This retrospective study analyzed the demographic outcomes, treatment outcomes, and toxicity data in a single-center cohort of 178 patients who received RT for prostate cancer between January 2012 and December 2018. The patients were divided into two groups: young-older (65-74) and older (≥75 years). Patients with clinically (T1-4 and N0M0) TNM stage (5) and histologically proven adenocarcinoma, who received RT treatment, with pretreatment prostate-specific antigen (baseline PSA) levels and total Gleason scores (GS), were evaluated. Patients with distant metastases at baseline and under 65 years old were excluded.

Patients were categorized using the National Comprehensive Cancer Network (NCCN) 2020 risk stratification as follows: low, T1-T2a, GS of 2-6, and PSA of <10 ng/mL; medium, T2b-T2c, GS of 7, or PSA of 10-20 ng/mL; and high, T3a-T4, GS of 8-10, or PSA of >20 ng/mL (6). PSA deficiency was defined using the Phoenix definition (rare, +2 ng/mL).

The study was approved by the Human Research Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2782, date: 9.03.2021) according to the Declaration of Helsinki. Informed consent was obtained from all patients after a thorough explanation of the study. All related laboratory and pathology results were obtained from the hospital data, and data related to the treatment follow-up were obtained from the clinical files.

Radiotherapy Data

All patients were diagnosed with a biopsy before the treatment. Definitive RT was applied as intensity-modulated therapy or volumetric modulated arc therapy. External beam RT was administered at 1.8-2.0 Gy daily fractions with 6 MV photon beams, 5 days a week. The pelvic region was added to the RT area in patients with pelvic lymph node involvement and those with >15% risk of lymph node involvement according to the Roach formula (7). A total dose of 46 Gy was given to the pelvic region, 54 Gy to the seminal vesicle (SV), and 76-78 Gy to the prostate. Gross tumor volume included the primary prostate. The clinical target volume was defined as pelvic lymph nodes (CTV3), SV + prostate (CTV2), and prostate only (CTV1). The planning treatment volume was defined as a pelvic lymph node margin of 0.7 mm. CTV2 and CTV1 were defined as 8 mm in all directions and 5 mm in the posterior direction. Local RT (prostate only) was applied to patients in the intermediate and low-risk groups according to the NCCN risk stratification.

Outcomes and Follow-Up

The BFS, MFS, and OS rates were examined in each patient group treated with these two treatment modalities. BFS, MFS, and OS were defined as the time from RP/RT until the biochemical failure, metastasis, and death of any cause, respectively.

Treatment toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 4.0 (8). During RT, patients were assessed at least once a week with a clinical examination and blood counts analyses. After RT, the patients' PSA levels were checked every 3 months in the first 2 years and abdominal/pelvic tomography and bone scanning were performed every 6 months. Follow-up was done every 6 months for 2-5 years, and once a year after 5 years. During the follow-up period, prostate-specific membrane antigen positron emission tomography/computed tomography and multiparametric magnetic resonance examination were requested in patients with suspected local or regional recurrence and distant metastasis.

Statistical Analysis

The mean, standard deviation, and median values were used in presenting descriptive analyzes. Categorical variables were compared using the Fisher's exact test and the Mann-Whitney U test to evaluate non-parametric variables between the two groups. BFS, MFS, and OS were evaluated using the Kaplan-Meier analysis. The univariate and multivariate Cox regression analysis was used to evaluate interactions between the two groups and prognostic variables for BFS outcome. All analyses were performed at a 95% confidence level with a 0.05 significance level using the Statistical Package for the Social Sciences 17.0 (SPSS Inc., Chicago, IL, USA) for the windows program.

Results

Retrospective data, available treatment features, and survival records of 178 patients diagnosed with prostate cancer and treated with RT were analyzed. Table 1 presents some baseline characteristics of the patients and their treatments. Pretreatment PSA, last PSA value, and Charlson comorbidity score were significantly different between the older and young-older groups (p=0.001, p=0.004, and p=0.012, respectively). The older group showed high pretreatment PSA value, last PSA value, and Charlson comorbidity score (5-6). ADT was used as a neoadjuvant for 6 months for a total of 2-3 years in patients with high risk. In the young-elderly, long ADT (2-3 years) was used in 54 (47%) patients and short ADT

Table 1. Comparison of patient characteristics according to age groups

Variables	Strata	Younger older (65-74 year) (n=115) (64.5%)	Older (≥75 year) (n=63) (35.5%)	p
Age	Mean	69.21	76.52	0.885
Pretreatment PSA	ng/dL	21.05 (1.8-146)	32.42 (1.5-770)	0.001[b]
T-stage	1-2	111 (96%)	62 (98%)	-
	3-4	108 (4%)	5 (2%)	0.296[a]
Gleason score	≥8	16 (13.9%)	11 (15.2%)	-
	≤6 and 7	99 (86.1%)	52 (92.6%)	0.540[a]
Risk category	High	57 (49.6%)	32 (50.8%)	-
	Low-intermediate	58 (49.4%)	31 (48.2%)	0.292[a]
RT doses	≥78Gy	40 (34.8%)	22 (34.9%)	-
	≤74Gy and 76 Gy	75 (65.2%)	41 (65.1%)	0.521[a]
Last PSA	ng/dL	0.9 (0.1-1.7)	4.5 (0.1-8.9)	0.004[b]
Hormonotherapy	Present	104 (90.4%)	36 (87.3%)	-
	No	11 (9.6%)	8 (12.7%)	0.380[a]
Charlson comorbidity score	2-4	77 (66.9%)	21 (31%)	-
	5-6	38 (33.1%)	42 (66.6%)	0.012[a]
Treatment modalities	IMRT	45 (39.1%)	36 (57.1%)	-
	VMAT	70 (60.9%)	27 (42.8%)	0.428[a]
Follow-up	-	68 (12-116)	60 (7-118)	-
Exitus	-	28 (24.3%)	22 (34.9%)	0.570[a]

PSA: Prostate-Specific antigen; a: Fisher's exact test, b: Mann-Whitney U test, IMRT: Intensity-modulated radiotherapy, VMAT: Volumetric modulated arc therapy

(6 months) in 54 (43.5%). In the elderly, long ADT was used in 31 (49.2%) patients and short ADT in 24 (38.1%). None of the other treatment or patient characteristics significantly differed between the groups.

Table 2 presents the treatment side effects according to age group. Acute hematological toxicity, such as leucopenia in 24 (38%) patients, was observed more frequently in the elderly (p=0.005). Non-hematological toxicity, such as diarrhea and proctitis, was observed in both age groups, without differences in the rates of these side effects between the groups (p≥0.005). Common late complications include rectal bleeding (10%) and fistula (4%) in the elderly. Rectal bleeding was statistically significant and more common in the elderly (p=0.003). Grade-3 and higher late complications occurred in two elderly (3%) and one young-elderly (1%). No grade 4 or 5 toxicity complications were found in either group.

At a median follow-up of 68 months (range: 12-116 months), 28 (24.3%) young-older patients were exitus, whereas 22 (34.9%) older patients were exitus at 60 months (range: 7-118 months). Biochemical recurrence was detected in nine patients and distant metastasis in eight patients in the young-older patient group, whereas 5 and 4 patients in the older patient group, respectively. The Kaplan-Meier analysis evaluated the BFS, MFS, and OS time (Figure 1). The 5-year BFS were 91.5% (young-older) and 93.4% (older). The 5-year MFS was 92.8% (young-older) and 93.1% (older). The 5-year OS were 86.4% (young-older) and 79.6% (older). No statistical difference was found in the BFS, MFS, and OS values in both groups.

No prognostic factors were found to affect the survival in univariate and multivariate cox regression analyzes for OS and MFS (p≥0.005). The multivariate Cox regression analysis for BFS (Table 3) found the RT dose of 76 Gy and 78 Gy as independent prognostic factors compared to 74 Gy (p=0.013 and p=0.007). According to the NCCN risk classification, the high risk of patients was observed as a borderline significant independent prognostic factor for BFS (p=0.051). In addition, high T-stage (T3-T4) was a prognostic factor for BFS in multivariate analysis (p=0.026).

Discussion

Age is one of the important factors influencing the treatment choice for clinicians. ADT was previously considered as a standard treatment in the elderly with prostate cancer. Since the 2000s, notable advances in technology, such as increased laparoscopic surgery, hypofractionation, and new RT techniques, were used in the elderly, and the use of ADT ceased to be standard. In addition, the International Association of Geriatric Oncology has recommended that healthy or fit elderly patients be treated like younger patients (9).

By 2030, 70% of all cancers are estimated to occur in patients aged 65 years and over (10). Old age is defined in many ways. Some articles take 70 years and above as the threshold value as elderly, whereas above 75 years in some studies (11). Our study compared the treatment results, treatment-related toxicity, and prognostic factors of patients with prostate cancer aged 65-74 years (young-old) and aged 75 years and over (old).

Tumor stage, GS, and initial PSA value are the most known prognostic factors for prostate cancer. In our study, the initial PSA value and the last PSA value were found to be higher (21.05 ng/dL vs 32.42 ng/dL and 0.9 ng/dL vs 4.5 ng/dL, respectively) in the elderly group and was statistically significant (p=0.001 and p=0.004), confirming that prostate cancer progresses more aggressively in older ages. Charlson comorbidity

Table 2. Acute and late toxicities according to age groups

Acute hematological toxicities	Younger older (65-74 year) (n=115) (64.5%)	Older (≥75 year) (n=63) (35.5%)	p
Anemia			
Grade 1-2	5 (4.3%)	8 (12%)	0.540
Grade 0	110 (95.7%)	55 (88%)	-
Leucopenia			
Grade 1-2	18 (15%)	24 (38%)	-
Grade 0	98 (85%)	39 (62%)	0.004
Thrombocytopenia			
Grade 1-2	14 (12%)	12 (19%)	-
Grade 0	99 (88%)	51 (81%)	0.780
Acute non-hematological toxicities			
Diarrhea			
Grade 1-2	8 (7%)	4 (6.3%)	-
Grade 0	107 (93%)	59 (93.7%)	0.877
Proctitis			
Grade 1-2	11 (9.6%)	4 (6.3%)	-
Grade 0	104 (90.4%)	59 (93.7%)	0.460
Late toxicities			
Rectal bleeding			
Present	4 (3%)	6 (10%)	0.003
Absent	112 (97%)	57 (90%)	-
Fistula			
Present	5 (5)	2 (4%)	0.896
Absent	110 (95)	61 (96%)	-
Any grade 3 toxicities	1 (1%)	2 (3%)	0.745

Table 3. Univariate and multivariate analysis for the BFS

		Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Variables	Strata	-	-	-	-
Age	(65-74 vs ≥75)	0.412 (0.244-1.011)	**0.041**	0.589 (0.323-1.074)	0.081
Pretreatment PSA	Ng/dL	1.010 (0.996-1.024)	0.192	-	-
T-stage	T1-2 vs T3-4	0.546 (0.444-1.200)	0.032	0.642 (0.356-1.089)	**0.026**
Gleason score	≤6	1	-	-	-
	7	0.471 (0.142-1.565)	0.219	-	-
	≥8	1.284 (0.270-6.102)	0.754	-	-
Risk category	Low	1	-	1	
	Intermediate	0.518 (0.422-1.116)	0.053	1.887 (0.608-5.849)	0.272
	High	0.673 (0.139-3.159)	**0.044**	1.199 (0.908-5.327)	**0.051**
RT doses	≤74 Gy	1		1	
	76 Gy	0.671 (0.679-1.943)	0.081	1.174 (0.44-0.690)	**0.013**
	≥78Gy	0.473 (0.553-1.109)	**0.021**	1.61 (0.430-0.601)	**0.007**
Last PSA	Ng/dL	0.773 (0.664-6.520)	0.881	-	-
Hormonotherapy	No	1	-	1	-
	Short (6 months)	0.606 (0.134-2.741)	0.602	-	-
	Long (2-3 year)	0.451 (0.131-1.556)	0.208	-	-
Charlson comorbidity score	2-4 vs 5-6	0.622 (0.215-1.800)	0.381	-	-
Treatment modalities	IMRT vs VMAT	0.272 (0.050-1.473)	0.131	-	-

RT: Radiotherapy, PSA: Prostate-specific antigen, IMRT: Intensity-modulated radiotherapy, VMAT: Volumetric modulated arc therapy

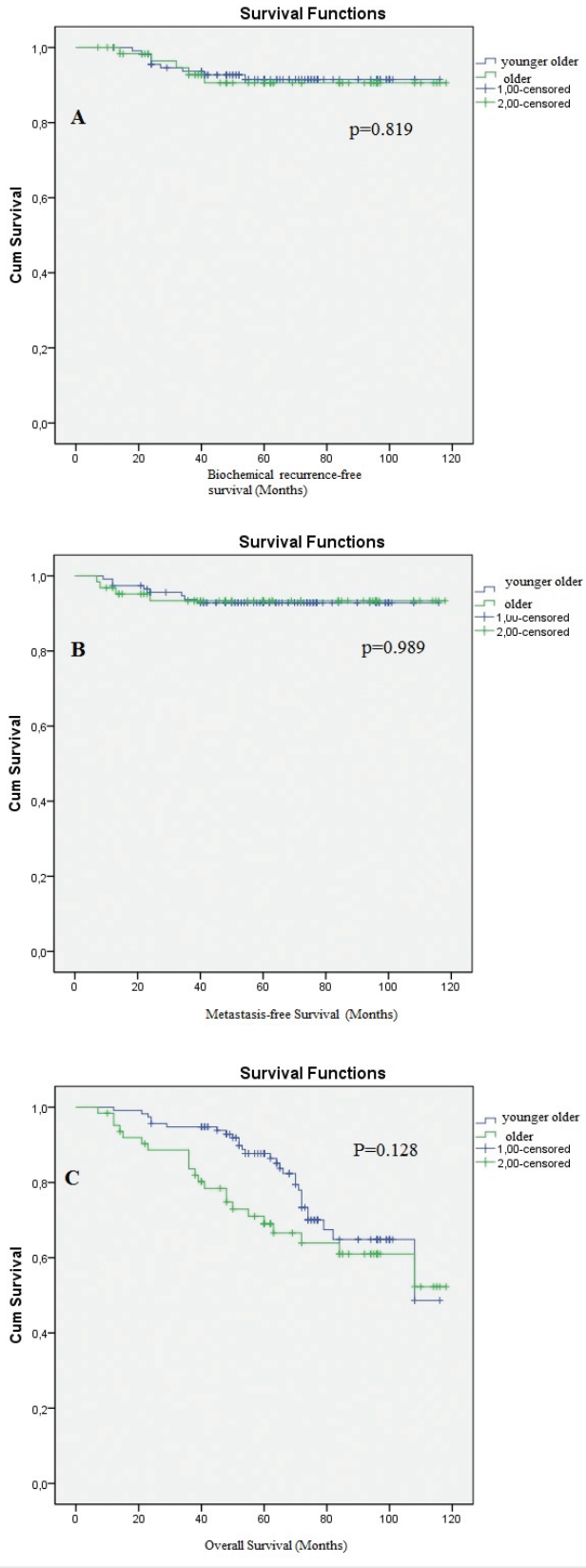

Figure 1. (A) Kaplan-Meier curve for the BFS, (B) Kaplan-Meier curve for the MFS, (C) Kaplan-Meier curve for the OS

BFS: Biochemical recurrence-free survival, MFS: Metastasis-free survival, OS: Overall survival

score is a parameter used in geriatric patients, and patients are scored according to their comorbidity (12). In our study, this score was naturally found to be higher in the elderly compared to the young-elderly. No statistical differences were found between the two groups in terms of T-stage, GS, NCCN risk categories, use of adjuvant or neoadjuvant ADT, RT dosage, and RT techniques (p>0.005).

No prognostic factors were found to affect the survival in univariate and multivariate cox regression analyzes for OS and MFS. High RT dosage for BFS was found to be a prognostic factor in univariate and multivariate analyzes. Many randomized studies (13-16) on prostate cancer observed that increasing the RT dosage increases the BFS, but not the OS. Similarly, in our multivariate analysis for the BFS, 76 Gy and ≥78 Gy RT doses were found to be an independent prognostic factor according to 74 Gy (p=0.013 and p=0.007). This result was consistent with the mentioned studies. High T-stage (T3-4) was found to be a prognostic factor for the BFS compared to lower T-stage (T1-2).

Another important issue in patients with prostate cancer is the inclusion of the pelvic area in the RT field. Current guidelines suggest that pelvic irradiation should be included in the treatment area in patients with a >15% involvement risk according to the Partin's table, clinical pelvic lymph node involvement, and high risk according to the NCCN guideline (6-7). However, pelvic RT application in the elderly increases acute toxicity and causes treatment discontinuation. Our clinic preferred to treat our patients aging ≥75 years with pelvic lymph node involvement with hormonotherapy rather than RT. Side effects were found to be similar in both groups since pelvic irradiation was preferred in younger patients. Among the acute hematological side effects, leukopenia (grades 1-2) and rectal bleeding (grades 1-2), among the late side effects, were more common in the elderly (p=0.004 and p=0.003, respectively).

Study Limitations

Our study had some limitations. First, the patients' quality of life after RT was not assessed. Second, the use of ADT increases the risk of fractures (17) and is associated with diabetes (18) and cardiovascular morbidity (19), requiring care, especially in the elderly. Side effects of ADT use in the elderly were not studied. Third, the elderly were in the higher risk category, and those receiving active surveillance and wait-and-see treatment were not included in the study.

Conclusion

According to our study results and literature findings, treatment outcomes, including survival times, are similar in the young-elderly and elderly. Based on the subgroup analyses, pretreatment PSA, last PSA, and Charlson comorbidity score treatment toxicities are higher in the elderly. RT dosage escalation was found to be the most important prognostic factor for all patients.

Ethics Committee Approval: The study was approved by the Human Research Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 2782, date: 9.03.2021) according to the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all patients after a thorough explanation of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Concept - Ö.M., B.Ö., C.A.; Design - B.İ., Ö.M., Ö.B.; Data Collection or Processing - B.İ., B.Ö., Ö.B., E.T., C.A.; Analysis or Interpretation - B.İ., B.Ö., E.T., C.A.; Literature Search - Ö.M., Ö.B., E.T., C.A.; Writing - B.İ., Ö.M.

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A Patient Having Multiple Fruit-Vegetable Allergies Presenting with Abdominal Pain

Karın Ağrısı Şikayeti ile Başvuran Hastada Çoklu Sebze-Meyve Alerjisi

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ABSTRACT

Allergy to fruits and vegetables are the most frequent food allergies in adolescents and adults. The most common phenotypes of fruit and vegetable allergy are pollen-food allergy syndrome (PFAS) (oral allergy syndrome) and lipid transfer protein (LTP) syndrome. In PFAS, fruit and vegetable allergy is caused by a prime sensitization to labile pollen allergens, e.g. Bet v 1 or profilin, and yielding generally mild phenotype, is made of local oropharyngeal symptoms. However, LTP syndrome occurs from a sensitization to LTPs, which are stable plant food allergens, often resulting systemic allergic reactions and moreover anaphylaxis. Component-resolved molecular diagnosis is crucial in directing the treatment of these patients. Existing therapeutic policies involve prevention and salvage medication, including epinephrine, for life-threatening LTP allergic reactions. Allergen specific pollen immunotherapy is not found to be helpful to manage PFAS, nevertheless sublingual immunotherapy against LTPs appears to be an encouraging treatment. Here, an interesting patient having abdominal pain for a long period of time whom later diagnosed by us with PFAS is discussed under the light of recent literature.

Keywords: Abdominal pain, vegetable, fruit, profilin, food allergy

ÖZ

Meyve ve sebzelere alerji, ergen ve erişkinlerde en sık rastlanan besin alerjisidir. Meyve ve sebze alerjisinin en sık görülen klinik şekli (fenotipi) polen-besin alerji sendromu (PFAS) (oral alerji sendromu) ve lipid transfer protein (LTP) sendromudur. PFAS'de, meyve ve sebze alerjisi dayanıksız (labil) Bet v 1 veya profilin gibi polen alerjenlerine primer duyarlaşma ile meydana gelir ve genellikle lokal orofaringeal semptomlarla giden hafif bir fenotipe yol açar. Fakat LTP sendromu, stabil bitki besin alerjeni olan LTP duyarlaşmasına bağlı oluşur ve sıklıkla sistemik alerjik semptomlara ve daha fazlası anafilaksiye yol açabilir. Bu hastaların tedavisini yönlendirmede, bileşene-dayalı moleküler teşhis yöntemi esastır. Mevcut tedavi stratejileri alerjenden korunma ve yaşamı tehdit eden LTP alerjik reaksiyonlarında epinefrin gibi kurtarıcı ilaç kullanımını içerir. Allerjen spesifik polen immünoterapisi PFAS'nin tedavisinde yararlı bulunmamış olmakla beraber, LTP'lerine karşı verilen sublingual immünoterapi ümit vadetmektedir. Burada, uzun süredir karın ağrısı olan ilginç bir hastanın PFAS tanısı konulması güncel literatür veriler ışığında tartışılacaktır.

Anahtar Kelimeler: Karın ağrısı, sebze, meyve, profilin, besin alerjisi

Introduction

Fruit and vegetable allergy is the most common food allergy in adolescents and adults (1-3). Multiple vegetable-fruit allergy is manifested by panallergen [profilin, lipid transfer proteins (LTP), etc] sensitivity (sensitization) in children and is reported to be common in the literature (1,2). Fruit-vegetable allergy occurs as a result of primary sensitization to the food or pollen allergen containing the panallergen (4).

Panallergen sensitivity is most commonly encountered in forms called pollen-food allergy syndrome (PFAS)/oral allergy syndrome (OAS) or LTP syndrome (5-8). PFAS results from primary sensitization to labile pollen allergens such as Bet v 1 or Profilin. Profilin is found in pollen and foods, and it causes food allergy as a result of sensitivity to labile allergen as a result of exposure to pollen from the respiratory tract. Ingestion of related food cross-reacting with pollen creates the PFAS phenotype with mild and local oropharyngeal reactions, and as a result, allergy to plant-derived foods usually develops. For example, there is a 55% chance of cross-reaction between birch and ragweed pollen and peach, apple and melon (1,2). LTP syndrome, on the other hand, causes food allergy due to a reaction to heat and enzymatic treatment stable allergens of non-pollen-related plant-derived foods. It often causes a more severe systemic and/or anaphylactic type of allergic reaction (8,9).

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Here, we describe the presentation and evaluation of a patient to our allergy outpatient clinic, with multiple vegetable-fruit allergy-related abdominal pain due to the development of PFAS, which we believe to have occurred as a result of sensitization of the panallergen profile.

Case Report

A 10-year-old male patient has complaints of abdominal pain and constipation since infancy, and he has had swelling of his eyes and lips (angioedema) in the last 3-4 years, during periods of increased abdominal pain and in spring months. In particular, the patient, whose relation with a food or nutrition could not be clearly defined, and who applied to the emergency department due to swelling of the eyes and lips, did not have urticarial rash at the same time. It was not evaluated as anaphylaxis or a similar clinical manifestation, and the swelling regressed with antihistamine treatment. The patient, who was examined inpatient and outpatient due to abdominal pain, was referred to the pediatric gastroenterology and pediatric rheumatology departments for examination purposes. No abnormal rheumatological or gastroenterological findings were detected in the examinations evaluated in two different centers. *FMF* gene analysis was negative. The patient was referred to the pediatric allergy clinic for evaluation due to swelling of the lips and eyes. According to the patient's anamnesis, there were also symptoms consistent with mild intermittent allergic rhinitis. There were no other features in the clinical and family history. The physical examination performed at the time of admission to the service was also completely normal.

In the skin prik tests of the patient, the tree pollen panel (cypress, sycamore, ash); cereal and grass pollen panel (various types of grasses, including English grass, Chenopodium, meadow grass) were found to be positive. A specific immunoglobulin E (IgE) scan was performed for dust mixture and other inhaled pollen related to the respiratory tract. A specific IgE value of >100 ku/L was found in the screening for inhaled allergens related to respiration, and a specific IgE value of 0.2 ku/L was found for the dust mixture. After the patient's complaints of abdominal pain were mostly after meals, a food allergy due to PFAS was suspected. Specific IgE values were examined for foods that the family suspected. According to the specific IgE values examined, the patient was admitted to the service for a pre-diagnosis of multiple (nuts, cereals, some vegetables and fruits that can be looked at) food allergy and a prick to prick test for verification purposes (Table 1). Skin prick tests were applied to the patient against 31 seasonal fruits and vegetables at 3-day intervals (Figure 1a-c). The prick to prick test results for kiwi, strawberry, banana, orange, tomato, boiled potato, carrot, walnut, apple, lemon, leek, parsley, tangerine, pear, green pepper, lettuce, radish, purple cabbage, corn, cucumber, eggplant, zucchini, cauliflower, cherry, spinach, black cabbage, onion, broccoli, pomegranate and quince are shown in the table (Table 2). Tests against 30 other foods, except boiled potatoes (probably not fresh), were positive. It was found out that when the patient ate foods that were positive for the test, his gastrointestinal complaints were accompanied frequently and more severe.

As a result of these tests, our patient was advised to take a diet for a certain period of time and come for a check-up. The patient who came to the control three months later informed us that he avoided foods that he was considered allergic to as much as possible, the most intense/severely positive foods, and that this diet itself reduced his complaints, especially abdominal pain, and benefited from the diet.

Afterwards, the patient was fed four strawberries from these foods, for which the skin prick test was significantly positive, and an oral provocation test was performed openly (by knowing what the patient ate). After the first strawberry was eaten without any problems, mild nasal itching and suspicious swelling under the right nipple developed when the second strawberry was eaten. At the time of eating the third strawberry, complaints of itching and mild abdominal pain appeared on the right eyelid and back. Since the patient's complaints were also indefinite and suspicious, the third strawberry was also finished. He also consumed the fourth strawberry without any additional problems. Despite the administration of the fourth strawberry, the complaint of

Table 1. Specific IgE values

Specific IgE	ku/L	Specific IgE	ku/L	Specific IgE	ku/L
The panel of nuts		**Grain panel**		**Meat-fish panel**	
Peanut	1.67	Wheat flour	1.07	Trout	<0.10
Nut	1.68	Corn	1.91	Salmon fish	<0.10
Walnut	0.80	Buckwheat	1.79	Codfish	<0.10
Fruit panel		Rice	4.67	Mutton	<0.10
Orange	9.70	**Milk-egg**		**Red meat**	<0.10
Strawberry	8.98	Cow's milk	<0.10	Beef	<0.10
Banana	2.42	Goat's milk	<0.10	Chicken	<0.10
Potato	1.74	α-Lactalbumin	<0.10	**Nutritional allergens**	
Kiwi	2.36	Casein	<0.10	Chocolate	<0.10
Vegetable panel		Yogurt	<0.10	Cocoa	<0.10
Tomato	7.85	Whole egg	<0.10	-	-
Soy bean	1.41	Egg yolk	<0.10	**Tree pollen**	
-	-	Egg white	<0.10	Platanus tree	43.10

IgE: Immunoglobulin E

Figure 1. Skin prick-to-prick test performed on different days in our patient (A-C)

abdominal pain remained mild, but the test was not continued. After the test and the next day, there was no increase or change in the complaints, and the abdominal pain completely disappeared.

Our patient was monitored with nutritional recommendations, and in the follow-up, it was noted that along with other complaints, abdominal pain was especially relieved in the patient with diet-appropriate nutrition. Although the PFAS usually forms a phenotype with mild and local oropharyngeal reactions, an adrenaline autoinjector was prescribed for our patient to use as a precaution in case of emergency, although its place in treatment is also controversial. Permission has been obtained from the patient's family for presentation.

Discussion

Food allergy in children occurs with a frequency of about 6-8%, and in adults with a frequency of 3-4% (1). It most often begins in the first two years of life. Fresh fruit allergy accounts for 1/3 of them, while vegetable allergy alone is responsible for 7% of all food allergies (2). Fresh fruit allergy is the most common food allergy that occurs above the age of five. It is known that food allergy to fruits from the Rosaceae family (apples, pears and peaches) develops most often (2). About 30% of children with food allergies have multiple food sensitivities. As mentioned above, pan-allergens in children (LTP, profilin, etc) its sensitization (sensitization) is manifested by multiple vegetable-fruit allergies and is frequent (1,2).

OAS is defined as the occurrence of symptoms such as oropharyngeal itching and angioedema in the lips, tongue, palate, ear and throat, which occur in a short time after ingestion of any food. Although it describes the reaction against plant-derived foods in patients with pollen allergy; The nomenclature of PFAS is found to be more accurate today, since systemic reactions can occur even without oral symptoms, although rarer, in these patients (2).

In PFAS, symptoms manifest as lip angioedema, mouth and throat itching, tingling and mild swelling immediately after ingestion of some uncooked fruits and vegetables. The findings result from a contact reaction in the oropharynx. Although oropharyngeal symptoms are seen more frequently, systemic symptoms are seen between 2-10%. Patients may apply for nausea and abdominal pain (5-7).

In our case, he was allergic to tree and grass pollen, and allergy to many plant foods was detected, and although the oropharyngeal complaints suggestive of PFAS were mild and less noticeable, especially abdominal pain came to the fore. Multiple vegetable-fruit allergies should be kept in mind, among other reasons, even in older patients who present with gastrointestinal complaints such as abdominal pain (5-7).

PFAS is generally considered to be a problem of adults, but it is rare in children. In a cross-sectional study conducted in 267 children aged 6-14 years, the overall prevalence of PFAS was found to be 8.9%, 8.8% in patients with allergic rhinitis, and 9.1% in asthmatics (7). If a patient has sensitivity to pollen, the prevalence of PFAS has been found to vary between 9.6-12.2% (5).

In a study conducted on 254 adults in Turkey, the rate of PFAS detected by patients' self-report was found to be 19.3%. Kiwi, peach, tomato, melon and watermelon were found among the most common causes. In the regression analysis, potential risk factors for PFAS were found to be asthma [odds ratio (OR): 2.4] and tree pollen sensitivity (OR: 2.9) (8). We know that our patient had mild allergic rhinitis symptoms in his history.

The gold standard in the diagnosis of multiple food allergies is food provocation tests (1,2). The fact that our patient showed positivity to tree pollen, cereal and grass pollen panels in the skin prick tests and that

Table 2. Raw (fresh) vegetable-fruit and prick to prick skin test results

Prick to prick test					
Kiwi	5x5	Tomato	10x5	Positive control (histamine)-I*	5x6
Strawberry	7x5	Potatoes (boiled)	2x2	Negative control	0x0
Banana	5x5	Carrot	7x8	Corn	4x4
Orange	4x4	Walnut	4x4		
Apple	3x3	Mandarin	8x5		
Lemon	5x5	Pear	3x3	Positive control (histamine)-II*	3x3
Leek	9x7	Green pepper	5x5		
Parsley	5x5	Lettuce	5x4		
Radish	6x6	Purple cabbage	4x4		
Cucumber	7x4	Spinach	9x6	Positive control (histamine)-III*	5x5
Eggplant	6x5	Black cabbage	6x5	Quince	3x2
Zucchini	8x5	Onion	5x5		
Cauliflower	6x4	Broccoli	3X3		
Sour cherry	4x4	Pomegranate	3X3		

*: Three series of tests conducted on three separate days are shown. All negative controls were 0x0 mm

he was allergic to different vegetables and fruits shows that our patient complies with the definition of PFAS. Likewise, in the single-blind oral provocation test performed with strawberry, the appearance of the complaints mentioned in the anamnesis confirmed that he had PFAS.

As in our patient, it is essential to exclude responsible foods from the diet in follow-up and treatment (4). As in our case, although it is difficult to diet against everything with multiple vegetable-fruit allergies, it can be done against the most obvious ones, as we have done. It is also reported that allergen-specific immunotherapy for pollen allergy has no place in the treatment of PFAS. Perhaps the benefit of sublingual immunotherapy in LTP syndrome is mentioned (1,2). Recently, although it cannot be used routinely due to its expensiveness, a dietary allergen that cross-reacts with the component-resolved molecular diagnosis method can be found in foods and a dietary intervention directed towards it may be more successful (10). Again, adrenaline autoinjector can be prescribed to the patient, especially for systemic/life-threatening allergic reactions related to LTP or PFAS (10,11).

Children with multiple food allergies should be followed closely in terms of growth and development retardation due to dietary restrictions (1,2). The patient should also be frequently evaluated in terms of asthma, other atopic diseases and inhalant allergen sensitivity (1,2).

Conclusion

PFAS, which usually presents with mild and local oropharyngeal reactions, should also be considered in patients with multiple vegetable-fruit allergies with complaints of abdominal pain.

Ethics

Informed Consent: Permission has been obtained from the patient's family for presentation.

Peer-review: Externally and internally peer-reviewed.

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