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JOURNAL OF ACADEMIC RESEARCH IN MEDICINE

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Section in a book: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. 2nd ed. St Louis: Mosby; 1974. p.273-85.

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Scientific or technical report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

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Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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Original Investigations

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Case Reports

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J Acad Res Med 2020;10(2):106-10

The Effect of Using a Dose of Prophylactic Antibiotics on Spondylodiscitis in Lumbar Disc Surgery

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ABSTRACT

Objective: Although spondylodiscitis seen after lumbar discectomy is very rare, its incidence has been reported to be around 0.1-18.8% by many different authors. The most common pathogen is *Staphylococcus aureus*.

Methods: Medical records of 1,154 patients who were operated in our hospital between 2007 and 2015 due to a single or two-level lumbar disc hernia were retrospectively extracted. Of these patients, 554 were female and 600 were male. Discectomy operation was performed in 1,062 of these patients with single-level and 91 with two-level lumbar microdiscectomy. All of these patients were given a prophylactic single dose of cefazolin sodium in accordance with the recommendations of the surgical antimicrobial prophylaxis guidelines during anesthesia. Spondylodiscitis developed in 12 patients (1.03%). Comorbidities in patients who developed spondylodiscitis, isolated pathogens, antibiotic susceptibility, antibiotics used, and hospital stay were noted.

Results: Of the 12 patients, 7 were female and 5 were male. Mean age was 45.75±14.16 years. Eleven of these patients underwent single level, one had 2 levels of lumbar microdiscectomy. Five patients underwent discectomy at L4-5 and 8 patients at L5-S1 levels. Three of these patients had *S. aureus* (25%), 4 had *Staphylococcus epidermidis* (33%) and 3 had *Escherichia coli* (25%) and 2 patients had no reproduction. The mean hospital stay was 29.45±3.98, and in patients without spondylodiscitöis it was 1.99±0.81, the two groups were significantly different from each other (p=0.0001).

Conclusion: Although most surgeons have a tendency to maintain antibiotic prophylaxis postoperatively or during hospitalization period, our study found that a single dose prophylactic antibiotic administered during anesthesia induction did not increase rate of spondylodiscitis by medical literature.

Keywords: Spondiylodiscitis, lumbar microdiscectomy, *Staphylococcus aureus*

INTRODUCTION

Although iatrogenic spondylodiscitis seen after lumbar disc surgery is very rare, its incidence has been reported by many different authors to be between 0.1-3% (1-15). Most articles on this topic are based on a retrospective case series. It is quite difficult to determine the true incidence of spondylodiscitis. Iatrogenic spondylodiscitis can be seen after discography, chemonucleosis, intradiscal operations (percutaneous laser disc decompression, nucleoplasty etc.), and lumbar disc hernia surgery. Although the infection rate in conventional discectomy is between 0.7% and 2.8%, there are authors who claim that this rate is higher in

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microdiscectomy (16). In addition, lumbar puncture, myelography and chemical sympathectomy can lead to distance contamination, causing discitis.

In terms of the development of spondylodiscitis, it is a matter of debate about whether the disc level is intra-operative contamination, from neighboring organs or hematogenous spread. The most common pathogen is *Staphylococcus aureus*. Diagnosis of spondylodiscitis is made by clinical laboratory and magnetic resonance imaging (MRI).

In some studies, despite adequate treatment for postoperative spondylodiscitis, the percentage of patients who could not continue under older study conditions was reported to be 66.7% and 87.5% (9,11,17), but only 44.6% of patients in a wide series of 7,493 surgeries and 90 spondylodiscitis has returned to their old professions (18). Prophylaxis is clearly important because of this negative result of postoperative spondylodiscitis. It is seen that perioperative intravenous antibiotics or irrigation with the antiseptic or antibiotic solution of the disc area are with irrigation is used, but postoperative spondylodiscitis has been significantly reduced (10,13).

The aim of this study is to define the incidence of spondylodiscitis in patients who underwent single-dose antibiotic prophylaxis under anesthesia induction and did not use prophylactic antibiotics in the postoperative period.

METHODS

Patient population and surgical technique: Medical records of 1,154 patients who were operated in our hospital between 2007 and 2015 due to a single or two-level lumbar disc hernia were retrospectively extracted. Patient consents were obtained. Five hundred fifty-four of these patients were female and 600 were male. Discectomy operation was performed in 1,062 of these patients with single level and 91 with two-level lumbar microsurgery. All patients were operated in prone position under general anesthesia in the operation room, and operated after sterile cover procedures. All patients underwent hemecircular laminectomy and foraminatomy and flavectomy to perform discectomy under the microscope. Attention was paid to hemostasis at the operation site and cartilage plates were not damaged, disc distance was not cured, but disc distances were irrigated with gentamicin serum at the end of the operation. All patients underwent a single dose of 1 g intramuscular cefazolin sodium antibiotic prophylaxis in accordance with the recommendations of the surgical antibiotic prophylaxis guidelines during anesthesia induction. During the 8-year follow-up period, 12 (1.03%) of the patients developed spondylodiscitis. Comorbidities, isolated pathogens, antibiotic susceptibilities, antibiotics used, and length of hospital stay were noted in the patients with spondylodiscitis.

Diagnosis of spondylodiscitis in the postoperative period: All patients were recorded by subtracting erythrocyte sedimentation rate (ESH) and complete blood count from the examinations performed before the operation. The first controls of the patients after discharge were made on the 15th day. MRI was performed on patients who had increasing back pain and/or leg pain in the postoperative period and applied to us again.

In cases such as ESH, white blood cell height at full blood count, hypointansity in the vertebrae adjacent to the disc operated on T1-weighted MRIs for control purposes in patients with high C-reactive protein (CRP) value, T2-weighted sections hyperintensity and contrast involvement in both end plates in contrast sections reduction of disc height; patients with clinical complaints and supporting laboratory findings was diagnosed with spondylodiscitis and hospitalized. After their hospitalization, tissue cultures were studied by taking a percutaneous biopsy from the disc distance and the pathogen was tried to be detected. Antibiotic infectious diseases, which are sensitive to patients with pathogen and antibiogram detected, were given as a result of consultation.

RESULTS

In our hospital, spondylodiscitis developed in 12 (1.03%) of 1,154 patients who had been operated for lumbar disc hernia and who underwent antibiotic prophylaxis during anesthesia induction only. The mean length of hospital stay at the time of operation was 1.99±0.81 days. Of the 12 patients diagnosed with spondylodiscitis, 7 were female and 5 were male. The mean age of these patients was 45.75±14.16 years. Eleven of these patients underwent a single level, 1 undervent two-level lumbar microdiscectomy. Five patients underwent microdiscectomy from L4-5 and 8 patients from L5-S1 levels. These patients were admitted to our outpatient clinic an average of 8.75±4.18 weeks after discharge, and a diagnosis of spondylodiscitis was made. Three of these patients had *S. aureus* (25%), 4 had *Staphylococcus epidermidis* (33%) and 3 had *Escherichia coli* (25%) and 2 patients had no reproduction. The patients were treated by the infection clinic, and the patients whose ESH and CRP values returned to normal under antibiotic treatment were discharged. The average hospital stay of these patients was 29.45±3.98 days, and in patients without spondylodiscitis 1.99±0.81 days, where the two groups were significantly different from each other (p=0.0001).

When the antibiotic susceptibilities of the bacteria obtained from cultures were examined, methicillin resistance was not detected in any of *S. aureus*, which reproduced in the tissue culture of 3 patients. In this case, it is sensitive to cefazoline given for prophylaxis. Methicillin resistance was observed in one of the *S. epidermidis* strains grown in 4 patients.

DISCUSSION

Postoperative spondylodiscitis is an unexpected condition with a rate of 0.1-3% that develops within 10 weeks after lumbar discectomy (10,19,20). Apart from lumbar disc surgery, as it can be seen in percutaneous procedures performed on the disc, discography, chemonucleosis, and ozone therapy, it is a severe complication due to its clinical course. Spinal instrumentation

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surgery in addition to lumbar microdiscectomy is one of the factors that increase the risk of infection. In spinal surgeries, the incidence of spondylodiscitis is up to 35% in some studies (21,22).

In addition to the clinical and laboratory methods, MRI is an important and valuable tool for diagnosis. In MRI, it shows decreased bone signal on T1-weighted MRI, increased bone signal on T2-weighted MRI, and gadolinium involvement in end plates adjacent to the disc, disc area infection with a sensitivity of 93% to 96% and a specificity between 92% and 97% (17,23). In advanced cases, the decrease in the height of the disc distance and erosive appearances in the adjacent cortical bone can also be seen (18,19). Although these views show the value of the radiological study once again, these findings have been shown in all patients who developed spondylodiscitis in our study. Prior to the use of MRI, technetium 99m diphosphonate and gallium 67 citrate bone scintigraphy screening was considered as a reliable test to ensure early detection of disc space infections (8). However, today in most patients, lumbar MRI is sufficient to diagnose together with increased ESH and CRP values with clinical (18,24,25). Apart from MRI imaging, computed tomography may show narrowing of the disk space and erosion of the adjacent cortical bone (18,19).

Large series of spondylodiscitis have been published before the routine use of MRI (2,9,12,26). The incidence of disc space infection reported in these series is likely to be very low, because the sensitivity of radiography and tomography is lower than that of MRI, especially for the detection of postoperative spondylodiscitis during the first 6 weeks after surgery (23). In most studies, no information about duration was given for follow-up examinations (7,17,18). In our study, postoperative spondylodiscitis incidence was 1.03% with single dose antibiotic prophylaxis.

Some authors argue that percutaneous disc biopsy is effective in making a diagnosis (14,19,24,27). Tissue culture with a biopsy taken from the disc distance is very valuable in eradicating the pathogen causing spondylodiscitis. Although biopsy can be easily taken under tomography or under fluoroscopy, the reported complication rates are low, but there is also a high false negative rate (28-30). In our study, all patients who were hospitalized with the diagnosis of spondylodiscitis were performed discal biopsies and pathogen was detected and appropriate antibiotic treatment was initiated.

Postoperative spondylodiscitis is an infection of disc distance caused by skin flora contamination. Often causes are *S. aureus* and *S. epidermidis* (19,24,31) Fraser et al. (32) have suggested that "aseptic" spondylodiscitis likewise begins with the contamination of the disc space with potentially infectious pathogens. In these cases, the infectious process is usually self-limiting and does not lead to severe clinical symptoms, positive cultures, positive discal biopsies and increase in ESH and CRP (24,30). According to the literature, the incidence of postoperative spondylodiscitis is up to 3.0% in patients who do not receive antibiotic prophylaxis (2-4,9,11,33). Infection rates from 0% to 3.0% have been reported for macro-surgical approaches (2,3,9,16,21,34). Infection rate in patients undergoing microsurgery techniques ranged from 0% to 2.5% (5,6,16,35). The effect of microscope use on incidence in lumbar surgeries is also a matter of debate. While Kho and Steudel (35) reported that the infection rate increased from 0% to 2.5% after using the microscope, Dauch (16) observed that the infection rate decreased from 2.8% to 0.4%.

There are a limited number of articles on lumbar discectomy, postoperative spondylodiscitis as a result of spinal infections and the effects of prophylactic intravenous antibiotic use. In some series, with the use of gentamicin, first or second generation cephalosporins, the rate of postoperative spondylodiscitis has been reported as 0-0.5% (3,10). Horwitz and Curtin (36) focused only on wound infections and reported a significant reduction in infection rates after lumbar disc surgery in patients using

Table 1. Demographic factors (standard deviation)

Age (years, mean ± SD)	43.05±12.58
Gender (n, %)	
Male	600 (52%)
Female	554 (48%)
Level (n, %)	
L2-3	110 (8.8%)
L3-4	140 (11.2%)
L4-5	444 (35.6%)
L5-S1	505 (44.4%)
Multilevel (n, %)	91
Hospitalization duration (days, mean ± SD)	1.99±0.81

SD: Standard deviation

Table 2. Summary of patients who developed spondylodiscitis

Patient ID	Gender	Age	Level	Pathogen	Week of application
1	Female	65	L5-S1	*Staphylococcus aureus*	10
2	Male	40	L5-S1	*Staphylococcus epidermidis*	6
3	Female	39	L4-5, L5-S1	*Staphylococcus epidermidis*	6
4	Female	23	L5-S1	*Escherichia Coli*	4
5	Male	61	L5-S1	No reproduction	4
6	Female	49	L5-S1	*Staphylococcus aureus*	10
7	Male	26	L4-5	*Escherichia Coli*	14
8	Female	41	L5-S1	*Escherichia Coli*	13
9	Female	38	L5-S1	*Staphylococcus aureus*	2
10	Male	58	L5-S1	No reproduction	13
11	Female	44	L5-S1	*Staphylococcus epidermidis*	13
12	Female	65	L5-S1	*Staphylococcus epidermidis*	10

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antibiotics. For spinal infection prophylaxis, a single dose of cefazolin sodium antibiotic is recommended for spinal surgery cases with or without instrumentation specified in the surgical guidelines (37). However, most surgeons tend to have patients use antibiotics in also postoperative period. The antibiotics used postoperatively can increase the antibiotic resistance of bacteria within the contaminated disc space. As a result of irrational antibiotic use, it can cause undesirable consequences such as cost, adverse effects, drug-drug interaction as well as antibiotic resistance. The incidence of spondylodiscitis in 1% of the patients we operated is within the values reported in the literature. Therefore, it was thought that the irrigation of the intervertebral disc distance in addition to a single dose of prophylactic antibiotics given to the patients was not caused by the insufficiency of the antibiotic given in terms of spectrum and duration. In our study, methicillin resistance was observed in only one patient in terms of antibiotic resistance when using single-dose antibiotics. Rational antibiotic use and antibiotic resistance are effective on the duration of spondylodiscitis treatment.

Washing the disc distance with antibiotic serums is a common practice among surgeons. However, there are few publications on this topic regarding the incidence of infectious complications after lumbar discectomy (38). In cases where the disc space cleaned after discectomy was irrigated with bacitracin and/or neomycin, the incidence of disc space infection was reported as between 0.2 and 1.2% (13). In cases where gentamicin, first or second generation cephalosporins are used, the incidence of postoperative spondylodiscitis has been reported between 0% and 0.5% (3,10,26). Gentamicin was used in irrigation fluid in our study. When we look at the sensitivities of organisms responsible for spondylodiscitis, 11 (91.6%) patients had sensitivity to gentamicin and cephalosporin. Gentamycin covers gram-positive and gram-negative bacteria, but can explain its effectiveness in preventing disc space infection.

In a study related to the topical applications of gentamycin, 72 patients who had osteomyelitis after orthopedic surgery, a collagenous sponge containing gentamicin was placed in the infected area and gentamicin levels in the drainage fluid were measured (31). Bactericidal gentamicin levels were found in the drainage fluid in the first 48 patients. It is possible to reach high antibiotic levels at the surgery area 72 hours after the operation. Based on these findings, in our study, the fact that the disc space infection is around 1% by irrigating the disc distance with a gentamicin solution may ensure that single dose antibiotic prophylaxis reaches bactericidal gentamicin and cephalosporin levels in the first postoperative days and is effective in preventing postoperative spondylodiscitis.

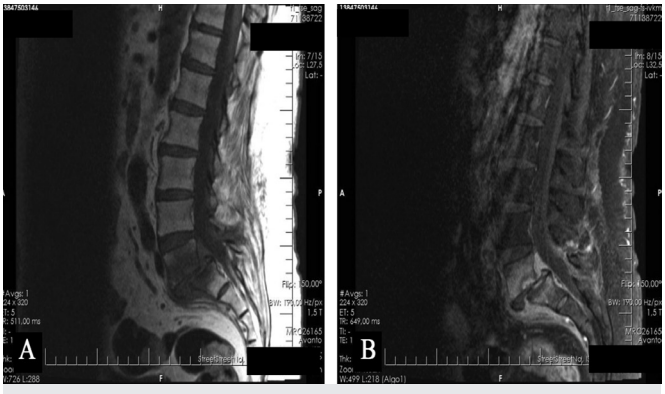

Figure 1. A) Image of discitis in L5-S1 level in T1A sagittal magnetic resonance (MR), **B)** image of discitis in L5-S1 level in contrasted T1A sagittal MR

Study Limitations

There are also limitations of our study. By its nature, it is a retrospective study based on patient file records. In our study, patients diagnosed with clinically advanced spondylodiscitis were examined, and those who were treated in subclinics or other clinics are not known. Although the patient population is not sufficient in terms of antibiotic resistance, objective results can be obtained by prospective studies.

CONCLUSION

Although most surgeons have a tendency to maintain antibiotic prophylaxis in the postoperative or in hospitalization period, our study shows that single dose prophylactic antibiotics performed only during anesthesia induction does not increase the rate of spondylodiscitis according to the medical literature.

Ethics Committee Approval: Retrospective study.

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

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Digoxin Levels and It's Stability in Different Blood Collection Tubes

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ABSTRACT

Objective: Digoxin is monitored because of its narrow range of therapeutic doses and risk of toxicity. Thus, we aimed to evaluate the effect of different blood collection tubes on digoxin levels and its stability.

Methods: Samples from 30 volunteers who received digoxin therapy were collected in 5 different tubes: no additive and gel-free glass tube (Z-tube) (reference tube), clot-activator tubes containing gel (Vacusera), clot-activator tubes containing gel (serum separator tube), barrier-free lithium heparinized tube (LiH), and new lithium heparinized tube with a barrier (Barricor). Digoxin levels in tubes were analyzed at 0 and 48 hours (h).

Results: No statistical difference was found between 0 and 48 h results in other tubes, except for LiH, and the difference in LiH was also not clinically significant. Digoxin levels in other tubes were not statistically different according to the reference tube, except for Barricor. The digoxin level in Barricor was clinically significantly higher than that in the reference tube. Although a strong correlation was found in the digoxin level between Barricor and Z-tubes, a proportional increase in digoxin level in Barricor was determined.

Conclusion: The digoxin levels in the tubes may be used interchangeably, except for Barricor. The reliability and accuracy of digoxin levels may be increased by the identification of a new therapeutic range for Barricor.

Keywords: Therapeutic drug monitoring, digoxin, specimen collection tube, serum, plasma

INTRODUCTION

Digoxin is a well-known prescribed medicine due to its positive inotropic effect in heart failure and reduction of ventricular rate in atrial fibrillation (1). In recent years, the recommended therapeutic range of digoxin in heart failure has been reduced from 0.8-2.0 to 0.5-0.9 ng/mL (2). The blood levels of digoxin need to be monitored because of its narrow range of therapeutic doses and the risk of toxicity.

Serum or plasma samples have been used in the monitoring of therapeutic drug levels as recommended by most manufacturers. To obtain these specimens, the manufacturers produce blood collection tubes with or without barrier and with or without additive. Because of its various advantages, plastic tubes with gel barriers, which are made from acrylic, polyester, or silicone, are preferred. In particular, blood tubes with gel barriers have more advantages, such as reducing the need for transfer to a secondary tube, minimizing cell-supernatant contact during storage,

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decreasing the risk of hemolysis and thrombolysis, increasing the stability of an analyte, and obtaining higher volumes of serum or plasma.

A gel separator has been reported to show absorption or adsorption effect, and therefore, this phenomenon may interfere with the analysis of certain therapeutic drugs. The effect changes depending on the hydrophobic structure of the drug, sample storage time, and sample volume (3-8). In addition, it is also stated that the elution of the gel material to sample may affect the analysis results (9). Therefore, the producers have developed new blood collection tubes with different structural barriers that can reduce the effect of gel and have better separation advantages. Although manufacturers aimed to produce blood collection tubes that can provide the most accurate and reliable results in the preanalytical process and are the best fit for clinical laboratories, laboratory specialists verify whether these blood collection tubes can meet their own needs in their clinical laboratory practice.

A number of studies have evaluated the effect of gel on drug levels and drug stability in tubes with gel due to the hydrophobic structure of digoxin. Most of these studies have been conducted *in vitro* in blood samples obtained by spiking an exogenous drug that cannot mimic protein binding and drug distribution in the circulation, and hence, it cannot directly reflect the *in vivo* status (3-5,10-12). Some studies were designed as *in vivo* and conducted in blood samples obtained from a small number of patients on digoxin treatment (7-8,13,14). However, no study was conducted on tubes consisting of a new-generation barrier on drug levels and drug stability. Therefore, the digoxin levels in four plastic tubes containing lithium heparinized with new-generation barrier, lithium heparinized without barrier, and gel with clot activator (two different brands) were compared with no additive and barrier-free glass tube (reference tube), and the stability of digoxin in each tube was also evaluated.

METHODS

Subjects

The study included 30 outpatients on digoxin treatment in the cardiology clinic and randomly selected volunteers. Blood samples were collected from volunteers between 08:00 and 10:00 AM after they fasted overnight [8-10 hours (h)]. Blood was collected from the antecubital vein into blood collection tubes. Detailed information about the study was provided to all participants before their participation, and their signed consents were obtained. This comparative analytical study was conducted in accordance with the Helsinki Declaration and approved by the Dokuz Eylül University Local Ethics Committee (approval number: 2016/26-32).

Methods

Blood samples from each individual were collected in five different types of tubes: a) No additive and gel-free glass tube [Becton Dickinson and Company (BD) Vacutainer ®Z-tube, 7 mL, 13×100 mm, catalog number 367615, NJ, USA] (Z-tube); b) a clot-activator tube containing gel (BD Vacutainer® SST II Advance tube, 5 mL, 13×100 mm, catalog number 367955, NJ, USA) serum separator tube (SST); c) a barrier-free lithium heparinized tube (BD Vacutainer ®BD Lithium Heparin, 4 mL, 13×75 mm, catalog number 368884, NJ, USA) (LiH); d) a newly produced lithium heparinized tube with a barrier (BD Vacutainer ®Barricor LH Plasma tube, 3 mL, 13×75 mm, catalog number 365031, NJ, USA) (Barricor); and e) a clot-activator tube containing gel (Vacusera Z-serum tube, 3.5 mL, 13×100 mm, catalog number 234303, İzmir, Turkey) (Vacusera).

A new-generation blood collection tube (Barricor) consists of two components: an elastomer top, which stretches during centrifugation and creates a seal on the inside wall of the tube at the end of centrifugation, and a high-density base, which uses the differential buoyancy between plasma and cells to ensure the separator orientates correctly during centrifugation.

Serum and plasma samples were separated according to manufacturers' centrifugation recommendations. Although the Z-tube, SST, LiH, and Vacusera tubes were centrifuged for 10 min at 1500 g, the Barricor tube was centrifuged for 10 minimum at 2700 g. After centrifugation, serum and plasma digoxin levels were immediately analyzed in the primer tubes. Serum (Z-tube) and plasma (LiH) in the primer tubes without a separator were transferred to the secondary tube to discontinue the cell-supernatant contact. To assess the stability of digoxin in different tubes, serum and plasma in the primer and secondary tubes were re-analyzed after being stored for 48 h at +4 °C. No visible hemolysis, lipemia, and icterus were detected in any serum and plasma samples. Care was taken to ensure that the tube sequences were random during the analysis period.

The digoxin levels were analyzed with a chemiluminescent method (ADVIA Centaur®DIG Lite Reagent, catalog number 110772, revised November 2011, Tarrytown, NY, USA) using the autoanalyzer (ADVIA Centaur XP, Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA). Daily internal quality control (IQC) for digoxin was performed using commercial IQC (Bio-Rad Lyphochek Immunoassay Plus Control, LOT number 40332, Bio-Rad Laboratories, CA, USA) at two different levels per day as part of routine laboratory practice. The within-run and between-run coefficient of variation values for the reagent were 4.0% and 3.9% for 0.83 ng/mL and 3.2% and 1.6% for 2.04 ng/mL, respectively.

The Z-tube was identified as the reference tube because it has no additive and is a gel-free glass tube, and the other plastic blood tubes might lead to an interference with the test results. This modality was also adopted from a study published by Dasgupta et al. (15,16).

Statistical Analysis

The SPSS 20.0 program (SPSS Inc., Chicago, USA) was used for all statistical analyses. The normality of the variables was tested with the Shapiro-Wilk test. Because all data show a

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normal distribution, statistical analyses were performed using parametric tests. Continuous variables were presented as mean and standard deviation (SD). The statistical difference between the sample results was evaluated using the paired t-test. While comparing digoxin results between 0 and 48 h, $p<0.05$ was considered statistically significant. While comparing digoxin levels of the 4 blood tubes with the reference tube, the Bonferroni method was used to adjust the value of the significance level, and $p<0.0125$ was considered statistically significant.

Clinically significant differences between digoxin concentrations based on the storage times (0 and 48 h) of each tube were assessed using the significant change method (17). In brief, the usual SD (USD) of 7 months' IQC data for digoxin was collected. The IQC with target mean that closely matched the mean of the 0-h digoxin levels was used to determine the USD. The significant change limit (SCL) was calculated as the mean of the 0-h digoxin levels in each tube ±2.8 USD. It was accepted as a clinically significant difference if the mean of the 48 h digoxin levels in each tube exceeded the SCL limit. Furthermore, the bias between the 0 and 48 h results was calculated with the formula as follows: [(mean of the 48 h results-mean of the 0-h results)/mean of the 0-h results] *100.

The clinical significance of digoxin concentrations between the compared and reference tubes at both 0 and 48 h was evaluated. The bias between the compared and reference tube results was calculated with the following formula: [(mean of the compared tube results-mean of the reference tube results)/ mean of the reference tube results] *100. The total allowable error was determined with the root mean square of the deviation according to RiliBAK of 14.00% (18). The total error was defined as bias (%) + 2CV (%) by the Clinical Laboratory Improvement Amendments (19). If 50% and 25% of the total error budget comes from systematic and random errors, respectively, the desirable quality specification for bias ($Bias_d$) (7.00%) was calculated with 50% of the total allowable error (14.00%). If the bias was higher than $Bias_d$, it was considered a clinically significant difference.

The digoxin levels in the compared and reference tubes were also compared using Passing and Bablok regression analyses, and subsequently, these results were visually demonstrated on Bland and Altman plots.

RESULTS

The mean and SD of digoxin levels determined in different tubes, SCLs, $Bias_d$, bias values, and statistical significance are shown in Table 1. The mean of the digoxin levels in each tube depending on the time is shown in Figure 1.

Although no statistical difference was found between the 0 and 48 h results in the Z-tube, Vacusera, SST, and Barricor tubes, the digoxin levels in LiH at 48 h increased statistically compared with 0 h. When SCLs were evaluated with regard to the stability of digoxin, the drug level in any tube did not exceed the limit. The bias between the 0 and 48 h results in all tubes was lower than $Bias_d$.

The digoxin levels in the LiH, Vacusera, and SST tubes at both 0 and 48 h were not statistically different according to the reference tube, but a statistically significant difference was found in the Barricor tube. The drug levels in the Barricor tube at both 0 and 48 h were higher than those in the reference tube. When assessed according to the $Bias_d$, the bias of digoxin results in LiH, Vacusera, and SST tubes were acceptable compared with the reference tube, except the Barricor tube at 0 h.

The digoxin levels obtained from the different tubes are shown using Passing and Bablok regression graphs and Bland and Altman plots in Figure 2. In the regression analyses, the digoxin levels between the LiH, Vacusera, and SST tubes with the Z-tube were strongly correlated, and any proportional or constant errors between tubes were not detected. Although the drug levels between the Barricor and Z-tubes were strongly correlated, a proportional error was found between the results of the Barricor and Z-tubes. According to the Bland-Altman plots, all paired data were within the confidence interval of agreement limits in comparison of all tubes with the Z-tube.

Table 1. Evaluation of digoxin stability according to different tubes and storage times

Tubes	0 h Mean ± SD (ng/mL)	48 h Mean ± SD (ng/mL)	Bias% and p-value between h		-SCL	+SCL	Bias% and p-value between reference and compared tubes at 0 h		Bias% and p-value between reference and compared tubes at 48 h		$Bias_d$%
											7.00
Z-tube	1.04±0.65	1.08±0.66	3.29	0.207	0.82	1.27					
LiH	1.04±0.62	1.10±0.66	5.96	0.020*	0.82	1.26	-0.29	0.874	2.29	0.036	
Vacusera	1.06±0.65	1.10±0.68	3.51	0.107	0.84	1.29	1.88	0.278	2.10	0.121	
SST	1.09±0.67	1.10±0.67	1.47	0.475	0.86	1.31	4.12	0.027	2.29	0.031	
Barricor	1.16±0.70	1.14±0.69	-1.62	0.357	0.93	1.38	10.70‡	<0.001†	5.44	<0.001†	

Z-tube: Glass tube without additive (reference tube), SST: clot-activator tube with gel, LiH: lithium heparin tube without gel, Barricor: lithium heparin tube with barrier, Vacusera: clot-activator tube with gel, SCL: significant change limit, $Bias_d$: desirable quality specifications for bias, Bias%: difference between the compared tube and reference tube results, p-value: significance value, *p<0.05 was considered statistically significant, †The level of significance was adjusted with Bonferroni's correction, and p<0.0125 was considered statistically significant, ‡Desirable quality specification for bias exceeded, SD: standard deviation

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DISCUSSION

Digoxin is one of the drugs that are frequently requested in therapeutic drug monitoring (TDM). In the current literature, there are different recommendations regarding the use of tubes with gel for TDM. The ADVIA Centaur systems, which produce the digoxin kit used in our laboratory, recommend that each laboratory should apply for TDM tests to its own specific tube manufacturer, but the recommended sample type is the serum. The manufacturer also stated that the samples should be stored at room temperature up to 8 h and at +4 °C after 8 h, and should be frozen at ≤-20 °C unless analyzed within 48 h.

The World Health Organization reports that plasma reflects the pathological condition of the patient better than serum (20). In the study published by the manufacturer of blood collection tube (BD) used in our laboratory, the digoxin levels in BD Barricor and BD plasma separator tubes were clinically acceptable compared with the BD SST; the digoxin levels in all tubes were stable for 48 h at room temperature and 7 days in the refrigerator (21). Therefore, we aimed to verify the statistical and clinical acceptability of differences in the LiH, Barricor, SST, and Vacusera tubes versus the Z-tube (reference tube) to evaluate the digoxin levels and stability in serum and plasma in our laboratory condition.

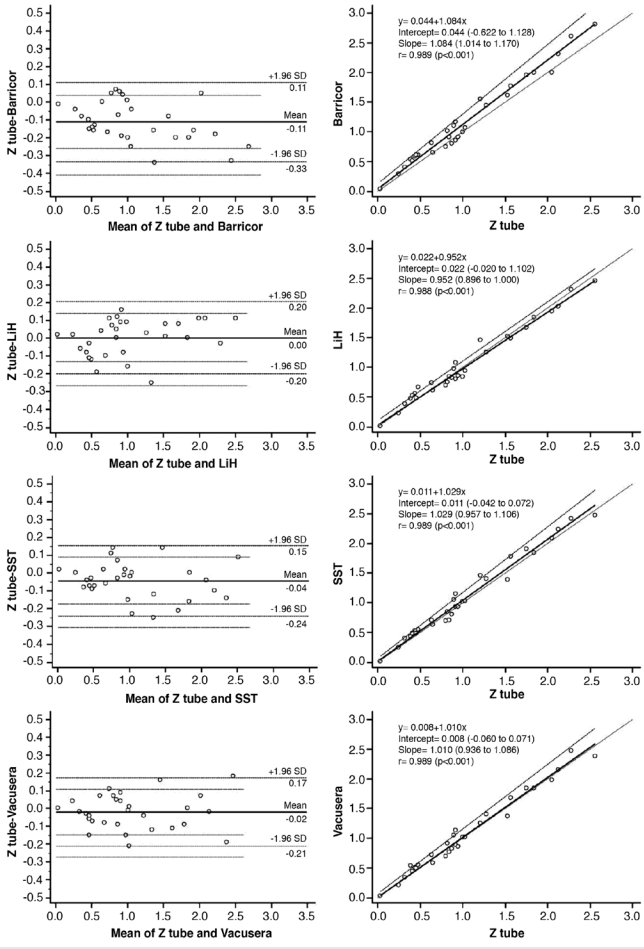

Figure 1. Bland-Altman plots and Passing-Bablok graphs for digoxin analyzed in five different types of blood collection tubes [Z-tube, glass tube without additive (reference tube)] at 0 h, SST: clot-activator tube with gel, LİH: lithium heparin tube without gel, Barricor: lithium heparin tube with barrier), Vacusera: clot-activator tube with gel. The solid, dashed, and identity lines in the Passing-Bablok regression graphs represent the regression line, its confidence intervals, and identity line (x=y), respectively. The thick solid, dashed, and thin solid in the Bland-Altman plots represent the mean difference, limits of agreement, and confidence intervals of limits of agreement, respectively

When the digoxin levels of LiH, Vacusera, and SST tubes were compared with those of the Z-tube at 0 h, the bias values were -0.29%, 1.88%, and 4.12%, respectively. The highest bias (10.70%) was in the Barricor tube and exceeded the $Bias_d$ limit (7.00%). The digoxin levels proportionally increased in the Barricor tube compared with the Z-tube. The digoxin level in a Barricor tube might possibly reflect real-time plasma digoxin level in relation with other tubes. Indeed, the digoxin metabolite in other tubes may be more trapped between cells and fibrin particles during blood clotting as seen in Z, Vacusera, or SST tubes. In the case of LiH tube, the digoxin levels were still lower than those in the Barricor tube despite both tubes using the same anticoagulant (Li heparin). The difference might be explained by the barrier effect in the Barricor tube, in which the drug metabolite was sprayed into the supernatant resulting to its effective separation. The drug levels in serum or plasma are preserved due to effective separation even in the presence of the barrier (a gel or not). The new barrier may also not absorb any significant amount of digoxin in the plasma because its structure is different from a gel structure.

At 48 h, only the bias between the Barricor and Z-tubes was statistically significant, but it did not exceed the $Bias_d$ limit. The

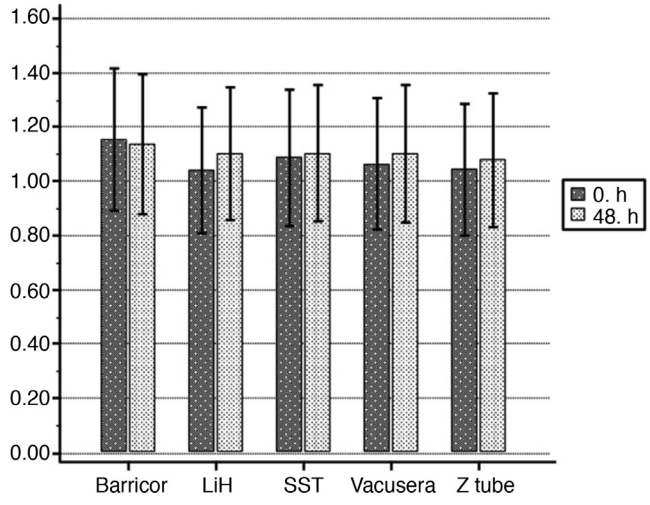

Figure 2. The comparison of digoxin level at 0 and 48 h obtained in different tubes. Z-tube, glass tube without additive (reference tube), SST: clot-activator tube with gel, LİH: lithium heparin tube without gel, Barricor: lithium heparin tube with barrier). Vacusera, clot-activator tube with gel. Data are shown as mean and 95% confidence interval for mean

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digoxin levels of the Z, LiH, Vacusera, and SST tubes showed a time-dependent increase, but those of the Barricor tube decreased at 48 h. Although the clinical significance of bias disappeared due to the increase in digoxin level of the reference tube and the decrease in digoxin level of the Barricor tube, statistical significance was preserved. The changes in other tubes except the LiH tube at 48 h were not statistically and clinically significant.

Boeynaems et al. (10) obtained comparable results between heparinized and non-heparinized plastic tubes with a glass tube. The digoxin levels of all three tubes were stable for 24 h. They considered that the plasma was interchangeable with serum in digoxin measurement (10). Chan et al. (22) detected a 5%-10% bias between the BD heparinized tube with gel (PST) and heparinized gel-free tube. In the study of Dukić et al. (13), the digoxin levels were compared in two plastic tubes with a gel barrier containing clot activator and lithium heparin. Similar to Boeynaems et al. (10), they showed that plasma or serum can be used interchangeably to measure the digoxin levels (13).

In this study, higher digoxin levels were found in the Barricor tubes compared with others, and no significant difference in any digoxin levels over time were accepted as evidence of the minimum effect of the new-generation barrier. Even if a glass tube was selected as a reference tube, it was estimated that the tubes with barrier better reflects digoxin levels in the matrix because of the barrier separating the cell-supernatant.

Dasgupta et al. (8) found that the increase in digoxin level at 24 h was not statistically significant in both tubes with gel separator and plane tube. Koch and Platoff (12) found a statistically significant increase in digoxin levels, depending on the time, in tubes with gel, but they could not explain its reason. Boeynaems et al. (10) showed that the digoxin levels in the glass tube without additive, heparinized, and heparin-free plastic tubes decreased in 24 h, but it was not statistically significant. Bailey et al. (11) reported that digoxin levels were stable up to 1 week in tubes with gel and plain tubes, and Landt et al. (4) reported that digoxin levels were stable up to 24 h in the tubes containing 3 different polymeric separators.

Study Limitations

Our study has also some limitations. Although our number of volunteers were compatible with local clinical validation of the blood collection tubes (23), it would be more convenient to include more volunteers. Another limitation was that the stability was evaluated only at 48 h due to both reagent and tube manufacturer specifying the stability for 48 h. Further studies involving different time periods can be chosen in case of different reagent/tube preferences.

CONCLUSION

The gel separator has been considered to have an absorption or adsorption effect, especially for hydrophobic therapeutic drugs. However, in studies to date, except for Koch and Platoff (12), the stability of serum and plasma digoxin in the different tubes has no significant time-dependent changes. Most likely, these differences can be attributed to differences in experimental procedures or conditions. In our study, because the most stable tube for digoxin was presumed to be SST containing gel, digoxin was not easily affected by the gel separator, similar to other hydrophobic drugs. Digoxin was the most stable in the SST tube, followed by the Barricor tube. The new-generation barrier makes a difference because the digoxin levels in the Barricor tube were higher than those in other tubes. This might be due to the Barricor tube being more efficient in separating between cells and supernatants. As a result, while the digoxin levels in the other tubes may be used interchangeably by existing therapeutic range, the reliability and accuracy of digoxin results may presumably increase by defining a new therapeutic range for the Barricor tube.

Ethics Committee Approval: Retrospective study.

Informed Consent: Detailed information about the study was provided to all participants before their participation, and their signed consents were obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.D.A., İ.K., H.S., C.D., Design - H.S., C.D.; Data Collection and/or Processing - S.D., M.Z.A., A.B.; Analysis and/or Interpretation - S.D., B.İ.B., M.Z.A., A.B.; Literature Search - F.D.A., İ.K., B.İ.B.; Writing Manuscript - F.D.A., İ.K., B.İ.B.

Conflict of Interest: The authors have no conflict of interest to declare.

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Is Vitamin D Important for Elderly Patients in Intensive Care?

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ABSTRACT

Objective: According to the World Health Organization's old age classification, 65-74 years is considered as young-old, 75-84 years as middle-old, and over 85 years as old-old. Effects of vitamin D on cardiac, renal, and endocrine diseases are closely associated with morbidity/mortality in intensive care units. This study evaluated the difference in vitamin D levels of intensive care patients below and above 75 years, and the associations between vitamin D levels and age as well as mortality/organ failure in both groups.

Methods: This study was designed as a retrospective, non-interventional, non-drug, observational clinical trial. Age, gender, vitamin D, and acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment scores on admission to the intensive care unit were recorded.

Results: Of all patients, 60 were female and 31 were male. The mean age was 77.7±13.8 years. There were 29 patients aged below 75 years and 62 patients above. The mean vitamin D level was 13.7510 ng/mL-1. The mean APACHE II score of patients of or above 75 years was significantly higher than that of patients below 75 years (p=0.024). There was a significant negative correlation between age and vitamin D in patients of or above 75 years (p=0.042).

Risk factors associated with vitamin D deficiency include age, gender, lifestyle, ethnic origin, diet, medical history, drugs, and acute critical illness. With aging, the concentration of 7-dehydrocholesterol in the skin decreases, as well as the vitamin D3-forming capacity of the skin. In this study lower vitamin D levels were detected with increasing age in intensive care unit patients.

Conclusion: No significant relationship was detected between age and vitamin D levels in patients below 75 years whereas a significant decrease in vitamin D level with increasing age was detected in patients of or above 75 years (p=0,042).

Keywords: Vitamin D, intensive care unit, elderly patient

INTRODUCTION

The definition made by the World Health Organization (WHO) as regards chronological age considers old age to be "65 years and older." According to the WHO's old age classification, 65-74 years is considered as young-old, 75-84 as middle-old, and over 85 years is as old-old (1).

The effects of vitamin D on cardiac, renal, and endocrine diseases are closely related to morbidity and mortality in intensive care units (2,3). Of 513 patients aged from 18 to 69 years, admitted in hospitals in Turkey, 51.8% had vitamin D insufficiency and 20.7% had vitamin D deficiency (4). The risk of vitamin D deficiency is higher in elderly people. Because they prefer to spend more

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time at home, they take less vitamin D, are more obese, and have weaker kidney functions (5).

This study evaluated the difference in vitamin D levels of intensive care patients below and above 75 years, and the associations between vitamin D levels and age as well as mortality/organ failure in both groups.

METHODS

This study was a retrospective, non-interventional, non-drug, observational clinical trial [Ethics Committee approval was received from the Giresun University Clinical Research Ethics Committee (approval number: 29/09/2017-11)]. Age, gender, vitamin D, and acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores of patients at anesthesiology, neurology, internal medicine, and coronary intensive care units were recorded. The patients were divided into 2 groups: below 75 years and of or above 75 years.

Statistical Analysis

SPSS 22.0 was used for statistical analyses and t-test was used to compare groups. Pearson's correlation analysis was used to evaluate intragroup correlations and $p<0.05$ was accepted as statistically significant.

RESULTS

Sixty patients were female and 31 were male. The mean age was 77.7±13.8 years. Twenty-nine patients were below 75 years, while 62 patients were at or above this age. The mean vitamin D level was 13.7510 ng/mL-1. The mean APACHE II score was 28.41 and the mean SOFA score was 7.78. The mean vitamin D level and APACHE II and SOFA scores are demonstrated in Table 1.

No significant difference could be found between the 2 groups in vitamin D levels (p=0.713). The mean APACHE II score of patients of or above 75 years was significantly higher than that of patients below 75 years (p=0.024). No significant difference could be detected between the two groups in mean SOFA scores (p=0.508). A comparison of the levels of vitamin D and the APACHE II and SOFA scores among the groups is shown in Table 2.

Intragroup comparisons showed a significant positive correlation between age and APACHE II score in the group below 75 years (p=0.012). There was a significant positive correlation between the APACHE II and the SOFA scores (p=0.000). There was no significant relationship between age and vitamin D levels (p=0.136), and no significant correlation was detected between vitamin D level and APACHE II and SOFA scores (p=0.923, p=0.488). Comparison of vitamin D level and APACHE II and SOFA scores in the group below 75 years is shown in Table 3.

Intragroup comparisons showed a significant negative relationship between age and vitamin D levels in patients of or above 75 years (p=0.042). No significant correlation was detected between age and APACHE II and SOFA scores (p=0.266 and p=0.687, respectively). There was no significant correlation between APACHE II and SOFA scores (p=0.187). No significant correlation was detected between vitamin D level and APACHE II and SOFA scores (p=0.154 and p=0.088, respectively). The comparison of vitamin D levels and APACHE II and SOFA scores in the group of or above 75 years is shown in Table 4. The correlation between age and vitamin D levels in patients of or above 75 years is shown in Figure 1.

DISCUSSION

Vitamin D affects many cells in addition to its effects on calcium and phosphorus metabolism and the skeletal system. Also, it is a hormone that has effects on many systems and diseases like immunomodulation and prevention of autoimmune diseases, some chronic diseases, and cancer development (6,7). Because of the immunomodulating effect of vitamin D and its relation to chronic diseases and age, the idea that it is also important in the course of critical patients is strengthened (8).

Table 1. Mean vitamin D levels and APACHE II and SOFA scores

	n	Minimum	Maximum	Mean	SD
Vitamin D ng/mL	91	3.00	52.76	13.7510	9.45736
APACHE II score	91	8	38	28.41	6.119
SOFA score	91	2	11	6.78	2.235

SD: Standard deviation, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment

Table 2. Comparison of vitamin D levels and APACHE II and SOFA scores between groups

	Age <75 (n=29)	Age >=75 (n=62)	p
	Mean ± SD	Mean ± SD	
Vitamin D ng/mL	14.288±11.888	13.500±8.179	0.713
APACHE II score	25.966±7.490	29.548±5.033	0.024
SOFA score	6.552±2.369	6.887±2.181	0.508

SD: Standard deviation, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment

Table 3. Comparisons of vitamin D levels and APACHE II and SOFA scores in the group below 75 years

		Vitamin D ng/mL	APACHE II score	SOFA score
Age	r	-0.284	0.458	0.186
	p	0.136	0.012	0.334
	n	29	29	29
Vitamin D ng/mL	r	-	0.019	0.134
	p	-	0.923	0.488
	n	-	29	29

SD: Standard deviation, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment

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Vitamin D can be synthesized endogenously or taken in the diet. It consists of two forms: cholecalciferol (Vitamin D3) and ergocalciferol (Vitamin D2). The majority of vitamin D in the body is Vitamin D3. Vitamin D2 is produced in plants and yeast (9). Endogenous vitamin D precursor 7-dehydrocholesterol, found in the epidermis, forms previtamin D3 after activation by ultraviolet B (10). With aging, the concentration of 7-dehydrocholesterol in the skin decreases as well as the vitamin D3-forming capacity of the skin (8).

Risk factors associated with vitamin D serum 25-hydroxyvitamin D [25(OH)D] deficiency include age, gender, lifestyle, ethnic origin, diet, medical history, drugs, and acute critical illness (11). Vitamin D levels below 20 ng/mL-1 are considered as a deficiency, between 20-30 ng/mL-1 as insufficiency, between 40-50 ng/mL-1 as optimal, and above 150 ng/mL-1 as toxic. The optimal serum vitamin D concentration is 30 ng/mL-1 (12,13).

Vitamin D deficiency may further deteriorate the aging of skeletal muscles. However, current evidence for the reversal of age-related muscular dysfunction with vitamin D supplementation is controversial, and rather than targeting too high vitamin D levels in elderly people, the safest option is to target conservative vitamin D levels sufficient for normal calcium homeostasis (14). Vitamin D deficiency should be treated per the severity of deficiency. In high-risk adults, serum 25(OH)D concentrations should be measured 3-4 months after the initiation of treatment and should be followed up for target levels (15).

Table 4. Comparisons of vitamin D level and APACHE II and SOFA scores in the group of or above 75 years

		Vitamin D ng/mL	APACHE II score	SOFA Score
Age	r	-0.259	0.143	0.052
	p	**0.042**	0.266	0.687
	n	62	62	62
Vitamin D ng/mL	r	-	-0.183	0.219
	p	-	0.154	0.088
	n	-	62	62

SD: Standard deviation, APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment

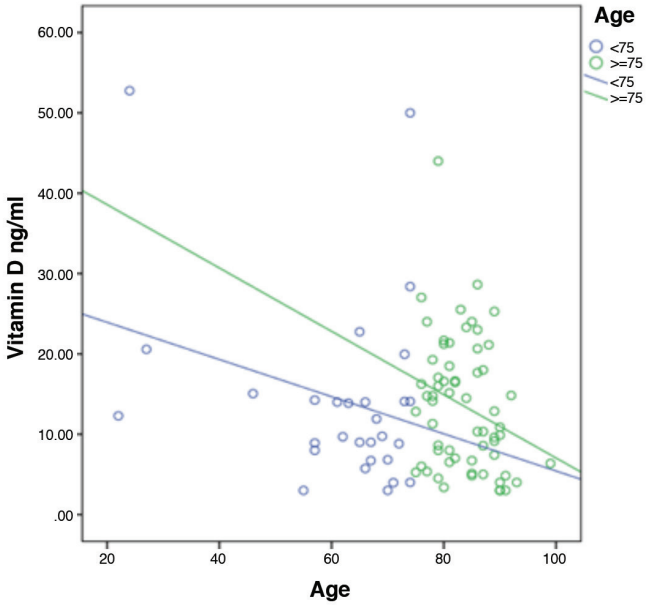

Figure 1. Correlation between age and vitamin D level in patients of or above 75 years

Patients in the intensive care unit are generally immobile and have multiple comorbidities. Their nutrition is impaired, exposure to sunlight is decreased, and they are at high risk for vitamin D deficiency (16).

In a study by Botros et al. (17) on Egyptian women, vitamin D deficiency was detected in 72.6% of breastfeeding women, 54% of pregnant women, 72% of childbearing age women, 39.5% of old age women, and 77.2% of geriatric age women. Vitamin D levels of women whose exposure to sunlight was poor, normal, or good were 14.1 ngmL-1, 14 ngmL-1, and 37 ngmL-1, respectively. In our study, 87.9% of patients were over 65 years. Of these patients, 96.9% had vitamin D levels below 20 ngmL-1, and the mean vitamin D level was 9.95 ngmL-1. A study in the United States also examined changes in vitamin D deficiency over the years and reported that serum 25(OH)D levels decreased by about 20% between 1988 and 2004, and the cause of this decrease was reported to be reduced exposure to sunlight (18).

Vitamin D deficiency is a predisposing factor for diabetes, left ventricular hypertrophy, congestive heart failure, hypertension, and chronic vascular inflammation (8,19,20). Some studies have shown that there is an increased association between vitamin D deficiency and pulmonary diseases, cardiovascular diseases, and cancer (21,22). It has also been shown that vitamin D supplementation reduces the incidence and mortality rate of these diseases (23-25).

The association between vitamin D deficiency and mortality in intensive care patients has been shown in different studies with controversial results. In a study conducted in intensive care patients, 25(OH)D and 1,25-dihydroxyvitamin D levels were found to be lower in patients who died (16,26). Another study reported that patients with 25(OH)D >60 nmol/L-1 had a mortality rate three times higher than patients with lower 25(OH)D levels (16,27). These studies performed with few patients resulted in conflicting outcomes and do not give definite results, raising the question "Is vitamin D important in intensive care patients?"

The prevalence of vitamin D deficiency exceeds 70% in intensive care patients. Lower levels of vitamin D in the intensive care unit are associated with higher infection rates, prolonged hospitalization, increased health costs, and increased mortality rates. There is an increased tissue demand for vitamin D in critical diseases (28). In a study by Arnson et al. (29) with 130 patients, vitamin D deficiency was detected in 82% of critically ill patients, and the mean vitamin D level was measured as 14.04±6.9 ngmL-1 (29). In our study, the mean vitamin D levels of all patients was 13.75±9.4

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ngmL-1, similar to vitamin D levels in this study. Most guidelines point to a cut-off value of 20 ngmL-1 for vitamin D deficiency, but the threshold value for intensive care patients has not yet been determined (13,30). Per literature, there is no clear cut-off value to define vitamin D deficiency, for the replacement or the dose/route of replacement in intensive care patients (13,30). Some authors suggest that organ failure, sepsis, and fluid deficiency and its treatment may change the level of vitamin D (31). However, in our study, there was no significant relationship between vitamin D levels and SOFA score, an indicator of organ failure, in both groups.

Vitamin D deficiency is among the risk factors that prolong the duration of hospital stay (32). A study conducted on patients admitted to an intensive care unit, with measured vitamin D levels, evaluated the duration of hospital stay, the risk of readmission to the intensive care unit, and mortality in 90 days. In this study, serum vitamin D level was positively correlated with a prolonged hospital stay, readmission to intensive care, and mortality within 90 days (28).

To promote the use of APACHE II in Turkey, it is provided online by the Ministry of Health. In this context, mortality can be calculated by this system after writing patient information and physiological values (33). Age was included in the APACHE II score as a factor affecting mortality independent of disease severity as it shows a decline in physiological reserves. The APACHE II score is the sum of 3 subscales: acute physiology score, age, and chronic health evaluation, with the highest value being 71. Mortality is 25% if the total APACHE II score is 25 and increases to 80% if the score is 35 points or higher (34,35). In our study, the mean APACHE II score of patients of or above 75 years was significantly higher than that of patients below 75 years.

In a retrospective study of patients treated in the intensive care unit with a diagnosis of sepsis and/or septic shock between 2006 and 2011, the vitamin D levels of patients when they are admitted to intensive care were compared with mortality rates within 30 days. In this study, vitamin D deficiency was found in 65 (54%) of 121 patients and the mortality rate was significantly higher in these patients (36). In another retrospective study, the mortality rates were evaluated in 3,509 patients whose vitamin D levels were measured and who had noncardiac surgery. High vitamin D levels were found to significantly decrease mortality rates. Also, vitamin D concentration was associated with mortality at the hospital, serious infection, and serious cardiovascular events (37). In contrast to these studies, there was no significant relationship between vitamin D levels and APACHE II scores, which indicate mortality, in both groups in our study.

There was a significant negative correlation between age and vitamin D in patients of or above 75 years in our study. In these patients, vitamin D levels decreased with increasing age. Inadequate vitamin D in the elderly adversely affects general health, speeds up the aging process, limits movement, and causes osteoporosis and brittleness in bones (38).

Vitamin D deficiency is associated with decreased muscle functions, impaired performance, and increased weakness. Supplementation of vitamin D, especially in the elderly, helps strengthen muscles (39). About one million people worldwide are thought to have vitamin D deficiency or insufficiency (19). In a study investigating the relationship between vitamin D status and the metabolic syndrome in the elderly, a negative correlation was found between vitamin D concentrations and the prevalence of the metabolic syndrome. Since vitamin D deficiency is widespread worldwide and the risk increases with age, the benefits of improving vitamin D levels in the elderly may be huge (40).

Study Limitations

The limitation of this study was the relatively small sample size.

CONCLUSION

We detected that vitamin D levels significantly decreased with age in patients of or over 75 years as per the literature. However, contrary to some studies linking low vitamin D levels with high mortality and organ failure especially in intensive care patients, there was no significant relationship between vitamin D levels and mortality/organ failure in our study. This result may be due to a limited number of patients. However, given that no clear consensus exists on critical vitamin D levels that require replacement in intensive care patients despite many studies that associate vitamin D levels and mortality/organ failure, we think that more comprehensive clinical studies with larger patient samples are warranted on this topic.

Ethics Committee Approval: This study was a retrospective, non-interventional, non-drug, observational clinical trial (Ethics Committee approval was received from the Giresun University Clinical Research Ethics Committee (approval number: 29/09/2017-11).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept - M.M.K., S.K., Ü.A.T.; Design - M.M.K., Ü.A.T.; Supervision - Ü.A.T.; Data Collection and/or Processing - M.M.K., S.K., Ü.A.T.; Analysis and/ or In1terpretation - S.K., Ü.A.T.; Literature Search - S.K.; Writing Manuscript - M.M.K., S.K.; Critical Review - Ü.A.T.

Conflict of Interest: The authors have no conflict of interest to declare.

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The Effect of Video Information on Preoperative Anxiety Levels in Patients Undergoing Total Knee Replacement

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ABSTRACT

Objective: The preoperative anxiety rate in patients waiting for elective surgery varies between 60% and 80%. We aimed to reduce preoperative anxiety in patients undergoing total knee replacement using a video demonstration of combined spinal-epidural anesthesia on a tablet computer.

Methods: Fifty adult patients, scheduled to undergo total knee replacement, were enrolled in a randomized controlled study. Anxiety levels were assessed using the State-trait Anxiety Inventory (STAI) and the Amsterdam Preoperative Anxiety and Information scale. The assessment was based on questionnaires completed by the patients. Patients were randomly divided into two groups: video and control groups. In the video group, a video demonstration of combined spinal-epidural anesthesia was provided, along with verbal information about the procedure. On the day of surgery, the same questionnaires were again completed for the assessment of anxiety levels.

Results: There were no significant differences between groups regarding age, sex, occupation, education, and previous history of anesthesia and surgery. The STAI scale scores were found to be significantly lower in the video group than in the control group ($p=0.000$; $p<0.005$). The Amsterdam Preoperative Anxiety and Information scale scores were found to be significantly lower in the video group compared to the control group ($p=0.000$; $p<0.05$).

Conclusion: New devices and technologies may be used in daily anesthetic practice to offer patient information more efficiently. This may help reduce preoperative anxiety levels among patients undergoing elective surgery.

Keywords: Anxiety, preoperative period, video recording, technology

INTRODUCTION

The incidence of preoperative anxiety among patients scheduled for elective surgery varies between 60% to 80% (1,2). Preoperative anxiety may necessitate a higher dose of anesthetic agents for the induction of anesthesia (3). The use of premedication before anesthesia and surgery aims to reduce patient anxiety (4).

Benzodiazepines are commonly used as anxiolytic agents. However, adequate preoperative counseling and positive reinforcement by hospital staff may reduce preoperative anxiety and the need for anxiolytic medication (5).

Total knee replacement results in severe postoperative pain and requires specialized care in the postoperative period (6). There are several advantages of regional compared to general anesthesia for total knee replacement (7,8). Combined spinal-epidural anesthesia, originally described by Soresi (9), is still considered one of the preferred techniques for lower extremity arthroplasty (7,8).

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Significant comorbidities are common among this patient population. Hence, it is important to choose an anesthetic technique that offers effective analgesia with relatively few side effects such as sedation, hypotension, and postoperative nausea and vomiting. In our clinic, when there is no contraindication, we prefer the combined spinal-epidural-anesthesia technique for total knee replacement to provide adequate analgesia in the postoperative period.

We aimed to reduce patient anxiety by a video demonstration of the planned anesthetic procedure along with verbal information on the night before surgery.

METHODS

The study was approved by the Namık Kemal University Observational Research Ethics Committee (approval number: 2014/92/12/06). Informed consent was obtained by the staff of the department of anesthesiology and reanimation from patients over 18 years of age, with American Society of Anesthesiologist-physical status (ASA-PS) I-II, who were scheduled to undergo total knee replacement at the clinic of orthopedics and traumatology.

Patients with ASA-PS III and above, mental disorders, altered conscious level, psychiatric illness on treatment, and those who were unable to cooperate for the study were excluded. We also excluded patients with contraindications for regional anesthesia, known history of allergy to local anesthetics, those who had previously participated in this study, and those who previously had a total knee replacement at our clinic of orthopedics and traumatology.

A preoperative evaluation was carried out in the anesthesia polyclinic. On the night before the surgery, the study was explained in detail to the patients, and written informed consent was obtained. Patients who refused to participate in the study were excluded.

Demographic information was collected from enrolled patients including age, sex, education level, and occupation. Information was collected on any previous history of surgery under anesthesia. Patients who had a history of regional anesthesia were considered to have undergone "regional anesthesia", even if they had been subjected to general anesthesia previously. Patients who had been subjected only to general anesthesia were considered to have undergone "general anesthesia", and those who had previously had local anesthesia alone were considered to have undergone "local anesthesia". Patient preferences regarding the choice of anesthetic technique were noted. All enrolled patients completed the State-Trait Anxiety Inventory (STAI) and the Amsterdam Preoperative Anxiety and Information scale (APAIS) questionnaires.

The STAI questionnaire includes has two sections; STAI-I, the State Anxiety Inventory, and STAI-II, the Trait Anxiety Inventory. There are 20 questions in each section. In the STAI-I section, possible responses to the current level of anxiety are: 1) not at all; 2) somewhat; 3) moderately so; 4) very much so. In the STAI-II section, the response to the frequency of feelings "in general" are: 1) almost never; 2) sometimes; 3) often; 4) almost always. In the STAI-I section, there are ten "reverse answers", numbered 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20. In the STAI-II section, there are seven "reverse answers", numbered 21, 26, 27, 30, 33, 36, and 39. After reverse scoring of responses as 1 to 4 and 4 to 1, the total STAI-I and STAI-II scores are calculated.

The APAIS form consists of six questions, including 1) I am worried about the anesthetic; 2) the anesthetic is on my mind continually; 3) I would like to know as much as possible about the anesthetic; 4) I am worried about the procedure; 5) the procedure is on my mind continually; 6) I would like to know as much as possible about the procedure. The patient is asked to answer each question using one of the following options: 1) not at all; 2) a little bit; 3) somewhat; 4) a lot; 5) extremely. The APAIS-A score reflects the anxiety level and is calculated by summing up the answers to questions 1, 2, 4, and 5. The APAIS-B score assesses the desire for information and is calculated by summing up the answers to questions 3 and 6. The final APAIS score is calculated by summing up the answers to all questions.

Patients were randomly divided into the "video" and "control" groups through computer-generated randomization. In the video group, a pre-recorded video clipping of the combined spinal-epidural anesthetic technique was demonstrated. In the control group, only the questionnaires were filled. We also provided verbal information regarding the anesthetic technique for the planned surgery to all the patients.

Patients were re-evaluated on the morning of the day of surgery. The STAI and APAIS questionnaires were completed once again and answers noted. Following this, patient preferences regarding the anesthetic technique were noted. Queries raised by patients were also addressed during this visit. All the visits and informing were done by the same anesthesiologist.

Statistical Analysis

We calculated a sample size of 14 subjects for the desired effect size with 80% power at a significance level of 5%.

Descriptive statistics are presented as mean with standard deviation, median with range, frequency, and ratio. The distribution of the variables was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for the analysis of quantitative independent data. The Wilcoxon test was used for analyzing dependent quantitative data. The chi-square test or Fisher's exact test was used to analyze qualitative independent data. A p-value of <0.05 was considered to indicate statistical significance. SPSS version 22.0 was used for all statistical analyses.

RESULTS

We initially included 52 patients in the study; however, two patients refused to participate later. Hence, 50 patients were enrolled (25 in each group). The mean age of patients was 63 years in the control group, compared to 66.28 years in the video group.

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There was no significant difference between groups in age, sex, occupation, education, and previous history of surgery under anesthesia. The preferred anesthetic technique was different between the video and the control groups. The response "I prefer the specialist's choice" was significantly higher than the "I prefer regional anesthesia" and "I prefer general anesthesia" responses in the video group compared to the control group (χ^2=0.005). Five patients in the video group preferred general anesthesia initially; however, they changed their minds and wished to undergo regional anesthesia after watching the video (Table 1).

The STAI-I scores on the night before surgery were not significantly different between the control (31.2±6.2) and the video groups (29.5±10); suggesting that patients in both groups had similar anxiety levels (p=0.120; p>0.05). In the video group, the STAI-I score on the morning of surgery (24.7±7.4) was significantly lower than in the control group (34.4±6.7) (p=0.000; p<0.05). The STAI-I score in the video group was significantly lower on the morning of surgery compared to the night before (29.5±10) (p=0.000; p<0.05). In the control group, the STAI-I score on the morning of surgery (34.4±6.7) was significantly higher than on the night before (31.2±6.2) (p=0.000; p<0.05), suggesting an increased level of anxiety on the morning of surgery. The STAI-I scores changed significantly between the night before and the morning of surgery in both groups (p=0.001; p<0.05). While the scores reduced in the video group, (-4.8±10.1) they increased in the control group (3.2±6) (Table 2).

Similar to the STAI-I score, the STAI-II score on the night before surgery was not significantly different between the

Table 1. Demographic information of patients

		Control group			Video group			p	
		Mean ± SD		Median	Mean ± SD		Median		
Age		63.0±9.9		62.0	66.3±8.0		67.0	0.109	m
Sex	**Male**	5	20.0%	-	1	4.0%	-	0.082	χ^2
	Female	20	80.0%	-	24	96.0%	-		
Occupation									
Housewife		18	72.0%	-	20	80.0%	-	0.415	χ^2
Retired		2	8.0%	-	3	12.0%	-		
Farmer		3	12.0%	-	2	8.0%	-		
Worker		2	8.0%	-	0	0.0%	-		
Education									
Illiterate		2	8.0%	-	5	20.0%	-	0.117	χ^2
Literate		2	8.0%	-	3	12.0%	-		
Primary school		17	68.0%	-	17	68.0%	-		
Secondary school		2	8.0%	-	0	0.0%	-		
High school		1	4.0%	-	0	0.0%	-		
University		1	4.0%	-	0	0.0%	-		
Operation history	**No**	4	16.0%	-	6	24.0%	-	0.480	χ^2
	Yes	21	84.0%	-	19	76.0%	-		
Type of anesthesia history									
General anesthesia		10	40.0%	-	7	28.0%	-	0.653	χ^2
Regional anesthesia		8	32.0%	-	10	40.0%	-		
Local anesthesia		3	12.0%	-	2	8.0%	-		
Anesthesia request									
Specialist's choice		7	28.0%	-	18	72.0%	-	**0.005**	χ^2
Regional anesthesia		9	36.0%	-	2	8.0%	-		
General anesthesia		9	36.0%	-	5	20.0%	-		

mMann-Whitney U test, χ^2Chi-square test, SD: Standard deviation

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control and the video groups (40.2±5.9 vs 39.3±8.6, p=0.899; p>0.05). In the video group, the STAI-II score on the morning of surgery (37.7±8) was significantly lower than in the control group (42.8±5.4); (p=0.029; p<0.05). The STAI-II score was also significantly lower on the morning of surgery compared to the night before in the video group (39.3±8.6); (p=0.000; p<0.05). In the control group, the STAI-II score on the morning of surgery (42.8±5.4) was significantly higher than on the night before (40.2±5.9); (p=0.000; p<0.05). The STAI-II scores changed significantly on the morning of surgery compared to the night before in both groups; (p=0.036; p<0.05). The scores reduced in the video group (-1.6±3.8) while they increased in the control group (2.6±7.5) (Table 2).

In the video group, the APAIS-A score on the night before surgery (12.8±4.7) was significantly higher than in the control group (7.6±4); (p=0.000; p<0.05). There was no significant difference in APAIS-A scores on the morning of surgery between the control (8.2±4.3) and the video groups (6.8±3.5) (p=0.287; p>0.05). The APAIS-A score on the morning of surgery (6.8±3.5) was significantly lower than on the night before (12.8±4.7) in the video group (p=0.000; p<0.05). In the control group, the APAIS-A score on the morning of surgery (8.2±4.3) was significantly higher than on the night before (7.6±4) (p=0.000; p<0.05). In both groups, the APAIS-A scores changed significantly between the night before and the morning of surgery (p=0.000; p<0.05). The scores reduced in the video group (-6.1±4.2) while they increased in the control group (0.5±3.5) (Table 2).

Table 2. The mean and median values of the STAI and the APAIS scores of patients

	Control group				Video group				p	
	Mean ± SD			Median	Mean ± SD			Median		
STAI-I										
Night	31.2	±	6.2	30.0	29.5	±	10.0	27.0	0.120	m
Morning	34.4	±	6.7	32.0	24.7	±	7.4	21.0	**0.000**	m
Night - morning change	3.2	±	6.0	2.0	-4.8	±	10.1	-6.0	**0.001**	m
Change within the group (p)	**0.000**			w	**0.000**			w		
STAI-II										
Night	40.2	±	5.9	40.0	39.3	±	8.6	40.0	0.899	m
Morning	42.8	±	5.4	43.0	37.7	±	8.0	38.0	**0.029**	m
Night - morning change	2.6	±	7.5	1.0	-1.6	±	3.8	0.0	**0.036**	m
Change within the group (p)	**0.000**			w	**0.000**			w		
APAIS-A										
Night	7.6	±	4.0	6.0	12.8	±	4.7	13.0	**0.000**	m
Morning	8.2	±	4.3	7.0	6.8	±	3.5	5.0	0.287	m
Night - morning change	0.5	±	3.5	0.0	-6.1	±	4.2	-4.0	**0.000**	m
Change within the group (p)	**0.000**			w	**0.000**			w		
APAIS-B										
Night	5.9	±	1.9	6.0	6.4	±	2.1	6.0	0.373	m
Morning	5.7	±	1.8	6.0	3.5	±	2.1	3.0	**0.000**	m
Night - morning change	−0.2	±	0.9	0.0	-2.9	±	3.4	-3.0	**0.000**	m
Change within the group (p)	**0.000**			w	**0.000**			w		
APAIS										
Night	13.0	±	4.7	12.0	19.2	±	5.5	20.0	**0.000**	m
Morning	13.9	±	5.4	11.0	10.2	±	4.1	8.0	**0.007**	m
Night - morning change	0.8	±	3.9	0.0	-9.0	±	5.7	-8.0	**0.000**	m
Change within the group (p)	**0.000**			w	**0.000**			w		

[m]Mann-Whitney U test, [w]Wilcoxon Test
STAI-I: The stait anxiety and information scale, STAI-II: The trait anxiety and information scale, APAIS: The Amsterdam preoperative anxiety and information scale, APAIS-A: The Amsterdam preoperative anxiety scale, APAIS-B: The Amsterdam preoperative information scale, SD: Standard deviation

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The APAIS-B score on the night before surgery was not significantly different between the control (5.9±1.9) and the video groups (6.4±2.1) (p=0.373; p>0.05). In the video group, the APAIS-B score on the morning of surgery (3.5±2.1) was significantly lower than in the control group (5.7±1.8) (p=0.000; p<0.05). The APAIS-B score was significantly lower on the morning of surgery compared to the night before (6.4±2.1) (p=0.000; p<0.05). The APAIS-B score on the morning of surgery (5.7±1.8) was significantly lower than on the night before (5.9±1.9) in the control group (p=0.000; p<0.05); however, the change in scores between the night before and the morning of surgery was significantly different between groups (p=0.000; p<0.05). The scores reduced more in the video group (-2.9±3.4) compared to the control group (-0.2±0.9) (Table 2).

The APAIS score on the night before was significantly higher in the video group (19.2±5.5) compared to the control group (13.0±4.7) (p=0.000; p<0.05). In the video group, the APAIS score on the morning of surgery (10.2±4.1) was significantly lower than in the control group (13.9±5.4) (p=0.007; p<0.05). In the video group, the APAIS score was lower on the morning of surgery compared to the night before (19.2±5.5) (p=0.000; p<0.05). In the control group, the APAIS score on the morning of surgery (13.9±5.4) was significantly higher than on the night before (13.0±4.7) (p=0.000; p<0.05). In both groups, APAIS scores changed significantly between the night before and the morning of surgery (p=0.000; p<0.05). The scores reduced in the video group (-9.0±5.7) while they increased in the control group (0.8±3.9) (Table 2).

DISCUSSION

The incidence of preoperative anxiety among the patients prior to elective surgery ranges between 60%-80% (1,2). Total knee replacement results in severe postoperative pain and requires special care in the postoperative period (6).

In our study, there were 88% and 12% of female and male patients, respectively. In the study by Kim et al. (10), including 47,961 patients who had total knee replacement between 2002 and 2005 in Korea, 91% were male patients compared to 9% of female patients. In the Souza et al. (11) study, 20.9% of 81 patients were men compared to 79.1% women. Sarban et al. (12) found that 35% of 34 patients who underwent total knee replacement were men compared to 65% of women. The sex distribution in our study was similar to previous studies.

Our study included housewives (76%), farmers (10%), and workers (4%). Retirees made up 10% of subjects. Franklin et al. (13) conducted a study that aimed to investigate the correlation between occupation and knee or hip replacement surgery in 1,408 patients. They found that 13% of 400 patients who had a history of knee replacement were housewives, while 23.7% were farmers, similar to our study.

In our study, 68% of the patients had completed primary school. Sağır et al. (14) aimed to assess the impact of patient information on preoperative anxiety levels in patients scheduled for surgery for inguinal hernia, anal fissure, hemorrhoids, and pilonidal sinus excision under spinal anesthesia. In this study, 42% of 210 patients had completed primary school, while 33% had completed high school.

In our study, 20% of patients had no previous history of surgery under anesthesia. Among the 40 patients who had undergone surgery under anesthesia, 42.5% had undergone general anesthesia, while 45% had undergone regional anesthesia. Shevde and Panagopoulos (15) found in their study of 800 patients regarding knowledge, attitude, and concerns regarding anesthesia that 31.7% of the patients had never experienced anesthesia or undergone surgery. Jlala et al. (16) assessed anxiety levels after patient information and found that 22.4% of patients had never been anesthetized previously.

In a previous study by Sağır et al. (14), basal anxiety levels were assessed using the STAI-I test preoperatively in the anesthesia polyclinic. Patients were divided into the visual and control groups. In the visual group, patients were given a colored visual catalog while in the control group, only written information was provided. Patients were asked to complete the STAI-I form before premedication and at 8 hours postoperatively. No significant difference in the STAI-I scores was observed at baseline and 8 hours postoperatively between groups. However, there was a significant decrease in postoperative compared to the basal anxiety scores in both groups. In the preoperative period, there was an increase in scores in the control group compared to the baseline; no change was seen in the visual group.

In our study, there was a significant decrease in the STAI-I and STAI-II scores on the morning of surgery in the video group compared to the control group. We believe that the video demonstration was effective in reducing anxiety levels on the morning of surgery compared to the night before.

Jlala et al. (16) assessed patients 2 weeks before elective surgery. After measuring the basal anxiety score levels, patients in the intervention arm were shown a video recording of a peripheral neural block or subarachnoid block. Patients in the control group received routine care. On the day of surgery, all patients completed the STAI and Visual Analog scale (VAS) questionnaires 2-3 hours before surgery. The questionnaires were again completed 2 to 8 hours postoperatively. No difference was noted in the STAI scores between groups on the first assessment, 2 weeks before surgery. There was an increase in anxiety levels by the STAI-I scores in the control group immediately before surgery; however, patients who had watched the video demonstration were found to be less anxious. Postoperatively, there was a significant decrease in anxiety levels in both the groups compared to the basal scores. On postoperative assessment, patients who had watched the video demonstration were found to be less anxious compared to the control group. The findings of the present study are similar.

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Taşdemir et al. (17) studied the impact of preoperative information on patient anxiety levels in 107 American Society of Anesthesiology class I-II patients between 18 and 70 years, scheduled to undergo ear, nose, and throat surgery. In the preoperative period, patients completed the STAI-I form before preoperative counseling and information regarding general anesthesia. The forms were completed again 4 and 6 hours postoperatively. Anxiety scores were significantly less in the postoperative period. In our study, we did not assess postoperative anxiety.

Salzwedel et al. (18) studied 209 patients who were scheduled to undergo general, urological, orthopedic, and trauma surgery. They categorized patients into three groups. An educational video was shown to one group of patients before the pre-anesthetic evaluation, while another group was shown the video after the pre-anesthetic evaluation. The control group did not receive video demonstration. Patients completed the STAI and VAS forms before and after the pre-anesthetic evaluation and the educational video; no significant changes were observed between groups.

We studied a homogenous group of patients who were scheduled to undergo total knee replacement by the orthopedics and traumatology department. The patients had no contraindication to combined spinal-epidural anesthesia. We believe that a more homogenous group of patients, who were provided with more specific information, resulted in reduced anxiety levels.

In a randomized controlled study by Oliphant et al. (19), patients scheduled to undergo surgery for prolapse or incontinence were shown a preoperative video regarding clean intermittent catheterization. STAI forms were completed before and after the video. A decrease in anxiety scores was observed in the video group compared to the control group.

Bondy et al. (20) contacted patients by telephone preoperatively and sent an information CD regarding general and regional anesthesia along with STAI and demographic information. Patients who watched the CD and completed the forms were asked to complete the STAI forms again preoperatively. When compared to written information, visual information was found to be much more effective in decreasing preoperative anxiety, establishing the importance of visual information in a video format, corroborating the findings of our study.

Study Limitations

STAI forms have 40 questions in total. Thus, the patients might have had difficulties while filling the forms.

CONCLUSION

Patients scheduled to undergo elective surgery may experience severe anxiety in the preoperative period. Preoperative anxiety is a serious problem that needs to be addressed adequately. We included patients scheduled to undergo total knee replacement which often leads to severe postoperative pain. We aimed to measure and to decrease anxiety levels by providing detailed information through a video and audio demonstration. We observed that the anxiety levels decreased significantly following detailed information offered in a multimedia format.

Ethics Committee Approval: The study was approved by the Namık Kemal University, Observational Research Ethics Committee (approval number: 2014/92/12/06).

Informed Consent: It was obtained.

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Supero-inferior Thyroidectomy Technique in Papillary Thyroid Carcinoma: Preliminary Results of Thirteen Cases with Intraoperative Nerve Monitoring

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ABSTRACT

Objective: This study aimed to investigate the novel use of a surgical technique using intraoperative nerve monitoring (IONM) technology in conjunction with supero-inferior thyroid dissection technique for selected cases of diagnosed papillary carcinoma. We also aimed to determine the minimal stimulation thresholds for the recurrent laryngeal nerve (RLN) before its insertion into the larynx through the cricothyroid membrane.

Methods: In this retrospective analysis, 13 consecutive patients (11 women, 2 men) aged 42-71 years (median, 53 years) who underwent total thyroidectomy with a preoperative diagnosis of papillary thyroid carcinoma only were included. The supero-inferior dissection technique has been detailed within the manuscript. After completion of thyroidectomy, the minimum current enough to stimulate the RLN at the most distal point was measured and recorded.

Results: The mean minimum stimulation current was 0.26±0.07 mA and 0.25±0.07 mA on the left and right sides, respectively. No permanent or transient RLN paralysis was observed postoperatively.

Conclusion: The supero-inferior dissection technique may have advantages, such as identification of the RLN in a constant point even in non-recurrent cases and low complication rates, but it still requires delicate and careful dissection based on our experience and should be combined with the IONM technique, if possible.

Keywords: Post-dissection current, recurrent laryngeal nerve, surgical technique

INTRODUCTION

Thyroidectomy is among the most commonly performed cervical surgery in countries that are endemic goiter regions. The main goal when treating thyroid diseases surgically is to present the patient with high quality of life by keeping the risk of complications to a minimum. The most common postoperative complications are hypoparathyroidism and recurrent laryngeal nerve (RLN) paralysis. The rates of RLN injury in total thyroidectomy cases can be as high as 10%; however, published rates of RLN injury are thought to be underestimated because less satisfactory results are less commonly presented, and complication rates from low-volume clinics tend to be higher (1-3).

Monitoring the laryngeal nerves during thyroidectomy has been increasingly used over the past 20 years. Intraoperative nerve monitoring (IONM) aids in the differentiation of RLNs from other tissues during thyroidectomy, facilitates identification of

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anatomical variations of RLN, and controls nerve integrity at the end of the surgery. The use of IONM has been advocated for high-risk thyroidectomy cases, such as reoperation, thyroidectomy for malignancy, thyrotoxicosis, and retrosternal goiter, where the rate of RLN palsy is considered to be higher (4-6).

Two different RLN identification methods are used during thyroidectomy. The classical approach involves locating the RLN in the tracheoesophageal groove and following it in the superior direction (infero-superior method), whereas the other approach identifies the nerve where it enters the larynx after superior pedicle ligation (supero-inferior), generally thought to be a high-risk method (7).

This retrospective cohort study elaborates a novel surgical technique using IONM in conjunction with supero-inferior dissection technique for selected cases of diagnosed papillary carcinoma. We also aimed to determine the minimal stimulation thresholds for RLN before its insertion into the larynx through the cricothyroid membrane. To the best of our knowledge, this is the first preliminary report of the supero-inferior total thyroidectomy technique performed in malignancies combined with IONM of RLN published in the English literature.

METHODS

In this retrospective analysis, 13 consecutive patients (11 women, 2 men) aged 42-71 years (median, 53 years) who underwent total thyroidectomy with a preoperative diagnosis of papillary thyroid carcinoma (PTC) only were selected. The local ethics committee approved the study, and written informed consents were gathered from the patients preoperatively. The surgeries were performed between January 2012 and March 2014 in a tertiary medical center, and IONM (Medtronic NIM-Response system, Medtronic Xomed, Jacksonville, FL, USA) was used in all patients to localize the RLN on both sides. Patients with previous neck or thyroid surgery were excluded. All patients underwent complete neck ultrasonography. Neither perithyroidal soft tissue invasion nor lymph node metastasis was detected on ultrasonographic evaluation. PTC was diagnosed using fine-needle aspiration biopsy preoperatively. Fiberoptic laryngoscopic examination of the vocal folds was performed pre- and postoperatively, and no vocal fold pathologies were present preoperatively. IONM was used in a standardized set-up in accordance with the published Randolph and Dralle (8) guidelines. Nerve monitoring was accomplished by placing an electromyography (EMG) endotracheal tube in contact with the vocal folds and a stimulating surface probe. Short-acting myorelaxants were used only during the induction anesthesia to avoid interference with EMG recordings throughout the surgery.

A 5-7 cm Kocher incision below the level of the cricoid cartilage was made to expose the thyroid gland. After the strap muscles were separated, the middle thyroid vein was ligated, and the upper pole of thyroid gland was extensively exposed by sharp and blunt dissection from the carotid sheath laterally and the trachea and cricothyroid muscle medially. The branches of superior thyroid artery were ligated separately to prevent injury to the external branch of the superior laryngeal nerve. After the ligation of upper pole vessels in close proximity to the gland, the upper pole was released, and it was possible to tract this part laterally with the help of Babcock forceps. A careful and bloodless dissection was continued under the level of the cricothyroid muscle, and the RLN was roughly identified at the point where the nerve entered the larynx with the aid of IONM by using a minimum of 1.5 mA stimulation current (Figure 1, 2), and after clearly identifying the RLN, the dissection was extended downwards by tunneling and spreading the tissues overlying the RLN. After the completion of thyroidectomy, the minimum current enough to stimulate the RLN at the most distal point was measured and recorded.

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 statistical package (SPSS, Chicago, USA). Mean and median values were used for parametric and non-parametric variables, respectively, as results of descriptive statistics.

RESULTS

The median follow-up period was 5.5 months. Three patients had multicentric/multifocal disease. Tumor node metastasis staging system was used for postoperative clinical staging. One patient had T1a (≤1 cm), three patients had T1b, eight patients had T2, and one patient had T3a tumors. Neither lymph node metastasis nor perithyroidal soft tissue invasion was detected in any of the patients. All patients but one with micropapillary thyroid cancer underwent radioactive iodine therapy treatment. Patients were followed up in 4 month intervals with routine physical examination and thyroglobulin levels. The mean current was 0.26±0.07 and 0.25±0.07 mA on the left and right sides, respectively (Table 1). No permanent or transient RLN paralysis was observed postoperative. One patient had hoarseness and dysphonia on the first postoperative day and during videolaryngoscopic examination, where generalized vocal fold edema and areas of minor hemorrhage on both sides with intact mucosa and normal vocal fold mobility were observed. This condition was thought to be a result of repeated stimulation of the RLNs in contact with the endolaryngeal tube during surgery, and it was managed with a single dose of intravenous prednisolone (1 mg/kg) and vocal rest. Two other patients developed hypocalcemia in the early postoperative period, but they became normocalcemic during their follow-up.

DISCUSSION

Intraoperative neuromonitoring is the gold standard for imaging and functional testing of the recurrent nerve during thyroid surgery, and this tool requires an experienced use of the EMG an intraoperative adaptation of the resection strategy (i.e., infero-superior, supero-inferior approach, etc.), especially in cases of planned bilateral total thyroidectomy. In addition to increasing intraoperative safety and facilitating the surgical procedure,

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especially in the case of high-risk interventions, medical malpractice lawsuits are taking their effect in many countries in favor of routine use of IONM in thyroid surgery. The guidelines published by the American Academy of Otolaryngology-Head and Neck Surgery and the German Association of Endocrine Surgeons also advise the routine use of IONM in thyroid surgery to protect vocal cord function (7-9), whereas the American Head and Neck Society endorses its utilization in thyroid cancer cases, particularly in patients with RLN palsy (1).

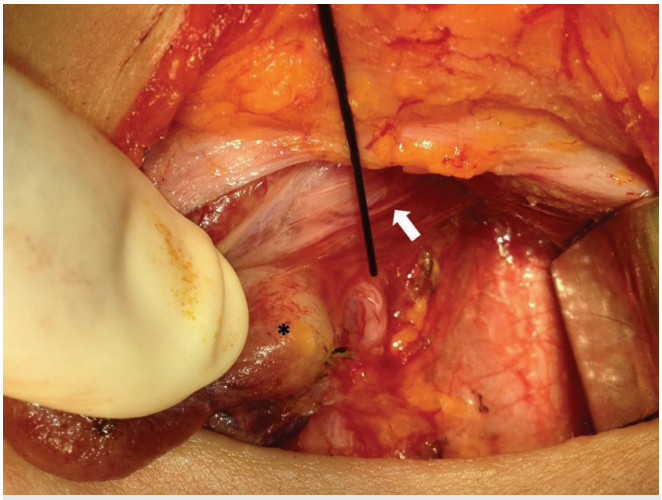

Figure 1. Intraoperative photo of left thyroid lobe (asterisk) after releasing the upper pole. The tip of the intraoperative nerve monitoring probe points at the left recurrent laryngeal nerve entering the larynx. The white arrow shows external branch of the superior laryngeal nerve

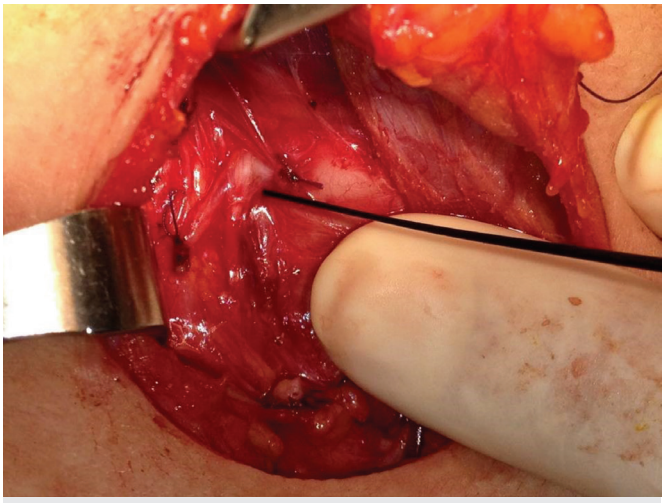

Figure 2. Photo documentation of the right recurrent laryngeal nerve (RLN) (tip of the probe) after completion of the surgery. The detection of minimal RLN stimulation threshold was performed at the most distal point through its infero-superior course

Table 1. Post-dissection minimum stimulation thresholds of the RLN

	Right (n=13)	Left (n=13)	Range (minimum)
Mean ± SEM	0.26±0.07 mA	0.25±0.07 mA	0.15±0.40 mA

SEM: Standard error of the mean, RLN: Recurrent laryngeal nerve

Although 1.5 mA stimulation current was used at the beginning of the surgery to roughly localize and map the neural structure overlaid by different types of tissues, proceeding with dissection, the minimal stimulation current needed for RLN to achieve a minimum EMG activity was >100 μV at its point of entry into the laryngeal region through the cricothyroid membrane. This point is presumed to be the most stable and reliable landmark in the RLN course, especially in non-recurrent variations. The detection of minimal stimulation threshold at the closest point to the larynx was made possible by using a descending method, thus lowering the stimulating current by 0.5 mA gradually until the EMG response on the screen was not recognizable. The mean minimum current at the end of the surgery was 0.26±0.07 and 0.25±0.07 mA on the left and right sides, respectively. Only few studies in the literature investigated the stimulation thresholds in vivo: Choby et al. (10) found that the mean postresection RLN minimum threshold level was 0.47 mA (range: 0.20-1.0 mA), although the point of measurement through the course of the nerve has not been mentioned in the article. Using the same NIM-RESPONSE monitoring system, the RLNs were monitored after thyroidectomy and parathyroidectomy in another prospective study, and the mean post-dissection stimulation threshold at the distal extremities of the nerve was 0.36 mA (range: 0.10-0.80 mA), and the authors claimed that this great variability of thresholds could be explained by the degree of nerve dissection or the differences of nerve exposure to the stimulation electrode from one case to another because the nerve covered by a small amount of surrounding tissue, such as adipose or connective tissue, would require more intense stimulation (11). However, we managed to gather the most precise stimulation thresholds as possible with the closest proximity to the inlet of the RLN to the laryngeal region by using the supero-inferior dissection technique.

Postoperative vocal fold edema and hemorrhage can cause hoarseness due to relative vocal cord immobility with normal stimulation signal, which occurred in one of the patients; but normal mobility will be regained after the edema subsides (1). This issue points out the importance of pre- and postoperative laryngoscopic examination of the vocal cord function to diminish medicolegal liability and to differentiate previous vocal fold pathologies, such as vocal polyps or even pre-existing vocal cord paralysis (12).

In certain circumstances, such as reoperation, large goiters, cancers with extrathyroidal extension, and patients with very short neck, the RLN cannot be easily identified at the point where it crosses the inferior thyroid artery; thus, it could be wiser to look for it at its only constant anatomical point where it penetrates the laryngeal membrane at the top of the tracheoesophageal groove (13). This supero-inferior dissection technique was first described in 1988 by Guerrier (14). Although the supero-inferior dissection technique may have some advantages, such as identifying the RLN in a very constant point even in non-recurrent cases and low

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complication rates (7), it still requires more delicate and careful dissection based on our experience and should be combined with the IONM technique, if possible. Our sample size was relatively small due to the retrospective nature of the study, which included only cases with a preoperative diagnosis of PTC requiring total thyroidectomy, and the aim of this manuscript was to mainly describe the surgical technique and set the standard mean post-dissection stimulation threshold of the RLN.

Study Limitations

The relatively small sample size and retrospective design are the main limitations of our study.

CONCLUSION

We aimed to investigate the use of IONM in conjunction with the supero-inferior thyroid dissection technique in elective bilateral total thyroidectomy for selected cases of preoperatively diagnosed PTC. Because inadvertent and repetitive use of high stimulus thresholds during such surgeries can fatigue the nerve cells and will potentially lead to postoperative paresis, the use of minimum currents for nerve stimulation is important. The supero-inferior dissection technique has advantages, such as identifying the RLN in a very constant point even in non-recurrent cases and low complication rates, but it still requires delicate and meticulous dissection based on our experience and should combined with IONM, if possible.

Ethics Committee Approval: The local ethics committee approved the study.

Informed Consent: Written informed consents were gathered from the patients preoperatively.

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Author Contributions: Concept - A.S.İ., K.Ç.K.; Design - A.S.İ., K.Ç.K.; Supervision - A.S.İ., K.Ç.K.; Resources - A.S.İ., K.Ç.K.; Materials - A.S.İ.; Data Collection and/or Processing - A.S.İ.; Analysis and/ or Interpretation - A.S.İ.; Literature Search - A.S.İ., K.Ç.K.; Writing Manuscript - A.S.İ.; Critical Review - A.S.İ., K.Ç.K.

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Cost Analysis in Knee Revision Arthroplasty: A Study at the Research and Training Hospital in Turkey

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ABSTRACT

Objective: This study aimed to investigate the costs covered by the hospital during inpatient treatment of patients who underwent knee revision arthroplasty in the orthopedics and traumatology clinics of a public hospital and compare with the invoiced amount.

Methods: The demographic information and revision reasons of 50 patients who underwent total knee revision arthroplasty in a public hospital between 01.01.2016 and 30.09.2017 were determined using hospital information management system records. The patients were categorized into two groups: septic and aseptic. For each patient, the costs of medical consumables, medicine/serum, medical treatment, surgery, anesthesia, imaging services, laboratory procedures, blood and blood products, meal and companion costs, device depreciation expenses, consultation, control examination, preoperative patient preparation stage, surgery, visit and other costs were calculated separately during inpatient treatment.

Results: The average total cost of a patient was 24,005.00 TL, whereas the average invoice amount was 21,490.00 TL, with a difference of 2,515.00 TL. This difference was 3,193.00 TL and 2,166.00 TL in the septic and aseptic groups, respectively. In the septic group, the duration of hospital stay, medication, treatment, surgery, anesthesia, laboratory, imaging, blood center, consultation, visit, meal cost, total cost, and invoice amount were significantly higher than the aseptic group (p□0.05).

Conclusion: Regulations by the social security institution are needed to ensure the fiscal sustainability of the public hospital's. In addition, following the medical and technical innovations in revision surgery can help reduce the costs.

Keywords: Revision, knee joint, arthroplasty, cost analysis, hospital economics

INTRODUCTION

The Nationwide Inpatient Sample (United States) surveys of hospital discharge records projected the demand for primary total knee arthroplasty (TKA) to increase by 673% from 450,000 (95% prediction interval, 425,000 to 477,000) in 2005 to 3.48 million procedures (95% prediction interval, 2.95 to 4.14 million) by 2030. The results of the same report projected the TKA revisions to increase from 38,300 (95% prediction interval, 32,600 to 44,300) in 2005 to 268,200 (95% prediction interval, 192,700 to 381,400) by 2030 (an increase of 601%) (1).

For an economical operation and sustainability of a hospital, the costs of complex cases requiring higher budgets should cover the variable costs per patient, which enables to cover the hospital's total fixed costs by the income from other more common procedures (2).

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The calculation of the costs of the services in hospital's is a difficult issue because common costs are wide in hospitals, diverse health services are offered, and the complexity of service units causes difficulties in cost estimations. Public hospitals offer profit-free services, and no direct relationship is found between the income from service provision and cost of services. It is only possible to determine whether a hospital gains or losses from a surgery by determining the costs in a real or real-like way. Diagnostic and treatment methods of health services financed by the Social Security Institution (SSI) in our country are indicated in the Health Practice Notifications (HPN) and annex lists, and HPN scores are compared in line with the opinions of experts based on the difficulty of the procedures (3,4). The SSI considering the cost estimates based on scientific cost analysis studies should be useful to determine the reimbursement prices to the hospitals (5).

This study aimed to investigate the costs covered by the hospital during the inpatient treatment of patients who underwent knee revision arthroplasty in the orthopedics and traumatology clinics of a public hospital and compare with the invoiced amount.

METHODS

After obtaining institutional review board approval, the demographic information and revision reasons of 50 patients who underwent total knee revision arthroplasty in a public hospital between 1 January, 2016 and 30 September, 2017 were determined using the Hospital Information Management System (HIMS) records. All total revision procedures due to infection and component loosening were included. The patients were categorized into two groups: septic and aseptic.

The treatment costs of patients in public hospitals in Turkey are maintained according to the lists in the Health Application Notification (HAN) and annexes in the appendix announced by the SSI. In these lists, a code has been determined for each surgical procedure, and the amount to be paid to the institution is indicated by the codes. The physician enters the code of each surgical procedure. In this study, the data of the patients with the code for total hip revision arthroplasty were included, but those with partial revision arthroplasty code were excluded. Two-stage revision arthroplasty surgeries in patients with septic origin were included. The duration and cost of hospitalization for each stage were added to the data set for each patient and included in the study.

For each patient, the costs of medical consumables (revision tibia and femur component, gloves, sutures, etc.), medicine/serum costs, medical treatment costs (injections, transfusion, arterial catheterization, wound debridement, enema, vascular access, etc.), costs of surgery and anesthesia procedures (revision knee arthroplasty, joint debridement, implant removal, spacer application, anesthesia, epidural block, etc.), costs of imaging services (direct graph, length graph, MR, CT, reporting, etc.), costs of laboratory procedures (biochemistry, microbiology, etc.), costs of blood and blood products (erythrocyte suspension, FFP, etc.), patient meals and companion costs, device depreciation expenses, consultation, control examination, preoperative patient preparation stage, surgery, visit and other costs were calculated separately during the impatient treatment, and the cost of each patient covered by the hospital was determined after calculating the sum of all the abovementioned costs.

While doing these calculations, after the amounts of all the goods and services covered for each patient during inpatient treatment are determined through HIMS, the average purchasing unit prices of the goods and services used for these patients from the hospital purchasing unit, the goods and services procurement contracts, the point multiples determined by the laboratory and imaging service procurements, the billings paid to the Red Crescent Blood Center, the main scores and coefficients to be paid for the processes in the HPN annex lists, data of the salary trust department, warehouse records, data from other related units, and the expense determination tables in the cost analysis studies published by the Ministry of Health were used (4).

In accordance with the applicable legislation, the invoices according to the HPN and annex lists have been determined for each patient from the hospital records. The total costs covered and SSI bill amounts were compared to determine the difference. The study was approved by the University of Health Sciences, Metin Sabancı Baltalimanı Training and Research Hospital Expertise Education Committee in Medicine Observational Research Ethics Committee (approval number:16.10.2017-16). The demographic information was determined using HIMS records.

Statistical Analysis

The mean, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics. The distribution of the variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data, and chi-squared test was used in the analysis of qualitative independent data. SPSS 22.0 program (IBM Corp., Released 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA) was used in the analyses.

RESULTS

Of the 50 patients, 37 were women, and 13 were men, with a mean age of 69 years. The aseptic and septic groups were composed of 33 and 17 patients, respectively. Table 1 shows the data of patients undergoing knee revision arthroplasty and their costs. The average cost of a patient was 24,005.00 TL (Turkish Lira), whereas the average invoice amount was 21,490.00 TL, with a difference of 2,515.00 TL. When comparing patients who underwent surgeries for septic and aseptic reasons, the average cost of the surgery (two-stage) for septic and reasons was 28,968.00 TL and 21,448.00 TL, respectively, whereas the invoice amount was 25,775.00 TL and 19,282.00 TL, with a difference of 3,193.00 TL and 2,166.00 TL, respectively.

The age and sex distribution, duration of the surgery, medical expenditure, patient acceptance, operation team, device depreciation, and companion expenses did not differ significantly

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in the aseptic and septic groups (p>0.05). In the septic group, the duration of hospital stay, medication, treatment, surgery, anesthesia, laboratory, imaging, blood center, consultation, visits, meal costs, total cost, and invoice amount were significantly higher than the aseptic group (p<0.05) (Table 2).

DISCUSSION

The main purpose of the studies on the total cost of patients during inpatient treatment is to find possible ways to reduce the costs based on health care without compromising the quality of the health care services (6-10). However, cost analysis is difficult and time consuming. Administrative, financial, and medical data should be reliable to establish the direct cost. Necessary regulations must be made to ensure the presentation of the money spent on the patient when requested and the motivation of the staff responsible for providing services to the patient at the first instance should be increased, and the functionality in fulfilling their responsibility should be ensured (10).

In this study, the payment of the patients who underwent revision knee arthroplasty during inpatient treatment based on HPN prices by the SSI was made below the hospitalization cost. When the literature is examined, similar results are found in studies conducted by unit cost analysis (11). Because the number of patients who underwent revision knee arthroplasty is expected to increase in the future (1), we believe that SSI needs to make corrective actions, such as revision of HPN prices in revision knee arthroplasty to ensure the sustainability of financial resources in public hospitals.

Similar studies have reported that septic knee revision arthroplasty is significantly more costly than aseptic knee revision arthroplasty (12-14). In our study, the cost of inpatient treatment for septic-based revision knee arthroplasty was approximately 7,520.00 TL more than that for aseptic-based revision knee arthroplasty.

In the literature, blood products and drug expenditures are significantly higher in the inpatient treatment of septic-based revision surgery, and while analyzing the costs covered by the hospital in the cost analysis of septic total knee revision surgeries, two separate hospitalizations for the two-stage revision and personnel costs should be included in the costs (14). This study is significant because all costs during inpatient treatment covered by the hospital are calculated, and the duration of hospitalization, medicine, treatment, surgery, anesthesia, laboratory, imaging, blood center, consultation, visits, meal costs, total costs, and

Table 1. Descriptive statistics of the data

Descriptive statistics of the data								
		Minimum-maximum			**Median**	**Mean ± SD (n, %)**		
Age		4.,0	-	84,0	68.5	68.6	±	7.6
Gender	Female					37		74.0%
	Male					13		26.0%
Surgery time (min)		120.0	-	300.0	180.0	188.1	±	41.7
Length of stay (days)		2.0	-	174.0	14.0	24.4	±	33.2
Medical consumption expenses (TL)		6832	-	48801	13,449	14,932	±	7591
Drug expenditures (TL)		17.1	-	4461.7	196.9	531.3	±	924.6
Treatment expenses (TL)		271.8	-	3882.4	521.9	784.2	±	706.3
Operation, anesthesia expenses (TL)		1141.9	-	9796.9	1746.3	2009.0	±	1384.4
Laboratory expenses (TL)		20.0	-	773.0	75.7	118.4	±	129.9
Imaging expenses (TL)		1.5	-	188.5	18.1	29.9	±	34.1
Blood and blood product expenses (TL)		0.0	-	6907.5	664.0	1023.3	±	1191.5
Consulting expenses (TL)		24.1	-	1349.6	132.6	230.9	±	287.1
Patient admission expenses (TL)		113.0	-	113.0	113.0	113.0	±	0.0
Surgical team expenses (TL)		707.1	-	1767.7	1060.6	1108.5	±	245.5
Device depreciation expenses (TL)		29.4	-	72.9	43.9	45.8	±	10.1
Visit Team and other expenses (TL)		216.8	-	18,859.9	1517.5	2642.5	±	3593.8
Patient meal expenses (TL)		30.3	-	2636.1	212.1	369.4	±	502.3
Companion expenditures (TL)		0.0	-	374.6	20.1	66.9	±	92.7
Total cost (TL)		**9924**	**-**	**82,767**	**19,961**	**24,005**	**±**	**14,094**
Invoice amount (TL)		**7687**	**-**	**109,005**	**17,423**	**21,490**	**±**	**16,301**

SD: standard deviation, min: minute, TL: Turkish lira

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Table 2. Comparison of septic and aseptic revision knee arthroplasty data

Comparison of septic and aseptic revision knee arthroplasty data											
		Aseptic				Septic				p	
		Mean ± SD (n, %)			Median	Mean ± SD (n, %)			Median		
Age		67.9	±	7.6	68.0	70.0	±	7.6	71.0	0.485	m
Sex	Female	25		75.8%		12		70.6%		0.693	χ^2
	Male	8		24.2%		5		29.4%			
Surgery time (min)		188.5	±	39.3	180.0	187.4	±	47.1	180.0	0.967	m
Length of stay (days)		16.5	±	27.2	7.0	39.7	±	38.8	29.0	0.000	m
Medical consumption expenses (TL)		14690	±	8659	12564	15402	±	5114	14465	0.108	m
Drug expenditures (TL)		231.6	±	562.5	106.9	1113.3	±	1200.0	658.2	0.000	m
Treatment expenses (TL)		554.1	±	416.0	392.2	1230.7	±	927.7	815.4	0.000	m
Operation. Anesthesia expenses (TL)		1696.1	±	769.2	1479.3	2616.5	±	2022.9	2191.4	0.006	m
Laboratory expenses (TL)		81.9	±	88.3	61.1	189.3	±	167.4	153.0	0.000	m
Imaging expenses (TL)		25.3	±	36.5	12.7	38.8	±	27.5	26.5	0.002	m
Blood and blood product expenses (TL)		675.7	±	707.4	538.0	1697.9	±	1616.7	1044.4	0.000	m
Consulting expenses (TL)		135.8	±	199.4	96.4	415.4	±	343.5	337.4	0.000	m
Patient Admission expenses (TL)		113.0	±	0.0	113.0	113.0	±	0.0	113.0	1.000	m
Surgical team expenses (TL)		1110.8	±	231.8	1060.6	1103.9	±	277.6	1060.6	0.967	m
Device depreciation expenses (TL)		45.9	±	9.5	43.9	45.6	±	11.4	43.9	0.967	m
Visit team and other expenses (TL)		1786.8	±	2951.4	758.7	4303.7	±	4205.9	3143.3	0.000	m
Patient meal expenses (TL)		249.7	±	412.5	106.1	601.5	±	587.9	439.4	0.000	m
Companion expenditures (TL)		51.5	±	80.6	13.4	96.8	±	109.1	93.7	0.130	m
Total cost (TL)		**21,448**	**±**	**13,438**	**18,083**	**28,968**	**±**	**14,406**	**26,236**	**0.001**	**m**
Invoice amount (TL)		**19,282**	**±**	**11,905**	**15,307**	**25,775**	**±**	**22,378**	**19,168**	**0.038**	**m**

[m]Mann-Whitney U test, χ^2Chi-squared test, SD: standard deviation, min: minute, TL: Turkish lira

billing costs in the septic group were significantly higher than the aseptic group ($p<0.05$).

Factors causing infection include obesity, diabetes mellitus, male sex, American Society of Anesthesiologists score of ≥3, diagnosis of osteonecrosis, diagnosis of posttraumatic arthritis, quadriceps-release exposure, and operative time as a risk factor, with a 9% increased risk per 15 minimum increment. High-risk patients should be counseled, and modifiable clinical conditions should be optimized (15).

For long-term survival, total knee prosthesis is required to be aligned in neutral or with a slight anatomic valgus (16). Navigation should be applied to improve the results of TKA in line with the limb and component alignment (17).

Blood loss constitutes a significant cost item for the hospital. To reduce bleeding, techniques, such as skin heating, gentle soft tissue dissection during surgery, use of a new bipolar electrocautery device, use of cardiac stent, and if not contraindicated, discontinuation of anticoagulant drugs, and use of preoperative intra- and postoperative tranexamic acid drugs, can be applied (18,19).

Studies conducted to shorten the length of hospital stay may be an appropriate attempt to reduce the cost of inpatient treatment. Patients undergoing revision TKA for non-septic reasons may be included in fast-track protocols. Outcome seems to be similar to those of primary TKA regarding length of stay, morbidity, and satisfaction (20).

Study Limitations

In the literature, the mean length of hospitalization of revision knee arthroplasty surgeries is reported to be shorter (21). We can explain the longer duration of hospitalization in our study with the lack of adequate home care services after discharge in our country; thus, pain control and rehabilitation process of the patients in the early postoperative period are performed in the hospitals. In addition, the reasons for the longer hospitalization period in patients undergoing septic revision knee surgery include inclusion of two-stage revision arthroplasty surgeries in the study, inclusion of the cost and duration of each step, and process of hospitalization for spacer and spacer revision to the data set of each patient, the use of some antibiotics parenterally administered in two-stage revision surgeries (aztreonam, vancomycin, imipenem, meropenem, linezolid, ertapenem, doripenem, sulbactam,

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kolistimetat, cefuroxime sodium, and daptomycin) being possible only during hospitalization according to the HAN (3), and inability to discharge the patient until antibiotic treatment is completed.

CONCLUSION

As a result, to ensure the financial sustainability of the public hospital in the inpatient treatment of the patients who underwent this surgery, there is a need for the SSI to adjust, such as increasing the HPN prices. In addition, following the medical and technical innovations in revision surgery can help reduce the costs.

Ethics Committee Approval: The study was approved by the Metin Sabancı Baltalimanı Training and Research Hospital Expertise Education Committee in Medicine Observational Research Ethics Committee (approval number: 16.10.2017-16).

Informed Consent: The demographic information were determined through hospital information management system records.

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A Comparison of the Clinical Features and Intraoperative Findings in Cholesteatoma Patients with and without Sinus Tympani Invasion

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ABSTRACT

Objective: The sinus tympani (ST) comprise one of the most hidden areas in the human body. It is one of the most common locations of residual cholesteatomas and is in close proximity with the facial nerve and stapes. These characteristics render ST as a key factor in chronic otitis media surgeries. This study aimed to investigate the clinical features and intraoperative findings of cholesteatoma patients with and without ST invasion (STI).

Methods: One hundred and fifty-one cholesteatoma patients who had undergone the canal wall-down procedure at our center were retrospectively reviewed. They were categorized into two groups: cholesteatoma patients with and without STI. Comparisons were made between the two groups in terms of the disease duration, surgical technique, rate of facial canal dehiscence (FCD), and number of locations of FCD and erosion of the stapes suprastructure. The mean hearing gain of the patients who underwent hearing reconstruction was compared between both groups.

Results: The rates of disease duration >5 years, radical mastoidectomy surgery, and erosion of the stapes suprastructure were significantly higher in patients with STI than in those without STI. Mean hearing gain was significantly higher in patients without STI than in those with STI. The numbers of locations and rate of FCD were also significantly higher in patients with STI than in those without STI.

Conclusion: The presence of STI in cholesteatoma patients is a significant intraoperative finding for the predicting the extent of FCD. STI should serve as a warning to surgeons because it indicates a potential for less functional outcomes due to erosion of the stapes suprastructure.

Keywords: Sinus tympani, cholesteatoma, facial canal, stapes suprastructure

INTRODUCTION

The sinus tympani (ST) are one of the most obscure areas in the human body. It lies medial to the pyramidal eminence, stapedial muscle, and facial nerve and lateral to the vestibule and posterior semicircular canal (1). The ST is clinically important during chronic otitis media surgery because of the risk of cholesteatoma recurrence due to the incomplete removal of the growth from the ST and conductive hearing loss due to its close proximity with the oval window and stapes suprastructure (2,3).The cholesteatoma

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located at the ST may come in contact with the stapes for a longer period with a higher pressure and may lead to erosion of the stapes suprastructure and less favorable functional outcomes.

The close proximity of the ST with the facial nerve makes the nerve more vulnerable during cholesteatoma surgery, especially if dehiscence is present in the bone covering the nerve (4-14). The facial canal dehiscence (FCD) may be caused by developmental bony defects or bony erosion caused by the enzymatic or pressure effect of cholesteatoma located at the ST. An unobserved FCD in the vicinity of the ST may be a risk factor for iatrogenic facial paralysis during the removal of cholesteatoma from the ST.

In this study, we aimed to compare the clinical features and intraoperative findings in cholesteatoma patients with and without ST invasion (STI).

METHODS

The study protocol was approved by the local ethical committee (approval number: E-18-1859, date: 11 April, 2018). Overall, 151 cholesteatoma patients (85 males, 66 females; 15-80 years of age; average age 42.9 years) who had undergone the canal wall-down procedure (CWDP) [51 radical mastoidectomy (RM), 100 modified radical mastoidectomy (MRM)] at our tertiary referral center between January 2010 and December 2017 were retrospectively reviewed. All the patients underwent otoscopic examination and audiometric investigation. Preoperative imaging of the temporal bone was obtained for all the patients and included high-resolution computed tomography (HRCT) or magnetic resonance imaging. The diagnosis of cholesteatoma was confirmed by histopathological examination. The disease duration, type of surgeries, hearing gain, and operation records, including information about the facial canal, STI, and stapes integrity, were documented for all the patients. The patients were categorized into two groups: cholesteatoma with STI and cholesteatoma without STI.

Our main indicators for CWDP were extensive cholesteatoma advancing into the mastoid and beyond, eustachian tube (antero-medial to the ossicles) or ST, extensive damage of the external auditory canal by disease, failure of previous canal wall-up surgery with recurrent cholesteatoma from epitympanic retraction pockets, patients with poor preoperative auditory thresholds, complicated cases, and the patients whose postoperative follow-up constitutes a problem. Patients who had undergone a revision tympanomastoidectomy and those with aural or intracranial complications were excluded from the study.

Intraoperative Findings

FCD observations were made with an operating microscope and confirmed by palpation with a blunt pick. We used the Moody and Lambert (13) classification for describing the FCD location. FCD located at the tympanic segment (TS) of the nerve was divided into three groups: [pure tympanic (PT); directly superior to the oval window], [geniculate ganglion (GG); proximal to the cochleariform process], and [mastoid genu (MG); distal to the oval window]. Combinations of PT, GG, and MG were also calculated. Dehiscence occurring in the mastoid segment of the nerve was noted as mastoid.

To evaluate the extent of cholesteatoma, the posterior canal wall was lowered to the level of the facial ridge. In patients where the cholesteatoma extended into the ST, the cholesteatoma was removed from the ST with a blunt pick and cottonoid.

Ossicular Reconstruction in CWDP

Ossicular chain reconstruction was performed in the presence of an intact and/or mobile stapes and good cochlear function. The integrity of the stapes suprastructure was assessed by the presence or absence of stapes footplates. Footplate mobility was evaluated by eliciting the round window reflex. Temporalis fascia graft was placed under the remnant of the anterior tympanic membrane and over the enlarged inferior canal wall. A small piece of cartilage (conchal) was placed between the fascia graft and stapes head. If the stapes suprastructure was absent and footplate mobile, we used titanium ossicular replacement prosthesis with a cartilage cap and place it between the footplate and temporalis fascia graft.

All the procedures performed were in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants prior to surgery.

All the patients underwent preoperative and postoperative (at 6 months) pure-tone audiometry measurements at 0.5, 1, 2, and 4 kHz and at 3 kHz frequencies using an Interacoustic AC-40 (Middelfart, Denmark) clinical audiometer. The average of the values at 2 and 4 kHz was used to calculate the value for 3 kHz. Preoperative and postoperative air and bone conduction thresholds were measured at these four frequencies. The air-bone gap (ABG) was calculated as the average difference between the air and bone conductions at four frequencies (0.5, 1, 2, and 3 kHz).

Statistical Analysis

The SPSS statistical software (SPSS 21.0 for Windows, Inc., Chicago, IL, USA) was used for data analysis. Quantitative data were presented as mean ± standard deviation or median and interquartile range and categorical variables were presented as percentages. The data was tested for normal distribution using the Kolmogorov-Smirnov test. Student's t-test or Mann-Whitney U tests, as appropriate, were used to compare continuous variables. Chi-square test was used to identify statistically significant differences between categorical variables. A 2-tailed $p<0.05$ was considered significant.

Results

A total of 151 patients (mean age: 36.2±13.2 years) with 151 operated ears (80 left, 71 right) who met the aforementioned criteria were evaluated. The overall STI rate was 41.7% (63 patients).

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The disease duration was ≥5 years in 31 patients (20.5%) and <5 years in the remaining 120 patients (79.5%). STI was observed in 57 of 120 patients (47.5%) with a disease duration ≥5 years and in 6 of 31 patients (19.4%) with a disease duration <5 years. The rate of the disease duration ≥5 years was significantly higher in patients with STI than in those without STI (p=0.005, Table 1).

Overall, 36 of 63 patients (57.1%) with STI and 15 of 88 patients (17%) without STI had undergone RM and this difference was statistically significant (p<0.001, Table 2).

The mean preoperative ABG was 33.3±5.2 dB in patients with STI and 29.2±6.1 dB in those without STI. There was a statistically significant difference between the groups in terms of preoperative ABG (p<0.001). The mean postoperative ABG was 30.8±5.9 dB in patients with STI and 22.6±5.1 dB in patients without STI. There was a statistically significant difference between the groups in terms of postoperative ABG (p<0.001). The mean hearing gain was 2.4±1.1 dB in patients with STI and 6.5±5.8 dB in those without STI and this difference was statistically significant (p<0.001).

The overall FCD rate was 33.8% and FCD was observed in 34 of 63 patients (54%) with STI and 17 of 88 patients (19.3%) without STI. Among the 51 patients with FCD, dehiscence was located at the TS in 47 patients (92%). The locations of dehiscence were as follows: GG, 2 patients (4.2%); PT, 13 patients (27.6%); MG, 4 patients (8.6%); PT+GG, 9 patients (19.2%); PT+MG, 10 patients (21.2%); and GG+PT+MG, 9 patients (19.2%). Overall, 4 patients (8%) had both tympanic and mastoid segment dehiscence. There were at least 2 locations of FCD in 31 of 34 patients (96.9%) with STI and 1 of 17 patients (6.2%) without STI (Figure 1). There was a statistically significant difference between the groups in terms of the number of FCD location (p<0.001, Table 3).

Erosion of the stapes suprastructure was observed in 46 of 63 patients (73%) with STI and in 37 of 88 patients (42%) without STI. There was a statistically significant difference between both groups in terms of erosion of the stapes suprastructure (p<0.001, Table 3).

Discussion

The ST has always been considered as important during cholesteatoma surgery due to its inability to be directly visualized under microscopes and because it is the most common location of residual cholesteatomas (2,3,15,16). The ST also has a critical anatomical proximity with the facial canal, and this proximity obstructs its surgical manipulation, especially when there is an anatomical defect or variation in the canal. The specificity and sensitivity of imaging systems are low for the detection of perioperative FCD (17). Therefore, ear surgeons should be familiar with the pathologies having a high likelihood of observing FCD, especially in cholesteatoma patients. Sometimes, surgeons may reasonably approach the facial nerve path more carefully and even risk the incomplete removal of the cholesteatoma when FCD is intraoperatively observed. FCD had been previously demonstrated to negatively affect surgical outcomes, including suboptimal hearing results and a potential requirement for revision surgery (18).

In our study, 63 of 151 patients (41.7%) had cholesteatoma invading into the ST. The disease duration was ≥5 years in 57 of 63 patients (90.4%) with STI and in 63 of 88 patients (70.1%) without STI. A longer disease duration prior to the surgery may provide insight into the extent of the disease in the ST. Overall, 36 of 63 (57%) with STI and 15 of 88 (17%) without STI had undergone RM. These results indicated that the extent of cholesteatoma into the ST affects a surgeon's choice for RM (p<0.001). The assessment of

Table 1. Disease duration in cholesteatoma patients with and without STI

Disease duration	STI (+) (n=63)	STI (-) (n=88)	Total (n=151)	p
Less than 5 years	6 (9%)	25 (28%)	31 (20%)	0.005*
More than 5 years	57(91%)	63 (72%)	120 (80%)	

N: Number of patients, STI: sinus tympani invasion, *p<0.05

Table 2. Distribution of the type of surgery according to STI

Type of surgery	STI (+) (n=63)	STI (-) (n=88)	Total (n=151)	p
Radical mastoidectomy	36 (57.1%)	15 (17%)	51 (33.7%)	<0.001*
Modified radical mastoidectomy	27 (42.9%)	73 (83%)	100 (66.3%)	

n: Number of patients, STI: sinus tympani invasion, *p<0.05

Table 3. Incidence of facial canal dehiscence and stapes suprastructure erosion according to the groups

	STI (+) (n=63)	STI (-) (n=88)	Total (n=151)	p
Facial canal dehiscence	34 (54%)	17 (19.3%)	51 (33.8%)	<0.001*
One location	3 (3.1%)	16 (93.8%)	19 (37%)	<0.001*
More than one location	31 (96.9%)	1 (6.2%)	32 (63%)	
Stape suprastructure erosion	46 (73%)	37 (42%)	83 (55%)	<0.001*

n: Number of patients, STI: sinus tympani invasion, *p<0.05

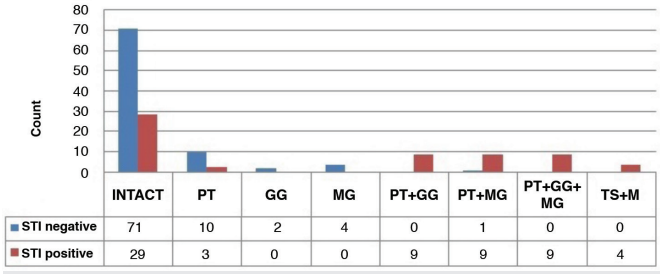

Figure 1. Status of the facial canal and sites of facial canal dehiscence with respect to STI
STI: Sinus tympani invasion, PT: pure tympanic, GG: geniculate ganglion, MG: mastoid genu, TS: tympanic segment, M: mastoid

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ossicular chain defects could explain the tendency of performing RM in patients with STI. We assessed the integrity of the stapes suprastructure according to the proximity of the oval window and stapes with ST. Our results demonstrated that the stapes suprastructure was eroded in 46 patients (73%) with STI and in 37 patients (42%) without STI. The close proximity of the ST with the stapes may cause the cholesteatoma to come in contact with the stapes for a longer period and with a higher pressure. The absence of the stapes suprastructure may complicate ossicular reconstruction.

Postoperative hearing outcomes were found to be better in cholesteatoma patients with the presence of the stapes suprastructure (19). Hence, STI resulting from cholesteatoma should alert surgeons regrading potentially less functional outcomes, and the preoperative evaluation of STI by HRCT may provide insights concerning the integrity of the stapes suprastructure.

FCD may be caused by developmental defects due to failure during the ossification process of the bony canal or bony erosion caused by cholesteatoma and inflammation (20). The mechanism of bony erosion resulting from cholesteatoma has indicated that bony erosion is due to the enzymatic or compression effect of cholesteatoma (21). The rate of dehiscence was reportedly higher (ranging between 55% and 72%) in other anatomical studies (22-24). Yetiser et al. (10) have reported an FCD rate of 11% in non-cholesteatoma patients. Bayazit et al. (20) have reported an FCD rate of 8.9% in non-cholesteatoma patients and 18.4% in cholesteatoma patients, whereas Ozbek et al. (14) have reported this rate at 37.2% in cholesteatoma patients. In the series of Magliulo et al. (17), which comprised 336 patients who had undergone mastoidectomy for cholesteatoma, this rate was reported as 27.1%. Selesnick and Lynn-Macrae (4) reported this rate at 33% during primary surgery and 35% during revision surgery. Moreover, Genc et al. (25) have reported this rate at 32.7% in cholesteatoma patients.

However, no healthy controls were analyzed in our study. The rate of FCD was 33.8%, which is similar to the results of Genc et al. (25) (32.7%) and Selesnick and Lynn-Macrae (4) (33%). The likely cause for this high percentage was that most of the patients included in our study had delayed or extensive disease. Our clinical approach for extensive cholesteatoma is CWDP. By this approach, we could accurately remove pathological growth from the middle ear and evaluate the FCD. The FCD rate was found to be significantly higher (54%) in patients with STI than in patients without STI, possibly due to a longer duration of contact of the cholesteatoma with the bony canal covering the facial nerve in the middle ear. Magliulo et al. (17) found that the risk for FCD was approximately 3.5 times more likely in patients with disease duration □5 years. These findings indicate that the longer pressure and enzymatic effects of the cholesteatoma mass on the bony canal results in a higher incidence of FCD or microdehiscence is enzymatically enlarged by cholesteatoma with time. This theory is supported by the fact that the disease duration was significantly longer in patients with STI than in those without STI.

Hence, we may conclude that the gross dehiscence of the facial canal may be due to prolonged contact with cholesteatoma or enlargement of a microdehiscence resulting from the disease. Conversely, it can be stated that cholesteatoma located at the ST may cause erosion in the adjacent bony structures as it expands. The pressure effect may increase when the cholesteatoma in the ST enlarges. Due to the pressure and enzymatic effects of cholesteatoma in this narrow space, the microdehiscence on the facial canal can be transformed into a macrodehiscence.

Previous studies have demonstrated that the most common location of dehiscence is the TS of the facial canal. Reportedly, FCD was also mainly observed in the tympanic region (92%). When we divided the number of locations of the tympanic dehiscences into three groups, the most common sites of dehiscence were the PT, MG, and GG, respectively. However, only mastoid dehiscence was not observed. The bony canal surrounding the facial nerve in the TS is quite thin; therefore, pathologies in the middle ear, i.e., cholesteatoma, infections, and inflammation, may directly damage the facial canal in these locations. In patients with STI, dehiscence was found at more than one location in 31 patients (96.9%). The number of dehiscence locations was correlated with STI. In patients with STI, dehiscence was observed at PT+GG in 9, PT+MG in 9, PT+GG+MG in 9, and T+M in 4 patients. Hence, we may conclude that cholesteatomas invading the ST were more aggressive and extensive in terms of FCD, and a significant correlation was noted between STI and the extent of dehiscence. It should be kept in mind that the presence of dehiscence at one segment of the facial canal in patients with STI may indicate the presence of additional dehiscence at other regions of the canal.

Study Limitations

There are two limitations to be addressed in this study. Firstly, some personal biases may have crept in during the evaluation of the surgical findings. Secondly, in retrospective studies, some of the records obtained from medical charts may be incomplete or lost in the course of time, leading to missing data. Further prospective studies can provide more reliable and accurate data.

CONCLUSION

FCD may be a challenging issue during cholesteatoma surgery, even for experienced surgeons. Dehiscence is more common in patients when cholesteatoma invades the ST. Our study indicates that FCD is present in more than half of cholesteatoma patients with STI. Hence, for patients in whom STI is intraoperatively observed, their facial nerve is likely at risk. The presence of STI in cholesteatoma patients is a significant finding for the prediction and extent of FCD. Ear surgeons must cautiously evaluate the intraoperative findings that may suggest FCD, such as the presence of STI, especially in patients with extensive cholesteatoma. Hence, the prevention of facial injury should be a priority while operating upon cholesteatoma patients with

STI. STI should serve as a warning to surgeons as it indicates a potential for less functional outcomes due to erosion of the stapes suprastructure in cholesteatoma patients.

Ethics Committee Approval: The study protocol was approved by the local ethical committee (approval number: E-18-1859, date: 11.04.2018).

Informed Consent: Written informed consent was obtained from all individual participants prior to surgery.

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Contribution of Fluorodeoxyglucose-Positron Emission Tomography Late Imaging to Diagnosis and Correlation with Histopathology in Invasive Lobular Breast Cancer

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ABSTRACT

Objective: The aim of this study was to investigate the correlation between primary lesion and contralateral breast tissue metabolic parameters in standard and delayed images obtained on preoperative F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) and the correlation with pathological variables of primary lesion in invasive lobular breast cancer (ILC).

Methods: Seventeen ILC cases in which standard and late FDG-PET imaging were performed between 2007 and 2018 were included in the study. SUV_{max}, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) values and change rates (Δ) of primary malignant lesion and contralateral breast control area were recorded. T and N-stages, histological and nuclear grades of primary malignancy, estrogen receptor (ER), progesterone receptor, presence of human epidermal growth factor receptor (HER)-2 and Ki-67 values are compared with FDG-PET values.

Results: No statistically significant correlation was found between metabolic parameters and histopathological components of 17 ILC patients (median age: 45 years) after surgery (11 breast conserving surgery, 6 mastectomy). Among the metabolic parameters obtained from contralateral breast tissue, SUV_{max}-based ones [standard(s)-SUV_{max}, late(g)-SUV_{max}, ΔSUV_{max}] showed statistically significant differences with malignancy ($p<0.000$).

Conclusion: Especially the negative median value of the control SUV_{max} suggests that late imaging may provide additional contribution, especially in the dense breast tissue, in the ILC with high probability of multifocality/multicentricity. Although there was no statistically significant difference with histopathological components, parallel results (such as high Δ-TLG in presence of lymph node metastasis, HER-2 positive and high SUV_{max}, MTV and TLG median values in ER negative cases) were seen with the literature mostly consisting of invasive ductal carcinoma. Confirmation of this important information obtained only from ILC patients is required in multicentre studies or meta-analyzes in which the number of cases will be higher.

Keywords: FDG-PET, late imaging, metabolic parameter, invasive lobular cancer

INTRODUCTION

Breast cancer is the most common type of cancer in women and ranks second after lung cancer in cancer-related deaths. Early diagnosis, more accurate and intervention-free staging, treatment follow-up and determining prognosis are the most important processes in determining the approach to breast cancer. 50-70% of breast cancers are invasive ductal carcinoma (IDC), 5-15% are invasive lobular cancer (ILC), 1-6% mucinous carcinoma and 1-2% tubular carcinoma (1).

In the diagnosis process, Magnetic resonance imaging is generally the method used especially in dens breast tissue and ILC, although it is required to have more sensitive non-invasive complementary

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methods due to increasing unnecessary biopsy count because of low specificity (72%), limitations in axillary lymph node staging and not being able to screen for distant metastases (2).

Although F-18-fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging has a high sensitivity and specificity in showing malignant lesions, its sensitivity in breast cancer is limited. In meta-analysis, it is reported that the overall sensitivity of FDG-PET in detecting primary breast cancer is 64-96%, specificity 73-100%, positive predictive value 81-100%, negative predictive value 52-89% (3). While the sensitivity of FDG-PET is 57% in tumors smaller than 1 cm in diameter, it exceeds 90% in tumors larger than 1 cm in diameter (4). False positivity can be seen in benign lesions such as fibroadenoma, ductal adenoma and inflammation. However, there are also studies reporting that FDG-PET is better than conventional methods in the initial evaluation of patients, especially enabling the detection of infraclavicular, supraclavicular and internal mammarian lymph nodes and occult distant metastases (5).

Glut-1 and hexokinase expression, number of live tumor cells, histological subgroup, microvascular density and inflammatory cell presence in breast cancer are the major factors affecting FDG involvement (6). The main factors explaining low FDG involvement seen in ILCs are lower tumor cell density, diffuse infiltration in the surrounding tissue, low Glut-1 expression, and low proliferation rate (7). It is known that estrogen and progesterone receptor (PR) negative, HER-2 expression positive tumors show higher FDG involvement compared to receptor positive and HER-2 negative tumors (8).

The clinical systemic contribution of PET is reported to be low due to the low FDG affinity in mucinous (1-6%) and tubular (1-2%) cancers, which occur less frequently with ILC, which constitutes 10-15% of breast cancers (9,10). For these reasons, the contribution of FDG-PET to IDC was mostly evaluated in the studies, and the ILC was found in a limited number of studies or was not included in the study due to low sensitivity (4,11).

The very low density of glucose-6-phosphatase enzyme in the tumor cell causes FDG to continue to accumulate. It is known that late imaging contributes to the diagnosis in malignancies, where the imaging quality will be optimal as much as the radiopharmaceutical half-life allows (12). There are many studies reporting that late image in FDG-PET in breast cancer significantly increases sensitivity and specificity (13-26). However, these studies mostly consist of IDC patients.

As the breast tissue density increases, FDG involvement is higher, and in this case primary lesion visualization has a negative effect on the ILC with low FDG involvement potential. In this retrospective study, it was aimed to investigate the contribution of metabolic parameters obtained from primary lesion and contralateral breast tissue and late images taken in preoperative FDG-PET in the ILC, where clinical diagnosis and staging of breast cancer is particularly difficult, to predict diagnosis and also the correlation of histopathological variables with primary lesion.

METHODS

Seventeen patients diagnosed with ILC applied to the nuclear medicine, molecular imaging and radionuclide treatment department for staging in purpose of FDG-PET test between 2007 and 2018, who underwent surgery for breast and axilla within 5-30 days after FDG-PET were included in the study. 50-70 minimum after 5-9 mCi FDG given intravenously, standard 7-9 bed length and between vertex and mid-crus and; 160-200 minimum later, late imaging of 2 bed areas covering the neck and thorax regions made with GE Discovery IQ-5 ring and GE Discovery 710 PET/computed tomography devices. The images were evaluated with the PETVCAR program at GE AW workstation. Metabolic tumor volume (s-MTV, g-MTV) and total lesion glycolysis (s-TLG, g-TLG) semicantitative tissue analysis values and exchange rates (Δ=late draft value-standard draft value/standard draft value x100) calculated from the area of interest drawn according to the relative threshold of 40% and above of SUV_{max} were recorded with primary malignant lesion SUV_{max} [standart(s)-SUV_{max}, late(g)-SUV_{max}] values. In the presence of multifocal/multicentric malignancy, the lesion with the highest SUV_{max} was included in the study. As the control group, the same semi-quantitative tissue analysis values and change rates were obtained from the area of mirror image in the opposite breast parenchyma. T and N-stages of primary malignancy, histological and nuclear grades, estrogen receptor (ER), PR, presence of human epidermal growth factor receptor (HER)-2 and Ki-67 values obtained from pathology of mastectomy (6 patients) or breast-conserving surgery (11 patients) are evaluated with semi-quantitative tissue analysis results obtained from FDG-PET. The presence of the estrogen or PR (1% and above) was considered as receptor positivity. The fact that Ki-67 was 14% and above was classified as a high proliferation index. HER-2 overexpression was evaluated as immunohistochemically positive, and HER-2 amplification was detected by fluorescent in-situ hybridization method in cases with 0/1+ immunohistochemistry.

Statistical Analysis

Since the data did not conform to the normal distribution, given as median and interval, in the dependent variable analysis (between the patient and healthy breast) Wilcoxon sign order test is used; Mann-Whitney U test was used only as an independent variable analysis for comparing the patient group within itself. $P<0.05$ was accepted as the statistical significance limit.

The primary outcome measure of the study is to investigate whether late imaging FDG involvement in the ILC contributes to the diagnosis prediction; secondary outcome measure is the relationship of FDG involvement amount with metastasis and histopathological variables (histological and nuclear grade, ER, PR and HER-2 presence, Ki-67).

Ethical Approval and Informed Consent

The study was conducted in accordance with the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013) and the authors declared that the study was carried out with ethical principles in accordance with the Helsinki Declaration. Patient consent could not be obtained due to the retrospective study structure.

RESULTS

Demographic features and histopathological characteristics of 17 patients included in the study, which were undergo surgery with the diagnosis of ILC, are presented in Table 1. After median 32 days (30±28 days), breast protecting surgery was performed in 11 patients (76%) and mastectomy (24%) in 6 patients. Ten of the cases are pT1, 6 of them are pT2, and only 1 patient is pT3.

The comparison of the primary malignancy and control tissue analysis values of the cases obtained in FDG-PET is given in Table 2. Accordingly, a significant difference was observed in the values obtained from the control interest area with malignancy in the SUV_{max} based values of s-SUV_{max}, g-SUV_{max} and Δ-SUV_{max}. In addition, the negative rate of median change in the control group in Δ-SUV_{max} and Δ-TLG indicates that the difference in involvement between the non-malignant breast parenchyma and malignancy has increased in the late image (Figure 1).

Of the 7 cases with lymph node metastasis, the patient with the highest SUV_{max} value in the group, metastatic lymph node was visualized in the late image and the primary malignancy Δ-SUV_{max}value was 62 (Figure 2).

DISCUSSION

Diagnosis of ILC and staging distant metastasis with lymph node after diagnosis is one of the most clinically difficult malignancies. The most important reasons for this are the fact that the tumor is seen as a tissue thickening rather than a mass formation due to the fact that it does not cause a stromal reaction and rarely observed microcalcification, which is the most important clinical finding in early diagnosis (27-29).

It is known that invasive triple negative tumors (TNT) in breast cancer have higher FDG affinity than non-TNTs (30) and grad 3 tumors have higher FDG affinity compared to grade 1-2 tumors (31). In addition, as well as tumor histopathology, microvascularization and hypoxia level affect FDG-PET radiopharmaceutical affinity (32).

There are many factors such as low tumor cell density, diffuse infiltration in the surrounding tissue, low Glut-1 expression, and low proliferation rate, explaining the low FDG involvement of FDG-PET in ILCs.

Many different metabolic parameters such as SUV, MTV, TLG have been used to increase sensitivity and specificity in breast tumors.

Table 1. Demographic characteristics and histopathological characteristics of invasive lobular cancer cases (n=17)

Age - year	
Median (range)	45 (35-62)
T-stage (n, %)	
T1	10 (59)
T2	6 (35)
T3	1 (6)
N-stage (n, %)	
N0	10 (59)
N1	7 (47)
ER (n, %)	
+	10 (59)
-	7 (41)
PR (n, %)	
+	10 (59)
-	7 (41)
Nuclear grade (n, %)	
1	5 (29)
2	8 (47)
3	4 (24)
Histological grade (n, %)	
1	5 (29)
2	8 (47)
3	4 (24)
HER-2 (n, %)	
+	9 (53)
-	8 (47)
Ki-67 (n, %)	
High (≥14)	11 (65)
Low (<14)	6 (35)

ER: Estrogen receptor, PR: progesterone receptor, HER: human epidermal growth factor receptor

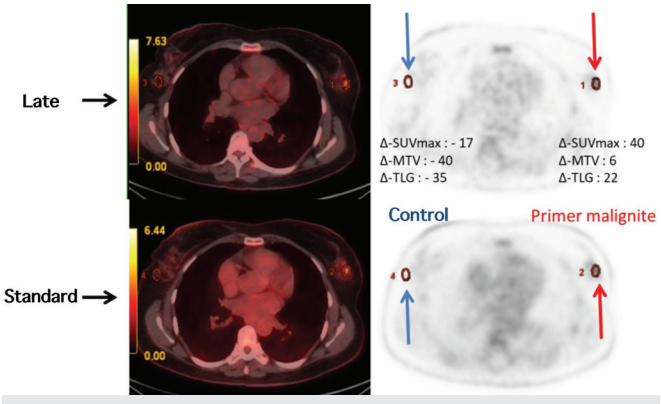

Figure 1. Fluorodeoxyglucose-positron emission tomography standard and late images; Left breast lower-inner quadrant invasive lobular cancer interest (red arrow) and contralateral breast same quadrant interest (blue arrow)
MTV: Metabolic tumor volume, TLG: total lesion glycolysis

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The majority of cases are more common IDC in nearly all of the researches. In 6 studies investigating the contribution of late imaging with FDG-PET in breast cancer, the first bibliography of 2/56, 3/66, 13/86, 2/53, 8/48 and 2/38, respectively, was included in the studies and the rate was only 9% (30/347) (18-20, 24-26). There is no study of ILC cases.

The correlation of tumor heterogeneity with aggressive malignancy has been demonstrated in many tumors. In the study of Garcia-Vicente et al. (19), it was predicted that increase in heterogeneity in late images may provide more meaningful prognostic information (18). In our study, Δ-TLG value to be 50 (median: 9) in our 2 cases who had lymph node metastasis is a finding that supports this.

Caprio et al. (26) shared that D-SUV_{max}, obtained by late imaging of FDG-PET in 8-ILC, 40-IDC and 11 benign breast lesions, increased significantly in malignancy and decreased significantly in benign lesions (25). In cases with local recurrence and distant metastasis, 13 of them were ILC and 86 of them were invasive breast cancer, Hildebrandt et al. (21) reported that more malignancy could be detected by decreasing background activity in late images (20).

Breast density can vary widely with age and weight. The higher FDG involvement in the dens breast tissue is a reason that reduces sensitivity in the ILC, which can show low FDG affinity. In our study, the control Δ-SUV_{max} median value obtained from the contralateral breast tissue is -10. In our study, in which Δ-SUV_{max} (median: 53) was significantly different in ILC, it was thought that late imaging may contribute additionally to the visualization of the ILC, which has a high probability of multifocality/multicentricity, especially in the dense breast tissue.

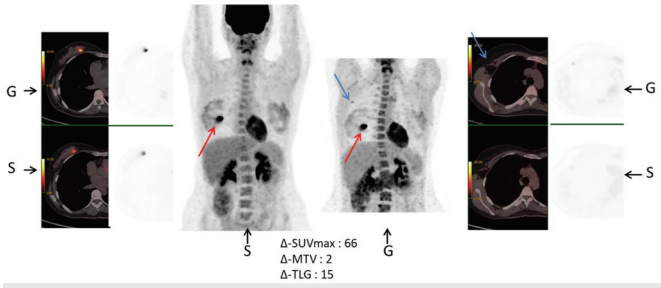

Figure 2. Fluorodeoxyglucose (FDG)-positron emission tomography standard (S) and late (G) images; Right breast lower-inner quadrant invasive lobular cancer (red arrow), FDG involvement in late image visualized in the right central axillary metastatic lymph node (blue arrow)
MTV: Metabolic tumor volume, TLG: total lesion glycolysis

Garcia-Vicente et al. (19) reported no additional contributions in the group where they assessed late imaging in 66 invasive breast cancers, of which only 3 cases were the ILC.

In the study that Sasada et al. (22) evaluated a total of 1122 invasive breast cancers, 30 of which were ILC, in late imaging, the value we defined as Δ in our study is expressed as retention index (RI). Although there was no significant difference in our study, SUV_{max} in the HER-2 positive group is higher than the group where MTV and TLG median values were negative (Table 2).

In the study investigating the contribution of late imaging in 53 invasive breast cancers where only 2 cases were ILC, it was reported that there was low ER positivity and high HER-2 expression in the group with high RI (24). In our study, it was shared in Table 3 that the ER negative cases were more significant in the SUV_{max} and the SUV_{max}, MTV and TLG median values were higher than the positive group.

In a study of Lee et al. (27), late imaging showed more significant correlation with prognostic factors in 38 invasive breast cancer cases, 2 of which were ILC. A similar correlation has been reported even when the late image was taken earlier (100 minimum) (26). This result will shorten the total examination period and can be taken into consideration in the next studies. In this low-incidence patient group, it is also possible to explain the lack of a statistically significant correlation between primary malignancy tissue analysis values and histopathological variables, since we did not have enough cases to reach statistical significance in our study.

CONCLUSION

In our study, it is foreseen that in the ILC, which has low FDG-PET sensitivity, the information obtained from the contralateral breast parenchyma and especially lateral image in the dorsal breast tissue, will contribute significantly. No statistically significant correlation was found with histopathological variables. However, parallel results were observed when compared to studies mostly composed of IDC patients. Δ-TLG is high in the group with lymph node metastasis; in HER-2 positive and ER negative cases, SUV_{max}, MTV and TLG median values are higher than HER-2 negative and ER positive groups. This important information needs to be confirmed by meta-analyzes or multicentre studies where the number of cases will be higher.

Tablo 2. Primer malignite ve kontrol ilgi alanının metabolik parametreleri ve değişim oranları

Average (range)	s-SUV_{max}	g-SUV_{max}	Δ-SUV_{max}	s-MTV	g-MTV	Δ-MTV	s-TLG	g-TLG	Δ-TLG
Primary malignancy	5.11* (21.58)	7.59 (36.10)	49 (33)	4.74 (17.18)	4.70 (16.69)	-1 (70)	9.56 (33.08)	10.71 (21.31)	1 (11)
Control	1.04 (1.79)	0.93 (4.01)	-11 (9.51)	2.40 (2.95)	2.24 (2.66)	-1 (66)	3.88 (1.31)	3.06 (2.30)	-2 (16)
p	<0.000**	<0.000	<0.000	0.36	0.83	0.36	0.049	0.04	0.06

*Values are given as median (range), ** p<0.05 was accepted as the statistical significance limit, MTV: metabolic tumor volume, TLG: total lesion glycolysis

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Tablo 3. Semikantitatif doku analiz değerleri ile histopatolojik değişkenler arasındaki ilişki

Δ-TLG	16 (123) 8 (152)	12 (123) 9 (152)	8 (122) 12 (123)	18 (152) 10 (123)	29 (39) 9 (111) 18 (152)	15 (39) 23 (199) -5 (40)	9 (152) 16 (123)	19 (76) 8 (199)
g-TLG	10.81 (41.11) 7.16 (19.16)	8.41 (41.11) 7.50 (13.47)	8.89 (11.97) 7.33 (42.26)	4.55 (12.26) 7.50 (41.11)	5.60 (3.80) 11.96 (41.11) 3.29 (32.27)	6.26 (5.96) 11.96 (42.38) 8.02 (32.14)	7.16 (19.16) 11.60 (41.11)	5.02 (12.13) 10.42 (42.38)
s-TLG	8.84 (9.21) 6.86 (19.92)	8.45 (29.21) 6.86 (12.43)	8.25 (11.57) 7.49 (30.66)	4.27 (9.52) 8.13 (29.21)	4.68 (4.36) 9.56 (26.41) 2.48 (28.48)	5.70 (5.63) 9.56 (30.92) 8.51 (28.22)	6.86 (19.92) 10.30 (29.21)	4.55 (9.26) 10.19 (30.92)
Δ-MTV	2 (172) -12 (102)	4 (172) -12 (102)	13 (50) -5 (172)	7 (103) -1 (172)	-14 (3) 1 (107) 14 (138)	-2 (29) 1 (172) -13 (68)	-1 (103) 4 (172)	2 (138) 1 (137)
g-MTV	3.57 (17.03) 1.65 (17.79)	3.67 (17.19) 1.36 (6.98)	6.55 (6.98) 2.17 (17.19)	3.17 (6.98) 2.69 (17.19)	2.68 (2.64) 4.65 (17.19) 1.56 (17.63)	3.34 (3.29) 1.58 (17.79) 4.33 (16.64)	2.69 (17.79) 3.11 (17.03)	2.69 (4.31) 3.56 (17.79)
s-MTV	4.52 (14.46) 2.70 (14.80)	4.52 (14.46) 2.15 (6.21)	6.23 (6.56) 3.51 (14.46)	3.69 (6.21) 4.32 (14.46)	3.08 (2.95) 4.72 (13.84) 13.93 (138.44)	3.34 (2.95) 4.72 (14.80)-13.10 (67.91)	2.70 (14.80) 4.52 (14.46)	2.37 (4.38) 5.06 (15.29)
Δ-SUV_{max}	53 (108) 49 (43)	49 (108) 57 (43)	57 (23) 49 (108)	48 (35) 49 (108)	48 (43) 49 (96) 53 (59)	43 (43) 57 (90) 36 (55)	49 (47) 54 (108)	49 (43) 53 (108)
g-SUV_{max}	5.93 (34.90) 3.93 (5.49)	5.93 (9.24) 3.99 (36.10)	4.35 (4.28) 4.40 (35.57)	3.81 (1.76) 4.99 (35.57)	4.24 (0.62) 6.87 (35.57) 4.13 (9.77)	4.77 (4.08) 4.02 (36.10) 6.21 (8.72)	4.02 (5.49) 9.91 (34.90)	4.25 (4.37) 5.61 (36.10)
s-SUV_{max}	4.16 (21.52)* 2.69 (4.21)	4.16 (9.14) 2.85 (21.58)	3.24 (2.71) 2.99 (21.52)	2.50 (1.59) 3.96 (21.52)	2.90 (0.43) 4.36 (21.52) 2.59 (9.20)	3.54 (2.33) 2.85 (21.58) 4.54 (8.70)	2.85 (4.21) 6.99 (21.52)	2.86 (2.87) 3.80 (21.58)
Patients (n)	**T-stage**	**N-stage**	**ER**	**PR**	**Nuclear grade**	**Histological grade**	**HER-2**	**Ki-67**
	T1 (10) T2-T3 (7)	N0 (10) N1 (7)	- (3) + (14)	- (4) + (13)	1 (2) 2 (9) 3 (6)	1 (4) 2 (9) 3 (4)	- (11) + (6)	<14 (7) ≥14 (10)

*Values are given as median (range) and no difference p <0.05 has been detected, MTV: metabolic tumor volume, TLG: total lesion glycolysis

Ethics Committee Approval: Retrospective study.

Informed Consent: Patient consent could not be obtained due to the retrospective study structure.

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The Effects of HPV Test on Anxiety, Emotion and Depression in Women

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ABSTRACT

Objective: Human papillomavirus (HPV) test is an important health screening test included in most national screening programs covering millions of women worldwide. HPV is a sexually transmitted virus, which may cause anxiety and depression in women. This study aimed at comparing the anxiety levels using a Hamilton Anxiety Rating scale and the depression levels using a Beck Depression Inventory between women who tested positive for HPV and those who tested negative.

Methods: Three hundred women who underwent HPV testing between 01.08.2017-01.11.2017 were randomly selected. The subjects were scored on the Beck Depression Inventory and Hamilton Anxiety Rating scale by the investigator through a face-to-face interview.

Results: No statistically significant differences were observed between 187 HPV (+) and 113 HPV (–) patients with respect to the depression and anxiety scores (p=0.183 and p=0.306, respectively). While a weak negative but significant correlation was found between the time from the HPV test report date and the anxiety scores, a moderate, negative correlation was observed between the length of this time period and the depression scores. Furthermore, strong negative correlations were observed between the times elapsed from the diagnosis and the anxiety and depression scores in patients who received their results at a family health center.

Conclusion: The most serious impact of getting a positive test result for HPV occurred during relatively earlier periods and in those who received their results at a family health center. Unwanted HPV-related effects may be prevented by giving appropriate support to the right population at the very beginning.

Keywords: HPV, anxiety, depression

INTRODUCTION

Cervical cancer is one of the prominent malignancies of female genital tract. Although the importance of smear tests is surely incontestable, the importance and value of Human papillomavirus (HPV) screenings are also gradually increasing. Currently, HPV screening and vaccination programs are running in many countries (1-6).

Overall, testing positive for HPV is considered to have mental, physical, familial, or even social consequences on women. However, these consequences have been investigated by only a limited number of studies so far.

Although underestimated, several previous studies have emphasized the importance of psychosocial impact of HPV tests and the need for further studies. As mentioned earlier, cervical

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cancer screenings are included in most national programs worldwide, and the significance of HPV tests for public health has been strongly emphasized (7).

A positive HPV test may cause fear, anxiety, stress, and sexual dysfunction, as well as raise accusations and questions about trust in relationships (8-11). Women who have tested positive for HPV may feel stigmatized and experience a feeling of guilt, sadness, and shame while indulging in sexual act (7,9,11,12). Moreover, experiencing troubles with explanations, disclosures, and trust in relationships may eventually increase anxiety (9). Also, the association between adequate public awareness of HPV and cervical cancer have not been fully understood (13-15).

Reports from several studies have indicated that initially, a positive HPV test is more likely to bring psychological problems than an abnormal smear result (7,11); this is because unlike women who have an abnormal Pap smear result, HPV (+) women are more prone to feel stigmatized and shame (16).

Finally, the approach to an HPV (+) woman should differ from that to a woman with an abnormal smear test result. In our country, an HPV test has a widespread use and is included in routine screening programs. Therefore, we believe that it is pertinent to increase the public understanding of the effects of this test on women and appropriate approaches to this issue.

In this study, we aimed at assessing the effects of testing positive for HPV on anxiety, mood, and depression in women.

METHODS

This cross-sectional and observational study included women who were directly referred to the Outpatient Clinics of Obstetrics and Gynecology of our hospital for an HPV testing and the HPV (+) women referred from other health centers during the study period (1 August, 2017 to 11 November, 2017).

A total of 187 HPV (+) women, aged 20-70 years, who met the inclusion criteria were included in the study group, while 113 HPV (–) aged-matched women were included in the control group. The exclusion criteria of the study included chronic diseases, the use of medicines that might affect the mood including antidepressants, antipsychotics, and sedatives, alcohol and/or any chemical substance addiction, and any other conditions that might lead to sexual dysfunction including vaginal stenosis, vagina dryness, active vaginitis, vaginismus, hymenal stenosis, and vagina atrophy.

Furthermore, the study data were collected by the investigator through face-to-face interviews conducted between 1 August, 2017 and 11 November, 2017. All subjects in both the study and control groups completed two psychiatric questionnaires including the Beck Depression Inventory and the Hamilton Anxiety Rating scale.

While the dependent variables in this study consisted of anxiety and depression in HPV (+) subjects, the independent variables included sociodemographic and biodemographic characteristics (such as age, educational attainment, income level, occupational status, number of children) and time from HPV test report date.

The study protocol was submitted to the Institutional Review Board and ethics approval was obtained on July 25, 2017 [Institutional Review Board (approval number: 2017/514/111/6)]. A written informed consent form was obtained from all patients prior to the study.

Statistical Analysis

Data were analyzed using the SPSS software version 17.0. The normality of the variables was assessed using histogram graphics and the Kolmogorov-Smirnov test. The descriptive statistics included means, standard deviation, minimum, and maximum. Moreover, the 2×2 contingency Pearson's chi-square and Fisher's exact tests were used for the comparisons. Additionally, while the Mann-Whitney U test was used for the comparisons of non-normally distributed (non-parametric) data between two groups, the Kruskal-Wallis test was used to compare more than two groups. Besides, the Spearman's Correlation test was used for intergroup comparisons of numerical data. A p-value <0.05 was considered as statistically significant.

RESULTS

Of the 300 studied subjects, 35.67% were elementary school graduates, 77% were married, 49% were unemployed, and 48.33% had a monthly income ranging from 1,500 to 4,500 TL. The mean age of the participants was 42.19±9.29 years and the mean number of children per subject was 1.98±1.27.

Interestingly, the analysis of the demographic characteristics by HPV results did not reveal any statistically significant associations between HPV results and age, educational attainment, marital status, number of children, income level, Beck Depression Inventory, and Hamilton Anxiety Rating scale scores (p>0.05).

In addition, no statistically significant associations were observed between the analysis of Beck Depression Inventory and Hamilton Anxiety Rating scale scores by HPV results (p>0.05).

Moreover, the analysis of the distribution of demographic characteristics by HPV results indicated that the rates of HPV (+) subjects were higher among employees (58.33%), unemployed women (53.74%), and pensioners (60%) than in students (0%) (p:0.009) (Table 1).

The analysis of the mean age, number of children, and Beck Depression Inventory and Hamilton Anxiety Rating scale scores by the HPV results revealed that Beck Depression Inventory scores were lower in HPV (–) subjects (11.93±8.86) compared to the HPV (+) subjects (14.13±9.08) (p=0.029) (Table 2).

Further, the analysis of age, educational attainment, number of children, income level, Beck Depression Inventory and Hamilton Anxiety Rating scale scores by the time from HPV testing revealed a very weak significant negative correlation (r= -0.167) between the time from HPV testing and Hamilton Anxiety Rating scale

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scores (p=0.004). However, no significant correlation was found between the duration of HPV infection and the mean age, educational attainment, number of children, income level, and Beck Depression Inventory scores (p>0.05).

The analysis of Beck Depression Inventory and Hamilton Anxiety Rating scale scores by the time from HPV testing in HPV (+) patients revealed significant correlations between the time from HPV testing and the Beck Depression Inventory and Hamilton Anxiety Rating scale scores: a statistically significant moderate negative correlation was found between the time from HPV test report date and the Beck Depression Inventory scores in HPV (+) patients (r= -0.404) (p<0.01), as well as between the time from HPV test report date and the Hamilton Anxiety Rating scale scores in HPV (+) patients (r= -0.436) (p<0.01).

Table 1. Demographic characteristics of patients according to the human papillomavirus results

		HPV result						p
		Positive		Negative		Positive at family health center		
		n	%	n	%	n	%	
Age	<40	73	(58.40)	40	(32.00)	12	(9.60)	0.059
	>40	95	(54.29)	73	(41.71)	7	(4.00)	
Education	Illiterate	5	(83.33)	1	(16.67)	0	(0.00)	0.820
	Primary school	58	(54.21)	39	(36.45)	10	(9.35)	
	Middle school	31	(55.36)	22	(39.29)	3	(5.36)	
	High school	41	(56.94)	28	(38.89)	3	(4.17)	
	University and above	33	(55.93)	23	(38.98)	3	(5.08)	
Marital status	Married	122	(52.81)	95	(41.13)	14	(6.06)	0.260
	Single	11	(64.71)	5	(29.41)	1	(5.88)	
	Widow	35	(67.31)	13	(25.00)	4	(7.69)	
Job	Working	77	(58.33)	48	(36.36)	7	(5.30)	0.009
	Not working	79	(53.74)	57	(38.78)	11	(7.48)	
	Retired	12	(60.00)	8	(40.00)	0	(0.00)	
	Student	0	(0.00)	0	(0.00)	1	(100.00)	
Number of children	2 and less	119	(57.77)	77	(37.38)	10	(4.85)	0.266
	3 and more	49	(52.13)	36	(38.30)	9	(9.57)	
Beck1	Normal	62	(52.10)	49	(41.18)	8	(6.72)	0.244
	Mild	56	(53.85)	43	(41.35)	5	(4.81)	
	Moderate	36	(63.16)	15	(26.32)	6	(10.53)	
	Severe	14	(70.00)	6	(30.00)	0	(0.00)	
Beck2	No depression	62	(52.10)	49	(41.18)	8	(6.72)	0.541
	There is depression	106	(58.56)	64	(35.36)	11	(6.08)	
Hamilton1	None	29	(48.33)	27	(45.00)	4	(6.67)	0.325
	Minor	84	(57.93)	49	(33.79)	12	(8.28)	
	Major	55	(57.89)	37	(38.95)	3	(3.16)	
Hamilton2	No anxiety	29	(48.33)	27	(45.00)	4	(6.67)	0.392
	There is anxiety	139	(57.92)	86	(35.83)	15	(6.25)	

HPV: Human papillomavirus

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Table 2. Average of age, number of children, Beck and Hamilton values according to the human papillomavirus result

	HPV result				p
	Negative		Positive		
	Average	± SD	Average	± SD	
Age	42.41	±9.39	42.06	±9.25	0.469
Number of children	2.02	±1.21	1.96	±1.30	0.596
Beck	11.93	±8.86	14.13	±9.08	0.029
Hamilton	12.27	±8.17	11.97	±7.40	0.991

HPV: Human papillomavirus, SD: standard deviation

The correlation analysis of the Beck Depression Inventory and Hamilton Anxiety Rating scale scores by the time from HPV testing in HPV (+) subjects who underwent an HPV testing at the Family Health Center (FHC) revealed a significant correlation between the time from HPV test report date and the Beck Depression Inventory and Hamilton Anxiety Rating scale scores. However, in patients who underwent HPV testing at the FHC, a strong negative correlation was found between the time from HPV test report date and the Beck Depression Inventory ($r= -0.611$) ($p<0.01$), as well as between the time from HPV test report date and the Hamilton Anxiety Rating scale scores ($r= -0.436$) ($p<0.01$).

DISCUSSION

In the present study, the states of depression and anxiety was assessed in a total of 300 subjects, including 187 HPV (+) women and 113 HPV (–) women. Moreover, no statistically significant differences were found between the HPV (+) and (–) women with respect to their depression and anxiety scores ($p=0.183$, $p=0.306$, respectively). Although the difference did not reach the level of significance, the higher numerical values detected in all HPV (+) groups in comparison to the HPV (–) groups were remarkable. While 73% of the subjects who scored in the moderate range and 70% who scored in the severe range on the Beck Depression Inventory were in the HPV (+) group, 66% of the subjects who scored in the minor anxiety range and 61% who scored in the major anxiety range on the Hamilton Anxiety Rating scale were in the HPV (+) group.

Moreover, the analysis of the depression scores by the age and number of children revealed significantly lower scores in the HPV (–) group in comparison to the HPV (+) group ($p=0.029$).

The time interval between the HPV test report date and the assessment date has been considered important in this patient group, as these patients may experience an acute anxiety and stress when they get test results. The fear of cancer may cause a tendency to undergo interventional procedures, colposcopic examinations, and biopsies in these patients, and they may even force their physician to perform these procedures. As a result, even the unnecessary interventions, and tissue sampling procedures may be performed.

A literature search revealed evidence from several studies indicating that the level of stress might be significantly increased initially after getting a positive HPV test result. Quantitative studies support that a positive HPV test is more likely to bring psychological load than an abnormal smear result and that this effect may lessen over time (17). In our study, the subjects were assessed at five different time intervals; "the first two weeks," "week 2 to week 4," "month 1 to month 3," "month 6 to month 12," and "after month 12." The assessment of anxiety and depression scores pointed out a negative, week but significant correlation between anxiety scores and the time from the HPV test report date. In other words, initial anxiety scores were significantly higher after getting a positive HPV test result. The assessment of depression scores by the same time intervals revealed a negative, moderate, significant correlation between the time from the positive HPV test report date and depression scores. In other words, initial depression scores were significantly higher after getting a positive HPV test result.

Furthermore, HPV positivity is typically associated with increased anxiety and depression scores, and intense fear and anxiety especially in the early period. This increasing fear and anxiety decreases with the help of researches, medical examinations, interviews, and explanations.

Another point to consider in this patient group is the site where the diagnosis was made. In our country, cervical HPV screening programs are performed by FHCs. All women over the age of 30 years are covered by routine screening programs and may undergo HPV testing. Test results are revealed to patients for the first time at FHCs. While women who test negative for HPV are not referred to other centers, those who test positive are referred to gynecologic oncology outpatient clinics at tertiary healthcare facilities. After getting a positive test result, patients are advised to contact a reference center. Negative interactions may be minimized if during this process, patients receive correct, and adequate information from a specialist in this field.

In this study, a strong negative correlation was also found between the test report date and anxiety and depression scores in subjects who were tested for HPV at an FHC. This finding might have resulted from inadequate information provided to the patients at FHCs as well as the inclusion of the

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patients from FHCs in the study in earlier periods after getting a positive test result.

In a study conducted in the United Kingdom in 2007, Waller et al. (18) informed 811 undergraduates about HPV and asked them to imagine themselves as being tested positive for HPV. Subsequently, they were asked about the levels of stigma, shame, and anxiety that they would experience. It was found that the awareness of high prevalence of HPV may reduce negative feelings and also anxiety, in general. They concluded that raising awareness of high prevalence of HPV through public health messages may alleviate negative psychosocial consequences (18).

In another study investigating the social and psychological consequences of HPV testing, McCaffery et al. (9) emphasized that the effects of abnormal smear tests had been adequately investigated until then, however, as a sexually transmitted disease, HPV might lead to anxiety and distress in addition to these negative effects. In particular, due fear of disclosure, patients experience difficulty explaining the situation to their spouse or even to their own family (9).

A sensitive approach is important even when informing patients about their positive HPV results to protect them from exposure to negative psychological effects. Kahn et al. (12) made recommendations on how to approach a patient at the time of HPV test result release. They recommended that correct information should be given in a sensitive and non-judgmental manner, and stated that an educational protocol might help women to understand HPV and its consequences. They emphasized that unwanted psychosocial consequences might be minimized by promoting health-improving behaviors, safe sexual habits, and regular cervical screening in adolescent girls (12).

Initially, a significant increase is observed in the anxiety and depression scores in patients who test positive for HPV. However, over time, these increased scores return to their normal levels.

We believe that patients can overcome these critical early periods of time with minimal negative impact if social factors are considered and correct and thorough information is provided at the very beginning with due diligence and a sensitive approach that would alleviate their fear.

In order to reduce depression and anxiety, it would be appropriate for the specialist obstetricians, psychologists, and psychiatrists to provide explanations and psychological support to patients.

CONCLUSION

When women first learn about their HPV carrier status, a significant increase in their anxiety and depression scores is observed at the beginning; however, this impact lessens over time. An appropriate support during this period is pertinent to protect patients from psychosocial traumas.

Ethics Committee Approval: The study protocol was submitted to the (institutional review board and ethics approval was obtained on July 25, 2017 (institutional review board approval number: 2017/514/111/6).

Informed Consent: A written informed consent form was obtained from all patients prior to the study.

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Assessment of Speech Intelligibility in Free-field Sound Chamber at Different Signal Noise Ratios

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ABSTRACT

Objective: In the presence of background noise, understanding speech is challenging for any listener, especially for those with serious hearing loss. This study aimed to determine speech intelligibility of normal-hearing adults in quiet and noisy free fields.

Methods: This study included 77 volunteers with normal hearing aged between 18 and 30 years (mean: 22.25±2.7 years). Speech intelligibility scores were determined using the non-adaptive method at different signal-to-noise ratios (SNRs) and changing the noise direction (front and rear).

Results: The mean ± standard deviation of the adaptive matrix speech reception threshold in quiet for 50% intelligibility was 22.69±3 dB sound pressure level. Speech intelligibility scores obtained at -10, -5, and 0 dB SNRs were significantly different when the noise was presented from the front to rear direction ($p<0.05$). Better speech intelligibility scores were obtained when noise was presented from the rear.

Conclusion: The standard audiometric test battery does not measure speech intelligibility in noisy environments. Therefore, speech intelligibility in the noise test developed and normalized in the native language of the patient should be used in the evaluation. Because our study was conducted in free field, the results could be used in the evaluation of patients using cochlear implants and hearing aids in free field.

Keywords: Speech audiometry, speech intelligibility in noise, signal-to-noise ratio, speech reception threshold, Turkish matrix sentence test

INTRODUCTION

Better speech perception is essential to improve communication. Understanding speech in the presence of background noise is challenging for any listener, especially for those with serious hearing loss. In our daily life, our environments are often noisy. The most common complaint by normal individuals and patients with hearing loss is the difficulty in understanding speech in noisy environments.

Most speech audiometry tests evaluate the performance of the listener in a quiet environment. However, the signal-to-noise ratio (SNR) and speech perception performance in background noise are of paramount importance because individuals have to understand speech in the presence of other signals found in their natural environments. Hence, speech-in-noise tests were developed. Speech-in-noise tests are also useful for adjusting classroom acoustics, setting hearing aids, hearing screening, and in the field of telecommunications (1).

Monosyllabic/polysyllabic words or phrases may be used as the test material in speech tests. Although the use of words offers the advantage of testing speech in an isolated way, the use of materials, such as long sentences, offers the advantage of testing more than one word at a time. Therefore, the use of sentences as the material is more efficient in a speech discrimination

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performance assessment (2). The use of sentences also means that the test better reflects communication in daily life. The matrix test was first prepared in Swedish by Hagerman (3). In 1999, Wagener et al. (4) detailed the test by attempting to create a natural prosody and adapted it to German.

Despite the limited word material [a sentence composed of 5-word types (e.g., verb, noun, subject, etc.) with 10 different words for each type], 100,000 combinations are possible. Phonetic distribution has been carried out in accordance with the language of the test. In practice, because the material provides an unlimited number of sentences, the matrix sentence test suitable for use in research and rehabilitation requires repeated testing (5). The matrix test in Turkish used in this study was created in 2015 (6).

This study aimed to determine the speech discrimination scores (SDSs) of young adults with normal hearing in quiet and noisy free fields. Because testing cochlear implant (CI) and hearing aid users with headphones is impractical, normative data are required for the noisy free field. Additionally, the placement and direction of the microphone in the hearing aid and CIs has an effect on understanding speech in noise. Therefore, the difference in subjects' speech intelligibility performance in relation to the direction of the noise was obtained.

METHODS

This study was constructed and conducted in compliance with the Helsinki Declaration of ethical standards and approved by the institutional ethics committee. Ethics committee approval was received from the İstanbul university-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee for approval of the study (approval number: 83045809-604.01.02). All participants were informed in detail about the procedures of this study and signed an informed consent form.

This study included 77 native Turkish speakers aged between 18 and 30 years (55 women, 22 men). Their mean age was 22.25±2.7 years. All volunteers underwent otoscopic examination and tympanometric measurements. Subsequently, pure tone and speech audiometry test batteries were conducted. All participants had hearing thresholds better than 15 dB between 250 and 8000 Hz. They had <10 dB air-bone gap between 250 and 4000 Hz. All study participants had type A tympanograms. The participants' speech reception thresholds (SRTs) and SDSs were determined before the Turkish matrix test measurements.

The speech intelligibility scores were measured using the Turkish matrix test in quiet and noisy environments. As recommended by Wagener et al. (4), two practice sessions (one in a quiet environment and one in a noisy environment) took place before the measurements (7).

Measurement Setup

The subjects were situated in a double-walled sound chamber containing two speakers, one in front and one behind the subject at an azimuth of 180°. An audiometer (AURICAL Aud; Otometrics, Denmark) with the "Oldenburg Measurement Applications (HörTech, Germany)" software was used. Figure 1 illustrates the measurement setup.

The Turkish adaptive and non-adaptive matrix test was used to measure the subjects' speech intelligibility in quiet and noisy environments. The test lists composed of 20 sentences were used as test material. The noise stimulus was a bubble noise set to continuous mode at 65 dB SPL. The measurements listed in Table 1 were conducted for all subjects. If necessary, the subjects were allowed to take a break.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 for Windows (IBM Corporation, New York, USA). The normality of the variables was assessed using the Shapiro-Wilk test provided by the SPSS software. The significance of the difference between measurements was analyzed using the Mann-Whitney U test. The correlation analysis was conducted by applying the Spearman rho test. The results were considered significant if $p \leq 0.05$.

RESULTS

For each subject, the pure tone thresholds were measured in free field for 500, 1000, 2000, and 4000 Hz, and the pure tone averages (PTAs) were calculated. The mean ± standard deviation (SD) of the PTA was 3.73±2.8 dB HL. The SDSs of all subjects measured in quiet free field were >88%.

Table 2 shows the mean ± SD of the matrix test measurements, and Figure 2 shows the mean speech intelligibility of the subjects for different SNRs and noise presentation conditions. As shown in Figure 2, the performance differences between the two conditions increased as the SNR decreased.

Table 3 shows the difference between the performances when the noise is from different directions. The intelligibility scores obtained at -10, -5, and 0 dB SNR when noise was from the rear were significantly different from the scores when noise was from the front ($p<0.05$).

The adaptive matrix SRT in noise values were also obtained for different SNRs when noise and signal were both from the front, and this difference was also statistically significant ($p<0.05$). The performances remained unchanged as the SNR increased; hence, statistically significant differences were not found for +5 and +10 dB SNR. This effect can be seen in Table 4.

DISCUSSION

The standard audiometric test battery does not measure speech intelligibility in noise (8). The SRT is a test based on the signal-to-

Figure 1. Measurement setup

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speech ratio where the patient understands 50% of the sentences. Although they are currently used to diagnose hearing loss, speech tests with single-syllable word lists do not reflect everyday listening conditions. Although the speech reception performance of a patient using hearing aid or CI is good in a quiet environment, it is disturbed in noisy listening conditions. Therefore, speech intelligibility in noise tests has been developed in different languages.

Although the developed tests are useful due to the correct SRT estimation, the use of a limited number of words, phrases, or sentences is not suitable for repeated testing. For example, the quick speech in noise (QuickSIN) test is composed of 1800 key words used in 360 different sentences (9).

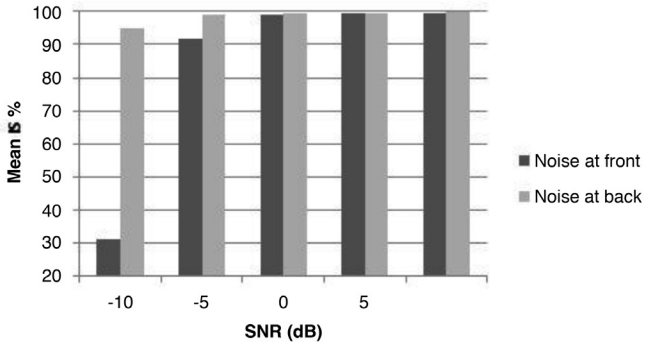

Figure 2. Mean speech intelligibility scores of subjects for different signal-to-noise ratios
SNR: Signal-to-noise-ratios

Table 1. Measurements conducted for each subject

No	Measurement	Direction of noise
1	Adaptive matrix SRT in quiet (50%)	-
2	Adaptive matrix SRT in noise (50%)	Noise in front
3	Adaptive matrix SRT in noise (50%)	Noise in rear
4	Non-adaptive intelligibility score in quiet (65 dB SPL)	-
5	Non-adaptive intelligibility score in noise (-10 dB SNR)	Noise in front
6	Non-adaptive intelligibility score in noise (-5 dB SNR)	Noise in front
7	Non-adaptive intelligibility score in noise (0 dB SNR)	Noise in front
8	Non-adaptive intelligibility score in noise (5 dB SNR)	Noise in front
9	Non-adaptive intelligibility score in noise (10 dB SNR)	Noise in front
10	Non-adaptive intelligibility score in noise (-10 dB SNR)	Noise in rear
11	Non-adaptive intelligibility score in noise (-5 dB SNR)	Noise in rear
12	Non-adaptive intelligibility score in noise (0 dB SNR)	Noise in rear
13	Non-adaptive intelligibility score in noise (5 dB SNR)	Noise in rear
14	Non-adaptive intelligibility score in noise (10 dB SNR)	Noise in rear

dB: Decibel, SNR: signal to noise ratio, SPL: Sound pressure level, SRT: speech reception threshold

Table 2. Descriptive statistics of measurements

Measurements	Speech position	Noise position	Measured values (mean ± SD)
Adaptive matrix SRT in quiet (50%)	Front	-	22.69±3.0 dB SPL
Adaptive matrix SRT in noise (50%)	Front	Front	-7.92±0.8 dB SNR
Adaptive matrix SRT in noise (50%)	Front	Rear	-15.12±2.8 dB SNR
Non-adaptive intelligibility score in quiet	Front	-	99.16±1.6%
Non-adaptive intelligibility score in quiet (-10 dB SNR)	Front	Front	31.10±11.9%
Non-adaptive intelligibility score in quiet (-5 dB SNR)	Front	Front	91.84±6.3%
Non-adaptive intelligibility score in quiet (0 dB SNR)	Front	Front	98.87±1.5%
Non-adaptive intelligibility score in quiet (5 dB SNR)	Front	Front	99.38±1.4%
Non-adaptive intelligibility score in quiet (10 dB SNR)	Front	Front	99.53±1.3%
Non-adaptive intelligibility score in quiet (-10 dB SNR)	Front	Rear	95.01±4.6%
Non-adaptive intelligibility score in quiet (-5 dB SNR)	Front	Rear	98.95±1.5%
Non-adaptive intelligibility score in quiet (0 dB SNR)	Front	Rear	99.27±1.6%
Non-adaptive intelligibility score in quiet (5 dB SNR)	Front	Rear	99.65±1%
Non-adaptive intelligibility score in quiet (10 dB SNR)	Front	Rear	99.81±0.5%

dB: Decibel, SD: standard deviation, SNR: signal to noise ratio, SPL: sound pressure level, SRT: speech reception threshold

Table 3. Test statistics of the Turkish matrix test for a grouping variable of direction (front versus rear)

	U	p
Adaptive matrix SRT in noise (50%)	154.5	<0.0010
Non-adaptive intelligibility score in noise (SNR: -10dB)	0.0	<0.0010
Non-adaptive intelligibility score in noise (SNR: -5 dB)	381.5	<0.0001
Non-adaptive intelligibility score in noise (SNR: 0 dB)	2285.5	0.006
Non-adaptive intelligibility score in noise (SNR: +5 dB)	2692.5	0.170
Non-adaptive intelligibility score in noise (SNR: +10 dB)	2793.0	0.326

dB: Decibel, SNR: signal to noise ratio, SRT: speech reception threshold

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Table 4. Test statistics of the matrix test for a grouping variable of performance differences.

Performance difference at different SNR values (noise in front)	U	p
−10 dB SNR vs −5 dB SNR	0.000	<0.001
−5 dB SNR vs 0 dB SNR	468.0	<0.001
0 dB SNR vs +5 dB SNR	2550.5	0.101
+5 dB SNR vs +10dB SNR	2887.0	0.711

dB: Decibel; SNR: signal to noise ratio

The matrix test was developed to remove this limitation and normalized to normal hearing by adapting to different languages. The literature shows that the normalizations were made on different numbers of participants. For example, in a study consisting 20 participants with normal hearing, the mean SRT of the German matrix test was -7.1±0.2 dB (4). In the Finnish matrix test, the SRT was -9.7±0.7 dB (5). In this study, the number of participants was 77, and the mean SRT was -7.92±0.8 dB.

Because patients using hearing aids and CIs are tested in free field in this study, normalization values for these situations were obtained. Therefore, the tests were made in free field, and speech and noise stimuli were given from loudspeakers. The results can be discussed under the following headings.

The influence of direction to understand speech in noise: As sound travels through the external ear canal, diffractions and resonance are produced due to the head and the structure of the pinna and concha. These diffractions and resonance cause linear distortions in the transfer characteristics of the external ear canal. This change in the transfer characteristics of the external ear canal provides important cues for speech understanding in noise. Nilsson et al. (10) measured the speech discrimination thresholds of 150 young adults in the presence of noise using HINT test and placing loudspeakers in different positions. In the study, the speech stimulus was presented at 0°, and the noise stimulus at 0°, 90°, and 270° azimuth. The study showed that the spatial separation between the speech and noise lowered the speech discrimination thresholds by an average of 7.42 dB.

With the aim of measuring the directional effects on intelligibility, individuals in this study were assessed by giving noise stimuli from the front and rear directions at different SNRs. Different SDSs were obtained at the same SNR when the speech stimulus was at 0°, and the noise stimulus was presented at 0° and 180° azimuth. For example, Table 3 shows that at the SNR of -10 dB, the subjects' ability to discern speech differed significantly (noise, 0° and 180° azimuth, 31.10±11.9 and 95.01±4.6). Similar results were obtained at -5 dB SNR ($p<0.05$). However, as given in Table 3, for SNR of 0, +5, and +10 dB, the participants' ability to understand speech was at a maximum level, independent from the noise and location of the signal. Therefore, a statistical difference in intelligibility scores was not found when the noise direction was changed for those SNRs. While comparing the performance between the cases when the noise was from the front and rear directions, it was thought that the significant improvement in the SRT values was due to the shadow effects of the head, pinna, and concha. When noise comes from behind, the person's ability to understand speech improves, and they are able to distinguish speech in lower SNRs. These data are similar to other studies in the literature (11). Based on this result, it is thought that when the SNR is low (such as in classroom), positioning the speech source in front of the listener and the noise in the back will increase speech comprehension performance.

The effect of level of noise on understanding speech: As shown in Figure 2, when the speech and noise stimuli are from the front, the mean speech intelligibility score values decrease much more as the SNR value decreases. Table 4 shows these performance differences. As shown in the table, while the performance differences between 10 and 5 dB SNRs and between 5 and 0 dB SNRs are statistically insignificant, the performance differences between 0 and -5 dB SNRs and between -5 and -10 dB SNRs are statistically significant ($p<0.05$). This result shows that at low SNRs, the mean intelligibility scores are worse, even in normal-hearing individuals. This causes difficulty in understanding speech.

This performance reduction is observed even at higher SNRs in individuals using CI or hearing aid. According to Polat et al. (12), the mean intelligibility performance difference between + 5 and 0 dB SNRs was approximately 14% when both stimuli were given from the front in CI users. According to the results in this study, the performance difference at the same SNRs is <1%. When the results of both studies are compared, individuals using CIs have been shown to be more affected by noisy environments.

Study Limitations

Our study has some limitations. First, because sex is not supposed to be a factor in hearing performance at this age group, the number of men and women were not kept equal in the study group. Second, the data were obtained from a limited group; thus, the results may not reflect the general population. Besides, the volunteers who agreed to participate in the survey consisted of university students or hospital personnel. Therefore, the results may be influenced by the education level of the study group.

CONCLUSION

This study aimed to determine the speech intelligibility performance of young adults with normal hearing in quiet and noisy free fields for different SNRs. Studies in the literature have shown that the scores of non-native participants are much lower, even if they have the same hearing thresholds as native speakers (13). For this reason, every patients' test of understanding speech in noise should be conducted in their native language. The normalization data were obtained by increasing the number of people and by choosing only native Turkish speakers.

This normalization data are more valuable for free-field tests because the tests in this study were performed in free field.

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These data can be used as a guide to assess speech recognition performance of CI and hearing aid users.

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Ethics Committee Approval: Ethics committee approval was received from the İstanbul university-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee for approval of the study (approval number: 83045809-604.01.02).

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Investigation of Sexual Dysfunction in Premenopausal Women with Urinary Incontinence

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ABSTRACT

Objective: In this study, "Female Sexual Dysfunction (FSD)" was investigated in women who applied to our urology outpatient clinics who suffered from urinary incontinence (UI) and healthy women who did not have UI to evaluate the effect of UI and incontinence types on Female Sexual Functions (FSF).

Methods: A total of 220 female patients who applied to urology and incontinence outpatient clinics between October-December 2016 were included in the study. Of these 220 female cases, 110 of them were patients without complaints of UI. In patients with complaints of UI, type of UI has been identified "female sexual function Index (FSFI)" test was used to determine FSF status in all cases.

Results: The rate of KCD was found to be 60% (n=66) in the UI group and 36.4% (n=40) in the control group. The rate of FSD was significantly higher in the UI group (p□0.05). When the FSFI scores were evaluated, FSFI desire, arousal, lubrication, orgasm, satisfaction scores were significantly lower in the UI group than those in the control group (p□0.05). When urge, stress, mixed incontinence groups were evaluated, there were no significant differences between FSFI scores and sexual dysfunction status (p□0.05).

Conclusion: In our study, we found that UI is one of the factors that increase incidence of sexual dysfunction. Therefore, we think that the cases with UI complaints should be evaluated in terms of FSD. In addition, when we looked at UI types separately to evaluate the effects of UI on sexual dysfunction, we found that there was no significant difference between them in terms of influencing sexuality.

Keywords: Urinary incontinence, female sexual dysfunction, premenopausal, urogynecology

INTRODUCTION

Urinary incontinence (UI) is a social and hygienic disease that can occur at any age, is common and affects life negatively. UI is a complex problem that occurs for different reasons. It is not just a medical problem. It also affects the quality of life, which is defined as physical, psychological, economic and social well-being. Although the frequency of UI increases with age, it can be seen not only in the elderly population but also in the young and middle-aged population (1).

Female sexual dysfunction (FSD) is a common disease and its incidence varies between 19 and 50% in the literature (2). UI can impair women's sexual health to various degrees. Causes

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such as psychological pressure, fear of UI during sexual intercourse and worry of bad smell play a role in the etiology (3). It is reported that UI causes FSD and the frequency of sexual dysfunction varies between 26% and 43% in the female group with incontinence (4).

Studies investigating the effect of UI types (stress-urge-mixt) on female sexual functions are available in the literature. In some studies, it has been found that incontinence types do not make any difference in affecting sexuality (5). In another study evaluating the effect of UI on sexual functions in our country, it was shown that the effect of mixed UI on sexual functions was higher than other groups (6).

Sexual functions are an important part of quality of life. The self-confidence of women who miss urine significantly decreases, becoming ashamed, avoiding the relationship and ultimately this situation negatively affects the sexual pleasure of the woman (7). It is important that they are questioned in terms of sexual function in the evaluation of UI cases in the light of this information.

In this study, we investigated the rates of female sexual dysfunciton in healthy women with similar demographic characteristics, UI complaints and aimed to evaluate the effect of UI on female sexual function.

METHODS

A total of 220 female patients who were admitted to the urology and incontinence polyclinics between October 2016 and December 2016 were included in our study. Of these 220 female cases, 110 have complaints of UI; the other 110 were randomized cases without UI.

The subjects included in the study were sexually active and married women, all of whom were in the premenosal period. Patients who were pregnant or breastfeeding, patients with a history of gynecological operations, and patients with a history of malignancy were not included in the study.

Patients filled out questionnaire forms themselves, in a relaxed and quiet environment. The age, education status, occupation, monthly income, age of marriage, duration of marriage, status and number of children, whether they have a chronic disease, history of surgery were questioned and recorded.

The type of UI in patients with UI was determined by taking into account the standardization determined by the International incontinence Association and accompanied by questionnaire forms. They were questioned about how long they had been urinating. The International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) questionnaire was filled out to determine the effects of UI on quality of life.

In all cases, the "Female Sexual Function Index" (FSFI) test, developed by Rosen et al. as a multidimensional scale in 2000, was used to determine female sexual function status. FSFI is a test that we use frequently, with Turkish validity and reliability studies consisting of 6 sections (sexual desire, arousal, lubrication, orgasm, satisfaction, pain) and 19 questions, evaluating sexual function and problems in the last 4 weeks. The scores obtained in the subheadings were multiplied by their own coefficient, resulting in the subheadings and total points, with a total score of 2 to 36. In our study, the threshold for FSFI was considered to be 23. The study was approved by the Clinical Research Ethics Committee of the Gaziosmanpaşa Training and Research Hospital.

Statistical Analysis

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by Kolmogorov- Simirnov test. Kruskal-Wallis, 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. SPSS program was used for analysis. The reference p value was <0.05.

RESULTS

The patients were randomized into two groups: group 1 (case group-UI), group 2 (control group). There were no statistically significant differences between these two groups in terms of socio-demographic data, presence of chronic disease, drug use, history of previous surgery (p>0.05) (Table 1).

In group 1 (n=110), urgency was present in 28 (25.5%) of cases, stress in 24 (21.8%) and mixt UI in 58 (52.7%). Of these patients, 56 (50.9%) did not receive any treatment, while 54 (49.1%) had a history of treatment.

When we evaluated all the FSFI scores, all scores in group 1 except pain score were significantly lower than those in group 2 (p=0.05). When FSFI total scores were evaluated, the rate of sexual dysfunction in group 1 was significantly higher than in group 2 (60%-36.4%) (p=0.05) (Table 2).

In group 1, there was no statistically significant difference between the two groups in comparison to the individual socio-demographic data of the patients with UI types (urge-stress-mixt incontinence). The mean age of the cases was 36, 41.3 and 40.1 years, respectively.

In this study, ICIQ-SF questionnaire was completed to determine the effects of UI on quality of life in patients with incontinence. Accordingly, the ICIQ-SF score did not differ significantly in urge, stress, mixt incontinence groups.

FSFI scores and sexual dysfunction rates in urge, stress, mixt incontinence groups were not significantly different (p>0.05). There were 66 cases of sexual dysfunction and UI, 16 cases of urgency, 14 cases of stress and 36 cases of mixt type incontinence. There was no significant difference in the incidence of sexual dysfunction among all three groups (p>0.05) (Table 3).

DISCUSSION

Sexual function in humans consists of a series of reactions involving complex interactions of psychological, physiological

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and behavioral components (8). FSD is a common disease and its incidence in the literature varies between 19-50% (2). A national study conducted in Canada found sexual dysfunction in 39% of the 18-44 age group (9). Age is an important factor in some of the factors that affect women's sexual health. In our study, the rate of sexual dysfunction was significantly increased with older age. Similarly, Cayan et al. (10) and Lukacz et al. (11) also determined that female sexuality is negatively affected with increasing age. However, Lauman et al. (12) stated that the rate of FSD was higher in young women.

In our study, we found that the rate of FSD decreases as the level of education increases. In line with our findings, there are studies that have found that low education level increases the risk of sexual dysfunction (13,14). Some studies in the literature also questioned the educational status of the woman's partner (15). In our study, it is a handicap to not know the educational status of the woman's partner. It may be thought that the high level of education of the woman or her partner may be a helpful factor in the issues such as sharing the current problem between couples and applying for the necessary professional help.

In our study, we found that the increase in duration of marriage and the low age of first marriage increased the likelihood of sexual dysfunction. Singh et al. (16) similarly found that the longer the duration of marriage, the greater the frequency of FSD. These findings can be explained by the increase of factors that lead to the risk of developing FSD, such as the progression of age and the presence of chronic disease as the duration of marriage increases.

Although the pathophysiology of UI has not been fully clarified, its negative effect on sexual function is known. Psychological pressure, fear of UI during sexual intercourse and anxiety of bad smell play a role in the etiology (3). The first study on the relationship between UI and FSD was conducted by Scott and Hsueh (17) and published in 1979. There are studies (4) reporting that the frequency of FSD varies between 26% and 43% in patients with UI. Shaw (18) also reported that 46% of patients with UI and lower urinary system complaints were

Table 1. Socio-demographic data of the cases

	Group 1 (case group)		Group 2 (control group)		p
	Mean ± SD (n, %)	Med	Mean ± SD (n, %)	Med	
Age (year)	39.3±8.7	43.0	36.6±9.4	38.0	0.052[m]
BMI (kg/m^2)	29.5±5.3	28.4	28.8±4.3	28.1	0.466[m]
Educational status					
Primary school	16 (14.5%)	-	6 (5.5%)		
Secondary school	52 (47.3%)	-	50 (45.5%)		
High school	10 (9.1%)	-	28 (25.5%)	0.134[χ²]	
University	24 (21.8%)	-	18 (16.4%)		
Post graduate	8 (7.3%)	-	8 (7.3%)		
Occupation					
Housewife	82 (74.5%)	-	69 (62.7%)		
Worker	12 (10.9%)	-	23 (20.9%)	0.058[χ²]	
Memur	16 (14.5%)	-	16 (14.5%)		
Monthly income					
None	84 (76.4%)	-	67 (60.9%)		
<1500 TL	12 (10.9%)	-	25 (22.7%)	0.063[χ²]	
1500-3000	8 (7.3%)	-	12 (10.9%)		
>3000 TL	6 (5.5%)	-	6 (5.5%)		
Dating					
Arranged	70 (63.6%)	-	78 (70.9%)	0.250[χ²]	
Friendship	40 (36.4%)	-	32 (29.1%)		
Number of children	2.5±1.3	3.0	2.4±1.4	2.0	0.398[m]

[m]Mann-Whitney U test, χ²chi-square test, SD: Standard deviation, , BMI: Body mass index

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Table 2. Comparison of Female Sexual Function Index score data of cases

		Group 1 (case group)		Group 2 (control group)		p
		Mean ± SD	Med	Mean ± SD	Med	
FSFI						
Desire		3.2±1.1	3.6	4.1±1.0	4.2	**0,000^{m}**
Arousal		3.3±1.1	3.3	4.0±1.0	3.6	**0,000^{m}**
Lubrication		4.0±.8	3.9	4.3±.7	4.5	**0,005^{m}**
Orgasm		3.4±1.3	3.6	4.3±1.0	4.0	**0,000^{m}**
Satisfaction		3.6±1.3	3.6	4.2±1.1	4.0	**0,000^{m}**
Pain		4.0±1.4	4.0	4.0±1.0	4.0	0,555^{m}
Total		21.4±5.1	22.0	24.9±4.7	24.3	**0,000^{m}**
Sexual dysfunction	(+)	66	%60	40	%36.4	**0,003$^{\chi^2}$**
	(-)	44	%40	70	%63.6	

^{m}Mann-Whitney U test, χ^2chi-square test, SD: Standard deviation, FSFI: Female Sexual Function Index

Table 3. Comparison of Female Sexual Function Index score data in urinary incontinence cases

		Urge Incontinence		Stress Incontinence		Mixt Incontinence		p
		Mean ± SD	Med	Mean ± SD	Med	Mean ± SD	Med	
FSFI								
Desire		3.5±1.1	3.6	3.3±1.3	3.3	3.1±1.1	3.6	0,246^{K}
Arousal		3.3±1.0	3.3	3.2±1.3	3.0	3.3±1.1	3.3	0,785^{K}
Lubrication		4.0±0.7	3.9	3.8±0.8	3.9	4.1±0.8	4.2	0,105^{K}
Orgasm		3.2±1.2	3.4	3.7±1.5	3.8	3.3±1.3	3.6	0,367^{K}
Satisfaction		3.8±1.0	3.8	3.5±1.5	3.2	3.6±1.3	3.6	0,501^{K}
Pain		3.9±1.1	3.8	3.6±1.6	3.6	4.1±1.4	4.4	0,205^{K}
Total		21.7±4.6	22.0	21.0±5.8	19.7	21.5±5.1	22.8	0,830^{K}
Sexual dysfunction	(+)	16	%57	14	%58.3	36	%62.1	0,962$^{\chi^2}$
	(-)	12	%43	10	%41.7	22	%37.9	

^{K}Kruskal-wallis, χ^2chi-square test, , SD: Standard deviation, FSFI: Female Sexual Function Index

found to have sexual dysfunction. In a study conducted by Turhan (13) in Turkey, FSFI threshold value was taken as 22.7 and sexual dysfunction was detected in 48.3% of all cases, 34% of cases in the reproductive period and 54% of cases with UI in the reproductive period. In our study, we considered FSFI threshold as 23 and found the rate of sexual dysfunction as 48.18% in all cases (n=220). This ratio was found to be 60% in the patients with UI (group 1) and 36.4% in the control group (group 2). When we looked at FSFI total scores, the rate of sexual dysfunction in the UI group was significantly higher than in the control group (60%-36.4%). The results we found were parallel to those in similar studies (6-8).

In our study, when we evaluated FSFI scores according to UI types, we could not find a significant difference in terms of FSFI scores. Similarly, Turhan (13) and Urwitz-Lane and Özel (5) also found that there was no statistically significant difference between the UI types in terms of FSFI scores in reproductive incontinence cases. When we look at the literature, we see different results. Güdücü and Keser Özcan (19) states that the sexual function of women with mixt incontinence is worse than that of women with stress and urge type incontinence. In another study conducted in Iran, mixt UI was found to affect sexual function more than stress and urge type incontinence (20). Gordon et al. (21) stated that the sexual function scores of mixt incontinence patients were higher than those of stress incontinence patients.

Sexual functions are an important part of quality of life. The self-esteem of women who miss urine decreases are

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embarrassed and they escape from the relationship. As a result, this situation prevents them from enjoying sexuality. In addition, the relationship of the couple and the marriage institution can be negatively affected. Yip et al. (22) found that emotional problems related to sexual satisfaction and UI in patients with stress incontinence, and decreased sexual satisfaction in patients with overactive bladder negatively affect the marriage.

It should be kept in mind that incontinence treatment can have a positive effect on sexual function and overall quality of life. Arslan et al. (23) found significant increase in FSFI scores in follow-up after transobturator tape (TOT) operation due to stress UI (SUI). In a recent metaanalysis evaluating sexual function after SUI surgery, 55.5% of all SUI surgeries [TOT, transvaginal tape (TVT)], Burch colposusception, autologous facial sling) reported no changes in sexual symptoms, 31.9% improvement and 13.1% worsening. Sexual symptoms for miduretral sling operations were reported to be 56.7% unchanged, 33.9% improved, and 9.4% worsened. When the improvement rates in symptoms were compared, no significant difference was found between both midurethral sling operations (TOT and TVT) (24). As stated by Ayyıldız et al. (25), information should be given that patients who are planning to have a vaginal intervention due to UI may experience some sexual function parameters such as dyspareunia, even if a general sexual dysfunction does not develop. This information also shows that the treatment that will be performed will provide significant improvement in sexual function and therefore in the quality of life of the partners.

Study Limitations

The fact that our study was single-centered and that couples were not evaluated in terms of sexual function can be seen as a limitation. In addition, UI cases could be treated and re-evaluated in terms of sexual function, and may provide additional contribution to the study.

CONCLUSION

Considering the incidence of continent cutaneous diversion and UI together, sexual function must be questioned in patients with UI. In addition to similar studies in the literature, we would like to identify this situation and emphasize that the treatment should be planned. It should be kept in mind that incontinence can negatively affect sexual functions when patients are left without treatment, and this can decrease quality of life and get a vicious circle.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of the Gaziosmanpaşa Training and Research hospital.

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Effects of Leptin, Resistin, and *PPAR-Gama* Gene Variants on Obese Patients with Acute Coronary Syndrome in the Turkish Population

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ABSTRACT

Objective: Obesity and acute coronary syndrome (ACS) are common health problems of recent years. There are many candidate genes related to the genetic infrastructure of ACS and obesity. This study aimed to investigate the association of Leptin glutamine to arginine substitution (Gln223Arg), Resistin-420 Cytosine/Guanine (C/G), and proliferator-activated receptor-gamma (PPAR-γ) proline to alanine substitution (Pro12Ala) polymorphisms in obese patients with ACS in the Turkish population.

Methods: Fifty obese patients concurrently diagnosed with ACS and 42 healthy controls were included in this study. These polymorphisms were analyzed using the polymerase chain reaction-restriction fragment length polymorphism and agarose gel electrophoresis methods.

Results: The PPAR-γ Pro12Ala polymorphism Pro/Ala genotype (p=0.001) was found to be higher in the obese patients with ACS, while the (Proline/Proline) genotype (p=0.001) was significantly higher in the control group. The GC genotype (p=0.045) distribution of Resistin-420 C/G was found to be significantly higher in the controls compared to the patient group.

Conclusion: Our study presents new findings that the PPAR-γ Pro12Ala polymorphism Pro/Ala genotype is a risk factor for ACS in obese individuals, whereas Resistin-420 C/G polymorphism GC genotype and PPAR-γ Pro12Ala polymorphism Pro/Pro genotype may be protective factors for ACS in obese individuals.

Keywords: Acute coronary syndrome, leptin, resistin, PPAR-γ, gene polymorphism, PCR-RFLP

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INTRODUCTION

Acute coronary syndrome (ACS) is the most common reason for emergency department visits and hospital admissions. ACS is one of the most important health problems causing morbidity, mortality, and reduced quality of life in today's society (1). Obesity is a multifactorial disease characterized by an excessive increase in the amount of body fat, adversely affecting health and the quality of life, reducing the lifespan, and causing many metabolic diseases (2). According to the World Health Organization's reports, obesity affects more than 700 million people worldwide and nearly 2.3 billion people are overweight (3). Obese individuals have a higher frequency of cardiovascular risk factors and have higher morbidity and mortality rates related to cardiovascular diseases (4). Previously, many studies showed that some gene polymorphisms are associated with obesity and cardiovascular diseases (5,6). Leptin, which is one of these genes, is expressed in adipocytes and regulates adipose-tissue mass, food intake, energy expenditure, and body weight (7). Many studies have demonstrated that the leptin gene or leptin receptor gene polymorphisms regulate obesity and cardiovascular pathogenesis (8,9). Resistin is a novel hormone that is secreted by adipocytes and its gene is located on chromosome 19p13.2 (10). Resistin-420 Cytosine/Guanine (C/G) polymorphism, located in the promoter region of the resistin gene, was reported to be associated with the regulation of resistin gene expression and serum resistin level (11). In addition, an association has been shown between the Resistin-420 C/G variant and diabetes, obesity, and cardiovascular disease in several studies (12-14). The peroxisome proliferator-activated receptor-gamma (PPAR-γ), localized on chromosome 3p25, is another related gene that is mainly expressed in adipose tissue, the colon, and macrophages. PPAR-γ plays a role in adipocyte differentiation and in the regulation of insulin responses, and it is linked to numerous diseases such as obesity, diabetes, atherosclerosis, and cancer (15).

It is suggested that Leptin Glutamine to Arginine substitution (Gln223Arg), Resistin-420 C/G, and PPAR-γ *proline to alanine substitution (Pro12Ala)* gene polymorphisms play an important role in the development of diabetes, obesity, and cardiovascular disease. However, there is no previous study that has investigated the combined effect of the variations of *Leptin, Resistin, and PPAR-γ* genes on the pathogenesis of ACS among obese patients in the Turkish population. Therefore, this study is the first to investigate the possible associations of *Leptin Gln223Arg, Resistin-420 C/G, and PPAR-γ Pro12Ala* gene polymorphisms together in obese patients with ACS.

METHODS

Ethical Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the İstanbul Faculty of Medicine Ethical Committee, İstanbul University (approval number: 2012/1590-1251). All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Study Group

The *Leptin Gln223Arg, Resistin-420 C/G, and PPAR-γ Pro12Ala* gene polymorphisms were investigated in 42 healthy subjects without any heart disease and 50 patients diagnosed with obesity and ACS. The patients were selected from the Medicana Bahçelievler Hospital, Clinic of Cardiovascular Surgery in İstanbul, Turkey.

The patient group consisted of obese patients [body mass index (BMI) □30] who were diagnosed with ACS in the hospital and whose samples were collected. ST segment elevated q positive or non-ST segment elevated, but enzyme positive patients were included into this group. Unstable angina pectoris patients were excluded. The control group consisted of people who were working in the same hospital, recruited via a survey. Particularly, the lack of a family history was the main criteria for maintaining the survey. While creating the control group, the age range was matched with that of the patient group.

DNA Isolation and Genotyping

In EDTA containing tubes, 10 mL of venous blood samples were obtained from the participants. Samples were stored at -20 °C until the genomic DNA isolation was performed using the salting out method (16). The PPAR-γ Pro12Ala, Resistin-420 C/G, and Leptin Gln223Arg polymorphisms were analyzed using the polymerase chain reaction (PCR)-restriction fragment length polymorphism methods. For detection of PPAR-γ Pro12Ala, Resistin-420 C/G, and Leptin Gln223Arg, 500 ng genomic DNA was amplified with 10x reaction buffer (10 mM Tris-HCl, 50 mM of KCl, 1.75 mM MgCl2), 2.5 mM of each dNTP, 100 pmol/μL of each primer, and 0.1 unit Taq polymerase (Invitrogen) in a 25 μL reaction volume. The annealing temperatures for Leptin Gln223Arg, Resistin-420 C/G, and PPAR-γ Pro12Ala polymorphisms were 64 °C, 63 °C, and 58 °C, respectively.

Used primers, restriction enzymes, and interpretations for determining Leptin Gln223Arg, Resistin-420 C/G, and PPAR-γ Pro12Ala polymorphisms are shown in Table 1.

Evaluation of the MspI, BpiI, and BstUI Restriction Enzyme Digestion Results

The PCR yield of the Leptin Gln223Arg polymorphism was 421 bp and the bands obtained following digestion with MspI were 294 and 127 bp, only if the polymorphism was present. Therefore, a single band of 421 bp was appraised as Thymin/Thymin (TT) (wild type, TT), 294 and 127 bp as Cytosine/Cytosine (CC) (mutant type, CC), and 421, 294, and 127 bp as Cytosine/Thymine (CT) (heterozygous type, CT) (Figure 1).

In order to evaluate the Resistin-420 C/G polymorphism, BpiI restriction enzyme was utilized. A single band of 533 was

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appraised as Guanine/Guanine (GG) (329 and 204 bp as CC (mutant type, CC), and 533, 329 and 204 bp as Guanine/Cytosine (GC) (heterozygous type, GC) (Figure 2).

The PCR yield of the PPAR-γ Pro12Ala polymorphism was 270 bp and the bands obtained following digestion with BstUI were 227 and 43 bp, only if the polymorphism was present. Therefore, a single band of 270 bp was appraised as Proline/Proline (Pro/Pro) (wild type, Pro/Pro), 227 and 43 bp as Ala/Ala (mutant type, Ala/Ala: Alanine/Alanine), and 270, 227, and 43 bp as Proline/Alanine (Pro/Ala) (heterozygous type, Pro/Ala) (Figure 3).

Statistical Analysis

Statistical analysis was performed using SPSS version 11.5 (SPSS Inc, Chicago, USA). The chi-square (χ^2) test, Fischer's exact test, and Student's t-test were used for comparison of the numerical variables between the groups. Allele frequencies were calculated by the gene counting method. Chi-square (χ^2) test was used for the comparison of clinical and non-clinical parameters and alleles. Student's t-test and ANOVA test were performed to compare the genotypes with more than two variables. Values of $p<0.05$ were considered as statistically significant.

RESULTS

Fifty obese patients with ACS and 42 healthy controls were included in the analyses. The mean ages of the patient and control groups were 61.56±8.92 and 60.34±12.55 years, respectively. No significant difference was found between the patients and the

Table 1. Polymerase Chain Reaction–Restriction Fragment Length Polymorphism-Based Assay of Leptin GLN223ARG, Resistin-420 C/G, and PPAR-γ PRO12ALA SNPs

SNPs	Primers	Restriction enzymes	Interpretation (bp)
PPAR-γ PRO12ALA	**Forward Primer:** 5′-GCCAATTCAAGCCCAGTC-3′ **Reverse Primer:** 5′-GATATGTTTGCAGCAAGTG AATCATAAGGAATCGCTTTCCG-3′	BstUI	**PP:** 270 **AA:** 227+43 **PA:** 270+227+43
Resistin - 420 C/G	**Forward Primer:** 5′- TGTCATTCTCACCCACAG ACA-3′ **Reverse primer:** 5′- TGGGCTCAGCTAACCAA ATC-3′	BpiI	**GG:** 533 **CC:** 329+204 **GC:** 533+329+204
Leptin GLN223ARG	**Forward Primer:** 5′-ACCCTTTAAGCTGGGTGT CCCAAATAG-3′ **Reverse Primer:** 5′- CTAGCAAATATTTTTGTAA GCAATT-3′	MspI	**TT:** 421 **CC:** 294+127 **CT:** 421+294+127

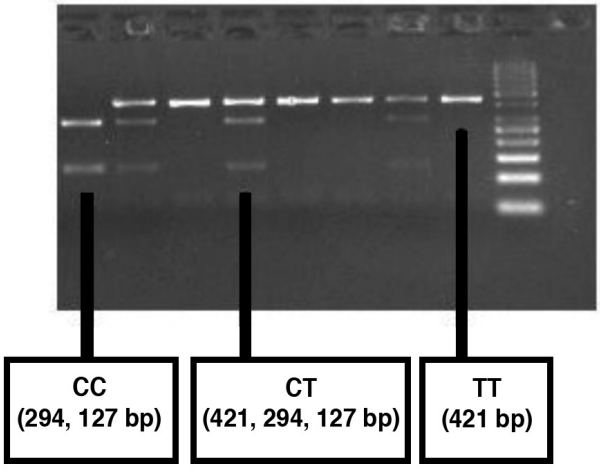

Figure 1. Gel photograph showing PCR-RFLP assay for genotyping of Leptin Gln223Arg polymorphism
PCR-RFLP: Polymerase chain reaction restriction-fragment length polymorphism, CC: cytosine-cytosine, CT: cytosine/thymine, TT: thymin/thymin

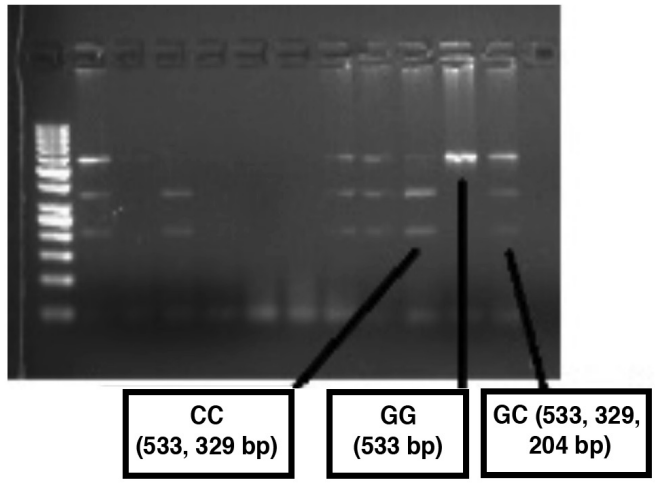

Figure 2. Gel photograph showing PCR-RFLP assay for genotyping of Resistin-420 C/G polymorphism
PCR-RFLP: Polymerase chain reaction restriction-fragment length polymorphism, CC: cytosine-cytosine, GG: guanine/guanine, GC: Guanine/Cytosine

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controls in terms of age. Demographic parameters of the study groups are shown in Table 2. BMI [p=0.001, 95% confidence interval (CI): 5.63-8.25], very-low-density lipoprotein-cholesterol (p=0.001, 95% CI: 9.94-30.00), and triglyceride (p=0.001, 95% CI: 49.87-150.29) levels were found to be significantly higher in the patient group compared to the controls. Also, LDL-cholesterol (p=0.002, 95% CI: 10.77-44.15) and high-density lipoproteins-cholesterol (p=0.001, 95% CI: 8.65-18.28) levels were found to be higher in the controls than in the patient group. In addition, 66% of individuals in the patient group were also diagnosed with hypertension and 36% with diabetes mellitus (DM).

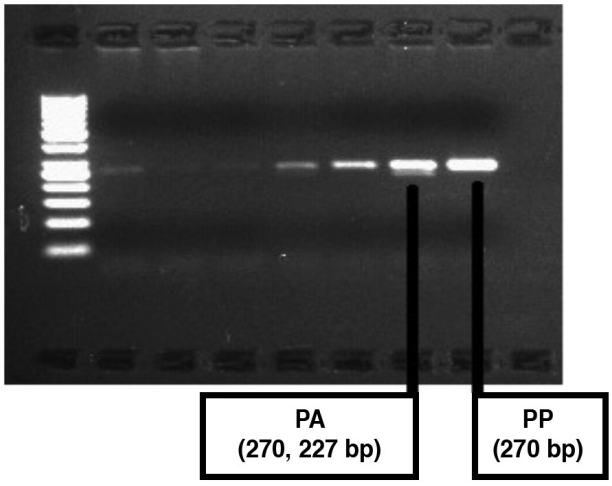

Figure 3. Gel photograph showing PCR-RFLP assay for genotyping of PPAR-γ Pro12Ala polymorphism
PCR-RFLP: Polymerase chain reaction restriction-fragment length polymorphism

When we evaluated the study groups in terms of the PPAR-γ Pro12Ala genotype and allele frequencies, none of the individuals in either group showed the Ala/Ala genotype. In the patient group, Pro/Ala genotype was found to be significantly higher compared to the controls (p=0.001, 95% CI: 3.82-17.22). Due to the absence of the Ala/Ala genotype, carrying the mutant Ala/Ala allele presents as the Pro/Ala genotype. The Pro/Pro genotype frequency was determined to be significantly higher in the control group compared to the patient group (p=0.001, 95% CI: 0.004-0.202) (Table 3). The allele and genotype frequencies of Leptin Gln223Arg polymorphism were not significantly different between the patient group and controls (Table 3). According to the results of the statistical analysis of Resistin-420 C/G polymorphism, the GC genotype distribution was determined to be significantly

Table 2. Demographic characteristics of obesity with ACS patients and healthy controls

Demographic parameters	Patient (n=50)	Control (n=42)	p
Age (year)	(61.56±8.92)	(60.34±12.55)	-
Gender (F/M)	17/33	14/28	-
Body mass index (kg/m^2)	(32.75±2.76)[a]	(25.81±3.42)	0.001
Presence of hypertension (%)	66%	-	-
Presence of diabetes mellitus (%)	36%	-	-
Presence of KOAH (%)	8%	-	-
LDL-cholesterol (mg/dL)	(103.84±43.05)	(131.30±37.50)[a]	0.002
Triglyceride (mg/dL)	(216.18±168.22)[a]	(116.09±51.79)	0.001
Total cholesterol (mg/dL)	(185.41±61.83)	(206.38±43.21)	-
HDL-cholesterol (mg/dL)	(38.34±9.75)	(51.80±13.43)[a]	0.001
VLDL-cholesterol (mg/dL)	(43.23±33.64)[a]	(23.26±10.26)	0.001
AST (mg/dL)	(30.54±14.03)	-	-
ALT (mg/dL)	(36.89±20.41)	-	-
BUN (mg/dL)	(19.50±9.02)	-	-
Hematocrit	(40.49±5.18)	-	-
Platelet	(266.18±52.29)	-	-
Urea	(38.55±13.06)	-	-
WBC	(7.63±2.17)	-	-
INR	(1.06±0.14)	-	-
Sedimentation	(35.36±25.82)	-	-

Values are reported as number of patients, n: number of individuals, SD: standard deviation, [a]p<0.05 denoted statistically significant, F: female, M: male, ACS: acute coronary syndrome, KOAH: Chronic Obstructive Pulmonary disease, HDL: high-density lipoproteins, VLDL: very-low-density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, WBC: white blood cell, INR: international normalized ratio

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higher in the controls compared to the patient group [p=0.045, χ^2: 4.033, odds ratio (OR): 1.364, 95% CI: 1.003-1.854] (Table 3).

When we investigated the association between demographic parameters and Leptin Gln223Arg, Resistin-420 C/G, and PPAR-γ Pro12Ala genotype distribution, the Leptin GG genotype carriers had significantly higher BMIs compared to heterozygote carriers in the patient group.

There were no significant differences between other polymorphisms and demographic parameters in both study groups (Table 3).

DISCUSSION

Leptin receptor Gln223Arg polymorphism is one of the most frequently encountered leptin receptor polymorphisms (17). Leptin Gln223Arg polymorphism falls within the region encoding the extracellular domain of the leptin receptor. Therefore, the amino-acid changes consecutively, leading to a change from a neutral to a positive charge of the molecule, in the extracellular domain of the receptor that represents a typical leptin-binding site and it was suggested that a change of charge could significantly affect the functionality of the receptor (18,19). Leptin Gln223Arg polymorphism affected the development process of coronary artery disease via facilitating the deposition of HDL cholesterol on blood vessel walls (20). While some studies have reported that Leptin Gln223Arg polymorphism has been associated with BMI, high blood pressure, obesity, lipids, and insulin resistance, other studies did not find any association with these parameters (21).

Although Leptin receptor Gln223Arg polymorphism has not been associated with lipid parameters in obese or normal-weight persons before (22,23), some studies showed that it may increase the risk of obesity and/or obesity-related diseases in different populations (24-26). In obese children, no association was found between Leptin Gln223Arg polymorphism and obesity, leptin, insulin resistance, and metabolic abnormalities (27). Similarly, Okada et al. (28) have found no association between Leptin Gln223Arg polymorphism and serum lipid profiles of Japanese obese children. Leptin Gln223Arg polymorphism was found not to be associated with obesity in Turkish children with metabolic syndrome (29). There was no difference in the genotype frequencies of Leptin Gln223Arg polymorphism between obese and non-obese adolescents (18). Yang et al. (30) selected fifteen studies for their meta-analysis. They reported a significant association between decreased risk of obesity and the Leptin Gln223Arg polymorphism. Overweight or obese subjects had significantly higher frequencies of the Arg223 homozygous allele of the Leptin Gln223Arg polymorphism (31). In a study conducted in the Iranian population, it has been suggested that carrying the G allele increases the risk of non-ST-segment elevation myocardial infarction (32). In another study, Leptin Gln223Arg polymorphism has not been associated with the risk of coronary artery disease and hypertension in the Iranian population (33). Aijälä et al. (34) have reported that no impact on incidence for cardiovascular events or death was detected between Leptin Gln223Arg polymorphism. Also, Shi et al. (20) have demonstrated that Leptin Gln223Arg polymorphism showed a significant difference between coronary artery disease patients and healthy controls neither genotypes nor alleles in China population. In the represented study, we found no association between the Leptin Gln223Arg polymorphism and obese patients with ACS in the Turkish population. A meta-

Table 3. Genotype and allele frequencies of patients and controls for Leptin GLN223ARG, Resistin - 420 C/G, and PPAR-γ PRO12ALA polymorphisms

SNPs	Genotype and alleles	Patient (n=50) (n, %)	Control (n 42) (n, %)	p
Leptin GLN223ARG	AA	14 (28)	18 (42.90)	-
	GG	2 (4)	3 (7.10)	-
	AG	34 (68)	21 (50)	-
	A allele	62 (62)	57 (67.85)	-
	G allele	38 (38)	27 (32.15)	-
PPAR-γ PRO12ALA	PP	6 (12)	38 (97.40)[a]	0.001
	AA	0	0	-
	PA	44 (88)[a]	1 (2.60)	0.001
	P allele	56 (56)	77 (98.71)	-
	A allele	44 (44)	1 (1.29)	-
Resistin-420 C/G	GG	9 (20.5)	5 (12.5)	-
	CC	10 (22.7)	4 (10)	-
	GC	25 (56.8)	31 (77.5)[a]	0.045
	G	43 (48.86)	41 (51.25)	-
	C	45 (51.14)	39 (48.75)	-

Values are reported as number of patients (percentage of total group). [a]p<0.05 denoted statistically significant. PPAR-γ: peroxisome proliferator-activated receptor-gamma, GG: guanine/guanine, CC: cytosine-cytosine, GC: Guanine/Cytosine

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analysis showed that Leptin Gln223Arg polymorphism was not significantly associated with cardiovascular disease risk, but have claimed that these findings are still unclear, because the frequency of the 223Arg allele was highly varied in different ethnicities (8).

The resistin gene coding resistin is found on chromosome 19p13; Resistin-420C/G polymorphism reported at promoter as well as on coding sequences. One of the most frequently studied polymorphisms, C to G substitution at -420 position in the 5′ flanking region of the gene showed altered resistin gene expression (mRNA levels) in abdominal fat with increased serum resistin level (35). This polymorphism has independently been associated with cardiovascular risk factors, such as insulin resistance, type 2 diabetes mellitus (T2DM), obesity, hypertension, dyslipidemia, and metabolic syndrome, as well as with coronary heart disease (arteriosclerosis, coronary artery disease, idiopathic dilated cardiomyopathy) (36-39). In a meta-analysis, G allele of Resistin-420 C/G polymorphism was reported as a risk factor for obesity (40). The Resistin-420 GG genotype was significantly associated with obesity, impaired glucose tolerance, and T2DM in a Egyptian population (41). G/G genotypes and G alleles for Resistin-420 C/G polymorphism were significantly associated with T2DM and cardiovascular disease in Egyptian diabetic patients (12). Also, Nakashima et al. (42) have reported that carrying the GG genotype and G allele increased cardiovascular disease risk. In a Chinese population, subjects with CG and GG genotypes had an increased risk of coronary artery disease compared to CC carriers (11). Hoffman et al. (43) did not find any association between Resistin-420 C/G polymorphism and coronary artery disease in Caucasians. Hussain et al. (44) reported that elevated serum resistin levels and carrying the G allele for Resistin-420 C/G polymorphism may be associated with hypertrophic cardiomyopathy. In the Chinese population, no significant difference in the distribution of genotypes and allele frequencies of -420 C/G polymorphism has been found in T2DM patients and coronary heart disease patients (45). Resistin-420 C/G polymorphism has been found associated with increased obesity and metabolic syndrome, but it is not different in subjects with high cardiovascular diseases such as myocardial infarction (46). Resistin-420 C/G polymorphism was not associated with metabolic syndrome or coronary atherosclerosis in nondiabetic Caucasians (47). According to our results, the GC genotype distribution for Resistin-420 C/G polymorphism was determined to be significantly higher in the control group compared to obese patients with ACS; therefore, it can be said that GC genotype for Resistin-420 C/G polymorphism is protective for ACS in obese patients in the Turkish population.

PPAR is a member of the nuclear hormone receptor family. There are three subtypes of PPAR: α, δ, and γ (48). The PPAR-γ plays a pivotal role on local vasculature in several critical aspects of atherothrombosis, including lipid metabolism and foam cell responses (49). A point mutation found on the B exon of the NH2-terminal of PPAR-γ, substitution of proline with alanine at position 12, the Pro12Ala polymorphism, which causes an amino-acid substitution in its ligand-independent activation domain, and a moderate decrease in its transcriptional activity (50,51). PPAR-γ expression has also been found in atherosclerotic lesions and macrophages, suggesting that PPAR-γ may influence atherogenic processes, and polymorphisms of PPAR-γ may modulate individual susceptibility to T2DM, insulin resistance, obesity, and related traits associated with coronary heart disease (48,49,52). Dedoussis et al. (53) reported that carrying the Ala allele for PPAR-γ Pro12Ala polymorphism is a risk factor for adiposity in children. Pro12Ala and/or Ala12Ala polymorphisms of the *PPAR-γ* gene have been found to be associated with obesity (54-57). The Ala/Ala genotype of the *PPAR-γ* gene was found to be associated with obesity and insulin resistance in Asian Indians (58). In a meta-analysis, it was notified that the PPAR-γ Pro12Ala polymorphism might be a risk factor for obesity susceptibility (59). On the contrary, some studies showed that the PPAR-γ Pro12Ala polymorphism is not associated with obesity in different populations (60,61). The relationship between the PPAR-γ Pro12Ala polymorphism and coronary diseases were investigated in previous studies. No association has been found between PPAR-γ Pro12Ala with ACS and coronary artery disease (62-64). In meta-analysis studies, the PPAR-γ Pro12Ala polymorphism was not associated with coronary heart disease (49,65). Wang et al. (66) reported that although the 12Ala is not an independent risk factor for obesity, the PPAR-γ Pro12Ala polymorphism is associated with increased risk of myocardial infarction in Han Chinese in Hohhot. In one study, the 12Ala allele in PPAR-γ correlated with a significantly increased coronary artery disease extent in men (67), whereas in another study, it was reported that this allele had a protective effect for cardiovascular disease (68). No association was found with coronary artery disease and PPAR-γ Pro12Ala polymorphism in Italian and Korean population (69,70), whereas in the Turkish population, it was reported that carrying the 12Ala allele increased the risk of coronary artery disease (71). In the represented study, we found that the PPAR-γ Pro12Ala polymorphism Pro/Ala genotype was found to be higher in the obese patients with ACS, while the Pro/Pro genotype was significantly higher in the control group. According to our results, it can be concluded that PPAR-γ Pro12Ala polymorphism Pro/Ala genotype may be a risk factor for ACS in obesity patients, while the Pro/Pro genotype may be a protective factor for ACS in obesity.

Finally, regarding the results of this study, and showing compliance with the previous ones, *PPAR-γ Pro12Ala* gene polymorphism may play a role in the development of ACS in obesity. Our results need to be confirmed in larger cohorts in order to improve the understanding of their role in the development of ACS in obesity patients.

Study Limitation

We believe that the small sample size in our study affected our results, and further studies with larger sample groups are needed to specifically clarify the role of the Leptin Gln223Arg, *Resistin-420 C/G*, and *PPAR-γ Pro12Ala* gene polymorphisms in the pathogenesis of ACS in obese patients. However, even with

the limited number of participants included in our study, we think that our findings will contribute to the understanding of the molecular mechanisms of ACS in obesity.

CONCLUSION

To date, no study had simultaneously evaluated the Leptin Gln223Arg, Resistin-420 C/G, and PPAR-γ Pro12Ala polymorphisms in obese patients with ACS. Thus, our study is the first to focus on the above-mentioned polymorphisms in obese patients with ACS and we believe that it might be a relevant source of data for the further studies.

Ethics Committee Approval: This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the İstanbul Medical Faculty Ethical Committee, İstanbul University (approval number: 2012/1590-1251).

Informed Consent: All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

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A Comparison of Exercise Tolerance, Measures of Cardiac Response to Exercise and Serum Markers in Chronic Obstructive Pulmonary Disease

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ABSTRACT

Objective: This study investigates the relationship between cardiac response measures and serum markers with exercise performance in patients with chronic obstructive pulmonary disease (COPD).

Methods: A total of 90 patients with stable COPD, diagnosed based on clinical findings and the GOLD spirometric criteria were included in this study. Each patient completed pulmonary function and lung diffusion tests, a six-minute walking test (6MWT), a Modified Medical Research Council Dyspnea scale, and a St. George Respiratory Questionnaire. The patient's height and body weight were obtained, and the body mass index was calculated. Serum pro-brain natriuretic peptide (pro-BNP), tumor necrosis factor-α, interleukin-6 (IL-6), IL-8, transferrin, and C-reactive protein levels were measured.

Results: After the evaluation of exercise tolerance with a 6MWT, exercise performance was found to be significantly associated with spirometric measurements, the level of dyspnea, quality of life, and serum pro-BNP levels. When the measures of cardiac response to exercise were evaluated, significant relationships were noted between systolic pressure and pulse differences, and the distance walked in a 6MWT.

Conclusion: We believe that the many factors that determine exercise tolerance in COPD patients are interrelated. A clear demonstration of these relationships may, in the long-term, change the perspective of both the clinical course of the disease and its treatment strategies.

Keywords: COPD, Pro-BNP, transferrin, exercise performance, 6-minutes walking test

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a slow-developing, chronic, and progressive disorder of the respiratory system. Treatment is based on the patient's symptoms, given that there is currently no treatment that may prevent the development or cure of COPD (1). Dyspnea is the most common symptom seen in COPD and is the leading cause of functional loss. It, therefore, plays an essential role in the choice of medication for COPD. The perceived level of dyspnea is considered as a marker of the patient's quality of life (2).

Musculoskeletal dysfunction and weakness are among the most common systemic effects of COPD and are frequently accompanied by a loss of fat-free mass. The loss of muscle mass is accompanied by muscle weakness, and this is a significant predictor of exercise capacity in COPD patients, irrespective of disease severity (3-5).

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In COPD patients, increased levels of tumor necrosis factor (TNF-α), interleukin 6 (IL-6), and IL-8, and decreased levels of calcium in the mitochondria may induce apoptosis in all body cells, including muscle cells, leading to a decreased body mass index (BMI) and weight loss (6,7).

Pro-B-type natriuretic peptide (Pro-BNP) is synthesized in response to a decrease in ventricular myocytes (8), and plasma pro-BNP levels are elevated in COPD patients that developed pulmonary hypertension and right ventricular overload (9). There are no studies on pro-BNP levels in stable COPD patients with no cor pulmonale or pulmonary hypertension (10).

A six-minute walking test (6MWT) is a valid and reliable test for the objective measurement of functional exercise capacity in individuals with pulmonary or cardiovascular diseases. The test is simple, reproducible, inexpensive, and well-tolerated. It better reflects the ability of a patient to engage in daily life activities compared to other walking tests (11-14). In this study, we compare the functional exercise capacity of COPD patients based on a 6MWT with measurements of cardiac response to exercise and serum markers.

METHODS

Patient selection: The study population included 90 patients with stable COPD, including 82 men and 8 women, selected from among the patients who were referred to our Clinics of Pulmonology Outpatient between February 2010 and April 2012, and who were invited to take part in this study through face-to-face interviews or telephone contacts.

A written informed consent was obtained from each patient. Ethics committee approval was received from the University Clinical Research Ethics Committee for approval of the study (approval number: 2010.03, date: 15.01.2010). Written permission was obtained from University Medical School Dean's Office in order to conduct the study in the Chest Diseases Clinic of Research and Application Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study inclusion criteria: Patients with a clinical picture consistent with COPD, diagnosed based on the GOLD spirometric criteria, and stable disease (no COPD exacerbation within the last six weeks) were included in this study.

Study exclusion criteria: Patients with severe physical disabilities who were unable to take the 6MWT, myocardial infarction or unstable angina within the last one month, or a history of heart failure were excluded from this study.

Our work conforms to the Helsinki declaration. This study was approved by the local research ethics committee, and all patients were informed about this study and provided written informed consent for their participation. The patients underwent physical examinations and clinical evaluations. To measure the severity of dyspnea and identify the COPD stage, all patients performed pulmonary function and lung diffusion tests and were assessed according to the Modified Medical Research Council (mMRC) dyspnea scale. Exercise performance was evaluated by a 6MWT. Height and body weight were obtained and BMI was calculated.

Pulmonary function test: This was performed by a pulmonary function test nurse in the pulmonary function test laboratories of our clinics using a Masterscope JLAB V5.22.1.50 (Cardinal Health, Germany, Hoechberg, 2006) spirometry device.

Lung diffusion test: This was carried out using a Vmax Encore 229 (Viasys Respiratory Care, ABD, California, 2008) device, based on the single-breath diffusing capacity of lung for carbon monoxide (DLCO) method.

Modified Medical Research Council Dyspnea scale: This scale is used to measure the shortness of breath that develops during walking or working, and differentiates five stages.

Six-minute walking test: This test was used to measure exercise capacity based on the recommendations of the American Thoracic Society. The total distance walked was measured and recorded at the end of the test.

St. George Respiratory Questionnaire: This is a self-administered questionnaire, standardized specifically for airway disorders, and includes questions related to three aspects of the disorder, including symptoms (8 questions), activity (16 questions) and impact (26 questions) (14).

Blood samples: TNF-α, IL-6, and IL-8 levels were measured twice using a high-precision enzyme-linked immunosorbent assay (Biosource, Nivelles, Belgium). C-reactive protein (CRP) levels were measured using a latex-enhanced immunonephelometry (Siemens, Dublin, Ireland). Plasma pro-BNP levels were measured through an electrochemiluminescence immunoassay using an Elecsys 2010 system (Roche Diagnostics, Mannheim, Germany). Transferrin levels were measured using the ELISA method.

Skinfold thickness measurement: Triceps measurements were obtained vertically from the midpoint of the distance between the acromion and olecranon while the arms were left to rest freely on either side of the body.

Statistical Analysis

The data were analyzed using SPSS Package Software version 15.0 (IBM Corporation, Armonk, New York, USA). Descriptive data were presented as numbers, percentages, means, standard deviations, medians, and minimum-maximum values. Categorical data were analyzed with a chi-square test, while a Kruskal-Wallis test was used to compare continuous variables. Correlation analyses were carried out with Spearman, Pearson, and Kendall's Tau tests, and correlation power values were interpreted as follows: 0.00-0.24, weak; 0.25-0.49, moderate; 0.50-0.74, strong; and 0.75-1.00, very strong. $P<0.05$ were considered statistically significant.

RESULTS

There were 82 men and 8 women included in this study, with a mean age of 59.7±5.8 years. Most patients were in the GOLD-stage 2 (64.4%) and mMRC 2 (55.6%) groups (Table 1).

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When measuring exercise tolerance using the 6MWT, the minimum and maximum walking distances were 180 and 671 meters, respectively, with a mean walking distance of 494.16±88.57 meters.

Based on the GOLD spirometric staging, the relationship between the St. George Respiratory Questionnaire (SGRQ) scores and the total distance walked in the 6MWT was examined, using Spearman's correlation test (Table 2).

In patients with stage 1 COPD (FEV1 ≥80%), a significant negative correlation was identified between the SGRQ symptom score and the total distance walked in 6MWT (rho: -0.611, p=0.009), and the SGRQ total score was found to have a significant negative but weak correlation with the 6MWT distance (rho: -0.493, p=0.044).

In patients with stage 2 COPD (FEV1 51%-79%), the SGRQ activity, impact, and total scores had significant negative but weak correlations with total distance walked in the 6MWT (for the activity score, rho: -0.532, p=0.0001; for the impact score, rho: -0.370, p=0.004; for the total score, rho: -0.390, p=0.003). Table 3 shows the relationships between the 6MWT distance and other parameters investigated in this study (Table 3).

A significant moderate negative correlation was found between the 6MWT walking distance and pro-BNP levels (rho: -0.435; p=0.003). Post-test forced vital capacity (FVC) and FEV1 values had a significant moderate positive correlation with walking distance (For FVC, rho: 0.354; p=0.001; for FEV1, rho: 0.332 p=0.001). On the other hand, a weak positive correlation was found between the DLCO value and total walking distance (rho: 0.212; p=0.048), and a significant weak negative correlation between BMI and total walking distance (rho: -0.217; p=0.039). A moderate negative correlation was found between total distance walked in 6MWT and the degree of dyspnea at the end of the test (rho: -0.451; p□0.01).

Values recorded during the 6MWT had a moderate negative correlation with the SGRQ symptom, impact, and total scores (rho: -0.364, p□0.001; rho: -0.384, p□0.001; rho: -0.449, p□0.001, respectively), and a significant strong negative correlation with the SGRQ activity scores (rho: -0.524, p□0.001).

The total walking distance had a moderate negative correlation with the level of dyspnea experienced after the test (rho: -0.311;

Table 1. GOLD and mMRC stages of patients

Stage	Patient (n, %)
GOLD 1	17 (18.9)
GOLD 2	58 (64.4)
GOLD 3	14 (15.6)
GOLD 4	1 (1.1)
mMRC 1	19 (21.1)
mMRC 2	50 (55.6)
mMRC 3	18 (20)
mMRC 4	3 (3.3)

GOLD: mMRC: Modified medical research council

Table 2. Relationship between total walking distance and COPD stage based on GOLD spirometric measurement criteria (Spearman correlation) (rho: correlation coefficient)

Stage	SGRQ score	Total distance	
Stage 1 (FEV1 %≥80)	Symptom score	**p=0.009**	**rho=-0.611**
	Activity score	p=0.084	rho=-0.431
	Impact score	p=0.142	rho=-0.372
	Total	**p=0.044**	**rho=-0.493**
Stage 2 (FEV1 %51-79)	Symptom score	p=0.063	rho=-0.245
	Activity score	**p=0.0001**	**rho=-0.532**
	Impact score	**p=0.004**	**rho=-0.370**
	Total	**p=0.003**	**rho=-0.390**
Stage 3 (FEV1 %31-50)	Symptom score	p=0.503	rho=-0.196
	Activity score	p=0.792	rho=0.078
	Impact score	p=0.881	rho=-0.04
	Total	p=0.994	rho=-0.002

SGRQ: St. George respiratory questionnaire

Table 3. Relationships between 6MWT distance and other investigated parameters

Investigated parameter	Associated-rho	Significance-p
Serum Pro-BNP levels	-0.435	0.003
Post-test FVC	0.354	0.001
Post-test FEV1	0.332	0.001
DLCO	0.212	0.048
BMI	-0.217	0.039
SGRQ total**	-0.449	□0.01
SGRQ-symptoms	-0.364	□0.01
SGRQ activity	-0.524	□0.01
SGRQ-impact	-0.384	□0.01
MRC*	-0.451	□0.01
Level of dyspnea at the end of the test	-0.311	0.003
Before/after the test - Pulse difference	0.348	0.001
Systolic blood pressure difference before/after test	0.266	0.01
Triceps skinfold thickness**	-0.266	0.01

*The relationship between the total Six-minute Walking test (6MWT) distance and the medical research council was analyzed with a Kendall's Tau test, **The relationships between the total 6MWT distance, the St. George respiratory questionnaire scores, and triceps skinfold thickness were analyzed with a Spearman's correlation test
Pro-BNP: Brain natriuretic peptide, 6MWT: Six-minute Walking test, MRC: Medical Research Council, SGRQ: St. George respiratory questionnaire, FVC: forced vital capacity

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p=0.003), and positive moderate correlations with the pulse and systolic pressure differences recorded after the test (rho: 0.348, p=0.001; rho: 0.266, p=0.01). The relationship between the total walking distance and triceps skinfold thickness, as a marker of nutrition, was investigated. The 6MWT distance had a moderate negative correlation with triceps thickness (rho: -0.266, p=0.01) and with BMI (rho: -0.274, p□0.01).

DISCUSSION

In the present study, a 6MWT was used to evaluate the exercise capacity of COPD patients, as an easy-to-implement and practical test, and a correlation was identified between the performance of daily life activities of patients and their 6MWT results (15).

In line with the findings in the literature, we identified a relationship between the 6MWT distances and SGRQ scores of mMRC stage 1 and stage 2 COPD patients, which indicates that the quality of life of COPD patients becomes poorer as their exercise capacity decreases. Three percent of the patients in this study had very severe (stage 4), and 18% had severe (stage 3) COPD. This insufficient number of patients with severe levels of the disease may represent an important limitation of our study.

While the source of systemic inflammation in COPD has yet to be identified, there have been some suggested mechanisms. Smoking may result in systemic inflammation even in the absence of airway obstruction, and may also cause extrapulmonary conditions (3,4).

Another opinion suggests that inflammation in the lungs is an important source of systemic inflammation. Proinflammatory molecules, such as TNF-α and IL-1, IL-6, IL-8 and transforming growth factor beta, which are released from the inflammatory cells into the lung parenchyma, flow from the lungs and enter into the systemic circulation, leading to the activation of inflammatory cells and eventually causing systemic inflammation (3,16).

In addition to its contribution to the extrapulmonary effects of COPD, the severity of systemic inflammation is also directly associated with poor quality of life, increased airway limitation, and decreased exercise tolerance in COPD patients (3). In our study, we could not find a significant correlation between exercise capacity and inflammatory markers.

Garcia-Rio et al. (17) found out that the exercise tolerance measured using a 6MWT was negatively proportional to serum CRP, IL-6, and IL-8 levels contrary to our results. Several cross-sectional studies have reported significant relationships between plasma CRP levels, disease severity, quality of life, exercise capacity, treatment response, and mortality (18,19). Similar to our findings, however, Gagnon et al. (20) could not find a significant relationship between plasma IL-6 levels and exercise capacity in patients with mild COPD. The relationship between hyperinflation and inflammation is an interesting hypothesis that merits further investigation.

We identified a moderate negative correlation between 6MWT distance and pro-BNP levels. According to Stols's hypothesis, BNP levels that increase in the presence of COPD as the small pulmonary arteries contract due to hypoxia result in increased pulmonary arterial pressure and cardiac stress (21).

In a study that evaluated cardiopulmonary exercise test (CPET) findings and BNP levels in COPD patients, Eroğlu et al. (22) identified a negative correlation between BNP levels and CPET parameters in patients with dyspnea and isolated left ventricular diastolic dysfunction. They suggested that BNP levels may be a beneficial biomarker of limited exercise capacity in patients with moderate to severe COPD (22).

Gas diffusion is impaired in COPD due to alveolar destruction and vascular bed loss (23). Consistent with the literature, we identified a positive correlation between 6MWT and DLCO (24,25).

Dyspnea is the most common symptom among COPD patients. The former is chronic, progressive, and persistent. COPD patients frequently develop dynamic hyperinflation during exercise that limits their daily activities (25). We evaluated the severity of dyspnea using the mMRC scale and identified a correlation between 6MWT and dyspnea severity. This finding is consistent with previous studies in which strong correlations are reported between exercise capacity and dyspnea severity experienced during exercise. (23-25).

We also identified significant correlations between 6MWT distance and pre-/post-test pulse and systolic blood pressure differences. Pulse response during the test is an important parameter regarding cardiac response to exercise, guiding the investigation of heart failure in patients with limited exercise capacity.

We evaluated malnutrition levels based on BMI and triceps skin thickness. The 6MWT distance of our patients was negatively correlated with BMI and triceps skin thickness. Malnutrition is associated with structural and metabolic changes in the peripheral respiratory muscles, and so may exacerbate shortness of breath and impair exercise tolerance and quality of life (26). While many previous studies have failed to identify a correlation between body weight and 6MWT distance, nutritional support significantly increased the distance walked in 6MWT (27-29).

Study Limitations

The limitations of the study include the collection of study data from a single center and the small sample size. Also, as this is a cross-sectional study, cause-effect analysis cannot be performed.

CONCLUSION

The data reported over recent years suggest that exercise performance in COPD patients may be a direct or indirect predictor of survival. While this process involves rather complex associations, it is specific for each patient. In this regard, all factors that reduce exercise capacity should be identified and eliminated to increase the patients' quality of life and survival as much as possible.

The data collected in this study and the relevant analyses suggest that there are numerous and interrelated factors that affect

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exercise performance in COPD patients. Appropriately designed studies conducted with larger patient cohorts are required to demonstrate these relationships more clearly.

Ethics Committee Approval: Ethics committee approval was received from the University Clinical Research Ethics Committee for approval of the study (15.01.2010, Approval No. 2010.03). Written permission was obtained from University Medical School Dean's Office in order to conduct the study in the Chest Diseases Clinic of Research and Application Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: A written informed consent was obtained from each patient.

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Topographic Evaluation of Acute Isolated Unilateral Thalamic Infarctions on Diffusion-weighted Imaging

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ABSTRACT

Objective: The thalamus plays a major role in regulating arousal, consciousness, and activity. Distinct vascular distribution of the thalamus causes different syndromic presentations of thalamic nuclei infarctions. During the evaluation of acute thalamic infarction, it is important to determine the thalamic vascular zone that is affected. This study aimed to assess the topography of acute isolated unilateral thalamic infarction on diffusion-weighted imaging, and to investigate the distribution of classic and variant type thalamic infarctions.

Methods: The imaging database of the 336 consecutive patients with acute thalamic infarction admitted to the radiology department between January 2015 and February 2020 were retrospectively reviewed. Specifically, patients with acute isolated unilateral thalamic infarction were included. The most affected thalamic territory, variant/classical territory rates, and the comparison of age and gender were evaluated.

Results: A total of 141 patients (classic territory group: 104, variant territory group: 37) were reviewed. The ratio of affected classic territory to variant territory was 2.8. Affected classic territories were inferolateral (n=68), anterior (n=25), paramedian (n=11), and posterior (n=0). Affected variant territories were posterolateral (n=18), central (n=13), and anteromedian (n=6). Comparing the patients in both groups, age, sex, and side were similar, p=0.435, p=0.71, and p=0.85, respectively. Relevant arteries did not have stenosis in 96.2% of patients, and no significant difference was observed between both groups, p=0.631.

Conclusion: In isolated acute unilateral thalamic ischemia, the ratio of the affected variant to the classic territory was approximately 1/3. Therefore, during the radiologic evaluation of acute thalamic ischemia, a variant thalamic territory should be considered in the presence of infarction that does not fit the classic territory, in order to avoid clinical-radiological discrepancies.

Keywords: Thalamus, infarction, arteries, magnetic resonance imaging

INTRODUCTION

Thalamic infarctions constitute approximately 11%-14% of acute ischemic strokes of the posterior circulation, most of which are unilateral (1). Thalamic infarctions are classified traditionally into four groups based on the territories supplied by four main arteries: anterior, paramedian, inferolateral, and posterior. This classification was initially based on neuroanatomic and neuropathologic data. However, this classification is recently based on imaging techniques, especially diffusion-weighted imaging (DWI), in the acute stage (2).

The thalami are fed by perforating branches of the anterior and posterior circulation (3). The territories of the thalamus can be subdivided traditionally into four groups based on the supplying arteries: anterior, paramedian, inferolateral, and posterior (4-6). The anterior territory is supplied by the tuberothalamic arteries (polar artery), which is the largest branch of the posterior communicating artery (PComA).

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The paramedian territory is supplied by the paramedian (thalamoperforating) arteries that originates from the P1 segment of the posterior cerebral artery (PCA). The inferolateral territory is fed by inferolateral (thalamogeniculate) arteries that arise as individual vessels from the distal P2 segment of the PCA. The posterior territory is supplied by the posterior choroidal arteries (PChA). The posterior choroid group usually includes one or two medial and one to six lateral PChAs. Medial PChA generally arises from the distal P1 or proximal P2 segments of the PCA. Lateral PChA arises directly from the PCA (distal P2 or proximal P3 segments) or from a branch of the PCA (3-5).

In addition to the classic vascular territories described above, there are also three variant vascular territories: anteromedian, central, and posterolateral. These variant areas can be due to variant vascular distribution or border-zone ischemia (2,4,5). The anteromedian territory is formed by combining the classic anterior and paramedian territories. It involves the posterior part of the anterior territory and the anterior part of the paramedian territory. The central territory involves parts of all the four adjacent classic territories and it is located in the central part of the thalamus. The posterolateral territory is formed by combining classic inferolateral and posterior territories. It involves the posterior part of the inferolateral territory and anterior part of the posterior territory (2,4,5,7).

The clinical spectrum of thalamic infarction can vary depending on the affected territories. Specifically, infarction located on variant territories may confuse the clinical-radiological presentation of a thalamic ischemic stroke. Therefore, it is important to recognize the classic and variant territories of the thalamus. This study aimed to evaluate the topographic patterns of isolated unilateral thalamic infarctions and to investigate the distribution of classic and variant type thalamic infarctions on DWI.

METHODS

Ethics, Study Design and Patients

Ethics committee approval was received for this study from the Ethics Committee of Taksim Training and Research Hospital (approval number: 81, date: 19/05/2020).

The imaging database of the 336 consecutive patients with acute thalamic infarction admitted to our radiology department between January 2015 and February 2020 was reviewed retrospectively on a PACS imaging workstation (Infinitt PACS; Infinitt Healthcare, Seoul, Republic of Korea). The primary imaging criteria for inclusion was isolated unithalamic infarction on DWI, whereas bithalamic infarctions, PCA territory infarctions involving the thalamus, accompanying infarcts in other vascular territories, and unithalamic abnormal signal intensity due to causes other than arterial infarctions such as tumor, deep venous thrombosis, and hemorrhage were excluded. After the exclusions, the final cohort consisted of 141 patients (77 females and 64 males with a mean age of 66.1±12.8) of the 336 investigated DWI. Then, the final population was divided into two groups: classic group (n=104) and variant group (n=37).

Imaging Protocols

DWIs were obtained using two 1.5 T-magnetic resonance imaging units (GE Signa HDxt and Signa Explorer; GE, Milwaukee, WI, USA). DWIs were acquired in the axial plane with parameters field of view: 25 mm, repetition time: 5000 ms, echo time: 100 ms, acquisition time: 1, number of excitations: 1, and b values of 0 and 1000 s/mm^2, isotropically weighted. DWI yielded 20 contiguous slices that were 7 mm thick and axial-oblique. Apparent diffusion coefficient (ADC) map was automatically generated from the DWI at b= 0 and b=1000 s/mm^2. We checked the ADC maps to ensure that "real" diffusion disturbance occurred. A visual evaluation was performed. Besides, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) were evaluated to investigate the relevant arteries of the thalamus.

Imaging Analysis

All the DWIs were evaluated by a radiologist with significant experience in neuroradiology (S.N.D. with 11 years in neuroradiology) on a PACS imaging workstation. The radiologist was blinded to the neurologic symptoms during the retrospective imaging review.

All the DWIs were reviewed with regard to the location of the thalamic infarction based on previous templates of classic and variant thalamic territories.

In CTA or MRA examinations, the stenosis of relevant arteries was evaluated.

Topography of Thalamic Infarctions

Classic thalamic infarctions were assigned four vascular zones based on previously published territory templates (3-5): anterior, paramedian, inferolateral, and dorsal (Figure 1). Isolated posterior territory infarction was not observed in this study. Therefore, to depict the posterior territory, posterior territory infarction accompanying to PCA infarction was used was shown in Figure 1d.

Variant thalamic infarctions were assigned into three vascular zones based on previously published territory templates (2,7): anteromedian, central, and posterolateral (Figure 2).

The relevant arteries were basilar artery, PCA, and PcomA.

Statistical Analysis

IBM SPSS version 22.0 software was used for the data analysis. Normality checks were performed by the Shapiro-Wilk test, and by drawing histograms, Q-Q plots, and box plots. Data were expressed as mean, standard deviation, minimum, maximum, frequency, and percentage. The two categories of non-normally distributed variables were analyzed using the Mann-Whitney U test. T test was used to compare the nominal variables. The significance level was taken as $p<0.05$ and bidirectional

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RESULTS

The final cohort consisted of 141 patients (41.9%) with isolated unilateral thalamic infarctions. Thalamic infarctions were located in classic territories in 104 (73.8%) patients and in variant territories in 37 (26.2%) patients. The ratio of affected classic territory to variant territory was 2.8.

In the total cohort, 64 (45.4%) patients were males and 77 (54.6) were females. The thalamic infarction was located on the right side in 59 patients (41.8%) and on the left side in 82 (58.2%). Comparing the patients in the classic and variant groups, the age, sex, and affected side were similar for both, with p=0.435, 0.761, and 0.852, respectively.

The relevant artery was investigated for 80 (56.7%) patients. CTA was performed for 84.8% of patients (n=67), and MRA for 15.2% (n=12). No stenosis was observed in 77 patients (96.2%). There was more than 50% stenosis in 2 patients (2.5%), and <50% stenosis in one patient (1.3%). No significant difference in relevant artery stenosis was observed between the classic and variant groups, p=0.631.

Table 1 summarizes the patient demographics.

Regarding the vascular territory of the thalamus, the anterior territory was involved in 25 patients (17.8%), paramedian in 11 (7.8%), inferolateral in 68 (48.2%), posterior in 0 (0.0%), anteromedian in 7 (4.9%), central in 12 (8.5%), and posterolateral in 19 (13.5%) patients. While infarctions were most commonly identified in the inferolateral territory, the posterior territory was not involved in any of the patients.

Regarding the classic vascular territory of the thalamus, the anterior territory was involved in 25 patients (24%), paramedian in 11 (10.6%), inferolateral in 68 (65.4%), and posterior in 0 (0.0%). Inferolateral territory was the most frequently affected classic territory. However, the isolated posterior territory infarction was not observed in any patient.

Regarding the variant vascular territory of the thalamus, the anteromedian territory was involved in 6 patients (16.2%), central in 13 (35.1%), and posterolateral in 18 (48.7%). The posterolateral territory was the most frequently affected variant territory.

Table 2 shows the distribution of the thalamic infarctions with vascular zones.

DISCUSSION

In the present study, the topographic pattern of isolated unilateral thalamic infarctions on DWIs was evaluated based on the relevant vascular zones. Several interesting findings were obtained. First, isolated unilateral thalamic infarctions constituted 41.6% of all

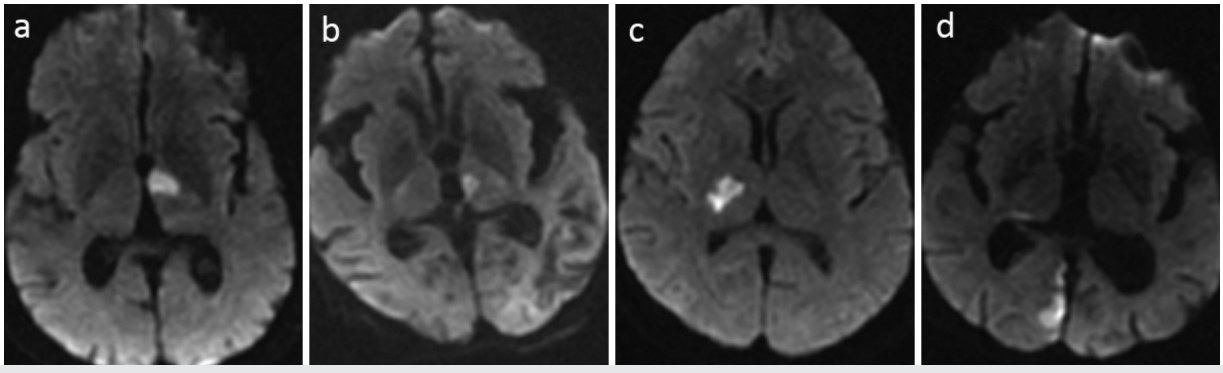

Figure 1. The classic territories of the thalamus on the DWI: anterior (a), paramedian (b), inferolateral (c), and posterior (d). The posterior territory infarction (d) was depicted from the PCA territory infarction because an isolated posterior territory infarction was not detected
DWI: Diffusion weighted imaging, PCA: posterior cerebral artery

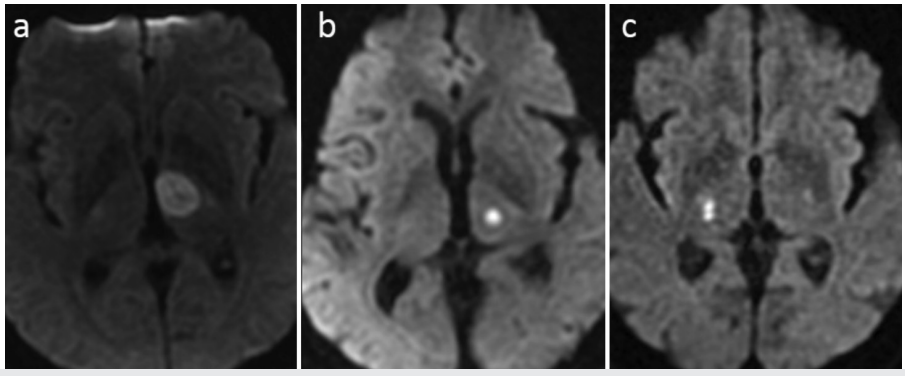

Figure 2. The variant territories of the thalamus on the DWI: anteromedian (a), central (b), and posterolateral (c)
DWI: Diffusion weighted imaging

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thalamic infarctions. Second, the ratio of the involved variant territory to the classic territory was approximately 1/3. Third, while the inferolateral territory was the most frequently affected in all the isolated unilateral thalamic infarctions, the isolated posterior territory infarct was not observed. Fourth, regarding the most frequently affected territory in classic and variant groups, whereas the inferolateral territory was the most frequently affected territory in the classic group, the posterolateral territory was in the variant group. Fifth, the relevant artery did not have any stenosis in 96.2% of patients. Comparing patients in the classic group and variant group, the results of relevant artery stenosis were similar for both.

In the literature, previous studies focused on the clinical-radiologic relationship of acute unilateral thalamic infarction without considering the isolated or a part of the PCA infarction. Meanwhile, this study consisted of only isolated unilateral thalamic infarctions and included a large number of patients. The present study also focused on the type of thalamic infarctions based on the affected vascular territory: classic and variant.

The ratio of isolated unilateral thalamic infarction in all the thalamic infarctions was similar with that of previous studies (8). Considering the affected vascular territory of the thalamic infarction, the variant group constituted approximately 1/3 of the isolated acute unilateral thalamic infarction, consistent with the literature (2).

Regarding the topography of the involved classic territory in previous studies, the inferolateral territory was the most frequently affected in all the studies, whereas the rates of the other territories varied between studies (8-12). Particularly, previous studies have reported various rates of isolated paramedian territory infarction and isolated posterior territory infarction. However, Wang et al. (8) did not report any isolated paramedian territory infarction, and Pezzini et al. (10) did not reveal any isolated posterior territory infarction. In present study, the inferolateral territory was affected the most, consistent with previous studies (8-12). Besides, while the isolated paramedian territory was observed, the isolated posterior territory infarction was not detected. Although this result was consistent with the findings of Pezzini et al. (10), it was contrary to those of Wang et al. (8). The isolated posterior territory infarctions are the least common infarction of the thalamus. The posterior territory of the thalamus has rich anastomosis; therefore, infarction that locates only the posterior territory could be very rare. Posterior territory infarctions are usually a part of the PCA territory infarction (13-16). In addition, there may be some difficulties especially in differentiating between the classic posterior territory and variant posterolateral territory. The previous studies also did not separately describe the variant territories.

Table 1. Summary of patient demographics in the total cohort

	Classic group (n=104)	Variant group (n=37)	Total cohort (n=141)
Gender (n, %)			
Male	48 (46.2%)	16 (43.2%)	64 (45.4%)
Female	56 (53.8%)	21 (56.8%)	77 (54.6%)
Age (mean/range)	66.6 (24-96)	64.6 (33-89)	66.1 (24-96)
Affected side (n, %)			
Right side	44 (42.3%)	15 (40.5%)	59 (41.8%)
Left side	60 (57.7%)	22 (59.5%)	82 (58.2%)
Stenosis of relevant arteries (n, %)	58 (55.8%)	22(59.5%)	80 (56.7%)
≥50% stenosis	2 (3.4%)	0 (0.0%)	2 (2.5%)
<50% stenosis	1(1.7%)	0 (0.0%)	1 (1.3%)
No stenosis	55 (94.9%)	22 (100%)	77 (96.2%)

There are few reports that investigated the variant territories of the thalamus (2,7). Kumral et al. (7) evaluated the acute multiple variant type thalamic infarction and they reported that the most commonly affected variant territory was posterolateral in unilateral thalamic infarction. Carrera et al. (2) investigated the isolated variant thalamic infarction. They reported the distribution of affected variant territories such as the anteromedian (n=9), posterolateral (n=8), and central (n=4). In present study, the most frequently affected variant territory was posterolateral, consistent with results of Kumral et al. (7). However, the least frequently affected variant territory was anteromedian, contrary to the findings of Carrera et al. (2). The frequency of the affected variant territory in the present study was different from previous studies. The discrepancy regarding the frequency of the affected variant territory among different studies may be as a result of the small sample size. Therefore, variant thalamic infarction needs to be evaluated in large series.

In addition, in this present study that evaluated relevant arteries were by CTA or MRA, large artery disease was not observed in both the sclassic and variant group. Therefore, this result can support the fact that variant territory can be as a result of variant vascular distribution rather than border-zone ischemia. Both Kumral et al. (7) and Carrera et al. (2) also reported that the most frequent cause of stroke was cardioembolism, and not large artery disease.

Table 2. The distribution of the thalamic infarctions according to vascular zones

	Total cohort (n=141)
Classic thalamic territory (n, %)	104 (73.8%)
Anterior	25 (24%)
Paramedian	11 (10.6%)
Inferolateral	68 (65.4%)
Posterior	0 (0.0%)
Variant thalamic territory (n, %)	37 (26.2%)
Anteromedian	6 (16.2%)
Central	13 (35.1%)
Inferolateral	18 (48.7%)

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Study Limitations

Several limitations to this study need to be acknowledged. First, the study was retrospective and is subject to all the limitations of this study design. Second, it was a single-center study. Third, only a small number of infarctions were present for certain vascular territories. Forth, the CTA or MRA examination could not be performed in all the patients.

CONCLUSION

The affected territory in acute isolated thalamic infarction can be in the variant group in approximately 1/3 of patients. Regarding the classic and variant groups, the most frequently affected territories were inferolateral and posterolateral, respectively. Therefore, in daily practice, during the evaluation of acute thalamic infarction on DWI, the infarction area needs to be sought for more carefully, whether it fits the classic territory or not. This is because an accurate topographic evaluation is important to avoid clinical-radiological discrepancies.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Taksim Training and Research Hospital (approval number: 81, date: 19/05/2020).

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The Efficacy of Voice Therapy in Call Center Agents with Disphonia

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ABSTRACT

Objective: In this prospective research, voice therapy results of 13 call center employees with voice problems were evaluated.

Methods: Thirteen call center employees (13 women) with voice problems who underwent voice therapy between September 2012 and January 2013 were included in the study. All patients underwent videolaryngostroboscopy prior to voice therapy. Before and after therapy, voice recordings were analyzed with Praat Program, voice handicap index-10 (VHI-10), maximum phonation time (MPT), s/z ratio values and diet passage readings for perceptual evaluation (GRBAS) were obtained. The results were statistically compared.

Results: A statistically significant differences between VHI, MPT and s/z ratio and GRBAS was obtained before and after sound therapy ($p<0.05$).

Conclusion: Call center employees who experience voice problems benefit from voice therapy while the existing workload density continues.

Keywords: Voice therapy, voice disorder, call center

INTRODUCTION

Vocation-related voice problems are most common (38% to 80%) in teachers (1,2). The second occupational group followed by 68% are call center employees (3). The first call center was established in the late 1960s by a federal judge's decision by the Ford firm to allow customers to report faulty cars to the company (4). The Call Centers Association states that the number of customer representatives in call centers reached ninety-one thousand people in 2017 and that they expect the number to rise to ninety-five thousand people in 2018 (5). Studies on call centers have shown that working in Call Centers is a stressful job (6). Tüfekçioğlu (7) stated that 37.7% of call center customer representatives experienced hoarseness in a study conducted in three different regions in Turkey. The voice complaints that occur in professional voice users such as call center employees are mostly hoarseness, tonal deterioration, narrowing of the voice range, weakness in the voice, and voice fatigue (3,8,9). The accompanying complaints are shortness of breath, feeling stuck in the throat, feeling dry in the throat, sore throat and difficulty talking (3,8,9). Chronic vocal problems can lead to benign vocal cord pathologies. Muscular tension dysphonia develops due to the misuse of the voice during phonation and habitual behaviors that are harmful to the voice. The tension in the neck muscles is noticeable to the eye even when talking, and the voice comes out tense, hoarse and muffled. Vocal nodules are associated with excessive or improper use of sound. The nodule is a small white or greyish protrusion located in the anterior 1/3 on the

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free edge of the vocal cords. Vocal cord polyps are unilateral lesions in contrast to vocal nodules. The Reinke cavity is located under the epithelium layer of the vocal cords. Reinke edema is a bilateral diffuse polyposis of this cavity. In later stages, the polypoid feature can progress enough to disrupt breathing. Its etiology includes smoking, allergies and chronic irritation (10-12).

In this study, the call center employees who experienced voice problems and who were diagnosed with vocal nodules, muscle tension dysphonia, reinke edema, vocal polyps and vocal cysts as a result of larengostroboscopic evaluation were investigated whether they benefit from voice therapy while their workload intensity continued.

METHOD

In this prospective study, 37 patients who applied to İstanbul Anatomica Hospital with the complaint of hoarseness and were diagnosed with vocal nodule, muscle tension dysphonia, Reinke edema, vocal polyps, vocal cysts as a result of ear nose throat examination and video-laryngostroboscopic evaluation between September 2012 and January 2013 were included. The data of 13 clients who completed voice therapy were evaluated from these clients. Data from 24 clients who did not complete the therapy were excluded from the study.

Laryngeal structures of all clients were evaluated by an otolaryngologist during rest, flat / i / and glide-containing / i / fonation with videolaryngostroboscopy. Objective and subjective sound assessments of the clients were made before and after therapy. Maximum phonation time (MPT), s/z ratio, F0, intensity, jitter, shimmer, HNR parameters were examined from objective evaluations; aerodynamic and acoustic parameters. The Praat program was used in acoustic analysis of sound. In subjective evaluations, the client's voice was evaluated by voice handicap index (VHI-10) and the client's voice was evaluated by two clinicians with GRBAS. In the MPT evaluation, the clients were asked to expirate with /i/ vocal after a deep inspiration, and this process was repeated three times. The scores from each client were averaged. In order to evaluate the s/z ratio of aerodynamic parameters, individuals were asked to expirate with /s/ and /z/ consonants after a deep inspiration, and this process was repeated 3 times. The scores from each client were averaged.

Within the scope of voice therapy, vocal hygiene and diaphragm breathing training were given in two groups, but voice exercises and laryngeal massage were applied to each client in the form of a specific therapy program. Voice therapy was performed 1 time per week. Each session lasted 35-40 minutes and a total therapy period of 4 weeks.

Within the scope of vocal hygiene training; the clients were informed about different forms of vocal rest, suggestions to prevent reflux, not speaking in noisy places, resting the voice occasionally while talking, avoiding extreme behaviors related to phonation, speaking at the middle pitch and violence level, increasing hydration, avoiding substances-foods and drinks that could harm the sound. The diet and medical treatment of the clients suffering from reflux was started by the ear nose throat physician.

Statistical Analysis

SPSS package program was used for statistical analysis of the findings. Statistical analysis of changes before and after voice therapy was evaluated using paired sample t-test in SPSS program. P values less than 0.05 were considered statistically significant.

RESULTS

Thirteen (100%) of the clients included in the study were women. Reinke edema was found in 1 of the clients, polyp in 1, muscle tension dysphonia in 3, bilateral vocal nodules in eight. When the values obtained before and after voice therapy were compared, a statistically significant difference was obtained ($p<0.05$) (Table 1-3).

Table 1. Acoustic values before and after therapy

	Before therapy	After therapy	t-value	p-value
F0	217	212	0.726	0.482
Intensity	90	91	-1.554	0.146
Jitter	0.22	0.15	3.081	0.010
Shimmer	1.24	0.72	2.576	0.024
HNR	20	24	-2.725	0.018

Table 2. Pre-and post-therapy MPT, s/z, VHI-10 values

	Before therapy	After therapy	t-value	p-value
MPT	13	18	-6.624	0.000
s/z	1.3	1.1	1.342	0.204
SHI-10	13	9	3.679	0.003

MPT: Maximum phonation time, VHI: Voice handicap index

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Table 3. Pre-and post-therapy GRBAS scores

	Before therapy	After therapy	t-value	p-value
g	1.6	1.1	3.207	0.008
r	1.6	1	4.382	0.001
b	1	1	0.562	0.584
a	0	0	-	-
s	1.4	0.5	5.500	0.000
Total GRBAS	5.6	3.7	6.218	0.000

DISCUSSION

Voice therapy can be defined as an effort to restore the voice to the highest level possible to meet the occupational, emotional and social needs of the patient (13). In our study, VHI-10, GRBAS, MPT, s/z ratio, F0, intensity, jitter, shimmer, HNR parameters data obtained before and after the therapy of adult clients with vocal cord nodule, vocal cord polyps, reinke edema and muscle tension dysphonia statistically compared.

Bengisu et al. (10) found a statistically significant difference in jitter and shimmer parameters after the therapy compared with the pre-therapy in 19 of 20 patients with muscle tension dysphonia. de Oliveira et al. (14) found significant improvement in jitter values with voice therapy in their study with forty-eight call center employees, but they could not reveal a difference in other acoustic analysis parameters or perceptual evaluation scores. The results we found in the study show a similarity in the significant statistical changes seen in the jitter and shimmer parameters compared to previous publications.

Treole and Trudeau (15) found that 13 clients with bilateral vocal nodules had no statistically significant difference in MPT and s/z ratio compared with pre-therapy and post-therapy. Eryılmaz et al. (16) had statistically significant differences in VHI-10, MPT and s/z ratio compared with pre-therapy and post-therapy of 40 adult clients with vocal cord nodules. Unlike the research of Treole and Trudeau (15), in our study, a statistically significant difference was found in the MPT values after the therapy compared with the pre-therapy. When our results are compared with the results of the studies of Eryılmaz et al. (16), The significant statistical changes seen in SHI-10 and MPT scores show a similarity.

Holmberg et al. (17) administered voice therapy to eleven clients with bilateral vocal nodules. As a result, they found that voice therapy had a positive effect on perceptual evaluation and sound quality.

Symptoms such as feeling stuck in the throat and need for frequent throat clearing of mucus, even if there were no serious voice complaints in Call Center employees (18). In this study conducted by Lehto et al. (18), It was found that more than 60% of the employees had a change in their vocal habits, and no negative results were found in any subject receiving therapy. In their subsequent study, the same group of researchers questioned the long-term vocal complaints of their patients who underwent short-term therapy 1-1.5 years later by questionnaires and found significant improvement in complaints such as hoarseness and vocal tension compared to the group who did not receive therapy (19).

CONCLUSION

As a result, in our study, a statistically significant improvement was obtained in the jitter, shimmer and HNR parameters, VHI-10, MPT, general GRBAS and GRBAS sub-scores, g, r and s-scores, compared before and after voice therapy ($p<0.05$).

Ethics Committee Approval: Ethics committee approval was not received.

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Cervical Lipoleiomyoma: Case Report

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ABSTRACT

Lipoleiomyomas are uncommon benign neoplasms composed of various mixtures of long intersecting bundles of bland smooth-muscle cells and mature adipocytes. These tumors are most commonly located in the uterine corpus, but rarely may be found in other locations, including the cervix, ovary, broad ligament, and retroperitoneum.

Keywords: Lipoleiomyoma, cervical

INTRODUCTION

Uterine lipoleiomyomas are rare (0.03%-0.20%) benign neoplasms known as a specific type of leiomyoma. These tumors are composed of a mixture of smooth muscle cells and mature adipocytes. They are most commonly found in the uterine corpus, but rarely can found in other localizations, such as the cervix, ovary, broad ligament, and retroperitoneum (1).

Most of the patients are asymptomatic peri or postmenopausal women. In fact, uterine lipoleiomyomas are clinically similar to leiomyomas and do not require treatment if they are asymptomatic. These tumors can be mixed with other gynecological conditions such as mature teratoma, well-differentiated liposarcoma and atypical lipoma (2,3). Therefore, surgical excision of these tumors and definitive histopathological diagnosis are important.

Here, an extremely rare case of cervical lipoleiomyoma diagnosed with postoperative histopathological examination in the premenopausal patient is presented with the consent of the patient.

CASE PRESENTATION

A 39-year-old G2P2 female patient applied with complaints of inguinal pain, which was more significant during sexual intercourse. In bimanual examination, a hard, solid cervical mass with a diameter of 7-8 cm was detected, which was protruded into the vagina, the borders of which were not clearly separated from the uterus. Magnetic resonance imaging (MRI) showed mass lesions with smooth lobulated contours filling the vagina, pushing the cervix into the superiora and anteriorly, showing intense contrast involvement in heterogeneous T2 signal intensity in a measure of 83x73x60 mm (Figure 1). Hemoglobin: 10.3 g/dL, hematocrit: 31.2%, serum glutamic oxaloacetic transaminase: 20 U/L, serum glutamic pyruvic transaminase: 16 U/L, cancer antigen (CA)125; 20.1 U/mL, carcinoembryonic antigen: 1.18 ng/mL, CA19-9: 8.6 ng/mL, CA: 15-3 26.8 U/mL. 8 cm diameter solid mass originating from the cervical region was detected in the patient who was operated with pfannenstiel incision under general anesthesia. Hysterectomy and bilateral salpingectomy were performed (Figure 2). The patient was discharged on the third postoperative day, and

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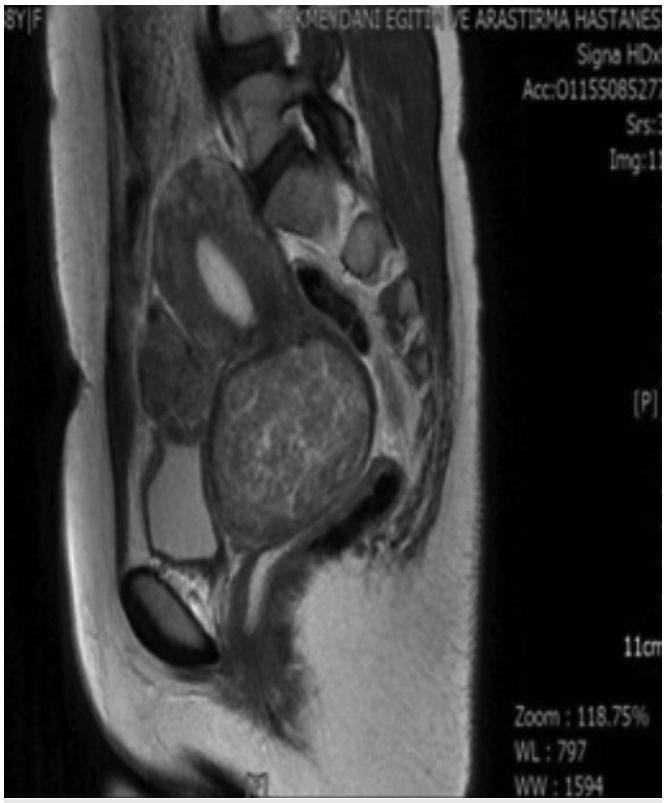

Figure 1. Preoperative magnetic resonance image

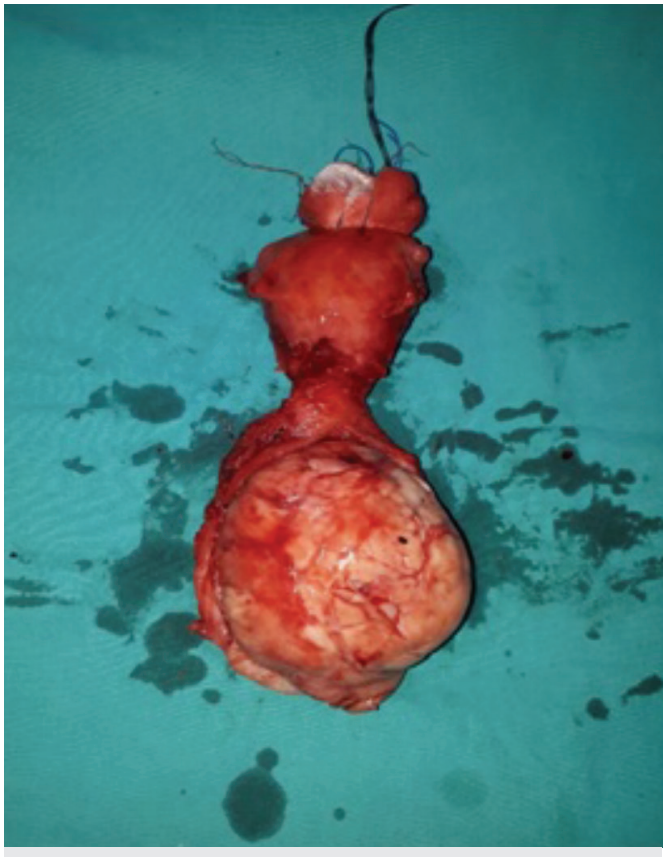

Figure 2. Postoperative histopathological specimen

the result of postoperative pathology was reported as cervical lipoleiomyom.

Informed consent was obtained.

DISCUSSION

Cervical leiomyoma is the most common cervical benign tumor that develops in the cervical muscle tissue, usually 0.5-1 cm diameter, single, straight structure, hard and similar to uterine myomas. Cervical fibroids constitute 1-2% of total fibroids and are observed in 3 different ways: interstitial, supravaginal and polypoidal. Supravaginal fibroids can push the uterus to the superior by surrounding the entire cervical canal. They can also be unilateral or bilateral, intramural or subserosal and can extend into the pelvis. Symptoms may differ depending on the direction of growth of the fibroid. Growing fibroids can cause symptoms related to mechanical pressure in neighboring organs, causing dysuria, urinary incontinence, ureteral obstruction, dyspareunia, or blockage of the cervix (4).

Uterine lipoleiomyoma is a rare mesenchymal neoplasm and is often described as a variant of uterine leiomyoma. It constitutes less than 0.2% of benign uterine tumors. Lipoleiomyoma consists of a mixture of smooth muscle and mature adipose tissue. The origin of the lipomatosis lesions of the uterus is a matter of debate; possible causes are the wrong placement of adipose cells in the embryological period, metaplasia of muscle and connective tissue cells to adipose cells, lipocytic differentiation of primitive connective tissue cells, infiltration of perivascular adipose cells around the vessel during the operation or connective tissue degeneration (5).

Imaging plays an important role in intrauterine localization and determination of adipose tissue content. In ultrasonographic examination, it presents as hyperechoic masses partially covered with a hypoechoic area. The hypoechoic area is interpreted as the myometrium surrounding the adipose tissue component. In computed tomography, the mass lesion is observed as the dominant hypodense area from the well-limited adipose tissue that separates from the uterus. In MRI examination, lipomatous component is observed in high signal intensity on T1-weighted images. The lipomatous component can be confirmed using the adipose suppression technique (6).

Similar uterine tumors that should be considered in differential diagnosis are angiolipoma, angiomyolipoma, lipoid degenerated leiomyoma, atypical lipoma and well-differentiated liposarcoma. Immunocytochemical studies confirm the complex histogenesis of these tumors that may arise from mesenchymal immature cells or direct transformation of smooth muscle cells into adipocytes. Additional gynecological malignancies from the uterus, cervix or ovaries have been reported in 18.8% of patients. Therefore, patients with uterine lipoleiomyomas should be subjected to detailed clinical and pathological evaluation in order not to overlook the coexistent gynecological malignancy. As a result of long-term follow-up of uterine lipoleiomyomas, it has been shown

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that such cases progress in benign character and that such cases do not cause any recurrence or death due to disease as isolated (7).

CONCLUSION

Although cervical lipoleiomyomas are much more rare than those of uterine origin, the symptoms of both are similar to typical leiomyomas. It is frequently seen in perimenopausal or postmenopausal women, rarely in premenopausal women. The definitive diagnosis is made by postoperative histopathological examination.

Informed Consent: It was obtained.

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Conflict of Interest: The authors have no conflict of interest to declare.

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The Phenomenon of Acute Renal Failure in Patients with Chronic Use of Wild Tobacco

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ABSTRACT

In patients with acute renal failure (ARF), the differential diagnosis may be more difficult than expected. Especially in young adults without additional diseases, it may not be considered in the diagnosis that an ARF can develop on the basis of chronic renal failure (CRF). In this case, ARF developed on the basis of CRF was presented in the light of literature in a young male patient who presented to the emergency department with ARF and who used chronic wild tobacco in his anamnesis.

Keywords: Acute renal failure, chronic renal failure, wild tobacco, Nicotiana Rustica Linn

INTRODUCTION

Wild tobacco (Nicotina Rustica Linn) is a smokeless tobacco used in our country, especially in the southeastern and eastern Mediterranean region, in place of cigarettes or with cigarettes. It is used by placing it in the oral mucosa (1). Chronic use of wild tobacco has been shown to cause many pathologies including oral mucosa cancers and respiratory problems in the long term (2). It has also been shown that blood pressure and heart rate increase in a short time after taking wild tobacco (3). Acute changes in the body after wild tobacco can reveal the underlying pathologies. In this case, acute kidney damage after the use of wild tobacco showed us that the patient had an undiagnosed chronic kidney failure.

CASE PRESENTATION

A 28-year-old male patient was admitted to the emergency room with respiratory distress and abdominal pain and on his first physical examination he was tachypneic (respiratory rate: 40/minute), hypertensive [tension (TA): 180/100 mmHg] and agitated. The blood gas taken under mask oxygen (6 L/minute) in the emergency room is determined to be pH: 7.22, pCO_2: 27 mmHg, pO_2: 36 mmHg, SO_2: 49%, Lac: 1.3 mmol 1/L, HCO_3: 11 meq/L, BE: -15 mmol l/L. It has been decided that the patient who was consulted will be interned in the intensive care unit. After being taken to intensive care, the patient was observed to be SpO_2: 50% under 3 L/minute mask oxygen and was intubated orotracheal and began to support invasive mechanical ventilation. While in volume control mode, PEEP was set to 8 cm H_2O and FiO_2 0.6. It was learned from the relatives of the patient that there was an increasingly severe respiratory distress in the past month, and he had applied to the emergency department several times. He had also swelling (like edema) on his foot recently and this situation regressed spontaneously. In the interrogation made in terms of substance use, it was found that the patient was a chronic wild tobacco (Nicotina Rustica Linn) user and chewed the wild tobacco before applying to the emergency room. Biochemistry

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parameters resulted in urea: 381 mg/dL-1, creatinine: 25.12 mg/dL, sodium: 126 mmol/L, calcium: 3.9 mmol/L, potassium: 5.5 mmol/L. From the moment he was admitted to the hospital, his anuria was present and therefore continuous venovenous hemodiafiltration (CVVHDF) was initiated with acute renal failure (ARF) in mind. Upon determination of hemoglobin value 4.7 gr/dL, 3 unite erythrocyte suspension replacement was performed. Sedation was provided by infusion of remifentanil 0.2 mcq/kg/minute. The patient's nasal, phlegm and urine cultures were sent. The hepatitis markers were negative. Bilateral widespread infitrations were detected in chest X-ray and thorax tomography (Figure 1, 2). Acid resistant staining/ Erlich-Ziehl-Neelsen was studied in terms of tuberculosis and it was observed to be negative. The patient underwent a renal ultrasound and was found an increase in parenchyma echogenity. On bedside echocardiography, ejection fraction was 60%, heart cavities and valve structures were normal, but pericardial effusion (uremic pericarditis) was detected. In the 6th hour of the intensive care follow-up, there was a decrease in the biochemistry values examined under CVVHDF (urea: 272 mg/dL, creatinine: 16.89 mg/dL). In the SIMV-P mode as a result of arteriel blood gas, FiO_2: 0.4, Ph: 7.34, pO_2:58 mmHg, PcO_2:35 mmHg, SO_2: 90%, BE: -5 mmol/L. On the second day of intensive care follow-up, the patient's anuria continued. The patient's procalcitonin value was 19 ng/mL and piperacillin-tazobactam, moxifloxacin and linezolid treatment was started by the infectious disease consultant. Urea: 29 mg/dL-1, creatinine: 2.07 mg/dL-1 decreased in the third day of follow-up (Table 1). However, due to the absence of urine output, he was consulted with internal medicine specialist. With the recommendation of internist parathyroid hormone level was requested and parathyroid ultrasound was performed upon high results (parathormon: 412 pg/dL, normal values: 12-88 pg/mL). However, a pathological lesion was not found. The patient was consulted to the nephrology clinic and was diagnosed with ARF, which developed on the basis of chronic kidney failure. The patient was extubated on the 7th day of hospitalization. The patient was transferred to the another hospital to be able to start a routine dialysis program. Our patient, who was a foreign national, remained in our follow-up only for one day after being extubated, and no communication could be established after he was referred to the another hospital and therefore no written consent could be obtained.

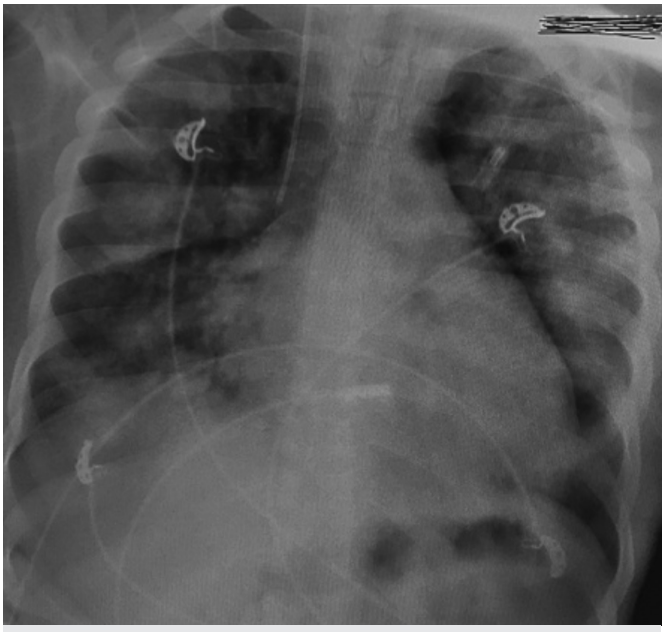


Figure 1. Chest X-ray

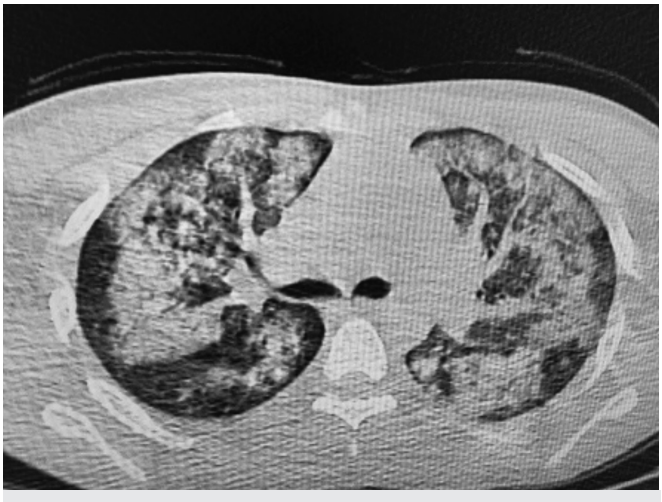


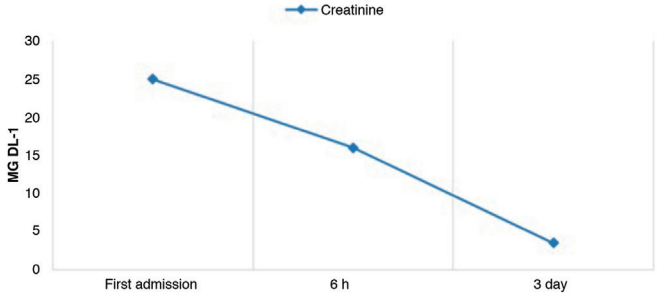
Figure 2. Thorax tomography

DISCUSSION

Although chronic renal failure occurs in older populations with comorbid diseases, it can also be detected in younger patients admitted to hospital in an ARF status. In young patients admitted to hospital with ARF, CRF is not usually considered (4).

The absence of a history of additional disease in the anamnesis highlights conditions such as intoxication. There are many cases in the literature about ARF as a result of intoxication (5,6). In our case, the fact that the patient was a user of chronic wild tobacco (Nicotiana Rustica Linn) and chewed wild tobacco before applying to the emergency room did not make us think about the diagnosis of chronic renal failure. It has been found that chronic marash powder abuse is mostly associated with oral cavity lesions (3). Although there is no correlation between chronic wild tobacco and ARF, Sucakli et al. (7) found that carotis intima media thickness increased compared to those who did not use it, and this caused systolic and diastolic blood pressure elevation. On the other

Table 1. Creatinine values under continuous venovenous hemodiafiltration in patient's intensive care follow-up



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hand, Keten et al. (3) measured systolic-diastolic blood pressures and heart rate at 5, 10, 15, and 20 minutes after the use of wild tobacco and found that wild tobacco significantly increased both blood pressure and heart rate (4). Tobacco products have also been shown to increase the risk of developing chronic kidney failure (8,9). In the light of this information, we would like to draw attention to the fact that wild tobacco may be effective in the development of ARF on the basis of chronic renal failure.

The diagnosis of CRF was made after anamnesis, clinical observation, and consultation with the nephrology clinic. In the patient's history, especially in the last month, episodes of respiratory distress and intermittent bilateral lower limb edema have suggested an underlying CRF clinical picture. Serious anemia (Hgb: 4.7 g/dL-1) observed in the patient at the first admission can be seen due to erythropoietin deficiency in patients with CRF (10). During the follow-up of the patient, decrease in urea-creatinine level with CVVHDF and anuria led us to the diagnosis of CRF.

CONCLUSION

Chronic renal failure may remain asymptomatic for a long time in young patients (11). If these patients have not been screened before, they usually apply to the hospital in the clinical picture of ARF and they are diagnosed with CRF. Therefore, it should be kept in mind that if an ARF clinical picture is observed in young adults, there may be an ARF picture on the basis of CRF. Also, it should be remembered that there may be a risk of developing CRF in the use of wild tobacco and may lead to the development of ARF.

Informed Consent: Our patient, who was a foreign national, remained in our follow-up only for one day after being extubated, and no communication could be established after he was referred to the another clinic, and therefore no written consent could be obtained.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept - S.S., Ü.Y., Ü.A.T.; Design - S.S.; Supervision - Ü.A.T.; Resources - İ.A., Ü.Y.; Materials - İ.A.; Data Collection and/or Processing - S.S.; Analysis and/or Interpretation - S.S.; Literature Search - S.S.; Writing Manuscript - S.S.; Critical Review - S.S., Ü.A.T.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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Cases with Gastrointestinal System Findings and Diagnosed with Malignancy Outside the Gastrointestinal System; Case Series

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ABSTRACT

In these case series, patients admitted to pediatric gastroenterology outpatient clinic with gastrointestinal complaints in the last year and diagnosed with malignancy after the examinations were discussed. Nine patients diagnosed with malignancy were evaluated with biochemical, imaging and histopathological methods. One of the patients, aged 4 months 8 years, was diagnosed with Burkitt's leukemia, two were diagnosed with Burkitt's lymphoma, the other two were diagnosed with neuroblastoma while two were diagnosed with posterior fossa tumor, two were diagnosed with Langerhans cell histiocytosis. All patients were referred to the pediatric oncology service for further treatment. We think that patients presenting with gastrointestinal findings should be evaluated in more detail by general pediatricians before they are referred to minor outpatient clinics.

Keywords: Non-gastrointestinal system, malignancy, childhood

INTRODUCTION

Vomiting, abdominal distention, abdominal pain and weight loss are common symptoms and signs that are common in pediatric practice. These general signs and symptoms are frequently followed with different diagnoses. However, the fact that these symptoms are long-lasting, insistent, and multiple and coexisting should bring to mind the neoplastic diseases in differential diagnosis. Abdominal bloating may be due to diffuse growth of intra-abdominal organs or it may be handled as a separate tumor. The palpated mass may be due to a simple cause such as fechaloma, as well as gastrointestinal system anomalies, cysts, inflammatory diseases or benign neoplasms. Depending on the location of the mass, there may be symptoms such as constipation and vomiting. The mass can often be noticed by the family in the form of swelling, stiffness, or asymmetry in the abdomen while the child is being dressed or bathing. But masses inside the abdomen, especially those in the retroperitoneal region, often escape the attention of the child's family until they reach large sizes (1,2). Another rare, sometimes life-threatening disease is Langerhans cell histiocytosis, which is caused by skin lesions. This disease can often be treated as a cow's milk allergy, especially due to rashes in the body and clinical signs such as diaper dermatitis (3,4). For differential diagnosis, good anamnesis, good systemic physical examination, laboratory and imaging support are required.

In this article, patients who were referred from general pediatric polyclinics to pediatric gastroenterology polyclinics for further examination and treatment with gastrointestinal system symptoms

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and who were diagnosed with malignancy after examinations are discussed.

CASE PRESENTATION

Case 1

A 3-year-old male patient was brought to the pediatric gastroenterology outpatient clinic with complaints of abdominal bloating and abdominal pain. In his history, it was learned that she had been diagnosed with abdominal pain, anorexia for two months, and not gaining weight since the last one month, despite the outpatient clinic admissions, weight loss increased gradually. On physical examination, the general condition of the case, whose body weight and height was below 3 percentile, was moderate, cachectic and fond-looking, and the eyeballs were collapsed. Respiratory examination was natural. Peak heart rate in the cardiovascular system was 140/min and rhythmic. A 2/6 severity systolic murmur was detected in the apex. Organomegaly could not be palpated since abdominal distention was excessive. Laboratory investigations were hemoglobin (Hgb): 10 gr/dL, hematocrit (Hct): 30%, white blood cell: 8380/mm^3, platelet count: 44,000/mm^3. Aspartate transaminase (AST): 56 U/L alanine transaminase (ALT): 9 U/L, gamma-glutamyl transpeptidase (GGT) 20 U/L, alkaline phosphatase (ALP) 79 U/L, total protein 5.4 g/dL, albumin 2.9 g/dL, urea 28 mg/dL, creatinine 0.17 mg/dL, iron 40 ng/dL, iron binding capacity 206 ng/dL, ferritin: 21 ng/dL. Immunoglobulin (Ig)A was 36 mg/dL, IgG 686 mg/dL, IgM 49 mg/dL. Atypical cell was not detected in peripheral smear. In abdominal ultrasonography (USG), no pathology other than fechaloma was detected. EMA IgA and EMA IgG examination of the patient who had a hard poop production 3 times a week was negative. Abdominal distension gradually increased and abdominal tomography [computed tomography (CT)] showed dilatation of the bowel loops and an increase in the thickness of the bowel in the right hepatic flexor. Neuron specific enolase (NSE), lactate dehydrogenase (LDH), urine vanillylmandelic acid (VMA) and ß human chorionic gonadotropin (HCG) levels were normal for the differential diagnosis of neuroblastoma. A hard mass with uncertain borders was found around the navel. In repeated abdominal USG, hypoechoic nodular areas of 7x6.5 mm and 7x7.5 mm in the left lobe in the parenchyma (metastatic areas associated with possible lymphoproliferative process defined in the epigastrium), gathered together in the midline, epigastrium, mass appearance. Thin walled hypoechoic lesions of millimeter sizes were observed in both kidneys, the largest of which was 7 mm in diameter in the right kidney. Repeated abdominal CT showed increased kidney sizes (metastasis) and a mass in the hepatic flexura in the right colon. In laboratory studies of the case with intermittent fever, alkaline hydration was started with the pre-diagnosis of malignancy on calcium 13.6 mg/dL and uric acid 7.8 mg/dL. L3-type lymphoblasts containing vacuoles were seen in 40% of bone marrow aspiration and stoplasmas. Burkitt was diagnosed with leukemia and underwent chemotherapy at a pediatric oncology clinic. Case was excitus caused by sepsis.

Case 2

A 9-month-old girl was brought with the complaint of abdominal distention since a week. It was learned that there was no history of maternal-parental consanguinity, that she was born as a result of uneventful pregnancy and that there was no feature in the postnatal period. In her physical examination, her weight was 10 kg (90 per) and her height was 67 cm (3-10 per). Her general condition was medium, pale and her respiratory and cardiovascular system examinations were normal. The liver of the patient with abdominal distension was to reach the inguinal area and his spleen was palpated 5 cm. Laboratory investigations were Hgb: 7.1 gr/dL, Hct: 28% L/dL, white blood: 3420/mm^3, Platelet: 97,000/mm^3, AST: 25 U/L, ALT: 30 U/L, GGT: 20 U, ALP: 272 U/L, T protein: 7.5 gr/dL, Albumin: 4.3 gr/dL, urea: 17 mg/dL, creatinine: 0.8 mg/dL, iron: 67 mg/total iron binding capacity: 215 mg/dL, ferritin: 188 mg/L, IgA: 31 mg/dL, IgG: 817 mg/dL, IgM: 45 mg/dl, LDH: 640 IU/L, Uric acid: 8.2 mg/dL and prothrombin time resulted normally. Hepatitis A, B and TORCH panel were negative. Atypical cell was not seen in peripheral smear. In abdominal USG, liver and spleen were large and liver parenchyma was observed homogeneously. Intestinal colon thickening and adjacent mesenteric lymphadenopathies adjacent to the intestine segments causing a mass appearance in the colon in the lower right quadrant of the abdomen were interpreted as a preliminary diagnosis of Burkitt lymphoma. Computerized CT revealed hepatosplenomegaly, paraaortocaval mass and lymphadenopathy. Burkitt lymphoma was diagnosed as a result of examination of laparoscopic biopsy material.

Case 3

A 3-year-old girl was brought in with a complaint of difficulty breathing. In her story, it was stated that since 15 days of restlessness, abdominal pain and abdominal bloating, she suddenly complained of difficulty in breathing and had difficulty urinating during the day. She was 13 kg (25 per) in weight and 96 cm (25-50 per) in physical examination. The general condition of the patient was fond, restless, agitated, pale-looking and dyspneic and tachycardic. The presence of organomegaly could not be evaluated because there was an advanced degree of distension in the abdomen. Laboratory examinations were Hgb: 7.6 gr/dL, Hct: 30%, white blood: 12420/mm^3, PLT: 70,000/mm^3. AST: 28 u/L ALT: 33 u/L, GGT: 21 U/L, ALP: 172 U/L, T protein: 7.6 g/dL, Albumin: 4.3 gr/dL, urea: 16 mg/dL, creatinine : 0.6 mg/dL, iron: 78 mg/dL, total iron binding capacity: 115 mg/dL, ferritin: 128 mg/L, IgA: 32 mg/dL, IgG: 916 mg/dL, IgM: 52 mg/dL, prothrombin time: 88%. LDH 842 IU/L, uric acid: 10.2 mg/dL, hepatitis A, B, and TORCH panel were negative. In abdominal USG, liver and spleen were large and liver parenchyma was observed homogeneously. Cells compatible with lymphoblasts were seen in peripheral smear. The patient, who was followed up in the intensive care unit, died on the third day of his hospitalization due to respiratory and renal failure. As a result of the examination of the post-mortem biopsy material, the case was diagnosed with Burkit lymphoma.

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Case 4, 5

Two 4-month-old female patient applied for bloating in the abdomen for 3 days. It was learned that the patients who had no complaints in their history had previously noticed bloating in the abdomen and had repeatedly applied to a doctor because of their increasing complaints. In their physical exams, one's weight was 7200 g (90 per) in length 61 cm (25 per), the other's weight was 7000 g (75-90 p), height 60 cm (25 p). The general condition of these cases was moderate, fever 36 °C, respiratory sounds were bilaterally equal, normal and the number of breaths per minute was 35, cardiovascular system examinations were normal. The liver of patients with abdominal distention was palpable in the inguinal and spleen midclavics and 5-6 cm. In laboratory investigations, Hgb: 11.9 gr/dL, Hct: 30%, white blood: 19,200/mm^3, platelet: 219,000/mm^3, AST: 25 U/L, ALT: 32 U/L, GGT: 23 U/L, ALP: 201 U/L, T protein: 7.8 g/dL, albumin: 4.2 gr/dL, urea: 22 mg/dL, creatinine: 0.7 mg/dL, iron: 78 mg/dL, total iron binding capacity: 215 mg/dL, ferritin: 178 mg/L, IgA: 34 mg/dL, IgG: 616 mg/dL, IgM: 42 mg/dL, Prothrombin time 89% and acid phosphatase: 8.1 were detected. Hepatitis A, B and TORCH panel were negative. Liver, spleen and liver parenchyma were heterogeneous in the abdominal USG of both cases. There were no atypical cells in the bone marrow aspiration examination. The NSE average was 81.4 (high) and VMA >1000 (very high). Gaucher's disease enzyme levels in both cases were also found to be normal. The cases were diagnosed with neuroblastoma as a result of the observation of small blue cells in histopathological investigations of liver biopsies.

Case 6

A two-year-old baby boy was brought with vomiting after feeding. In his history, it was learned that he had vomited after each feeding since his birth and that there was a slowdown in weight gain. No feature was found in the history and history of the case. On physical examination, the general condition of the patient, whose weight was 11 kg (25 per) and 84 cm (25-50 per) in length, was good and active. Respiratory and cardiovascular system of the patient was normal and organomegaly was not detected. Laboratory examinations were Hgb: 10.6 gr/dL, Hct: 32%, white blood: 7420/mm^3, platelet: 370,000/mm^3. No characteristics were observed in the abdominal USG of the patient with normal serum electrolytes, liver and renal functions. Anti-reflux treatment was recommended. Although there was no improvement in complaints in the follow-up, there was no characteristic in the fundus oculi examination of the case. However, he was referred to neurosurgery because of mass determination in posterior fossa in computerised brain tomography.

Case 7

An eight-year-old male patient was brought to the pediatric gastroenterology outpatient clinic with the complaint of vomiting. It has been learned that there have been vomiting attacks, especially in the morning, for six months, gastritis and vomiting treatments have been given in repeated polyclinic applications, but morning vomiting has been increasing since the last few days. His physical examination revealed a weight of 26 kg (50 per) and a height of 127 cm (50 per), and his general condition was moderate, fever 36 °C, and his color was pale. Respiratory examination was normal, peak heart rate: 80 min/rhythmic, liver and spleen were not palpable. Hb: 12 gr/dL, Hct: 38%, white blood cell: 7880/mm3, platelet count: 344,000/mm^3. AST: 36 U/l, ALT: 29 U/l, GGT: 21U/L, ALP: 269 U/L, total protein 6.4 gr/dL, Albumin 3.9 gr/dL, urea 28 mg/dL, creatinine 0.17 mg/dL were detected. Bilateral papil edema was detected in the fundus oculi examination and cranial CT revealed a mass in the posterior cavity and the patient was referred to neurosurgery.

Case 8

A nine-month-old girl was brought to our pediatric emergency clinic with complaints of fever, abdominal distention and paleness since two months. In her history, it has been learned that they have been using various antibiotics for recurrent outpatient clinic applications due to intermittent fever and abdominal bloating for five months, but abdominal bloating and paleness have increased since the last few days. In her physical examination; weight was 8000 gr and length was 67 cm (50 percentile), general condition was medium, fever 38 °C, color was pale. Respiratory examination was normal. The PHR was 120 min/rhythmic. Systolic murmur at the apex was 1/6. The liver of the patient with abdominal distension was 5 cm past the edge of the midclavicular line and costa. The spleen was palpated at 4 cm and medium hardness. Laboratory investigations were Hgb: 10 gr/dL, Hct: 31%, leukocyte count: 4380/mm^3, platelet count: 144,000/mm^3. AST: 56 U/L, ALT: 49 U/L, GGT 20 U/L, ALP: 279 U/L, total protein: 5.4 gr/dL, albumin: 2.9 gr/dL, urea: 28 mg/dL, creatinine: 0.17 mg/dL, iron: 30 ng/dL, iron binding capacity 406 ng/dL, ferritin: 10 ng/dL, vitamin B12: 189 pg/mL, folic acid: 7 ng/mL, IgA 208 mg/dL, IgG: 686 mg/dL, IgM It was 49 mg/dL. Alpha fetoprotein, NSE, fibrinogen levels were normal. Microcytic anemia was detected in its peripheral spread. Hepatosplenomegaly was present in the abdominal USG and parenchyma was homogenous. The case with pancytopenia and fever was treated with antibiotics. In addition, Cytomegalovirus, Epstein-Barr virus, Parvovirus IgM, hepatitis A, B and C panel were found to be negative. Microcytic anemia was present in the bone marrow aspiration examination, hemophagocytosis and atypical cells were not found. In addition to anaemia, tachypnea, tachycardia, cardiac failure and 40% prothrombin activity, the patient was transfused with erythrocyte suspension and freshly frozen plasma. TORCH IgM, Grubel-Widal and Wright tests of the case were negative. Ammonia, urine-blood aminoacid levels, Alpha-1 antitrypsin levels, tests for Gaucher disease, Niemann-Pick A and B enzyme levels were normal and no pathology was detected in the eye-bottom examination. Repeated bone marrow biopsy was evaluated as normocellular. However, acid was also found in the case that started jaundice, T bilirubin 5 mg/dL and D bilirubin 4 mg/dL. In the case of hypoalbuminemia and international normalized ratio: 2, hemorrhagic papular lesions of various sizes were observed in both palms and on the back of the hand while preparing for liver transplantation. The

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case was diagnosed as Langerhans cell histiocytosis after the widespread CD1 a antigen positive histiocytes were observed in histopathological examination of skin biopsy material from lesions. He was referred to an oncology clinic.

Case 9

The seven-month-old girl was brought with a complaint of rash on the body, which has been for two months. She has been using antifungal, antibiotic and corticosteroid creams with her diaper rash due to rash, itching and crusting, which has been continuing for two months in her body, especially in the folds of the body to be more than two months, continuing since the last four weeks also increasing the redness. It was learned that he was referred to the gastroenterology outpatient clinic with a diagnosis of allergy. On physical examination, weight: 7 kg (25 pairs), height: 67 cm (50 pairs) and general condition was moderate. In addition to the common erythematous, patched papular-looking lesions on the neck, trunk, the structure of the nails was disrupted and there were hemorrhagic lesions in some erythematous areas. Respiratory and cardiovascular system examinations were normal. Liver was 3 cm in the midclavicular line, and her spleen was palpated by 2 cm. Laboratory investigations were Hgb: 10.1 g/dL, Hct: 31%, white blood: 4420/mm^3, platelet: 207,000/mm^3. The diagnosis of langerhans cell histiocytosis was made in the histopathological examination of the skin punch biopsy material taken from the patient with normal liver, kidney functions and serum electrolytes. Verbal consent was obtained from all cases.

DISCUSSION

Malignant diseases are not uncommon in childhood and adolescence and can always appear with different clinical signs and symptoms. Tumors that occupy the abdomen in childhood may appear with different clinical findings in different localizations. Most tumors that show intraabdominal location give symptoms such as abdominal pain, bloating, nausea, vomiting, constipation or diarrhea. However, most abdominal masses in children are asymptomatic and often noticed by family or doctor during routine examination. Sometimes the cases are taken to the doctor with complaints such as pain, vomiting and constipation due to the mass (2). Burkitt lymphoma is a fast-growing malignant tumor. In non-Hodgkin lymphoma, which is the nonendemic form that causes abdominal mass, clinical findings vary depending on the localization of the tumor. In 35% of the patients, the tumor is localized in the abdominal region. It may originate from all lymphoid tissue in the intestinal wall, including the abdominal lymph nodes as well as the ileocecal region, the appendage and the ascending colon (5-7). Our three cases were brought in with abdominal bloating and abdominal pain. In one of the cases, a mass was detected in the colon, while the other two cases, were diagnosed with Burkitt lymphoma. Neuroblastoma is the most common extracranial solid tumor seen in childhood and accounts for 7% of childhood tumors (8). Since neuroblastoma can develop from any part of the sympathetic nerve chain, the location and clinic of the tumor are very variable and vary by age. Neuroblastoma cases usually do not have any complaints. Although the tumor is mostly found by chance during the examinations, 65% are located in the abdomen (9,10). Increased urine catecholamine metabolites (VMA, HVA) are very important in the diagnosis of neuroblastoma. Two of our cases (patients 4 and 5) were brought with the complaint of bloating in the abdomen, and a diagnosis of neuroblastoma was made as a result of the examinations. Brain tumors are the most common solid tumor seen in childhood. It constitutes 20% of cancers seen in children. It is the second most common malignant disease under the age of 15 after leukemias. Brain tumors are clinically grouped according to infratentorial and supratentorial localization. Medulloblastoma, which is one of the infratentorial tumors and located in the posterior fossa, is the most common brain tumor in the child age group (25%). It accounts for 30-40% of all posterior fossa tumors. This tumor is seen more in boys than in girls, but peaks at ages 5-9 (11,12). One of our cases was two years old, the other was 8 years old, and both were admitted with morning vomiting. After the examinations, they were diagnosed with posterior fossa tumor, which is common in this age group as stated in the literature. Langerhans cell histiocytosis is a rare disease characterized by abnormal histiocyte proliferation, whose etiology has not yet been fully elucidated. This disease, which has an annual incidence of 3-4 per million, can occur at any age in childhood. Itchy erythematous papules, vesiculopustules, petechiae, erosion and ulcerations are seen in the groin. There may be atrophy in the inguinal folds. Systemically, anemia, diarrhea, hepatosplenomegaly, bone involvement and lymphoadenopathies can be detected. The definitive diagnosis is made by showing the CD1a surface antigen immunohistochemically in the biopsy samples taken from skin or bone lesions or by showing the langerhans cells under the electron microscope. Chemotherapy (vinblastin and etoposide), local radiotherapy or isolated curettage can be applied in treatment (3,4). In one of our two cases, the first finding was rash on the body, but in the other, the first finding was organomegaly. However, hemorrhagic papular lesions of various sizes were observed in both palms. LCH was diagnosed by histopathological examination of skin biopsy of both cases. Malignant diseases should be kept in mind in cases presenting with hepatosplenomegaly, persistent fever and pallor as in these cases presenting with various gastrointestinal findings.

As a result, as with any disease, knowledge, awareness, correct synthesis and appropriate approach are required in the diagnosis of neoplastic diseases. Therefore, the complaints of the gastrointestinal tract are primarily a symptom of a gastroenterological disease, but may also concern other clinical departments, especially oncology. Patients presenting with these non-specific complaints, which are the precursors of many diseases such as vomiting, dermatological findings, abdominal bloating, should be directed to the minor clinics after being evaluated in more detail by general pediatricians.

Informed Consent: Verbal consent was obtained from all cases.

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Angiolipoma-like Atypical Lipomatous Tumor/Well-differentiated Liposarcoma

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ABSTRACT

Lipomas are benign mesenchymal neoplasms. Angiolipoma is a variant of ordinary lipomas, characterized by adipocytic cells as well as capillary vascular clusters. Atypical lipomatous tumors are local aggressive mesenchymal neoplasms which include atypical stromal cells. They frequently arise in the deep thigh of the lower extremity. They have four histologic subtypes. So far, there aren't any case of angiolipoma with malignant transformation or atypical lipomatous tumor with angiolipoma-like areas in the English literature. Here we presented a case of atypical lipomatous tumor which was quite like angiolipoma. It was composed of mature fat with focal cytologic atypia and also accompanying diffuse capillary vessels. If there is a large-diameter and deeply located angiolipoma-like lesion, careful examination is required to rule out a liposarcoma. Liposarcomas may be rarely dedifferentiate or metastatic. It is not possible to verify that if the case is a variant of liposarcoma or it is a malignant transformation of angiolipoma.

Keywords: Atypical lipomatous tumor, liposarcoma, angiolipoma, malign transformation, angioliposarcoma

INTRODUCTION

Atypical lipomatous tumors are locally aggressive mesenchymal tumors. They are composed of mature fats with variably sized adipocytes, bands of fibrotic stroma, and also have atypical stromal cells. Areas of fat necrosis are observed, especially at the peripheral localization of the large lesions. These tumors are frequently observed in the deep locations of the thigh, followed by the retroperitoneum, trunk, head and neck region, and spermatic cord. They are predominantly seen in the middle and older ages. Atypical lipomatous tumors have four histologic subtypes, including lipoma-like, sclerosing, inflammatory, and spindle cell histologic subtypes. The lipoma-like subtype is the most common.

Diffuse capillary vascular structures are unusual event in atypical lipomatous tumor. This pattern is very similar to angiolipoma. Angiolipomas are benign tumors composed of mature adipocytes and intermingled with small and thin-walled vessels with intraluminal fibrin thrombi. Angiolipomas constitute 6%-17% of all lipomas (1). They were first described by Bowen (2) in 1912. The nature of these lesions was first documented in 1960 by Howard and Helwig (3). In 1974, Lin and Lin (1) divided them into two; infiltrating and non-infiltrating groups based on their biological behavior. Infiltrating angiolipomas are characterized by a non-capsulated tumor extended into surrounding tissues. Non-infiltrating angiolipomas are encapsulated.

İn this study, we presented a case of atypical lipomatous tumor composed of mature fat with focal cytologic atypia and diffuse capillary vessels. It was similar to angiolipoma. To our knowledge, it is probably the first case in English literature.

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CASE PRESENTATION

A 75-year-old male patient was admitted to an orthopedic clinic with complaints of a palpable mass in his back. The mobile mass lesion under the latissimus dorsi muscle was excised. No metastatic lesion was detected by computed tomography (CT) scans. Macroscopic examination revealed that the mass lesion was covered by a thin incomplete capsule.

The cut surface of the lesion had a dirty yellow color, with an appearance of mature fat (Figure 1). Most of the neoplastic adipocytic cells had similar sizes and shapes (Figure 2A-C). There were also scattered capillary vascular clusters within the lesion and capillary vascular structures were usually located in the periphery of the lesion. Endothelial cells of capillary structures were benign. The adipocytes size in different parts of the lesion varied from small to large compared to normal (Figure 2D and Figure 3A, B). In addition, there were atypical stromal cells and rare lipoblasts in fibrous septa (Figure 3A-C). Atypic stromal cells rarely showed pleomorphism and there were sparse mitotic activities (Figure 3D). Immunohistochemically, capillary structures expressed CD34 (Figure 4A); atypical stromal cells expressed murine double minute 2 (MDM2), cyclin-dependent kinase 4 (CDK4), and p16 (Figure 4B, C); and scattered atypical stromal cells expressed S100 protein (Figure 4D). Analysis of MDM2 by fluorescence in situ hybridization (FISH) showed clusters of red signals in the neoplastic cells. Red signal clusters in neoplastic stromal cells indicated the presence of amplification/overexpression of the MDM2 protein (Figure 5). The patient was discharged without any complications and after ten months of follow-up, there was no recurrence as determined by endoscopic evaluation and CT examination.

Consent form was taken from the patient.

DISCUSSION

Angiolipoma is a variant of ordinary lipomas characterized by adipocytes as well as capillary vascular clusters. We did not find any case of angiolipoma with malignant transformation or an atypical lipomatous tumor with angiolipoma-like areas in the English literature. Due to the atypical stromal cells in the lipomatous areas and the presence of widespread capillary vessels, it may be misdiagnosed as angiolipoma. Differential diagnosis of angiolipoma depends on the density of the capillary vessels. Hypovascular angiolipomas are differentiated from ordinary lipoma by the presence of fibrin thrombi, meanwhile cellular angiolipomas may be confused with Kaposi's sarcoma or spindle cell hemangioma. Although they do not contain clustered vessels with small thrombi, spindle cell hemangiomas unlike angiolipoma, contain large cavernous vascular structures and large calcified thrombi (phleboliths).

Infiltrative angiolipomas are localized in the deep soft tissue (1,4), not encapsulated, and can be mixed more often with

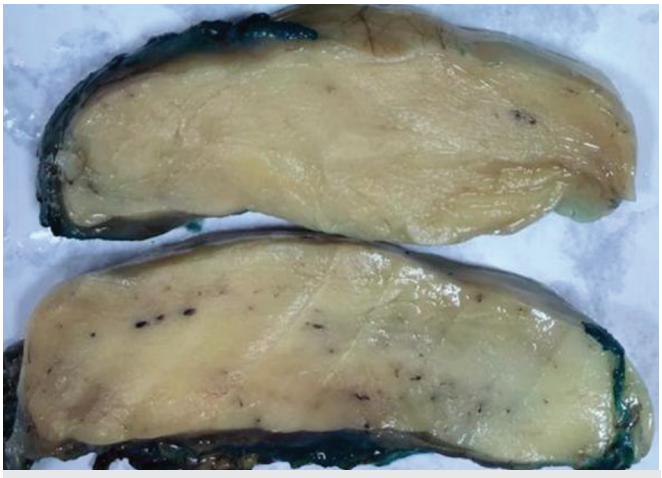

Figure 1. Tumor is covered by a thin fibrous capsule. The cut surface shows a dirty yellow color with a mature fatty tissue appearance

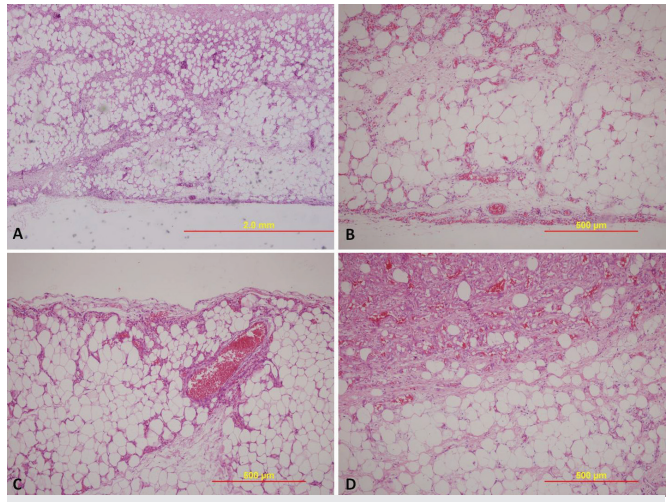

Figure 2. A, B, C) Hematoxylin and eosin (H&E), x100: Adipocytic cells are usually similar in size and shape, and there are some capillary vascular clusters scattered within the lesion. **D)** H&E, x200: Adipocytic cells have different sizes and shapes in some areas

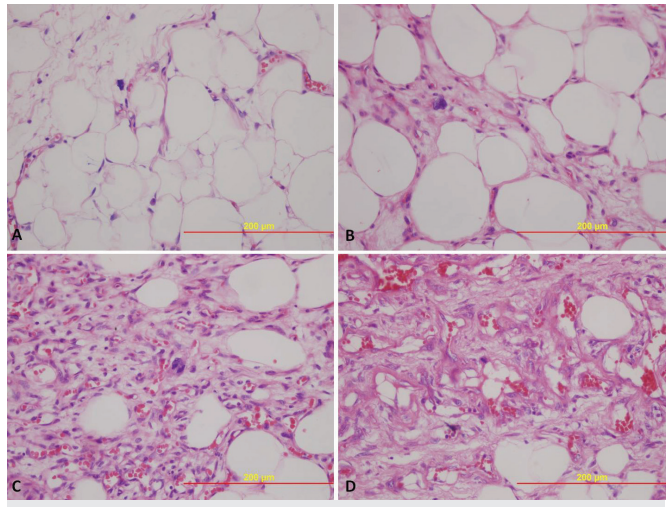

Figure 3. A, B, C) Hematoxylin & eosin (H&E), x400: Atypical stromal cells in the fibrous septa. **D)** H&E, x400: Capillary structures

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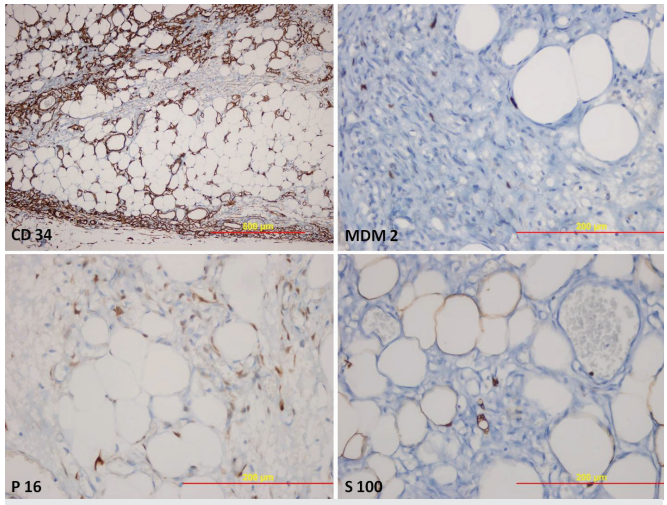

Figure 4. CD34x200: Capillary structures. MDM2, x400: Atypical stromal cells. CDK4, x400: Atypical stromal cells. P16: Atypical stromal cells. S-100x400: Atypical stromal cells
MDM2: Murine double minute 2, CDK4: cyclin-dependent kinase 4

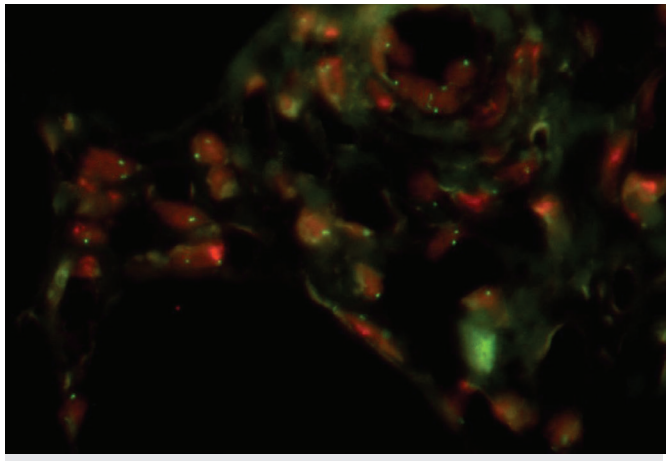

Figure 5. FISH: MDM2 amplification and overexpression
FISH: Fluorescence in situ hybridization, MDM2: murine double minute 2

angiosarcoma. Our case was located deeply under the muscle in the back, but it was circumscribed and had lobulated margins.

Angiosarcoma and Kaposi's sarcoma in this case were considered in the differential diagnosis due to the focal capillary vascular proliferation detected in the mature adipose tissue. There were fascicular endothelial proliferations consisting of more spindle cells than angiolipoma in Kaposi's sarcoma. There were also blood-filled slit-like spaces, extravasated erythrocytes, and periodic acid-Schiff [PAS (+)] hyaline globules in Kaposi's sarcoma, but no fibrin thrombi. Immunohistochemical studies showed that Kaposi's sarcoma endothelial cells expressed human herpesvirus 8. In angiosarcoma, the vascular structures dissected fatty tissue, collagen fibers, and other tissues. The endothelial cells of the vascular structures were atypical, multi-layered, and showed tufting toward the lumen. There were no fibrin thrombi in capillary vessels in angiosarcoma.

Our case was diagnosed as angiolipoma-like atypical lipomatous tumor/well-differentiated liposarcoma due to the presence of diffuse capillary proliferations in the atypical lipomatous tumor.

The presence of atypical stromal cells is important to differentiate atypical lipomatous tumor from a lipoma. Thway et al. (5) had reported that p16, CDK4, and MDM2 were useful immunohistochemical markers for the distinction of lipoma and an atypical lipomatous tumor. In addition, we have also showed MDM2 amplification by FISH. MDM2 amplification is a finding that supports malignant transformation. The co-occurrence of angiolipoma and atypical lipomatous tumor has been reported by Christodoulidou et al. (6) in a case presentation. However, angiolipoma and atypical lipomatous tumors were seen in the paratesticular area and in contralateral localizations. However, in our case, angiolipomatous areas and atypical lipomatous tumor were intermingled with each other.

Fibrin thrombi are usually seen in angiomatous lesions, caused by microtrauma. They are usually seen in subcutanous angiolipomas and not in angiolipoma-like areas in our case. In the literature like in our case, angiolipomas in the gastric, colonic and rectal locations without fibrin thrombi have been reported (7-9). The absence of fibrin thrombi in the deep soft tissue may be associated with less trauma in these areas.

In our case, it was noticed that the adipocyte cells in fatty tissues, which contained dense capillary vessels showed different sizes and shapes. The diagnosis was atypical lipomatous tumor because of the presence of rare atypical stromal cells and lipoblasts in fibrous septa in these areas. Is the present case a new variant of liposarcoma? It can be discussed because of the diffuse capillary vessels similar to angiolipoma. However, some liposarcoma types have areas with branched capillaries, and a form with extensive capillary vascular proliferation has not yet been defined.

Can the atypical stromal cells and lipoblasts detected in the lipomatous areas in this case be the evidence of the malignant transformation of an angiolipoma? However, soft tissue textbooks report that angiolipomas are always benign or there is no evidence that these lesions ever undergo malignant transformation (10,11).

Angiolipoma-like atypical lipomatous tumors and angioliposarcoma or malignant transformation of angiolipoma have not yet been described in the literature. We defined our case as an atypical lipomatous tumor/well-differentiated liposarcoma due to the atypical stromal cells and lipoblasts observed in the angiolipoma-like and lipomatous areas. In conclusion, the possibility of atypical lipomatous tumor/well-differentiated liposarcoma in large and deeply located angiolipoma-like lesions should be excluded.

Informed Consent: Consent form was taken from the patient.

Peer-review: Externally peer-reviewed.

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Is Mucopolysaccharidosis a Cause of Sleep and Speech Disorders? Report of Four Cases?

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ABSTRACT

Mucopolysaccharidosis type III (MPS 3) is an autosomal recessive disorder caused by a deficiency of one of the four enzymes involved in the lysosomal degradation of heparan sulfate (HS). It is often unrecognized or misdiagnosed in children as an idiopathic developmental/speech delay, attention deficit/hyperactivity disorder (ADHD), and/or autism spectrum disorder. It is characterized by progressive mental deterioration and behavioral problems with dysmorphic facial features and mild somatic signs. We report on children with ADHD who were repeatedly admitted to the pediatric psychiatry department for sleep disturbances, hyperactivity, and speech delay; and to the emergency department with accidental corrosive substance ingestion. Children with mental retardation, coarse face, and hypertrichosis were referred to the pediatric gastroenterology department for preliminary diagnosis of MPS. Lysosomal enzyme activity examinations in leukocytes revealed increased levels of total glycosaminoglycans, heparin, and HS, and decreased HS sulphamidase activity, leading to the diagnosis of MPS III.

Keywords: Children; mucopolysaccharidosis, sanfilippo, attention deficit/hyperactivity disorder

Introduction

Mucopolysaccharidoses (MPSs) are a group of seven inherited metabolic disorders that are characterized by the absence or deficiency of specific lysosomal enzymes that lead to the accumulation of glycosaminoglycans (GAGs) within the lysosomes. MPS type III (or Sanfilippo syndrome) is the most common type and is composed of four different subtypes: type A (OMIM #252900), type B (OMIM #252920), type C (OMIM #252930), and type D (OMIM #252940). Each subtype is caused by a deficiency of a different enzyme in the catabolic pathway of heparan sulfate (HS), a type of GAG. MPSs comprise 11 lysosomal diseases, each with an absence of a specific step in the degradation of GAGs that leads to their accumulation in tissues and to a range of clinical consequences, including central nervous system (CNS) impairment, depending on the type of the MPS (1,2).

Seven types of MPS disorders caused by deficiencies of 10 different enzymes are as follows: MPS I (Hurler MIM 607014, Hurler-Scheie MIM 607015, Scheie MIM 607016), MPS II (Hunter syndrome MIM 309900), MPS III A (MIM 252900), B (OMIM 252920), C (MIM 252930), or D (MIM 252940) (Sanfilippo syndrome), MPS IV A (MIM 253000) or B (MIM 253010) (Morquio syndrome), MPS VI (Maroteaux-Lamy syndrome, MIM 253200), MPS VII (Sly disease, MIM 253220), and MPS IX (MIM 601492) (1). The clinical symptoms vary widely across the different subtypes (1).

MPSs are a group of inherited metabolic disorders caused by a deficiency of lysosomal enzymes that take part in the

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degradation of GAGs: HS, dermatan sulfate, keratan sulfate, and hyaluronic acid. They are inherited as an autosomal recessive trait except for type II that has an X-linked recessive inheritance. The incidence of all types of MPSs is around 1.8-4.5 per 100,000 live births (1,3). MPS I (Hurler syndrome), II (Hunter syndrome), III (Sanfilippo diseases), and VII (Sly diseases) are associated with CNS involvement.

MPSs are characterized by three phases that begin after a period of apparently normal development.

In the first phase, generally starting between the ages of 1 and 3 years, a slowing or plateauing of cognitive development becomes apparent; often speech is more noticeably affected than the other functions (4). Motor development usually progresses normally during this stage. The second phase starts at approximately 3-4 years of age and is characterized by progressive cognitive deterioration and the emergence of behavioral difficulties (hyperactivity, impulsivity, obstinacy, anxious behaviors and autism-like behaviors) and sleep disturbances (4-8). In the early stages of neuropathic forms of MPS, particularly MPS III, developmental delay or regression of skills may be the only prominent manifestation. They are usually misdiagnosed as attention deficit/hyperactivity disorder (ADHD) and/or autism spectrum disorders in this phase. The third stage begins, usually in the teenage years, with the onset of severe dementia and decline of motor functions. Swallowing difficulties and spasticity emerge, and patients usually die at the end of the second or beginning of the third decade of life (4-8).

GAGs serve as natural biomarkers for these diseases, as MPSs are primarily associated with their accumulation. There are different subclasses of GAGs that can be accumulated according to the specific enzymatic defect. This accumulation can also vary according to the residual levels of enzyme activity, type of genetic variant, and environmental factors (9).

We report four cases with ADHD, followed by the pediatric psychiatry department, who were admitted to pediatric emergency department with corrosive substance ingestion and diagnosed with MPS III A.

CASE PRESENTATION

Case 1

A 9-year-old girl was admitted to the pediatric emergency department after she ingested a corrosive substance. Upper gastrointestinal tract endoscopy revealed no pathology; however, she suffered from severe behavioral disorder, hyperactivity, mental retardation, speech disorder, coarse face, and hypertrichosis.

Her parents were first-degree relatives. She was reported to have acquired head control by the 3rd month of life, was able to walk at 2 years, and started to talk at 2.5 years; however, her speech did not improve. She was admitted to the pediatric psychiatry department for sleep disturbances, hyperactivity, and speech delay.

She had severe behavioral disorder, hyperactivity, mental retardation, speech disorder, coarse face and hypertrichosis. Her laboratory investigations revealed normal complete blood count, liver function, serum copper, ceruloplasmin, alpha 1-antitrypsin levels, and thyroid function. Hepatitis A, B, and C were ruled out on serology. Urinary GAGS were significantly increased. The lysosomal enzyme activity was assessed in leukocytes and showed that total GAG levels were 63.5 mg/mmol; levels of creatinin, heparin, and HS were increased; whereas, HS sulphamidase activity was decreased (0 nmol/mg protein/17 h) compared with the normal reference range (3.2±20.4 nmol/mg protein/17 h). She was thus diagnosed with MPS III A.

Chest radiography revealed beaking of vertebral bodies and oar shaped ribs (Figure 1). Abdominal USG showed hepatosplenomegaly. Echocardiography and ophthalmic examinations were normal. Severe sensorineural hearing loss was detected.

Case 2

An 11-year-old boy was admitted to the pediatric emergency department after ingesting a corrosive substance.

Upper gastrointestinal tract endoscopy revealed mild hyperemia. He had severe behavioral disorder, hyperactivity, mental retardation, speech disorder, coarse face, and hypertrichosis, similar to his sibling.

He had previously been admitted to the pediatric psychiatry department several times for walk and speech delay. He had severe mental retardation, hyperactivity, speech disorder, and sleep disturbances since he was 6 years old and was diagnosed with ADHD. His physical examination was unremarkable except for the presence of a coarse face and hypertrichosis. There was no organomegaly.

His laboratory investigations revealed normal complete blood count, liver function, serum copper, ceruloplasmin, alpha 1-antitrypsin levels, and thyroid function. Hepatitis A, B, and C were ruled out. Urinary GAGs were increased. Total GAG levels

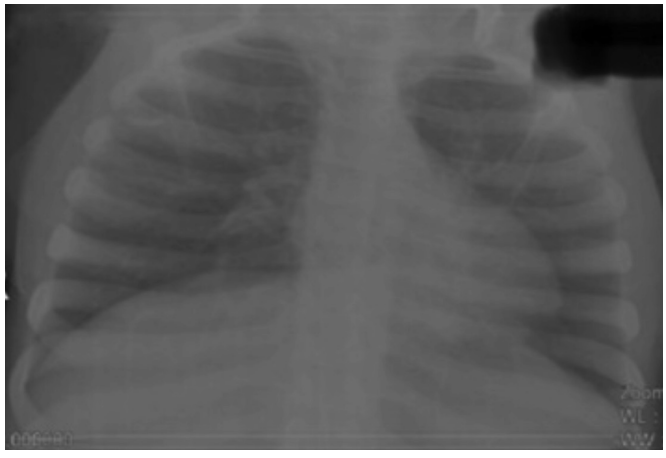

Figure 1. Chest radiograph showing beaking of vertebral bodies and oar shape ribs

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were 41.8 mg/mmol; levels of creatinin, heparin, and HS were increased; whereas, HS sulphamidase activity was decreased (0.1 nmol/mg protein/17 h). He was diagnosed with MPS III A. Chest radiograph revealed beaking of vertebral bodies and oar shaped ribs. Sensorineural hearing loss was observed; while, echocardiography and ophthalmic examinations were normal.

Case 3

A 4.5-year-old boy was admitted to the pediatric emergency department after ingesting a corrosive substance (bleach). Upper gastrointestinal tract endoscopy revealed no pathology.

His history revealed no consanguinity. He had agitation, hyperactivity, and short sleep duration. He had started to talk and walk after 2.5 years, and had been followed-up by pediatric psychiatry department for the last 6 months with the diagnosis ADHD.

His physical examination revealed a coarse face, roughness of the hands and feet. There was no organomegaly. The lysosomal enzyme activity was approximately 0 nmol/mg protein/17 h that led to the diagnosis of MPS III A. He had no skeletal abnormalities or hearing loss.

Case 4

A 14-year-old boy was admitted to the pediatric emergency department with complaints of corrosive substance ingestion. Upper gastrointestinal tract endoscopy revealed linear erosions and hyperemia. His oral intake was stopped and proton-pump inhibitors were administered.

His history revealed no consanguinity. He had started to talk at 4.5 years, and suffered from sleep disorders since the age of 8 years. He had been admitted to the pediatric psychiatry department many times with the suspicion of ADHD.

His physical examination revealed a coarse face, hypertrichosis, and roughness of the hands and feet. He had hearing loss and skeletal abnormalities. Liver was palpable 3 cm below right costal margin. His laboratory investigations were normal. As the lysosomal enzyme activity was 0 nmol/mg protein/17 h, a diagnosis of MPS III A was made. A repeat endoscopy performed 1 week later was unremarkable.

Written informed consents were obtained from all the patients and/or their parents.

DISCUSSION

MPS III A is an autosomal recessive disorder caused by a deficiency of heparan N-sulphatase that is involved in the lysosomal degradation of HS. It is reportedly the most severe form, with an earlier onset and faster progression of symptoms than in the other types of MPSs (3-6,8). MPS III A is characterized by progressive mental retardation, speech delay, sleep disturbances, and behavioral disorders (3-11). It has been reported that 40.6% of the patients talked after the 15th month of life, 7.2% of them walked after the 18th month, and 26.1% had both delayed talking and walking (5). The patients were usually diagnosed at 3-4.5 years of age (5,10).

The first clinical symptoms reported by Meyer et al. (5) included behavioral and sleep disturbances; whereas, speech (48%) and behavioral disorders (9%) were cited as the first symptoms by Buhrman et al. (10). Our patients were admitted to the pediatric psychiatry department for sleep disorders, hyperactivity, and delayed speech and walking. No clinical improvement occurred during their follow-up period. The diagnosis of MPS was based on the physical signs, such as a coarse face (flat nasal bridge, thickened lips, low set ears, macroglossia, short neck, hypertrichosis, etc.), hepatosplenomegaly, broad hands, and short fingers.

Although, skeletal abnormalities are less prominent in MPS III than in the other types of MPS, regular imaging of the spine, hips, and the lower extremities is recommended in these patients (12). Three of our patients had skeletal abnormalities.

Leukocytes and/or skin fibroblast cultures are the gold standard for establishing the diagnosis and determining the subtype of MPS. Prenatal diagnosis is possible, and familial carriers can be identified by molecular genetic testing. There is no specific enzyme replacement therapy; however, hematopoietic stem cell transplantation can be used (13).

In conclusion, MPSs can be easily misdiagnosed as other common diseases seen in children, and this can result in their inappropriate management. Therefore, pediatricians, pediatric psychiatrists, and physicians must suspect MPSs in patients who present with hyperactivity, speech delay or deterioration, autism-like behavioral disorders, and motor developmental delay, even in the absence of apparent features like coarse face.

Informed Consent: Written informed consents were obtained from all the patients and/or their parents.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - N.U.; Concept - N.U., D.K.; Design - N.U., D.K., R.G.; Data Collection and/or Processing - N.U., R.G.; Analysis and/or Interpretation - N.U., D.K.; Literature Search - D.K.; Writing Manuscript - D.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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