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Clinical findings, treatments and obstetric results of pregnant women diagnosed with coronavirus disease 2019

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Ethics Committee Approval
The study was approved by the local Ethics Committee of University of Health Sciences, Umraniye Training and Research Hospital (approval number: 2020/308).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Coronavirus disease 2019 (COVID-19), which causes acute respiratory disease, is an emergency that concerns global public health. Limited data are available on coronavirus disease 2019 in pregnant women. We aimed to evaluate the characteristic features and perinatal results of pregnant women diagnosed with COVID-19.

Methods: This retrospective cohort study was conducted in a Training and Research Hospital. Clinical records and perinatal results of 84 pregnant women and 46 newborns diagnosed with coronavirus disease 2019 in a pandemic hospital on the Asian side of Istanbul between March 29-June 30, 2020, were retrospectively analyzed.

Results: The mean maternal age of the patients was 28.8 (5.6) (17-43) years. The most common symptoms were cough (41.7%), shortness of breath (26.2%), fever (19%), myalgia and malaise (19%). Fifteen percent of patients were in the first trimester, 20.2% were in the second and 64.3% were in the third trimester. Sixty-two percent of the pregnant women were PCR positive and 38.1% had clinical or radiological findings. CT was performed in 27 patients, and lung findings were observed in 23. Among all, 29.8% of the patients received inpatient treatment and 70.2% received outpatient treatment or follow-up. Medical treatment was given to 42.9% of the patients. Sixty percent of the hospitalized pregnant women were admitted to the adult intensive care unit and 3.6% (3/84) resulted in maternal death. Thirteen newborns (28.2%) were admitted to the neonatal intensive care unit. Fever was seen in 6.5% (3/46), dyspnea, in 15.2% (7/46), and pneumonia, in 13% (6/46) of the hospitalized newborns. PCR was performed only in newborns admitted to the neonatal unit. All neonatal PCR tests were negative. Death due to sepsis was seen in 3 newborns.

Conclusion: COVID-19 can cause preterm labor in pregnant women. Lymphocyte, thrombocyte, and CRP values may be useful in clinical follow-up and treatment. PCR positivity decrease and CT findings increase with clinical severity.

Keywords: COVID-19, Pandemic, Pneumonia, Pregnancy, Pregnancy outcomes, Pregnant women, Preterm birth, SARS-CoV-2, Vertical transmission

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Introduction

Due to suppressed immunity and physiological changes during pregnancy, the transmission of viral infections poses a risk for the mother and the baby [1]. Suppression of the mother's immunity to prevent the fetus from being affected and physiological dyspnea caused by changes in the lung complex render pregnant women more vulnerable to viral diseases [1]. An enveloped, segmented, and single-stranded RNA virus from the betacoronaviridae family, coronavirus disease 2019 (COVID-19) causing Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) emerged in Wuhan in 2019 and caused major health problems all over the world. SARS (severe acute respiratory syndrome) in 2003 and MERS (Middle East respiratory syndrome) in 2012 caused high mortality among pregnant women. Coronavirus disease 2019 (COVID-19) poses a risk in pregnant women due to the above-mentioned physiological reasons [2]. The coronavirus can cause illness ranging from a mild cold to pneumonia and is spread mainly by droplets [3]. Mothers infected with the virus may be asymptomatic or may present with clinical symptoms such as fever, dry cough, dyspnea, and myalgia [4]. Radiological demonstration of lung involvement is helpful in diagnosis [4]. The gold standard for definitive diagnosis is the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test [5]. With this study, we aimed to evaluate the clinical features, laboratory, and radiological findings and perinatal results of 84 pregnant women and 46 newborns with suspected or diagnosed COVID-19.

Materials and methods

This retrospective cohort study was conducted in Health Sciences University, Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology. All pregnant women with a diagnosis or suspicion of COVID-19 who visited our hospital since the beginning of the pandemic were included in the study. Data were collected between March-June 2020. Ethical approval was obtained from the local Ethics Committee of Health Sciences University Umraniye Training and Research Hospital (Approval number 2020 / 308).

Of the pregnant women, 52 patients with positive RT-PCR tests and 32 patients with symptoms and radiological findings but negative RT-PCR tests were included in the study. Asymptomatic pregnant women with negative RT-PCR tests were excluded.

Complaints of pregnant patients (fever, cough, shortness of breath, weakness, myalgia, etc.), demographic (age, BMI, additional disease) details, week of gestation according to last menstrual period, the severity of infection (asymptomatic, mild, moderate, severe), patient follow-up data (outpatient, inpatient, intensive care need), laboratory values (complete blood count, liver and kidney functions, electrolytes, CRP, ferritin, fibrinogen, D-dimer, coagulation tests), treatments administered, data regarding the pregnancy and its complications (abortus, stillbirth, preterm birth, maternal mortality), gestational age at birth, mode of delivery, cesarean section indication, complications, neonatal birth weight, Apgar scores, neonatal intensive care unit (NICU) admission data and neonatal outcomes were collected. Pregnant women with a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test evaluated with nasal and pharyngeal swab samples, and those with negative PCR tests but having symptoms or positive CT findings were diagnosed with COVID-19.

Patients were evaluated according to the severity of symptoms and test results. Asymptomatic or mildly symptomatic patients were followed at home under quarantine. The patients were divided into Group 1 (asymptomatic, mild) and Group 2 (moderate and severe) according to their symptoms. The mild form of COVID-19 was characterized by fever with a body temperature below 38.5°C, cough, fatigue, sore throat, and the absence of clinical signs of moderate to severe disease. Those with moderate/severe clinical symptoms were followed up in the hospital. Moderate disease symptoms included a fever of 38.5°C and higher, respiratory rate of more than 22/minute, shortness of breath during physical activity, pneumonia confirmed by CT scan, and an oxygen saturation of more than 95%. Severe symptoms of the disease included a respiratory rate of more than 30/minute, an oxygen saturation of 94% and lower, PaO_2 / $FiO_2 \leq 300$ mmHg, progression of lung damage (≥50% increase of damaged tissue in 24-48 hours), impaired consciousness and unstable hemodynamics [6].

Patients were advised to visit the emergency department if their symptoms increased, or their general condition deteriorated. Radiological imaging was performed with posteroanterior (PA) chest radiography or Thoracic CT scan in eligible patients during pregnancy. The consent form was obtained before the procedure, and the entire abdomen was covered with a lead blanket during scanning and the fetus was protected from radiation. Thoracic CT scans were performed in the postpartum period in symptomatic patients with positive RT-PCR tests who did not undergo imaging. Thoracic CT scan and posteroanterior (PA) chest radiography findings were evaluated by a radiologist and/or chest diseases specialist.

In light of the recommendations of the Scientific Committee of the Ministry of Health, the treatments of the patients were determined by the infection and chest diseases specialists. Daily laboratory tests were requested from the hospitalized patients and weekly PCR tests were performed. Oxygen support was given to all patients with nasal cannula/face mask, and patients were monitored with ECG.

Medical treatment included lopinavir/ritonavir, 2 tablets twice daily for 10 days (Kaletra 200 mg/50 Tab), or favipravir at a loading dose of 1600 mg twice a day and a maintenance dose of 600 mg twice a day for 5 days (Favicovir 200 mg Tab), or Hydroxychloroquine 200 mg twice a day for 5 days (Plaquenil 200mg Tab) administered orally. In addition, 4000IU Enoxaparin sodium (Enox 4000/0.4 ml) was administered subcutaneously once a day, azithromycin 500 mg tablet was given perorally on the first day, and 250 mg perorally daily on the following 4 days, ceftriaxone 1000 mg was administered intravenously twice a day. Plasma therapy was given to eligible patients and patients with clinical worsening. Mothers whose clinical conditions worsened and those with viable pregnancies (24 weeks) were delivered by cesarean section. Necessary isolation measures were taken during the operation. The newborns were isolated and 1st and 5th minute Apgar scores, birth weight, neonatal sepsis findings, neonatal

intensive care admission, clinical symptoms, and RT-PCR results were noted.

Statistical analysis

Continuous variables were expressed as Mean (SD), and categorical variables were given as numbers and percentages. The paired-sample t-test and Wilcoxon Signed Rank test were used to compare the laboratory findings both before and after treatment. Pearson`s chi-square, likelihood chi-square (for the tables when expected values in cells were less than 5), and Fisher`s exact tests were used to assess qualitative variables. A *P*-value <0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS) (version 22) was used for analysis.

Results

The demographic characteristics of patients with diagnosed or suspected COVID-19 are summarized in Table 1. The mean age and BMI of the patients was 28.8 (5.6) (17-43) years and 25.4 (3.1) kg/m^2, respectively. The mean week of gestation was 28.2 (11.1). Out of 84 patients, 13 (15.5%) were smokers and 19 (22.6%) had concomitant diseases. Among all, 15.5% of the patients were in the first trimester, 20.2% were in the second and 64.3% were in the third trimester. PCR test positivity rate was 61.9% and 38.1% had clinical or radiological findings. CT was performed in 27 patients and positive lung findings were observed in 23.

Table 1: Demographic and baseline characteristics, and clinical outcomes of coronavirus disease-2019 in pregnant women

	Values
Age (years)	28.7 (5.6) (17 - 43)
BMI (kg/m^2)	25.4 (3.1) (20 - 35)
Gestational age on admission (week)	28.1 (1.1) (4 - 40)
1st Trimester	13 (15.5%)
2nd Trimester	17 (20.2%)
3rd Trimester	54 (64.3%)
Parity	1.1 (1.1) (0 - 5)
Comorbidities	19 (22 6%)
Diabetes mellitus	4 (4.8%)
Hypothyroidism	4 (4.8%)
Chronic hypertension	3 (3.6%)
Asthma	2 (2.4%)
Other	6 (7.4%)
Smoking	
Yes	13 (15 5%)
No	71 (84 5%)
Symptoms	
Cough n (%)	35 (41.7%)
Shortness of breath n (%)	22 (26.2%)
Fever n (%)	16 (19%)
Myalgia and weakness n (%)	16 (19%)
Headache n (%)	12 (14 3%)
Sore throat n (%)	8 (9.5%)
Loss of taste n (%)	3 (3.6%)
Diarrhea n (%)	3 (3.6%)
No symptoms n (%)	18 (21.4%)
Diagnosis	
RT-PCR	52 (61.9%)
CT	23 (27.3%)
Diagnosed by Symptom Only	9 (38.1%)
Thorax CT findings (n=27)	
Ground-glass opacity n (%)	22 (74%)
Patchy shadowing n (%)	15 (55%)
Atelectasis or pleural effusion n (%)	10 (37%)
No finding n (%)	4 (14%)
No treatment n (%)	48 (57.1%)
Treatment n %	36 (42.8%)
Supplemental O2 n (%)	25 (29.8%)
Hydroxychloroquine n (%)	7 (8.3%)
Invasive mechanical ventilation n (%)	5 (6%)
Antiviral therapy n (%)	29 (24.4%)
Antibiotic therapy n (%)	18 (21.3%)
Anticoagulant therapy n (%)	36 42.8%
Disease severity	
Moderate to severe n (%)	25 (29.8%)
Asymptomatic and mild n (%)	59 (70.2%)
Follow-up	
Inpatient n (%)	25 (29.8%)
Outpatient n (%)	59 (70.2%)

The mean time between the onset of complaints and hospital admission was 2.1 (1.62) (0-7) days. Cough, fever, sore throat, headache, shortness of breath, myalgia and malaise, diarrhea, loss of taste and other symptoms were seen in 41.7%, 19%, 9.5%, 14.3%, 26.2%, 19%, 3.6%, 3.6%, and 7.1% of the patients. The rate of asymptomatic patients was 21.4%.

29.8% of the patients received inpatient and 70.2% received outpatient treatment. Medical treatment was administered to 42.9% of the patients. Five patients (6%) were admitted to the adult intensive care unit and 3 (3.6%) died. The mean duration of hospitalization was 6.6 (4.9) (range 18) days. Pregnancy and fetal results are summarized in Table 2.

Table 2: Perinatal outcomes of coronavirus disease-2019 in pregnant women

	Values
Pregnancy complications	
Preeclampsia n (%)	4 (4.8 %)
Oligohydramnios n (%)	3 (3.6%)
Cholestasis n (%)	3 (3.6%)
Gestational Diabetes Mellitus n (%)	1 (1.2%)
Preterm labor n (%)	23 (27.4%)
PROM n (%)	2 (2.4%)
Delivery method	
Ongoing pregnancy n (%)	35 (41.6%)
Abortus n (%)	3 (3.6%)
Vaginal delivery n (%)	14 (16.7%)
Cesarean delivery n (%)	32 (38.1%)
Indication of cesarean delivery	
Previous uterine surgery	10 (12%)
Fetal distress	7 (8.3%)
Clinical outcomes of newborns (n=46)	
Neonatal birthweight (g) mean (SD)	3190.7 (773.5)
Apgar 1st min. mean (SD)	7.8 (1.8)
Apgar 5th min. mean (SD)	9.3 (0.9)
Transferred to NICU n (%)	13 (28.2%)
Neonatal symptoms	
Fever n (%)	3 (6.5%)
Dyspnea n (%)	7 (15.2%)
Pneumonia n (%)	6 (13%)
Neonatal death n (%)	3 (5.3%)
Neonatal RT-PCR(+)	0

PROM: Preterm Rupture of Membranes, RT-PCR: The real-time reverse transcription polymerase chain reaction

Pregnancies of 41.7% (35/84) of the patients continued, 3.6% (3/84) had an abortion and 54.8% (46/84) gave live births. Cesarean section was performed in 31.12% of deliveries, while 16.7% had normal birth. Forty-six babies were born.

The mean 1st and 5th minute Apgar scores of the newborns were 7.8 (1.8) (3-9) and 9.3 (0.9), respectively. The mean birth weight was 3190.7 (773.5) grams. Thirteen of the forty-six of newborns (28.2%) were admitted to the neonatal intensive care unit, among which fever was observed in 6.5% (3/46), dyspnea in 15.2% (7/46), and pneumonia in 13% (6/46). The COVID-19 PCR tests of the newborns admitted to the intensive care were negative. Mortality was observed in 3 newborns.

Comparison of demographic characteristics and laboratory values is summarized in Table 3. Significant differences were observed between Group 1 and Group 2 in terms of PCR and CT results (P=0.045, P=0.002). There was less PCR positivity and more CT findings in Group 2 compared to Group 1. Significant differences were observed between the groups in terms of fetal distress (p=0.001), birth weight of the newborns and neonatal intensive care need (p=0.002, p=0.006, respectively).

Table 3: Comparison of groups according to the clinical severity of the patients

	Total	Group 1 asymptomatic/ mild	Group 2 moderate/ severe	*P*-value
Age (years) mean (SD)	28.7 (5.6) (17-43)	28.4 (5.7) (17-43)	29.6 (5.3) (20-38)	0.702
BMI (kg/m^{2}) mean (SD)	25.4 (3.1) (20-35)	25.2 (2.9) (21-34)	26 (3.5) (20-30)	0.483
Gestational age on admission (week) mean (SD)	28.1 (11.1) (4-40)	28.2 (11.7) (4-40)	26.6 (10.6) (6-39)	0.297
1st Trimester	13 (15.5%)	10 (11.9%)	3 (3.6%)	
2nd Trimester	17 (20.2%)	11 (13.1%)	6 (7.1%)	
3rd Trimester	54 (64.3%)	38 (45.2%)	16 (19%)	
Parity mean (SD) range	1.1 (1.1) (0-5)	1.1 (1) (0-5)	1.2 (1.1) (0-4)	0.883
Additional disease	19 (22.6%)	11 (13.1%)	8 (9.5%)	0.181
Diabetes mellitus	4 (4.8%)	2 (2.4%)	2 (2.4%)	
Hypothyroidism	4 (4.8%)	3 (3.6%)	1 (1.2%)	
Chronic hypertension	3 (3.6%)	1 (1.2%)	2 (2.4%)	
Asthma	2 (2.4%)	-	2 (2.4%)	
Other	6 (7.4%)	4 (4.8%)	2 (2.4)	
Smoking				0.566
Yes	13 (15.5%)	10 (11.9%)	3 (3.6%)	
No	71 (84.5%)	49 (58.3%)	22 (26.2%)	
Symptoms				
Cough n (%)	35 (41.7%)	21 (35.6%)	14 (56.0%)	0.083
Shortness of breath n (%)	22 (26.2%)	15 (17.9%)	7 (8.5%)	0.806
Fever n (%)	16 (19%)	12 (14.3%)	4 (4.8%)	0.643
Myalgia and weakness n (%)	16 (19 %)	11 (13.1%)	5 (6%)	NS
Headache n (%)	12 (14.3%)	7 (8.5%)	5 (6%)	NS
Sore throat n (%)	8 (9.5%)	5 (6%)	3 (3.6%)	NS
Loss of taste n (%)	3 (3.6%)	2 (2.4%)	1 (1.2%)	NS
Diarrhea n (%)	3 (3.6%)	1 (1.2%)	2 (2.4%)	NS
No symptoms n (%)	18 (21.4%)			
Diagnosis				
RT-PCR	52 (61.9%)	31 (36.9%)	19 (22.6%)	0.045*
CT	23 (27.3%)	13 (15.5%)	14 (16.7%)	0.002*
Diagnosed by Symptom Only	9 (38.1%)			
Delivery method				
Ongoing pregnancy	35 (41.6%)			
Abortus n (%)	3 (3.6%)	2 (2.4%)	1 (1.2%)	NS
Vaginal delivery n (%)	14 (16.7%)	9 (10.7%)	5 (6%)	0.594
Cesarean delivery n (%)	32 (38.1%)	23 (27.4%)	9 (10.7%)	0.797
Indication of cesarean delivery				
Previous uterine surgery	10 (12%)	7 (8.3)	3 (3.5%)	0.986
Fetal distress	7 (8.3%)	-	7 (8.3%)	0.001*
Clinical outcomes of newborns (n=56)				
Neonatal birthweight (gr)	3190.7 (773.5)	3397.6 (748.9)	2681 (591.5)	0.002*
Transferred to NICU n (%)	14 (25%)	5 (9%)	9 (16%)	0.006*
Neonatal death n (%)	3 (5.3%)	2 (3.5%)	1 (1.7%)	NS
Laboratory findings				
Leucocytes (10^{9}/L) mean (SD)	9.6 (3.45)	9.8 (3.3)	9.2 (3.7)	0.472
Lymphocytes(10^{9}/L) mean (SD)	1.55 (0.64)	1.68 (0.63)	1.25 (0.57)	0.004*
Platelets 10^{3}/mm3 mean (SD)	226.8 (68.8)	240.1 (59.7)	195.4 (79.3)	0.016*
CRP (mg/dL) mean (SD)	3.1 (4.11)	2.02 (3.40)	5.7 (4.49)	0.001*
Ferritin (ng/ml) mean (SD)	102.6 (134)	75 (121.3)	98.3 (135.9)	0.870
Fibrinogen (mg/dl) mean (SD)	498 (131)	528.5 (134.1)	478.7 (123.6)	0.311
D-dimer (ng/ml) mean (SD)	2073.4 (1310.7)	2005.1 (1323.9)	2043.5 (1246.9)	0.941
AST (U/L) mean (SD)	59.8 (115.8)	23.2 (14.7)	92.9 (153.4)	0.051
ALT (U/L) mean (SD)	53.1 (105)	22.5 (35.9)	99.1 (151.4)	0.033*

AST: Aspartate aminotransferase enzyme, ALT: Alanine aminotransferase enzyme, CRP: C-reactive protein, CT: Computer Tomography, RT-PCR: The real-time reverse transcription polymerase chain reaction, NICU: neonatal intensive care unit, (*) There is significant difference between the Group 1 and the Group 2 (P<0.05).

Discussion

In the literature, the average age of pregnant women with COVID-19 positive ranges between 29-32 years. It has been reported that pregnant women positive for COVID-19 are mostly in the 3rd trimester [7]. In a study conducted on 50 pregnant women with a positive COVID-19 PCR tests, the mean age was 30 years, and the mean week of gestation was 36 weeks [8]. In a case series of 116 patients, the mean age was reported as 30.8 (24-41) years and the gestational week as 38 (IQR 36-39) weeks [9]. In addition, in a study involving 388 patients from 22 different cities and 73 centers, the mean age of the patients was 32.2 years, and the mean week of gestation was 30.6 (9.5) weeks [10]. In our study, the mean age of the patients was 28.8 (5.6) years, and the mean gestational week was 28.2 (11.1) weeks. Among them, 15.5% were in the first trimester, 20.2%, in the second trimester and 64.3%, in the third trimester.

The data of symptomatic patients differ in the literature. While fever was observed in 87% of patients in Yang et al.'s study [11], another study found fever in 17.3% [12]. Jie et al. [9] reported that the most common symptom was fever with a rate of 50.9% (59/116), which was followed by cough (28.4%, 33/116). In a systematic review of 108 pregnant women, 68% of the patients had fever, 34% had persistent dry cough, 12% had dyspnea, and 6% had diarrhea. [13]. In another publication, 52.1% of the patients had cough, 44.1% had fever, 15.5% had shortness of breath, and 24% of the patients were asymptomatic [10]. In our study, the rates of cough, shortness of breath and headache were 41.7%, 26.2%, and 14.3%, respectively. The rate of asymptomatic patients was 21.4%.

Although the diagnosis of COVID-19 was made by PCR, the value of diagnosis with thoracic CT is higher due to the high PCR false negativity [12]. In another study, 96.3% (104/108) of pregnant women with a clinical diagnosis of COVID-19 had pneumonia in thoracic CT scans [9]. In a study conducted on 388 pregnant women, CT was obtained in 56 patients (14.4%), among which bilateral multifocal involvement was observed in 80.4% (45/56) [10]. In our study, 52 (61.95%) patients were diagnosed by PCR tests, and 32 (38%) were diagnosed clinically and radiologically. Chest CT was performed in 27 patients, and COVID-19 lung findings were observed in 23. The most common lung findings included ground-glass opacity (74%) and patchy shadowing (55%). The diagnostic value of CT was high. PCR positivity decreased and thorax CT findings increased with disease severity.

It has been reported that laboratory values of IL-6 and CRP can provide information about the severity and course of the disease in a study conducted on 140 patients [14]. In another study of 58 patients, CRP and procalcitonin values were significantly associated with disease severity [12]. In a study by Naudi et al. [7], 70% of the patients who gave birth by cesarean section had high CRP values and 59% had lymphopenia. In another study involving 116 pregnant women, lymphopenia was observed in 44% of the patients, leukopenia in 24.1%, and high CRP in 44% [9]. Comparing with the control group in 61 patients, Justin et al. [15] reported that low WBC and platelet counts in COVID-19 positive patients indicated the severity of the disease. The majority of patients had decreased white blood cell, platelet, and lymphocyte count and increased alanine aminotransferase and aspartate transaminase values. In our study, lymphocyte and platelet count decreased, and CRP and ALT values increased with disease severity. We think that lymphocyte, CRP, and platelet count are valuable in the follow-up and treatment of the disease.

It has been reported that antibiotics, antivirals, anticoagulants, corticosteroids, and plasma are given in the treatment of the disease since it is a viral infection [16]. In a study conducted with 61 COVID-19 positive pregnant women (n = 54), they did not give any treatment to those who were not severely ill (supplemental O_2, hydroxychloroquine, remdesivir, antibiotics, steroid use, mechanical ventilation, ICU admission). In a multicenter study of 388 patients, 222 (57.2%) patients were not treated. Among the rest, hydroxychloroquine was given to 90 patients (23.2%), antibiotics, to 79 (20.4%), azithromycin to 58

(14.9%), LMWH to 87 (22.4%), and antiviral agents (lopinavir / ritonavir) were given to 72 patients (18.6%) [10]. Studies suggest administering a prophylactic dose of low molecular weight heparin (LMWH) for hospitalized patients due to the increased risk of intravascular thrombosis in COVID-19 positive patients [17]. In our study, 36 patients received treatment, and low molecular weight heparin (LMWH) was administered to all. Medical treatments given in addition to LMWH were favipravir (21.4% of patients), lopinavir/ritonavir (13%), hydroxychloroquine (8.3%), ceftriaxone (16.6%), and azithromycin (4.7%).

In a study, only 2 of 48 COVID-19 positive pregnant women gave birth via normal vaginal delivery and 39% had premature birth [8]. In another study involving 52 pregnant women, preterm labor occurred in 15.3% of the patients [12]. In a small series of 5 cases, stillbirth was reported as a result of chorioamnionitis, secondary to infection [18]. In the study of Yang et al. including 118 pregnant women, the rates of preterm labor, neonatal asphyxia and stillbirth were 21.3%, 1.2%, and 1.2%, respectively [11]. There was one spontaneous abortion in 116 cases, preterm labor in 21.2%, and Preterm Rupture of Membranes (PROM) in 6.1%. Severe asphyxia occurred in 1 out of 100 newborns [11]. The worldwide preterm birth rate is estimated to be around 11% (5% in Europe, 18% in Africa) [19]. In our study, 41.6% of pregnancies continued, 27.4% resulted in preterm labor, 3.6% in abortion, and 2.4% in PROM. We noticed that the rate of preterm birth increased with COVID19.

In a study, 85 (85.9%) of pregnant women with COVID-19 gave birth by cesarean section and 14 (14.1%) by vaginal delivery [20]. In other studies, 92% of COVID-19 pregnant women gave birth by cesarean section and 8% by vaginal delivery. Fetal distress was reported as the most common cesarean indication [21, 22]. In our study, 38.1% of women delivered by cesarean section and 16.7% by normal vaginal delivery. The most common cause of cesarean section in clinically severe COVID-19 patients was fetal distress.

Recent studies have shown that most newborns born to infected mothers are asymptomatic and there is only limited evidence of vertical transmission [23]. However, many studies have shown that there is no vertical transition (amniotic fluid, cord blood, neonatal throat swab samples, Breastmilk samples) [8, 20, 21, 24]. Neonatal death was reported in 5 (2.0%) of 251 COVID-19 pregnancies (3 due to prematurity and 2 due to sepsis), and only one (0.4%) of 251 live-born newborns was RT-PCR positive after birth [10]. In the study conducted by Zhu et al., one of the babies of nine COVID-19 positive mothers died, while five were hospitalized in the neonatal intensive care unit [25]. In their study, Yang et al. reported neonatal death in only 1.2% [11]. In our study, 28.2% (13/46) of the neonates were admitted to the neonatal intensive care unit. Three newborn mortalities were observed (2 due to sepsis, 1 prematurity), none of which were COVID-19-positive. The rate of low birth weight (LBW) and hospitalization in the neonatal unit significantly increased in the infants of mothers with severe symptoms.

In a multi-center study, 11.1% of 388 pregnant women with COVID-19 were hospitalized in the intensive care unit, 9.3% required mechanical ventilation (36/388), and maternal death occurred in 0.8% [10]. In another study, 7 pregnant women were reported, 2 were admitted to the intensive care unit, and all survived [26]. In a COVID-19 series of 116 cases, 8 patients were admitted to the intensive care unit, but the authors reported maternal death [9]. In a study conducted in Turkey, 4 of 56 pregnant women who were positive for COVID-19 died, 2 of which were admitted to the intensive care unit [12]. In our study, 5 pregnant women were admitted to the intensive care unit, 3 maternal deaths were observed and among them, only 1 pregnant woman had an additional disease.

Conclusions

The coronavirus disease 2019 may cause preterm labor. In pregnant women, radiological diagnosis with thorax CT scans may be more accurate than PCR tests. Based on our results, lymphocyte, CRP, and thrombocyte values may be useful laboratory findings in clinical follow-up and treatment.

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Comparison of conventional surgical method and eversion technique in carotid endarterectomy operations

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Ethics Committee Approval
Adana Numune Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (02.12.2013 ANEAH.EK/91)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Carotid endarterectomy is a highly effective and safe operation for preventing the risk of stroke in patients with symptomatic internal carotid artery stenosis. Several surgical techniques were described and available: Conventional carotid endarterectomy (CCEA) and eversion carotid endarterectomy (ECEA) are the two most common. Superiority of these two techniques to one another has not yet been clearly demonstrated. We aim to demonstrate the surgical and clinical experience of our institution regarding these two approaches.

Methods: In this retrospective cohort study, forty-three consecutive patients operated for symptomatic carotid stenosis were divided into two groups according to the preferred surgical method (CCEA and ECEA), and compared in terms of postoperative hospital stay, use of shunts and antibiotics, early (30-day) complications, long-term restenosis, and mortality rates.

Results: Demographic data and preoperative stenosis rates were similar between the two groups ($P>0.05$). In the CCEA group, subjects had a significantly longer clamping time (19.3 (4.1) vs 15.4 (3.4) min., $P=0.002$) and significant differences were found between operative time (35.1 (3.2) vs 28.7 (4.3) min) and need for shunting (25.7% vs 2.1%, $P<0.001$). CCEA patients had a higher percentage of antibiotic use (49.8% vs. 31.1%, $P=0.04$). Hematoma rates, complications during follow up, including stroke, heart attack, and mortality rate were similar between the groups, along with re-stenosis ($P=0.754$) and survival rates ($P=0.241$), according to Kaplan-Meier analysis.

Conclusions: Our results showed that ECEA was a convenient surgical technique and more advantageous compared to CCEA with respect to early and long term follow up results. ECEA can be performed within a significantly shorter operative time and may decrease the necessity for shunting, although it may require specific experience.

Keywords: Carotid stenosis, Eversion carotid endarterectomy, Conventional carotid endarterectomy

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Introduction

According to the World Health Organization, cerebrovascular diseases are the second most common cause of death worldwide following ischemic heart diseases [1]. Up to 8-10% of cerebrovascular events occur in the internal carotid artery [2]. Detection and treatment of the disease are very important in terms of health expenditures as well as preventing possible labor and function loss. The European Society for Vascular Surgery guidelines for management of extracranial carotid disease recommend carotid endarterectomy (CEA) for all symptomatic patients with a carotid stenosis of 70-99% [3]. CEA has been widely performed all over the world with increasing popularity and effectiveness since the 1980s. Perioperative stroke rate was 6.2% in CEA operations, which is shown to be quite safe compared to medical treatment or carotid stenting procedures [4].

Two methods are widely used for endarterectomy. The eversion carotid endarterectomy technique was first described by DeBakey [5]. In this technique, the internal carotid artery (ICA) is transected and separated from the common carotid artery at the level of its origin. The plaque inside the internal carotid artery is everted and removed and anastomosis is performed again with CCA. The plaque causing stenosis is reached with a longitudinal incision extending towards the ICA through the CCA in conventional carotid endarterectomy (CCEA). The arteriotomy incision on the carotid artery is closed by patching or primary suturing after removal of the plaque. This study aims to compare the early and mid-term results of these two methods.

Materials and methods

In this retrospective cohort study, the data of forty-three consecutive patients who were operated between 2013 and 2014 were reviewed. The patients were divided into two groups according to the operation technique used (ECEA and CCEA). Adana Numune Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (02.12.2013 ANEAH.EK/91) approved this study. Patients who were operated on for the second time due to restenosis or underwent an additional surgical procedure in the same session due to other concomitant pathologies were excluded from the study. All subjects were evaluated by Doppler USG and computed tomography angiography or conventional angiography before the procedure. A team of at least one neurovascular specialist and at least one cardiovascular surgeon assessed all patients before surgical intervention. The eligibility of the patients for the surgical procedure was decided by the same team together with the imaging results. Optimal medical treatment was arranged for all patients before the procedure. All demographic data and clinical information were recorded. The data obtained during the operation, the use of a shunt, length of hospital stay, the incidence of perioperative cerebrovascular events, complications such as bleeding or hematoma requiring re-intervention in the early period (first 30 days), and significant (>50%) restenosis rates in long-term (1 year) follow-ups were noted.

All operations were performed under general anesthesia. Heparin was administered to the patients at 5000-6000 units/kg during the operation. Patients were followed up with routine monitoring and intermittent neurological examination for at least 24 hours in the vascular surgery intensive care unit after the operation. Doppler USG examination was performed to evaluate restenosis at the 12th and 18th months.

Statistical analysis

All data, retrospectively obtained from the clinical documents and hospital registry, were analyzed using Statistical Package for Social Sciences (SPSS for Windows, v.20.0; Chicago, IL, USA). Imaging and laboratory results, as well as operation notes were reviewed. Student-t test was used to evaluate statistical significance. A *P*-value <0.05 was considered significant.

Results

Demographic data and preoperative stenosis rates were similar between the groups. In the CCEA group, clamping (19.3 (4.1) vs 15.4 (3.4) min., *P=0.002*) and operative times were significantly longer (35.1 (3.2) vs 28.7 (4.3) min, *P=0.001*), and patients had a higher rate of antibiotic use (49.8% vs. 31.1%, *P*=0.04) (Table 1).

Table 1: Demographic and clinical data of patients

	CCEA (n=24)	ECEA (n=19)	*P*-value
Mean age (SD)	66.1(6.0)	66.8 (5.3)	0.685
Gender (male)	19 (79.2 %)	14 (73.2%)	0.817
Hypertension	8 (33.3 %)	7 (36.8 %)	0.152
Diabetes Mellitus	15 (62.5 %)	11 (57.9 %)	0.083
Hyperlipidemia	17 (70.8 %)	10 (52.6 %)	0.241
Current Smoker	16 (66.7 %)	11 (57.9 %)	0.068
Peripheral Vascular Disease	14 (58.3 %)	10 (52.6 %)	0.704
Ischemic Heart Disease	8 (33.3 %)	8 (42.1 %)	0.230
Symptomatic ICA disease	19 (79.2 %)	15 (78.9 %)	0.078
Previous cerebral infarct	19 (79.2 %)	16 (84%)	0.105
Preoperative medications			
Acetylsalicylic Acid	20 (83%)	15(78.9%)	0.681
Beta blocker	15 (62.5%)	11(57.8%)	0.083
ACE inhibitors	12 (50%)	11(57.8%)	0.360
Anticoagulant	2(8.3%)	0	0.241

The complication rates observed in the early postoperative period (within the first 30 days) did not differ between the two groups (Table 2).

Table 2: Intraoperative and early period (30 days) outcomes

	CCEA	ECEA	*P*-value
Operative Time (min), mean (SD)	92.7 (12.3)	74.9 (9.2)	0.001
Clamping Time (min), mean (SD)	19.3 (4.1)	15.4 (3.4)	0.002
Length of Stay in Hospital mean (SD)	2.54 (1.1)	2.37 (0.9)	0.734
Dysrhythmia, n (%)	0	1	0.387
Local cranial nerve injury	2 (8.3%)	1 (5.3%)	0.871
Stroke	0	0	-
Myocardial Infarction	1(2.3 %)	1(5,3%)	0.624
Death	0	0	-
Bleeding	2 (8.3%)	1 (5.3%)	0.871
Wound Infection (surface)	1(2.3 %)	0	0.582

Cranial nerve injuries (hypoglossal nerve, laryngeal nerve, recurrent laryngeal nerve, and glossopharyngeal nerve) at the surgical site were observed at a similar rate in both groups. Local nerve damage symptoms resolved in all patients in the following months. Superficial wound infection and hematoma rates were similar between the two groups. Neither deep wound infection, nor major stroke was observed in any patient in the early postoperative period. Protamine was not administered to reverse anticoagulation in any of the patients. Early complications are summarized in Table 2. Complications during the follow-up period, including stroke, heart attack, mortality rate, and according to Kaplan-Meier analysis, restenosis (*P*=0.754) and survival rates (*P*=0.241) were not significantly different between the groups (Figures 1, 2).

Figure 1: Kaplan-Meier analysis of no restenosis rates (The log-rank *P*=0.754)

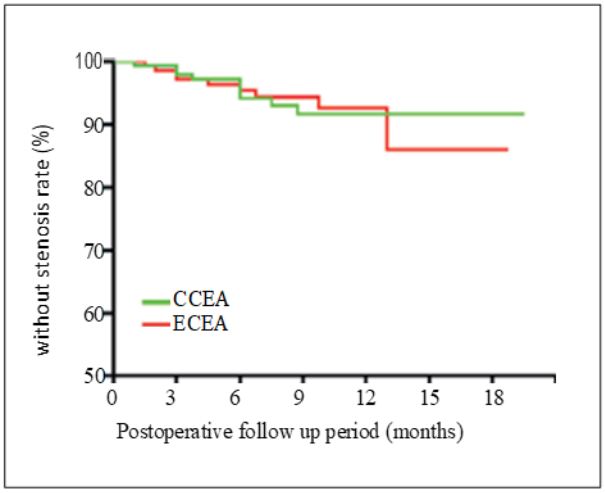
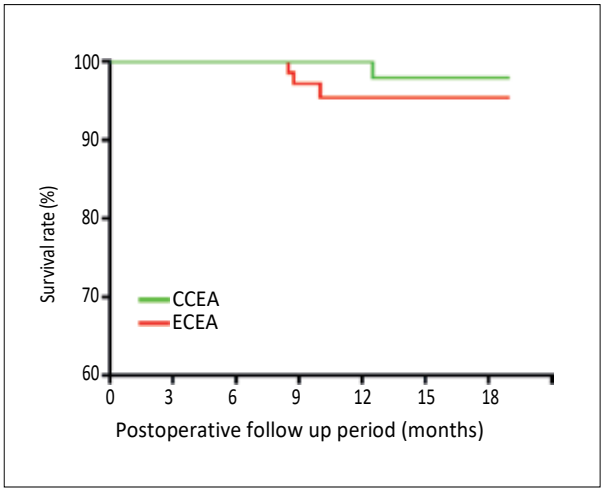


Figure 2: Kaplan-Meier analysis of survival rates (The log-rank test *P*=0.241)



Discussion

The eversion technique has become an alternative operative method with at least as much popularity as the conventional method. No superiority was demonstrated between the two methods in the early and late periods, similar to our study [6].

Surgically, endarterectomy is known to be superior to medical treatment than endovascular stenting [7]. The superiority of surgery can only be achieved by lower perioperative major complications and long-term restenosis rates. Therefore, it is very important that carotid surgery is performed by experienced surgeons in centers with sufficient experience of the procedure, as emphasized in the guidelines. A healthy evaluation, especially in terms of lesion localization, and implementing the most suitable method to the patient will yield optimum success in surgical results, even though both methods can be used in each patient in the centers that meet these conditions. Patients were operated on after the method was determined preoperatively without randomization in our study. ECEA is preferred more in lesions limited to ICA or those with a small association with the CCA, whereas CCEA is preferred in our own clinic, especially in lesions largely associated with CCA. We think that this selection played a role in the lower restenosis and stroke rates among our patients compared to the literature. There was no difference between the two groups in terms of efficacy and reliability in our study. Similarly, no difference was found between the two methods in terms of safety and efficacy in many randomized studies and meta-analyses [7-9]. Cross-clamp times were significantly shorter in ECEA patients, although this did not result in clinical advantage perioperatively. However, it may provide the opportunity to perform surgery within a safer time in patients with contralateral carotid lesions or intracranial vascular damage.

The incidence of infection has been reported around 1% in CCEA cases in which prosthetic patches were used [10]. Gram-positive staphylococci and streptococci have been identified as the most important responsible pathogens leading to bacterial infection [11]. It is important to consider this in routine antibiotic prophylaxis to eliminate the risk of infection. Superficial infection was observed in one patient in the CCEA group in our study; therefore, treatment did not require surgical debridement and revision. Especially infections of prosthetic patches may lead to severe conditions that cannot be compensated if the infection is not carefully managed.

Different results have been presented regarding shunt use. The idea of maintaining brain perfusion during the procedure seems very attractive. However, the use of shunts also has its own complications. It may be necessary to enlarge the arteriotomy to place the shunt, which may extend the cross-clamp time during placement. In addition, improperly placed shunts may cause embolisms. M. Jamil et al. showed that routine shunt use did not affect perioperative results [12]. On the other hand, there are studies indicating that selective and routine shunt use reduce the incidence of stroke [13, 14].

Arteriotomy incision is closed with a patch in CCEA operations in our practice. ECEA method was shown to be associated with relative risk reduction of 28% and 25% in 30-day and one-year stroke/death rates, respectively (30-day stroke/death: OR 0.72, 95% CI 0.54-0.95; stroke/death at 1 year: HR 0.75, 95% CI 0.58-0.97) compared to ECEA and patchless CCEA method [8,15]. Primary closure of the arteriotomy incision forms a more favorable ground for restenosis during vascular remodeling even though stenosis is reduced with the removed plaque when a patch is not used. This leads to higher complication and mortality rates within 30 days and one year.

Larger patient groups are needed to evaluate some data more healthily since our study was conducted among a limited patient group. The lack of evaluation of plaque morphologies constitutes another weakness of the study.

Conclusions

The results we reached in this study with a limited group of patients showed that both ECEA and CCEA operations were safe methods with very low complication rates. No significant clinical difference was observed in 12-month and 18-month long-term follow-ups in terms of safety and durability.

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The effect of bilateral tubal ligation on menopause age and symptoms

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Abstract

Background/Aim: Bilateral tubal ligation (BTL) is an effective and safe method for family planning; however, the blood supply of the ovaries may be affected during the procedure. There is suspicion that women may enter menopause early once BTL is performed. Although some studies in the literature have evaluated bilateral tubal ligation's effect on ovarian reserves and function, studies investigating its effect on menopause age and symptoms are lacking. The aim of this study was to investigate the effect of bilateral tubal ligation on menopause age and symptoms, eliminate women's hesitations, and guide the clinicians.

Methods: Two hundred postmenopausal women with no comorbidities which may affect the ovarian reserve and menopause symptom severity were included in this case-control study. One hundred women who had undergone bilateral tubal ligation constituted the bilateral tubal ligation (BTL) group, while 100 women who had not undergone any surgery, including bilateral tubal ligation, and who had not received medical treatment and naturally gone through menopause, constituted the control group. Data of all patients regarding menopause age, obstetric history, and educational status were collected. The 'Menopause Rating Scale' was applied to the groups to assess the severity of menopause symptoms. Bilateral tubal ligation age was recorded for the study group. The results were compared using statistical methods.

Results: The mean menopause ages of the bilateral tubal ligation and control groups were 48.30 (3.5) and 47.67 (4.3) years, respectively (P=0.250). The two groups were similar in terms of somatic (P=0.744), psychological (P=0.930), and urogenital (P=0.477) menopause symptoms. The mean age at which bilateral tubal ligation was performed in the bilateral tubal ligation group was 37.33 (4.6) years.

Conclusion: The bilateral tubal ligation procedure did not affect menopause age or the severity of menopause symptoms.

Keywords: Contraception, Bilateral tubal ligation, Menopause age, Menopause symptoms

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Introduction

'Menopause' is defined as the permanent loss of menstruation due to the loss of ovarian function [1]. One-fifth of the world's female population is in menopause, and according to data published in 2019, women's life expectancy is 74.2 years [2]. With increased quality and access to health services, life expectancy has increased, along with the proportion of the female population in menopause [3]. During menopause, somatic, psychological, and urogenital complaints may occur, including hot flashes, cardiovascular diseases, anxiety, irritability, personality changes, physical and mental fatigue, depression, genital atrophy, sexual problems, and pelvic floor dysfunction [4].

Meanwhile, the subject of family planning has been on the agenda of people for a long time. Bilateral tubal ligation (BTL) is an easy-to-perform, effective, and economical contraceptive method. In addition to these positive aspects, it has been reported to protect against tubal and ovarian cancers [5]. However, during the tubal ligation procedure, anastomoses between the uterine and ovarian arteries may be affected, and blood supply to the ovaries may be impaired. Furthermore, the reduced paracrine, endocrine and neural stimulation of the ovaries resulting from tubal damage may adversely affect ovarian function and the severity of menopause symptoms. Although some studies in the literature evaluated BTL's short-term effects on ovarian reserves and function, studies investigating BTL's long-term effects on menopause age and symptoms are lacking.

The current study, therefore, compares women who have undergone BTL with women who have not undergone the procedure in terms of menopause age and the severity of menopause symptoms.

Materials and methods

This case-control study was conducted at the Gynecology and Obstetrics Clinic of Mersin University Hospital between 30 January 2019-31 May 2019. Before beginning this research, approval for the study was obtained from the Mersin University Clinical Research Ethics Committee on January 23, 2019, with the decision number 2019/48.

The BTL Group: The hospital records were reviewed retrospectively, and women who had undergone the BTL procedure at Mersin University Hospital using the Pomeroy method were invited to the Gynecology and Obstetrics Clinic for an interview. Among the participants who accepted this invitation, women who were in menopause constituted the study's BTL group.

The control group: Women who visited the gynecological outpatient clinic at Mersin University Hospital for routine menopause control were evaluated, and those who did not have any comorbidities, had not undergone the BTL procedure, and agreed to participate in the study were included in the control group.

Exclusion criteria: Women with a history of smoking, radiation exposure, radiotherapy and chemotherapy, premature ovarian insufficiency, previous ovarian surgery, and previous myomectomy – all of which might affect the ovarian reserve – were not included in the study. Additionally, women with thyroid diseases, cardiac diseases, pheochromocytoma, leukemia, pancreatic tumors, migraine, Parkinson's disease, breast cancer, and psychiatric diseases – all of which might affect the severity of menopause symptoms – were also excluded from the study (Figure 1).

All participants were informed of the study's aim and content, as well as the confidentiality of any collected data, which participants were told would be used for scientific purposes only. The women who agreed to participate were included in the study. Interviews were conducted face-to-face by the same investigator (YI) in both the BTL and control groups. To avoid bias, the first participants for both groups who met the criteria were included in the study. The menopause rating scale was applied in a separate room alone and without any intervention.

Power analysis was used to determine the sample size, which revealed that 100 participants in each group were needed for a power of 80% at α=0.05.

Both groups were asked about their socio-demographic characteristics, such as current age, onset age of menopause, gravida, parity, living children, number of miscarriages and abortions, educational status, and chronic diseases. Considering symptoms in the first year of menopause, the women were asked to answer the questions in the 'Menopause Rating Scale' (MRS). The women in the BTL group were also asked about the age at which they had undergone bilateral tubal ligation. Both groups were compared in terms of menopause age, demographic features, answers to the MRS questions, and somatic, psychological, and urogenital symptoms. Furthermore, the BTL and control groups were evaluated for gravida, parity, and educational status.

Menopause Rating Scale

To determine the severity of menopausal complaints and their effect on women's quality of life, the Turkish version of the scale (the original scale had been developed by Schneider, Heinemann, et al. [6] in German in 1992) was validated as a reliable and valid measurement tool [7].

The Menopause Rating Scale is a Likert-type scale comprising 11 items. For each item, the following options are available: '0: None', '1: Mild', '2: Moderate', '3: Severe', and '4: Extremely Severe'. Items 1, 2, 3, and 11 use three subgroups to evaluate somatic complaints. Items 4, 5, 6, and 7 evaluate psychological complaints. Finally, items 8, 9, and 10 evaluate urogenital complaints. The Cronbach's alpha reliability coefficient value was 0.65 for somatic symptoms, 0.79 for psychological symptoms, 0.72 for urogenital symptoms, and 0.84 in total. The scale is evaluated by finding the sum of the points assigned for each item. This evaluation results in a total score between 0 and 44. The higher the total score, the higher the severity of menopausal complaints and the lower the quality of life [7].

Statistical analysis

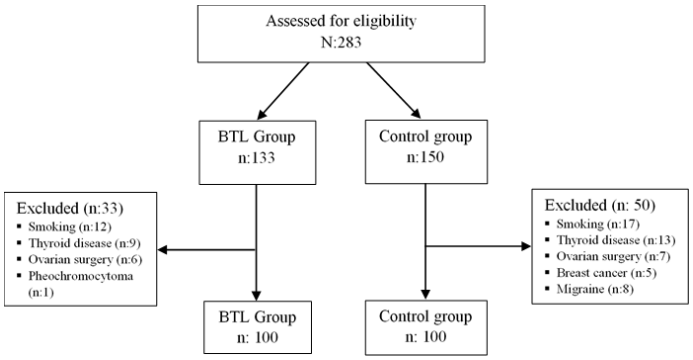
In this study, Statistical Package for Social Sciences (SPSS) 21.0 (SPSS Inc. Chicago, IL, USA) was used for statistical analysis. The Shapiro-Wilk test was used to check whether the data were normally distributed among each group. The mean and standard deviations were used as descriptive statistics for the normally distributed data, and the medians and percentages were used for the non–normally distributed data. The Mann-Whitney U test was used to assess differences between two non-normally

distributed groups. The results were evaluated at a 95% confidence interval and a $P<0.05$ significance level.

Results

The number of samples as determined by power analysis was reached by interviewing a total of 283 participants, including 133 from the BTL group and 150 from the control group. As they did not meet the criteria, 33 participants in the BTL group and 50 in the control group were excluded from the study. The reasons for these women's exclusion are provided in detail in the flowchart below (Figure 1).

Figure 1: Flowchart of study



The mean ages of the patients in the BTL and control groups were 53.5 (4.6) years and 54.0 (5.0) years, respectively (P=0.031). The mean age of menopause in the BTL and control groups were 48.3 (3.5) years and 47.7 (4.3) years, respectively (P=0.250). patients in the BTL group had undergone BTL operation at a mean age of 37.3 (4.7) years, and the group's mean time from undergoing the BTL procedure to menopause was 10.3 (5.2) years. No differences were observed between the groups in terms of gravida (P=0.100), parity (P=0.200), educational status (P=0.270) (Table 1), or in the severity of somatic (P=0.744), psychological (P=0.930), and urogenital (P=0.477) complaints related to menopause (Table 2).

Table 1: Descriptive Statistics Between the Groups

Descriptive Information	BTL group (n=100)	Control group (n=100)	*P*-value
Mean Age	53.5 (4.6)	54.0 (5.0)	0.31
Gravida	4.5 (2.2)	3.9 (2.0)	0.10
Parity	3.7 (2.0)	3.0 (1.6)	0.20
Menopause age	48.3 (3.5)	47.7 (4.2)	0.25
BTL age	37.3 (4.6)	-	-
Time after BTL (years)	10.2 (5.2)	-	-
Educational Status;			
Illiterate/primary school	56 (56%)	64 (64%)	0.27
Secondary/high school	35 (36%)	28 (28%)	
Undergraduate/Postgraduate	9 (9%)	8 (8%)	

BTL: Bilateral tubal ligation, SD: Standard deviation, Mean (SD) values are given. Educational status is indicated by numbers and percentages.

Table 2. Distribution of menopausal complaints by groups

	BTL group (n=100)	Control group (n=100)	*P*-value
Somatic Complaints	5.7 (3.0)	5.5 (3.1)	0.744
Psychological Complaints	5.5 (3.2)	5.6 (2.0)	0.930
Urogenital Complaints	3.4 (2.2)	3.2 (2.5)	0.477
Total	14.7 (6.8)	14.5 (8.0)	0.731

Mean (SD) values are given

Discussion

Bilateral tubal ligation is a popular family planning procedure, performed upon women's requests. In a recent study, Gurbuz et al. [8] reported that family planning methods do not negatively affect the quality of life. On the other hand, the menopause period decreases the quality of life of women. Whether BTL affects menopause age and menopause symptoms are important because menopause constitutes at least one-third of women's lives and, if it starts at an early age, its negative effects will be prolonged [2, 3]. The current study clearly emphasizes that no differences were observed between women with and without BTL in menopause age and menopausal complaints. Furthermore, the mean menopause age in this study was consistent with the mean natural menopause age in Turkey.

In our literature review, we found only one study evaluating BTL's effect on menopausal age [9], and we did not find any study interpreting BTL's effect on menopausal symptoms. In 2019, Ainsworth et al. compared various tubal ligation methods' effects on menopausal age and found the mean age of women who entered menopause naturally to be 50.1 years. The mean menopause age was 50.9 years in the cautery method, 51.1 years in the Pomeroy method, 50.1 years in the Hulka and Filshie clip systems, and 50 years in unknown BTL methods. No statistically significant differences were observed between the menopause ages in terms of various BTL methods and the mean menopause age of women who had entered menopause naturally. In Ainsworth et al.'s study, the mean age at which women underwent the BTL procedure was 36–37 years [9]. In our study, the mean age at which women underwent the BTL procedure was 37.3 years.

Ovarian reserve tests can be used to predict menopause age [10], and numerous studies in the literature have investigated tubal sterilization procedures' effects on ovarian reserves. These studies have reported that tubal surgery does not adversely affect ovarian reserves [11-17]. However, some publications have contradicted these studies [18, 19]. In most of the above-mentioned studies, hormonal markers (such as FSH, LH, E2, and AMH), and ultrasonographic findings (such as ovarian or uterine artery Doppler indices and antral follicle counts) were used in the preoperative and postoperative short terms to evaluate ovarian reserves or function. Our study differs from previous studies in the literature in that it evaluates both menopause age and symptom severity in the postoperative long term, comparing the perspectives of women who have undergone BTL to the control group.

The reason why BTL does not affect menopause age can be explained by the fact that tubal ligation is usually performed from avascular areas. Also, the formation of new anastomoses after the procedure, the recanalization of ligated vascular ends, and the compensatory dilatation of other vascular structures involved in ovarian blood supply meet the need for ovarian blood as a result of the procedure. In parallel to this hypothesis, some studies have evaluated the effect of different BTL procedures such as laparoscopic electrocoagulation, the Pomeroy method, and fimbriectomy on ovarian stromal and utero ovarian artery blood flow parameters in women and found no statistically significant differences between preoperative and postoperative values [20-22].

Studies have also examined subjects' reporting a decrease in ovarian reserves, arguing the antithesis of the previously mentioned findings [18, 19]. The factors underlying this difference may be the ligation of the dominant vessels from the uterine or ovarian arteries in the ovarian blood supply, depending on the anatomical variations of ovarian vascularization. While the ovarian blood supply is normally provided by both the

ovarian and uterine arteries, in some women, it may be predominantly provided by either the ovarian or uterine arteries.

Modern medicine aims to improve quality of life and prolong lifespans. For this reason, quality-of-life scales have recently become a particularly important research area. The Menopause Rating Scale is frequently used in clinical practice because it measures the severity of menopausal complaints quantitatively and determines their effect on the quality of life. This scale was compared with scales measuring the severity of menopause symptoms – such as the Kupperman index and Nottingham Health Profile – and it was found to be more realistic, easier to apply, and more reliable in evaluating menopausal complaints [23]. Moreover, a 2018 study found that the mean MRS scores were 12.88 (8.39) for women who had not menstruated for one year and 9.93 (9.11) for women who had not menstruated for more than one year, and the difference between these two groups was statistically significant [24]. Therefore, in our study, women were asked to answer questions on the MRS while considering their complaints in the first year of menopause.

Both groups were found to have symptoms that impaired their quality of life, but no statistically significant difference was observed between the groups. Decreased quality of life for menopausal women has also been reported in various publications [25]. Blumel et al. [26] reported that menopausal women have worse quality-of-life scores than premenopausal women in the vasomotor, psychosocial, physical, and sexual domains. In addition, hot flashes (a somatic complaint) have been reported as the most disturbing quality of life symptom [27].

The current study's strength is that it directly investigates BTL's effect on menopause age and menopause symptoms, unlike other studies evaluating ovarian reserve tests – such as E2, FSH, LH, and AMH – which indirectly affect menopause age. The mean age of women in the BTL and control groups during the data collection period may be considered a limitation of the current study because women may have difficulty remembering their complaints from early menopause due to a long time has elapsed since its onset. In recent years, after the revelation of the relationship between ovarian cancer and tubal epithelium, salpingectomy has become more popular in tubal sterilization. However, since BTL is reversible and salpingectomy is irreversible, BTL is often preferred – especially among young women. Since most women who have undergone salpingectomy for contraceptive purposes are not yet menopausal, no long-term results have been obtained.

Conclusion

The results of this study demonstrate that BTL does not affect menopause age, or the severity of somatic, psychological, and urogenital complaints related to menopause. We think our study will contribute to better informing patients and improving counseling in family planning practices.

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Research article

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What is the role of oxidative stress in the development of diabetic peripheral neuropathy?

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Ethics Committee Approval
The study was approved by Bozok University Clinical Research Ethics Committee and written consent was obtained from the patients (Research protocol no: 2020-01-07, decision no: 2017-KAEK-189_2020.01.08_16, date: 08.01.2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Diabetic peripheral neuropathy (DPN) is a clinical entity affecting approximately half of the patients with diabetes, impairing the quality of life. Patients usually do not receive full welfare despite medical treatment. This study aimed to evaluate the relationship between DPN and oxidative stress.
Methods: A single-center, clinical study was conducted on 80 patients with type 2 diabetes with and without peripheral neuropathy. Glucose, glycosylated hemoglobin (HbA1c), total oxidant capacity (status) (TOS), and total antioxidant capacity (status) (TAS) levels were assessed from blood samples collected from these individuals. Oxidative stress index (OSI) was calculated by the division of TOS to TAS.
Results: TAS levels were within the normal range while TOS and OSI levels were higher compared to individuals without diabetes in both groups. There was no significant difference between the groups in terms of TOS (P=0.26), TAS (P=0.85), and OSI (P=0.32) levels.
Conclusion: In our study, no relationship was found between DPN and oxidative stress. Further studies involving a larger number of diabetic patients with and without DPN are required to clarify the role of oxidative stress in the development of DPN.

Keywords: Diabetic peripheral neuropathy, Total oxidant status, Total antioxidant status, Oxidative stress, Oxidative stress index

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Introduction

Diabetes is a worldwide metabolic disease with high morbidity and mortality rates due to its macrovascular and microvascular complications. The complex sequence of events leading to cellular failures in response to high glucose levels is not fully explained. Structural and functional disorders of the peripheral nervous system in diabetic patients are described as diabetic peripheral neuropathy (DPN), provided that other etiological factors are excluded. Many factors may contribute to the pathogenesis of DPN such as genetic predisposition, endoneurial hypoxia or ischemia, increased oxidative stress, increased glycosylation end-products, lack of growth factors, or immune mechanisms. The long-term high blood glucose level is the initial inducing factor [1].

Oxidative stress has an important role in the pathogenesis and late complications of diabetes. As a result of having one or more unshared electrons, free radicals are very reactive, and they tend to grab electrons from other atoms or molecules to fill their outer energy levels [2]. In diabetes mellitus, oxidative stress can occur because of the increased production of reactive oxygen species (ROS) including superoxide (O_2^-) radicals, hydroxide radicals (HO^-), and hydrogen peroxide (H_2O_2), and/or inadequacy of antioxidant defense systems [3]. An increase in ROS production is related to protein glycosylation and/or autoxidation of glucose under hyperglycemic conditions. The reason for the inadequacy of neutralization of free radicals is related to the inadequacy of enzymatic and nonenzymatic radical scavengers (antioxidants) [4]. In the literature, the relationship between DPN and oxidative stress in a real-life setting has not been explained clearly. The aim of this study was to evaluate the relationship between DPN and oxidative stress among the patient with type II diabetes.

Materials and methods

Study population

This single-center, prospective clinical study including type 2 diabetes and DPN patients aged between 31-81 years was conducted between January-October 2020. The definition of type II Diabetes Mellitus was made as follows: **a**. At least 8-hour fasting plasma glucose (FPG) ≥ 126 mg/dl **b**. Randomized plasma glucose ≥ 200 mg/dl with diabetes symptoms **c.** In Oral Glucose Tolerance Test (OGTT), 2nd-hour plasma glucose ≥ 200 mg/dl, HbA1c ≥ 6.5% [5]. Exclusion criteria were as follows: The diagnosis of non-diabetic neuropathy, any drug use for neuropathy within the last 6 months, vasculitis, renal failure (glomerular filtration rate less than 90 ml/min), liver failure (liver transaminase levels more than two times of the upper limit), vitamin B12 deficiency, vitamin D deficiency, thyroid pathology, chronic/acute infection findings, cancer diagnosis and/or treatment. A hundred patients with DPN were consecutively assessed in terms of the inclusion and exclusion criteria. Sample size analysis performed at a 5% Margin of Error, 80% Power and a Standard Effect Size of 0.81 revealed that 24 patients were needed in each group. A total of 20 patients were excluded from the study due to the exclusion criteria. Finally, 80 diabetic patients fulfilling the criteria who agreed to participate in the study were included in the analyses. The patients were divided into two groups as the patients with and without DPN. After a detailed physical examination of all patients, fasting venous blood samples were obtained and routine hematological and biochemical tests were performed accordingly. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meter.

Assessment of peripheral neuropathy

Peripheral neuropathy was diagnosed according to EMG findings (nerve conduction velocity, amplitude, and distal latency) and Douleur Neuropathique 4 (DN4) questionnaire. Sensory and motor nerve conduction studies were performed on the median, ulnar, peroneal, and tibial motor nerves, and median, ulnar, and sural sensory nerves with an electromyography (EMG) device (Medelec Synergy; Oxford Instruments; Surrey, UK) by the same neurologist. DN4 survey includes 7 items related to symptoms and 3 items related to neuropathic pain. A total score of 4 or more indicates neuropathic pain. In a developmental study, DN4 showed 83% sensitivity and 90 % specificity in the diagnosis of neuropathic pain [6]. The Turkish version of DN4, used in our study, was validated for the Turkish population [7].

Biochemical analysis

Venous blood samples were collected from the antecubital vein of each patient after a 12-hour overnight fast, and 10 ml samples of venous blood were taken into a biochemistry tube. Their sera were separated with centrifugation at 3000 rpm for 10 min. All material was stored at – 80 °C until analysis.

Serum TOS and TAS were determined with Rel Assay Diagnostics kit (Mega Tıp, Gaziantep, Turkey, developed by Erel) and Oxidative Stress Index (OSI) values were calculated. Total oxidant status (TOS) was measured as described by the manufacturer's protocol. In this method, the oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. Ferric ion produces a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide and the results were expressed in terms of μmol H_2O_2 equivalent/L of serum.

Total antioxidant status (TAS) was measured in the sera by the generation of 2,2′-azino-di-(3-ethylbenzthiazoline sulphonate) (ATBS) radical cation using the commercial kit according to the manufacturer's manual.

The ratio of TOS to TAS was used as the oxidative stress index (OSI) and calculated as follows: OSI (arbitrary units) = [(TOS, μmol H_2O_2/L) / (TAS, mmol Trolox equiv./L)].

Statistical analysis

All analyses were performed using SPSS version 23.0 (IBM Co., NY, USA). The suitability of the data to normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. Independent samples t-test and Mann-Whitney U test were used to compare the differences between continuous variables, and chi-square (χ 2) test was used to assess the differences between categorical variables. The relationships between the variables were evaluated by the Pearson Correlation test. One-Sample t-test was used to compare variables with reference values. Descriptive statistics included mean (SD), median 25th-75th percentiles, and percentage. *P*-value <0.05 was considered statistically significant in all tests.

Results

Of 80 patients with type 2 diabetes, 58 were female. The group with DPN had significantly more female patients, higher BMI, bigger waist circumference, and longer duration of diabetes; however, fasting glucose level, creatinine and HBA1c levels of both groups were statistically similar (Table 1).

Table 1: Demographic and laboratory data of diabetic patients with and without diabetic peripheral neuropathy

Variables	Without Peripheral Neuropathy (n= 40)	With Peripheral Neuropathy (n=40)	*P*-value
Age (years)	60.03 (11.78) (31-81)	58.90 (9.31) (41-77)	0.64
Gender (female/ male)	24 (66%) / 16 (40%)	34 (85%) / 6 (15%)	0.012
BMI (kg/m^2)	30.17 (4.35) (22.76-38.96)	33.38 (5.57) (23.51-44.30)	0.005
Waist circumference (cm)	106.35 (7.80) (86-129)	113 (10.15) (97-137)	0.001
Duration of diabetes (years)	8.30 (6.26) (1-30)	11.25 (7.05) (1-35)	0.028
Fasting glucose (mg/ dL)	175.88 (82.33) (85-499)	169.10 (78.98) (84-437)	0.61
Creatinine (mg/ dL)	0.95 (0.31) (0.42-1.89)	0.97 (0.61) (0.39-4.46)	0.36
Glycosylated hemoglobin A1c (%)	7.70 (1.83) (4.8-11.89)	7.55 (1.67) (4.89-12.20)	0.70

Values are expressed as n (%), mean (SD) (minimum-maximum), median (25-75th percentiles), BMI: body mass index

Although TOS levels of both groups were higher than the reference range (5.00 - 8.00 μmol H_2O_2 equivalent/L), there was no statistically significant difference between diabetic patients with and without peripheral neuropathy concerning TOS levels (*P*=0.26). TAS levels of both groups were within reference values (1.4 - 2.0 mmol Trolox equivalent/L). Similarly, no significant difference was found between diabetic patients with and without peripheral neuropathy with respect to TAS levels (*P*=0.85). Although the OSI values in both groups were higher than the reference range (2.50 - 5.72), there was no statistically significant difference between diabetic patients with and without DPN (*P*=0.32). TOS, TAS, and OSI data of diabetic patients with and without peripheral neuropathy are summarized in Table 2.

Table 2: TOS, TAS and OSI measurements of diabetic patients with and without diabetic peripheral neuropathy

Variables	Reference Range	Without Peripheral Neuropathy (n= 40)	With Peripheral Neuropathy (n=40)	*P*-value
TOS (μmol H2O2 equivalent / L)	5.00 - 8.00	34.02 (13.43) (10.99-55.57)	37.31 (13.26) (9.28-52.97)	0.26
TAS (mmol Trolox equivalent/L)	1.4 - 2.0	1.78 (0.19) (1.20-2.17)	1.77 (0.19) (1.43-2.26)	0.85
OSI (TOS/TAS)	2.5 - 5.72	19.40 (8.11) (6.03-38.13)	21.20 (7.89) (5.72-35.15)	0.32

Values were expressed as mean (SD) (minimum-maximum). TOS: total oxidant status, TAS: total antioxidant status, OSI: oxidative stress index

In correlation analyses, parameters related to oxidative stress had no significant correlation with fasting glucose, HbA1c, duration of diabetes, BMI, or waist circumference (*P*>0.05 for each).

Discussion

Diabetes is a worldwide metabolic disease with high morbidity and mortality rates due to its macrovascular and microvascular complications. Oxidative stress has a prominent role in the pathogenesis and late complications of diabetes [1]. Structural and functional disorders of the peripheral nervous system in diabetic patients are described as diabetic peripheral neuropathy (DPN), provided that other etiological factors are excluded. Many factors may contribute to the pathogenesis of DPN such as genetic predisposition, endoneurial hypoxia or ischemia, increased oxidative stress, increased glycosylation end products, lack of growth factors or immune mechanisms.

In a study by Inci et al. [8], the TOS, TAS, and OSI values of healthy subjects were compared with those of diabetic nephropathy patients, and all were significantly greater among the diabetic nephropathy patients compared to controls. However, in this study, diabetic patients with and without diabetic nephropathy were not compared. In another study, serum TOS levels and OSI values of patients with diabetic nephropathy were significantly higher compared to those of healthy subjects. TAS was low in the blood of diabetic nephropathy patients [9]. In our study, we also found that TOS and OSI parameters were significantly higher in patients with diabetes. This data may support the idea that the patients with diabetes have higher oxidative stress, which may play a role in the development of diabetic complications.

In a study by Kasznicki et al. [10], catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPX), and total antioxidant status (TAS) were examined in diabetic patients with and without DPN, and healthy control groups. A significant decrease of SOD, GPX, and nonsignificant decrease of CAT, and TAS status were seen in type II DM patients with neuropathy compared to type II DM patients without neuropathy and the control group. In our study, only serum TAS levels were measured, and similar to this study, no statistically significant difference was found between diabetic patients with and without neuropathy.

Sayın et al. [11] evaluated serum prolidase activity, TAS, malondialdehyde (MDA), and nitric oxide (NO) levels. Serum MDA and NO levels were significantly higher in patients with DPN compared to the control group, while prolidase activity and TAS levels were lower in the patients with DPN. In our study, TAS levels were within the normal range in both groups. In our study, the data of patients with and without diabetic neuropathy were compared, in contrast to Sayın et al.'s study, which cannot provide precise information about the role of oxidative stress in diabetic neuropathy.

In a study which evaluated plasma 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$), superoxide anion ($O_2^{\cdot-}$), peroxynitrite ($ONOO^-$), vitamin E to lipid ratio, and vitamin C, only superoxide anion ($O_2^{\cdot-}$) was significantly higher in diabetic patients with neuropathy compared to those without. Vitamin E to lipid ratio and vitamin C, which are regarded as antioxidants, were significantly lower in those with neuropathy [12].

In the study conducted by Uzar et al. [1], TOS and OSI levels were higher, but TAS levels were lower in diabetic patients with and without DPN compared to healthy subjects. However, they could not find a significant difference between diabetic patients with and without DNP with respect to these parameters. They stated that this may support the role of oxidative stress in the pathogenesis of diabetes mellitus. In our study, TOS and OSI levels in patients with and without DPN were also significantly higher than the reference range, while TAS level was not.

Limitations

One potential limitation is the cross-sectional study design. In addition, the number of diabetic patients with or without DPN was limited. However, this is a preliminary study giving us an idea about oxidative stress in DPN based on TOS, TAS, and OSI.

Conclusion

These data support the increase of oxidative stress in diabetic patients. There was no significant difference between these parameters among diabetic patients with and without DPN in our study, which may yield controversial results in terms of the role of oxidative stress in DPN. However, our study included a small number of diabetic patients. Further studies involving a larger number of diabetic patients with and without DPN are required to clarify the role of oxidative stress in the development of DPN.

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Effects of treatment with hydroxychloroquine and azithromycin on the index of cardiac electrophysiological balance in patients with COVID-19: A retrospective cohort study

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Ethics Committee Approval
This study was approved by the ethics committee of Gazi Yaşargil Education and Research Hospital with the decision numbered 452 and dated April 28, 2020.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The common cardiac toxicities of hydroxychloroquine (HCQ) and azithromycin (AZ) are not well defined in COVID-19 patients. Index of cardiac electrophysiological balance (iCEB) is used as a novel risk marker for drug-induced arrhythmias. The purpose of this study was to evaluate ventricular repolarization using iCEB and other conventional ECG parameters such as the end of electrocardiographic T wave (Tp-e) interval, Tp-e/QT ratio, and Tp-e/ heart rate-corrected QT (QTc) ratio in COVID-19 patients treated with HCQ and AZ.

Methods: This retrospective study enrolled 164 patients diagnosed with COVID-19 pneumonia in the Emergency Department (ED) and then transferred to the ward or the intensive care unit in April 2020.

Results: A total of 164 patients with a mean age of 47 (18) years (range: 18-97 years) included 83 (50.6%) females. There were 38 and 126 patients in Groups HTQ and HTQ+AZ, respectively. On the 5th day of hospitalization, all patients' heart rates were significantly lower (P<0.001), while QTc, QT max (V5-V6), QTmin, Tp-e (V5-V6), and iCEB values were significantly higher (P=0.01 and P<0.001 for the rest, respectively) compared to the basal values measured in the ED (P<0.001). iCEB values of the HTZ+AZ group were significantly higher than those of the HTQ group (P=0.03). iCEBc strongly positively correlated with Tp-e/QT (V5), and strongly negatively correlated with Tp-e (V5).

Conclusion: The iCEB values were increased after HTQ and AZ treatment among COVID-19 patients, and strongly correlated with Tp-e and Tp-e/QT. iCEB is a simple, non-invasive method that can be a useful marker to evaluate ventricular repolarization in COVID-19 patients.

Keywords: COVID-19, Hydroxychloroquine, Azithromycin, ECG, iCEB, Tp-e interval

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Introduction

In December 2019, cases of pneumonia, caused by a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurred in Wuhan, China [1]. The World Health Organization has announced the official name of this disease as coronavirus disease 2019 (COVID-19) [2]. Repositioning of old drugs for use as a possible therapeutic agent to treat COVID-19 can be an attractive approach because knowledge on clinical safety, efficacy profile, side effects, and drug interactions are well defined [3].

In the previous severe acute respiratory syndrome (SARS) outbreak, hydroxychloroquine (HCQ) was confirmed to have antiviral activity in vitro [4]. This suggests that HCQ may be a possible therapeutic agent for patients with COVID-19. Based on available evidence, an authorization was published by the United States Food and Drug Administration to permit the use of HCQ and chloroquine treatment in COVID-19 patients [5]. Also, in a previous study, HCQ treatment in combination with azithromycin (AZ) was related to viral load decrease/dissolution in COVID-19 patients [6]. According to the Diagnosis and Treatment of COVID-19 Pneumonia (trial 13 April) recommended by Turkey's National Health Commission, all hospitalized patients diagnosed with COVID -19 pneumonia should be treated with HCQ, in combination with AZ for five days [7]. The common cardiac toxicities of HCQ and AZ are not well defined in COVID-19 patients. Few studies have evaluated adverse events potentially linked to the use of HCQ or chloroquine and AZ in COVID-19 patients, including electrophysiological cardiac conditions of prolonged QT and arrhythmia [8–10].

Fatal arrhythmias can be caused by electrophysiological changes during ventricular repolarization [11]. In a previous clinical study, QT interval (QT) and corrected QT interval (QTc) were reported to predict ventricular arrhythmias and sudden death [12]. Few studies suggested that Tp-e interval and Tp-e/QT ratio were novel electrocardiogram (ECG) parameters to assess ventricular repolarization and associated with malignant ventricular arrhythmias [13–15]. A novel marker index of cardio-electrophysiological balance (iCEB), measured as QT interval divided by QRS duration, is an ECG-based derivative of cardiac wavelength λ (λ = conduction velocity x effective refractory period or QT/QRS). Cardiac wavelength λ is related to arrhythmogenesis: Drugs that decrease the wavelength are may raise the risk for non-TdP VT or VF while drugs that increase wavelength may raise the risk for TdP [16, 17]. ICEB projects the balance between cardiac repolarization and depolarization of the action potential, similar to cardiac wavelength λ [18].

The purpose of this study was to evaluate ventricular repolarization using iCEB and other conventional ECG parameters such as the end of electrocardiographic T wave (Tp-e) interval, Tp-e/QT ratio, and Tp-e/QTc ratio in COVID-19 patients treated with HCQ and AZ.

Materials and methods

This is a retrospective cohort study. The institutional ethics board of the Gazi Yasargil Training and Research Hospital, an affiliate of the University of Health Sciences, reviewed and approved this retrospective study (decision date: 28 April 2020, no: 452).

Patients

This study enrolled 164 patients who were diagnosed with COVID-19 in the emergency department and then transferred to the ward or the intensive care unit of a tertiary hospital in Diyarbakır, Turkey, in April 2020. The diagnoses were made according to the Diagnosis and Treatment of Novel Coronavirus Pneumonia (trial 13 April) recommended by Turkey's National Health Commission [7]. The inclusion criteria were as follows: A) Having an epidemiological history, B) Having a non-contrast chest computed tomography (CT) with signs of pneumonia in the emergency department, C) Being 18 years of age or older. All hospitalized patients diagnosed with COVID -19 pneumonia were treated with hydroxychloroquine 400 mg twice a day followed by 200 mg twice a day for 4 days, in combination with azithromycin 500 mg orally a day for 5 days [7]. Patients who stayed in the hospital for less than five days, treated for acute electrolyte imbalance and/or were on antiarrhythmic drugs were excluded from this study, in addition to those who used any drugs (antibiotics, antifungals, antipsychotics) associated with QTc prolongation in addition to standard treatment in the first five days. Patients were divided into two groups, as those treated with only hydroxychloroquine (Group HCQ) and those treated with a combination of hydroxychloroquine and azithromycin (Group HCQ + AZ).

Sociodemographic information such as age, gender, as well as past medical histories such as hypertension, chronic obstructive pulmonary disease, diabetes mellitus, cardiac disease, chronic kidney disease, dementia, malignancy, vitals, laboratory results, ECG parameters were compared.

Electrocardiogram (ECG) analysis

Initial ECGs were obtained in the emergency department and after the completion of treatment (on the 5th day of hospitalization). ECGs were obtained at a rate of 25 mm/s, while patients were in resting position (Nihon Kohden, Tokyo, Japan,). All ECGs were recorded to a computer to reduce error measurements. A software (Adobe Photoshop**, Adobe Systems**, CC 2015, San Jose, CA, USA) was used for 400% magnification. All ECGs were evaluated for electrocardiographic repolarization parameters manually. Measurement of ECG parameters and evaluation of heart conduction disorders were examined by a cardiologist blinded to all clinical features of the study population. The QT interval was measured from the onset of the QRS complex until the end of the T wave. The longest QT intervals in V_5 and V_6 leads were considered QT maximum and the shortest QT interval in any lead was considered QT minimum. Corrected QT intervals were calculated according to Bazett's formula ($QTc = QT/\sqrt{RR}$). The interval from T peak to T end was defined as Tp-Te which was measured on leads V5 and V6. Tp-Te/QT ratio was calculated separately on V5 and V6. ICEB was calculated by dividing QT interval by QRS interval and iCEBc was calculated by dividing QT_c interval by QRS interval in the leads V5-V6.

Statistical analysis

SPSS version 22.0 (IBM SPSS Statistics for Windows, Armonk, United States of America) was used for statistical analysis. Descriptive statistics were presented as frequency and percentage for categorical variables and mean and standard deviation for numerical variables. When conditions for normal distribution were not met, comparisons for two independent

groups were performed using the Mann-Whitney test. To analyze the interaction between measures and treatments, repeated-measures analysis of variance (ANOVA) was used. Spearman correlation test was utilized to evaluate the relationship between QT, QTc, Tp-e, Tp-e/QTc, and ICEB parameters. *P*-values below 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics of study patients

The demographic features, vitals, laboratory parameters, and outcomes of the study population are summarized in Table 1. A total of 164 patients with a mean of 47 (18) years (range, 18-97 years) included 83 (50.6%) females. Thirty-eight patients were treated with hydroxychloroquine only (HCQ group), and 126 patients received a combination of hydroxychloroquine and azithromycin (HCQ + AZ group). The demographic data, vital parameters, and comorbidities of the two groups were similar (Table 1). There was no significant difference between the HCQ group and HCQ + AZ group in terms of admission to the ward or the intensive care unit and length of hospital stay (Table 1). Of 164 patients, the positive reverse transcription-polymerase chain reaction (RT-PCR) tests of 71 (43.3%) were positive, among which 18 patients belonged to the HCQ group (47.4%). The RT-PCR positivity rates were similar between the two groups (P=0.69). The mortality rate in the study population was 5.5% (n=9). HCQ group had 2 (5.3%) in-hospital patient deaths, while the HCQ+AZ group had 7 (5.6%) (P=1). Among all, 17.7% had hypertension, 8.5% had cardiovascular diseases, and 15.9% had diabetes. Nineteen cases with comorbidities (11.6%) were admitted to the intensive care unit (Table 1).

Table 1: Demographics and comorbidities of patients by survival or non-survival during hospitalization

	Total (n=164)	Group HCQ (n=38)	Group HCQ + AZ (n=126)	*P*-value
Age (years/old)	47.7 (18.9)	44.8 (19.7)	48.6 (18.7)	0.27
Sex (n,%)				0.64
Female	83 (50.6)	21 (55.3)	62 (49.2)	
Male	81 (49.4)	17 (44.7)	64 (50.8)	
Comorbidities at baseline (n, %)				
Hypertension	29 (17.7)	8 (21.1)	21 (16.7)	0.71
Diabetes	26 (15.9)	4 (10.5)	22 (17.5)	0.44
COPD-asthma	8 (4.9)	1 (2.6)	7 (5.6)	0.68
Cardiovascular disease	14 (8.5)	3 (7.9)	11 (8.7)	1
Cancer story	3 (1.8)	2 (5.3)	1 (0.8)	0.13
Chronic kidney disease	7 (4.3)	1 (2.6)	6 (4.8)	1
Other comorbidities	9 (5.5)	0 (0.0)	9 (7.21)	0.12
Length of stay (days)	9.8 (6.4)	8.6 (4.47)	10.1 (6.9)	0.82
Systolic BP (mmHg)	118 (16)	118 (13)	118.4 (17)	0.86
Diastolic BP (mmHg)	72.7 (9.7)	71.7 (7)	73 (10)	0.75
Fever (^{0}C)	37.1 (0.7)	37.0 (0.7)	37.1 (0.7)	0.55
Pulse (per minute)	90 (17)	91 (19)	90 (2)	0.77
SPO_2 (%)	96 (3)	97 (3)	96 (3)	0.25
D Dimer (0-243 ng/ml)	328.9 (495)	270.05 (341)	346.6 (533)	0.72
Troponin (0-0.16 ng/ml)	0.1 (0.1)	0.1 (0.01)	0.1 (0.15)	0.91
Hospitalization (n,%)				0.24
Non-ICU	145 (88.4)	36 (94.7)	109 (86.5)	
ICU	19 (11.6)	2 (5.3)	17 (13.5)	

Data are mean (SD) or n (%). HCQ: hydroxychloroquine, AZ: azithromycin, COPD: chronic obstructive pulmonary disease, BP: blood pressure, SPO2: oxygen saturation, ICU: intensive care unit

Clinical laboratory data

All laboratory tests of all patients, performed on admission and the 5th day of hospitalization, were compared (Table 2). The effect of HCQ and HCQ + AZ on biochemical parameters were similar on the 5th day of hospitalization (P>0.05) (Table 2).

Table 2: Laboratory parameters

	Total (n=164) n (%)	Group HCQ (n=38) n (%)	Group HCQ + AZ (n=126) n (%)	*P*-value **
WBC (4.000-10.000/mm^3)				0.652
in ED	7.85 (6)	6.70 (3)	8.19 (6.3)	
5th day	7.07 (5)	6.16 (2)	7.35 (5.2)	
P-value *	0.044			
Neutrophil (2.000-7.000/mm^3)				0.695
in ED	5.4 (4)	4.65 (3)	5.62 (4.1)	
5th day	4.32 (2)	3.77 (2)	4.5 (2.4)	
P-value *	0.002			
Lymphocyte (800-4000/mm^3)				0.659
in ED	1.58 (0.7)	1.48 (0.7)	1.61 (0.7)	
5th day	2.07 (3.5)	1.77 (0.7)	2.17 (4)	
P-value *	0.164			
Platelet (150.000-450.000/mm^3)				0.776
in ED	233.8 (8)	219.02 (65.8)	238.32 (87.2)	
5th day	266.2 (8)	254.23 (72)	269.81 (83.1)	
P-value *	<0.001			
Hemoglobin (11-16 gr/dl)				0.051
in ED	13.5 (2)	13.29 (2.4)	13.6 (1.8)	
5th day	13.1 (1.9)	13.1 (2.3)	13.02 (1.8)	
P-value *	<0.001			
Hematocrit (37-54 %)				0.046
in ED	41.8 (5.3)	40.9 (6.8)	42.1 (4.8)	
5th day	40.4 (5.2)	40.4 (6.5)	40.3 (4.8)	
P-value *	<0.001			
C-reactive protein (0-5 mg/L)				0.675
in ED	43.1 (62.4)	40.9 (72)	43.6 (60)	
5th day	35.9 (59.6)	30.8 (61)	37.5 (59.3)	
P-value *	0.083			
Calcium (8,8-10,6 mg/dl)				0.443
in ED	8.7 (0.5)	8.7 (0.5)	8.7 (0.5)	
5th day	8.4 (0.5)	8.4 (0.6)	8.4 (0.5)	
P-value *	<0.001			
Chlorine (98-107 mmol/l)				0.897
in ED	103.8 (3.2)	103.7 (3.7)	103.8 (3.1)	
5th day	104.7 (3.4)	104.6 (4.2)	104.8 (3.1)	
P-value *	0.007			
LDH (135-225 U/l)				0.33
in ED	254.4 (104.6)	241.2 (122.4)	258.4 (99)	
5th day	268.5 (150.2)	238.2 (123.4)	277.7 (156.7)	
P-value *	0.479			
Potassium (3.5-5.2 mEq/L)				0.38
in ED	4.03 (4.3)	4.0 (0.4)	4.0 (0.4)	
5th day	4.3 (0.5)	4.2 (0.5)	4.3 (0.5)	
P-value *	<0.001			
Sodium (134-146 mEq/L)				0.821
in ED	137.2 (2.9)	137.1 (2.7)	137.7 (3)	
5th day	138.4 (2.5)	138.4 (2)	138.4 (2.7)	
P-value *	<0.001			

HCQ: hydroxychloroquine, AZ: azithromycin, WBC: white blood cell, ED: emergency department, LDH: lactate dehydrogenase, *within subjects, **between subjects

Electrocardiogram data

All patients' ECGs were obtained in the emergency department and after the treatment was completed (on the 5th day of hospitalization) (Table 3). On the 5th day of hospitalization, heart rates (HR) were significantly lower compared to those obtained in the emergency department (P<0.001), while QTc, QT maximum (V5-V6), QT minimum, Tp-e (V5-V6) and ICEB values were significantly higher (P=0.01 and P<0.001 for the rest, respectively). The changes in QT max (V5-V6), QT minimum, Tp-e (V5-V6), and QTc values were similar between the groups. The iCEB values of the HCQ+AZ group were significantly higher than those of the HCQ group (P=0.03).

The iCEBc values had changed insignificantly in all patients from admission until the 5th day of hospitalization; they were increased in the HCQ+AZ group and decreased in the HCQ group.

iCEBc was strongly correlated with Tp-e/QT (V5), strongly negatively correlated with Tp-e (V5), and weakly correlated with QTc and QT (Table 4).

Table 3: Electrocardiogram parameters

	Total (n=164) n (%)	Group HCQ (n=38) n (%)	Group HCQ + AZ (n=126) n (%)	*P*-value **
Heart rate (bpm)				0.856
in ED	89.9 (16.6)	90.9 (19.02)	89.7 (16)	
5th day	79.6 (14.3)	80.2 (16.52)	79.5 (13.7)	
P-value *	0			
V_5 QT max (ms)				0,128
in ED	350.2 (51.3)	356.4 (52.6)	348.38 (5)	
5th day	390.9 (70.5)	381.7 (53.1)	393.66 (7)	
P-value *	0			
V_6 QT max (ms)				0.155
in ED	349.9 (52.1)	356.0 (54.1)	348.06 (51.6)	
5th day	390.6 (69.8)	381.7 (53.1)	393.33 (74)	
P-value *	0			
QT min (ms)				0.166
in ED	327.0 (5)	329.6 (46.6)	326.3 (48.8)	
5th day	363.6 (7)	350.4 (60.3)	367.6 (69.4)	
P-value *	0			
DII QRS (ms)				0.432
in ED	98.51 (24.7)	100.4 (30.9)	97.9 (22.6)	
5th day	101.9 (60)	96.9 (17.9)	103.4 (67.8)	
P-value *	0.869			
V_5 QRS (ms)				0.423
in ED	100 (22.6)	99.1 (22)	101.5 (16.9)	
5th day	99.4 (21)	101.5 (17)	98.8 (22.1)	
P-value *	0,836			
V_6 QRS (ms)				0.471
in ED	98.8 (23.7)	97.9 (23.1)	99.1 (24)	
5th day	98.9 (20.6)	100.8 (18.0)	98.4 (21.4)	
P-value *	0.668			
V_5 Tp-e (ms)				0.387
in ED	81.3 (21.7)	82.1 (25.2)	81 (20.6)	
5th day	91.8 (25.5)	89.2 (26.9)	92.6 (25.1)	
P-value *	0			
V_6 Tp-e(ms)				0.45
in ED	80.9 (21.8)	81.4 (26.2)	80.8 (20.3)	
5th day	91.8 (25.5)	89.2 (26.9)	92.5 (25.2)	
P-value *	0			
QTc (ms)				0.06
in ED	423.7 (49.4)	432.2 (48.4)	421.1 (49.6)	
5th day	444.2 (60.1)	436.1 (53.1)	446.7 (62.1)	
P-value *	0.012			
iCEB (QT/QRS)				0.03
in ED	3.6 (0.7)	3.7 (0.8)	3.59 (0.7)	
5th day	4.0 (0.7)	3.8 (0.7)	4.06 (0.7)	
P-value *	0			
iCEBc (QTc/QRS)				0.03
in ED	4.4 (0.8)	4.5 (0.9)	4.3 (0.8)	
5th day	4.6 (0.8)	4.4 (0.9)	4.6 (0.7)	
P-value *	0.354			
V_5 Tp-e/QT				0.96
in ED	0.2 (0.04)	0.23 (0.05)	0.23 (0.04)	
5th day	0.2 (0.05)	0.23 (0.05)	0.23 (0.05)	
P-value *	0.469			
V_5 Tp-e/QTc				0.93
in ED	0.19 (0.1)	0.18 (0.05)	0.19 (0.04)	
5th day	0.20 (0.1)	0.20 (0.04)	0.20 (0.04)	
P-value *	0.003			
V_6 Tp-e/QT				0.88
in ED	0.23 (0.05)	0.22 (0.1)	0.23 (0.1)	
5th day	0.23 (0.05)	0.23 (0.1)	0.23 (0.1)	
P-value *	0.37			

Data are represented as mean values (standard deviation); *within subjects; **between subjects; ED: emergency department, max: maximum, min: minimum, iCEB: index of cardio-electrophysiological balance

Table 4: Spearman correlation test for index of cardio-electrophysiological balance (iCEB) and corrected index of cardio-electrophysiological balance ($iCEB_C$)

	iCEB		$iCEB_C$	
	P-value	R	*P*-value	R
QT	0.15	−0.11	0	−0.32
QTc	0.18	0.1	0	0.326
V_5 Tp-e	0.38	0.69	0	−0.69
V_6 Tp-e	0.007	0.21	0.93	−0.006
V_5 Tp-e/QT	0.046	0.15	0	0.88
V_6 Tp-e/QT	0.57	0.04	0.009	−0.2
Tp-e/QTc	0.51	0.05	0.01	−0.2

Discussion

This is the first human study to demonstrate the clinical usability of iCEB as a predictor of arrhythmias in COVID-19 patients treated with HCQ and AZ. We believe that increased iCEB values are due to HCQ and AZ treatment which increases ventricular repolarization heterogeneity and ventricular arrhythmias. iCEB may a more sensitive marker than QT prolongation in predicting the risk of multi-drug arrhythmia.

In this study, the most prevalent comorbidities were hypertension (17.7%), diabetes (15.9%), and cardiovascular disease (8.5%). The literature offers few studies about the incidence of comorbidities among COVID-19 patients. Yang et al. assessed the prevalence of comorbidities in COVID-19 patients in a meta-analysis and found various underlying diseases, including hypertension (21.1%), cardiovascular (8.4%,) and respiratory system diseases (1.5%) [19]. Another meta-analysis by Li et al. examined comorbidity incidence among COVID-19 cases and reported the most prevalent as hypertension (17.1%), diabetes (9.7%) cardio-cerebrovascular diseases (16.4%) [20].

Few studies have evaluated adverse events potentially linked to the use of HCQ and AZ in patients with COVID-19, including electrophysiological cardiac conditions of prolonged QT and arrhythmia [8–10]. Arrhythmic events frequently encountered in COVID-19 patients and drugs used in treatment also have a pro-arrhythmic effect. COVID-19 causes direct and indirect damage to the cardiovascular system at varying levels [20]. In COVID-19 patients, HCQ, used as a possible therapeutic agent, can lead to QT interval prolongation and Torsades de Pointes (TdP). Erythromycin, azithromycin, clarithromycin, telithromycin, and roxithromycin are listed either as drugs that are definitely or possibly linked to TdP [21]. Possible therapeutic agents (HCQ, AZ, lopinavir/ritonavir, remdesivir, and others) for treatment of COVID-19 carry a risk of inducing ventricular arrhythmia. This side effect is uncommon, but co-prescription of other drugs like azithromycin could improve that risk [22]. Previous studies reported that treatment with chloroquine (HCQ) combined with AZ in COVID-19 patients had cardiovascular side effects of QT interval prolongation. This side effect could be a mechanism that predisposes to ventricular arrhythmias [23,24]. However, it is known that TdP will not develop in all patients with drug-induced QTc prolongation [22].

Yayla et al. reported that the increase in the distribution of ventricular repolarization was related to lethal arrhythmias [25]. Yontar et al. suggested that Tp-e interval, Tp-e/QT, and Tp-e/QTc rations were better ECG parameters to assess ventricular repolarization than QT parameters [26]. Alsancak et al. reported that patients with two or three-vessel coronary artery ectasia had a higher Tp-e and Tpe/QT ratio than those with one vessel coronary artery ectasia [27]. A new non-invasive marker, ICEB, projects the balance between cardiac depolarization and repolarization, similar to cardiac wavelength λ, which is related to arrhythmogenesis [16,17,28]. Our study is the first report evaluating iCEB, which was increased in COVID-19 patients treated with HCQ and AZ. We believe that increased iCEB values due to HCQ and AZ treatment in COVID-19 patients increases ventricular repolarization heterogeneity and ventricular arrhythmias. Lu et al. reported that iCEB projected the balance between the depolarization (changes QRS duration) and repolarization (changes QT interval) of the cardiac action potential. Also, they suggested that iCEB predicts potency of drug-related arrhythmia risk beyond long QT and TdP [29].

Robyns et al. reported that iCEB was more useful than the other ECG parameters in predicting ventricular arrhythmia

risk, particularly for its potency to differentiate between long-QT belong arrhythmias and TdP [18].

Limitations

This study had some limitations. First, we measured electrocardiographic repolarization parameters manually. The others are its single-center design and the limited number of patients. Additional long-term and large-scale studies are required to confirm and clarify our data.

Conclusion

Based on our results, the iCEB values increased after HCQ and AZ treatment in COVID-19 patients. Also, iCEBc values strongly correlated with Tp-e and Tp-e/QT. We think that iCEB is a simple, non-invasive method that can be a beneficial marker to evaluate ventricular repolarization in COVID-19 patients.

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Clinical outcomes in lower extremity deep vein thrombosis treated with a direct oral anticoagulant: A retrospective cohort study

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The ethical approval was obtained from the Ethics Committee of the Medical Faculty of the Erciyes University (number 2019/491).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Rivaroxaban and apixaban were shown to be non-inferior and somewhat superior to warfarin in preventing pulmonary embolization and venous complications. However, there is still a need for further evidence concerning the efficacy and safety of direct oral anticoagulants in the treatment of patients with deep vein thrombosis **(**DVT) and pulmonary embolism (PE). This study aimed to analyze patients with DVT and PE who received a direct oral anticoagulant (apixaban) during their hospitalization and thereafter.

Methods: Data of all consecutive subjects admitted for lower limb DVT who received apixaban for DVT treatment in our department between January 2015-April 2019 were analyzed. Apixaban was directly administered after the diagnosis of DVT in 68 subjects, following discontinuation of warfarin due to the lack of success in maintaining appropriate INR values in 56 subjects and following the discontinuation of the rivaroxaban due to gastrointestinal complications in 7 subjects.

Results: Apixaban was administered for a median duration of 12.0 (12.0-24.0) months. The most common predisposing factors for venous thromboembolism were thrombophilia and major surgery history. Among all, 62.59% of the DVT were at and proximal to the femoral vein. Concomitant PE was encountered in 16.03% of the study subjects. Those with distal DVT and those who received apixaban immediately after diagnosis of the DVT less frequently developed PE compared to those who received post-rivaroxaban or post-warfarin apixaban. Treatment with apixaban leads to a significant decline in D-dimer levels from the first month of the treatment ($P<0.001$). Recurrent DVT and PE occur in 10% and 16%, respectively, under apixaban treatment.

Conclusions: Among patients with proximal DVT, those receiving apixaban following a period of treatment with rivaroxaban or warfarin compared to direct administration constitute the majority of the PE cases. Apixaban seems like an effective treatment option in patients with DVT and PE.

Keywords: Deep vein thrombosis, Direct oral anticoagulant, Apixaban, Recurrence, Pulmonary embolism, Anticoagulation

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Introduction

Deep vein thrombosis (DVT) which commonly affects the lower limb has an incidence of 1.6 per 1000 of the general population [1, 2]. Distal lower limb veins are the most frequently affected sites with a rate of 40% [3]. Femoral, common femoral, and iliac veins are involved in about 55% of the cases. Surgery under general anesthesia, prolonged hospitalization, pregnancy, cesarean section, estrogen therapy, and leg injury are common transient predisposing factors for the development of lower limb DVT [4], while an active malignancy or inflammatory bowel disease and systemic lupus erythematosus are persistent risk factors [5].

Deep vein thrombosis was shown to lead to excessive morbidity due to post-thrombotic syndrome and venous ulceration, which are encountered in one-third of the subjects [6]. However, PE develops in 6-32% of the subjects with DVT and may be fatal in 5%-10% of cases [7, 8]. Anticoagulation with low-molecular-weight heparin (LMWH) and warfarin are traditionally used in the treatment of DVT to prevent clot extension and embolization. However, recent guidelines from NICE and ACCP recommend direct oral anticoagulants (DOACs) as a first-line treatment for DVT [9]. Rivaroxaban and apixaban, which do not require initial treatment with LMWH before the commencement of the DOAC, were shown to be non-inferior and somewhat superior to warfarin in the prevention of pulmonary embolization and venous complications [10, 11]. However, there is still a need for further evidence concerning the efficacy and safety of DOACs in the treatment of patients with DVT and PE.

This study aimed to analyze patients with DVT and PE who received apixaban during their hospitalization and thereafter.

Materials and methods

In this cohort study, data of all consecutive subjects admitted for lower limb DVT who received apixaban for the treatment of the DVT in Erciyes University Medical School, Department of Cardiovascular Surgery between January 2015 and April 2019 were analyzed.

Ethical approval was obtained from the Ethics Committee of the Medical Faculty of the Erciyes University (number 2019/491). Written informed consent was obtained from all subjects and the study was conducted following the Helsinki declaration.

The criteria for inclusion in the study were as follows: Being over 18 years of age, DVT confirmed by Doppler ultrasonography, post-warfarin, post-rivaroxaban, or direct apixaban treatment initiation. Those receiving warfarin, LMWH, and DOACs other than apixaban were not included in the final analysis. Exclusion criteria were as follows: Creatinine clearance <25 mL/min, presence of advanced liver failure, moderate to high-risk PE, and contraindications for anticoagulant treatment. Apixaban was directly administered after the diagnosis of the DVT in 68 subjects, following discontinuation of warfarin due to the lack of success in maintaining appropriate INR values in 56 subjects and following the discontinuation of the rivaroxaban due to gastrointestinal complications in 7 subjects. Apixaban was administered 10 mg twice daily for the first 7 days. After completion of the first week, the dose was adjusted to 5 mg twice daily.

The patients who used apixaban were followed up closely in our clinic with complete medical records. Thus, all patients who received apixaban were included in the study.

Demographic data including age, gender, and previous medical history, D-dimer results, and ultrasonography findings including the location of the DVT were retrieved from an institutional digital database. Factors associated with recurrent DVT, PE, and the locations of the DVT were analyzed.

Statistical analysis

Statistical analyses were conducted using SPSS for Windows, version 17 (SPSS, Chicago, IL, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were presented as mean (standard deviation) or median (1^{st} and 3^{rd} quartiles) according to data distribution and categorical variables as frequency (n) and percentage (%). Pairwise comparisons were performed using Student's t-test, Mann–Whitney U-test, $\chi 2$ -test, or Fisher's exact test, where appropriate. Friedman test was used for comparison of baseline, 1^{st} month, and 3^{rd}-month D-dimer measurements. A two-sided *P*-value of ≤ 0.05 was interpreted as statistically significant.

Results

Longitudinal data was available for 131 subjects (mean age: 56.73 (18.31) years, 48.86% males). The demographic characteristics of the study group are listed in Table 1. Apixaban was administered for a median duration of 12.0 (12.0-24.0) months. The most common predisposing factors for venous thromboembolism were thrombophilia and major surgery history with rates of 25.19%, and 16.79%, respectively. Among all, 62.59% of the DVTs were at or proximal to the femoral vein. Concomitant PE was encountered in 16.03% of the study subjects. D-dimer levels at first and sixth months of the treatment were lower than baseline values [1050.0 (550.0-1080.0) µg/L, 750.0 (550.0–1080.0) µg/L vs. 1200.0 (8900.0-2700.0) µg/L, $P<0.001$]. Baseline D-dimer levels of subjects with a sub-femoral DVT were lower than that of the subjects with a DVT located at the femoral vein or proximal to it [980.0(765.0 - 14600) µg/L vs. 1765.0(987.5 - 3815.0) µg/L, $P<0.001$].

Table 1: Demographic and clinical characteristic of the study patients

	n=131
Age, years	56.73 (18.31)
Gender	
Female, n	67 (51.40%)
Male, n	64(48.86%)
D-dimer baseline	1200.0(895.0-2600.0)
D-dimer 1st month	1050.0(750.0-2200.0)
D-dimer 6th month	750.0 (550.0-1080.0)
BMI, kg/m^2	27.6 (3.75)
Apixaban duration, months	12.0 (12.0-24.0)
Location of the DVT	
Sub-femoral, n	49 (37.40%)
Femoral and above, n	82 (62.59%)
Coronary artery disease, n	17 (12.97%)
Atrial fibrillation, n	25 (19.08%)
Hypertension, n	39 (29.77%)
Previous malignancy, n	18 (13.74%)
Recurrent DVT, n	13 (9.92%)
Predisposing factors	
Major Surgery History, n	22 (16.79%)
Thrombophilia, n	33 (25.19%)
Immobilization, n	11 (8.39%)
Active cancer, n	11 (8.39%)
Concomitant Pulmonary Embolism, n	21 (16.03%)

Recurrent DVT occurred in 13 (10%) patients, the data of which are presented in Table 2. Thrombophilia was more frequent among subjects with recurrent DVTs compared to those without (61.54% vs. 21.19%, $P<0.001$). There were 21 (16%) patients with concomitant PE (Table 3). The DVTs of 95.24% of the subjects with PE were at the femoral vein or proximal to it. Thrombophilia (47.62% vs. 20.91%, $P=0.010$), history of major surgery (42.86% vs. 11.82%, $P<0.001$) and malignancy (38.1% vs. 9.09%, $P<0.001$) were more frequent in subjects with PE compared to those without. Those who received apixaban immediately after diagnosis of the DVT less frequently developed PE compared to those who received post-rivaroxaban or post-warfarin apixaban ($P<0.001$).

Table 2: Comparison of the demographic and clinical features of the subjects with and without recurrent deep vein thrombosis

	Recurrent DVT		*P*-value
	Yes (*n*=13)	No (*n*=118)	
Age, years	50.23 (14.99)	57.44 (18.55)	0.179
Male gender, n	6(46.15%)	58(49.15%)	1.000
BMI, kg/m2	27.69 (2.75)	27.54 (3.86)	0.892
Atrial fibrillation, n	0(0.0%)	25(21.2%)	0.065
Coronary artery disease, n	2(15.38%)	15(12.7%)	0.785
Hypertension, n	2(15.38%)	37(31.36%)	0.232
Previous malignancy, n	0(0.0%)	18(15.25%)	0.129
Major surgery, n	3(23.08%)	19(16.1%)	0.523
Thrombophilia, n	25(61.54%)	8(21.19%)	<0.001
Immobilization, n	0(0.0%)	11(9.32%)	0.250
Active cancer, n	0(0.0%)	11(9.32%)	0.250

Table 3: Comparison of the demographic and clinical features of the subjects with and without pulmonary embolism

	Pulmonary Embolism		*P*-value
	Yes (n=21)	No (n=110)	
DVT location			
Subfemoral, n	1(4.76%)	48(43.64%)	<0.001
Femoral and above, n	20(95.24%)	62(56.36%)	
Major surgery, n	9(42.86%)	13(11.82%)	<0.001
Thrombophilia, n	10(47.62%)	23(20.91%)	0.010
Immobilization, n	3(14.29%)	8(7.27%)	0.288
Hypertension, n	6(28.57%)	33(30.0%)	0.896
Female gender, n	15(71.43%)	52(47.27%)	0.042
Coronary artery disease, n	2(9.52%)	15(13.64%)	0.607
Atrial fibrillation, n	0(0.0%)	25(22.73%)	0.015
Previous malignancy, n	8(38.1%)	10(9.09%)	<0.001
Apixaban administration			
Direct Apixaban, n	3(14.29%)	65(59.09%)	<0.001
Post-Rivaroxaban, n	2(19.52%)	5(4.54%)	
Post-Warfarin, n	16(76.19%)	40(36.36%)	
Recurrent DVT, n	4(19.05%)	9(8.18%)	0.127
Active cancer, n	3(14.29%)	8(7.27%)	0.288

Discussion

Venous thromboembolism, which includes DVT and PE, is a significant source of morbidity and mortality. Recurrent DVT, *post-pulmonary embolism syndrome*, chronic thromboembolic pulmonary hypertension, and post-thrombotic syndrome are long-term complications of venous thromboembolism [12]. Proximal DVT of the lower extremities, symptomatic calf vein (distal) DVT, and PE require immediate treatment with anticoagulant agents unless anticoagulation is contraindicated because of high bleeding risk [13]. More aggressive therapies, such as systemic thrombolysis, catheter-directed thrombolysis, pharmaco-mechanical therapies, or surgical intervention are reserved for patients with PE and complicated proximal DVT [14].

Anticoagulants are the first-line agents in the treatment of DVT both in the acute and extended treatment phases. Unfractionated heparin, LMWH, warfarin, fondaparinux, and DOACs are used for this purpose. LMWHs are used in the first week of DVT for transitioning to warfarin, dabigatran, or edoxaban for long-term anticoagulation and the agents of choice in pregnant women and those with malignancies [15, 16]. Apixaban and rivaroxaban do not need a pretreatment period with LMWH before administration and can be used as monotherapy for the initial treatment of DVT [17]. Lack of the need for INR monitoring in long-term treatment, rapid onset of action, and shorter half-life make DOACs the most popular treatment option due to more predictable anticoagulant effects. The earlier EINSTEIN-DVT study has shown that rivaroxaban was non-inferior to warfarin in terms of safety and efficacy in the acute treatment of DVT [10]. Further research including patients with PE has demonstrated that rivaroxaban was also non-inferior to warfarin in this patient population [18]. Moreover, major bleeding events were less frequent in patients receiving rivaroxaban compared to those receiving warfarin in the EINSTEIN-PE study. Apixaban, another oral factor Xa inhibitor, was non-inferior to conventional warfarin therapy for the treatment of acute venous thromboembolism with less bleeding risk in the AMPLIFY trial [11]. Nevertheless, there is currently no head-to-head comparison of DOACs in the treatment of patients with DVT. Real-life data concerning the use of apixaban and clinical and demographical features of the subjects who received apixaban for DVT are also limited.

Findings of the present study indicate that thrombophilia and history of a major surgery were the most common underlying causes for the development of DVT. Previous data indicate that inherited deficiency of protein C, protein S, and antithrombin, and mutations in factor V and prothrombin genes account for up to one-third of the cases with venous thromboembolism [5, 8, 19]. Prolonged immobilization after a major surgical procedure has also been reported as an important risk factor for the development of DVT [20]. We found that one-half of the DVTs were at or proximal to the femoral vein. Recurrent DVT occurred in 10 % and PE occurred in 16% of the study population. Thrombophilia and history of a recent major surgery were more common in those who developed PE compared to those who did not. Those directly receiving apixaban compared to the subjects receiving apixaban after warfarin or rivaroxaban tend to have less PE. Majority of the subjects who developed PE while receiving treatment for DVT were prescribed apixaban following discontinuation of warfarin due to inappropriate INR during follow-up. We speculate that subjects directly receiving apixaban compared to those receiving apixaban following a period of treatment with rivaroxaban or warfarin may have a lower risk for the development of PE. However, further research is required to address whether apixaban is superior to warfarin in the prevention of PE in DVT.

Subjects with femoral or supra-femoral DVTs constituted 95% of the PE cases whereas only 5% of the patients with PE had distal DVT. Previous evidence indicates a higher risk of PE in proximal lower extremity DVT compared to distal DVT.

Limitations

The current study has some limitations. First, the study was conducted retrospectively and in a single center, both of which limit the generalizability. Second, the study did not contain a control group. Lastly, the follow-up of patients was not long.

Conclusion

The majority of the DVT occurs in proximal veins of the lower extremity and thrombophilia and history of major surgery are the most common predisposing factors. Treatment with apixaban leads to a significant decline in D-dimer levels from the first month of the treatment. Recurrent DVT and PE occur in 10%

and 16%, respectively, under apixaban treatment. Those with proximal DVTs and receiving apixaban following a period of treatment with rivaroxaban or warfarin compared to direct administration constitute the majority of the PE cases.

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An effective method to reduce the risk of endophthalmitis after intravitreal injection (IVI): Application of 0.25% povidone-iodine

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Ethics Committee Approval
The study was approved by Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (No: 2020/134).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The most important complication after intravitreal injection (IVI) is endophthalmitis, which can result in severe vision loss. This study aims to investigate the effect of 0.25% povidone-iodine (PI) application before IVI on the incidence of endophthalmitis in patients who received intravitreal anti-vascular endothelial growth factor (anti-VEGF) injection.

Methods: A total of 15345 intravitreal anti-VEGF injections and nine endophthalmitis cases after IVI performed at the outpatient injection room of a single university hospital between January 2017 and January 2020 were included in this retrospective cohort study. Before July 2018, after applying 10% PI around the eyes and 5% PI on the eyes, an eyelid speculum was inserted, and the injection was performed. After this date, in addition to these steps, after placing a speculum and determining the injection site with a caliper, 3-4 drops of 0.25% PI were applied just before injection. Topical antibiotics were not used before or after the injection.

Results: Nine cases of endophthalmitis were detected in 3 years. The most common symptoms were vision loss (9/9) and pain in the eye (7/9). All cases had conjunctival hyperemia, cells-hypopyon in the anterior chamber, and cells in the vitreous. The time between injection and re-visiting the clinic due to endophthalmitis symptoms ranged between 2-6 days, and visual acuity varied between hand motion and 0.2. While the number of endophthalmitis cases before July 2018 was 8 (8/8330) in 1.5 years, after the addition of 0.25% PI application to the protocol, only 1 case of endophthalmitis (1/7015) was seen in the last 1.5 years. The rate of endophthalmitis had decreased significantly (P=0.037).

Conclusion: Since July 2018, the addition of 0.25% PI to the standard IVI protocol just before injection has significantly reduced endophthalmitis rates. With this method, endophthalmitis rates may be decreased despite the increasing number of IVIs.

Keywords: Anti-vascular endothelial growth factor, Endophthalmitis, Hypopion, Intravitreal injection, Povidone-iodine

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Introduction

The first known intravitreal injection (IVI) was performed in 1911 with the introduction of air into the eye for retinal detachment [1]. Since then, IVI has become a common treatment method after proven medical benefits of intravitreal administration of anti-VEGF agents in the treatment of diabetic retinopathy (DRP), age-related macular degeneration (AMD), retinal vein occlusion (RVO), and retinopathy of prematurity (ROP) [2]. During this procedure, patients usually undergo an intensive follow-up and injection regimen at four- or six-week intervals per the available therapeutic methods [3].

Literature indicates that the most serious complication of the IVI is endophthalmitis [4]. It usually results in poor visual prognosis despite rapid diagnosis and treatment with intravitreal antibiotics or vitrectomy. The incidence of endophthalmitis after IVI ranges between 0.02% and 0.26% [5, 6].

PI, which has antimicrobial activity against bacteria, yeasts, other fungi, and particular viruses, possesses low toxicity for human tissues and cells. Use of the 5% PI solution as antisepsis on the ocular surface is strongly suggested before intraocular surgery [7]. To prevent any possible contamination through the displacement of pathogens on the eyelids and conjunctiva or the treating ophthalmologist's mucosa while speaking to the patient during the application [8, 9], a short process of topical antibiotic is generally used routinely. However, recent studies report that repeated post-injection topical antibiotics do not only reduce the risk of endophthalmitis but may also increase the antibiotic resistance of the ocular flora [10, 11]. Therefore, PI seems to be a more potent agent than antibiotics for infection prophylaxis in IVIs [12].

Due to its potential toxic effect on cells, it is vital to determine the ideal effective concentration and exposure time of the PI. There is a widespread misconception that higher concentrations of PI, such as 10% and 5%, have higher bactericidal activity, and entail a noticeably short contact time. Indeed, a study has revealed that the release of free iodine becomes more difficult as povidone-iodine concentration increases, and diluting the solution facilitates iodine release [13]. The concentration of free iodine has been reported in this literature as 13 ppm in a 0.01% PI solution, 24 ppm in a 0.1% solution,13 ppm in a 1% solution, and 5 ppm in a 10% solution. The time needed for bactericidal effect is shorter for 0.1 to 1.0% PI (20-30 sec.) compared to 2.5 to 10% PI (30 to 120 sec.). The 0.25% PI, when applied to the ocular surface, is diluted with tears, and yields 0.1% concentration, which has the highest and fastest bactericidal effect [14, 15]. This retrospective study focused on investigating the effect of an ophthalmic solution containing 0.25% PI in preventing endophthalmitis.

Materials and methods

This study was performed in adherence to the tenets of the Declaration of Helsinki and approved by Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (No: 2020/134). The files of 15345 IVI patients who received anti-VEGF between January 2017 and January 2020 were reviewed. The files of 9 patients who developed endophthalmitis after the injection were analyzed in detail. Endophthalmitis was diagnosed clinically, and vitreous samples were sent for microbial cultures.

All IVIs were performed by an ophthalmologist at Abant Izzet Baysal University Hospital in an injection room, which is separated from the outpatient clinic and equipped with a bed and a microscope. Since IVI drugs are not provided by the hospital in our country, the drugs are prescribed to the patients, who obtain them from the pharmacy. It was questioned whether the necessary conditions were met during the transport of the drug, the drug was not administered in suspicious cases which did not meet the cold chain conditions and prescribed again. All IVIs in our clinic are performed per the standards specified in the Euretina guideline. Doctors and nurses working in the injection room wear disposable bonnets, surgical masks, and overshoes, and change them twice a day (morning and afternoon). The patient, wearing his/her clothes wears a bonnet, a mask, and overshoe before entering the injection room, is instructed to lie on the bed. While performing the injection, the doctor and the nurse refrain from talking, sneezing, and coughing.

Until July 2018, standard IVI application was performed by applying 10% PI around the periocular area and the ocular surface was irrigated with 5% PI. After this date, in addition to these steps, 3-4 drops of 0.25% PI diluted in physiological saline were applied immediately after the determination of the injection site with a caliper on the globe.

In our clinic, the new method of IVI application is as follows:

- After topical anesthesia application (0.5% proparacaine hydrochloride), ocular surface, lid margins, and fornix are irrigated with 5% PI, and periocular skin is cleaned with 10% PI.
- The eye is covered with a sterile eye drape and an eye speculum is inserted.
- According to the lens condition of the patient, the area 3.5 or 4 mm from the limbus is visualized in the superotemporal quadrant.
- Since 0.25% PI is effective for approximately 20-30 seconds [15], immediately after placing the valve speculum and marking the injection site, 3-4 drops of 0.25% PI are applied to the marked conjunctival area once (This is the added step to our standard IVI application protocol after June 2018). If the time between the marking of the injection site and performing the injection is more than 20 seconds, the injection site is re-irrigated with 0.25% PI just before IVI.
- Then, to prevent the vitreous and the injected drug from spilling out, the conjunctiva is slid with a sterile cotton swab and a total of 0.05 mL of anti-VEGF is slowly injected into the vitreous with a 30-gauge needle tip (at a 90° angle to the sclera, targeting the center of the globe).
- When the medicine in the syringe is finished, the needle tip is withdrawn at the same angle without applying any tampon to the conjunctiva. After injection, no eye patch is worn.
- At the end of the procedure, the patient is taken to the resting room without applying other topical antibiotics or PI. Patients are informed about the symptoms of endophthalmitis, and follow-up appointments are made.

Table 1: Characteristics of endophthalmitis cases

	Case1	Case2	Case 3	Case4	Case 5	Case 6	Case 7	Case 8	Case 9
Gender	F	F	M	M	F	F	M	M	M
Age	64	76	87	67	68	75	70	74	76
Diagnosis	DRP	DRP	AMD	DRP	AMD	AMD	DRP	AMD	DRP
Applied agent	IVR	IVA	IVA	IVR	IVA	IVA	IVA	IVA	IVA
Number of injections administered	14	3	2	2	12	9	3	4	4
VA before endophthalmitis	0.8	0.3	CF 5m	0.7	0.4	0.2	0.5	0.6	0.4
VA at endophthalmitis presentation	0.1	CF 3m	HM	0.2	CF 1m	CF 5m	0.1	0.1	HM
Final VA (Sixth month)	0.5	0.1	1 mps	0.7	0.2	0.1	0.2	0.4	CF 5m
Treatment	IVAb	IVAb	IVAb+VRS	IVAb	IVAb+VRS	IVAb	IVAb+VRS	IVAb	IVAb+VRS
Application time to the clinic-day(s) (after IVI).	3	3	6	2	4	3	4	2	5
Application reasons	vision loss	vision loss	vision loss	vision loss	vision loss	vision loss	vision loss	vision loss	vision loss
Vitreal tap	+	+	+	-	+	+	-	+	+
Culture	CoNS	CoNS	S. epidermidis	No growth	S. epidermidis	CoNS	No growth	No growth	CoNS
Where come from	City center	district	district	district	district	City center	center	out of province	district
Phakic status	Psph	Ph	Psph	Ph	Ph	Psph	Psph	Ph	Ph

AMD: Age-related macular degeneration, CF: Count fingers, CoNS: Coagulase-negative Staphylococcus, DRP: Diabetic retinopathy, HM: Hand motion, IVA: Intravitreal Aflibercept, IVAb: Intravitreal antibiotics, IVI: Intravitreal injection, IVR: Intravitreal Ranibizumab, Ph: Phakic, Psph: Pseudophakic, VA: Visual Acuity, VRS: Vitreoretinal surgery

Statistical analysis

In this study, the data were analyzed using SPSS statistical software package, version 25.0 (SPSS Inc., Chicago, IL, USA). The data were reported as mean (standard deviation (SD)) for each data set. $P<0.05$ indicated statistical significance. The statistical analyses of the data were performed with the Chi-square test.

Results

Nine endophthalmitis cases were seen after 15345 IVI applications (Table 1), five of which were males. These patients' ages ranged between 64-87 years. Aflibercept and ranibizumab were administered to 7 and 2 of 9 endophthalmitis patients, respectively. Three patients, two of which received ranibizumab and one of which received aflibercept, resided in the city center while 5 patients receiving aflibercept resided in other districts in our city. One patient receiving aflibercept resided outside the province. Six patients bought their medicine from the pharmacy on the day of injection and three had bought it one day before. All drugs were delivered to us with an ice pack.

Vision loss (9/9) and eye pain (7/9) were the most common reasons for admission to the hospital. Conjunctival hyperemia, cells-hypopyon in the anterior chamber, and cells in the vitreous were present in all patients. The admission time to the clinic was 2-6 days after IVI, and visual acuity varied between hand motion and 0.2. Vitreous sample cultures had positive results in 5/9 of the post-injection cases and coagulase-negative Staphylococcus reproduced in most. While vitreous tap was insufficient in 2 patients, culture was negative in 2 patients with signs of endophthalmitis, and these patients benefited from intravitreal antibiotic treatment. Vitrectomy was required in four patients. Five and four patients were followed up with diagnoses of DRP and AMD, respectively. The number of IVIs varied between 2-14 in cases with endophthalmitis.

While the number of endophthalmitis cases admitted to our clinic before July 2018 was 8 (8/8330) in 18 months, only 1 endophthalmitis case (1/7015) was observed in the 18 months after 0.25% PI application was added to the protocol. Adding 0.25% PI to the IVI protocol significantly decreased our endophthalmitis rate ($P=0.037$).

Discussion

The results of our 3-year study revealed a significant beneficial effect of 0.25% PI irrigation just before IVI in preventing endophthalmitis. This is evident from the fact that there was only one case of endophthalmitis (0.014 %) within the last 18 months.

Endophthalmitis can often be caused by conjunctiva or eyelid pathogens, as well as from the oral flora of the patient in the injection room and the healthcare professionals who perform the procedure [8, 9]. Chronic diseases including diabetes mellitus, hypertension, immunodeficiency, and glaucoma can also predispose to endophthalmitis [16, 17]. In our study, of 9 patients who developed endophthalmitis, 5 had DM and 3 had HT, while none had immunodeficiency. Spoilage of the used drug due to partial long-distance transport during which cold chain might be broken may be another possible cause of endophthalmitis. Indeed, 3 of the patients involved in the study resided in the city center while 6 had to travel a long distance. However, adding 0.25% PI to the protocol significantly decreased the endophthalmitis rate, which might indicate that probable spoilage of the drug has a limited effect on the endophthalmitis rate.

In the Euretina 2018 Update regarding IVI application and the reduction of endophthalmitis rates, it is emphasized that the ocular surface and its surroundings should be disinfected, sterile gloves and masks should be used, a 5% PI should be contacted with the conjunctiva for at least 30 seconds, and a sterile eyelid speculum should be worn. Drape use may not be necessary, and antibiotics before IVI are not required [18]. The emphasis on PI use and the unnecessary administration of antibiotics is remarkable. On the other hand, antibiotic use before and/or after IVI is still practiced widely even though it has been observed that the use of antibiotics in IVI causes antibiotic resistance in bacteria [10, 11]. In our clinic, antibiotics have not been used before and/or after IVI application. The PI application was updated as recommended in the Euretina 2018 update. In addition, a low PI concentration of 0.25% has also been added to the injection protocol just before the IVI application after marking the IVI site. Our results indicate the significant effect of this application.

Ophthalmologists have used different concentrations of PI to decrease endophthalmitis rates in several studies [19-21]. Hosseini et al. [19] have reported that using 5% PI for 15 minutes or 10% PI for 5 minutes can prevent the growth of most endophthalmitis bacterial isolates after cataract surgery. Pinna et

al. [20] have also found that 0.6% PI ophthalmic solution shows in vitro antimicrobial activity against S. epidermidis, S. aureus, P. aeruginosa, and Candida species. Likewise, another retrospective study has found a very low rate of endophthalmitis achieved by the protocol that includes irrigating the conjunctiva with 0.25% PI and waiting for at least 30 seconds before performing IVI [21]. In that report where 15144 cases were evaluated, none of the patients had suspected or proven endophthalmitis cases. Similarly, 0.25% PI was used also in our study, but we additionally irrigated the ocular surface with 3-4 drops of 0.25% PI only after the injection site was marked, rather than continuous irrigation. We did not wait for 30 seconds or use PI after the injection. No antibiotics were administered before or after IVI. After the change in protocol, the rates of endophthalmitis significantly decreased from 0.096% to 0.014%. This rate is lower than the data previously reported in the literature [6, 7, 22, 23].

Literature indicates that the fastest and most effective bactericidal effect of 0.25% PI drop onto the ocular surface can be achieved through the dilution with tear to 0.1% PI [14, 15]. Similarly, we have used 0.25% PI to obtain 0.1% PI concentration on the ocular surface. After marking the injection site with a caliper, this area was irrigated with 3-4 drops of 0.25% PI. It is essential to mention that the time between marking the intervention site and the injection should not exceed 20-30 seconds, as reported in the literature [15]. If that time is prolonged, the effect of 0.25% PI will decrease due to quick loss of free iodine concentration [15]. Since it is well known from the previous studies [24-27] that this PI form is not toxic to the epithelium, re-irrigation can be applied easily, as is the case in our study.

Studies have shown no toxic effects of PI when injected into the anterior chamber at low concentrations such as 0.5-1%, or the corneal epithelium at a concentration of 1%. However, it is toxic to the corneal epithelium at concentrations of 5% and above [24, 26]. During cataract surgeries, 0.25% PI did not have a toxic effect on the corneal endothelium with repeated irrigations [25]. None of our patients in this study had clinically significant toxic effects with 0.25% PI. Mild conjunctival hyperemia occurred in only a few patients, which was supposedly due to 5% PI and regressed spontaneously without treatment. No additional pathology/toxicity was seen during the whole procedure of this study.

Studies have shown that 5% PI used in eye surgeries and IVI applications temporarily eliminates conjunctival flora, bacteria reappear on the ocular surface after drape cover and speculum insertion and can pass into the eye with surgical instruments [4, 15]. With this problem in mind, a new method that can reduce endophthalmitis rates has been suggested in this study. We have reasons to believe that the key point of the endophthalmitis problem can be solved especially at this stage. We think that the bacteria that reappear on the ocular surface after covering the drape and placing the speculum can be eliminated with 0.25% PI drops, resulting in a significant decrease in endophthalmitis rates.

Limitations

There were certain limitations in the study. As this study was retrospective, the patients' comorbid diseases, continuously used drugs, regular follow-up, and treatment protocols, and long-term vision loss could not be questioned adequately. Since vitrectomy operations were not performed in our clinic, patients who developed endophthalmitis and needed vitrectomy were referred to external centers, and difficulties were experienced in their long-term follow-up. The study period and the number of cases may have been limited to show that our endophthalmitis rates have decreased significantly. However, we think that despite all these limitations, the positive results obtained from a total of 15345 IVIs applied to the eye in 3 years are significant.

Conclusion

Upon the preliminary results of this study, we believe that our study can lead to reduced post-injection endophthalmitis rates. Since antisepsis with 0.25% PI is simple, safe for ocular tissues, effective, and cheap, it can also be used in all kinds of IVIs. Further studies on large series are needed to confirm the usefulness of PI and other measures in post-injection endophthalmitis.

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A randomized controlled trial of closure or non-closure of subcutaneous fatty tissue after midline vertical incision

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Ethics Committee Approval
Bursa Uludag University Faculty of Medicine Clinical Research Ethics Board, Date: 12.02.2019, Number: 2019-3/19
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: There are limited studies that evaluate the closure of subcutaneous tissue, particularly among gynecologic oncology patients, a group with a high rate of obesity and more co-morbidities. This prospective randomized controlled study aimed to assess the effects of subcutaneous closure versus non-closure on wound complication rate in patients with subcutaneous tissue thicknesses of more than >4 cm.
Methods: All patients with a subcutaneous tissue depth≥4 cm measured with ultrasonography and undergoing gynecologic surgery via a midline vertical incision from February 2019 to March 2020 in the gynecologic oncology department at a teaching hospital were considered for inclusion. Patients were intraoperatively and sequentially randomized as 1:1 only when the measurement of subcutaneous tissue depth was verified to be 4 cm or more.
Results: A total of 82 patients who underwent randomization were assigned to undergo or not undergo subcutaneous closure with sutures (41 patients each). Subcutaneous wound depth (mean: 6.36 cm, range: 4-11 cm), vertical incision length (mean: 24.32 cm, 12-36 cm), body mass index (33.82 kg/m^2, 19.6-52 kg/m^2) were similarly distributed between the groups (P>0.05 for all). Wound complications were observed in 17 (20.7%) patients. Wound infection occurred in two patients in the closure group as compared to three patients in the control group (P=0.644). Seroma and wound dehiscence were seen more often in the control group, but neither of these findings reached statistical significance (P=0.077, P=0.284).
Conclusion: We found no significant differences in the rate of surgical wound complications with suture approximation of the subcutaneous tissue in patients with 4 cm or more subcutaneous thickness undergoing gynecologic surgery via a vertical midline incision.

Keywords: Subcutaneous closure, Obesity, Wound complication, Midline vertical incision

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Introduction

Obese patients have a high rate of surgical incision complications including wound dehiscence, infection, and subcutaneous seroma or hematoma after gynecologic surgery. In patients with BMI ≥30 kg/m^2 who underwent surgery through a midline vertical incision, wound complication rates as high as 46% have been reported [1, 2]. The increase in wound complications was attributed more specifically to the thickness of the subcutaneous tissue [3, 4].

A prospective study on 150 patients undergoing hysterectomy reported that the wound infection rate was proportional to the thickness of subcutaneous tissue. Wound infection rates in patients with a subcutaneous fat thickness of 3, 4, 5, ≥6cm were 15%, 17%, 21%, and 40% respectively [3].

Wound complications in obese patients are possibly associated with insufficient vascular supply of the subcutaneous tissue, hematoma formation, and serous fluid collection [5].

There have been multiple studies to determine the most appropriate technique for surgical abdominal wall incision closure, yet there is still a debate about this. Many of these studies are retrospective and limited by their lack of standardization of surgical methods, patient selection criteria, and definitions of wound complications [6, 7].

There are limited studies evaluating the closure of subcutaneous tissue, particularly in gynecologic oncology patients, a group with a high rate of obesity and other co-morbidities. Although the closure of subcutaneous tissue may prevent dead space, hence decrease serous fluid collection, additional suture materials have the potential of increasing the risk of wound infection.

This prospective randomized controlled study aimed to assess the effect of subcutaneous closure versus non-closure on wound complication rate in women with subcutaneous tissue depths of ≥4 cm.

Materials and methods

All women with subcutaneous tissue depths≥4 cm measured with ultrasonography and undergoing elective gynecologic surgery via a midline vertical incision from February 2019 to March 2020 in the gynecologic oncology department at a teaching hospital were considered for inclusion. The study protocol was approved by Bursa Uludag University Faculty of Medicine Clinical Research Ethics Board on 12.02.2019 with the decision number 2019-3/19.

We intraoperatively and sequentially randomized patients as 1:1 when the measurement of subcutaneous fat thickness was verified as 4 cm or more. Exclusion criteria were a history of abdominal midline incision, a preexisting or repaired umbilical hernia, planned intestinal surgery or enterotomy, or not consenting to participate in the study. Traditionally, in surgical practice, there is a tendency for subcutaneous suturing in patients with thick subcutaneous adipose tissue. Because this is a non-blind randomized trial, 1:1 sequential randomization was strictly followed to avoid selection bias.

The surgical procedure for incision and closure of the wound was standardized. No subcutaneous drains were placed. All patients received antibiotic prophylaxis with cefazolin (if allergic, clindamycin) before the operation. An additional dose was administered if the operation lasted longer than three hours or the patient lost more than 1500 ml of blood.

The skin was incised using a scalpel, and subcutaneous tissue was incised using cutting electrocautery. At the end of the surgery, two looped polydioxanone sutures (PDS) were used to close the fascia, starting at the proximal and distal ends of the incision, and being knotted in the middle. Following fascia closure, the length of the incision and subcutaneous tissue thickness were measured via a sterile metallic ruler from the deepest part of the incision, from the fascia to the skin surface, to determine patient eligibility. The incision was irrigated with warm saline solution. In the subcutaneous closure group, subcutaneous tissue was closed with continuous running sutures using absorbable vicryl 2/0. Vicryl® is a synthetic suture absorbed in up to 70 days [8]. Closed suction drains were not used. The skin was closed with staples, which were removed in the second week.

All patients were seen in the second, fourth, and eighth weeks postoperatively in the outpatient clinic to assess the state of the surgical wound. They were examined to find out whether they have the following wound complications:

-Seroma or hematoma: Serous fluid accumulation or presence of blood in the subcutaneous space without signs of infection.

-Wound disruption: Spontaneous or iatrogenic dehiscence of the wound edges by more than 1 cm.

-Wound infection: Wound erythema and swelling requiring additional antibiotics or surgical management.

Additional demographic characteristics and perioperative data associated with wound complications were also noted.

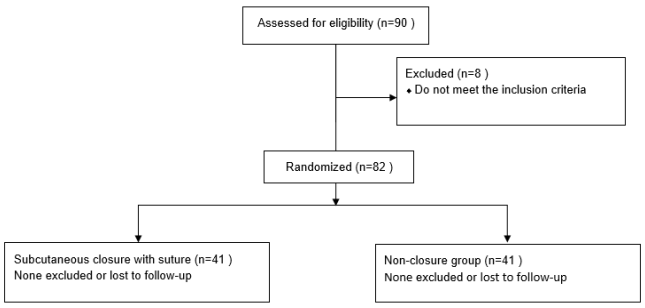
Statistical analysis

Descriptive statistics were analyzed. Fisher's exact test and Mann-Whitney's test were used to compare the percentages between groups. SPSS version 23.0 for Windows was used for statistical analysis. A *P*-value <0.05 was considered statistically significant.

Results

A total of 82 patients who underwent randomization to undergo subcutaneous closure with sutures or non-closure (n=41 in each group) were included in the analysis. No cases were lost during the 8-week follow-up after surgery (Figure 1).

Figure 1: Flow diagram of the study



The demographic and clinical characteristics of the closure and non-closure groups were similar (*P*>0.05 for all) (Table 1). The mean age of the patients at operation was 59.1 years (range: 37–80 years). Among all, 73.1% were operated on

with the diagnosis of malignancy. The most common surgical procedure in the cohort was hysterectomy with bilateral salpingo-oophorectomy and pelvic and/or paraaortic lymphadenectomy.

Subcutaneous wound depth (mean: 6.36 cm, range: 4-11 cm), vertical incision length (24.32 cm, range: 12-36 cm), body mass index (BMI) (33.82 kg/m^2, 19.6-52 kg/m^2) and other variables were similarly distributed between groups. Wound complications were observed in 17 (20.7%) patients (Table 2).

Table 1: Patients' characteristics

Parameters	Closure group (n=41) Mean (SD)	Non-closure group (n=41) Mean (SD)	*P*-value
Age (years)	60.3 (11.3)	57.9 (10.3)	0.316
Weight (kilogram)	85.5 (18.6)	81.4 (18.4)	0.267
Body mass index	34.7 (7.3)	32.9 (7.1)	0.235
Subcutaneous depth (cm)	6.5 (2.1)	6.2 (1.8)	0.480
Incision length (cm)	23.8 (5.9)	24.8 (4.8)	0.402
Duration of surgery (mins)	122 (46.6)	138 (56.7)	0.243

Table 2: Wound complications

	Closure group (n=41)	Non-closure group (n=41)	*P*-value
Cellulitis or infection	2	3	0.644
Wound dehiscence	3	4	0.692
Seroma or hematoma	2	7	0.077
Any complication	6	11	0.284

Wound infection occurred in two patients in the subcutaneous suture group as compared to three patients in the control group. One patient in each group was hospitalized and treated with vacuum-assisted closure (VAC). The other patients were treated only with antibiotics. Seroma and wound dehiscence were more frequent in the non-closure group, but neither of these findings reached statistical significance.

Discussion

The technique used for closing a vertical incision is crucial for wound complications. Suturing of the subcutaneous fatty tissue is recommended by several studies to close the dead space [9]. On the other hand, there is a possibility that the suture itself may act as foreign material and cause more wound infections than it prevents. Currently, there is no consensus on the method of subcutaneous closure. Therefore, our randomized study aimed to determine the role of subcutaneous closure in vertical midline incisions performed in patients with ≥4 cm subcutaneous thicknesses.

After a vertical midline incision, surgical site infection is reported in up to approximately 15% of patients [10]. This rate highly varies between different reports, which is probably very much related to different surgical procedures, cohorts, and definitions of infection. In the present trial, the surgical site infection rate was 6.1% in the whole study group. We observed no significant differences in the rate of surgical site infections between the closure and non-closure groups. In a Cochrane database, analyses evaluating subcutaneous tissue closure versus non-closure after abdominal surgical operations reported no significant differences in terms of surgical site infections between the two groups (RR 0.84; 95% CI 0.53 to 1.33; I2 = 0%) [7].

In our trial, we observed no significant differences in wound dehiscence rates between the subcutaneous closure and non-closure groups. A meta-analysis reviewed six trials on suture approximation after cesarean delivery and reported that subcutaneous closure in patients with more than 2 cm of subcutaneous thickness resulted in a 34% decrease in wound dehiscence [11]. On the other hand, Cardosi et al. [6] evaluated the subcutaneous tissue of vertical midline incisions with 3 cm or more of subcutaneous tissue and similar to our results, found that wound dehiscence rates did not significantly differ between the closure and non-closure groups (7.7% vs 11.7%, *P*=0.6). Lack of a standard definition for surgical wound dehiscence can make it difficult to compare results. Exposure to different physical tensile forces in transverse and vertical incisions may result in different results.

A prospective study of 60 patients with 2.5 cm or more subcutaneous tissue thickness evaluating the closure or non-closure of the subcutaneous space after gynecological surgery found no significant differences between the closed and unclosed groups. [12]. We found insignificantly fewer seromas in the closure group. The relatively small number of participants in the trial may explain this result.

Limitations

The major strength of our study is its prospective randomized controlled nature and evaluation of women with ≥4 cm subcutaneous fat thickness only. On the other hand, this study remains underpowered in terms of primary outcome due to the relatively small number of participants and a lower than anticipated rate of wound complications. However, determining the optimal means of reducing wound complications requires a multicenter randomized trial with much larger sample sizes.

Conclusion

We found no significant differences in the rate of surgical wound complications with suture approximation of the subcutaneous tissue in patients with 4 cm or more subcutaneous thickness undergoing gynecologic surgery via a vertical midline incision.

Subcutaneous closure has the potential to increase cost due to prolonged operation time and additional suture material. If subcutaneous closure has no remarkable benefit and costs more, it may not be routinely applied.

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Nutritional status and anxiety-depression relationship in hemodialysis patients

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Ethics Committee Approval
The ethics committee approval was obtained for the study from Harran University Medical School (74059997-050.04.04/ HRU/19.01.20)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Malnutrition is one of the determinants of most morbidity and mortality in end-stage renal failure (ESRD) patients receiving hemodialysis (HD). Depression is the most common psychological complication among these patients. This study aimed to determine the nutritional status and anxiety-depression level in hemodialysis patients and evaluate the relationship between the two.
Methods: This cross-sectional study included 55 routine hemodialysis patients over 18 years of age who were treated in the Department of Internal Diseases of a university hospital between November 2019 and January 2020. Two patients were excluded from the study due to renal transplantation. All patients filled out a two-part Hospital-Anxiety Depression Scale (HAD) and a two-part Mini Nutritional Assessment (MNA) questionnaire. The MNA-short form (MNA-SF) was first used to evaluate the malnutrition status of patients. Those who were identified as at-risk or malnourished with the MNA-SF were also asked to complete the long form. The HAD scale was used to evaluate the levels of depression and anxiety. SPSS 20 statistical package program for statistical analysis. $P<0.05$ was considered statistically significant.
Results: The mean age of the patients was 56.2 (15.9) years; 36 (66%) were female and 18 (34%) were male. Among all, 55.8% and 26.9% of the patients were at risk in terms of depression and anxiety, respectively. Depression prevalence was higher in patients with low MNA-SF scores ($P=0.001$) and comorbidities ($P=0.007$). In those with a low MNA-SF score ($P=0.001$), comorbidities ($P=0.008$), and high urea levels ($P=0.003$), anxiety was more common. In patients with an elevated risk of anxiety ($P=0.001$) and depression ($P=0.007$), malnutrition risk was significantly higher.
Conclusion: Depression is closely related to nutritional status in patients receiving chronic hemodialysis therapy and considered an independent risk factor for malnutrition. Early diagnosis and treatment of hemodialysis patients' psychological problems and regulation and control of nutrition programs can be practical interventions to improve the quality of life of these patients.

Keywords: Malnutrition, Hemodialysis, Anxiety-depression

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Introduction

More than 1.5 million individuals worldwide require dialysis treatment because of chronic kidney disease. CKD patients have a higher mortality rate than the general population [1]. Patients receiving long-term renal replacement therapy are also at increased risk of complications or even death during dialysis due to malnutrition [2]. Malnutrition in dialysis patients is a common and complex condition that occurs because of renal disease and comorbidities. The rate of malnutrition varies between 18-75% in hemodialysis patients and 10-50% in peritoneal dialysis patients, depending on the criteria with which the patient is evaluated [3,4]. The presence of malnutrition is one of the determinants of most morbidity and mortality in end-term renal failure (ESRD) patients receiving hemodialysis (HD). Malnutrition is associated with delays in recovery, increased hospitalization, and susceptibility to infection [5].

There is consensus that the first step in assessing nutritional status is to identify the "at-risk" condition using approved screening tools [6-8]. Malnutrition is an important problem in the rehabilitation and treatment process. One of the methods that can reveal the risk of malnutrition is the standard nutrition questionnaire [9]. A useful method for preliminary assessment of patients' nutritional status is the use of standard scales that assess nutritional levels. Such scales are completed easily and quickly, do not require any special equipment, and are therefore easily applicable by medical personnel [10].

Depression and anxiety are the most common psychological disorders in patients undergoing hemodialysis. The incidences of depression and anxiety range between 19-60% and 12-52%, respectively, in dialysis patients [11, 12]. Depression is associated with poor quality of life, concomitant diseases, increased risk of hospitalization, cardiovascular disease, malnutrition, poor patient compliance, mortality [13-15].

This study aimed to determine the nutritional status and anxiety-depression levels of patients with ESRD in a chronic hemodialysis treatment program and evaluate the relationship between the two.

Materials and methods

Study design

This cross-sectional study was conducted at a university hospital between November 2019 and January 2020 on dialysis patients (n=55) over the age of 18 years who received treatment in the Dialysis Unit. Two patients were excluded from the study due to renal transplantation. No sample was selected for the study, all patients were included (n=53). All patients received a Hospital-Anxiety Depression Inventory (HAD) and a Mini Nutritional Assessment (MNA), both consisting of two parts.

Mini Nutritional Assessment (MNA)

MNA consists of two parts, long and short. It evaluates four aspects of the nutritional/health status, including diet, anthropometry, global, and status of self-rating [16]. The MNA-SF was first used to evaluate the malnutrition status of patients. Those who were identified as at-risk or malnourished with the MNA-short form were also asked to complete the long form. The validity and reliability test of the Turkish version was conducted by Sarikaya in 2013. Kappa compliance of the scale was 0.801 [17].

Hospital-Anxiety Depression Scale (HAD)

It is a scale developed by Zigmond et al. [18] in 1983. The scale consists of 14 questions. The anxiety and depression levels of the patients are evaluated by 7 questions each. The validity and reliability study of the scale was performed in 1997 by Aydemir et al. [19]. Cronbach alpha coefficients were 0.85 for the anxiety subscale and 0.78 for the depression subscale.

Statistical analysis

SPSS 20 statistical package program was used for statistical analyses and $P<0.05$ was considered statistically significant. Conformity tests were conducted to evaluate the distribution of data with regards to normality. The socio-demographic characteristics, anxiety-depression levels, nutritional statuses of the participants were evaluated, and the relationship between the latter two were examined with Chi-square and Mann-Whitney U tests.

Ethical permission

Ethics committee approval was obtained for the study from Harran University Medical School (Dated 07/01/2019 and HRU / 19.1.20 decision No). The Hospital-Anxiety Depression Scale is valid, reliable, and open to general use. Permission was obtained for the use of the Mini Nutritional Test-Short Form. Oral and written information were given to each participant, and their written consents were obtained.

Results

The mean age of 53 patients included in the study was 56.2(15.9) years; 36 (66%) were female and 18 (34%) were male. Anthropometric measurements such as body mass and height were obtained, with which the body mass index (BMI) values were calculated. The mean duration of kidney disease was 6.5 (5.5) years, and the mean duration of dialysis treatment was 4.5 (4.2) years. Among all, 56.6% of the patients were illiterate, 71.7% were unemployed and 54.7% had comorbidities. The socio-demographic characteristics of the patients are shown in Table 1.

Table 1: Socio-demographic characteristics of the patients

Socio-demographic characteristics	Categories	Number (n)	Percentage (%)
Gender	Female / Male	35/18	66.0/34.0
Age group	49 years and below	14	26.4
	Between 50-59 years	19	35.8
	60 years and above	20	37.7
Educational status	Illiterate / Literate	30/23	56.6/44.4
Occupation	Worker / Unemployed	15/38	28.3/71.2
Marital status	Married / Single	36/17	67.9/32.1
Total		53	100.0

In terms of depression and anxiety, 55.8% and 26.9% of the patients, respectively, were at risk. The relationship between the anxiety-depression levels and socio-demographic, biochemical, clinical, and anthropometric data of the participants were examined. A statistically significant increase was found in the frequency of depression and anxiety in patients with low MNA-SF scores ($P=0.001$ and X^2: 24.66, and $P=0.001$ and X^2: 6.96, respectively) and comorbidities ($P=0.007$ and X^2: 6.96, and $P=0.008$ and X^2: 7.36, respectively). Anxiety was also significantly increased among patients with high urea levels ($P=0.003$ and MWU: 28.5).

Based on MNA-SF, fourteen patients (27.5%) were found risky in terms of malnutrition, who were then evaluated

with MNA-LF. Among them, 12 (71.4%) were at risk for malnutrition and 2 (14.3%) were malnourished. The patients did not differ in terms of socio-demographic and clinical characteristics according to nutritional status (Tables 2 and 3).

Table 2: Relationship of patients' nutritional status with some socio-demographic and clinical data

Characteristics	Categories	Nutrition Status		Statistical analysis	
		Normal (%)	At-risk (%)	*P*-value	X^2
Gender	Female / Male	73.5/70.6	26.5/29.4	0.53	0.04
Education	Illiterate / Literate	67.9/78.3	32.1/21.7	0.40	0.68
Occupation	Worker / Unemployed	73.3/72.2	26.7/27.8	0.61	0.07
Marital status	Married / Single	71.4/75.0	28.6/25.0	0.53	0.07
Smoking	Smoker/ Not smoker	75.8/66.7	24.2/33.3	0.45	0.48
Presence of comorbidity	Yes / No	75.0/69.6	25.0/30.4	0.66	0.18
Body mass index	Low/ Normal/ High	70.0/84.2/66.7	30.0/15.8/33.3	0.42	1.70
Blood pressure	Normal/ High	69.2/90.0	30.8/10.0	0.18	1.76

Table 3: Relationship of clinical data of patients with nutrition status

Characteristics	Nutrition Status		Statistical analysis	
	Normal	Vulnerable	*P*-value	MWU
Age (years)	57.3 (15.2)	55.9(16.2)	0.90	253.0
Kidney Disease Duration (years)	6.6 (5.1)	5.5 (5.9)	0.82	98.5
Dialysis Duration (years)	5.1 (4.4)	3.6 (3.5)	0.90	183.0
Kt/V	1.6 (0.3)	1.5 (0.3)	0.14	209.5
Hemoglobin (gr/dL)	10.6 (1.7)	10.0 (1.5)	0.49	196.5
Hematocrit (%)	33.9 (3.6)	35.9 (3.6)	0.39	217.5
Urea (mg/dL)	128.2 (37.9)	102.1 (47.5)	0.19	185.5
Creatinine (mg/dL)	13.6 (29.7)	6.8 (3.3)	0.90	182.0
Albumin (g/dL)	3.8 (0.6)	3.8 (0.3)	0.90	231.5
Calcium (mg/dL)	8.2 (0.9)	8.4 (0.8)	0.69	214.0
Phosphorus (mg/dL)	4.5 (1.4)	3.9 (1.5)	0.07	190.0
C-reactive protein (mg/dL)	1.1 (1.3)	1.4 (0.8)	0.90	235.5
Hemoglobin A1c (%)	7.2 (2.0)	6.5 (1.5)	0.38	52.0
High Density Lipoprotein (mg/dL)	33.0 (10.9)	36.5 (12.5)	0.68	218.5
Low Density Lipoprotein (mg/dL)	84.0 (22.0)	85.3 (35.0)	0.69	254.0
Triglycerides (mg/dL)	170.2 (98.1)	161.3 (135.0)	0.39	221.0
Vitamin D (ng/mL)	7.9 (4.1)	9.9 (8.9)	0.69	112.5
Vitamin B12 (pg/mL)	418.1 (347.5)	446.3 (188.5)	0.07	98.5
Folic acid (ng/mL)	10.5 (12.7)	7.0 (4.8)	0.85	150.0
Glucose (mg/dL)	133.5 (81.1)	148.1 (98.3)	0.69	243.0
Ferritin (ng/mL)	580.5 (460.2)	799.6 (1127.7)	0.82	258.0
Thyroid Stimulating Hormone (mIU/L)	1.9 (0.8)	1.7 (1.2)	0.39	185.5

The relationship between patients' anxiety-depression statuses and nutrition is shown in Table 4. The risk of malnutrition was significantly increased among patients who are at risk for anxiety (P=0.001) and depression (P=0.007).

Table 4: Relationship between patients' anxiety-depression status and nutrition

Characteristics	Categories	Nutrition Status		Statistical analysis	
		Normal (%)	At-risk (%)	*P*-value	X^2
Anxiety	Healthy	91.7	21.4	0.00	24.66
	Vulnerable	8.3	78.6		
Depression	Healthy	90.9	57.1	0.00	6.96
	Vulnerable	9.1	42.9		

Discussion

CKD and HD are important and global public health problems due to increased incidence, high treatment costs, and negative impact on the quality of life. Malnutrition, a common finding in individuals with CKD, is associated with increased mortality and morbidity. Malnutrition, by itself, also has a negative impact on anxiety and depression. Prevention of malnutrition may reduce the risk of anxiety and depression in patients [20]. Although nutritional status is assessed by various biochemical and physical parameters or nutritional assessment scores, most of these methods are not suitable for routine repetitive follow-up in dialysis patients as they are expensive or impractical. MNA is a common tool to rate the risk of malnutrition [21]. It is effective for screening and evaluating the risk of malnutrition in various settings (community, nursing homes, or institutions) or various health conditions (mental illness, cognitive impairment, dementia, stroke rehabilitation, cancer patients, or hemodialysis treatment patients) [22]. Most scoring systems for malnutrition use less reliable or less representative parameters in dialysis patients, and its association with mortality in this population may be unreasonable. The most striking example is the obesity paradox in which high BMI appears to be protective in dialysis patients [23]. In this study, we did not find a significant relationship between body mass index (BMI) and malnutrition risk.

The prevalence of malnutrition in patients with CKD is between 18-75% in HD patients and 10-50% in peritoneal dialysis patients, depending on the criteria with which the patient is evaluated. Malnutrition in chronic kidney failure usually results from decreased energy intake associated with uremic syndrome and systemic chronic inflammation [24]. In our study, 27.5% of the patients were at risk for malnutrition, similar to the literature. It is thought that the relationship between serum albumin and nutritional status is not clear, which reduces its effectiveness as a marker of malnutrition [25-27]. We found that the relationship between nutritional status and serum albumin was not statistically significant.

Depression is the most common psychological disorder among HD patients. Research has shown that depressive HD patients have high mortality rates and depressive symptoms are one of the important factors that determine the overall quality of life of patients. Similarly, in our study, we found that 26.9% and 55.8% of the patients had a risk of anxiety and depression, respectively [28]. Various factors are thought to contribute to this problem, including stress, sleep disturbance, anemia, and treatment methods [29]. Similarly, in this study, there was a significant relationship between malnutrition and anxiety-depression. In this context, it is thought that the risk of malnutrition will be reduced by early diagnosis and treatment of patients with depression and anxiety disorders.

Limitations

This study has some limitations, such as the lack of comparison with healthy controls and the sparse number of patients. It may be strengthened by comparing the variables of HD patients with a control group with normal kidney functions and increasing the number of patients. More studies are needed to help examine the risk of anxiety and depression in hemodialysis patients and identify factors that contribute to the associated outcomes.

Conclusions

Depression and anxiety are common psychological problems in patients receiving chronic hemodialysis. This is closely related to their nutritional status. Early diagnosis and treatment of psychological problems of hemodialysis patients and regulation and control of nutritional programs can be practical interventions to improve their quality of life.

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The pandemic's effect on discharge against medical advice from the emergency department

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Abstract

Background/Aim: Reasons for discharge against medical advice (DAMA) may vary according to countries' conditions and environmental or individual factors. Patients who choose to leave the hospital against the doctors' recommendations are at risk of inadequate treatment and increased rehospitalization risk. The COVID-19 disease has come to the fore with a pandemic and the atmosphere of fear and panic it creates. We aimed to investigate the effect of fear of the pandemic on DAMA.
Methods: This study was conducted in the emergency department (ED) of a tertiary hospital in Turkey. The characteristics of all patients who were discharged against medical advice and their reasons over six months at the beginning of the pandemic were examined prospectively.
Results: A total of 263 patients left the ED on various excuses against medical advice between February 6-August 31, 2020 (DAMA rate: 2.4‰). The most common complaint of patients discharged against medical advice was abdominal pain (27%). The top 3 most common causes of DAMA were the fear of being infected by COVID-19 (36.5%), the thought of being neglected (12.2%), and the month of Ramadan (11.4%).
Conclusion: The pandemic is an important reason for DAMA. Patients leave the hospital against medical advice with an avoidance-avoidance conflict during the COVID-19 pandemic. Defining dirty and clean areas within the emergency services with sharp boundaries and informing patients may prevent DAMA due to the fear of being infected with COVID-19. Physicians do not ignore the risk of progression to worse clinical outcomes in patients who discontinue treatment due to the pandemic.

Keywords: COVID-19, Discharge against medical advice, Emergency department, Pandemic

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Introduction

Discharge against medical advice (DAMA) refers to a condition where the patient leaves the hospital, hence interrupting the diagnosis and treatment process for any reason. DAMA is a confusing ethical problem for physicians. In recent years, concerns about patients with DAMA from the emergency department (ED) have been increasing worldwide. DAMA continues to be a significant problem affecting healthcare quality, with a ratio of 2.7% among ED discharges [1]. Patients who choose to leave the hospital against the doctor's recommendations are at risk of inadequate treatment and increase their rehospitalization risk [2]. Ethical issues regarding DAMA are still a critical dilemma. Although many doctors desire treatment to continue for the patient's benefit, they discharge the patient, respecting the patient's decision [3]. Link et al. [4] found the mortality rate of 57 patients with DAMA in a group of hospitals in the Virginia region to be 15.7% within one year. It has been reported that patients discharged against medical advice have 56% more healthcare costs in their readmissions than in their first admissions [5]. Some conditions that cause patients to request discharge in studies on DAMA are as follows: The patient feels well, socioeconomic conditions, alcohol-substance addiction, and dissatisfaction with health care [6-8].

Months before the coronavirus disease 2019 (COVID-19) pandemic reached Turkey, emergency medicine specialists were trying to raise awareness in their followers through social media posts [9]. Based on these data, it was also investigated whether the pandemic had an impact on DAMA. To the best of our knowledge, there is no study investigating the pandemic's effect on patients who leave the hospital against medical advice.

In this prospective study, we aimed to find solutions to these problems by determining DAMA patients' characteristics, the underlying reasons for the demand for discharge, whether they revisited the ED, their 1-month mortality, and why the doctor avoided discharging the patient in the first place. With this study, we also intended to raise awareness in patients and doctors on this subject.

Materials and methods

Study setting and design

This prospective, descriptive, and single-center study was conducted between February 6, 2020, and August 31, 2020, in the ED of a tertiary hospital in Çorum, Turkey. The study's ethics committee approval was obtained from the Hitit University Faculty of Medicine Clinical Research Ethics Committee (Approval ID: 2020/156, February 5, 2020).

The study was conducted in the ED of a tertiary hospital, which admits approximately 300,000 patients per year. Only adult patients aged 18 years and over are treated in this ED. Four to six general practitioners and 1-3 emergency medicine specialists work every day. The following characteristics of all patients with DAMA were examined and recorded over six months: Time of ED presentation, mode of presentation [self-presenting or by an emergency medical service (EMS)], admission complaint, triage code, demographic data (age, gender, comorbidities, place of residence (city/rural area), having health insurance), smoking and alcohol consumption habits, reasons for DAMA, whether the patient had a previous DAMA history, the reason why the doctor avoided discharging the patient in the first place, the diagnosis at discharge, length of stay in the ED, ED revisit within one month, revisit complaint and 1-month mortality status.

Selection of participants and measurements

Patients aged 18 years and over who left the hospital against medical advice were included in this study. Informed consent was obtained from each patient before the study. Hospital processes of the patients, such as diagnosis, examination, and treatment, were not intervened. One patient who did not state a reason for DAMA and two patients who did not give written consent were excluded from the study.

ED triage is an essential preliminary screening tool that divides emergency patients into urgency categories to prioritize patients for treatment and evaluation. In Turkey, color coding is used to determine patients' treatment priority admitted to the ED. Patients are divided into three categories according to the severity of their symptoms: Red (emergent), yellow (urgent), and green (nonurgent) [10]. According to this classification, the green code indicates patients without any acute symptoms. The yellow code indicates patients with immediate symptoms but who are not expected to die within hours. In contrast, the red code indicates patients with highly acute symptoms who are likely to die within minutes to hours if not intervened early.

The conditions causing DAMA, as stated by the patients, were grouped under the following subtitles: Fear of being infected with COVID-19 (the first case in our country was detected on March 11, 2020), thought of being neglected, and the Ramadan month effect (patients who are Muslim in our country fast in the 9^{th} month of the lunar calendar; the fasting starts before sunrise and ends at sunset, so people who fast often prefer to be at home in the evening), thought of waiting too long, feeling well, dissatisfaction with hospital conditions, avoiding the ED's chaotic environment, conflict with the healthcare staff, the desire to see their own doctor for follow-up, having jobs to catch up on, thought that the family would worry about them, and the desire to smoke.

Outcome

This study's primary outcomes were to determine both the factors leading to the discharge of patients from the ED against medical advice and DAMA patients' characteristics. The secondary outcome was to examine the ED revisits and one-month mortality of DAMA patients.

Statistical analysis

Descriptive statistics are presented as numbers and percentages. Continuous variables are presented as medians and minimum-maximum values, and categorical variables are presented as percentages. The normality condition for continuous variables was checked with the Shapiro-Wilk test. Differences between the two groups were analyzed using the Mann-Whitney U test. The relationship between two categorical variables was examined using Pearson's chi-square test and Fisher's exact test. IBM SPSS Statistics for Windows, Version 23 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses. A *P*-value of <0.05 was considered statistically significant.

Results

Approximately 300,000 patients are admitted annually to the ED, where the study was conducted. The number of ED visits was 111,853 during the study period (36% lower than the number of visits in the same period in the previous year).

Between February and August 2020, a total of 263 patients left the ED on various excuses against medical advice (DAMA rate: 2.4‰). The patients' median age was 32 (range: 18-90) years, and 51.7% were females. All patients with DAMA had health insurance. The most common complaints of patients who were discharged against medical advice were abdominal pain (27%), followed by headache (17.9%) and sore throat (16.3%). The most common diagnoses of these patients during their stay in the ED were pharyngitis (16.3%), followed by nonspecific abdominal pain (16%) and migraine (10.3%). It was found that 36.5% of patients with DAMA had histories of DAMA, and 90% of those admitted again within one month were admitted with the same complaint. During the study period, it was observed that *fear of being infected with COVID-19* was the most common reason, with a rate of 36.5% among all cases of DAMA. The second most common reason was *the thought of being neglected*, with 12.2%, while the sacred *month of Ramadan*, in which Muslims fast, was the third most common reason, with a rate of 11.4%. *Uncompleted diagnostic tests and treatment* constituted approximately 95% of why doctors did not discharge the patient (Table 1). No mortality was observed in any of the patients with DAMA within one month.

While patients without comorbidity and alcohol use were more worried about *being infected with COVID-19*, male individuals who smoked and drank alcohol claimed they were *neglected* as a justification for DAMA. Comorbid patients left the hospital to *avoid the ED's chaotic environment* against medical advice. The reasons for the *thought of being neglected* and *avoiding the ED's chaotic environment* were more effective on DAMA as age increased (P<0.05). A detailed comparison of the factors causing DAMA in terms of demographic characteristics is shown in Table 2.

The comparison between DAMA patients' hospital data and the cause of DAMA is as follows: (1) *Fear of being infected with COVID-19*: green code triage, no previous DAMA history, no emergency room revisit; (2) *Thought of being neglected*: Self-presenting, yellow code triage, no ED revisit, presenting between 18:00-23:59; (3) *The Ramadan month effect*: green code triage, no previous DAMA history; (4) *Feeling well*: self-presenting, yellow code triage, no ED revisit; (5) *Dissatisfaction with the hospital conditions*: self-presenting, admitted between 12:00-17:59, no previous DAMA history; and (6) *Avoiding the ED's chaotic environment*: self-presenting, yellow code triage, length of stay in the ED >1 hour, no ED revisit (P<0.05) (Table 3).

Table 1: The distribution of DAMA patients' characteristics, their reasons for leaving the hospital, their hospital processes, and ED revisits

Characteristics	n	%	Complaints	n	%	The reasons for DAMA	n	%
Age (years)	32 (18-90)*		Abdominal pain	71	27.0	The fear of being infected with COVID-19	96	36.5
Female	136	51.7	Headache	47	17.9	The thought of being neglected	32	12.2
Place of residence			Throat ache	43	16.3	Month of Ramadan effect	30	11.4
City center	254	96.6	Nausea	24	9.1	The thought of being awaited too long	23	8.7
District	9	3.4	Fall	22	8.4	Feeling well	20	7.6
Health insurance			Syncope	19	7.2	Dissatisfaction with hospital conditions	16	6.1
General	260	98.9	Chest pain	14	5.3	Avoiding the ED's chaotic environment	14	5.3
Private	3	1.1	Shortness of breath	9	3.4	Conflict with the healthcare staff	10	3.8
Known disease	42	16.0	Assault	3	1.1	The desire of seeing own doctor	9	3.4
Comorbidities**			Dizziness	2	0.8	Having jobs to catch up	6	2.3
COPD[a]	8	3.0	General condition disorder	2	0.8	The thought that the family will worry about	4	1.5
Hypertension	34	12.9	Seven other complaints[d]	7	2.7	The desire for smoking	3	1.1
Diabetes	6	2.3	Diagnosis			Why doctors are against it?		
CAD[b]	11	4.2	Pharyngitis	43	16.3	Uncompleted of diagnostic tests	166	63.1
Malignancy	1	0.4	Nonspecific abdominal pain	42	16.0	Uncompleted of treatment	82	31.2
CRF[c]	3	1.1	Migraine	27	10.3	Clinical instability	8	3.0
Cirrhosis	3	1.1	Soft tissue trauma	21	8.0	Desire to keep under observation for a while	6	2.3
Stroke	3	1.1	Renal colic	20	7.6	Feeling of his efforts being wasted	1	0.4
Smoking	97	36.9	Hypertension	20	7.6	Length of stay in the ED (hours)		
Alcohol use	62	23.6	Vertigo	19	7.2	1 or less	179	68.1
Admission time			Acute coronary syndrome	16	6.1	>1	84	31.9
00:00-05:59	8	3.0	Urinary tract infection	16	6.1	Previous DAMA history (+)	96	36.5
06:00-11:59	47	17.9	Syncope	10	3.8	ED revisit	21	8.0
12:00-17:59	106	40.3	COPD[a]	8	3.0	ED revisit complaint		
18:00-23:59	102	38.8	Ovarian cyst rupture	4	1.5	Same	19	90.5
Mode of presentation			Trauma to the pregnant	3	1.1	Different	2	9.5
Self-presenting	240	91.3	Excessive alcohol intake	3	1.1	ED revisit period		
By emergency medical service	23	8.7	Stroke	2	0.8	1-7 days	16	76.2
Green Code	180	68.4	Other diagnoses [e]	9	3.4	7-14 day	2	9.5
Yellow Code	83	31.6				15-28 days	3	14.3

*Median (min-max); ** Some patients had more than one comorbidity; [a]COPD: Chronic obstructive pulmonary disease; [b]CAD: Coronary artey disease; [c]CAD: Chronic renal failure; [d] seven complaints: traffic accident, melena, speech impairment, burn, drug overdose, itching, myalgia; [e] other diagnoses: sepsis, intracranial bleeding, acute renal failure, gastrointestinal bleeding, burn, drug intoxication, clavicula fracture, cellulite, urticaria; DAMA: discharge against medical advice; ED: emergency department; COVID-19: coronavirus disease 2019

Table 2: Evaluation of the reasons why patients leave the hospital against medical advice in terms of demographic characteristics

Reasons		Fear of being infected with COVID-19	Thought of being neglected	The Ramadan effect	Thought of being awaited too long	Feeling well	Dissatisfaction with hospital conditions	Avoiding the ED's chaotic environment	Other reasons *
Age, Median (IQR) **	No	32 (22)	31 (21)	32 (21)	32 (22)	32 (21)	32 (21)	32 (20)	-
	n	167	231	233	240	243	247	249	
	Yes	31.5 (19)	43 (13)	31 (23)	32 (19)	30 (29)	26.5 (42)	52.5 (50)	-
	n	96	32	30	23	20	16	14	
P-value		0.358	0.009	0.811	-	0.877	0.527	0.006	-
Gender									
Female (n=136)		57 (41.9)	10 (7.4)	23 (16.9)	8 (5.9)	10 (7.4)	5 (3.7)	8 (5.9)	15(10.9)
Male (n=127)		39 (30.7)	22 (17.3)	7 (5.5)	15 (11.8)	10 (7.9)	11 (8.7)	6 (4.7)	17(13.4)
P-value		0.059	0.013	0.004	0.089	0.873	0.091	0.676	-
Living place									
City Centre (n=254)		96 (37.8)	32 (12.6)	30 (11.8)	22 (8.7)	17 (6.7)	14 (5.5)	12 (4.7)	31(12.2)
District (n=9)		0 (0)	0 (0)	0 (0)	1 (11.1)	3 (33.3)	2 (22.2)	2 (22.2)	1(11.1)
P-value		0.124	0.088	0.489	0.704	0.021	0.040	0.004	-
Comorbidity									
Yes (n=221)		89 (40.3)	28 (12.7)	28 (12.7)	19 (8.6)	15 (6.8)	10 (4.5)	6 (2.7)	26(11.7)
No (n=42)		7 (16.7)	4 (9.5)	2 (4.8)	4 (9.5)	5 (11.9)	6 (14.3)	8 (19)	6(14.3)
P-value		0.004	0.568	0.188	0.771	0.335	0.027	<0.001	-
Smoking									
No (n=166)		58 (34.9)	3 (1.8)	28 (16.9)	18 (10.8)	15 (9)	13 (7.8)	8 (4.8)	23(13.8)
Yes (n=97)		38 (39.2)	29 (29.9)	2 (2.1)	5 (5.2)	5 (5.2)	3 (3.1)	6 (6.2)	9(9.3)
P-value		0.491	<0.001	<0.001	0.115	0.252	0.121	0.634	-
Alcohol									
No (n=201)		63 (31.3)	14 (7)	29 (14.4)	22 (10.9)	17 (8.5)	14 (7)	13 (6.5)	29(14.4)
Yes (n=62)		33 (53.2)	18 (29)	1 (1.6)	1 (1.6)	3 (4.8)	2 (3.2)	1 (1.6)	3(4.8)
P-value		0.002	<0.001	0.006	0.023	0.424	0.374	0.199	-

* The following reasons for DAMA could not be analyzed due to the insufficient sample size: conflict with the healthcare staff, the desire of seeing own doctor, having jobs to catch up, the thought that the family will worry about, the desire for smoking; ** IQR: Interquartile range; DAMA: discharge against medical advice; COVID-19: coronavirus disease 2019; ED: emergency department. Categorical variables are given as n (%) in the rows.

Table 3: Evaluation of the reasons why patients leave the hospital despite medical advice according to the factors in the hospital process

Reasons	Fear of being infected with COVID-19	Thought of being neglected	The Ramadan effect	Thought of being awaited too long	Feeling well	Dissatisfaction with hospital conditions	Avoiding the ED's chaotic environment	Other reasons *
Admission time								
00:00-05:59 (n=8)	2 (25)	0 (0)	0 (0)	1 (12.5)	3 (37.5)	0 (0)	2 (25)	0(0)
06:00-11:59 (n=47)	12 (25.5)	9 (19.1)	9 (19.1)	2 (4.3)	3 (6.4)	0 (0)	3 (6.4)	9(19.1)
12:00-17:59 (n=106)	38 (35.8)	17 (16)	13 (12.3)	8 (7.5)	5 (4.7)	12 (11.3)	6 (5.7)	7(6.6)
18:00-23:59 (n=102)	44 (43.1)	6 (5.9)	8 (7.8)	12 (11.8)	9 (8.8)	4 (3.9)	3 (2.9)	16(15.7)
P-value	0.183	0.037	0.159	0.374	0.030	0.031	0.079	-
Mode of presentation								
Self-presenting (n=240)	91 (37.9)	32 (13.3)	29 (12.1)	22 (9.2)	15 (6.3)	12 (5)	9 (3.8)	30(12.4)
By emergency medical service (n=23)	5 (21.7)	0 (0)	1 (4.3)	1 (4.3)	5 (21.7)	4 (17.4)	5 (21.7)	2(8.6)
P-value	0.124	0.088	0.489	0.704	0.021	0.040	0.004	-
Triage Area								
Green Code (n=180)	79 (43.9)	30 (16.7)	26 (14.4)	13 (7.2)	6 (3.3)	8 (4.4)	0 (0)	18(10)
Yellow Code (n=83)	17 (20.5)	2 (2.4)	4 (4.8)	10 (12)	14 (16.9)	8 (9.6)	14 (16.9)	14(16.9)
P-value	<0.001	0.001	0.022	0.198	<0.001	0.101	<0.001	-
Length of stay in the ED (hours)								
1 or less (n=179)	71 (39.7)	24 (13.4)	24 (13.4)	16 (8.9)	11 (6.1)	10 (5.6)	5 (2.8)	18(10.1)
>1 (n=84)	25 (29.8)	8 (9.5)	6 (7.1)	7 (8.3)	9 (10.7)	6 (7.1)	9 (10.7)	14(16.6)
P-value	0.120	0.369	0.136	0.871	0.192	0.623	0.015	-
Previous DAMA history?								
No (n=167)	73 (43.7)	14 (8.4)	26 (15.6)	15 (9)	13 (7.8)	4 (2.4)	6 (3.6)	16(9.5)
Yes (n=96)	23 (24)	18 (18.8)	4 (4.2)	8 (8.3)	7 (7.3)	12 (12.5)	8 (8.3)	16(18.6)
P-value	0.001	0.013	0.005	0.858	0.885	0.001	0.099	-
ED revisit								
No (n=242)	95 (39.3)	31 (12.8)	30 (12.4)	21 (8.7)	15 (6.2)	13 (5.4)	9 (3.7)	28(11.5)
Yes (n=21)	1 (4.8)	1 (4.8)	0 (0)	2 (9.5)	5 (23.8)	3 (14.3)	5 (23.8)	4(19)
P-value	0.002	0.486	0.145	0.704	0.014	0.125	0.002	-

* The following reasons for DAMA could not be analyzed due to the insufficient sample size: conflict with the healthcare staff, the desire of seeing their own doctor, having jobs to catch up, the thought that the family will worry, the desire for smoking; DAMA: discharge against medical advice; COVID-19: coronavirus disease 2019; ED: emergency department. Categorical variables are given as n (%) in the rows.

Discussion

The issue of patients deciding to discharge themselves is encountered every day in the ED, and despite its rarity, it carries growing importance. In our study, in which we aimed to reveal the factors that affect DAMA, we found that the pandemic effect and religious beliefs such as fasting and the thought of being neglected were highly influential in the DAMA decision. It was observed that the doctors opposed DAMA at a rate of 95% due to incomplete tests and treatment. The DAMA ratio was 2.4‰ in our study. DAMA's prevalence in the ED has been reported as 0.5-1.44% of admissions [11, 12].

The COVID-19 disease has come to the fore with a pandemic and the atmosphere of fear and panic it creates. The pandemic triggered anxiety and depression and led to behavioral changes [13]. Suggestions made to control the epidemic (social distance rules, curfew restrictions, closing down socializing environments), especially the information burden/pollution caused by social media, make significant contributions to society's tension [14]. One of the aims of this study was to examine whether this tension affected DAMA. It was determined that most patients wanted to be discharged against medical advice due to fear of being infected with COVID-19. Advanced age, comorbid diseases, and male sex are among the risk factors for deaths from COVID-19 [15-18]. However, age and sex were not influencing factors in the decision to leave the hospital due to fear of being infected with COVID-19 in our study.

Contrary to the presence of comorbidities, which are highly associated with COVID-19 mortality, we observed that those without comorbidities left the hospital because they were afraid of being infected with COVID-19. This may be because those with comorbid diseases think that they need more medical support. The fact that green code patients mostly choose DAMA due to COVID-19 supports this view. According to the US data for 2002-2011, lack of social security, male sex, and geographical region (northeast) are the most important triggering factors for DAMA [19]. Noohi et al. [20] stated that the most common cause of DAMA from the ED was feeling well. Eze et al. [21] cited patients' financial reasons and inadequate response to treatment as the most common reasons for DAMA. It was also reported that the presenting symptoms' regression or disappearance was one of the causes of DAMA [22]. Although the reasons for DAMA may vary according to the countries' conditions, based on our data, we concluded that the fear of being infected with COVID-19 was the most prominent cause of DAMA in 2020.

It is strikingly prominent in our study that, as one of the pandemic's hidden effects, patients abandon their treatment halfway through due to the fear of contamination and leave the hospital against medical advice. The pandemic also affects the treatment of patients who are not infected with COVID-19 and should not be ignored. It can be assumed that sick individuals experience an "avoidance-avoidance conflict" due to the anxiety created by the risk of COVID-19 transmission when being admitted to healthcare facilities. Patients who encounter two disadvantageous situations may prefer to interrupt their treatment in this conflict.

Revisits to the ED after DAMA can be considered an indicator of the current clinic's importance and severity. In a study conducted by El Sayed et al. [23] that included 1213 DAMA cases, it was found that 9.8% of the cases revisited the hospital within three days, there was no difference between the urgency in the revisit and the first visit, and 0.3% of patients had mortality within one month (however, they could not learn the fate of half of the patients). Jerrard et al. [22] stated that 34.5% of the patients with DAMA returned to the ED with regressed or ended symptoms, with a rate of 46.2%, and they did not detect any mortality within a month. In our study, 8% of DAMA patients returned to the ED, and 76.2% of these returns were in the first seven days. No mortality was observed within one month. It can be explained that patients with severe symptoms feel the need for revisits, and most DAMA cases have mild symptoms. Only 3% of DAMA patients are defined as critically ill patients by doctors, which supports this view.

It is a known fact that women have difficulties in all areas of life. In previous studies, it was observed that men were more frequently discharged from the hospital against medical advice [19-21]. In Nasir and Babalola's research [24], nearly 4 out of every 5 DAMA patients were male. In our study, 51.7% of DAMA patients were women, and the most common reason for leaving the hospital was Ramadan. During the month of Ramadan, Muslims, who make up almost the entire population of the country, fast. Fasting starts before sunrise and continues until sunset. There is serious food preparation for the ending of the fast at sundown. In almost all societies, women undertake preparing meals. The fact that women prefer DAMA more often in Ramadan when the food preparation burden is high shows that they also experience difficulties. The effect of Ramadan, which covers a total of 30 days in a working period of approximately six months, ranked third as a cause of DAMA (11.4%). This can be attributed to the patients' inadequate knowledge of which interventions can be performed during fasting and health professionals' inability to explain this issue [25].

Emergency crowds are increasing daily, making it difficult for emergency services to operate effectively. For this reason, triage protocols, in which patients are classified according to their clinical priorities, are practiced in many emergency services [26, 27]. This practice at admission to the ED determines the patients' severity and waiting times and is effective in reducing the ED crowd [27, 28]. Eze et al. [21] reported that most DAMA cases (64.6%) were nonemergency patients. Spooner et al. [19] stated that most DAMA cases were patients presenting with symptoms causing mild and moderate dysfunction (34.6% and 44%, respectively). In the center where this study was conducted, a color code triage system is used to prevent emergency service crowds and provide effective service. The majority of patients with DAMA (68.4%) consisted of patients without serious symptoms (green code). Patients with severe symptoms (yellow code) left the hospital because they felt well and wanted to avoid the ED's chaotic environment.

In contrast, patients with the green triage code left the hospital despite medical advice due to fear of being infected with COVID-19 and the impact of Ramadan. The fact that DAMA is more common in patients with green codes can be attributed to their awareness that their current symptoms are not suitable for ED visits. For patients with mild symptoms not to occupy the ED and be directed electively to the necessary units, smartphone applications with health information lines or clinical decision support systems can be created. In this way, nonchaotic ED environments can be provided for patients with severe symptoms.

The length of stay in the ED is a factor that is affected by many parameters and determines the quality of patient care. While designing the study related to the emergency service, the duration of stay in the ED is also evaluated, as is mortality. This approach aims to determine the issues that need to be considered to prevent mortality and emergency crowding. In the study of Shirani et al. [29], the majority of patients with DAMA stayed in the ED for <12 hours (63%), and only 4.5% of patients had DAMA due to a prolonged stay in the ED. In the study of El Sayed et al. [23] the average length of stay in the ED of DAMA cases was 3.8 ± 6.8 hours, and only 2.9% of the patients indicated a long waiting time as the reason for DAMA. In our study, 8.7% of patients with DAMA left the hospital thinking that they had waited too long. There was no significant difference between the reason and the duration of stay in the ED.

Patients brought in by ambulance are often expected to have severe symptoms. However, 8.7% of DAMA cases in our study were admitted by ambulance, and most (n=21, 91.3%) were green code patients. Unlike the patients brought by ambulance, self-presenting patients cited feeling well, not being satisfied with the hospital conditions, and avoiding the ED's chaotic environment as their reasons for DAMA. As mentioned

before, this difference can be explained by the fact that patients who need treatment know their well-being status and continue their treatment demands.

Limitations

The first limitation of this study was that it was performed in a single center. Second, there was no information about whether DAMA patients who left our hospital applied to another hospital. The third limitation was the lack of cost analysis. Fourth, we did not have data to compare the DAMA rate at the time of the study with the same period of previous years. Finally, the long-term outcomes of patients with DAMA were not examined.

Conclusion

The pandemic effect has also manifested itself in DAMA. This study calls not to ignore the risk of later progression to worse clinical outcomes in patients who discontinue treatment due to the pandemic. Patients leave the hospital against medical advice with an avoidance-avoidance conflict during the COVID-19 pandemic. Defining the dirty-clean areas of emergency services with sharp boundaries and informing patients may prevent DAMA due to the fear of being infected with COVID-19. Also, physicians should keep in mind that people's religious feelings in the regions where they work may play a role in refusing or accepting treatment.

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The contribution and histopathological correlation of MRI in BI-RADS category 4 solid lesions detected by ultrasonography

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Ethics Committee Approval
Approval for the study was obtained from the 'Non-invasive Clinical Research Ethics Committee' of Aydın Adnan Menderes University (No: 2018/1333), on February 22, 2018.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: BI-RADS category 4 breast lesions have widely varying malignancy rates and they are almost always evaluated with biopsy. However, especially in the 4a subgroup with a benign character of up to 98%, many patients undergo unnecessary invasive procedures. Breast MRI can be a good problem-solving method to reduce unnecessary invasive procedures, but there are very few publications on BI-RADS category 4 solid lesions. This study aimed to investigate the contribution of breast MRI in Breast Imaging Reporting and Data System (BI-RADS) category 4 solid mass lesions detected by Mammography and Ultrasonography.

Methods: In this retrospective cohort study, ultrasound reports of patients examined in the radiology breast imaging unit between January 2015 and December 2017 were reviewed. Cases reported as BI-RADS category 4 with a solid mass on ultrasonography were determined. Patients without histopathological diagnosis and/or breast MRI were excluded from the study. After the implementation of the exclusion criteria, 121 solid lesions of 104 female patients were included in the study. US and MRI images of the patients were re-evaluated by two radiologists and BI-RADS scoring was performed again. The obtained data were analyzed statistically together with histopathological data.

Results: With breast MRI, 74 of 121 BI-RADS category 4 lesions were downgraded while 13 lesions were upgraded. Of the 74 downgraded lesions, 61 were BI-RADS category 2 and 3, which do not require a biopsy. Only one of these lesions was histopathologically malignant. Of the 13 lesions upgraded, 6 were in BI-RADS category 5, two of which were benign. The sensitivity, specificity, positive and negative predictive values of MRI were 93.8%, 56.2%, 24.6%, and 98.3%, respectively.

Conclusion: In our study, breast MRI reduced the BI-RADS categories to 2 and 3 in approximately half of the BI-RADS category 4 solid lesions detected by ultrasound. Therefore, problem-solving MRI may be useful to avoid unnecessary invasive procedures in these patients.

Keywords: BI-RADS category 4, Breast ultrasonography, Breast MRI, Breast cancer, Solid breast lesions

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Introduction

Breast Ultrasonography (US) is a widely used imaging modality to evaluate breast abnormalities of young women, and in those with dense breast tissue due to low sensitivity of mammography (MG). Due to high dependence on the operator, the sensitivity and specificity of US vary between the studies. Previous studies reported 81-98% sensitivity, 33-89% specificity, 13-68% positive predictive value (PPV), and 92-100% negative predictive value (NPV) for US Breast Imaging and Data System (BI-RADS) classification [1].

Breast magnetic resonance imaging (MRI) is the most sensitive method to detect breast cancer (90-95%), although it has relatively low specificity (37-72%) when compared with MG and US [2,3]. There are recent studies that report that the specificity of breast MRI has increased in parallel with the developing technology [4, 5]. Although it has a high false-positive predictive value, negative breast MRI safely excludes malignancy with a high negative predictivity (91.7-100%) [4, 6]. Therefore, especially in selected cases, breast MRI use is increasing day by day in addition to conventional breast assessment methods for diagnostic and problem-solving purposes [7, 8]. Although MRI falls into the American College of Radiology (ACR) BI-RADS classifications published in 2003, the MRI guidelines for BI-RADS category 4 lesions are not fully specified [9].

The malignancy risks of BI-RADS category 4 breast lesions vary widely (2-95%) and they are evaluated in 3 subgroups. BI-RADS category 4a has low (2-10%), 4b has moderate (10-50%) and 4c has high (50-95%) malignancy possibility [10]. Although the probability of benignity reaches 98% especially in the BI-RADS category 4a, these lesions are considered to require pathological correlation rather than problem-solving MRI due to the risk of malignancy [10,11]. However, we think that breast MRI may reduce the need for biopsy due to its high sensitivity and negative predictive value.

This study aimed to investigate the contribution of breast MRI and its predictivity in reducing invasive biopsy procedures in BI-RADS category 4 solid mass lesions detected by MG and US.

Materials and methods

Approval for the study was obtained from the 'Non-invasive Clinical Research Ethics Committee of our institution (No: 2018/1333) on February 22, 2018.

Patient selection

A total of 2143 patients who underwent breast US in our clinic between January 2015 and December 2017 were scanned retrospectively. Images of 353 patients with BI-RADS category 4 in their radiological report were re-evaluated. Patients whose biopsy results were unavailable and who did not have MRIs were excluded from the study. A total of 121 lesions of 104 cases which were found to have solid mass showing suspicious malignant characteristics (BI-RADS category 4) were included in the study.

Mammography and tomosynthesis imaging

MG was performed in Mammomat Inspiration (Siemens, Erlangen, Germany), with standard craniocaudal (CC) and mediolateral oblique (MLO) views and additional views (lateral, spot compression, etc.) when necessary.

Tomosynthesis was performed in the MLO position with the tube moving at an arch angle of 25°. The resulting projection images were reconstructed with a cross-sectional thickness of 1 mm. MG and tomosynthesis images were evaluated on an MG-specific Workstation (MammoReport, Siemens, Erlangen, Germany).

MG examination was performed in all patients over 45 years of age and/or patients with a high risk of malignancy. All MG images were evaluated by or under the supervision of a 13-year-experienced radiologist.

Ultrasound imaging

All US examinations were performed on Acuson Antares (Siemens, Erlangen, Germany) ultrasound device. Sonograms were obtained with a 6-13 MHz wide band matrix transducer on breast preset. Patients under 45 years of age and without additional malignancy risk were evaluated by US alone. Patients over the age of 45 years and/or high risk of malignancy were first evaluated with MG, then US. All US examinations were performed by or under the supervision of a 13-year-experienced radiologist.

Magnetic resonance imaging

All breast MRIs of the patients were performed in a 1.5 T MRI device (Achieva, Philips MS, Eindhoven, The Netherlands), with a dedicated 7-channel nozzle coil, in the prone position. Breast MRI parameters were as follows: First, axial T1W spin-echo sequence (TR / TE: 454 / 10ms, FOV: 300, Matrix: 432, section thickness 3mm); next, axial T2W short tau invasion recovery (STIR: TR (TE: 2000/173 msec, FOV: 300, Matrix: 432, 2 mm section thickness) images were obtained. In the dynamic examination, axial 3D T1W gradient-echo sequence (THRIVE: TR / TE: 7 / 3.4 msec, matrix: 352, FOV: 340, flip angle 10º, 1 mm section thickness) was repeated 6 times in precontrast and postcontrast. Gadolinium contrast agent 0.1 mM/kg (Gadoteratmeglumine, Dotarem®, Guerbet, France; Gadobutrol, Gadovist®, Bayer Healthcare, Germany; Gadodiamide, Omniscan®, GE Healthcare, USA) was administered intravenously at 2 ml/sec with an automatic injector (Medrad Spectris Solaris EP, Bayer Radiology Solutions, Whippany, NJ, USA) and washed with 10 ml saline. MR images were evaluated on a mammography-specific Workstation (MammoReport, Siemens, Erlangen, Germany).

Image evaluation

The images of the patients who were diagnosed as BI-RADS category 4 in MG and US were re-evaluated by two radiologists with 13 years of experience in breast imaging by examining US, MG, and MRI findings with a common consensus.

All cases were re-classified with US and MG images using the fifth edition of the ACR BI-RADS Atlas [11,12]. The masses with partially circumscribed margins, complex cystic and solid lesions were noted as category 4a, masses with indistinct margins and/or amorphous or fine pleomorphic calcifications were considered category 4b, and masses with new indistinct margins and/or fine linear calcifications were recorded as category 4c. Masses with spiculated or irregular margins,

architectural distortion, skin/nipple retractions, and/or fine linear or linear branching calcifications were considered category 5.

Breast MRIs of all patients were also re-evaluated by a radiologist with 13 years of breast radiology experience, and the lesions were divided into three groups as focus, mass, and non-mass enhancement. In a mass lesion, irregular shape, microlobulated contour, and indistinct margin were considered suspicious and noted as BI-RADS category 4. An oval or round-shaped mass with a smooth margin was considered benign. Lesions with high T1 and T2 signals were considered benign, and low or medium T2 signals were considered suspicious. Homogeneous, heterogeneous, and circular enhancement patterns were considered suspicious in mass lesions. Enhancement of the internal septa was interpreted as a marker of malignancy (BI-RADS category 5), and internal septal structures without enhancement were interpreted in favor of benignity (BI-RADS category 3). In addition to the enhancement patterns, contrast kinetic curves of all mass lesions were obtained. Lesions with persistent (type 1) kinetic curves were considered benign, while lesions showing plateau (type 2) or wash-out (type 3) were suspicious for malignancy. In the non-mass enhancement group, the distribution and shape of the lesion were evaluated. Ductal, linear, segmental, and regional non-mass enhancements were considered suspicious. Considering the morphology of the lesions, T1 and T2 signal characteristics, enhancement patterns and kinetics, and associated findings (adenopathy, skin/nipple retractions or invasions, etc.) all lesions were re-classified according to the fifth edition of ACR BI-RADS Atlas [13].

Histopathological examination

All lesions of patients were histopathologically evaluated. In some patients, histopathological sampling was obtained by imaging-guided percutaneous tru-cut biopsy method, and in others, by surgical excision. Percutaneous biopsy was performed with US-guided 14G cutting needle biopsy with an automatic gun (Magnum, Bard biopsy systems, Tempe, USA). The obtained specimens were evaluated by a single pathologist working specifically on breast pathology.

Statistical analysis

A total of 121 lesions of 104 patients were included in the study. Re-evaluated MG, US, and MRI findings and BI-RADS scores, histopathological diagnosis of the lesions, and demographic data of the patients were recorded as numbers and percentages. SPSS version 22.0 was used for statistical analysis. Kolmogorov Smirnov test was used for normality analysis. Pearson's and Spearman correlation tests were utilized in normally and non-normally distributed data, respectively. Histopathological diagnosis was considered the gold standard diagnostic method. Accordingly, sensitivity, specificity, negative and positive predictive values, and accuracy rates of the examinations were calculated.

Results

A total of 121 lesions of 104 patients were examined. The mean age of the patients was 50.60 ± 8.83 (27-71) years. Sixty-two (59.6%) patients were in the premenopausal period. Ten (9.6%) of the patients had a risk factor.

According to MG and US BI-RADS, 70 (57.9%) were BI-RADS category 4a, 22 (18.2%) were BI-RADS category 4b and 29 (24.0%) were BI-RADS category 4c. MRI findings of these lesions are shown in Table 1.

Of the 121 BI-RADS category 4 solid lesions identified in US, 13 (10.7%) were upgraded, and 74 (61.2%) were downgraded after MRI. Of the 6 lesions upgraded to MRI BI-RADS category 5, one was category 4a and 5 were category 4c. Seven lesions were upgraded with MRI between category 4 subgroups, of these, 3 were upgraded from 4a to 4b, and 4, from 4a to 4c. With MRI, 17 of 74 lesions were downgraded to category 2, 44 lesions were downgraded to category 3, which did not require biopsy. Thirteen lesions were downgraded among category 4 subgroups and did not cause any change in clinical approach. MRI BI-RADS distribution according to BI-RADS category 4 subtypes is shown in Table 2.

Table 1: Distribution of lesions with MRI findings according to BIRADS subtypes

MRI findings	MG + US BI-RADS Categories		
	Category 4a (n=70)	Category 4b (n=22)	Category 4c (n=27)
Mass (n=95)	59 (84.3%)	15 (68.2%)	21 (72.4%)
Non-mass enhancement (n=8)	3 (4.3%)	2 (9.1%)	3 (10.3%)
Focus (n=18)	8 (11.4%)	5 (22.7%)	5 (17.3%)

MG: mammography, US; ultrasonography, MRI: magnetic resonance imaging, BI-RADS: breast imaging reporting and data system

Table 2: MRI BI-RADS classification of lesions according to MRI findings

MRI BI-RADS	MG + US BI-RADS Categories		
	Category 4a (n=70)	Category 4b (n=22)	Category 4c (n=29)
Category 1 (n=0)	---	---	---
Category 2 (n=17)	12 (17.1%)*	4 (18.2%)*	1 (3.5%)*
Category 3 (n=44)	30 (42.8%)*	9 (40.9%)*	5 (17.2%)*
Category 4a (n=32)	20 (28.6%)	3 (13.6%)*	9 (31.0%)*
Category 4b (n=10)	3 (4.3%)	6 (27.3%)	1 (3.5%)*
Category 4c (n=12)	4 (5.7%)	---	8 (27.6%)
Category 5 (n=6)	1 (1.5%)	---	5 (17.2%)

MG: mammography, US; ultrasonography, MRI: magnetic resonance imaging, BI-RADS: breast imaging reporting and data system

Seven of 13 upgraded lesions with MRI and three of 74 downgraded lesions were histopathologically diagnosed as malignant. Only one of these 3 lesions was downgraded into the group that did not require biopsy (BI-RADS category 3) (false-negative rate 1/74 = 1.3%) Histopathological classification of cases that had been upgraded or downgraded by MRI according to BI-RADS category 4 subtypes is shown in Tables 3.

Table 3: Histopathological results of MRI-upgraded and MRI-downgraded cases

MG + US BI-RADS Categories	Benign lesions							Malign lesions			
	FA	SA	IDP	Atypic IDP	ADH	FCD	other	IDC	DCIS	other	Total
MRI upgraded lesions											
Category 4a	2	1	1	0	0	0	1	2	1	0	8
Category 4b	0	0	0	0	0	0	0	0	0	0	0
Category 4c	0	1	0	0	0	0	0	3	0	1	5
Total	2	2	1	0	0	0	1	5	1	1	13
MRI downgraded lesions											
Category 4a	13	6	2	2	4	4	10	1	0	0	42
Category 4b	8	2	0	1	0	0	5	0	0	0	16
Category 4c	5	2	0	0	0	0	7	2	0	0	16
Total	26	10	2	3	4	4	22	3	0	0	74

MG: mammography, US: ultrasonography, BI-RADS: breast imaging reporting and data system, MRI: magnetic resonance imaging, FA: fibroadenoma, SA: sclerosing adenosis, IDP: intraductal papilloma, ADH: atypic ductal hyperplasia, FCD: fibrocystic disease, IDC: intraductal carcinoma, DCIS: ductal carcinoma in-sutu

Histopathological findings

According to the histopathological examination of 121 lesions' specimens obtained through US-guided core needle biopsies, 107 (88.4%) were benign and 14 (11.6%) were malignant. The distribution of histopathological examinations according to BI-RADS subtypes is shown in Table 4.

Due to clinical-pathological incompatibility, surgical excision was performed in 30 of 107 lesions which were diagnosed as benign in the core needle biopsy. Twenty-eight

(93.3%) of these lesions were diagnosed as benign and 2 (6.7%) were diagnosed as malignant.

Table 4: Histopathological distribution according to BIRADS subtypes

Pathological diagnosis	MG + US BI-RADS Category			MRI BI-RADS Category						
	4a	4b	4c	1	2	3	4a	4b	4c	5
Benign										
FA (n=35)	20	9	6	0	6	19	6	3	1	0
SA (n=20)	11	5	4	0	4	4	6	4	1	1
IDP (n=3)	3	0	0	0	0	2	0	0	1	0
A. IDP (n=4)	2	1	1	0	1	2	0	0	1	0
ADH (n=5)	5	0	0	0	0	4	1	0	0	0
FCD (n=4)	3	1	0	0	1	2	0	1	0	0
others (n=34)	20	6	8	0	5	10	15	2	1	1
Malign										
DCIS (n=1)	1	0	0	0	0	0	0	0	1	0
IDC (n=13)	5	0	8	0	0	1	4	0	5	3
others (n=2)	0	0	2	0	0	0	0	0	1	1
Total (n=121)	70	22	29	0	17	44	32	10	12	6

MG: mammography, US: ultrasonography, BI-RADS: breast imaging reporting and data system, MRI: magnetic resonance imaging, FA: fibroadenoma, SA: sclerosing adenosis, IDP: intraductal papilloma, ADH: atypic ductal hyperplasia, FCD: fibrocystic disease, DCIS: ductal carcinoma in-sutu, IDC: intraductal carcinoma

In total, 39 of 121 lesions underwent surgical excision. Sixteen of 18 (88.9%) lesions in BI-RADS category 4a were diagnosed as benign and 2 (11.1%) were malignant; all 4 lesions in BI-RADS category 4b were diagnosed as benign, and 8 of 17 (47.1%) lesions in BI-RADS category 4c were diagnosed as benign and 9 (52.9%) were diagnosed as malignant.

Sixty-four (91.4%) of the 70 lesions in BI-RADS category 4a were diagnosed as benign, 6 (8.6%) were diagnosed as malignant. All 22 lesions (65.5%) in BI-RADS category 4b and 29 BI-RADS category 4c lesions were diagnosed as benign, while ten (34.5%) BI-RADS 4c lesions were diagnosed as malignant.

In our study, the sensitivity, specificity, PPV, and NPV of MRI were 93.8%, 56.2%, 24.6%, and 98.3%, respectively. Two patient samples whose BI-RADS category was upgraded and downgraded as a result of the MRI examination were given in Figure 1 and Figure 2, respectively.

Figure 1: A 51-year-old female patient who had an operation history due to right breast invasive ductal carcinoma. a: A smooth solid lesion with minimal size increase was detected in the left upper outer quadrant in the follow-up ultrasonography (US), b: No vascularization was found in Doppler US, and considered as BI-RADS category 4a, c: On T2 weighted MRI images, the lesion was hyperintense, d: On Diffusion Weighted Images the lesion was hyperintense, e: The lesion was enhanced in postcontrast series, f: The time-contrast curve chart of the irregular margined lesion shows a plateau enhancement (type 2 pattern). (f: vertical axis indicates the percentage of enhancement, and the horizontal axis indicates the time in seconds). Due to irregular margins and enhancement pattern, the BI-RADS category of the lesion was upgraded to 5. Micropapillary type invasive ductal carcinoma was diagnosed with biopsy.

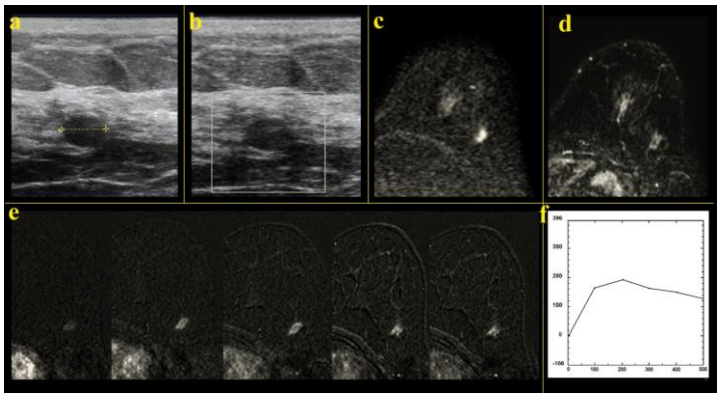
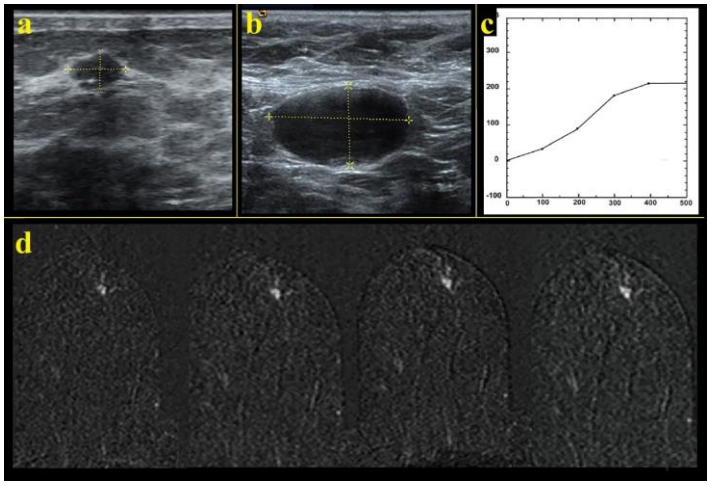


Figure 2: A 61-year-old female patient; an asymmetrically increased density in the retroareolar area of the right breast was found in routine follow-up mammography (MG). The patient was evaluated by ultrasonography (US), a: A solid lobulated contoured solid mass (BI-RADS category 4b) was detected in this region, b: In the ipsilateral axilla, a suspected lymphadenomegaly (LAM) was found, c: The lesion has a persistent enhancement (type 1 pattern) on time-contrast curve chart, d: Dynamic contrast T1W images showed the persistent enhancement of the lesion. Although the T2 hyperintensity and enhancement pattern indicate benignity, the lesion was accepted as BIRADS 4a due to the presence of axillary LAM. Biopsy was performed for suspicion of malignancy, and the lesion was reported as benign ductal hyperplasia and the axillary lymph node was reported as reactive lymphoid hyperplasia.



Discussion

In the present study, we determined that MRI provides a more accurate classification of BI-RADS category 4 solid lesions detected in US, and we think it can be used as a problem solver in the evaluation of these lesions. We found that MRI is more useful in detecting possible malignant findings and referring to biopsy when compared with MG and US. Therefore, problem-solving MRI may contribute to the prevention of unnecessary biopsies, especially for BI-RADS category 4a lesions, which are mostly benign.

BI-RADS category 4 lesions represent a wide range of imaging findings including solid mass with 2-95% malignancy risk, asymmetry, architectural distortion, and calcifications. With the addition of MRI images, mass or non-mass enhancement is also considered within this range. Because of the risk of malignancy, a generally accepted approach is to evaluate these lesions by biopsy [10, 11]. However, since the risk of malignancy is very low, especially in BI-RADS category 4a lesions, new approaches such as problem-solving MRI are needed to reduce the indication for invasive biopsy. In our study, we found that 74 of 121 (61%) breast masses in BI-RADS 4 as categorized by MG and US were downgraded by problem-solving breast MRI and 61 of the 74 downgraded lesions were classified as stage 2 or 3. In terms of BI-RADS category 4a, in 42 (60%) of 70 solid lesions, BI-RADS categories were downgraded to 2 and 3, which did not require biopsy. On histopathological examinations, three lesions were reported as malign in the downgraded group, and only one of them (1.6%) was in the benign spectrum (BI-RADS category 3) on MRI. The malignancy rate was 53.9% (7/13 lesions) in upgraded cases. These findings show that MRI determines the need for biopsy with greater accuracy and significantly contributes to MG and US.

Although studies with problem-solving MRI in breast imaging report some reservations, especially false-positive diagnoses, they are increasing day by day. However, the number

of studies on BI-RADS category 4 lesions is quite low. In our literature review, we did not find any studies conducted on solid lesions only. In almost all studies with BI-RADS category 4 lesions, MRI has a prominent advantage in the recognition of malignant-benign features [14-19]. In most of these studies, false negativity rates of MRI were almost 0% and this finding is very promising in terms of MRI evaluation reducing unnecessary invasive procedures. In the present study, only one patient had false-negative lesions with MRI and our negative predictive value was very high (98.4%), close to the literature. Strobel et al. [18] evaluated 353 BI-RADS category 4 lesions in 340 women with problem-solving MRI and concluded that MRI detected lesions better and reduced the need for biopsy. They found 100% negative predictive value in all cases except microcalcification clusters, without distinguishing solid lesions, and reported that diagnostic MRI could be an alternative assessment tool to biopsy. On the other hand, Giess et al. [19] reported that US has an important contribution in defining the lesion in patients with suspicious mammography findings. However, they stated that radiologists needed problem-solving MRI in 12% of cases despite US. They predicted that, in these cases, breast MRI differentiated malignancy with high sensitivity and negative predictive values and that the problem-solving MRI could reduce the need for biopsy.

The main concern for problem-solving MRI was that breast MRI was in the process of development and the lack of standardization in interpretation. However, in parallel with technological advances, the experience gained in the differentiation of benign-malignant lesions on breast MRI and specialization in this field indicate that it can be used to reduce biopsy indications [9, 17-19]. Another concern is that although MRI is useful in solving certain problems, false positivity values are high. In a study they conducted, Strobel et al. [18] reported that the rate of false positivity was 2.3% and they had benign but high-risk lesions (such as atypical ductal hyperplasia). While the PPV was 73% in the study of Strobel et al., it was reported as 31.9% in the study of Giess et al. [19]. In our study, false positivity rates remained at 24.6%, lower than the literature. This result may be due to interpretative differences, study design (especially lesion selection), high physician-patient anxiety, or local differences.

Limitations

Due to the retrospective planning of the study, there may be differences in the evaluation of images and lesion management among radiologists. The obtained sample may not have represented the real population completely since some lesions were not included in the study because biopsy or operation was performed without MRI due to different opinions and because some lesions were monitored only with US. Another limitation is that the predictions of breast MRI on all solid lesions cannot be determined due to the absence of BI-RADS category 3 and 5 solid lesions in the study. However, since BI-RADS category 3 and 5 lesions do not generally present a problem in BI-RADS classification, and because biopsy is recommended although a great majority of BI-RADS category 4 lesions are benign, these lesions were used in our study to prevent unnecessary biopsies.

Conclusion

In this study, breast MRI reduced the BI-RADS categories to 2 and 3 in approximately half of the BI-RADS category 4 solid lesions detected by ultrasound. Therefore, we think that problem-solving MRI may be useful to avoid unnecessary invasive procedures in these patients.

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Clinical examination and fundus photography in diabetic retinopathy screening

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Ethics Committee Approval
Adnan Menderes University Faculty of Medicine Ethics Committee approved the study [Protocol No: 2016/927].
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: An increasing number of patients and an ophthalmologist shortage in some areas necessitate reaching more patients in a shorter time to decrease the burden of devastating visual complications of diabetic retinopathy (DR). Screening and diagnosing DR using fundus photographs may save time and effort. In this study, we aimed to report the results of DR screening in a Turkish treatment-naive diabetes mellitus (DM) patient group by examining fundus photographs taken with ETDRS protocol and compare them with clinical examination and optical coherence tomography (OCT) findings.

Methods: Two hundred and ninety-two eyes of 150 DR treatment-naive DM patients were included in this cross-sectional study. Complete ophthalmic examination was performed by a single examiner. Fundus photograph acquisition according to ETDRS protocol and OCT were performed by an experienced technician. Fundus photographs were evaluated by the same examiner who was blinded to patient names, at the end of the study period.

Results: Two hundred and ninety-two eyes of 150 DR treatment-naive DM patients' findings were evaluated. According to stereoscopic fundus examination, 76 (26%) eyes showed no signs of DR, 76 (26%) eyes showed mild non-proliferative diabetic retinopathy (NPDR) signs, 44 eyes (15.1%) showed moderate NPDR signs, 78 eyes (26.7%) showed severe NPDR signs, and 18 eyes (6.2%) showed PDR signs. According to images acquired with the ETDRS protocol, 79 (27.1%) eyes showed no signs of DR, 81 (27.7%) eyes showed mild NPDR signs, 50 eyes (17.1%) showed moderate NPDR signs, 68 eyes (23.3%) showed severe NPDR signs, and 14 eyes (4.8%) showed PDR signs. Clinical examination and fundus photography showed substantial agreement in detecting DR severity (Kappa value: 0.78, $P<0.001$). Diabetic macular edema (DME) was present in 106 and 68 eyes according to OCT and ETDRS fundus photographs, respectively. These two methods showed moderate agreement in detecting DME (Kappa value: 0.57, $P<0.001$). ETDRS fundus photography is an effective method for screening DR severity in a Turkish DR population. When patients with no evident DR findings were excluded, we found a statistically significant negative correlation ($P<0.001$, Spearman Rho coefficient: -0.306) between central retinal thickness and best-corrected visual acuity, as expected.

Conclusion: For screening DR severity, ETDRS fundus photography is an effective method in a Turkish DR population.

Keywords: Diabetic retinopathy, Optical coherence tomography, Clinical examination, Fundus photography

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Introduction

Diabetes Mellitus (DM) is a chronic disease caused by ineffectiveness or deficiency of the insulin hormone [1]. Long-term hyperglycemia causes damage leading to loss of function and insufficiency [2]. Diabetic retinopathy (DR) is the leading cause of legal blindness all over the world [3]. DR prevalence is 34.6% in DM patients aged over 40 years, whereas sight-threatening DR prevalence is %10.2 in the same population [4, 5]. The most important risk factor for DR is the duration of the disease [6]. Once DR begins, glycemic control outweighs disease duration for predicting progression [7, 8]. Recommended first eye examination is the moment of diagnosis for type 1 and five years after the diagnosis for type 2 DM [9].

Despite advanced DR stages, patients can still have good visual acuity. The increasing number of patients necessitates reaching more patients in a shorter time. In this study, we aimed to compare clinical examination, optical coherence tomography (OCT), and fundus photography findings of treatment-naive DM patients. Also, OCT findings were evaluated with respect to DR stage and HbA1C levels.

Materials and methods

In this prospective study, treatment-naive 150 DM patients with DR were enrolled from the Endocrinology department.

Spearman correlation coefficient calculated from the diabetic retinopathy staging table in the "Nonmydriatic Ultrawide Field Retinal Imaging Compared with Dilated Standard 7-Field 35-mm Photography and Retinal Specialist Examination for Evaluation of Diabetic Retinopathy" study was used for power analysis at a tolerance rate of 7%, alpha value of 0.05 and statistical power of 0.80. Based on the results, at least 123 cases were needed.

Patients with DR treatment history, posterior segment pathologies other than DR, posterior segment surgery history, media opacity blocking fundus view were excluded from the study. Age, gender, duration of DM, a medication used for DM and duration of usage, HbA1C levels within the last three months of enrolment, and other systemic diseases were recorded. A complete ophthalmologic examination including best-corrected visual acuity (BCVA), intraocular pressure (IOP) anterior segment, and dilated fundus examination findings were recorded by one ophthalmologist. One technician performed OCT scans and took fundus photographs according to the ETDRS protocol. Dilated fundus findings were recorded using a +90D lens by one ophthalmologist. International clinical diabetic retinopathy disease severity scale (10) was used for grading DR. After dilated fundus examination, an experienced technician performed OCT scans and took fundus photographs with Kowa VX-20 (Kowa Company, Ltd, Aichi, Japan) according to the ETDRS protocol. Fundus photographs were evaluated at the end of the patient enrolment period by the same ophthalmologist blinded to the patient names. OCT scans were performed in a dusky room with Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA, USA) macular cube 512x128 protocol. Scans with a signal strength of 7/10 or more were recorded for evaluation. Central retinal thickness (CRT) values were recorded from OCT scans. HbA1C levels were obtained from endocrinology records. DR grades decided with dilated fundus examination and fundus photographs were compared. Consistency between OCT and examination findings was analyzed.

Statistical analysis

For statistical analysis, Statistical Package for the Social Sciences 17 [SPSS] program was used. For the analysis of quantitative data, compatibility with normal distribution was examined with the Kolmogorov-Smirnov test; parametric methods were used in the analysis of variables with normal distribution, and non-parametric methods were used in the analysis of variables without normal distribution. The Mann-Whitney U test was used to compare independent binary groups. Spearman Rho test was used to examine the correlations of quantitative data with each other. In the comparison of categorical data, the Pearson Chi-square test was used. Quantitative data are expressed in the tables as mean (standard deviation). Categorical data are expressed in numbers (n) and percentages (%). The data were analyzed at a 95% confidence level and a *p*-value of less than 0.05 was considered significant. The agreement of DR stages between the methods was transferred to the crosstab. Kappa values were calculated and interpreted according to the Landis and Koch classification (0-0.20, slight, 0.21–0.40, fair, 0.41–0.60, moderate, 0.61–0.80, substantial, 0.81–1.00, almost perfect). For every patient included in the study, written informed consent was obtained. Adnan Menderes University Faculty of Medicine Ethics Committee approved the study [Protocol No: 2016/927]. This study was performed in line with the principles of the Declaration of Helsinki.

Results

Two hundred and ninety-two eyes of 150 patients (79 females (52.6%), 71 males (47. 4%)) were enrolled. Only one eye was included in eight patients. The mean age of the patients was 61.71(8.85) years. The mean duration of DM was 12.02(7.2) years and mean HbA1C levels within the last three months were %6.96 (1.27). Seventy-eight (%52) patients were using oral antidiabetic agents only, while 72 patients (48%) were on insulin. The mean best-corrected visual acuity (BCVA) of the whole patient group was 0.64 (0.30) and the mean intraocular pressure (IOP) measured with a pneumatic tonometer was 15.36 (2.90) mmHg (Table 1).

Table 1: Patient demographics according to DR severity and overall patient group

		Diabetic Retinopathy Severity					
		No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Overall
Age	Mean	59.63	64.42	63.16	60.99	58.28	61.69
	SD	7.89	8.23	8.05	10.46	5.92	8.85
HbA1c	Mean	6.47	6.96	7.22	7.08	7.31	6.92
	SD	1.26	1.28	1.15	1.12	1.67	1.27
Visual Acuity	Mean	0.84	0.68	0.55	0.51	0.46	0.64
	SD	0.22	0.28	0.27	0.31	0.31	0.30
IOP	Mean	16.03	15.88	14.48	14.91	14.39	15.36
	SD	2.80	3.40	2.45	2.67	1.97	2.90
DM Duration	Mean	8.97	12.50	11.66	14.19	15.28	12.08
	SD	7.08	6.80	6.76	7.31	6.11	7.23
	N	76	76	44	78	18	292

DR: Diabetic retinopathy, NPDR: non-Proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, HbA1c: Hemoglobin A1c, IOP: Intraocular pressure, DM: Diabetes mellitus, SD: Standard deviation

According to stereoscopic fundus examination, 76 eyes (26%) showed no signs of DR, 76 eyes (26%) showed mild non-proliferative diabetic retinopathy (NPDR) signs, 44 eyes (%15.1)

showed moderate NPDR signs, 78 eyes (%26.7) showed severe NPDR signs and 18 eyes (6.2%) showed proliferative diabetic retinopathy (PDR) signs. According to images acquired with the ETDRS protocol, 79 eyes (27.1%) showed no signs of DR, 81 eyes (27.7%) showed mild NPDR signs, 50 eyes (17.1%) showed moderate NPDR signs, 68 eyes (23.3%) showed severe NPDR signs, and 14 eyes (4.8%) showed PDR signs. According to Field 2 image acquired with ETDRS protocol, 98 eyes (33.5%) showed no signs of DR, 84 eyes (28.8%) showed mild NPDR signs, 52 eyes (17.8%) showed moderate NPDR signs, 48 eyes (16.4%) showed severe NPDR signs, and 10 eyes (3.4%) showed PDR signs. Clinical examination and ETDRS fundus photographs showed a significant substantial agreement in detecting DR severity (Kappa value: 0.78 $P<0.001$) (Table 2).

Diabetic macular edema (DME) was diagnosed in 106 eyes with OCT, while 100 eyes had DME according to stereoscopic fundus examination. The sensitivity and specificity of detecting DME with stereoscopic fundus examination were 76.4% and 89.8%, respectively (Table 3). These two methods showed substantial agreement in detecting DME (Kappa value: 0.67; $P<0.001$). According to images acquired with the ETDRS protocol, 68 eyes were diagnosed with DME. When compared with the OCT data, these two methods showed a significant moderate agreement in detecting DME (Kappa value: 0.57, $P<0.001$).

Table 2: Cross-tabulation of diabetic retinopathy (DR) severity staging with clinical examination and ETDRS fundus photography

			Clinical Examination Stage					
			No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Total
ETDRS Fundus Photography Stage	No DR	N	69	8	2	0	0	79
		%	90.8%	10.5%	4.5%	0.0%	0.0%	27.1%
	Mild NPDR	N	7	62	7	5	0	81
		%	9.2%	81.6%	15.9%	6.4%	0.0%	27.7%
	Moderate NPDR	N	0	6	34	8	2	50
		%	0.0%	7.9%	77.3%	10.3%	11.1%	17.2%
	Severe NPDR	N	0	0	1	65	2	68
		%	0.0%	0.0%	2.3%	83.3%	11.1%	23.3%
	PDR	N	0	0	0	0	14	14
		%	0.0%	0.0%	0.0%	0.0%	77.8%	4.7%
Total		N	76	76	44	78	18	
		%	100.0%	100.0%	100.0%	100.0%	100.0%	

DR: Diabetic retinopathy, NPDR: non-Proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, ETDRS: Early treatment diabetic retinopathy study

Table 3: OCT and clinical examination cross-tabulation for DME detection

			OCT		Total
			Normal	Edema	
Clinical Examination	Normal	N	167	25	192
		%	89.8%	23.6%	65.8%
	Edema	N	19	81	100
		%	10.2%	76.4%	34.2%
Total		N	186	106	292
		%	100.0%	100.0%	100.0%

OCT: Optical coherence tomography

Central retinal thickness (CRT) and BCVA had an insignificant negative correlation (Spearman Rho coefficient: -0.104) ($P=0.076$). When patients with no evident DR findings were excluded, a statistically significant negative correlation ($P<0.001$, Spearman Rho coefficient: -0.306) was found between CRT and BCVA.

The mean HbA1c levels of patients were 6.0% (5.7-6.7) in those with no apparent DR findings, 6.8% (6.1-7.47) in the mild NPDR, 7.1% (6.3-8.2) in the moderate NPDR, 7.05% (6.5-7.3) in the severe NPDR and 7.4% (5.82-8.1) in the PDR groups. HbA1c levels of the no apparent DR findings group were lower than those of all other groups (mild $P=0.013$, moderate $P<0.001$, severe $P<0.001$, and PDR $P=0.023$).

Median CRT of patients with no apparent DR findings was 253.5 µm (237.25-276), while they were 262 µm (239-331.75) in the mild NPDR, 280.5 µm (245.25-357) in the moderate NPDR, 258 µm (224-299.75) in the severe NPDR and 308.5 µm (250.5-384.5) in the PDR groups. As we compared median CRT of patients with respect to DR stages, we found a significant difference ($P=0.044$) between PDR and no apparent DR findings groups.

According to DR stages, the median BCVA of patients with mild, moderate, and severe NPDR, PDR and no apparent DR findings were 0.7 (0.5-0.9), 0.6 (0.32-0.70), 0.5 (0.2-0.8), 0.55 (0.1-0.72) and 1.0 (0.7-1.0), respectively. Patients with no apparent DR findings had better BCVA than patients with moderate NPDR ($P<0.001$), severe NPDR ($P<0.001$), and PDR ($P<0.001$). Also, patients with mild NPDR had better BCVA than those with severe NPDR ($P=0.01$).

A significantly low negative correlation was found between BCVA and HbA1C levels of patients (Spearman Rho: -0.159, $P=0.006$). BCVA was compared according to the drug used for DM regulation. BCVA of the patients in the insulin group was significantly lower than those in the OAD group ($P<0.001$). The HbA1C values of the group using insulin for DM regulation were higher than those using OAD, as expected ($P<0.001$). The CRT retinal thickness values of the insulin users were higher than those of OAD users ($P=0.036$).

Discussion

The number of patients with DM is increasing day by day. It is predicted that the prevalence will approach 600 million in 2035 and a potential diabetes epidemic could develop in Asia [11]. Diabetic retinopathy, which is the most common cause of vision loss and preventable blindness in the working-age group in developed countries, also increases among all causes of visual loss [12, 13]. Considering the incidence of DM and predictions, DR-related complications can lead to serious loss of labor and an increase in treatment costs in the working-age group [14]. Besides, as a result of DR, patients' quality of life can decrease. In the absence of other serious complications due to DM, the quality-of-life score was significantly lower in 148 patients with DR compared to the control group [15].

The UK National Institute of Clinical Excellence reported that the test to be used for DR screening should have a sensitivity of at least 80% and a specificity of at least 95% [16]. Defined by the ETDRS group, stereoscopic colored fundus photographs taken from seven areas is the gold standard photography method in DR screening [17]. This method has been reported to be useful in detecting areas of DME and small neovascularization [18]. This method is a little more time-consuming than wide-angle and very wide-angle fundus photography. However, the quality of wide-angle and very wide-angle fundus photographs taken without dilatation can be reduced in media opacities and small pupillary openings [19]. Very wide-angle fundus photography may be timesaving but may lead to misinterpretations due to reduced image quality. As a result, the patient may be diagnosed with a lower or higher stage than the fundus findings. Depending on this, unnecessary

treatment can be started or there may be a delay in receiving the necessary treatment.

In his study, Vujosevic et al. [20] compared the results of single and multiple digital colored non-mydriatic retinal images in DR screening with fundus photographs taken according to the ETDRS protocol. The Kappa agreement value was 0.56 for evaluating the DR severity of ETDRS fundus photographs and single retinal images. In our study, the kappa agreement value of the ETDRS fundus photograph taken from the fovea was 0.68 for DR staging. This value shows a statistically significant agreement. In our study, the reason for the higher agreement value can be explained by pupillary dilation.

OCT can provide detailed information about retinal thickness with high reproducibility. Browning et al. compared the relationship between retinal thickness and BCVA in 251 eyes with DME of 210 patients. According to the results, a moderate correlation was found between BCVA and OCT central retinal thickness. Although there was a moderate correlation in the discussion section, there was a significant variation in the BCVA of patients with similar or equal retinal thickness. Better BCVA was found in many eyes with relatively high retinal thickness, while lower BCVAs were detected in many eyes with near-normal retinal thickness [21]. Considering this data, it may not be correct to comment on BCVA with central retinal thickness only. In our study, there was no statistically significant correlation between central retinal thickness and BCVA (P=0.076, Spearman Rho coefficient: -0.104). However, in patients with DR findings at any stage, there was a statistically significant negative correlation between central retinal thickness and BCVA (P<0.001, Spearman Rho coefficient: -0,306). It should be kept in mind that other retinal pathologies might be present in DM patients, which may decrease BCVA levels, except for central retinal thickness increase.

In a study in which the effects of macular ischemia on BCVA were investigated by Sim et al. among DR patients, ischemia in the papillomacular retinal nerve fiber band had a strong relationship with low BCVA regardless of the foveal avascular zone and macular edema [22]. As seen in the study by Sim et al. [23], there is not always a significant relationship between central retinal thickness and BCVA, depending on other factors. In our study, in patients with DR findings at any stage, we found a significant but low negative correlation (P<0.001, Spearman Rho coefficient: -0.306) between central retinal thickness and BCVA. In our study, the correlation between BCVA and central retinal thickness may be low depending on the presence of patients with low BCVA due to ischemia. In the guideline published by AAO for DR in 2016, evaluation with FFA is recommended in presence of unexplained poor BCVA with fundus examination and OCT findings. It is predictable to increase the correlation between BCVA and central retinal thickness when excluding patients with ischemia with FFA.

In the study of Nunes et al. [24], the correlation between increased retinal thickness and BCVA in patients with CSME was evaluated in 62 eyes. The eyes included in the study were grouped according to the presence of retinal thickening in the central 500-µm area. In 19 eyes, there was no increase in retinal thickness in the central 500-µm area; there was no correlation between retinal thickness and BCVA in these eyes (R = 0.062). A moderate correlation was found between the BCVA and retinal thickness in 43 eyes with an increase in retinal thickness in the central 500-µm area (R = -0.459). In this study, it was reported that the correlation between retinal thickness and BCVA was found in 48.8% of patients even if there was an increase in retinal thickness in the central 500 µm area. In addition, there was no correlation between retinal thickness and HbA1C levels in this study. Although retinal thickness measurements with OCT provide useful information about macular edema, it is not a reliable marker alone in the evaluation of visual loss. In addition, the status of photoreceptor cells in the areas with macular edema is also effective on BCVA.

In a study conducted by Özdek et al. [25], 195 eyes of 110 DM patients were evaluated with OCT, FFA, and clinical examination. In this study, there was an increase in retinal thickness in 148 eyes with OCT; clinical examination revealed a retinal thickness increase in 112 eyes. Compliance of DME findings obtained from OCT with clinical examination was 77%. In our study, this ratio was 76.4%. In the study performed by Özdek et al., 36 eyes (24.3%) had retinal thickening in OCT while clinical examination did not reveal any. In our study, 25 of 106 eyes (23.6%) with retinal thickening in OCT were missed during fundus examination. Clinical examination is an effective method for detecting DME. However, in patients with suspected DME in clinical examination, evaluation should be performed with OCT.

Hyperglycemia is one of the most important risk factors for the development of DR and DME. In a meta-analysis of three broad population-based studies, a gradual relationship was found between the level of glycemia and the incidence of retinopathy [26]. Strict glycemic control (Hb1C <7%) has been reported to reduce the risk of DR development and progression in both type 1 and type 2 DM patients [27]. In our study, in 128 eyes of 66 patients with HbA1C values above 7%, PDR (9.4%) was found in 12 eyes and severe PODR (32.8%), in 42 eyes. PDR was detected in 6 eyes of 164 eyes of 84 patients with HbA1C value below 7% and severe PODR was found in 22 eyes (22%). According to the data obtained from our study, the DR severity phase of the patients increased with HbA1C levels. According to these data, our study also found that HbA1C levels are an important marker for DR development and progression.

Browning et al. compared the relationship between retinal thickness and severity of DR in 383 eyes of 383 patients. Patients with no apparent DR findings, mild NPDR, moderate NPDR, severe NPDR and PDR findings and those with retarded PDR findings had a central retinal thickness of 208(22), 198(25), 204(26), 224(38), and 205(27) µm, respectively. As the severity of DR increased, the likelihood of an increase in macular thickness was also reported to increase. While 15% of eyes with severe NPDR and PDR findings did not show edema in the clinical examination, macular thickening was detected by OCT. In our study, central retinal thickness measurements were 257(30), 290(81), 311(100), 271(82), and 335(115) µm for patients with mild NPDR, moderate NPDR, severe NPDR, and PDR, respectively [28]. In 5.2% of eyes with severe PODR and PDR findings, clinical examination revealed no signs of edema, but retinal thickening was detected with OCT.

In a multi-center prospective study conducted by Garcia-Serrano et al. in Spain, 8244 DM patients were compared in terms of indirect ophthalmoscope and DR screening results after pupil dilatation. The rate of participation in the screening program was 84.1% [29]. Among all, 91.3% of patients had undergone fundus examination at least once. 3.4% of patients were referred to a hospital for treatment. The total cost of the screening program was €53173 and the average cost per patient was 8.87 €. With the help of the screening program, it was predicted that vision loss was delayed for four years after the treatment of 93 patients who needed laser treatment [30]. Considering the possible loss of labor and treatment costs, it was concluded that the total cost of treatment and loss of labor force in two working patients were above the budget used for screening of 8244 patients in this study. Garcia Serrano et al. emphasized the need to create regular screening programs to prevent visual loss due to DR. With the awareness of individuals at risk, it is possible to achieve significant gains both in terms of community health, treatment costs, and labor loss.

Conclusions

In our study, clinical examination and fundus photographs taken according to the ETDRS protocol are suitable methods for detecting and evaluating DR severity. Dilated fundus examination is the method of choice for determining the severity of DR. The fundus photographs taken with the ETDRS protocol is another effective method for DR staging. In our study, these two methods showed significant agreement. Field 2 fundus photography in the ETDRS protocol showed moderate agreement with clinical examination. This method is also useful for detecting the severity of DR, although not as effective as the ETDRS protocol.

OCT is gaining value in the diagnosis of DME. Findings obtained by OCT detect minimal thickness increases that cannot be detected by fundus examination. It also provides quantitative data to compare with the previous findings during patient follow-up. The diagnosis of DME based on the clinical examination and OCT findings showed a statistically significant agreement. The clinical examination showed a sensitivity of 76.4%, specificity of 89.8%, and accuracy of 84.8% in detecting DME. The fundus examination performed after the pupil dilatation showed that an increase in OCT was detected in a significant portion of the cases with retinal thickness.

Considering the increasing number of DM patients, prompt diagnosis and initiation of treatment are of vital importance to prevent possible vision loss. Delays in treatment increase the number of patients in need of care as well as the risk of loss of workforce. In the diagnosis of DR and DME, there is a need for screening programs with high sensitivity and patient compliance, which can be applied quickly to the population at risk with high sensitivity and specificity.

The most prominent strength of our study is the evaluation of treatment-naive DM patients. Evaluation of fundus photographs and examination of patients were conducted by one ophthalmologist. Although the ophthalmologist was blinded to the patient data, an independent observer might have been a better option.

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Cytogenetic analysis in couples with recurrent pregnancy loss

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Recurrent pregnancy loss (RPL), described as the loss of two or more pregnancies before 24 weeks of pregnancy, remains a concern for both the couples and the clinicians. Genetic factors tend to be strongly linked to reproductive failure among different etiologies. Our goal was to determine the rates and kinds of chromosomal defects in couples who had repeated pregnancy losses and a history of miscarriage in the first trimester.

Methods: This cross sectional study was conducted at a single tertiary center over a 3-year period. Couples who visited the outpatient clinic due to recurrent pregnancy loss and underwent tests to investigate the etiology were included in the study. Ages, number of abortions and genetic results of the patients were recorded. A total of 253 pairs had been tested for karyotype. Conventional cytogenetic method was used to identify chromosomal aberrations.

Results: Of 506 cases, chromosomal abnormalities were present in 15 (2.9%). Women were more frequently affected than men, with prevalences of 1.9% and 0.98%, respectively. Eight of the 15 cases (53.3%) showed structural deviations and 2 (13.3%) had numerical abnormalities. Additionally, 5 (33.3%) individuals were found to have chromosome variants.

Conclusion: Pregnancy loss is a major adverse life event, and the recurring nature of RPL can intensify the grief experienced. Aside from routine analyses of couples on anatomical, endocrine, and infection factors, these findings suggest that cytogenetic testing is required for an accurate approach to determine the cause of recurrent miscarriages.

Keywords: Chromosomal abnormalities, Cytogenetics, Recurrent pregnancy loss, Translocation

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Introduction

The term "pregnancy loss" refers to the spontaneous termination of a pregnancy before the fetus reaches viability. The phrase encompasses all miscarriages from conception to the 24th week of pregnancy [1]. There has been considerable debate in the literature about the definition of recurrent pregnancy loss (RPL) and, more specifically, to what extent this definition should be expanded or narrowed depending on the number of losses and whether they are consecutive. The number of pregnancy losses needed to meet the requirements for recurrent miscarriage is unknown, but ESHRE guidelines classify RPL as the loss of two or more consecutive pregnancies before 24 weeks of gestation [2]. This definition includes both spontaneous conception and pregnancy losses after ART but excludes ectopic and molar pregnancies and implantation failure. However, some researchers feel that even a spontaneous loss deserves consideration. RPL affects about 15% of births and concerns 1% of the general population [3].

It's difficult to pinpoint the exact cause of RPL because of its multifactorial existence. Despite comprehensive research over a decade to determine the underlying causes, the exact cause of pregnancy loss is only known in around half of the cases. After that, 50% of couples are diagnosed with idiopathic or unexplained RPL [4]. Uterine malformations, thrombophilic disorders, infections, immune dysfunction, multiple endocrine disorders, and parental chromosomal anomalies have all been suggested as contributing factors to pregnancy loss, either alone or in combination. Genetic factors tend to be strongly linked to reproductive failure through a variety of etiologies [5, 6]. Chromosomal etiology is very common in miscarriages, with chromosome abnormalities in the fetus accounting for 29 percent to 60 percent of abortions in the first trimester. A chromosomal abnormality in a partner affects between 3% and 6% of RM pairs, which is ten times higher than in the general population [7]. This chromosomal abnormality has been linked to either a balanced reciprocal translocation carrier parent or a recurrent numerical abnormality that is not normally inherited but can lead to recurrent miscarriages. Furthermore, carriers of chromosomal rearrangements are more likely to produce dysfunctional gametes, which can result in infertility, RPL, and malformations in infants. Balanced reciprocal translocation, Robertsonian translocation, gonosomal mosaic, and inversions are all examples of karyotype changes [8, 9].

While significant chromosomal anomalies and balanced chromosomal rearrangements found in couples who experience recurrent pregnancy loss are recognized as valid etiologies, the utility of preimplantation genetic diagnosis (PGD) is debatable. Fischer et al. [10], on the other hand, proposed that PGD would favor pregnant carrier couples with a history of RPL, increasing the likelihood of a healthy pregnancy significantly. While few structural rearrangements occur spontaneously, the majority tend to be hereditary, so couples with more than two pregnancy losses should undergo cytogenetic analysis and receive genetic counseling to rule out the likelihood of structural rearrangement.

The study's aim was to find out the rate and kinds of chromosomal defects in couples with recurrent pregnancy loss and a history of first-trimester miscarriage.

Materials and methods

This was a retrospective study at a single tertiary center over a 3-year period. The present study was approved by Süleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee (05.04.2017 -73). Couples who visited to the outpatient clinic due to recurrent pregnancy loss (2 or more pregnancy losses) and underwent testing to investigate the etiology were included in the study. Ages, number of abortions and genetic results of the patients were recorded. A total of 253 pairs had been tested for karyotype. All patient samples were subjected to chromosome analysis using peripheral blood. Ordinary cytogenetic procedures were used to prepare metaphase chromosome preparations from peripheral blood cultures. RHG banding was used to conduct cytogenetic research. All patients had 20 metaphases examined, but anomalies and mosaic states required the study to be expanded to 50 metaphases. The chromosomal anomalies have been identified according to the International Human Cytogenetic Nomenclature System (ISCN 2009).

Results

The study included 253 couples (506 cases) with a history of recurrent miscarriage. The female and male partners' median ages were 33.94 (0.70) years and 35.61 (3.94) years, respectively. The number of recurrent abortions per pair ranged from 2 to 7 (Table 1). Chromosomal abnormalities were found in 15 cases (2.9 percent). Women were affected more frequently than men, with prevalence rates of 1.9 percent and 0.98 percent, respectively. Eight of the fifteen cases (53.3 percent) had structural deviations, and two (13.3 percent) had numerical deviations. Additionally, 5 (33.3 percent) individuals were found to have chromosome variants. Among the structural abnormalities that make up the largest group of chromosome anomalies, reciprocal translocations including chromosomes 1, 2, 7, 11, and 21 were observed in 3 cases. In one case, robertsonian translocation including chromosomes 13, 14 was observed. Inversion in chromosome 8 was observed in 3 cases. One of the 2 cases with numerical anomaly had mosaic with monosomy 45 X and the other had 47 XXX karyotype. In addition to these main chromosomal anomalies, pericentric inversion of chromosome 9 was observed in 4 cases. Chromosomal anomalies detected in patients are summarized in Table 2.

Table 1: Demographic data of patients

The median age of the female partner (yr)	33.94(0.70)
The median age of the male partner (yr)	35.61(3.94)
The mean body mass index for females	21.7(1.4)
The mean body mass index for males	19(1.2)
The mean number of abortions	2.3(0.8) (2 to 7 abortions/pairs)
The percentage of consanguineous marriages among couples	22.5%

Table 2: Cytogenetic findings of patients

Cytogenetic findings	Number of miscarriages	Maternal/paternal age
46 XY t(1,2) (p36,p23)	7	34
46 XX t(7,21) (p22,q22)	3	28
46 XX t(1,11) (p3,q13)	3	26
45 XX rob (13,14) (q10,q10)	4	36
47 XX+mar	2	33
46 XX inv (8) (q22q24.3)	3	24
46 XX inv (8) (p23q13)	5	29
46 XY inv (8) (p23q13)	5	37
47 XXX	3	27
Mos 45 X (5)/46, XX (25)	2	25
46 XX inv (9) (p11q13)	4	31
46 XX inv (9) (p11q13)	2	28
46 XY inv (9) (p11q13)	3	37
46 XY inv (9) (p11q13)	2	29
46 XX 13ps+	2	30

Of the 253 couples, 57 (22.5%) were consanguineous marriages. One pair with chromosomal anomaly was consanguineous marriage, and inv 8 (p23q13) karyotype was observed in this couple.

Discussion

The inefficiency of human reproduction is evidenced by the fact that a large percentage of all pregnancies do not succeed in a live birth. Miscarriage occurs in approximately 15-20% of all clinically recognized pregnancies, and total pregnancy loss is predicted to be 30% -50% [11]. The cause of most miscarriages before 12 weeks of pregnancy can be attributed to fetal aneuploidy.

For both the patient and the clinician, recurrent abortion remains a daunting process. In the first and second trimesters, chromosomal defects are the most common cause of spontaneous abortions, with a prevalence of approximately 70% during the first 6 weeks, 50% before 10 weeks, and 5% after 12 weeks [12]. The majority of fetal chromosome defects are de novo, according to numerous cytogenetic studies, and parental karyotypes appear normal. Various research, on the other hand, have been performed to assess the prevalence of chromosomal defects among couples who have had repeated miscarriages. This prevalence varies between 2.7 and 13.9 percent [13, 14]. These discrepancies may be due to variations in sample size and requirements.

The products of conception in translocation carrier pairs may have a regular karyotype, a balanced structural chromosome abnormality, or an unbalanced structural chromosome abnormality. The final scenario will result in a fetus being miscarried, a child being stillborn, or a child being born with serious congenital defects and significant mental disabilities [15].

The inversion of chromosome number 9 occurs with a high frequency of structural heteromorphism, a natural variation that is inherited by the family as a mendelian trait. Despite widespread disagreement, most cytogeneticists conclude that this variation is a harmless chromosomal polymorphism of the standard human karyotype [16]. The incidence is projected to be 1-3 percent of the general population, with Asians having the lowest rate with 0.25 percent. Among various species, inv (9) (p11q12) and inv (9) (p11q13) are the most common [17]. It's debatable whether heteromorphism will cause disease. Inv (9) has been linked to infertility and multiple abortions, according to Ueharas et al. [18]. Rodriquez et al. [19] believed Yq + was not linked to birth failure, while Genest et al. [20] assumed Yq + was linked to repeated miscarriages. In addition to habitual abortion, chromosome 9 inversions have also been associated with other diseases such as schizophrenia, bipolar disorders, mental retardation, hermaphroditism, obstetric infertility, and undescended testis [21, 22]. Infertility, repeated miscarriages, hydatidiform molar pregnancies, azoospermia, congenital abnormalities, growth retardation, and its association with irregular phenotype have all been recorded [23,24]. Garcia-Peiró et al. [25] investigated the sperm DNA integrity of a male patient with infertility and inv (9) karyotype and discovered high sperm DNA fragmentation, considerable meiotic changes, abnormal aneuploidy, and abnormal seminogram parameters, all of which can cause chromosomal imbalance in the generation. The higher incidence of Down syndrome and other abnormalities in the lineage of these carriers have been documented [26]. Although polymorphic variants containing pericentric inversions of chromosomes 9 and Y are said to be common in the general population, chromosomal inversions and polymorphic variants in recurrent pregnancy loss must be considered to determine future risk and provide better genetic counseling.

The most common chromosomal abnormalities found in this study, as recorded in other studies, are structural chromosomal abnormalities. According to the literature, chromosomal structural disorders affect 0.7 percent of the normal population, 2.2 percent of which had a miscarriage once, 4.8 percent of which had a miscarriage twice, and 5 percent of which had miscarriages three times [6, 9]. Translocations (reciprocal translocations, Robertsonian translocations, inversions, deletions, and duplications) are the most common structural chromosomal abnormalities in recurrent miscarriages [1, 3]. Balanced translocation prevalence among couples ranges from recurrent miscarriage to 0-31% in different studies. When one partner of a couple has a balanced chromosome translocation, the chances of miscarriage nearly double. A balanced translocation in a partner is found in 3-5 percent of couples who have recurrent miscarriages [6, 9, 15].

The male to female ratio of chromosomal rearrangement in our sample was 1: 2. Female predominance appears to be because chromosome abnormalities in fertile females may be linked to male infertility. Testart et al. [27] reported a higher frequency of translocation and inversion (3.6: 1) in men compared to women in a study conducted in couples who received intracytoplasmic sperm injection treatment. Due to poor mobility recorded in spermatozoa with a high prevalence of structural chromosome abnormalities, male reciprocal translocation carriers may expect a lower fertility rate.

Many Middle Eastern and Arab cultures and communities, including our own, practice consanguineous marriage. Because of the development of autosomal recessive gene mutations inherited from a shared ancestor, offspring of consanguineous relationships may be at a higher risk for genetic disorders. The more closely the parents are related biologically, the more likely their children would inherit similar copies of one or more harmful recessive genes. For example, first cousins are thought to share 12.5 percent (1/8) of their genes. As a result, their descendants would be homozygous (or, more specifically, autozygous) at 6.25 percent (1/16) of their gene loci on average (that is, they will receive identical copies of the gene from each parent at these sites in their genome). As determined in various studies, the rate of abortion among related couples is significantly higher compared to unrelated couples [28, 29]. It may not be possible to find the gene locus associated with poor obstetric outcome with standard karyotype analysis. As advanced genetic analysis becomes widespread, it may be possible to obtain PGD support by revealing the genetic defects in these couples.

Finally, our findings support previous research [3-6] that found an increase in the number of balanced chromosomal translocations in couples who have had two or more miscarriages compared to the general population. Couples with RPL are less likely to have numerical chromosomal anomalies. Sex

chromosome aneuploidy is the most common type of these anomalies, which occur infrequently.

Limitations

The limitations of our study include its retrospective nature, lack of genetic analysis results of the conception materials, and the fact that it does not include advanced examinations other than standard karyotype analysis.

Conclusion

Pregnancy loss is a major adverse life event. Our findings suggest that parental chromosomal disorders play a significant role and karyotype analysis is a clinically useful test in cases of recurrent pregnancy loss. Multidisciplinary approaches involving an obstetrician and a clinical geneticist will aid in the achievement of positive outcomes in these patients.

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Research article

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Comparison of hearing reconstruction techniques in tympanosclerosis with stapes fixation

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Ethics Committee Approval
The study was approved by Kocaeli University Ethics Committee of Non-Invasive Clinical Research with the approval number of GOKAEK 2021/3.30 on February 5, 2021, and informed consent was obtained from all patients. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Surgery for tympanosclerosis with stapes fixation for hearing reconstruction is controversial, with many reports in the relevant literature advocate opposing suggestions. The primary aims were to evaluate hearing improvement with varied hearing reconstruction techniques performed for tympanosclerosis with stapes fixation.

Methods: Patients with tympanosclerosis and stapes fixation, whose hearing impairment was reconstructed surgically and who were followed for 1-5 years were reviewed in this retrospective cohort study. The audiological outcomes of reconstruction methods, including mobilization, partial ossicular replacement prosthesis (PORP), total ossicular replacement prosthesis (TORP), and teflon pistons (TP) were documented.

Results: The study included 76 ears of 76 patients; 29 ears in the mobilization technique group, 28 ears in the PORP technique group, 10 ears in the TORP technique group, and 9 ears in the TP technique group. When postoperative and preoperative hearing were evaluated, the mobilization and PORP techniques showed statistically significant improvement in both air conduction threshold gain and air-bone gap closure ($P<0.05$). Although some improvement was observed with the TORP and TP techniques, it was not significant ($P>0.05$). Bone conduction threshold showed no significant deterioration in any techniques.

Conclusion: For hearing gain, mobilization and PORP were effective in tympanosclerosis patients with stapes fixation after removal of sclerotic plaques, whereas the TORP and TP techniques did not show significant improvement. It can be concluded that, if a functionally mobile stapes cannot be achieved, it is not advisable to perform TORP replacement or a stapedotomy. However, these methods may still be used in carefully selected patients and be successful in some.

Keywords: Tympanosclerosis, Stapes fixation, Hearing reconstruction, Ossicular replacement prosthesis, Ossicular mobilization

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Introduction

The tympanic membrane, tympanic cavity, and mastoid cavity sometimes contain calcareous plaques, a condition known as tympanosclerosis. Dense fibrous and collagenous connective tissue with scattered calcification, hyaline degeneration, and few cells were observed in histological studies [1]. Deposition of calcareous plaques usually causes conductive-type hearing loss at lower frequencies, initially due to ossicular fixation. As the disease progresses, hearing loss may be detectable at all frequencies due to the mass effect of plaques. If the disease affects the cochlea, sensorineural hearing loss can also occur [2]. There is no proven and effective medical treatment for tympanosclerosis. Thus, to date, surgery is the only effective option to treat this pathology, although surgery remains controversial due to concerns about long-term refixation and sensorineural hearing loss during stapedotomy.

Ossicular mobilization is the initial step in all types of tympanosclerosis surgery. If total mobilization can be achieved, the procedure can be concluded. However, if total mobilization is not possible, a further appropriate hearing reconstruction technique should be selected. Placement of partial ossicular replacement prosthesis (PORP), total ossicular replacement prosthesis (TORP) or Teflon pistons (TP) are options for ossicular continuity [3, 4], but all these techniques carry the risk of hearing deterioration, especially after performing a stapedectomy. This makes the surgical decision-making challenging in some patients. Rehabilitation with hearing aids is an alternative choice [5], but it has its own disadvantages. Therefore, single stage surgery is still promising to obtain functional hearing in selected patients.

The aim was to evaluate hearing improvement following the use of a range of reconstruction techniques including mobilization only, PORP, TORP, and TP and to further compare subsequent postoperative hearing outcome when these techniques were performed for tympanosclerosis with stapes fixation.

Materials and methods

Patients with tympanosclerotic middle ears who were treated surgically between January 2016 and November 2018 at a tertiary center were retrospectively assessed. Patients who had stapes and/or oval window fixation, were Wielinga-Kerr Classification Groups 3 and 4 [6], who were treated surgically, had a hearing reconstruction performed at the same or second stage, and had been diagnosed as tympanosclerosis by pathological examination were included in this study. Wielinga-Kerr group 1 and 2 patients, patients who had less than 12 months of follow-up or who refused second stage operation were excluded. Patients whose stapes could not be mobilized and could not be replaced with a TP were also excluded.

The study was approved by Kocaeli University Ethics Committee of Non-Invasive Clinical Research with the approval number of GOKAEK 2021/3.30 on February 5, 2021, and informed consent was obtained from all patients.

Patients and reconstruction techniques

Patients were evaluated by sex, tympanic membrane status, presence of cholesteatoma, preoperative and the postoperative air-conduction thresholds (ACT), bone-conduction thresholds (BCT) and air-bone gap (ABG).

Patients were evaluated by four techniques depending on the method of hearing reconstruction: Technique 1- The mobilization technique, Technique 2- The PORP technique, Technique 3- The TORP technique, and Technique 4- The TP technique. All prostheses were Kurz® (Dusslingen/Germany) titanium ossicular prostheses.

Operative procedure

Tympanoplasty was defined as grafting of the tympanic membrane and exploration of the middle ear for the purpose of this study. After the removal of pathological tissues, all available ossicles were first mobilized. Then, additional hearing reconstruction(s), if needed, was performed according to the status of the middle ear and ossicular chain.

The evaluation of ossicular mobility began with the assessment of the malleus with a needle manipulation. If the malleus was not mobile, the incudostapedial joint was disrupted and the stapes was palpated individually. If attic fixation was detected, the incudomalleolar joint was detached, the incus was removed, and the prosthesis was positioned between the malleus and the stapes or footplate. Patients who had both attic fixation coupled with stapes fixation and where the mobilization of one or both was unsuccessful were excluded from the study. In patients undergoing TORP or PORP, the prosthesis was placed between the graft or malleus and stapes suprastructure or footplate. In all TP cases, the small fenestration technique was performed as a standard stapedotomy procedure.

The TORP was a further choice for ossicular reconstruction. Due to the nature of tympanosclerosis, destruction of ossicles is infrequent [6]. The reason for the use of TORP was usually absent or weakened stapes suprastructure.

Sclerotic plaques were removed under microscopic vision. Plaques between the stapedial crura and around the footplate were carefully and gently removed using a needle. When at all possible, the sclerotic mass was removed from the surgical field and stapes mobilization was assessed with round window movement under the highest magnification. The plaques over the lateral semicircular canal and the facial canal were dealt with using maximum precision. On the facial canal projection, as much of the plaque was removed as possible, with the help of a facial nerve stimulator, until it had no effect on the ossicular or ventilation system which was then restored. After removing all sclerotic plaques, additional hearing reconstruction techniques were performed, if ossicular continuity or mobilization could not be achieved.

In general, mobilization was the first step and also the only intervention for all patients if adequate motility was achieved. In the absence or weakness of stapes suprastructure, TORP was used. Ossicular discontinuity was managed with PORP. The patients whose stapes could not be mobilized were treated with TP, if feasible.

Audiological analysis

Audiometric evaluations were performed according to ISO standards using an Interacoustic AC40 (Interacoustic, Middelfart, Denmark) and obtained no earlier than one month before surgery, and postoperative measurements were made at the most recent recorded physical examination

after surgery. All techniques were evaluated according to hearing thresholds and the proportion of patients with a postoperative ABG less than 20 dB.

Statistical analysis

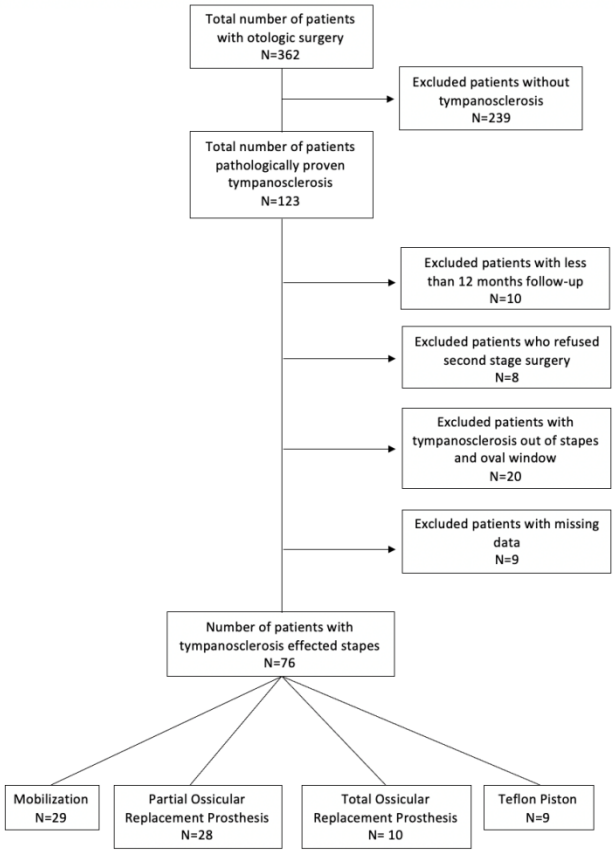
All statistical analyses were performed using SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov tests were used to test the normality of data distribution. Continuous variables were expressed as mean (standard deviation (SD)), median (25^{th}-75th percentiles, i.e., the interquartile range (IQR)). Categorical variables were expressed as counts (percentages). Comparisons of normally distributed continuous paired variables between the times were performed using the paired samples t-test and two-way ANOVA. Comparisons of non-normally distributed continuous variables between the times were performed using the Wilcoxon t-test, and Friedman analysis of variance by ranks. A *P* value <0.05 was considered statistically significant.

Results

General information

At a tertiary center, 123 patients with ears pathologically confirmed as tympanosclerosis were identified between the years 2016-2018. Of these, ten patients with a follow-up of less than 12 months, eight patients who refused second stage surgery, twenty patients falling into Wielinga-Kerr group 1 and 2 (tympanosclerosis not involving the stapes and oval window), and nine patients with missing data were excluded. Thus, a total of 47 patients were excluded. Seventy-six ears of 76 patients were included in the study and analyzed (Figure 1). There were no patients who had both ears operated in the study cohort.

Figure 1: Flow diagram of the study



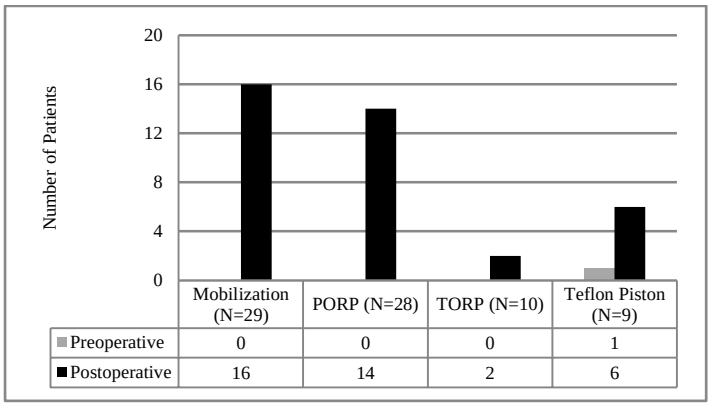
The patients were aged between 18 and 61 years with a median (IQR) age of 28.0 (22.0-35.6) years. Fifty-two (68.4%) were female, and 24 (31.6%) were male. The patients were followed for a median (range) of 41.8 (12-60) months.

Tympanic membrane perforation was detected in 65 patients (85.5%). There were seven patients (9.2%) affected by cholesteatoma, but no recurrence was observed during follow-up. Tympanoplasty without mastoidectomy was performed in 16 patients (21.1%), intact canal wall (CWU) mastoidectomy in 41 patients (53.9%), and canal wall down (CWD) mastoidectomy in 19 patients (25.0%).

Reconstruction methods and audiological assessment

There were 29 patients in the mobilization group, 28 patients in the PORP group, 10 patients in the TORP group, and nine patients in the TP group. The median follow-up time was 42 months for all groups. The mobilization group was followed for a median (IQR) of 42.0 (28.2-50.5) months, the PORP group for 39.0 (22.5-49.0) months, the TORP group for 40.5 (22.5-51.8) months, and the TP group for 49.7 (29.0-55.9) months. Follow-up times did not differ significantly between these groups (*P*>0.05). Figure 2 shows the pre-operative and the post-operative ABGs of all groups, and Table 1 summarizes the audiological and statistical results. The details of all groups are given below.

Figure 2: The preoperative and the post-operative ABG less than 20 dB of all groups



PORP: Partial ossicular replacement prosthesis; TORP: Total ossicular replacement prosthesis.

Table 1: The evaluation of average of hearing thresholds according to techniques

		Preoperative Median (25th-75th)	Postoperative Median (25th-75th)	*P*-value
Mobilization (n=29)	ACT	47.5 (45.0-54.4)	36.3 (24.5-56.9)	0.001
	BCT	17.5 (13.8-22.6)	15.0 (9.4-21.3)	0.130
	ABG	30.0 (26.9-35.0)	18.0 (13.9-32.9)	0.005
PORP (n=28)	ACT	53.8 (44.1-60.1)	43.9 (27.5-54.4)	0.002
	BCT	14.0 (10.0-20.0)	14.0 (11.5-21.9)	0.380
	ABG	34.4 (30.1-45.8)	22.0 (16.6-33.6)	0.001
TORP (n=10)	ACT	58.9 (48.4-63.8)	46.9 (31.3-53.8)	0.102
	BCT	20.0 (14.7-27.5)	16.8 (13.4-23.4)	0.343
	ABG	35.9 (28.4-45.2)	26.9 (18.4-33.8)	0.058
TP (n=9)	ACT	48.0 (45.0-48.9)	31.3 (25.6-46.3)	0.139
	BCT	15.0 (11.0-21.9)	12.0 (8.8-25.0)	0.888
	ABG	30.0 (23.8-39.0)	19.0 (16.4-24.4)	0.173

ACT: Air-Conduction Threshold BCT: Bone-Conduction Threshold ABG: Air-Bone Gap PORP: partial ossicular replacement prosthesis; TORP: total ossicular replacement prosthesis; TP: Teflon Piston; ACT: air-conduction threshold; ABG: air-bone gap. (Unit: dB) Data given as median (25. percentile; 75. percentile).

Group 1: Mobilization (n=29). In all surgeries in this study, mobilization was the first step. Patients who did not require additional reconstructions were included in this group. Adequate ossicular mobility were achieved in 29 patients (38.1%) with mobilization only. Four patients (13.8%) required revision surgery with the mobilization procedure. Tympanoplasty was performed in six (20.7%), CWU in 19 (65.5%), and CWD in four (13.8%) patients. The graft success

rate was 86.2% (25 patients). Cholesteatoma was present in three patients (10.3%).

A postoperative ABG <20 was achieved in 16 patients (55.2%). The ACT levels significantly improved from a median of 47.5 dB to a median of 36.3 dB (P=0.001). The ABG levels improved from a median of 30.0 dB to a median of 18.0 dB (P=0.005). The BCT levels tended to improve from 17.5 to 15.0 dB, but without statistical significance (P=0.130).

Group 2: PORP (n=28). In this cohort, the most applied prosthesis was the PORP. The PORP was positioned between the manubrium mallei and the stapes in 18 patients (64.3%), and between a cartilage under-graft and stapes in 10 patients (35.7%). Tympanoplasty was performed in five (17.9%), CWU in 12 (42.9%), and CWD in 11 (39.3%) patients within this group. Four revision surgeries (14.3%) were performed due to prosthesis displacement in two patients, and tympanic membrane perforation in two patients. Cholesteatoma were removed in two patients (7.1%).

The PORP group had a success rate of 50.0% (14 patients) with postoperative ABG less than 20 dB. The ACT levels improved from a median of 53.8 dB to a median of 43.9 dB (P=0.002). The ABG levels improved from a median of 34.4 dB to a median of 22.0 dB (P=0.001). There was no change in BCT levels with a postoperative median of 14.0 dB compared to preoperative levels of 14.0 dB (P=0.380).

Group 3: TORP (n=10). The TORP was positioned between the manubrium mallei and the stapes footplate in three patients (30.0%), and between a cartilage under-graft and the stapes footplate in seven patients (70.0%). Tympanoplasty was performed in two (20%), CWU in four (40%), and CWD in four patients (40%). Only one (10.0%) revision surgery for tympanic membrane perforation was carried out. Cholesteatoma was removed in two patients (20.0%).

There were two (20.0%) patients with less than 20 dB postoperative ABG (defined as success). In the TORP group, improvement was achieved in all three assessments (ACT, ABG, and BCT), with no statistical significance. The ACT levels improved from a median of 58.9 dB to a median of 46.9 dB (P=0.102), the ABG levels from a median of 35.9 dB to a median of 26.9 dB (P=0.058) and the BCT levels from 20.0 to 16.8 dB (P=0.343).

Group 4: TP (n=9). The least used prosthesis in our patients was TP. Stapedotomy was performed in nine patients (11.9%) who had no mobile stapes footplate. We removed all plaques wherever possible. After the middle ear and oval window were freed from plaques, we manually controlled the fixation. If stapes fixation persisted, we mostly preferred to wait and perform a second stage surgery. Two-stage surgery was performed in six patients (66.7%), and a single-stage surgery was performed in the remaining three patients (33.3%). Tympanoplasty was performed in three (33.3%) and CWU, in six patients (66.7%). Three (33.3%) revision surgeries (fat myringoplasties) for tympanic membrane reconstruction were performed in this group. Cholesteatoma was encountered in two patients (20.0%) in the first stage of their surgery.

A less than 20 dB postoperative ABG was achieved in six patients (66.7%). In the TP group, improvement was evident in all three assessments (ACT, BCT, and ABG) but there was again no statistical significance. The ACT levels improved from a median of 48.0 dB to a median of 31.3 dB (P=0.139), the ABG levels improved from a median of 30.0 dB to a median of 19.0 dB (P=0.173), and the BCT levels improved from 15.0 to 12.0 dB (P=0.888).

Complications

Graft failure occurred in 10 patients (13.2%) and prosthesis dislocation, in two patients (2.6%). Six were corrected with minor interventions, such as fat myringoplasty. The remaining graft failures and prosthesis dislocations were revised under general anesthesia with a tympanoplasty procedure, as described. No major complications, including total hearing loss or facial paralysis, were noted.

Discussion

Tympanosclerosis is a mass disease in the middle ear, affecting the tympanic membrane, and the mastoid cavity. Although the surgical treatment of tympanosclerosis remains controversial, especially when there is stapes involvement [7], surgery is justified for hearing reconstruction [8]. Surgery begins with the removal of calcareous deposits. When all irreversible or mobility-effecting deposits are removed, ossicular chain mobility should be assessed using at least basic methods. Our practice is to always palpate the ossicular chain with a needle, and if any movement of the round window after the mobilization was observed, the procedure for hearing reconstruction was considered complete without any further intervention. If no movement was observed, additional reconstruction strategies were used, depending on the status of the ossicular chain.

Mobilization, or sole use of mobilization, is a controversial procedure in the management of fixed stapes in tympanosclerosis. Some authors are opposed to the notion that the mobilized ossicles will become fixed again in a short time or that satisfactory hearing results cannot be achieved with mobilization alone [9, 10]. However, our results demonstrated no significant long-term deterioration in the mobilization group over a median 42 month-follow-up period, as previously reported [11, 12], and in support of this viewpoint. The concerns about re-fixation requirement in mobilized ossicles are somewhat allayed by these satisfactory results.

The limit for ossicular mobilization is also controversial. Having a mobile and healthy stapes without any intervention seems sufficient, but our major focus in this study was damaged and fixed stapes, due to tympanosclerosis. All stapes ossicles of patients in this study were damaged and no patient in the cohort had healthy stapes in the affected ear. After mobilization, if the movement of the round window appeared sufficient, it was deemed sufficient to finish the procedure. However, the main issue is an accurate evaluation of ossicular mobility. Although the round window reflex is not a reliable method, due to simplicity, economy, and practicality, it is certainly a pragmatic option for evaluation of stapes mobility. The implementation of new, objective techniques to assess ossicular motility will provide more detailed and precise information about which technique should be applied. Wales et al. [13] experimented with minimally invasive laser vibrometry for an objective evaluation of the ossicles in temporal bones. In the future, after mobilization, surgeons may utilize such methods

to decide whether to perform an additional hearing reconstruction.

After stapes mobilization, if the malleus and/or incus were defective or had to be removed, the PORP was the prosthesis of choice for hearing reconstruction in our patients. Wan *et al.* showed that the results of PORP for mobile stapes and attic fixation were statistically better than those of mobilization alone [14], but our results showed no significant difference between PORP and the mobilization group according to ACT gain, ABG gain, and BCT loss. Since our samples sizes were larger, we believe that our results are more reliable. Thus, we suggest that mobilization is as effective as PORP. Proper removal of the plaques and efficient mobilization are the key points. In addition, selection of patients in which mobilization is sufficient and for which a PORP is required are also important. We believe that it is particularly important to preserve anatomical structures as much as possible to utilize them in reconstruction, despite the fact that they may display a mass effect and causere-fixation [12].

TORP was the preferred prosthesis for ossicular reconstruction in our patients when the stapes suprastructure was absent or weakened, and the footplate was mobile. Although the likelihood of ossicular destruction in tympanosclerosis is considered low [6], we encountered relatively high rates of stapes suprastructure defects. The reason for this might be the high number of patients with cholesteatoma and the deleterious effect of late hospital admission. The TORP group did not show significant hearing improvement, which is in contrast to the study of De Vos *et al* [15]. These authors stated that the design of TORP increased stability and has equal performance with PORP. Stability was provided for the titanium prosthesis we used by placing gel foams around the TORP. Encouragingly, TORP displacement was not observed, although two dislocations in the PORP group were identified during follow-ups. In our patients, there was also a tendency to improve in both the ACT and the ABG levels in the TORP group, but this was not significant. It is our opinion that both PORP and TORP have their own advantages and disadvantages. PORP has functional superiority, but it also has a higher risk of re-fixation. TORP has a lower risk of ongoing sclerosis but is placed in a less favorable position in the middle ear. Our preference is for PORP rather than TORP when a functional stapes is present.

The TORP group had the least (Postoperative ABG <20 dB) hearing success (20%). The extraction of plaques on the oval window with a defective stapes suprastructure is more challenging due to the risk of footplate dislocation and worsened hearing. This restrains the surgeon from further removal causing the poorest ABG gain in the TORP group.

Prosthesis extrusion rates ranged from 0 to 5% in a previous report [16]. To overcome this complication, prostheses (PORP and_TORP) were placed under a cartilage graft or the manubrium mallei, which avoided direct contact with the fascia graft. We believe that the main reasons why we did not encounter any prosthesis extrusion were cartilage graft placement and meticulous surgical procedure. Only two patients required revision for non-functional hearing gain in the PORP group: One due to displacement towards the promontorium and the other due to synechia with the bony annulus.

The main question in the management of tympanosclerosis is whether to force mobilization or perform a stapedotomy. The reasons for this discussion are the risk of sensorineural hearing loss and facial nerve damage [17]. Some authors favor mobilization and others favor stapedotomy [3, 7, 8]. There was no hearing deterioration or facial nerve damage in any of our patients and we did not observe any significant improvement in the stapedotomy group, suggesting that further intervention was not necessary. A hearing aid may be a safer option than performing a stapedotomy, based on our results.

Stapedotomies were usually performed at the second stage (71.4%), as suggested by Bayazıt et al. [10]. Deciding whether to undergo second stage surgery may be difficult for patients. In our center, eight patients refused to undergo a second operation and were excluded from the study. The single-stage patients (33.3%) had dry ears with only sclerotic plaques with anterior small perforations. Thus, we could not compare single- and two-stage stapedotomy surgery statistically because of insufficient numbers of stapedotomies at the first stage of the operation. Future studies with higher number of patients would provide more data for this comparison.

In the TP group, ABG insignificantly decreased. Six out of nine patients (66.7%) had a postoperative ABG of less than 20 dB in the TP group and the median ACT was 31.3 dB, both of which are acceptable for communicative hearing. The low numbers of patients in this group may have made statistical analysis unreliable.

The general success rate in all groups was 50.0% in the long term (median 42 months), according to a success criterion of a postoperative ABG less than 20 dB. Teufert and De La Cruz compared short-term and long-term results for up to 9.5 years. They reported a success rate of 64.6% in the short term and 65.3% in the long term using this same criterion. They also showed no significant deterioration over the time [11]. Therefore, given the results of Teufert and De La Cruz's and the present study, we suggest that re-fixation of the ossicles and deterioration of the audiological results is unlikely to be of concern.

The co-existence of cholesteatoma with tympanosclerosis was 9.2% in our study. Our finding was consistent with the lower end of the rate (4-30%) reported by Kaur [18]. Of course, the presence of cholesteatoma in patients with tympanosclerosis complicates the surgery. However, we believe that, with appropriate surgical treatment, it should not hinder achieving hearing gain, as also reported by Weiss et al. [19].

Limitation

There are limitations to this study, including its retrospective and single-center design. A further limitation of the study was the small population of patients in the TORP and the TP groups compared to the other groups. It is also important to note the limitations inherent in gathering data through a hospital registry review process. Future research with higher number of patients and prospective design should be done for more certainty.

Conclusion

We recommend surgical intervention for these patients. To obtain a mobile stapes is the key point for hearing

improvement. If stapes mobilization cannot be achieved after removal of tympanosclerotic plaques, any additional intervention, such as TORP or stapedotomy, is generally not recommended. We suggest that these techniques may still be performed in some selected patients by our long-term hearing outcomes.

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Is there a relationship between lower lumbar disc herniation and multifidus muscle volume in postmenopausal women?

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Ethics Committee Approval
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Abstract

Background/Aim: Lumbar disc herniation (LDH) is the most common cause of low back pain. It can also cause radiculopathy, sciatica, loss of sensation and motor loss due to pressure on the nerve roots. The multifidus muscle protects the lumbar axis. The aim of this study is to investigate the relationship between volumetric measurements and the degree of atrophy in the multifidus muscles with LDH in postmenopausal women.

Methods: This case-control, retrospective study included 207 postmenopausal women with disc herniation on lumbar magnetic resonance imaging (MRI) and 183 reproductive period-premenopausal women with a mean age of 47.12 (10.07) years who were admittd to Adıyaman Training and Research Hospital between March 2020 and March 2021. LDH was detected at L4-L5 and L5-S1 levels on axial T2W lumbar MRI images. At these levels, the multifidus muscle volume was measured from the superior and inferior end plates of the vertebral bodies. The measurement of total volume was called multifidus total muscle volume (M-TMV), and the measurement made from the area without fat infiltration was called multifidus functional muscle volume (M-FMV). The M-TMV/FMV value was obtained to determine the degree of fat atrophy. Statistical analyses were performed, in which $P<0.05$ was considered statistically significant.

Results: The mean age of women in postmenopausal period with L4-L5 and L5-S1 intervertebral disc degeneration was 66.27 (12.33) years (57-84 years). M-TMV and M-FMV values were significantly lower and M-TMV / FMV values were significantly higher in postmenopausal women compared to the control group ($P<0.001$). In ROC analysis, the sensitivity and specificity of M-TMV / FMV above a cut-off value of 1.67 in diagnosing LDH at L4-L5 in postmenopausal women were 96.1%, and 73.7%, respectively, while the sensitivity and specificity of M-TMV / FMV above a cut-off value of 1.46 in diagnosing LDH at L5-S1 were 89.3%, and 71.4% ($P<0.001$), respectively.

Conclusions: This study reveals that in patients suffering from LDH in the postmenopausal period, atrophy of the multifidus muscle has negative effects and volumetric measurements of these muscles can be diagnostic in determining the degree of LDH. While planning LDH treatment in postmenopausal women, muscle strengthening programs planned after MRI evaluation may be beneficial for reducing symptoms.

Keywords: Lumbar disc herniation, Multifidus muscle, Muscle degeneration, Fatty infiltration

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Introduction

Lumbar disc herniation (LDH) is the most common cause of low back pain in adults. Disc herniation causes radicular pain, loss of sensation or motor weakness as a result of compression on ventral / dorsal nerve roots [1]. The most common levels of LDH are L4-L5, L5-S1 and more rarely, L3-4 [2]. Although the pathogenesis of disc herniation has not been determined precisely, anatomical causes are blamed [3, 4]. Physiologically, the bone and muscle structures of the spine can prevent damage and stenosis of the nerve roots by maintaining stability [5]. Primary muscles involved in the stabilization of the spine are abdominal muscles, psoas muscle and multifidus muscles. The most important muscle group that plays a role in providing local stabilization of the spine is the multifidus muscles, which constitute the largest back muscle group in the lumbosacral region [6, 7]. Multifidus muscles provide physiological lordosis and play a role in the equal distribution of pressure on the intervertebral discs by controlling the stability of the spine [8]. In previous studies, it has been shown that there is a relationship between pathologies such as disc degeneration, scoliosis, radiculopathy and multifidus muscle degeneration [9, 10]. In addition, radiological examinations revealed that degenerative changes in other paravertebral muscle groups and fatty atrophy in LDH patients are also common findings [11, 12].

Although it has been shown in recent studies that multifidus muscles are associated with LDH, there is no study examining age and menopausal status [13]. It has been stated that in the postmenopausal period, women may have more severe LDH than male patients of the same age due to a significant decrease in estrogen concentrations [14, 15]. However, there is no current study investigating the effect of the presence and degree of degeneration in the multifidus muscle on disc herniation in female patients in the postmenopausal period.

The aim of this study is to investigate the relationship between volumetric measurements and the degree of atrophy in the multifidus muscles with LDH in postmenopausal women.

Materials and methods

Patient characteristics

There were 12873 women in the postmenopausal period who visited the gynecology outpatient clinic between March 2020 and March 2021. The age and clinical information of the patients were obtained from the hospital database KARMED. A total 532 patients low back pain complaints who underwent lumbar MRI were identified. Of these patients, 325 patients with motion artifacts on lumbar MRIs, kyphosis in the lumbar axis and / or scoliosis were excluded from the study. After the implementation of these criteria, 207 patients were included. Ethics approval was obtained from Adıyaman University Non-Interventional Research Ethics Committee (2021 / 04-13). This study was carried out in accordance with the Declaration of Helsinki.

Inclusion criteria were being aged 55 years and above, having lumbar disc degeneration and herniation and unilateral or bilateral nerve root compression at L4-L5 and L5-S1 levels.

Having lumbar axis disorders such as spondylolisthesis (>3 mm) or scoliosis (>10), having undergone surgery for reasons such as lumbar disc herniation, spinal stenosis, history of spinal neoplasm, previous spinal infection (spondylodiscitis, tuberculosis, brucellosis, etc.) or other malignancies constituted the exclusion criteria.

One hundred eighty-three women between the ages of 40-50 years in the reproductive-premenopausal period were included in our study as the control group.

Imaging parameters

Lumbar MRI images were obtained in supine position using a 1.5-T MRI scanner (Gyroscan Intera, Philips Medical Systems, Best, The Netherlands. Imaging parameters were as follows: In sagittal T2-weighted images from T12 to sacrum, TR / TE 2980 / 122.6, matrix, size: 208 x 320, recovery time: 3,000--3,600 ms, echo time: 87--114 ms and slice thickness: 4 mm). In axial T2-weighted images from T12 to S1, TR / TE 2980 / 122.6, matrix size 208 x 320, recovery time: 3,000–3,600 ms, echo time: 87–114 ms, and slice thickness: 4 mm.

Evaluation of disc herniation

The degree of intervertebral disc herniation was determined by sagittal T2W images, and grade 2 and grade 3 patients were included in the study [16].

Evaluation of muscle degeneration

Multifidus muscle was evaluated from axial T2W images. Fatty infiltration involving <10% of normal muscle tissue was considered Grade 1 atrophy, fatty infiltration between 10-50% of normal muscle tissue was considered Grade II atrophy and severe irregular diffuse fatty infiltration (>50% fat infiltration in normal muscle tissue) was considered Grade III atrophy [17].

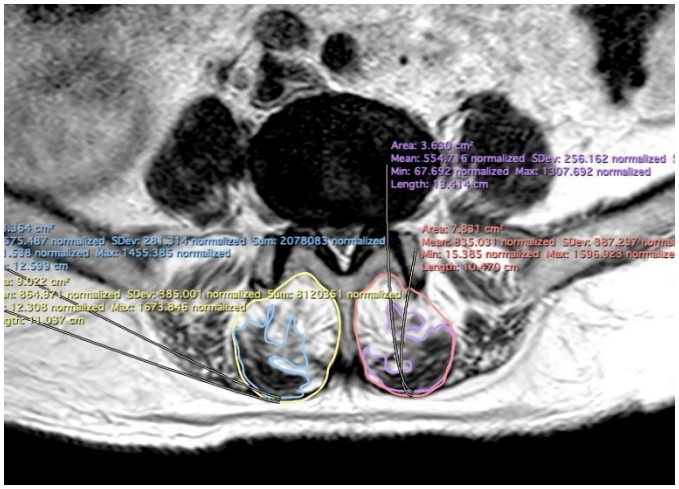
Paraspinal muscle measurements

Images were obtained from KARMED imaging system in DICOM format. Axial and sagittal T2W images were processed using the Horos operating system. The degree of degeneration was detected from sagittal T2W images. Measurements were made at the level of the superior and inferior endplates of the L5 vertebra from the axial T2A sections at the level of disc herniation in those with L4-L5 LDH, and at the level of the superior and inferior endplates of the S1 vertebra at the level of disc herniation in those with L5-S1 LDH. First, the total muscle volume (TMV) of the muscles was measured by hand drawing (Figure 1). Then, the functional muscle volume (FMV), excluding fat infiltration, was measured. FMV/TMV value was calculated to determine the degree of fat infiltration. The total value was obtained by calculating each value separately as right and left. The data obtained for L4-L5 and L5-S1 levels were collected, and the volumetric measurements were made.

Statistical analysis

Statistical analyses were performed using SPSS 22 (International Business Machines Corp., Armonk, New York). Kolmogrow-Smirnov test was used to evaluate normality assumption. Mann Whitney U test was used to compare non-normally distributed independent groups, and ROC analysis was performed to evaluate the diagnostic effectiveness of M-TMV, M-FMV and M-TMV/M-FMV in LDH. Binary logistic regression analysis was used to assess the relationship between LDH, fatty atrophy degree and M-TMV, P-TMV, M-FMV, T-FMV values. A *P*-value <0.05 was considered significant.

Figure 1: Multifidus muscle volume measurements on T2 weighted axial images



Results

In the postmenopausal period, the mean age of women with intervertebral disc degeneration at L4-L5 and L5-S1 levels was 66.27 (12.33) years (57-84 years). The mean age of patients in the control group was 47.12 (10.07) years (40-49 years).

When compared with the control group, the M-TMV, M-FMV values of postmenopausal women had significantly decreased and M-TMV / FMV ratio had significantly increased at both LDH levels (P<0.001) (Table 1).

Table 1: Comparison of postmenopausal women with lumbar disc herniation and control group multifidus muscle volumes

		Groups		
		Control Group	Postmenopausal women	*P*-value
L4-L5	M-TMV	1092.2 (139.4)	788.7 (99.3)	<0.001
	M-FMV	917.9 (104.7)	433.2 (89.1)	<0.001
	M-TMV/FMV	1.18 (0.07)	1.82 (0.23)	<0.001
L5-S1	M-TMV	1157.4 (212.3)	871.3 (103.2)	<0.001
	M-FMV	1089.3 (121.9)	539.9 (92.7)	<0.001
	M-TMV/FMV	1.06 (0.07)	1.61 (0.17)	<0.001

M-TMM: Multifidus-Total muscle volume; M-FMV: Multifidus functional muscle volume; M-TMV/FMV: Multifidus total muscle volume/functional muscle volume

ROC analysis was performed to determine the effectiveness of M-TMV, M-FMV values and M-TMV/FMV ratio in diagnosing LDH in postmenapausal women. M-TMV / FMV values were strongly diagnostic for LDH at L4-L5 and L5-S1 levels (P<0.001): The sensitivity and specificity of M-TMV / FMV above a cut-off value of 1.67 in diagnosing LDH at L4-L5 in postmenopausal women were 96.1%, and 73.7%, respectively, while the sensitivity and specificity of M-TMV / FMV above a cut-off value of 1.46 in diagnosing LDH at L5-S1 were 89.3%, and 71.4% (P<0.001), respectively (Table 2) (Figure 2).

Table 2: Visibility results and cut off values of multifidus muscle volume measurements

	AUC	*P*-value	Cut-off	Sensitivity	Specificity
M-TMV/FMV (L4-L5)	0.883	<0.001	1.67	96.1	73.7
M-TMV/FMV (L5-S1)	0.872	<0.001	1.46	89.3	71.4

M-TMV/FMV: Multifidus total muscle volume/functional muscle volume, AUC: Area under curve

Binary logistic regression analysis was performed to analyze the correlation between LDH, age, fatty atrophy degree, and M-TMV, M-FMV, M-TMV / FMV values in the postmenopausal period. All these factors increased the risk of LDH in postmenopausal women (P<0.001 for each). Among them, M-TMV / FMV value increased the LDH risk by 3.9 in postmenopausal women, while the degree of fatty infiltration doubled it (Table 3).

Table 3: Multivariate Logistic Regression Analysis

	B	*P*-value	Exp(B)	95% CI	
				Lower	Upper
Age	1.394	<0.001	3.42	2.12	7.89
Fatty infiltration grade	1.034	<0.001	3.008	2.512	4.328
M-TMV	-0.703	<0.001	2.312	1.212	3.211
M-FMV	-1.682	<0.001	4.237	2.832	9.183
M-TMV/FMV	3.921	<0.001	8.451	5.291	11.430

M-TMV: Multifidus-Total muscle volume, M-FMV: Multifidus functional muscle volume, M-TMV/FMV: Multifidus total muscle volume/functional muscle volume

Discussion

The results of this study show that lumbar disc herniation may occur due to a decrease in functional muscle in the multifidus muscles, and fatty atrophy is a risk factor for LDH in postmenopausal women. This finding supports other studies investigating the relationship of lumbar disc degeneration with the multifidus muscles [11, 17].

The compression in the nerve root causes denervation and atrophy due to structural changes in the lumbar multifidus muscles [18]. The multifidus muscle plays an important role in protecting the lumbar lordosis and the intervertebral discs by preventing movements such as sudden flexion. It does this by not only providing the necessary muscle strength for stabilization, but also by contributing to the nucleus pulposus and anulus fibrosus in the disc structure [19]. It also supplies support by reducing the pressure in the intervertebral disc at the L5-S1 segment. Restricting daily movements and reducing use is a common trend in patients suffering from LDH. This may result in atrophy due to reduced denervation of the muscles. The innervation of the multifidus muscle occurs through the medial branch of the dorsal ramus of the L5 nerve root. Denervation occurs with stenosis due to LDH in this nerve [18]. In the light of this information, it is not coincidental that there is a decrease in the total volume and functional volume in the multifidus muscle in postmenopausal female patients in our study, and these atrophic changes may have caused LDH at the L4-L5 and L5-S1 levels and secondary nerve root compression.

In a previous study, the degree of degeneration in the multifidus muscle was associated with disc degeneration [20]. The volume of multifidus in women with LDH was significantly different compared to the control group. In addition, the decrease in the functional volume of the multifidus muscle was highly diagnostic for determining LDH in postmenopausal women. To the best of our knowledge, this study is the first in which the cut-off value of the multifidus muscle volume can is determined to diagnose LDH.

This study reveals the relationship between the grade of fatty atrophic changes, which we distinguished visually, with LDH and shows that it is a reliable method in clinical evaluation. This result supports those of other studies in the literature [12, 21]. In another study, although the degree of multifidus fatty infiltration was superior to cross-sectional evaluation in patients with LDH [22], our study showed that cut-off values obtained in volumetric measurements provide superiority in diagnosis.

In previous studies, mild atrophic changes were found in the multifidus muscle after LDH surgery [23, 24]. However, weakness in the paraspinal muscles can be reversed with rehabilitation and exercise programs [25]. Choi et al. showed that lumbar extension strengthening exercises have positive effects on muscles after LDH surgery [26]. The main patient group included and investigated in our study are female patients in the

postmenopausal period. Preferring surgical treatment methods, especially in the elderly female patient group, may be difficult due to additional morbidities. According to the results of our study, it is thought that exercises and rehabilitation practices that strengthen the detected muscle groups may be beneficial. Therefore, MRIs to be performed before treatment may be useful in determining appropriate treatment methods.

Limitations

This study has some limitations. First, disc herniations at the lower levels (L4-L5 and L5-S1) were analyzed first. For this reason, evaluation of LDH at higher levels is limited. Second, our patients consisted of only postmenopausal women. This should be considered before applying our results to the general population. Another limitation of our study is that it is retrospective. Although derived from the hospital database, this may cause bias.

Conclusion

This study reveals that in patients suffering from LDH in the postmenopausal period, atrophy of the multifidus muscle has negative effects and volumetric measurements of these muscles can be diagnostic in determining the degree of LDH. While planning LDH treatment in postmenopausal women, muscle strengthening programs planned after MRI evaluation may be beneficial in reducing symptoms.

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The association of TNFα -238 G/A gene polymorphism with alopecia areata

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Ethics Committee Approval
Kutahya Health Sciences University, School of Medicine, Ethical Committee, 2019/01-4.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Alopecia areata (AA), which is characterized by hair loss, is an inflammatory autoimmune disease. Tumor necrosis factor-alpha (TNFα) is a potent proinflammatory cytokine that has a highly significant role in inflammatory and immune responses. The aim of this study is to evaluate whether there is a relationship between TNFα -238 G/A gene polymorphism and AA in the Turkish population.

Methods: In this case-control study, the frequency of TNFα-238 G/A gene polymorphism and its relationship with some clinical parameters of AA patients were investigated. Seventy-eight AA patients and 78 healthy individuals were included in our study. TNFα -238 G/A polymorphism was evaluated by the PCR-RFLP method.

Results: The distribution of TNFα -238 G/A genotypes was significantly different between patients and control subjects (P<0.001). Frequency of genotypes GG and AA in AA patients (53.8 and 6.4%, respectively) were evidently lower compared to the controls (59 and 25.6%, respectively). Individuals with AA genotype had a lower risk of AA disease (odds ratio (OR)=0.27; 95% CI=0.09-0.79; relative risk (RR)=0.65 (0.49-0.86); P=0.013). GA genotype was significantly higher in patients with AA (39.7%) compared to the control group (15.4%) and an increased risk of patchy AA was observed (OR=2.82, 95% CI=1.28-6.21; RR=1.87 (1.11-3.15); P=0.008).

Conclusion: These results suggest that the TNFα -238 G/A gene polymorphism is associated with AA and individuals with GA genotype may have an increased risk of AA.

Keywords: TNFα, Gene polymorphism, Alopecia areata

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Introduction

Alopecia areata (AA) is an inflammatory autoimmune disorder characterized by non-scarring hair loss [1, 2]. The most affected area is the scalp; nevertheless, there are more serious clinical forms like alopecia universalis (AU) that induces hair loss throughout the whole body and alopecia totalis (AT), including all hair loss on the scalp [2, 3]. Currently, the etiopathogenesis of AA is yet unknown. A strong relationship exists between AA and autoimmune disorders, especially autoimmune thyroiditis, type 1 diabetes, vitiligo, and pernicious anemia. Nearly 20% of the affected individuals have a positive family history, indicating a genetic predisposition. Thus, AA is regarded as a genetically determined immune-mediated disease [3].

The TNFα is a potent proinflammatory cytokine that plays a significant role in inflammatory and immune responses [4]. It is located on chromosome 6 in the class III region of the human leukocyte antigen (HLA). Studies have identified a number of single nucleotide polymorphisms in the promoter region [3, 4]. TNFα -238 G/A polymorphism is one of the few polymorphisms in the TNFα gene that alters the transcription of TNFα and regulates its production [5]. In the literature, TNFα -238 G/A gene polymorphism is reported to be related to diseases such as acne vulgaris, psoriasis, systemic lupus erythematosus, and rheumatoid arthritis [5-7].

Many polymorphisms associated with AA have been identified [8]. There is very limited literature on the correlation between TNFα gene polymorphism and AA patients. Therefore, the aim of the present study was to analyze the association between TNFα -238 G/A gene polymorphisms and Turkish AA patients to clarify if these polymorphisms influenced disease occurrence or led to increased disease risk.

Materials and methods

Subjects

This was a case-control study conducted on patients with patch AA and healthy individuals. The study was conducted with the approval of the Ethics Committee of Clinical Research at Kütahya University of Health Sciences (approval number: 2019/01-4). The sample size to be used in the study was calculated by Power analysis. The alpha error value was 0.05, and the power of the test was 0.95. As a result of the power analysis performed under these conditions, the total sample size was calculated as 156.

In our study, 78 patch AA patients (43 females, 35 males; mean age: 30.1 (1.16) years) were recruited from the dermatology outpatient clinic, Kutahya Health Sciences University. For the patients with patchy AA diagnosis (S1-S2), the AA investigational assessment guidelines were considered [9]. Demographic data, family history, duration of disease, nail dystrophy, autoimmune disease, and AA severity were recorded in all patients.

The control group comprised 30 females and 48 males with a mean age of 36.1 (1.74) years. They were healthy individuals who lived in the same geographical area, had no family history of AA and were free of any dermatological or autoimmune disease.

Genotyping

Blood samples were obtained from all subjects. DNA was isolated from blood by conducting the standard Phenol/chloroform extraction method. To analyze the TNFα -238 G/A gene polymorphisms assay, PCR based restriction fragment length polymorphism (RFLP) method was employed as described previously [7]. Three minutes of initial denaturation was performed for amplification at 94°C, which was followed by 35 cycles of 30 seconds at 94°C, 30 seconds at 60°C, and 1 minute at 72°C. Final extension involved 5 minutes at 72°C. The primer pairs used were 5′- ATC TGG AGG AAG CGG TAG TG-3′ and 5′- AGA AGA CCC CCC TCG GAA CC -3′. The 152 bp PCR product was digested with MspI (New England Biolabs, Ipswich, MA, USA) at 37 °C overnight after the amplification. Restriction fragments were separated on a 3% agarose gel stained with ethidium bromide, and under the ultraviolet (UV) illumination, the genotypes were identified. Wild-type (GG) was identified by the 133/19 bp fragment, heterozygotes (GA) by both the 133/19 bp and 152 bp, and the homozygote variant (AA) by only a 152 bp fragment. Due to its small size, the 19 bp fragment did not appear on the gel.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS 16). The distribution of the genotypes was evaluated with the $\chi 2$ test to analyze the Hardy–Weinberg equilibrium. The chi-square test was utilized to detect the correlation between TNFα -238 G/A gene polymorphisms and the clinical and demographic features. To evaluate the risk factors, the odds ratio (OR), and 95% confidence interval (CI) were used. All p values were 2-tailed, and confidence intervals were set at 95%. *P*-values of less than 0.05 indicated significance.

Results

Both clinical and demographic features of the AA patients are shown in Table 1. Age, gender, family history, duration of the disease, alopecia severity, nail dystrophy, and localization, and the presence of another autoimmune disease were analyzed. In our study, no relationship was found between the clinical and demographic characteristics of AA patients and TNFα -238 genotypes. However, genotype GA was found in 4 (12.9%) of AA patients with other autoimmune diseases (P=0.046) (Table 1).

The frequency of TNFα -238 G/A polymorphism genotypes in AA did not show an important discrepancy from the Hardy-Weinberg equilibrium (P=0.820), but there was a significant deviation from the controls (P<0.001) (Table 2).

The genotype frequency of TNFα -238 polymorphism was significantly different in the control and patient groups. It was found that 42 (53.8%) cases and 46 (59%) controls had GG genotype, while 31 (39.7%) cases and 12 (15.4%) controls had GA genotype, and 5 (6.4%) cases and 20 (25.6%) controls had AA genotype ($\chi 2$=17.5, df=2, P<0.001) (Table 3). As a reference, evaluation of the GG genotype revealed that the GA genotype was related with a higher risk of AA patients (OR=2.82; 95% CI=1.28-6.21; RR=1.87 (1.11-3.15); P=0.008), while the AA genotype was significantly linked with reduced

risk of AA disease (OR=0.27; 95% CI=0.09-0.79; RR=0.65 (0.49-0.86); *P*=0.013).

Table 1: Baseline clinical and demographical features of the study patients with AA stratified according to TNFα -238 G/A gene polymorphisms

Characteristic	Total n = 78	GG	GA	AA	*P*-value
Gender, male/female, n (%)	43/35 (55.1/44.9)	23/19 (54.8/45.2)	17/14 (54.8/45.2)	3/2 (60/40)	0.975
Age (years)	30.1 (1.16)	29.3 (1.60)	30.6 (1.85)	34.0 (4.77)	0.560
Disease duration (months)	8.66 (1.88)	10.7 (3.30)	6.84 (1.62)	3.0 (1.04)	0.503
Family history, n (%)	15 (19.2)	9 (21.4)	5 (16.1)	1 (20)	0.850
Nail dystrophy, n (%)	12 (15.4)	7 /16.7)	4 (12.9)	1 (20)	0.869
Alopecia severity					
<25%	62 (79.5)	33 (78.6)	24 (77.4)	5 (100)	0.498
25-50%	16 (20.5)	9 (21.4)	7 (22.6)	0 (0)	
Alopecia localization					
Scalp	52 (66.7)	27 (64.3)	22 (71)	3 (60)	0.778
Beard/Mustache	13 (16.7)	9 (21.4)	3 (9.7)	1 (20)	
Hair/Beard	12 (15.4)	5 (11.9)	6 (19.4)	1 (20)	
Body	1 (1.3)	1 (2.4)	0 (0)	0 (0)	
Other autoimmune disease	4 (5.1)	0 (0)	4 (12.9)	0 (0)	0.046*

Data were analyzed by analysis of variance and $\chi 2$ test. Mean plus standard error of the mean values are presented for age, disease duration. AA: alopecia areata, TNFα: tumor necrosis factor alpha, * *P*-value ≤0.05 is significant.

Table 2: Allele/Genotype frequencies and test of Hardy-Weinberg (HW) equilibrium

	Controls		Alopecia Areata	
	O	E	O	E
GG	46	34.6	42	42.3
GA	12	34.6	31	30.2
AA	20	8.6	5	5.3
	χ^2=33.3, df=2, *P*<0.001		χ^2=0.05, df=2, *P*=0.820	
f(G)	0.6667		0.7372	
f(A)	0.3333		0.2628	

f: observed frequency of each allele (G or A), O: observed genotype numbers, E: expected genotype numbers under a Hardy-Weinberg (HW) equilibrium assumption, $\chi 2$: Chi-square values, *P:* probability of difference

Table 3: Representation of genotype and allele frequencies of TNFα -238 G/A polymorphisms for patients and control groups

TNFα -238	AA patients n = 78 (%)	Controls n = 78 (%)	OR (95%CI)	RR (95% CI)	*P*-value
Genotypes					
GG	42 (53.8)	46 (59)	1	1	<0.001
GA	31 (39.7)	12 (15.4)	2.82 (1.28 - 6.21)	1.87 (1.11 - 3.15)	0.008
AA	5 (6.4)	20 (25.6)	0.27 (0.09 - 0.79)	0.65 (0.49 - 0.86)	0.013
	$\chi 2$=17.5, df=2, *P*<0.001				
G	115 (73.7)	104 (66.7)	-	-	
A	41 (26.3)	52 (33.3)	0.71 (0.43 - 1.16)	0.84 (0.67 - 1.06)	0.173
	$\chi 2$=1.85, df=1, *P*=0.173				

TNFα: tumor necrosis factor alpha, AA: alopecia areata, OR: odds ratio, 95% CI: 95% confidence interval, RR: relative risk. The statistically significant results are shown in bold.

The groups were similar in terms of allele frequency ($\chi 2$=1.85, df=1, *P*=0.173). G allele frequencies were found in 115 (73.7%) cases and 104 (66.7%) controls. Similarly, A allele frequencies were observed in 41 (26.3%) and 52 (33.3%) in cases and controls, respectively (OR=0.71, 95% CI=0.43-1.16; RR= 0.84 (0.67-1.06); *P*=0.173) (Table 3).

Discussion

In our study, the data of 156 individuals, including 78 AA patients and 78 control subjects, were collected from the dermatology outpatient clinic, Kutahya Health Sciences University, Turkey. We analyzed the function of the TNFα -238 G/A polymorphism in the development of patchy AA in the Turkish population and found a significant link between TNFα -238 G/A gene polymorphism and AA patients.

As far as we know, this study is the first to report the relationship between TNFα -238 G/A gene polymorphism and AA in the Turkish population. Therefore, it is not possible to compare the results of this study with others. Contrarily, Tan et al. [10] reported no association of alopecia areata with the polymorphisms of TNFα -238 G/A and TNFα -308 G/A. However, the relationship of TNFα -238 G/A gene polymorphism with other patient groups in other ethnic populations have also been reported. In the study performed by Aisha et al. [6], the authors found that the AA genotypes of TNFα -238 were related to an elevated risk of acne vulgaris. Rajesh et al. [7] reported that the TNFα -238 AA genotype was detected only in patients with moderate to severe psoriasis vulgaris. Another study suggested that TNFα -238 AA genotype significantly increased, while the GG genotype decreased in psoriasis, compared to the control group [11]. In various studies, the relationship between TNFα -238 G/A polymorphism and gastric disease risk were studied. In a study in the Chinese population, there was no significant relationship between the TNFα -238 GA genotype and gastric cancer, while another study reported that the TNFα -238 GA polymorphism is significantly related to the increased gastric cancer risk in Asians [12, 13]. It has been reported that TNFα -238 GA genotype was related to swollen joint count <5 as compared to the TNFα -238 GG genotype [14]. A recent study by Brinkman et al. [15] investigated TNFα -238 GA genotype and found it was associated with decreased radiologically detectable disease course. In another study, they reported that the TNFα -238 GG genotype was related to severe and unresponsive forms of rheumatoid arthritis in the Iranian population [16]. In our study, there was no significant difference in the allele frequencies of TNFα -238 G/A between AA patients and the control group. Szabó et al. [17] reported that there was no significant difference in genotype or allele frequencies between acne and control group in terms of TNFα -238 G/A gene polymorphism. Wang et al. [18] showed that the TNFα -238 A allele is related to elevated susceptibility to acne in Asians but not in European populations. Schmeling et al. [19] found that the TNFα -238 A allele was more prevalent in the psoriatic arthritis and juvenile idiopathic arthritis subgroup than the control group as well as in the non-psoriatic juvenile idiopathic arthritis patients. Aisha et al. [6] reported that patients with acne vulgaris had significantly higher TNFα -238 mutant A allele than healthy controls. In another study, TNFα -238 A allele was reported to raise the risk of psoriasis vulgaris in the Indian population [7]. In a study in the Tunisian population, they reported that the TNFα -238 A allele was significantly higher in non-small cell lung cancer patients than in the controls and that TNFα -238 G/A may be associated with elevated susceptibility to lung cancer [20].

Further analysis was performed to investigate the association between clinical and demographic features and TNFα -238 G/A genotypes of patients. According to these analyses, there was no relationship between TNFα -238 G/A genotypes and sex, age, disease duration, family history, nail dystrophy, and severity of the disease. Interestingly, however, there was a relationship between AA patients with another autoimmune disease and TNFα -238 GA genotype [4 (12.9%); *P*=0.046]. This result shows that the relationship between TNFα -238 G/A gene polymorphism and autoimmune diseases have a critical role in the development of AA.

AA pathogenesis remains incompletely understood. The cytokines may have a role in AA. In *in vitro* studies, TNFα inhibited hair follicle growth, indicating that it may play a significant role in AA [21]. Gohary et al. [22] showed that skin

TNFα levels were elevated in AA patients, which may indicate a significant role of TNFα in AA patients. Abdel Halim et al. [23] showed that both serum and tissue levels of TNFα in patients with AA were significantly higher than in the control group before and after treatment.

Limitations

To the best of our knowledge, this is the first study to investigate the relationship between TNFα -238 G/A and AA risk in the Turkish population. However, there were several limitations in our study: First, all subjects were Turkish, therefore extrapolation of our results to other ethnic groups is not possible. Second, although we did not have a restriction on the severity of the disease in our study, the participants were mild to moderate AA patients. This may stem from the limited number of patients and rarity of severe disease, such that alopecia totalis or alopecia universalis occur only in 2% of all AA cases [1]. Third, since serum TNFα levels of the participants were not measured, the relationship between TNFα -238 G/A gene polymorphism and serum TNFα level could not be demonstrated.

Conclusion

The findings of our present study proved an association between TNFα -238 G/A gene polymorphism and the susceptibility to patchy AA in the Turkish population. Our results show that TNFα -238 G/A gene polymorphism might have a role in patchy AA and the GA genotype may confer an increased risk of disease while the AA genotype has a lower risk for patchy AA in the Turkish population. It is not obvious if the relationship with TNFα -238 G/A gene polymorphism is dependent on the disease type. Hence, the data is not precise. Larger-scale studies on different ethnic groups, including other Alopecia clinical forms, are needed to further clarify their role in disease development. As AA is a multifactorial disease, their interaction with disease triggering factors, environmental factors, and other genetic studies, including gene-gene and gene-environment interactions, are needed for more clarification of disease pathogenesis.

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Different fresh gas flows in prone position under general anesthesia: comparison of costs and effects on airway and endotracheal cuff pressures

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The study was approved by the Research Ethics Committee, Faculty of Medicine, Tekirdağ Namık Kemal University on 04.02.2020 with protocol number 2019.236.12.11.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Many studies have been performed on different fresh gas flows for general anesthesia. In this study, we aimed to compare the costs, airway, and endotracheal cuff pressures of different fresh flows (low, medium, high) of patients receiving general anesthesia in the prone position.
Methods: A total of 150 ASA I-II patients over the age of 18 years who underwent lumbar vertebral surgery in prone position were included in this retrospective cohort study. Patients were divided into three groups: Low-flow (n=50, fresh gas flow: 1 l/min), medium-flow (n=50, fresh gas flow: 2 l/min) and high-flow (n=50, fresh gas flow: 4 l/min). In addition to the preoperative heart rates, peripheral oxygen saturation, mean arterial pressures, endotracheal cuff pressures, airway peak and plateau pressures in the first 60 minutes (as 0^{th}, 15^{th}, 30^{th}, 45^{th}, 60^{th} minutes) were noted, and the amount of inhaled gases (sevoflurane, oxygen, nitrogen protoxide) based on the data of the device were recorded to evaluate cost.
Results: The two groups were similar in terms of hemodynamics, airway, and endotracheal cuff pressures. Regarding cost, there was a significant difference in the low-flow anesthesia group in terms of inhaled anesthetic agents, oxygen, and nitrogen protoxide.
Conclusion: With modern anesthesia machines, it is unnecessary to avoid low-flow anesthesia applications. However, we recommend that the fresh gas flow be more than 2 l/min for anesthetists lacking experience or those who do not prefer low-flow anesthesia.

Keywords: Low-flow anesthesia, Prone position, General anesthesia, Sevoflurane

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Introduction

The fresh gas used in the anesthesia machine is classified according to the amount of flow. According to this classification, low flow is defined as 0.5-1 liter (l)/minute (min), medium flow, as 1-2 l/min and high flow, as 2-4 l/min. Low-flow anesthesia can be used in rebreathing systems in which 50% of the CO2 can return to the lungs after absorption [1]. In modern anesthesia machines, there are various types of equipment that provide varied fresh gas flow and regulate oxygen concentration [2]. Despite the high standards of modern anesthesia machines, 85-90% of anesthetists prefer high fresh gas flows [3]. Although low-flow anesthesia, which is widely used today, helps reduce cost, prevent environmental pollution, and preserve respiratory physiology [4], there are also publications warning about the risk of intraoperative hypoxia [5]. In low-flow anesthesia, fractional inspiratory oxygen amount (FiO_2) should not be less than 30% [6, 7]. It is considered not reasonable to avoid using low-flow anesthesia with modern anesthesia machines [8]. A study of general anesthetic agents advocated switching from desflurane to sevoflurane, based on the high cost, weak potency, and greater greenhouse effect of desflurane [9].

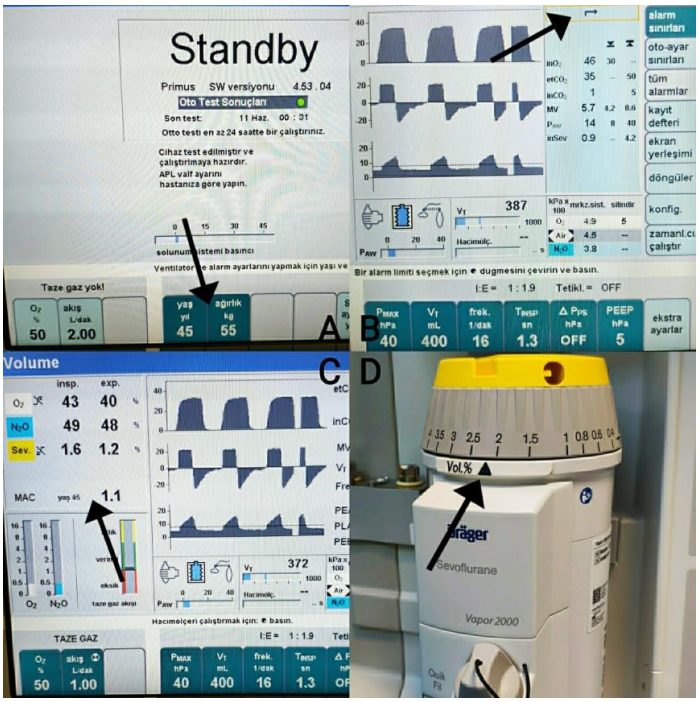
Our study aimed to compare airway peak (Ppeak) and plateau (Pplato) pressures, endotracheal tube cuff pressures, and costs with different fresh gas flow in patients who received general anesthesia with sevoflurane in the prone position while undergoing lumbar vertebral surgery.

Materials and methods

This study was carried out in Tekirdağ Namık Kemal University, Medical Faculty, Department of Anesthesiology and Reanimation after approval was obtained from the Faculty Hospital Ethics Committee (dated 04.02.2020, protocol number: 2019.236.12.11). As a result of the power analysis conducted, the required number of patients at 95% power and 95% confidence interval was 126. A total of 150 ASA I-II patients aged 18 years and over, planned to undergo elective lumbar disc surgery were included in the study. Patients were divided into three groups according to fresh gas flow: Low flow (group L) (1 l/min) (50 individuals), medium flow (group M) (2 l/min) (50 individuals) and high flow (group H) (4 l/min) (50 individuals). Patients excluded in the study were those with ASA scores other than ASA I-II, body mass index (BMI) >40 kg/m^2 and pregnant or breast-feeding women.

Leak checks and calibration of anesthesia machines were performed before each operation. Soda-lime (Drägersorb 800 plus) (Dräger Medical, Lübeck, Germany) was used as CO_2 absorbent, and Dräger Primus (Dräger Medical, Lübeck, Germany) was used as the anesthesia machine. All patients received standard premedication. The patients were monitored preoperatively on ECG, and heart rate (HR), noninvasive blood pressure (NIBP), and peripheral oxygen saturation (SpO_2) were noted. The patient's age and ideal weight (actual weight should not be preferred) were entered to adjust the appropriate MAC (minimum alveolar concentration) and tidal volume on the anesthesia machine before induction. The monitoring alarm limits were set (Alarm for FiO_2 should be set at 30% minimum). All patients were pre-oxygenated for 3 minutes before induction at 4 l/min with 100% oxygen. Following intubation, the patient was turned to prone position. Fresh gas flow was provided at low and medium flows of 4 l/min for 10 minutes and a high flow of 4 l/min throughout the entire case. After intubation, the sevoflurane vaporizer was adjusted so that the MAC value was 1.1-1.3, according to the age of the patient (Figure 1).

Figure 1: Switch to low-flow anesthesia. (Arrow A is the preoperative entry of patient's age and ideal weight into the machine, Arrow B is the setting of the alarm limits, Arrow C is the attempt to maintain the MAC value appropriate to the age between 1.1-1.3 (if the patient's hemodynamics allow), Arrow D is the vaporizer adjustment required for the MAC value that is provided)



During the administration of anesthesia, a mixture of 2 l/min oxygen and 2 l/min N2O were provided to Group H (1:1). After giving prone position, Group M and Group L were maintained with the same ratio (1:1). After 10 minutes, the fresh gas flows were reduced to 2 l/min and 1 l/min. End-tidal carbon dioxide ($EtCO_2$) was maintained between 30-35 mmHg. Sevoflurane was turned off in all three groups 5 minutes before the end of the operation, and the fresh gas flows of the medium and low groups were increased to 4 l/min and oxygen to 100% with the start of the surgical dressing. Patients with sufficient spontaneous breathing after decurarization with neostigmine 0.03 mg/kg and atropine 0.01 mg/kg were extubated and transported to the recovery unit.

In both groups, mean arterial pressure (MAP), SpO_2, heart rate (HR), endotracheal tube cuff pressure (ECP), Ppeak (PEAK) and Pplateau (PLAT) pressures (by decreasing this value if PEEP is given) in the first 60 minutes (as 0^{th}, 15^{th}, 30^{th}, 45^{th}, and 60^{th} minutes) were recorded. The duration of the operation and the amounts of oxygen, N_2O (nitrogen oxide) and total sevoflurane consumed (inhaled and used for the whole case) at the end of the operation were also noted.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 software. Mean, standard deviation, median, lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The Kolmogorov–Smirnov test was used to measure the distribution of variables. Kruskal-Wallis and Mann-Whitney U tests were used for quantitative independent data analysis. A Chi-square test was used to analyze independent

qualitative data. Pearson's and Spearman's rank correlation were used for correlation analysis. *P*-values of less than 0.05 indicated significance.

Results

The data of 150 patients were analyzed. The demographic and operational data of the patients are presented in Table 1. There was no statistically difference between the age and gender distribution of the patients in the low, medium and high-flow groups (*P*=0.450 and *P*=0.682 respectively). Demographic data of all groups were similar (height, weight, BMI: *P*=0.346, *P*=0.336 and *P*=0.878 respectively).

There was no significant difference between ASA values, or durations of operation in the low, medium, and high-flow groups (*P*>0.05 for all) (Table 2). In the low-flow group, the amount of oxygen, N_2O and sevoflurane used were significantly lower (*P*<0.05) than the medium flow and high-flow groups. In the medium-flow group, the amount of oxygen, N_2O and sevoflurane used were significantly lower (*P*<0.05) than the high-flow group. The amounts of sevoflurane inhaled in the low, medium, and high-flow groups did not differ significantly (*P*>0.05) (Table 2).

Table 1: Demographic and operational data of the patients

		Min-Max			Median	Mean (SD) / n-%	
Age		20.0	-	77.0	56.5	54.3	(12.4)
Gender	Male					52	34.7%
	Female					98	65.3%
Height		1.5	-	1.8	1.7	1.7	(0.1)
Weight		57.0	-	110.0	80.0	81.7	(11.6)
BMI		20.8	-	41.9	29.4	29.8	(4.4)
ASA	I					31	20.7%
	II					119	79.3%
Duration of the operation (min)		38.0	-	264.0	97.0	109.1	(47.5)
Oxygen (lt)		23.0	-	582.0	166.0	189.6	(88.3)
N_2O (lt)		31.0	-	544.0	94.5	119.4	(83.9)
Sevoflurane (ml)		7.0	-	129.0	21.0	26.6	(19.3)
Inhaled Sevoflurane (ml)		1.0	-	29.0	7.0	7.3	(4.1)
MAP		77.0	-	169	110.5	111.5	(17.1)
SpO_2		92.0	-	100.0	98.0	97.8	(2.1)
HR		51.0	-	116.0	80.0	81.4	(14.3)

Min-Max: Minimum-Maximum, Mean (SD) / n-%: Mean, standard deviation, number, percentage, BMI: Body mass index, ASA: American Society of Anesthesiologists, min: minute, lt: liter, ml: milliliter, MAP: Mean arterial pressure, SpO2: Peripheral oxygen saturation, HR: Heart rate.

In low, medium, and high-flow groups, 0th, 15th, 30th, 45th, 60th minute MAP, SpO_2, HR, ECP, PEAK, PLAT values were similar (*P*>0.05 for all) (Table 3).

Table 2: Data of the study groups

		Group L			Group M			Group H			*P*-value	
		Mean (SD) / n-%		Med	Mean (SD) / n-%		Med	Mean (SD) / n-%		Med		
Age		54.8	(12.5)	56.0	52.9	(12.8)	54.0	55.3	(12.1)	58.0	0.450	K
Gender	M	18	36.0%		15	30.0%		19	38.0%		0.682	X^2
	F	32	64.0%		35	70.0%		31	62.0%			
Height		1.7	(0.1)	1.7	1.6	(0.1)	1.7	1.7	(0.1)	1.7	0.346	K
Weight		83.2	(11.6)	80.0	79.3	(9.9)	80.0	82.7	(13.1)	80.0	0.336	K
BMI		29.9	(4.0)	29.4	29.5	(4.7)	29.4	29.9	(4.6)	29.2	0.878	K
ASA	I	14	28.0%		11	22.0%		6	12.0%		0.072	X^2
	II	36	72.0%		39	78.0%		44	88.0%			
Time (min.)		112.1	(52.2)	103.5	104.2	(43.8)	84.0	110.9	(46.8)	106.0	0.718	K
Oxygen (lt)		140.5	(35.0)	136.5	161.2	(47.7)	151.0	267.1	(104.1)	258.0	*0.000*	K
N_2O (lt)		63.9	(26.7)	56.0	104.9	(45.6)	86.5	189.5	(101.3)	168.0	*0.000*	K
Sev (ml)		15.8	(5.5)	15.0	22.3	(10.6)	20.0	41.7	(24.9)	35.5	*0.000*	K
Inh Sev (ml)		7.0	(3.2)	6.5	7.0	(3.9)	6.0	8.0	(4.9)	7.0	0.497	K

K: Kruskal-Wallis (Mann-Whitney U test) / X^2 Chi-square test, Med: Median, M: Male, F: Female, Sev: Sevoflurane consumed, Inh Sev: Inhaled sevoflurane, Mean (SD) / n-%: Mean, standard deviation, number, percentage, M: male, F: female, BMI: Body mass index, ASA: American Society of Anesthesiologists, min: minute, lt: liter, ml: milliliter

Table 3: MAP, SpO2, HR, ECP, PEAK, PLAT values

Minute	Group L			Group M			Group H			*P*-value	
	Mean (SD)		Median	Mean (SD)		Median	Mean (SD)		Median		
MAP											
0	107.4	(13.5)	109.0	109.0	(14.6)	107.5	117.9	(20.6)	115.5	*0.013*	K
15th	83.5	(14.8)	81.0	83.7	(13.1)	84.0	83.7	(14.1)	80.0	0.977	K
30th	85.4	(13.2)	84.5	90.8	(17.6)	88.0	82.7	(10.5)	82.0	0.054	K
45th	81.0	(11.1)	81.5	83.3	(13.1)	82.5	78.3	(14.3)	79.0	0.220	K
60th	88.4	(13.6)	88.0	89.2	(18.4)	86.0	82.7	(14.6)	83.5	0.182	K
SpO_2											
0	98.0	(2.0)	99.0	97.9	(1.9)	98.0	97.4	(2.4)	98.0	0.516	K
15th	99.4	(0.7)	99.0	99.4	(0.9)	100.0	99.0	(0.8)	99.0	0.052	K
30th	99.3	(0.9)	100.0	99.2	(1.0)	99.5	98.9	(0.9)	99.0	0.056	K
45th	99.3	(0.8)	99.5	99.2	(1.0)	100.0	99.0	(0.8)	99.0	0.092	K
60th	99.4	(0.8)	100.0	98.3	(6.2)	100.0	99.2	(0.8)	99.0	0.418	K
HR											
0	78.5	(11.8)	76.0	83.8	(15.2)	82.0	81.8	(15.3)	78.5	0.233	K
15th	77.7	(12.9)	74.0	76.2	(14.0)	73.5	70.8	(12.5)	71.5	0.054	K
30th	67.5	(10.0)	65.5	69.3	(11.2)	67.0	66.3	(11.4)	63.0	0.303	K
45th	67.9	(10.8)	66.0	67.2	(11.7)	63.5	65.1	(12.8)	61.0	0.252	K
60th	64.4	(8.1)	62.5	67.1	(12.6)	63.0	66.4	(10.9)	65.0	0.831	K
ECP											
15th	36.5	(3.9)	36.0	38.8	(4.4)	40.0	38.9	(4.9)	38.0	0.062	K
30th	44.3	(6.1)	44.0	46.8	(6.6)	47.5	45.8	(7.5)	45.5	0.071	K
45th	48.8	(7,3)	49.0	52.3	(7.8)	50.0	49.4	(9.6)	50.0	0.077	K
60th	56.7	(9.7)	55.5	61.7	(11.8)	60.0	56.8	(10.9)	57.0	0.127	K
PEAK											
15th	16.3	(3.4)	16.0	16.1	(3.6)	15.0	15.7	(3.4)	15.0	0.595	K
30th	17.5	(3.6)	17.0	17.5	(3.8)	17.0	16.4	(3.4)	17.0	0.280	K
45th	18.5	(5.8)	18.0	17.7	(3.6)	18.0	16.9	(3.4)	17.0	0.276	K
60th	18.0	(4.1)	18.0	17.6	(3.7)	17.0	16.6	(3.8)	17.0	0.281	K
PLAT											
15th	13.9	(3.3)	13.0	14.4	(4.0)	14.0	13.7	(3.1)	14.0	0.785	K
30th	15.3	(3.6)	15.5	15.4	(3.5)	15.0	14.5	(3.5)	15.0	0.395	K
45th	15.6	(4.0)	16.0	16.0	(3.8)	16.0	15.1	(3.2)	15.0	0.644	K
60th	15.8	(3.9)	16.0	15.9	(3.5)	16.0	15.1	(3.7)	15.5	0.564	K

K: Kruskal-Wallis (Mann-Whitney U test), Mean (SD): Mean, standard deviation, MAP: Mean arterial pressure, SpO2: Peripheral oxygen saturation, HR: Heart rate, ECP: Endotracheal tube cuff pressure, PEAK: Airway peak pressure, PLAT: Airway plateau pressure.

Discussion

Baker et al. [1] discussed the classification of the amount of fresh gas flow used in the anesthesia machine. According to this classification, metabolic flow is defined as 250 ml (milliliter) / min, minimal flow, as 250-500 ml/min, low flow, as 0.5-1 l/min, medium flow, as 1-2 l/min, high flow, as 2-4 l/min and very high flow, as >4 l/min. Low-flow anesthesia can be used in rebreathing systems in which 50% of the CO2 can return to the lungs after absorption. Our study was conducted in patients who received general anesthesia with low, medium, and high fresh gas flow in prone position. They were monitored on the Dräger Primus anesthesia machine. We used sevoflurane as an inhaled anesthetic agent. In their study, McGain et al. [9] and Chatrath et al. [10] suggested switching from desflurane to sevoflurane to minimize the cost and environmental impact of inhalation anesthesia, based on the high cost, low potency, and greater greenhouse gas effect of desflurane.

In our study, there was no significant difference between hemodynamic, endotracheal cuff, and airway pressures in low, medium, and high-flow groups. Hemodynamically, our results are similar to other studies [11-13]. With this result, we found that the use of low-flow anesthesia (even in prone position) has no drawbacks in terms of hemodynamics.

The patient's age and ideal weight (actual weight should not be preferred) were entered, and the device alarm limits were set to adjust the appropriate MAC and tidal volume on the anesthesia machine before the induction [6]. As the amount of fresh gas flow decreases in low-flow anesthesia, the difference between the oxygen concentration in the inspired gas increases. One of the essential concerns in low-flow anesthesia is that the patient breathes the hypoxic gas mixture through the rebreathing system. Therefore, FiO_2 must be continuously monitored [6, 14, 15]. However, thanks to the alarm limits in modern machines, these data and $InspCO_2$ can be monitored easily, and high flow may be switched to until the end of the case by increasing oxygen/air (or N_2O) mixing rates in favor of oxygen if necessary, or if there is an increase in $inspCO_2$. In our study, FiO_2 value did not fall below 40% in any of the cases. Since necessary changes were performed for soda-lime reaction, no other changes were required. During the operation, considering the hemodynamics in all groups, the sevoflurane vaporizer was adjusted according to the age-based algorithm of the anesthesia machine after intubation, so that the MAC value reached and stabilized at 1.1-1.3. Similar studies reported remaining within the recommended MAC limits (1-1.5) [16, 17].

It has been shown that low-flow anesthesia ensures the preservation of heat and moisture in the respiratory system, less air pollution, and lower costs [11, 18, 19]. In our study, we compared the amounts of sevoflurane and other gases consumed according to the different fresh gas flow in patients undergoing general anesthesia in the prone position in terms of cost. Accordingly, our groups were statistically similar with regards to operation duration, the amount of sevoflurane inhaled, and other data. The amount of sevoflurane consumed even in our low-flow (1lt/min) group (15.8 (5.5) ml) was twice the mean sevoflurane amount used by patients (7.0 (3.2) ml). While this ratio can increase to 5 times the amount of sevoflurane consumed in other groups, these results were similar to previous studies [20]. In terms of the amount of sevoflurane consumed, our low-flow group saved 62% on average compared to the high-flow group and 30% on average compared to the medium-flow group. In terms of nitrogen protoxide use, they saved 66% compared to high flow and 39% compared to medium flow. These rates remained at 47% and 13% for oxygen. Inhaler anesthetics rank second after muscle relaxants by constituting 20% of the cost. Inhaled anesthetic agents are more costly than other anesthetic drugs. It is known that the most important control mechanism of anesthetic gases in terms of cost is the amount of fresh gas flow [21]. Fresh gas flow control will prevent unnecessary costs to increase.

Although in terms of cost, the lack of evaluation of CO_2 absorbent (soda-lime) can be considered as a shortcoming of our study, it has been reported in other studies that the decrease in the cost with sevoflurane at low flow will be higher than with CO_2 absorbent [22]. However, for those with limited experience in the use of sevoflurane with low/minimal-flow anesthesia, fresh gas flow under 2 l/min is not recommended in circle-system anesthesia machines [23].

Recent studies concluded that, with modern anesthesia machines (the anesthesia machine we used was Dräger Primus), there is no reason why anesthetists managed fresh gas flow (even in prone position) to avoid low-flow anesthesia. The monitoring capabilities and alarms of modern anesthesia machines are sufficient to convince users that low-flow anesthesia will not put the patient under risk. However, for anesthetists who do not prefer low-flow anesthesia or have limited experience, our study recommended that the fresh gas flow should not exceed 2 lt/min.

Conclusion

By practice on low-flow anesthesia, and allowing better monitoring of patients (with monitor and machine settings), significant savings with be achieved. This training should be provided not only to physicians but also to anesthesia technicians who will follow up patients under general anesthesia. For those who do not prefer low-flow anesthesia, we do not recommend the use of a fresh gas flow of more than 2 l/min, which is considered the end of mid-flow anesthesia, and the starting point of high-flow.

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Prevalence and antibiotic resistance of bacterial pathogens in respiratory tract samples of geriatric patients

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Ethics Committee Approval
The ethics approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Karabuk University; No: 2021/452. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The frequency and severity of respiratory tract infections increase with aging. The aim of this study was to determine the bacterial profile of respiratory tract samples in geriatric patients and evaluate the antibiotic susceptibility patterns of the pathogens.

Methods: In this cross-sectional study, a total of 509 clinical samples which were obtained from 302 geriatric patients over 65 years of age and sent to the microbiology laboratory between June 2019-January 2021 were investigated retrospectively. The identification and antibiotic susceptibilities of strains were evaluated with BD-Phoenix-100 fully automated microbiology system.

Results: Of the 302 geriatric patients, 166 (%55) were males and 136 (%45) were females. The most isolated pathogens were *Klebsiella pneumoniae* (25.3%) *Pseudomonas aeruginosa* (22.5%) and *Acinetobacter baumannii* (10.2%), *Corynebacterium striatum* (7.3%), *Escherichia coli* (6.4%), *Staphylococcus aureus* (6.4%) and coagulase-negative staphylococci (4.2%). The production of ESBL in *Klebsiella pneumoniae* strains (52.3%) was higher than in *Escherichia coli* (41%) strains. All *Corynebacterium striatum* samples were resistant to ciprofloxacin, tetracycline, rifampin, and penicillin. Methicillin resistance among *Staphylococcus aureus* (MRSA) isolates was 22.7% and they were 100% susceptible to vancomycin and teicoplanin. Above 90% of *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* positive patients were hospitalized in intensive care units ($P<0.05$). The tobramycin-resistant *E. coli* and colistin-resistant A. *baumannii* rates were highest between 85-99 years of age ($P<0.05$).

Conclusion: K. *pneumoniae*, *P. aeruginosa* and *A. baumannii* were the most common pathogens in respiratory tract samples in geriatric patients, especially those hospitalized in the intensive care units. The antimicrobial resistance rates were higher in patients aged ≥85 years. Vancomycin and teicoplanin were the most effective antibiotics against MRSA. It is thought that the results will be useful in the preparation of treatment protocols and guiding physicians about the correct use of antibiotics.

Keywords: Antibiotic resistance, Geriatric patients, Respiratory tract samples

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Introduction

The World Health Organization has determined the age of 65 and above as 'old age' and, the United Nations has agreed that 60+ years may be denoted as 'old age' [1]. Elderly people are more susceptible to disease, syndromes, injuries, and sickness than adults. In addition, the atypical symptoms pose a diagnostic challenge in the elderly [2].

Respiratory tract infections are the most common cause of antibiotic use and the main causes of morbidity and mortality worldwide. The frequency and severity of respiratory tract infections increase with aging. Respiratory tract infections and pneumoniae accounted for nearly half of all infection-related hospitalizations in elderly individuals [3]. Many different groups of microorganisms can cause respiratory tract infections. The most common causative bacteria are *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes* [4, 5]. Also, extended spectrum beta-lactamase (ESBL) producing and carbapenem-resistant *Enterobacterales*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci species and multi-drug-resistant *Acinetobacter baumannii* are associated with both nosocomial and community-acquired infections. Multidrug-resistant *Acinetobacter baumannii*, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Enterobacter* species have become major concerns at hospital settings worldwide [5, 6].

Determining of the common pathogens that cause such infections and the patterns of resistance to existing antimicrobial drugs is crucial for defining therapeutic strategies. Bacterial pathogens responsible for respiratory tract infections and antibiotic resistance may vary by country, regions of the country, hospital, clinics and even clinic wards. Therefore, local surveillance data are required, which include detailed analysis of etiological factors [7].

The aim of this study was to determine the etiological agents causing respiratory tract infections in geriatric patients and evaluate the antibiotic susceptibility patterns of the pathogens, which would provide information to optimize accurate timely diagnosis, and treatment of the elderly patients.

Materials and methods

In this study, 509 respiratory tract samples obtained from 302 geriatric patients over 65 years of age and sent to the microbiology laboratory from various clinics such as the Intensive Care Unit, Chest Diseases, Internal Medicine, Palliative Care, Cardiology, Medical Oncology, General Surgery, Neurology, etc. in Karabuk University Training and Research Hospital between June 2019-January 2021 were investigated retrospectively. The other clinical samples test results, repeated patient results and the patients <65 years of age were excluded from this study. These results were obtained from the laboratory information system.

Clinical samples, including endotracheal aspirate (ETA), sputum, and bronchoalveolar lavage (BAL) were cultured on 5% sheep blood agar (RTA laboratories, Kocaeli, Turkey), Eosin Methylene Blue agar (EMB) (RTA), and Chocolate Agar (RTA) and incubated aerobically at 37°C for 24-48 hours.

The identification and antibiotic susceptibility of strains were determined with the BD/Phoenix-100 (Becton Dickinson, USA) automated system. Antibiotic susceptibility test results were evaluated as per EUCAST (The European Committee on Antimicrobial Susceptibility Testing) guidelines and the production of the ESBL (extended spectrum beta lactamase) enzyme was determined using the combined disk diffusion method [8]. The *E. coli* ATCC 25922, *S. aureus* ATCC 25923, and *P. aeruginosa* ATCC 27853 were used as quality control strains.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS for IBM-PC 20.0; SPSS Inc., USA). Descriptive statistics were stated as number (n), percentage (%), and median value. The Kolmogorov–Smirnov test was used to determine whether the variables were normally distributed. For the comparison of continuous variables, the two-sample t-test was used. The Pearson's Chi-squared test or Fisher's Exact test was used for comparison of categorical variables if applicable. A probability (*P*) value of <0.05 was considered statistically significant at 95% confidence interval.

Results

A total of 302 geriatric patients comprising 166 (%55) males and 136 (%45) females were included in the study. All the patients were >65 years of age and the median age of the patients was 79 (65-99) years.

In our study, 302 outpatients and inpatients were investigated, 84.4% (255/302) of which were hospitalized in the Intensive Care Unit, 7.9% (24/302), in Chest Diseases, 2.6% (8/302), in Internal Medicine, 2.3% (7/302), in Palliative Care, and 26 % (8/302) in Cardiology, Medical Oncology, General Surgery, Neurology, etc. A total of 509 clinical samples were examined, including 80% (410/509) endotracheal aspirates (ETA), 11% (53/509) sputum samples, 9% (46/509) bronchoalveolar lavage (BAL).

In 500 (98%) of 509 samples, pathogenic microorganisms were detected. No growth was observed in 9 samples (1.8%). Most isolated pathogens were Gram negative bacteria (68%, n=339), and the rate of Gram-positive bacteria was lower (20%, n=102). In the present study, 35 different pathogenic bacteria were isolated, and more than one microorganism growth was detected in 82 (27.1%) patients. The most isolated pathogens were *Klebsiella pneumoniae* (25.3%) *Pseudomonas aeruginosa* (22.5%) and *Acinetobacter baumannii* (10.2%), *Corynebacterium striatum* (7.3%), *Escherichia coli* (6.4%), *Staphylococcus aureus* (6.4%) and coagulase- negative staphylococci (CNS) (4.2%). The prevalence and distribution of the samples according to the isolated pathogens is shown in Table 1.

K. pneumoniae, *P. aeruginosa* and *A. baumannii* positivity were 93.4%, 92.9% and 90%, respectively, among patients hospitalized in the Intensive Care Units. The distribution of *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* positivity was examined according to clinics, which revealed that above

90% of positive patients were hospitalized in the intensive care units (P<0.05).

Table 1: The distribution of the samples according to the isolated pathogens

Pathogens	ETA		Sputum		BAL		TOTAL	
	n	%	n	%	n	%	n	%
Klebsiella pneumoniae	116	91.5	6	4.4	5	4.1	127	25.3
Pseudomonas aeruginosa	94	84	9	7.7	9	8.3	112	22.5
Acinetobacter baumannii	41	79.7	3	6.8	7	13.4	51	10.2
Corynebacterium striatum	34	94.1	1	1.3	2	4.6	37	7.3
Escherichia coli	21	67.1	8	24.9	3	8	32	6.4
Staphyloccocus aureus	30	92.4	-	-	2	7.6	32	6.4
*CNS**	14	66.6	4	16.9	3	16.5	21	4.2
Entorobacter cloacae	7	51.5	2	16.4	5	32.2	14	2.9
Klebsiella oxytoca	7	63.6	-	-	4	36.4	11	2.3
Serratia marcescens	6	85.7	1	14.3	-	-	7	1.4
Stenotophomonas maltophilia	5	83.3	1	14.3	1	14.3	7	1.4
Burkhoderia cepacia	6	85.7	1	14.3	-	-	7	1.4
Enterobacter aerogenes	6	85.7	1	14.3	-	-	7	1.4
Citrobacter spp.	5	83.3	-	-	1	16.7	6	1.3
Enterococcus faecalis	2	66.6	1	33.3	-	-	3	0.6
Candida albicans	1	33.3	1	33.3	1	33.3	3	0.6
Other *Corynebacterium spp.*	2	66.6	1	33.3	-	-	3	0.6
Chryseobacterium indologenes	2	100	-	-	-	-	2	0.4
Achromobacter spp.	2	100	-	-	-	-	2	0.4
Gamella haemolysans	-	-	2	100	-	-	2	0.4
Leuconostoc spp.	2	100	-	-	-	-	2	0.4
Other *Candida spp.*	1	50	1	50	-	-	2	0.4
Streptococcus acidominimus	-	-	2	100	-	-	2	0.4
Sphingomonas paucimobilis	-	-	-	-	2	100	2	0.4
Providencia stuartii	1	100	-	-	-	-	1	0.2
Entorobacter gergoviae	1	100	-	-	-	-	1	0.2
Streptococcus agalactiae	1	100	-	-	-	-	1	0.2
Delfia acidovorans	1	100	-	-	-	-	1	0.2
Enterococcus faecium	-	-	1	100	-	-	1	0.2
Moraxella catarrhalis	1	100	-	-	-	-	1	0.2
TOTAL	409	81.8	46	9.2	45	9	500	100

CNS*: coagulase-negative staphylococci, ETA: endotracheal aspirate, BAL: bronchoalveolar lavage

Antibiotic susceptibility test was performed on all the samples with pathogenic microorganism growth, and antibiotic resistance was detected in 50.4% (252/500). The pathogen with the highest antibiotic resistance was *K. pneumonia,* and it was mostly resistant to ciprofloxacin (95%) and amikacin (93.4%) (P<0.05). The second highest antibiotic resistance was found in *P. aeruginosa* against Levofloxacin (43%) and Cefepime (38%) (P>0.05). The third highest antibiotic resistance was against Ertapenem (100%), Tobramycin (100%) and Levofloxacin (95%), found in *A. baumannii* (P<0.05). Colistin resistance of *K. pneumoniae* and *A. baumanni* isolates were 24% and 5.1%, respectively. The antibiotic resistance profiles of the most isolated pathogens are shown in Table 2.

All *C. striatum* samples were resistant to ciprofloxacin (100%), tetracycline (100%), rifampin (100%), penicillin (98.2%) and clindamycin (82%), but susceptible to vancomycin and linezolid (P<0.05) (Table 2).

The rates of antibiotic resistance of *E. coli* to ciprofloxacin, TMP-SMX, gentamicin, and piperacillin-tazobactam were 92%, 62%, 22%, and 14%, respectively. The production of ESBL in *E. coli* strains was 41%. The production of ESBL in *K. pneumoniae* strains (52.3%) was a bit higher than that in E. coli (41%) strains (P>0.05).

Among *Staphylococcus aureus* isolates, 22.7% were methicillin-resistant (MRSA). MRSA isolates were 100% sensitive to vancomycin and teicoplanin (P<0.05).

The antimicrobial resistance results of the predominant organisms were investigated by age groups. Tobramycin-resistant *E. coli* and Colistin-resistant *A. baumannii* rates were highest between 85-99 years of age (P<0.05). Antimicrobial resistance results for the predominant organisms by age group are shown in Table 3.

Table 2: The antibiotic resistance profiles of the most isolated six pathogens

%	*Klebsiella pneumoniae* (n:127)	*Pseudomonas aeruginosa* (n:112)	*Acinetobacter baumannii* (n:51)	*Corynebacterium striatum* (n:37)	*Escherichia coli* (n:32)	*Staphylococcus aureus* (n:32)	*P*-value
AK	77.1*	6	79	0	4	4	0.03
AX	-	-	-	-	74	-	NA
AMC	93.4	-	-	0	-	-	NA
AM	100	-	-	0	92.5	-	0.73
SAM	97	-	-	-	65.3	-	0.46
FEP	92.3	36.2	-	-	65.3	-	0.54
CAZ	92.3	36	-	-	63	-	0.67
CRO	93.4	-	--	-	78	-	0.63
CXM	93.4	-		-	85	-	0.60
CIP	95*	34.2	95	100*	92.5	4	0.02
DA	-	-	-	74.5	-	19.2	0.57
CT	23	5.3	5.1	-	0	-	0.42
DAP	-	-	-	14.2	-	-	NA
E	-	-	-	25	-	23	0.73
ETP	77	-	100*	-	0	-	0.01
FF	-	-	-	0	0	0	0.01
FA	-	-	-	0	-	11.5	0.34
CN	80.4	16	89.3	82.2*	22.2	8	0.04
IPM	61.1	43	90.4	-	-	-	0.62
LEV	91.3	43.2	95*	14.2	92.5	4	0.02
LNZ	-	-	-	0	-	-	NA
MEM	64	34.5	91	-	0	-	0.65
MXF	-	-	-	0	-	4	0.31
OX	-	-	-	0	-	31	0.52
P	-	-	-	98.2*	-	85	0.03
TPZ	87	35.3	-	-	15	-	0.72
RA	-	-	-	100*	-	5.2	0.03
TE	55	-	-	100*	-	27	0.04
TOB	-	-	100*	-	-	-	0.02
SXT	83	-	77.3	33.3	63	11.5	0.47
TGC	-	-	7.1	-	-	-	NA
VA	-	-	-	0	-	-	NA

AK: Amikacin, AX: Amoxicillin, AMC: Amoxicillin/ Clavulanic acid, AM: Ampicillin, SAM: Ampicillin/Sulbactam, FEP: Cefepime, CAZ: Ceftazidime, CRO: Ceftriaxone, CXM: Cefuroxime, CIP: Ciprofloxacin, DA: Clindamycin, CT: Colistin, DAP: Daptomycin, E: Erythromycin, ETP: Ertapenem, FF: Fosfomycin, FA: Fusidic acid, CN: Gentamicin, IPM: İmipenem, LEV: Levofloxacin, LNZ: Linezolid, MEM: Meropenem, MXF: Moxifloxacin, OX: Oxacillin, P: Penicillin, TPZ: Piperacillin +Tazobactam, RA: Rifampin, TE: Tetracycline, TOB: Tobramycin, SXT: Trimethoprim + Sulfamethoxazole, TGC: Tigecycline, VA: Vancomycin; *P<0.05, NA: Not applicable

Table 3: Antimicrobial resistance results for the predominant organisms by age group

	Antimicrobial susceptibility by age group[a]								
	65-74 years old			75-84 years old			85-99 years old		
Pathogen organisms (EUCAST criteria)	n	R (%)	S (%)	n	R (%)	S (%)	n	R (%)	S (%)
Klebsiella pneumoniae	38			48			41		
AK		71.4	28.6		74.3	25.7		86.2	13.8
AMC		96.4	3.6		91.4	8.6		93.1	6.9
AM		100	-		100	-		100	-
SAM		100	-		91.4	8.6		100	-
FEP		96.4	3.6		85.7	14.3		96.6	3.4
CAZ		96.4	3.6		88.6	11.4		93.1	3.4
CRO		96.4	3.6		88.6	11.4		96.6	3.4
CXM		96.4	3.6		88.6	11.4		96.6	3.4
CIP		96.4	3.6		91.4	8.6		96.6	3.4
CT		33.3	-		13.8	-		25.9	3.7
9.8ETP		78.7	14.9		77.8	15.9		74.5	13.8
CN		75	25		80	20		86.2	24
IPM		65.2	13		63.9	27.9		54	3.4
LEV		92.9	3.6		88.6	8.6		93.1	3.4
MEM		69.6	21.7		67.2	24.1		54	24
TPZ		89.3	7.1		80	17.2		93.1	6.9
TE		82.1	17.9		77.1	22.9		89.7	6.9
SXT		52.9	11.8		66.7	8.3		43.5	4.3
Pseudomonas aeruginosa	28			38			46		
AK		10.8	89.2		8	88		11.3	82.3
FEP		50	50		22	78		45.2	54.8
CAZ		52.6	47.4		24	76		35.5	64.5
CIP		29.7	67.6		30	70		40.3	59.7
CT		6.5	-		2.3	6.8		7.3	-
CN		18.4	81.6		10.6	89.4		17.7	80.6
IPM		56.4	40		40.5	59.5		36.4	56.8
LEV		50	50		42	58		40.3	59.7
MEM		55.6	38.9		30.7	49.3		25.3	51.6
TPZ		52.6	47.4		20	80		37.1	62.9
Acinetobacter baumannii	11			16			24		
AK		88.9	11.1		100	-		80	20
CIP		100	-		100	-		100	-
CT		-	-		-	10		6.7*	6.7
ETP		-	-		100	-		100	-
CN		77.8	22.2		85.7	14.3		95	5
IPM		81.3	6.3		95.8	-		94.9	-
LEV		100	-		100	-		100	-
MEM		81.3	6.3		100	-		94.6	-
TOB		-	-		100	-		-	-
SXT		100	-		78.6	7.1		85	15
Corynebacterium striatum	11			15			11		
CIP		100	-		100	-		100	-
DA		76.5	23.5		76.2	23.8		70.6	23.5
DAP		50	-		-	-		-	-
CN		89.5	5.3		75	25		84.2	10.5
LNZ		-	100		-	100		-	94.4
P		100	-		100	-		94.4	5.6
RA		100	-		100	-		100	-
TE		100	-		100	-		100	-
SXT		-	-		50	50		-	-
VA		-	100		-	100		-	100
Escherichia coli	13			6			13		
AK		9.1	90.9		-	100		-	100
AX		81.8	18.1		80	20		63.6	27.4
AM		90.9	9.1		80	20		100	-
SAM		72.7	27.3		80	20		50	50
FEP		54.5	45.5		40	40		90	10
CAZ		63.6	27.3		40	60		72.7	9.1
CRO		63.6	36.4		60	40		100	-
CXM		81.8	18.1		60	40		100	-
CIP		81.8	9.1		100	-		100	-
CT		-	20		-	33.3		-	11.1
ETP		-	92.9		-	100		-	100
FF		-	-		-	-		-	100
CN		27.3	72.7		20	80		18.1	81.8
IMP		-	92.9		-	100		-	100
LEV		81.8	9.1		100	-		100	-
MEM		-	92.3		-	100		-	100
TPZ		18.1	63.6		20	40		9.1	72.7
TOB		-	-		-	-		100*	-
SXT		63.6	36.4		80	20		54.5	45.5
TGC		-	50		-	-		-	-
Staphylococcus aureus	5			16			11		
AK		-	100		7.7	92.3		-	100
CIP		-	100		7.7	92.3		-	100
DA		25	75		23.1	76.9		11.1	88.9
DAP		-	100		-	100		-	100
E		50	50		23.1	76.9		11.1	88.9
FF		-	100		-	100		-	100
FA		-	100		15.4	84.6		11.1	88.9
CN		-	100		15.4	84.6		-	100
LEV		-	100		7.7	92.3		-	100
LNZ		-	100		-	100		-	100
MXF		-	100		7.7	92.3		-	100
OX		25	75		30.8	69.2		33.3	66.7
P		50	50		84.6	15.14		100	-
RA		-	66.6		10	-		-	-
TEL		-	100		-	100		-	100
TE		25	75		30.8	69.2		22.2	77.8
SXT		-	100		7.7	92.3		22.2	77.8
VA		-	100		-	100		-	100

S: susceptible, R: resistant, *P<0.05, [a] Antimicrobial resistance was presented as % S and % R

Discussion

Respiratory tract infections are the most common diseases in the elderly and age is a major risk factor for both occurrence and severity of respiratory tract infections. There is insufficient data on the distribution and antimicrobial susceptibility rates of bacterial pathogens that cause respiratory tract infections. Therefore, determining common pathogens and their antimicrobial resistance profiles is crucial. In our study, the most isolated pathogens were Gram-negative bacteria (68%). Premalatha et al. [9] investigated 110 geriatric patients (>65 years) with lower respiratory tract infections and reported 60% Gram-negative bacilli and 9.1% Gram-positive cocci. *K. pneumoniae* (36.8%) was the most frequent pathogen, followed by *P. aeruginosa* (22.3%) and *A. baumannii* (11.8%). In the randomized study by Khattab et al. [10], *K. pneumoniae*, *P. aeroginosa* and *Acinetobacter spp*. were the most common organisms, followed by Methicillin-resistant *Staphylococcus aureus* and *E. coli* in lower respiratory tract infections. In the present study, in line with literature, the most isolated pathogens were *K. pneumoniae, P. aeruginosa, A. baumannii, C. striatum, E. coli* and *S. aureus* in geriatric patients with respiratory tract infections [9-11]. Moreover, above 90% of K. *pneumoniae, P. aeruginosa* and *A. baumannii* positive patients were hospitalized in the intensive care units. The most common nosocomial pathogens in respiratory tract infections are seen among intensive care unit patients and in geriatric hospitals [10-12].

Antibiotic resistance is an important health problem all over the world. It is known that long-term hospitalization and use of antibiotics increase the risk of emergence of multi-resistant microorganisms. Multidrug resistant Gram-negative bacteria studies have focused on *K. pneumoniae, E. coli* (ESBL, carbapenemase), *A. baumannii* and *P. aeruginosa*. In our study, *K. pneumoniae* (52%) was the most common pathogen and a potent ESBL producer and had the highest antibiotic resistance. In many studies, *K. pneumoniae* was the predominant ESBL producing organism, similar to our study [10-12]. Mu et al. [12] reported that 39 strains (31%) out of the total 126 isolates of *K. pneumoniae* were ESBL producers. *K. pneumoniae* and *E. coli* were the second highest ESBL producer strains with 41%. Lin et al. [13] investigated the ESBL producing *Enterobacterales* isolates in geriatric patients in respiratory care wards. They found that the prevalence of ESBL-producing isolates of *K. pneumoniae* and *E. coli*. were 69.7% and 39.5%, respectively. The studies suggest that the prevalence of ESBL worldwide in both *E. coli* and *K. pneumoniae* is markedly increasing and the risk factors for ESBL producing are exposure to antibiotic therapy, age, and length of hospitalization [14-16].

According to the results of National Antimicrobial Resistance Surveillance 2016 data in Turkey [17], multi-drug resistance was calculated as 83.5% in invasive *Acinetobacter* spp. isolates, and colistin resistance was 6.7%. In our study, carbapenem resistance was around 93% and colistin resistance was lower than the country average (5.1%) among *A. baumannii* isolates. Altay et al. [18] investigated the etiologic agents and their antimicrobial resistances in patients with respiratory tract infections in Turkey and found that the carbapenem resistance was around 40% among *K. pneumoniae* isolates. According to the results of surveillance in 2016 in Turkey [17], multi-drug resistance was 46.1% in invasive *K pneumoniae* isolates, and carbapenem resistance was 40%. Our results were higher compared to those in the literature, with 65% carbapenem resistance in *K. pneumoniae* isolates.

Corynebacterium striatum has been increasingly reported as an infectious agent in patients with long-term hospitalization. Formerly, it was susceptible to many drugs, but it has recently demonstrated high-level resistance to antibiotics such as macrolides, aminoglycosides etc. [19]. The increase in antimicrobial resistance of *C. striatum* is a great concern. Asgin et al. [20] investigated antimicrobial resistance and molecular epidemiology of 81 *C. striatum* strains and they reported that all *C. striatum* strains were resistant to penicillin, cefotaxime, ciprofloxacin, and tetracycline, but susceptible to vancomycin and linezolid. Similarly, in the present study, *C. striatum* showed resistance against most used antibiotics. All *C. striatum* samples were resistant to ciprofloxacin, tetracycline, rifampin, and penicillin, but susceptible to vancomycin and linezolid. Therefore, according to our antibiotic susceptibilities results, linezolid and vancomycin may be selected for the treatment of *C. striatum* infections.

One of the most well-known cases of antimicrobial resistance, Methicillin resistance in *Staphylococcus aureus* (MRSA), has been associated with high mortality rates every year [21]. According to National Antimicrobial Resistance Surveillance System 2016 data, MRSA in *S. aureus* isolates rate was 23.6% in Turkey [17]. EARS-Net 2016 [22] reported that the average rate of MRSA in *S. aureus* isolates is 13.7% in the European Union countries. Akgün and Sayıner [23] investigated 320 coagulase-positive *S. aureus* which were cultured from patients hospitalized in the intensive care unit and reported that the rate of MRSA in *S. aureus* isolates was 20.9% in Turkey. Khattab et al. [10] isolated 8.1% MRSA among the total isolates. They were 100% sensitive to vancomycin and teicoplanin. The present study agrees with the literature: Our rate of MRSA isolates was 22.7% and MRSA isolates were 100% sensitive to vancomycin and teicoplanin [9, 10, 13].

Age was significantly associated with differences in antimicrobial resistance for many pathogenic organisms [25, 26]. Adam et al. [26] investigated the association between age groups (children, adults, and the elderly) and antimicrobial resistance in the most identified pathogens. They reported that resistance rates are often higher among the elderly. In the present study, antimicrobial resistance rates were higher in patients >85 years of age. This may be associated with increased exposure to antimicrobial resistant organisms in long-term care facilities and frequent hospitalizations or high rate of multidrug resistance.

In the coming years, compared to non-resistant bacteria, resistant forms are expected to cause a double risk of developing a severe infections and triple risk of mortality [24].

Limitations

There are some limitations in this study. First, because this is a retrospective single-center study based on laboratory data, the data on the clinical findings and treatments of patients are not available. Second, the reference method for antibiotic susceptibility, the agar dilution test could not be performed.

Conclusion

The most encountered pathogens were *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*, *C. striatum*, *E. coli* and *S. aureus* in respiratory tract samples in geriatric patients. Above 90% of *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* positive geriatric patients were hospitalized in the intensive care units. The antimicrobial resistance rates were higher in patients above 85 years of age. Vancomycin and teicoplanin were the most effective antibiotics against MRSA. It is thought that the results will be useful in the preparation of treatment protocols and in guiding physicians about the correct use of antibiotics. The resistance profiles should be monitored regularly through active surveillance in geriatric patients.

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Risk factors and consequences of delayed graft function in renal transplantation

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The study approved by the Ondokuz Mayis University Clinical Research Ethics Committee (Approval number: 2020/510).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Delayed graft function (DGF) continues to be an important complication in patients who underwent kidney transplantation. Our study aimed to determine the rate of DGF and risk factors after renal transplantation at our center and explore DGF-related complications and outcomes.
Methods: Patients over 18 years of age who underwent kidney transplantation between January 2015 and January 2020 were evaluated. DGF was defined as the need for at least one dialysis session within the first week after renal transplantation. The factors affecting DGF were analyzed as the primary outcome, and discharge and additional complications, as the secondary outcomes.
Results: Data of 206 patients who underwent renal transplantation were analyzed, and delayed graft function (the need for at least one dialysis session within the first week after renal transplantation) was observed at a rate of 20.9%. A statistically significant relationship was observed between DGF and presence of diabetes mellitus, cadaver graft transplantation, higher cold ischemia time, need for postoperative erythrocyte suspension and fresh frozen plasma transfusion ($P<0.05$ for all). Graft loss was significantly higher in patients with DGF ($P=0.001$).
Conclusion: After renal transplantation, delayed graft function continues to occur at a high rate. Prevention of delayed graft function development will reduce graft loss rates.

Keywords: Kidney transplantation, Delayed graft function, Allograft rejection

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Introduction

Most cadaveric and some living-donor organ transplants show early dysfunction to some extent, leading to delayed graft function (DGF). Rarely, the graft never functions (primary dysfunction). DGF is a form of acute renal failure that results in post-transplantation oliguria. Optimization of donor and recipient management and improvements in diagnostic and therapeutic modalities have neither reduced the overall rates of this disorder nor mitigated its short- and long-term effects [1]. DGF is associated initially with ischemia-reperfusion injury, and triggered host inflammatory response and, ultimately, with decreased graft life and patient survival, and acute graft rejection [2]. The factors that affect DGF can be grouped as donor-related, recipient-related, and perioperative risk factors [3, 4].

Our aim in the study was to determine the rate of DGF and risk factors after renal transplantation at our center and explore DGF-related complications and outcomes.

Materials and methods

Our hospital's patient data system "Nucleus Medical System^{R}" and archived data records were used to retrieve data of patients who underwent renal transplantation at Ondokuz Mayıs University Medical Faculty Hospital between January 2015 and January 2020. It was a retrospective study approved by the Ondokuz Mayis University Clinical Research Ethics Committee (Approval number: 2020/510). The exclusion criteria were as follows: Being aged <18 years, mortality within the first week, inability to access screening data related to DGF, the presence of concomitant extra renal organ transplantation, and primary dysfunction after renal transplantation. All patients aged >18 years who underwent living-donor or cadaveric renal transplantation were included in this study.

DGF was defined as the need for at least one dialysis session within the first week after renal transplantation.

The following data were recorded: Patient demographics (e.g., age, body mass index (BMI), chronic diseases, and drugs used), human leukocyte antigen (HLA) matching, drugs used in anesthesia induction and their doses, drugs used in anesthesia maintenance and their doses, intraoperative fluid amounts, blood and blood products, inotropic and/or antihypertensive drugs and their doses, intraoperative vital signs (e.g., arterial blood pressure, pulse, body temperature, respiratory rate, SpO2, central venous pressure, and mechanical ventilation values), vital signs in the first postoperative week (e.g., arterial blood pressure, pulse, number of respiration, and body temperature), SpO2, daily urine amount, electrolyte values (Na, K, Mg, Cl, P, Ca), total blood count, blood urea nitrogen, creatinine values, daily and total postoperative fluid balance, blood and blood products used, and inotropic and/or antihypertensive drugs and their doses. Immunosuppressive protocol used after transplantation, and dialysis requirements in the first postoperative week were examined in terms of DGF. Parameters considered to affect DGF were evaluated by comparing them with the data of the non-DGF control group.

Statistical analysis

Demographic data were summarized using frequency (percent) or mean (standard deviation) depending on the data type. Fisher's exact tests and chi-squared tests were used to compare categorical variables, and one-way analysis of variance was used to compare continuous variables. Logistic regression models were utilized to assess the risk factors for mortality, graft loss, and DGF. Statistical analyses were performed using IBM SPSS Statistics 21.0 software. $P<0.05$ was considered statistically significant.

Results

The data of 206 patients who underwent renal transplantation were accessed. DGF was observed in 43 (20.9%) patients. Evaluation of the relationship between DGF and demographic data, HLA matching, and comorbidities revealed that DGF rates were higher in the presence of diabetes mellitus ($P=0.007$); however, there was no significant correlation between DGF and the other variables (Table1). Patients were not evaluated in terms of ABO blood group matching, as fully matching ABO group was a prerequisite for renal transplantation at our center. In total, 106 (51%) patients underwent cadaveric renal transplantation, while 100 (49%) underwent living-donor renal transplantation. Among the live donor transplants, 62 (62%) were first degree, 34 (34%) were second degree, 4 (4%) were third-degree relatives. No intraoperative or postoperative complications were encountered in transplants from living donors. There has been no mortality in living donors so far. DGF was observed in three (3%) recipients of living-donor kidneys and in 40 (37.7%) recipients of cadaveric kidneys ($P=0.011$). The mean cold ischemia times were 379 (60–1.140) minutes and 721 (70–1.200) minutes in the living and cadaveric donor groups, respectively, with a significant correlation between cold ischemia time and DGF ($P<0.01$). However, DGF was not significantly correlated with surgery duration, intraoperatively used crystalloid and colloid quantity, blood and blood product transfusion, or the rates of hypo- and hypertensive attacks developing intraoperatively (Table 2). According to the renal transplantation protocol followed at our center, regardless of patient weight, all adult patients were administered 500 mg methylprednisolone, 12.5 g mannitol, and 100 mg furosemide during the operation. Methylprednisolone, mannitol, and furosemide and their doses per kilogram of patient weight were studied to see if they correlated with DGF, but no significant difference was noted (Table 2). Of all patients included,192 (93.2%) underwent open and 14 (6.8%) underwent laparoscopic renal transplantation. The rate of DGF was significantly higher in patients who underwent laparoscopic renal transplantation ($P=0.026$). When the hemoglobin level, blood and blood product transfusions, and hemodynamic parameters of the patients undergoing renal transplantation were analyzed during the first postoperative week, DGF was found to significantly correlate with receiving freshly frozen plasma and erythrocytes suspension replacement ($P<0.05$), but not with the other variables (Table 3).

In patients with DGF, graft rejection rate was significantly higher ($P<0.05$) compared to those without DGF, while mortality rate and the duration of hospitalization were similar (Table 3).

Table 1: The relationship between demographic data and delayed graft function

	DGF (+) n=43	DGF (-) n=163	*P*-value
Age, year (mean,min-max)	44 (20-60)	42 (18-66)	0.364
BMI, kg/m^2 (mean, min-max)	23.4 ((14.8-32.8)	23.5 (14.1-35.4)	0.359
Sex (Female/Male) %	41.9/58.1	58.1/41.9	0.493
Diabetes Mellitus %	51.2	35.6	0.007
Hypertension %	51.2	50.9	0.623
Heart failure %	4.7	3.7	0.314
COPD %	0	1.2	0.999
Smoke %	37.5	9.2	0.062
HLA mismatches (%)			0.305
0	8 (18.6)	15 (9.2)	
1	8 (18.6)	36 (22.1)	
2	9 (20.9)	39 (23.9)	
3	12 (27.9)	42 (25.8)	
4	5 (11.6)	19 (11.7)	
5	-	2 (1.2)	
6	1 (2.3)	10 (6.1)	

COPD: Chronic Obstructive Pulmonary Disease, BMI: Body Mass Index, HLA: Human Leukocyte Antigen

Table 2: The relationship between intraoperative data and delayed graft function

	DGF (+) n=43	DGF(-) n=163	*P*-value
Surgery time, minute	225 (155-480)	209 (110-480)	0.075
Intraoperative crystalloid amount, ml	3045 (2000-5500)	2975 (1000-6000)	0.465
Intraoperative colloid%	7	8	0.684
Erythrocyte Suspension%	4.7	7.4	0.999
Fresh Frozen Plasma%	4.7	2.5	0.999
Intraoperative Hypotension%	16.3	14.1	0.606
Intraoperative Hypertension%	7	8	0.749
Steroid (mg / kg)	7.9 (5-14.2)	8.7 (3.7-26.3)	0.186
Mannitol (g / kg)	0.19 (0.01-0.37)	0.19 (0.01-0.39)	0.323
Furosemide (mg / kg)	1.5 (0.8-2.5)	1.6 (0.1-12)	0.391

Table 3: The relationship between postoperative data and delayed graft function.

	DGF (+) n=43	DGF(-) n=163	*P*-value
Postoperative Hemoglobin, mg / dl	7.7 (5-11)	8.4 (6.1-13)	0.359
Postoperative Hypotension%	16.3	18.4	0.473
Postoperative Hypertension%	69.8	65	0.535
Erythrocyte Suspension%	53.5	21.5	0.01
Fresh Frozen Plasma%	48.8	8.6	0.01
Mortality%	9	2.5	0.061
Graft loss%	27.9	2.5	0.001
Hospital stay, days	13(5-30)	11(4-34)	0.768

Discussion

DGF remains a significant complication after renal transplantation. In this retrospective study, the variables of renal transplantation process performed at our center and subsequent risk factors for DGF, and associated complications were examined.

In our study, 43 (20.9%) patients had DGF. In the literature, the rate varies widely between 2% and 50% [5]. In a study of 86,682 patients who underwent renal transplantation, the DGF rate was 21%, similar to our study [6] .

A crucial factor leading to DGF appears to be hypoperfusion-related cell damage, besides immunological factors. This process is further exacerbated by ischemia-reperfusion injury [7]. According to several studies focusing on DGF, donor-related risk factors include age, comorbidity, BMI, and final creatinine level, recipient-related risk factors include age, BMI, comorbidity, and race, and procedure-related risk factors include cold ischemia time and surgical duration [8, 9].

DGF rate is approximately 25% after cadaveric and 1%–8% after living-donor renal transplantations [10, 11]. The cadaveric donor transplantation procedure involves almost all risk factors for DGF (long cold ischemia time, ischemia-reperfusion injury, and donor-related comorbidities) [12]. In our study, DGF was significantly higher in the cadaveric group.

Lauronen et al. [13] evaluated 846 patients who underwent renal transplantation and reported that the cold ischemia time and DGF rate were significantly correlated. The mean cold ischemia time was 1,080 min in this study. A general opinion is that the cold ischemia time should be <12 h. [13-15]. In our study, the overall mean cold ischemia time was 450 (60–1.200) min, and there was a significant correlation between cold ischemia time and DGF. The cold ischemia time varied significantly between the living and cadaveric donor groups. However, when these two groups were evaluated separately for DGF and cold ischemia time, no significant correlation was observed between the two. The short cold ischemia times at our center compared with those reported in the literature can explain this.

HLA is considered an important biological barrier for successful transplantation [16]. However, modern immunosuppressive agents reduce the effect of HLA matching. In the revised UK Kidney Allocation Scheme, the HLA-A match is no longer required [17]. The European Renal Transplantation Guide still recommends HLA-A, HLA-B, and especially, HLA-DR matching as much as possible [18]. In a meta-analysis published by Shi et al., they emphasized that HLA mismatching is a prognostic factor, and in particular, HLA-DR matching is effective in graft survival [19]. The relationship between DGF and HLA subgroup and total matching was not shown in our study.

Diabetes mellitus increases ischemia-reperfusion injury due to chronic inflammatory process and increased oxidative stress [20]. Diabetes mellitus is mentioned in most studies as an independent risk factor for DGF [21, 22]. In addition, chronic renal insufficiency can cause significant changes in insulin metabolism and blood sugar regulation. According to the glomerular filtration rate, insulin clearance changes and hypoglycemia or hyperglycemic attacks may occur. In our study, similar to the literature, the presence of diabetes mellitus was identified as a facilitating factor for DGF.

Hemodynamic stability is very important in terms of graft perfusion, especially in the intra operative period [23]. Several factors such as anesthesia induction, anesthesia maintenance, proper fluid replacement, surgery duration, surgical technique (laparoscopic/open), and intra operative blood loss affect intra operative hemodynamics and organ perfusion. In our study, the patients were hemodynamically stable in the intra operative period; there was no significant difference between the DGF and non-DGF groups in terms of blood and blood product transfusion and fluid replacement. As the laparoscopic technique causes less blood loss, has shorter surgical duration and leads to more stable hemodynamics, it stands out in renal transplantation [24]. Although the number of patients was not evenly distributed (laparoscopic:14; open: 192), the DGF rate was lower in the open surgery group in our study. There was no difference between the two groups in terms of surgery duration, blood and blood product transfusion, and hemodynamic instability. Renal perfusion associated with increased intra-abdominal pressure during laparoscopic technique was a subject requiring further investigation.

Hypoperfusion, which is responsible for possible complications after transplantation, develops after insufficient oxygen delivery. Unless the concentration of hemoglobin, which is an important component of oxygen delivery, falls under the threshold (7 g/dl if there is no acute coronary syndrome), erythrocyte transfusion is not recommended, especially in intensive care patients, because of its possible side effects [25-

27]. In particular, multiple blood and blood product transfusions affect immunization through HLA, resulting in adverse effects such as acute graft rejection after transplantation [28]. In our study, hemoglobin levels were similar in patients with and without DGF in the first postoperative week. However, these similar hemoglobin levels were significant in patients with DGF receiving erythrocyte suspension and freshly frozen plasma.

DGF indicates hypoperfusion of not only the kidney but also the whole body. An increased mortality rate is expected in cases of hypoperfusion, ischemia-reperfusion injury, and possible comorbidities in patients with renal failure who require treatment regimens, such as immunosuppressive therapy, which have severe side effects [29]. Using hemodialysis for the treatment of patients with DGF may reduce early mortality rates. In our study, mortality rates in patients with DGF were similar. The duration of hospital stay was insignificantly higher in patients with DGF compared with those without. Graft loss rate was significantly higher in patients with DGF.

Limitations

This study has several limitations, the most prominent being its retrospective and single-center design. Donor data could not be evaluated due to the lack of recorded data on donors. Existing comorbidities and duration were interpreted in accordance with the data.

Conclusion

There are ongoing studies that focus on the risk factors and occurrence mechanism in DGF. Reducing DGF after renal transplantation may also decrease graft loss and mortality rates.

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Analysis of patients admitted to the emergency department with gunshot wounds

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Ethics Committee Approval
This study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/449). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: The incidence and nature of gunshot wounds differ between countries, and they are a prominent cause of mortality and morbidity. The primary assessment and treatment of patients with gunshot wounds in the emergency department are often highly complex. In this study, we aimed to investigate the effect of clinical findings and trauma scores on patient prognosis and mortality of patients who applied to the emergency department with gunshot wounds.

Methods: In this retrospective cohort study, records of patients with gunshot wounds were accessed from the archive. Patients' age, gender, time of admission to the emergency department, injured body regions, image reports, hospitalization status and mortality rates were analyzed. The Glasgow Coma Scale (GCS), Revised Trauma Score (RTS), Injury Severity Score (ISS) and Trauma and Injury Severity Score (TRISS) rates were calculated for all patients to predict prognosis.

Results: Most injuries (50.8%) and the highest mortality (66.7%) occurred between 16:01 and 24:00. The most common injuries were lower extremity injuries (63.9%) and upper extremity injuries (47.5%). The mean GCS, RTS, and ISS were 13 (3.6), 7.07 (2.23), and 12.36 (10.48), respectively, and the mean TRISS survival probability for penetrating trauma was 88.59%. Eighteen patients (29.5%) were treated and discharged from the emergency department, nineteen (31.2%) were admitted to the wards and 9 patients (14.8%), to the intensive care unit. In patients who died, GCS, RTS, and TRISS were significantly lower than in surviving patients, and the ISS was statistically significantly higher ($P<0.001$). Mortality rate was 9.8%.

Conclusion: Gunshot wounds can cause serious injuries associated with high mortality, especially in the head, chest, and abdomen. GCS, ISS, RTS and TRISS trauma score systems will be useful in predicting prognosis and mortality rates in gunshot wounds.

Keywords: Gunshot wounds, Glasgow coma scale, Injury severity score, Revised trauma score, Trauma and injury severity score

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Introduction

Gunshot wounds are one of the most important traumas affecting mortality and morbidity. Especially with the industrial development of firearms in the second half of the nineteenth century, the incidence of gunshot wounds increased worldwide [1, 2]. With the easy availability of firearms, mortality rates due to gunshot wounds are increasing in our country as well. The bullet rotates and advances along its rotation, which may lead to more serious injuries than the physician initially suspects [3]. Gunshot wounds can cause high morbidity and mortality due to concomitant organ and vascular injuries [1, 2].

In the emergency department (ED), the trauma patient who was seriously injured by a firearm should be evaluated and intervened rapidly for airway obstruction, tension pneumothorax, massive internal or external hemorrhage, open pneumothorax, flail chest, and cardiac tamponade [4].

Trauma scoring systems are used in emergency situations to provide fast and accurate triage to trauma patients and predict mortality. These scoring results provide information about the course of the disease and affect the treatment of the casualty. Trauma scores are calculated according to age, anatomical injury, and physiological findings [5].

This study aimed to examine the effects of clinical findings and trauma scores on prognosis and mortality by examining the patients who were admitted to the ED with gunshot wounds.

Materials and methods

This retrospective cohort study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/449 on 02/10/2020). Among 2601 forensic cases admitted to the ED of Afyonkarahisar Health Sciences University between 01.11.2019-01.11.2020, sixty-one (aged 0-90 years) were admitted to the emergency department with gunshot wounds. The patients' age, gender, time of admission to the ED, injured body regions, image reports, hospitalization status, trauma scores and mortality rates were retrospectively examined from the archive and analyzed.

Glasgow coma score (GCS) is a scoring system that helps evaluate consciousness after head trauma and predict of the prognosis in the preliminary period [6,7].

The Injury Severity Score (ISS) allows evaluation of the severity of existing lesions according to the anatomical region. The score ranges from 0 to 75. Traumas which score over 15 points in the ISS are considered severe [8].

Revised Trauma Score (RTS) is a scoring system that includes GCS, systolic blood pressure (SBP) and respiratory rate (RR). It is calculated with the formula RTS = (0.9368 x GCS) + (0.7326 x SBP) + (0.2908 x RR) and results in a score between 0-7.8408 [9].

Trauma and Injury Severity score (TRISS) is calculated using the ISS and the patient's age [10].

GCS, RTS, ISS and TRISS rates were calculated for all patients to predict prognosis.

Statistical analysis

Statistical analysis of the study was performed using SPSS version 22.0. The data were presented as mean, standard deviation and percentages. The Kolmogorov Smirnov test was used to determine the conformity of the data to normal distribution, which revealed that the data was non-normally distributed. Mann Whitney U test was used for pairwise group comparisons in which significant differences between measurements were evaluated, and Kruskal Wallis Test was used for multi-group comparisons. The results were evaluated at a 95% confidence interval, and P <0.05 was considered statistically significant.

Results

Sixty-one patients (95.1% male, 4.9% female) were admitted to the emergency department after a gunshot wound within one year. The mean age of all patients was 35.5 years (range: 5-87 years). Most events (50.8%) and the highest mortality (66.7%) occurred between 16:01-24:00. Gunshot wounds were most seen in November (16.4%). No significant relationship was detected between age and mortality (P=0.531, r=-0.063).

The most common injury sites of gunshot wounds were lower (n=39, 63.9%) and upper extremity injuries (n=29, 47.5%). More than one area of injury was seen in 25 (41%) patients.

The average trauma scores were calculated for all patients. The mean GCS, RTS, and ISS were 13 (3.6) (range: 3-15), 7.07 (2.23) (range: 0-7.84), and 12.36 (10.48) (range:1-54), respectively, and the mean TRISS survival probability for penetrating trauma was 88.59% (range: 0.24-99.45%). In patients who died, GCS, RTS and TRISS were significantly lower, and ISS was significantly higher compared to surviving patients (P<0.001). In total, nineteen patients had severe injury, hence an ISS of above 15 points. ISS of six patients who died ranged between 25-54.

The first blood test results of the patients admitted to the ED with gunshot wounds are given in Table 1. Ten patients required erythrocyte suspension transfusion. Forty-one patients (67.2%) had their blood alcohol levels measured in the ED, and four patients were found to have consumed alcohol. All cases (n=61) were reported to the judicial authorities.

Table 1: The first admission blood test results in the emergency department

Value	Median (min-max)	Mean (SD)
BUN (mg/dl)	15 (6.54-49.5)	18.26 (8.71)
Creatinine (mg/dL)	0.90 (0.28-1.5)	1.17 (1.87)
Sodium (mmol/L)	140 (133-150)	137.31 (19.54)
Chloride (mmol/L)	104 (94-118)	104.81 (4.37)
Potassium (mmol/L)	4.3 (2.2-7)	4.38 (0.77)
Calcium (mg/dL)	8.98 (7-10.8)	9.07 (0.76)
AST (U/L)	25.75 (10-381)	37.32 (50.67)
ALT (U/L)	19.4 (7-364)	31.68 (51.78)
Amylase (U/L)	49 (22-134)	53.11 (51.78)
APTT (sec)	25.30 (15.4-47.9)	26.88 (5.97)
WBC (10^3/uL)	13.18 (1.48-32.49)	13.52 (5.52)
Hb (g/dl)	13.60 (7-17.8)	13.49 (2.34)
PLT (10^3/uL)	227 (72-374)	229.81 (65.86)

BUN: Blood Urea Nitrogen, AST: Aspartate Aminotransferase, ALT: Alanine Transaminase, APTT: Activated Partial Thromboplastin Time, WBC: White Blood Cells, Hb: Hemoglobin, PLT: Platelet, SD: Standard Deviation

Extremity fractures and bullet fragments were detected by radiological methods. There were fractures in the upper and lower extremities in 4 and 15 patients, respectively. Bullet fragments were detected in the upper extremities of 16 patients, the lower extremities of 10 patients, the head and face of six patients, the thorax of five patients, and the abdomen of three patients. Six patients had severe vascular injury (arterial injury), three had nerve injury, two had tendon injury, one had an

amputated phalanx, one had a subarachnoid hemorrhage, and four patients had severe abdominal injury.

Consultations from other departments were requested for 53 patients (86.9%), but no consultation was needed for eight patients (13.1%). Most consultations were made to the Orthopedics & Traumatology Department (42.7%), (Table 2). Eighteen patients (29.5%) were treated and discharged from the ED, nineteen patients (31.2%) were hospitalized in the wards and nine patients (14.8%) were transported to the intensive care unit (ICU). Most patients were hospitalized in the Department of Orthopedics & Traumatology. Cardiopulmonary resuscitation was performed in five patients in the ED. Six patients (9.8%) died (four in the ED, one in the ICU and one in the operating room) within 24 hours (Table 2).

The GCS, RTS, ISS and TRISS of the patients hospitalized in the ward and the ICU significantly differed (P=0.036, P=0.039, P=0.009, and P=0.014, respectively). Patients admitted to the ICU had lower GCS, RTS and TRISS scores and higher ISS than those admitted to the ward (Table 3).

Table 2: Distribution of consulted specialties and hospitalization

		n	%
Distribution of consulted specialties	Orthopedic & Traumatology	41	42.7
	Plastic surgery	16	16.6
	Neurosurgery	11	11.5
	Cardiovascular surgery	9	9.4
	General surgery	8	8.3
	Thoracic surgery	4	4.2
	Others *	7	7.3
	Total	96	100
Distribution of hospitalization	Discharge from ED	18	29.5
	Hospitalized in service	19	31.2
	Hospitalized in ICU	9	14.8
	Treatment refusal	5	8.2
	Refer to another hospital	4	6.5
	Exitus	6	9.8
	Total	61	100

*Urology (2), ophthalmology (1), anesthesia (1), cardiology (1), gynecology (1), pediatric surgery (1). ICU: Intensive Care Unit, ED: Emergency Department.

Table 3: Hospitalization and scores

	Hospitalization N (%)	Hospitalized in service 19 (31.2%)	Hospitalized in ICU 9 (14.8%)	P-value
GCS	Median (min-max)	15 (15-15)	15 (3-15)	0.036
	Mean (SD)	15 (0)	13 (3.97)	
RTS	Median (min-max)	7.84 (7.55-7.84)	7.84 (2.93-7.84)	0.039
	Mean (SD)	7.83 (0.7)	7.05 (1.63)	
ISS	Median (min-max)	9 (4-19)	17 (8-32)	0.009
	Mean (SD)	10.7 (5.08)	19.7 (7.92)	
TRISS (%)	Median (min-max)	98.87 (96.24-99.33)	96.66 (8.41-99.13)	0.014
	Mean (SD)	98.56 (0.86)	84.34 (29.34)	

ICU: Intensive Care Unit, SD: Standard Deviation

Discussion

Due to the easy availability and portability of firearms, morbidity, and mortality rates due to gunshot wounds are increasing in our country as well as in the world [4]. The physician's recognition of the characteristic wound patterns in the trauma patient who was severely injured by a firearm in the ED can speed up the treatment. The diagnosis of the anticipated injuries is supported by imaging [11, 12].

Compatible with the literature, in this study, the patients who presented to the ED with gunshot wounds were young males aged 30-40 years [1, 3, 4, 13]. The average age of the patients who died was 28 years, and no significant relationship was detected between age and mortality (P=0.531, r=-0.063). The gunshot wounds mostly occurred between 18:00-24:00 [1,4]. Similarly, in this study, most of the gunshot wounds (50.8%) and highest mortality rate (66.7%) were observed between 16:01-24:00. Factors that determine rates of firearm violence vary by country [14], and include illicit drug trafficking, access to firearms, substance abuse including alcohol, mental health problems, firearm laws, and social and economic differences [14, 15]. Where guns are more common, controversy results in more deaths [16]. We attribute the increase in the number of cases between 16:01-24:00 to the fact that most people leave work, and the rate of heavy alcohol consumption is high during those hours.

In the study conducted by Meral et al. [4], patients were most admitted to the hospital with gunshot wounds in April (13.2%) and May (11.6%), whereas in our study, gunshot wounds most occurred in November. While Meral et al. [4] showed that 14.6% of the cases were injured in more than one body part, we found that this rate was 41% in our study. Similar to the other studies [3, 4], lower extremity was the most common site of injury in this study.

There are several studies on the effectiveness of scoring systems to predict survival in patients injured by firearms [1, 3, 13]. GCS, ISS, RTS and TRISS trauma scores are among the important scoring systems in predicting prognosis and mortality in emergency situations [5, 6, 13]. Traditionally, surgeons have analyzed trauma mortality to assess the quality of treatment and the effectiveness of care. The implementation of the TRISS scoring system in developing countries with western norms has not been widely reported [17]. The true incidence of injury-related deaths is generally higher in developing countries, which can be attributed to inadequate trauma care, and the quality of prehospital care, including the elapsed time until transportation to a hospital [17, 18]. In this case, the precaution to be taken should improve the pre-hospital first intervention phase and reduce the time until definitive treatment. In developing countries, all studies based on TRISS do not include ED deaths. It is advocated that the TRISS scoring system will be a comparative audit by showing differences in outcome between hospitals in developing countries and act as a catalyst to encourage changes that will improve performance [17]. Several studies have suggested that a relationship exists between injury severity and death in trauma patients [19-21]. In this study, the mean TRISS score for survival prediction for penetrating trauma was 88.59%. Similar to the literature [3], in patients who died, GCS, RTS and TRISS were significantly lower and ISS was significantly higher compared to the surviving patients. We think that trauma scores provide information about the course of the disease and affect the treatment of the casualty.

Studies reported the rates of extremity fractures due to gunshot wounds as 59%, 34.5% and 56.7% [3, 11, 22]. In our study, there were four fractures in the upper and 15 fractures in the lower extremities, as determined by radiological methods.

Urgent intervention is required when arterial damage occurs in the lower extremity, as it can result in limb loss or a lethal injury [11, 23]. Dorlac et al. [24] found that more than half of the patients who were injured by firearms died from excessive blood loss due to artery damage in the lower extremity. In the study conducted by Engelmann et al. [22], neurovascular injuries were detected in 43.1% of patients. In this study, two patients with upper extremity injuries had radial artery and one patient with lower extremity injury had crural artery injury. Erythrocyte suspensions were transfused to two patients, and no death occurred due to extremity artery injury. Three patients had nerve injury (sciatic nerve in two patients, peroneal nerve in one

patient) due to lower extremity trauma. It should not be forgotten that extremity traumas are life threatening due to the vascular and neural networks in this area and the anatomical neighborhoods of these structures.

In many studies, patients with gunshot injuries were mainly consulted to the Orthopedics & Traumatology Department [1, 3, 4], which was attributed to the prevalence of extremity injuries. This was followed by the plastic surgery department. In a cross-sectional study on gunshot wounds in ED patients, 7% of patients were admitted to the ICU [25] while this rate was 14.8% in our study.

Studies on gunshot wounds reported higher mortality rates than this study [3, 13]. Similar to the literature, in this study, deaths due to gunshot wounds generally occurred within the first day [3, 26]. Turgut et al. [1] found that the ISS of patients who died were significantly higher than those of survivors. Norouzi et al. [19] reported that an increase in ISS above 25 was directly related to an increased risk of death in injured patients. In our study, the injury severity score of six patients who died were above 25. As expected, high ISS is useful in predicting prognosis and mortality in patients with gunshot wounds.

There are many factors affecting morbidity and mortality in firearm injuries. Although bullets cause small holes in the skin, they can cause serious injuries associated with high mortality, especially in the head, thorax, and abdomen [3, 4, 27, 28]. Research emphasized that patients with abdominal injuries that cause high mortality should be intervened early and the hemorrhage should be controlled [27, 28]. In this study, the findings showed that two of the patients who died had isolated severe abdominal injuries and one had an isolated severe head-neck injury. Also, one patient who died with thoracic injury had accompanying head-neck and extremity injuries and the other patient had a concomitant abdominal injury.

Limitations

Limitations of our study included the lack of available information on morbidity and mortality after hospital discharge and the small number of the patients. It is recommended that further studies be performed with a larger number of patients.

Conclusion

The incidence of hospital admissions due to gunshot wounds, and the related mortality rates has increased over recent years. Gunshot wounds can cause serious injuries associated with high mortality, especially in the head, chest, and abdomen. This study suggests that the GCS, ISS, RTS and TRISS trauma scores systems can be useful in predicting prognosis and mortality rates in gunshot wounds.

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Evaluating the characteristics of spondylolisthesis in low back pain by radiography

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Ethics Committee Approval
The study was conducted with the approval of the Ethics Committee of the Faculty of Medicine of Eskisehir Osmangazi University (The decision no.: 35, date: 14.07.2020).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: In physical therapy and rehabilitation practices, it is important to diagnose radiographic spondylolisthesis for correct choice of exercise in patients with low back pain. There are different results about the rates and the characteristics of spondylolisthesis. The aims of this study were to compare the radiographical findings, and evaluate the frequency and the radiographic characteristics of spondylolisthesis according to gender.

Methods: Nine hundred and four patients with low back pain, who were over 18 years of age with records of age, gender, and lumbar spine radiographs (both anterior and lateral) were included in this retrospective cross sectional study. Three hundred and forty-eight patients (245 females, 103 males) who met our criteria were included in the study and reviewed for age, gender, and anterior/lateral-lumbar spine radiographies. Spine radiographies were assessed for the presence of spondylosis, scoliosis, fracture, flattening of the lordosis, hyperlordosis, sacralization, lumbarization and spondylolisthesis. The spondylolisthesis measurements were made according to the Meyerding Grading Scale. The levels and the pattern of anterior or posterior listhesis, and co-existing radiological findings such as osteophyte, sclerosis, intervertebral disk space narrowing and scoliosis, were noted.

Results: The rate of hyperlordosis (P=0.003) and spondylolisthesis (P=0.012) were significantly higher in females compared to males. The rate of spondylolisthesis among all patients was 11.4% (female/male ratio:2.95/1). All male patients and 91.5% of female patients with spondylolisthesis had it at the L5-S1 level only. Among all, 90.6% of spondylolisthesis patients had anterolisthesis and 79.1% had grade 1 spondylolisthesis according to Meyerding. The most common radiological findings were sclerosis (95%), osteophytes (62.5%), intervertebral disk narrowing (62.5%), scoliosis (37.5%) in spondylolisthesis patients.

Conclusion: The results of our study showed that hyperlordosis and spondylolisthesis were more common in females. The characteristics of spondylolisthesis include occurring mostly at one level only, being Meyerding grade 1 and showing anterolisthesis pattern. The most frequent coexisting radiological findings were sclerosis, osteophytes, and intervertebral disk narrowing. These result support the idea that the pathogenesis of spondylolisthesis is associated with spondylosis. The rate of spondylolisthesis was higher compared to many previous studies. Before deciding on an exercise, it is important to see the direct radiography of the patient with low back pain.

Keywords: Low back pain, Spondylolisthesis, Spondylosis

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Introduction

Spondylolisthesis is defined as the slippage (anterior or posterior) of a vertebral body relative to the next caudad vertebra [1]. It is one of the major causes of low back pain and disability [2], it mostly occurs in the lumbar region and is considered to have two major etiologies: Isthmic and degenerative [1]. Isthmic spondylolisthesis is associated with spondylolysis distinguished by fracture of the pars interarticularis and mostly occurs at L5-S1. Degenerative spondylolisthesis is associated with progressive degeneration of both intervertebral discs and facet joints with aging, and mostly occurs at L4-5 [3]. Despite usually being asymptomatic, neurogenic claudication and neurological symptoms can occur, such as pain in the legs, weakness, numbness due to spinal stenosis.

The incidence of spondylolisthesis is reported as 4-6% [4]. The prevalence of spondylolisthesis among 1147 patients with low back pain was 6% [5]. There are contradictory results about prevalence in males and females, it was 2.7% in elderly males, and 8.4% in elderly females in The Copenhagen Osteoarthritis Study [6]. In another study conducted on the elderly Chinese population, 25% of females and 19.1% of males had spondylolisthesis. There are also conflicting results about its relationship with age [7]. Horikawa et al. reported no significant correlation between the presence of spondylolisthesis and age in Japan [8]; however, Denard et al. reported that spondylolisthesis prevalence increased with age [9].

The pathogenesis of degenerative spondylolisthesis is multifactorial and starts with the degeneration of intervertebral discs and facet joints. Progressive degeneration can lead to instability [10]. Chanchairujira et al. reported that osteophyte formation may cause segment instability [11], and Wang et al. reported that intervertebral disc space narrowing can lead to degenerative lumbar spondylolisthesis [12]. There are also studies about other vertebral pathologies that increase the risk of spondylolisthesis. It was reported that the risk of spondylolisthesis increases four times in the presence of sacralization in L5 [4]. In another study on athletes, stress fractures were the most dominating cause of spondylolysis, which is associated with isthmic spondylolisthesis [13]. In a study investigating the relationship between scoliosis and spondylolisthesis, scoliosis was found in 42% of the patients with symptomatic spondylolisthesis [14].

Previous studies reported conflicting results about the gender-based comparison of radiographical findings. Some of them stated that spondylosis was more common in males [15], while the others stated otherwise [16]. Also, there are different results about the rates and the characteristics of spondylolisthesis.

In clinical practice, it is necessary to diagnose spondylolisthesis due to the exercise choice. Exercises which are given in spondylolisthesis differ from those needed in other conditions of low back pain [17].

This study aimed to assess radiographical findings in patients with low back pain as well as the frequency and the radiographic characteristics of spondylolisthesis according to gender.

Materials and methods

This retrospective analysis included patients with low back pain evaluated at the Department of Physical Medicine and Rehabilitation in Eskisehir City Hospital (Eskisehir, Turkey) between August 2019 and April 2020. Data were obtained from the hospital database and patient files. The medical records of 904 patients with low back pain (ICD-10: M48.06, M51, M51.0, M51.1, M53.3, M54.5, M54.4) were reviewed for age, gender, lumbar spine radiographs.

Patients over 18 years of age with records of age, sex, and lumbar spine radiographs (both anterior and lateral), were included in the study. Those under the age of 18 years, patients who do not have both anterior and lateral radiographs, and those with lumbar spine radiographs not suitable for accurate assessment were excluded from the study. A total of 348 (245 female, 103 male) patients who met the criteria were included.

Anterior and lateral radiographs obtained from T12 to S1 were interpreted by two physical therapy and rehabilitation specialists for the presence of osteophytes, intervertebral disk space narrowing, spondylosis, scoliosis, fracture, flattening of lordosis, hyperlordosis, sacralization, lumbarization and spondylolisthesis.

The spondylolisthesis measurements were made according to The Meyerding Grading Scale by the same specialists by dividing the slip distance by the caudad body width: No slip: Grade 0, 5-25% slippage: Grade 1, 26-50% slippage: Grade 2, 51-75% slippage: Grade 3, 76-100% slippage: Grade 4, complete slippage: Grade 5. Slips of less than 5% were not considered spondylolisthesis [18]. In our study, degenerative and isthmic spondylolisthesis were not evaluated due to the absence of oblique radiographies, and the results for anterolisthesis and retrolisthesis were present. This study did not differentiate between spondylolisthesis and spondylolytic spondylolisthesis because only lateral radiographs were obtained. Antero- and retrolisthesis are grouped under spondylolisthesis.

A loss of anterior, middle, and posterior vertebral height (>20%) or a crush fracture in the vertebra were evaluated as the presence of vertebral fracture [19]. Sclerosis, disk space narrowing, spur formation (osteophyte) indicated the presence of spondylosis [20]. Lumbar lordosis is defined as the angle between the line passing through the upper end plate of L1 vertebra and the sacral endplate. Normal lumbar lordosis is between 40 and 70 degrees when the L3-4 distance is considered as the peak point. A lordotic angle of less than 40 degrees indicated flattening of the lordosis and more than 70 degrees indicated hyperlordosis [21]. A Cobb angle of more than 10 degrees in the frontal plain was considered scoliosis [22]. Addition of sacral elements by the incorporation of L5 was evaluated as sacralization [23]. Separation of the S1 segment from the S2 segment was evaluated as lumbarization [24].

The study was conducted with the approval of the Council of Ethics of the Faculty of Medicine of Eskisehir Osmangazi University with the decision no 35 on 14.07.2020.

Statistical analysis

IBM SPSS Statistics 22.0 (SPSS Inc., Chicago, Illinois) program was used for statistical analysis. The categorical variables were evaluated with Chi-square tests and presented as numbers (n) and percentages (%). Descriptive statistics were

given as mean (standard deviation [SD]). A *P*-value<0.05 was considered significant.

Results

The radiograph qualities of 348 patients were high enough for analysis. Among them, 245 (70.4%) were females, and 103 (29.6%) were males. The overall mean age of the patients, and those of males and females were 47.7 (16.12) years, 45.6 (17.78) years, and 48.3 (15.79) years, respectively (range: 18-87 years).

Among all, %11.7 of the patients had normal radiographic findings. The most common finding in radiographs was spondylosis (75.8%) in both males (77.6%) and females (75.1%). The number and percentage of other radiological findings was shown in Table 1. Spondylolisthesis were seen in 11.4% of the patients, with a F:M ratio of 2.95:1. The rates of hyperlordosis (*P*=0.003) and spondylolisthesis (*P*=0.012) were significantly higher in females (Table 1).

Table 1: The comparison of radiological findings according to gender

	Female (n=245) (%)	Male (n=103) n (%)	*P*-value	Total (n=348) n (%)
Normal radiography	28 (11.4%)	13 (12.6%)	0.753	41 (11.7%)
Lumbarization	2 (0.8%)	2 (1.9%)	0.728	4 (1.1%)
Sacralization	2 (0.8%)	1 (0.9%)	0.887	3 (0.8%)
Hyperlordosis	28 (11.4%)	2 (1.9%)	0.003	30 (8.6%)
Fracture				
Fracture in L1	6 (2.4%)	5 (4.8%)	0.242	11 (3.1%)
Fracture in L2	3 (1.2%)	5 (4.8%)	0.095	8 (2.2%)
Multiple vertebral fractures	8 (3.2%)	2 (1.9%)	0.147	10 (2.8%)
Total	17 (6.9%)	12 (11.6%)	0.500	29 (8.3%)
Scoliosis	66 (26.9%)	22 (21.3%)	0.274	88 (25.2%)
Flattening of lumbar lordosis	62 (25.3%)	32 (31%)	0.269	94 (27%)
Spondylosis	184 (75.1%)	80 (77.6%)	0.609	264 (75.8%)
Spondylolisthesis	35 (14.2%)	5 (4.8%)	0.012	40 (11.4%)

We detected 43 spondylolistheses in 40 patients. Thirty-two of 35 female patients and all male patients had spondylolistheses at L5-S1 only. All males had Meyerding grade 1 spondylolisthesis, and all were in the form of anterolisthesis. Anterolistheses were seen in 90.6% all spondylolistheses, all single-level anterolistheses were at the L5-S1 in both females and males. Two anterolistheses were at two levels in females (At L2-3 and L5-S1 in one, and at L4-5 and L1-2 in the other patient). Most spondylolisthesis (79.1%) were Meyerding grade 1. Retrolisthesis was seen in only 3 (7.5%) patients, all of which were female and Meyerding grade 1. Two retrolistheses were at the L4-5 level, and the other retrolisthesis patient had slips at two levels (both L2-3 and L5-S1) (Table 2).

Table 2: The vertebral level and the grade of the spondylolisthesis patients

	L1-2 n(%)	L2-3 n(%)	L4-5 n(%)	L5-S1 n(%)	Total
Female					
Anterolisthesis grade 1	1 (2.3%)	1 (2.3%)	1 (2.3%)	22 (51.1%)	25 (58.1%)
Anterolisthesis grade 2				9 (20.9%)	9 (20.9%)
Retrolisthesis grade 1		1 (2.3%)	2 (4.6%)	1 (2.3%)	4 (9.3%)
Male					
Anterolisthesis grade 1				5 (11.6%)	5 (11.6%)
Total	1 (2.3%)	2 (4.6%)	3 (6.9%)	37 (86%)	43 (100%)

The most common coexisting radiological finding was end-plate sclerosis present in almost all patients with spondylolisthesis (95%), followed by osteophytes (62.5%) and intervertebral disc space narrowing (62.5%) (Table 3).

Table 3: Coexistence of other radiological findings according to gender in spondylolisthesis patients

	Spondylolisthesis in Female (n=35) n (%)	Spondylolisthesis in Male (n=5) n (%)	Total (n=40)
Hyperlordosis	5 (14.2)	0	5 (12.5%)
Flattening of the lumbar lordosis	6 (17.1)	0	6 (15%)
Fracture	5 (14.2)	1 (20%)	6 (15%)
Scoliosis	13 (37.1)	2 (40%)	15 (37.5%)
Intervertebral disc space narrowing	20 (57.1)	5 (100%)	25 (62.5%)
Osteophyte	23 (65.7)	2 (40%)	25 (62.5%)
Sclerosis	34 (97%)	4 (80%)	38 (95%)

Multiple findings could be observed in one spondylolisthesis patient

Discussion

The major finding of our study is the nearly doubled rates of lumbar spondylolisthesis in patients with low back pain than previously reported [5]. In the Framingham Heart Study, spondylolisthesis was found in 20.7% of studied population, similar to ours [15]. Another study in China reported the prevalence of spondylolisthesis as 25% among females, and 19.1% among males [7]. The female predominance in that study resembles our results. Although the rates of spondylolisthesis may differ with ethnic difference, it cannot be the major factor. In another study in Turkey, the spondylolisthesis ratio was 5%, less than half reported in our study [25].

Gender-based comparison of radiological findings have revealed conflicting results. Kalichman et al. [15] reported that spondylosis was more common in males, while Lee et al. [16] stated otherwise. In another study, scoliosis was more common among females [26]. Contrary to these studies, we found no significant differences between the genders in terms of spondylosis, scoliosis, and other findings. Only hyperlordosis and spondylolisthesis were more common in females with low back pain. Similar to our study, Stagnara et al. [27] reported that hyperlordosis was more common among females compared to males due to their greater buttock size. Furthermore, the lumbar lordosis angle and spondylolisthesis were related [28].

In our study, spondylolisthesis rate was higher among females. Other studies also reported similar findings, but differences were observed in female/male ratios [6,7,15]. The general belief is that it is approximately four times more common in women [4]. The F:M ratio in our study was 2.95:1. Similar to our study, Horikawa et al. reported the female/male ratio as 2.34:1 in Japan [8]. In a Chinese study, female/male ratio of lumbar spondylolisthesis was 1.3:1 [7] and the Copenhagen Osteoarthritis Study reported it as 6.1:1 [6]. The laxity in joints, pregnancy [29] and oophorectomy [30] are thought to be predisposing factors in spondylolisthesis. Also, intervertebral disc narrowing was more severe in women in some studies [31], which may lead to higher ratios of degenerative spondylolisthesis among women.

In our study, most female patients (91.5%), and all male patients had a slip at a single level. A chinese study reported the rate of multi-level slips as 13.8% among female subjects [7]. Denard et al. reported that 96% of listhesis were only at the vertebral level in 300 elderly males [32].

In previous studies, the rate of anterior spondylolisthesis was higher, similar to our study. Anterolisthesis rate in our study is high among both female and male spondylolisthesis patients (females: 91%, males: 100%) Although the rate in female was

similar to those in the previous studies, the rate in males were slightly higher than the other studies. He et al. reported the same rate (91%) of anterolisthesis with our study in 499 females with spondylolisthesis, however, male anterolisthesis rates (74%) were lower than our study [7]. This may be due to the low number of male patients with spondylolisthesis in our study.

Single spondylolistheses were all at L5-S1. In the Framingham Heart Study, isthmic types were mostly found at the L5-S1 spinal level, while the degenerative types were mostly at the L4-5 level [15]. Isthmic spondylolisthesis is mostly seen in male patients and at the L5-S1 level, and degenerative spondylolisthesis is mostly seen in female patients and at the L4-5 level [4]. Due to the absence of oblique spine radiographs, differentiation of isthmic and degenerative spondylolisthesis could not be evaluated. It is not known which type of spondylolisthesis rate is higher in our study.

Our study showed that all listheses of males and 76.3% listheses of females were Meyerding grade 1. Similar to our results, in many studies, grade 1 listhesis was much more common than the other grades. Denard et al. [32] reported that all listheses were classified as grade 1 according to the Meyerding Scale in 300 elderly men. The Chinese study reported that 94% of female patients with spondylolisthesis were Meyerding grade 1 [7].

There are limited studies investigating the relationship between spondylolisthesis and other radiological findings. It is known that progressive degeneration in intervertebral discs and facet joints and osteophyte formation can lead to pain and segment instability [10]. In our study, the most common radiological findings were sclerosis (95%), osteophytes (62.5%) and intervertebral disk narrowing (62.5%) in spondylolisthesis patients. This supports the idea that the pathogenesis of spondylolisthesis is associated with spondylosis. We also studied the relationship of other radiological findings with spondylolisthesis and found that while fracture rate was not high (15%), scoliosis rate was 37.5%. In published data, there is evidence regarding the relationship between degenerative scoliosis and lateral spondylolisthesis [33]. However, there are limited studies about the relationship of scoliosis and anterior-posterior spondylolisthesis. A study reported 42% scoliosis rate in patients with symptomatic spondylolisthesis [14]. This relationship between scoliosis and spondylolisthesis may be associated with the development of various curves due to the muscle contracture and increased pars interarticularis defects in scoliosis compared to the normal population [34]. It is known that the risk of spondylolisthesis increases four times in the presence of sacralization in L5 [4]; however, we had no patient with sacralization and spondylolisthesis in our study. In another study, the prevalence of sacralization was 5.1% [34], while it was 0.8% in ours. The lack of a relationship may be because of the low number of patients with sacralization.

Limitations

This study has some limitations. First, degenerative and isthmic spondylolisthesis was not investigated due to the absence of oblique radiographs. Also, because of retrospective design, we were not able to evaluate pain levels, functionality, pelvic inclination, or the degree of lordosis. Increased lumbar lordosis may impose additional stress on the spinal ligaments and play a role in spondylolisthesis pathogenesis. Further studies are needed which evaluate the relationship between degree of lordosis and spondylolisthesis. The strength of our study was not only evaluating the frequency, age and sex distribution, but also evaluating the relationship between spondylolisthesis and other radiological findings.

Conclusion

In this study, the rates and the characteristics of spondylolistheses was presented. In physical medicine and rehabilitation practice, it is important to differentiate spondylolisthesis because the choice of exercise differs accordingly. The rate of spondylolisthesis was higher compared to many previous studies. Most spondylolistheses occurred in females, higher rates of anterolistheses were observed compared to retrolisthesis, and most were grade 1 at the L5-S1 level. The most common radiological findings were sclerosis, osteophytes and intervertebral disk narrowing in spondylolisthesis patients. Our results support the idea that the pathogenesis of spondylolisthesis is associated with spondylosis.

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Stress and fluid restriction before anesthesia induction, investigation of the effects of the patient's clinic, endocrine responses, and the level of the Nesfatin-1

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Fırat University Faculty of Medicine Clinical Research Ethics Committee (01.11.2012 / 18-02) All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Preoperative fasting, fluid restriction and stress trigger many hormonal responses, one of which is the newly described Nefsatin-1. It has important effects on energy metabolism and stress. In this study, we aimed to examine the relationship between stress, fasting, fluid restriction, and Nesfatin-1.
Methods: A total of 100 ASA I-II adult patients between 18 and 60 years of age with no psychiatric, cardiovascular, or metabolic disorders, who were operated under general anesthesia for various reasons at Fırat University Hospital between June and November 2013 were included in this randomized prospective case-control study. Patients were categorized into fluid restriction (Group 1) and no-fluid restriction (Group 2) groups. These groups were further sub-categorized as those receiving (Groups 1A and 2A) and not receiving pre-medication (Group 1B and Group 2B). State Trait Anxiety Inventory was applied to all patients by an independent member of the research team before the surgical procedure. Also, blood samples were obtained 6-8 hours, 1 hour, and just before the induction to measure insulin, glucose, epinephrine, norepinephrine, cortisol, and Nesfatin-1 levels.
Results: In both groups, the test score for pre-operative anxiety was 44. While there were no differences in serum insulin levels between the study groups ($P>0.05$), serum glucose and epinephrine levels were higher in Group 1A than in other groups ($P<0.05$ for both). Except for the 2nd period, serum norepinephrine levels were elevated in all stages ($P<0.05$). Serum cortisol levels were higher in Group 2B ($P<0.05$), while serum Nesfatin-1 levels were higher in Group 2A ($P<0.05$).
Conclusion: According to our findings, the highest reflection of stress in patients, together with clinical and endocrine responses, coincided just before the induction period. Further studies are warranted before firmer conclusions can be drawn regarding the association between Nesfatin-1 and anxiety. We believe that if the pathophysiological mechanisms between anxiety and Nesfatin-1 are clarified, Nesfatin-1 targeting treatment approaches can be tried in the clinic.

Keywords: Surgery, Premedication, Fluid restriction, Anxiety, Nesfatin-1

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Introduction

Preoperative fasting and fluid restriction used in elective surgeries is a routine anesthetic preparation that reduces the risk of aspiration. However, this process can put the patient in distress both metabolically, physiologically, and psychologically [1]. Hunger, fluid restriction and emotional stress caused by surgery affect the pituitary hormones. Catabolic hormones such as cortisol, glucagon and catecholamines increase, while anabolic hormones such as insulin and testosterone are inhibited [2]. However, it is also known that emotional stress causes the release of adrenaline and noradrenaline from the suprarenal medulla [3].

Nesfatin-1 is a recently described saturation molecule in the hypothalamus and has multiple endocrine functions [4,5]. Nesfatin-1 has an autonomous and endocrine effect on energy expenditure and affects eating [6,7]. It also plays a role in the regulation of emotional and behavioral situations. In experimental animal models, Nesfatin-1 was activated in the rat brain in psychological stress [8]. Plasma Nesfatin-1 level was higher in patients with high anxiety compared to those with low anxiety. A significantly high correlation was found between plasma Nesfatin-1 level, total stress score and depression score [9]. We used the State-Trait Anxiety Inventory (STAI) test, which is the standard test for the measurement of anxiety in patients.

This study aimed to investigate the effects of stress and fluid restriction before anesthesia induction on the patients' clinical status, endocrine responses and the level of a new peptide-made hormone, Nesfatin-1.

Materials and methods

Previous studies were referenced for sample size. There were 100 patients, 25 patients in each group, with a minimum sample size at 0.05 alpha error and 0.8 beta error. Permission was obtained from Fırat University Faculty of Medicine Clinical Research Ethics Committee (01.11.2012 / 18-02). One hundred ASA 1-2 patients between the ages of 18-75 years who were operated between June-November 2013 at Fırat University Hospital were included in this randomized prospective case-control study. Patients with psychiatric, cardiovascular, and metabolic disorders were excluded.

The patients were randomly divided into two groups, as those with and without fluid restriction. Both groups were also randomly divided into 2 subgroups, as those who did and did not receive premedication. Randomization was provided by a closed envelope method by a blinded operating room staff who did not participate in the study.

Group 1 (n=50): These patients fasted and fluid-restricted preoperatively for 4-6 hours before induction.

Group 1A (n=25): These patients received premedication. Intramuscular (IM) midazolam (0.07 mg/kg) and intravenous (IV) atropine sulfate (0.0l mg/kg) were administered.

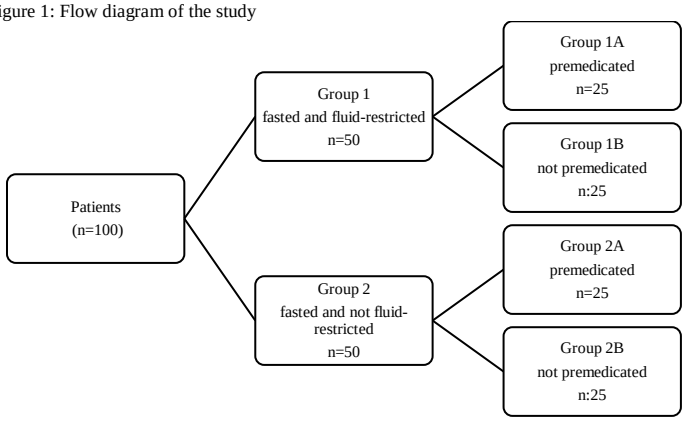
Group 1B (n=25): These patients did not receive any premedication.

Group 2 (n=50): These patients who fasted preoperatively did not restrict fluids until 1 hour before the induction of anesthesia.

Group 2A (n=25): These patients received premedication. IM midazolam (0.07 mg/kg) and IV atropine sulfate (0.0l mg/kg) were administered.

Group 2B (n=25): These patients did not receive premedication.

Figure 1: Flow diagram of the study



Demographic data of the patients were recorded. All patients received the (STAI) State-Trait Anxiety Inventory test which shows state and continuous anxiety before the operation (STAI 1, STAI 2). Systolic blood pressures (SAP), diastolic blood pressures (DAP) and heart rates were measured and recorded for 6 hours before the induction (period 1), 1 hour before induction (period 2) and immediately before induction (period 3). Within the same periods, Nesfatin-1, epinephrine, norepinephrine, glucose, insulin, and cortisol values were measured and recorded.

Statistical analysis

SPSS 12.0 (The Statistical Package for the Social Sciences, Chicago, USA) program was used for statistical analyses. The data were recorded as mean (SD). Variation analysis (ANOVA) was used in the analysis of parametric tests, and a post-Tukey HSD test was used when a significant difference was found in comparison between the groups. Paired t-test was used to compare repetitive measurements within the group. The relationship between patients' Nesfatin-1 levels and mood and anxiety disorders was evaluated with the Pearson correlation test. *P*-value <0.05 was considered significant.

Results

Demographic and hemodynamic data

Thirty-three percent (n=33) of the patients in the study were females. The mean age of Groups 1A, 1B, 2A and 2B were 30.16 (10.78) years, 32.84 (12.12) years, 26.48 (5.59) years, and 27.72 (7.80) years, respectively. The demographic data of the patients were similar between the groups ($P>0.05$) (Table1).

Table 1: Demographic data of patients

	Group 1		Group 2	
	Group 1A (n=25)	Group 1B (n=25)	Group 2A (n=25)	Group 2B (n=25)
Gender (M/F)	17/8	16/9	17/8	17/8
Age (year)	30.16 (10.78)	32.84 (12.12)	26.48 (5,59)	27.72 (7.80)
Weight (kg)	73.32 (9.24)	67.80(7.83)	70.36 (6.89)	73 (9.26)

The SAP, DAP and heart rate values did not differ among the groups ($P>0.05$). However, SAP values were significantly higher in all groups in the 3rd period compared to the 1st period ($P<0.05$). DAP values in the 2nd period were significantly higher in all groups compared to the 1st period ($P<0.05$). The heart rate values in period 2 were significantly

higher compared to period 1 (P<0.05). Time-dependent changes within the groups are given in Table 2.

Table 2: Hemodynamic changes in patients

	Period	Group 1		Group 2	
		Group 1A (n=25)	Group 1B (n=25)	Group 2A (n=25)	Group 2B (n=25)
Systolic blood pressure (mmHg)	1	113.96 (12.10)*	112 (11.18)*	107.80 (10.51)*	111.60(7.46)*
	2	118.84 (13.67)	114.00 (8.03)$^{\varphi}$	111.40 (9.41)$^{\varphi}$	113.80 (10.82)$^{\varphi}$
	3	125.56 (11.80)	124.24 (8.83)	128.04 (13.22)	125.00 (8.83)
Diastolic blood pressure (mmHg)	1	69.36 (7.17)	68.20 (9.00)	68.20 (8.88)$^{\&}$	71.00 (7.50)
	2	72.76 (10.74)	71.00 (8.03)	73.00 (7.77)	72.20 (6.62)
	3	76.28 (8.65)	76.32 (8.57)	77.60 (10.17)	75.88 (6.85)
Heart rate (Pulse / min)	1	79.64 (9.30)	76.36 (9.18)	73.04 (5.70)$^{\&}$	74.52 (7.26)$^{\&}$
	2	79.04 (13.47)	77.72 (7.19)	76.16 (6.23)	78.48 (9.06)
	3	79.52 (10.13)	75.24 (13.89)	78,16 (10.12)	77.92 (11.60)

Period 1: 6 hours before induction, Period 2: 1 hour before induction, Period 3: Just before induction. * P<0.05 Between Period 1 and Period 3. & Between Period 1 and Period 2. φ P<0.05 Between Period 2 and Period 3.

Biochemical parameters

Serum glucose values of group 1A significantly differed from the other groups in the 2nd period (P<0.05). Serum glucose values were significantly higher in Group 1A (81.68 (29.55)) compared to Group 2A (62.76 (27.14)), in group 1B (82.12 (17.87)) compared to group 2A, and in group 2B (84.32 (17.08)) compared to group 2A (P<0.05).

Insulin values were similar between the two groups (P>0.05; however, those of Group 2A were significantly higher in the 2nd period (4.68 (2.62)) compared to the first period (3.88 (2.70)). Cortisol level in group 2B was significantly higher than group 2A (P<0.05).

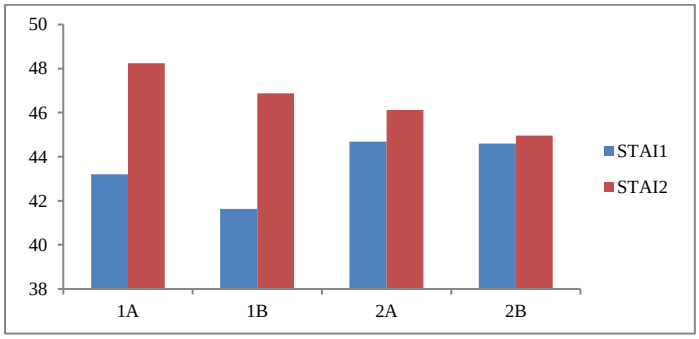
Epinephrine values in the 1st period were significantly higher in group 1A (70.67 (17.90)) compared to other groups (P<0.05). Likewise, epinephrine values in the 2. period were higher in group 1A (57.76 (18. 42)) than group 1B (46.21 (8.98)) and group 2A (43.98 (6.60)), in group 2B (56.20 (11.22)) than group 1B and 2A (P<0.05). Epinephrine values in the 3rd period were significantly higher in group 1A (76.79 (16.61)) compared to all other groups (P<0.05) and in group 1B (54.14 (8.12)) compared to Group 2A (42.14 (6.69)) (P<0.05). In the intergroup evaluation, while the norepinephrine value in group 1A was significantly higher in all periods (P<0.05), that in group 1B (430.36 (147.21)) was significantly higher in the 1st and 2nd periods compared to Groups 2A (172.40 (38. 33)) and 2B (133.44 (30.15)) (P<0.05). In addition, in the 3rd period, norepinephrine levels were significantly lower in group 1B (307.92 (97.28)) compared to group 1A (753.48 (188.72)) and in group 2A (198.32 (55. 90)) compared to group 2B (361.64 (165.63)) (P<0.05).

Serum Nesfatin-1 levels of group 2A was significantly higher than group 2B in inter-group evaluation (P<0.05). In intra-group evaluation, the level of Nesfatin1 in group 2A (21.08 (6.20)) was significantly higher in the 2nd period and that in group 1A was significantly higher in the 2nd period (15.24 (6.11)) compared to the 3rd period (17.78 (7. 86)) (P<0.05). According to the results of statistical analysis between all groups, changes in patients' biochemical parameters are summarized in Table 3.

STAI Test (State and Trait Anxiety Scale) analysis

The mean anxiety score was 44. Although there were no significant differences in STAI-1 between the groups, it was highest in group 2A (44.68) and lowest in group 1B (41.64) (P>0.05). Although STAI-2 scores were similar, it was highest in group 1A (48.24), and lowest in group 2B (44.96) (P>0.05) (Figure 2).

Figure 2: STAI Test Analysis



Discussion

The patient, who is informed about the need for an operation, faces a stressful situation. This anxiety reaches the maximum level especially in the preoperative preparation room. The main reason for this anxiety is pain and fear of not waking up after surgery [10-12]. Detailed information and premedication prior to the operation have an important role in the prevention of this preoperative incapability [9, 13]. This anxiety, pre-operative fasting, and fluid restriction significantly increase the level of stress. It induces various physiological, metabolic, and psychological responses to protect the body from this stress [3, 14]. The body's response is characterized by increased activation of catabolic and immunosuppressive hormones from the pituitary gland with activation of the sympathetic nervous system [15]. The aim of this study is to investigate the effects of stress and fluid restriction before anesthesia induction on patient clinic, endocrine responses, and a new peptide-made hormone, Nesfatin-1 level. The State-Continuity Anxiety Scale (STAI 1-STAI 2) is an easy-to-apply scale that can be answered by the individual as well as the patient's hemodynamic and biochemical data in the measurement of anxiety. Taşdemir et al. [16] showed that preoperative anxiety was significantly higher than postoperative anxiety. Domar et al. [17] found an average score of 45 preoperatively. In our study, according to the results of the statistical analysis for the STAI test, no significant differences were observed between the groups. The preoperative anxiety score in our study was 44 on average. This is similar to the results of other studies.

In our study, systolic and diastolic blood pressure values increased significantly just before induction in all groups. Although there were no statistically significant differences in the heart rate values between the groups, the intra-group evaluation increased significantly 1 hour before induction. This indicates that the anxiety caused by surgery increases as the time of operation approaches and premedication is not effective enough to prevent this.

The pituitary hormones secreted in response to stress and increased sympathetic activity cause the body to transition to a new state both hemodynamically and metabolically. Therefore, heart minute volume and tissue perfusion are increased, and body temperature rises. Blood glucose is increased with the increase of catabolic hormones such as cortisol, adrenaline, and insulin, in addition to glycolysis, gluconeogenesis, and lipolysis. The serum insulin levels in our study were similar in inter- and intra-group evaluations. Serum glucose levels of group 1A (fasted, fluid restricted and premedicated group) also showed a significant change compared to other groups. The high glucose levels of

group 1A may be due to the anxiety caused by fluid restriction. Catecholamines have important physiological effects in response to stress. They activate glycogenolysis, gluconeogenesis, lipolysis and ketogenesis in the liver. This is because they lower insulin and increase glucagon [18-20]. They also increase blood pressure and heart rate [21]. There are many stimuli that lead to catecholamine release, such as hypovolemia, hypoglycemia, hypoxemia, pain and fear. Hypovolemia is best correlated with catecholamine release [22]. In our research, epinephrine and norepinephrine levels were higher in group 1A compared to the other groups. These results support our view that hunger and fluid restriction increase the stress level. It is known that surgical stimulation, anesthesia, psychic, and emotional stress increase cortisol release [23]. Cortisol potentiates the effects of epinephrine and glucagon, causing hyperglycemia. It also activates gluconeogenesis, proteolysis, and lipolysis. As a result of all these processes, blood glucose rises and tries to supply the vital organs with the necessary energy.

Nesfatin-1 is a recently described molecule. Studies show that besides the central nervous system, it is secreted from the pancreas, adipose tissue, and gastric mucosa [7, 24-26]. It has been shown in human milk [27]. Food and water intake has been shown to increase Nesfatin-1 levels [7, 24, 28]. Stengel et al. [29] found low levels of Nesfatin-1 in rats that were fasted for 24 hours. Tsuchiya et al. [30] stated that there is a negative correlation between Nesfatin-1 and BMI. The increase of Nesfatin-1 secretes glucose-stimulated insulin from pancreatic beta cells [31, 32]. Foo et al. [7] showed that Nesfatin-1 administration decreases blood glucose level of hyperglycemic rats (type 2 DM) depending on the dose and time. Nesfatin-1 is also effective in the regulation of emotional and behavioral states. In experimental animal models, Nesfatin-1 activation in the rat brain increased psychological stress [8]. In their study, Hofmann et al. [33] found that plasma Nesfatin-1 level was higher in the group of high anxiety compared to patients with low anxiety**.** There was a statistically significant correlation between plasma Nesfatin-1 level, total stress score and depression score. Günay et al. [34] reported that Nesfatin-1 level was low in their study on normal weight men with general anxiety. In our study, the nestfatin-1 levels of only group 2A was significantly higher than group 2B. In the intra-group evaluation, Nesfatin1 level in group 2A was high in the second period.

The level of Nesfatin1 in Group1A was significantly higher in the 3rd period than in the 2nd period. Also, group 2A had the lowest glucose levels in comparison to other groups. This can be regarded as an indicator of the antihyperglycemic effect of Nesfatin-1. Based on our results, anxiety score was compatible in the STAI 1 test, but no correlation was observed in the STAI-2 test. We think this may be related to glucose level.

The limitations of this study are as follows: The study was performed only in operations involving general anesthesia. Therefore, the data were more limited as it did not include patients with regional anesthesia. In addition, it should be kept in mind that anxiety analyses are affected by the sociodemographic statuses of the patients.

Conclusion

According to our findings, the highest reflection of stress in patients seems to coincide with the clinical and endocrine responses just before the induction period. Preoperative fluid replacement and premedication maintain hemodynamic stability and contribute positively to energy balance by increasing the level of Nesfatin-1. If the pathophysiological mechanisms are clarified, we think that Nesfatin-1 can be used in the treatment of diseases affecting energy metabolisms such as diabetes and obesity, and in reducing perioperative complications.

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Biochemical analysis of serum mineral and vitamin levels in benign essential blepharospasm

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Ethics Committee Approval
The study protocol was approved by the institutional review board of Afyonkarahisar Health Sciences University Ethics Committee (Date: 05.02.2021, Acceptance code: 2021/139). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Benign essential blepharospasm (BEB) is a type of focal dystonia characterized by involuntary periocular muscle spasms, resulting in partial or complete eyelid closure. Though BEB has been linked to a variety of mineral and vitamin D deficiencies, its association with serum vitamin B_{12} has never been studied. We intended to determine the association between vitamin B_{12}, serum calcium, magnesium, phosphorus, and 25-(OH) vitamin D levels, and BEB severity and frequency.
Methods: This retrospective case-control study included 20 BEB patients who were followed-up and treated periodically with botulinum toxin injections in Afyonkarahisar Health Sciences University Department of Ophthalmology's Oculoplastic and Reconstructive Surgery Unit between January 2019 and January 2021. Twenty age- and gender-matched healthy individuals were also included. The Jankovic rating scale was used to determine the severity and frequency of BEB. Acquired data were assessed retrospectively in terms of age, gender, serum minerals, 25 (OH)-Vitamin D and Vitamin B_{12} levels.
Results: In this study, 20 BEB patients (F:M=14:6) and 20 healthy individuals (F:M=12:8) (P=0.321) were investigated. The mean ages of BEB patients and healthy individuals were 64.37 (4.21) and 63.83 (3.13) years, respectively (P=0.239). Compared to healthy individuals, BEB patients had significantly lower serum levels of 25-(OH) vitamin D (P=0.037), vitamin B_{12} (P=0.014) and calcium (P=0.011). In BEB patients, serum levels of 25-(OH) vitamin D (r=-0.375, P=0.043), calcium (r=-0.319, P=0.039), and vitamin B_{12} (r=-0.408, P=0.027) were all strongly negatively correlated with the Jankovic severity score.
Conclusion: A strong negative correlation between disease severity and decreased vitamin B_{12}, 25-(OH) vitamin D, and calcium in BEB patients indicated that, among other things, BEB may be a rare form of vitamin B_{12} deficiency. In the absence of an obvious cause for BEB, serum vitamin B_{12} testing, in addition to serum minerals and 25-(OH) vitamin D, may be useful.

Keywords: Benign essential blepharospasm, Vitamin B12, Magnesium, Phosphorus, Calcium, 25-(OH) vitamin D, Jankovic rating scale

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Introduction

Benign essential blepharospasm (BEB) is a type of focal dystonia characterized by involuntary spasms of the orbicularis oculi, corrugator, and procerus muscles that cause partial or complete closure of the eyelids. Symptoms of this condition include a slightly higher blink rate, involuntary eyelid closure, and functional blindness in some cases. BEB affects between 1.4 and 13.3 individuals per 100,000, with symptoms appearing between the fifth and seventh decades of life [1]. The annual mean incidence of BEB is reported as 0.10 ‰, with female and male incidences of 0.12 ‰ and 0.07 ‰, respectively [2]. Even though it is more common in females than in males, a potential explanation for women's predisposition to this disease is yet to be discovered [3, 4]. BEB patients may also experience mid-facial or lower-facial spasms, a condition known as Meige syndrome [5]. Although BEB etiology has not been fully clarified, potential contributions of basal ganglia (BG), and cortical process abnormalities, as well as genetic, and environmental factors have been reported [6]. Involuntary contractions of the orbicularis oculi muscle may lead to a continuous eyelid closure. A series of involuntary activation of periorbital muscles may also be associated with BEB. Treatment of BEB involves botulinum toxin injection, which is basically applied to periorbital areas to inhibit acetylcholine release at the neuromuscular junction, and thus induces temporary paralysis of the muscles responsible for dystonia [7, 8].

An involvement of calcium regulation in dystonia has been discussed at the cellular level. In both animal and human models, accompanying mutations have also been identified [9]. Hypocalcemia is associated with neuromuscular overstimulation, while hypercalcemia causes muscle pain, tenderness, weakness, and muscle spasm [10-12]. Extracellular calcium ions (Ca^{+2}) have been shown to be just as critical in central and peripheral neuronal functions as intracellular calcium ions [13]. Muscle strength and serum magnesium ion (Mg^{+2}), which is involved in muscle contraction and tone maintenance, have been related. Involuntary muscle contractions may occur in hypomagnesemia [14]. Hypermagnesemia, however, blocks calcium channels in all smooth, skeletal and/or cardiac muscle cells [15]. Phosphorus regulates a Ca^{+2}/ATPase pump responsible for muscle contraction and relaxation. An insoluble calcium phosphate precipitate formed by inorganic phosphate reduces Ca^{+2} ion release [16]. The 25-hydroxy (OH) vitamin D is essential for immune function, mineral homeostasis, and bone biology. Controlling the concentration of ionized calcium in extracellular and intracellular compartments is crucial. Hypocalcemia has also been related to a vitamin D deficiency [17]. In addition, muscle weakness may be caused by hypophosphatemia or vitamin D deficiency [18].

Vitamin B_{12} is an essential vitamin and must be supplied in the diet, primarily through foods such as meat, fish, eggs, milk, and liver [19]. Usually, the daily requirement for vitamin B_{12} is approximately 2 mg in adults [20]. Adults store 2-3 mg in their bodies, which means that many years of dietary deficiency is actually necessary until the disorder is clinically evident [21-23]. Vitamin B_{12} deficiency has been linked to a variety of neurological symptoms for over 150 years [24]. Myelopathy, large fiber neuropathy, optic atrophy, dementia, chronic seizures, psychosis, and mood disorders constitute the symptoms of vitamin B_{12} deficiency [25, 26]. Moreover, adults with cerebellar ataxia and extrapyramidal symptoms such as dystonia and chorea have been uncommonly reported [25, 27-30]. Apart from the parameters described above, the relationship between BEB and vitamin B_{12} level has never been investigated before, making the current research the first to determine the potential relationship between BEB and vitamin B_{12} level, among other things.

The aim of this study was to analyze serum calcium, magnesium, phosphorus, 25-(OH) vitamin D and vitamin B_{12} levels in BEB patients to determine whether there was a connection between these values and BEB severity and frequency.

Materials and methods

Study participants

This retrospective case-control study included 20 BEB patients who were followed-up and treated periodically with botulinum toxin injections in Afyonkarahisar Health Sciences University Department of Ophthalmology's Oculoplastic and Reconstructive Surgery Unit and Endocrinology clinics between January 2019 and January 2021. Twenty age- and gender-matched healthy individuals were also included for comparison. The study protocol complied with the ethical principles of the Declaration of Helsinki and received full approval from the institutional review board of Afyonkarahisar Health Sciences University Ethics Committee (Date: 05.02.2021, Acceptance code: 2021/139). Written informed consent was obtained prior to the study.

Inclusion and exclusion criteria

To rule out any potential neurological disorders, all patients underwent complete neurological examination. Patients who were followed up in the ophthalmology clinic with a diagnosis of BEB disease but without prior eyelid or intraocular surgery and/or any systemic disease that might affect eyelid movements were included in the study. However, patients with eyelid disorders secondary to any prior ocular trauma, underlying neurological disorders, prior thyroid and parathyroid surgery that may affect calcium metabolism, use of supplements such as vitamin B_{12}, vitamin D and magnesium, calcium and phosphorus, and presence of Meige Syndrome were excluded from the study.

Jankovic rating scale

The Jankovic rating scale, an existing clinical scale commonly used for grading BEB severity and frequency during the initial assessment and measuring therapeutic outcomes during patient follow-up, was used to determine the severity and frequency of BEB. As shown in Table 1, this scale rates severity and frequency separately, assigning a score of 0 to 4 to each [31]. 0 points are given in case there are no symptoms, while 4 points are given when the severity of BEB symptoms is maximum and most frequent. Total score is obtained from the sum of the two sub-scores. The Jankovic rating scale focuses primarily on the objective manifestations of BEB. However, this scale also includes some subjective symptoms, such as whether it neutralizes increased blinking and spasms due to its assessment by the physician. This clinical scale is relatively simple and can easily be used by both patients and physicians. Measurement

tests may be completed without the use of complicated equipment or scoring procedures. The Jankovic rating scale has some drawbacks, such as a lack of evaluation of how the patient's blepharospasm affects everyday activities and a lack of determination of small changes in BEB severity or frequency.

Table 1: Jankovic rating scale

Severity	Descriptions
0	No symptoms
1	Only under the influence of external stimuli (e.g. bright light, wind, reading, etc.)
2	Mild, spontaneous blinking (without spasms), clearly visible, sometimes troublesome, but without functional impairment
3	Moderate, clearly visible spasms of the eyelids; moderate deterioration
4	Severe, disruptive spasms of the eyelids, possibly involving other facial muscles
Frequency	Descriptions
0	No symptoms
1	Slightly increased flashing frequency
2	Eye flickering with an individual blink time of less than a second
3	Spasms of the eyelids that last more than a second; eyes open more than 50% of waking time
4	Functional blindness caused by prolonged closing of the eyes for more than 50% of the awakening time

Data from the respective groups were assessed retrospectively in terms of age, gender, serum mineral (calcium, magnesium, and phosphorus), 25-(OH) vitamin D and Vitamin B_{12} levels. In our laboratory, the normal ranges for serum calcium, magnesium, and phosphorus were 8.8 to 10.6 mg/dl, 1.8 to 2.6 mg/dl, and 2.5 to 4.5 mg/dl, respectively. Vitamin D deficiency was described as 25-(OH) vitamin D <20 ng/l and vitamin B12 deficiency was described as vitamin B12 <200 pg/ml.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 21.0 software package (SPSS Inc., Chicago IL, USA). The distribution of data was analyzed with the Kolmogorov Smirnov test. Continuous variables with normal distribution were presented as mean (SD). Categorical data were reported as number (frequency). Student's *t* test and Chi-square test were used to compare the data. Pearson's correlation analysis was performed for normally distributed data. $P<0.05$ was statistically significant.

Results

Twenty BEB patients and 20 healthy individuals were included in this study. Female-to-male ratios in BEB patients and healthy individuals were 14:6 and 12:8, respectively ($P=0.321$). The mean age was 64.37 (4.21) years in BEB patients and 63.83 (3.13) years in healthy individuals ($P=0.239$). Compared to healthy individuals, BEB patients were associated with statistically significantly lower levels of 25-(OH) vitamin D ($P=0.037$), vitamin B_{12} ($P=0.014$) and calcium ($P=0.011$), respectively. Besides, BEB patients had lower levels of phosphorus and magnesium than healthy individuals, although the difference was not statistically significant ($P=0.680$ and $P=0.340$, respectively) (Table 2).

Correlation analysis

In BEB patients, serum levels of 25-(OH) vitamin D (r=-0.375, $P=0.043$), calcium (r=-0.319, $P=0.039$), and vitamin B12 (r=-0.408, $P=0.027$) were all negatively correlated with the Jankovic severity score. No correlations were observed between the serum parameters of Group 1 patients and the Jankovic frequency score (Table 3).

Table 2: Vitamin and mineral serum levels in the respective study groups

Parameters	BEB patients mean (SD)	Healthy individuals mean (SD)	*P*-value
25-(OH) vitamin D (ng/ml)	16.58 (7.23)	19.23 (6.37)	0.037
Vitamin B_{12} (pg/ml)	274.11 (107.22)	380.13 (119.09)	0.014
Magnesium (mg/dl)	1.94 (0.36)	1.96 (0.28)	0.340
Phosphorus (mg/dl)	3.53 (0.98)	3.54 (0.66)	0.680
Calcium (mg/dl)	9.32 (0.38)	9.76 (0.29)	0.011

SD: Standard deviation, $P<0.05$ was considered statistically significant.

Table 3: Illustration of the Jankovic frequency and severity scores in BEB patients

Parameters	Jankovic frequency score		Jankovic severity score	
	Pearson's correlation coefficient (*r*)	*P*-value	Pearson's correlation coefficient (r)	*P*-value
25-(OH) vitamin D (ng/ml)	0.198	0.092	-0.371	0.043
Vitamin B_{12} (pg/ml)	0.162	0.103	-0.408	0.027
Magnesium (mg/dl)	0.136	0.53	0.208	0.328
Phosphorus (mg/dl)	0.228	0.384	0.271	0.491
Calcium (mg/dl)	0.201	0.168	-0.319	0.039

BEB: Benign esseantial blepharospasm; Pearson's correlation coefficient was considered significant if within 0.300-0.700; $P<0.05$ was considered statistically significant.

Discussion

In this study, BEB patients had significantly lower serum calcium and 25-(OH) vitamin D and insignificantly lower serum magnesium, and phosphorus levels compared to healthy individuals. In addition, the Jankovic severity score was strongly negatively correlated with serum calcium and 25-(OH) vitamin D in BEB patients. Few studies investigating serum calcium, magnesium, phosphorus, and/or 25-(OH) vitamin D levels in BEB patients have been reported with mixed results [32].

Most importantly, in addition to the above parameters, this study included, as far as we understand, the first assessment of serum vitamin B_{12} levels in these patients. In this regard, relative to healthy individuals, BEB patients had significantly lower serum vitamin B_{12} levels. Besides, in BEB patients, the Jankovic severity score was strongly negatively associated with serum vitamin B_{12}.

The precise mechanisms of BEB etiology are yet to be discovered. Involuntary spasms of the orbicularis oculi muscles often involving the corrugator supercilii and procerus, identified as eyelid protractor muscles, have been strongly correlated with BEB features [6]. The primary form of BEB has a gradual onset and occurs most frequently in middle-aged females, while secondary form is associated with BG, brainstem and thalamus lesions. Focal dystonia is one of the important distinctive findings of BEB. Dystonia is defined as an isolated or generalized disproportional contraction of muscles. It is a neurological movement disorder that results in forceful body bending, repetitive movements and/or sometimes painful abnormal postures [9, 33]. Its pathogenesis has been linked to disorders in BG and cerebellar circuits in the motor network with dyshomeostasis in mitochondrial dysfunction and dopamine as well as calcium signaling [8, 33].

Investigation of the relationship between acute dystonic reactions and serum calcium in 17 acute psychotic patients with non-primary dystonia reported no association between acute dystonia and serum calcium [34]. Also, while calcifications in BG, cerebellum, thalamus, and cerebral white matter have been identified in patients with autosomal dominant dystonia, serum calcium levels in these patients were within normal limits [35]. In this study, on the other hand, serum calcium levels in patients with BEB decreased significantly compared to healthy controls.

However, none of them had hypocalcemia and/or associated neuro-radiological findings. In view of this, although these findings demonstrate the relationship among dystonia, BG and Ca^{+2} homeostasis, the exact pathophysiology remains undisclosed.

The role of 25-(OH) vitamin D in muscle strength and contraction has been reported [36]. In 25-(OH) vitamin D deficiency, muscle strength may be maintained by increasing plasma phosphorus levels, supporting the notion that 25-(OH) vitamin D alone does not play a role in the function or activity of the skeletal muscles [37, 38]. However, the association between low 25-(OH) vitamin D and muscle weakness in the elderly has been reported in epidemiological studies [37, 39]. Further, the association of 25-(OH) vitamin D and phosphate metabolism has been known since Nicolaysen demonstrated an improvement in phosphate absorption in response to vitamin D [40]. Vitamin D increases plasma phosphate in low phosphate intake [41]. It is noteworthy that phosphate deficiency affects muscles with a slower metabolism and produces a slower sustainable response [42, 43]. Although little or no effect due to rapid metabolism has been observed in the fast-twitch muscle, the slow-twitch muscles have been associated with a higher concentration of phosphate use for a maximum muscle function. Indirect effect of 25-(OH) vitamin D on skeletal muscle has also been reported in some studies [18]. Vitamin D increases the intestinal absorption of phosphorus. However, a decrease in muscle strength is inevitable as the absorption of phosphorus decreases in 25-(OH) vitamin D deficiency. Although it remains unclear whether 25-(OH) vitamin D or phosphorus is directly responsible for muscle weakness, it is clear that 25-(OH) vitamin D plays a positive role in the metabolism of phosphorus. Similarly, in this study, levels of 25-(OH) vitamin D and phosphorus were lower in BEB patients compared to age- and gender-matched healthy individuals with statistically significant decreases in 25-(OH) vitamin D and non-significant decreases in serum phosphorus. The direct proportional decrease of these two parameters confirms the previous reports on their interrelated metabolism and the subsequent muscle physiology in dystonia or BEB.

Extrapyramidal involvement attributable to vitamin B_{12} deficiency is relatively uncommon in adults, with which the deficiency has been reported to be associated wıth focal dystonia, chorea, myoclonus, Parkinsonism and even ataxia [26, 28, 44, 45]. No prior reports of BEB in adults associated with vitamin B_{12} deficiency have been reported. In this study, however, in addition to significantly lower serum 25-(OH) vitamin D and calcium levels, BEB patients had significantly lower serum vitamin B_{12} levels compared to age and gender-matched health individuals. Moreover, the correlation analysis revealed a statistically significant negative correlation between vitamin B_{12} along with 25-(OH) vitamin D, calcium and the Jankovic severity score. These findings may indicate a potential collective relationship between serum vitamin B_{12} and BEB in adults, in addition to serum 25-(OH) vitamin D and calcium.

The mechanism for extrapyramidal involvement in serum vitamin B_{12} deficiency is not well comprehended. Vitamin B_{12} deficiency is the most frequent cause of hyperhomocysteinemia. Homocysteine is necessary for methionine methylation. It also possesses N-methyl-D-aspartate agonistic effect. By acting on the thalamo-cortical pathway, homocysteine may trigger excitatory activity in BG leading to dystonia and chorea [46]. Further, excess methyl level in B_{12} deficiency results in an increased e-methyl tetrahydrofolate level, which is characterized by kainic acid agonistic effect. Kainate has been noted to cause harm comparable to that seen in Huntington's disease in experimental animals [47]. Furthermore, methylmalonic acidemia, an inborn metabolism error, is typically associated with acute extrapyramidal syndrome in infants [48]. In patients with dystonia, increased plasma levels of homocysteine have been reported [19]. It has therefore been suggested that a high level of homocysteine may contribute to the onset and severity of dystonia, and that routine plasma homocysteine testing and treatment of these patients for hyperhomocysteinemia should also be recommended.

The authors recognize the drawbacks of this study. First, the retrospective nature of this study has limited the ability of the authors to discover prospective processes in relation to the association between BEB and serum levels of minerals and vitamins, particularly serum vitamin B_{12}. Second, homocysteine analysis was not performed in this study, which could allow prompt diagnosis of vitamin B12 deficiency. Third, residual influencing factors might have led to an unexplained analytical preference. Moreover, the size of the study population was just not high enough to improve the efficacy of the study.

While there are some drawbacks in this study, there are some strengths as well. As far as we know, in addition to serum calcium, magnesium, phosphate and 25-(OH) vitamin D, this may be the first study in which serum level of vitamin B_{12} was assessed in relation to BEB in a sample of patients and control subjects of the same ethnicity. There is a significant role of ethnicity in the selection of patients and control groups, even though extensive investigation has not yet been undertaken. The high average age of the study participants can foreseeably influence the outcome of BEB from the undiagnosed age-related neuro-degenerative conditions. Fortunately, all study groups were about the same age, which might at some stage alleviate the inherent preference of this study's clinical outcomes.

Conclusion

To conclude, in conjunction with other factors, whether vitamin B12 deficiency and BEB are coincidentally or causally related is not yet determined. The improvement in BEB after only cyanocobalamine supplementation is intriguing, implying a potential causal relationship. Thus, BEB may be a rare manifestation of vitamin B12 deficiency, and early detection is critical for reversing the associated hematological and neurological dysfunction. Significantly lower serum levels of 25-(OH) vitamin D and calcium were also found in BEB patients, as well as a strong negative correlation with disease severity. Moreover, serum magnesium and phosphorus levels were lower in BEB patients as compared to healthy individuals, though the difference was not significant. Long-term prospective studies may yield clinically valuable results in determining the role of calcium regulation and vitamin D involvement in BEB pathophysiology and changes in ion concentrations in BG, cerebrospinal fluid, serum, and orbicularis oculi muscle. In the absence of an apparent cause for BEB, serum vitamin B12 levels,

in addition to serum minerals and 25-(OH) vitamin D, may be worth testing.

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Incidental thorax imaging findings in abdominal computed tomography: Results of a tertiary center

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The study protocol was approved by the Adiyaman Training and Research Hospital Ethics Committee (2020/9-12).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Abdominal computed tomography (ACT) is a frequently used imaging modality. The large imaging area often results in the inclusion of lower sections of the thorax. It is known that some thoracic pathologies have symptoms that mimic upper abdominal pathologies. It is possible to detect many pathologies with careful examination of these levels. Previous studies have been conducted to detect incidental chest findings in imaging methods performed for emergency reasons such as trauma, but there is no study in the literature investigating incidental chest findings in ACT imaging. The aim of this study is to determine the incidental findings detected in thoracic sections included in abdominal computed tomography (CT) images and the prevalence of these findings in a tertiary center.

Methods: This descriptive study includes 1133 patients who were admitted to Adıyaman Training and Research Hospital between 2017-2020 due to abdominal pain, diarrhea, vomiting, weight loss, constipation, and recurrent urinary tract infection, and underwent abdominal CT scanning. The necessary local ethics committee approval was obtained. Incidental findings in thoracic areas shown in the abdominal CT images included mediastinal findings, infectious findings, pulmonary lesions, pleural findings, lung parenchyma and pleural findings.

Results: The mean age of the patients was 43.8 (18.7) years. Incidental findings were detected in 49.2% of the patients, the most common being those related to the lung parenchyma and the pleura (20.7%). The most common lung lesions were pulmonary nodules smaller than 1 cm (5%). In addition, 116 (10.2%) patients had infectious findings, among which the images of 31 (2.7%) suggested bacterial pneumonia factors, and 17 (1.5%) had interstitial pneumonia findings due to the SARS-CoV2 virus.

Conclusion: According to the results of this study, evaluation of pathologies detected incidentally in the thorax in ACT sections may affect the treatment of patients. In addition, evaluation, follow-up, and early treatment of lung nodules that can be detected incidentally can prevent possible advanced stage malignancies. Although the symptoms and clinical statuses of the patients are very useful in evaluating the images, examination of every structure included in the imaging field may play a role in the early diagnosis and treatment of some pathologies.

Keywords: Abdominal computed tomography, Chest computed tomography, COVID-19, Incidental findings, Pulmonary nodule

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Introduction

Major advances in computed tomography (CT) in the recent years provide radiologists with the opportunity for early diagnosis and treatment of many abdominal, thoracic, mediastinal, and cardiac pathologies. The early detection of pathologies such as lung cancer, hepatocellular carcinoma, gastrointestinal tumors, or aortic aneurysm may decrease mortality, but also cause misdiagnosis or over-diagnosis [1].

Another important factor in computed tomography (CT) evaluation by radiologists is the possibility of incidental findings. The rapid increase in the number of CT scans and the evaluation performance have made the detection of these findings easier. Incidental findings are generally defined as imaging abnormalities unrelated to the indication requiring CT imaging [2]. All abnormal findings that cannot be associated with the primary pathology before exposure fall into this group. These are divided into 4 groups to facilitate the examination and clinical evaluation: 1- Findings with results that need immediate treatment (e.g. newly diagnosed malignancy), 2- Findings with good prognoses but require follow-up (e.g. calcifications in the heart valves), 3- Findings with possible clinical / prognostic significance requiring follow-up (pulmonary nodules) and 4- Findings without a proven clinical/prognostic significance (sclerotic bone islands in the vertebrae) [2].

CT scans after trauma are used very commonly as they are a fast and effective diagnostic tool [3-5]. The rates of CT findings detected incidentally in trauma patients reach 45% [6]. Many studies have been conducted to determine these rates, and the clinical value of incidental findings has been investigated [7, 8].

A significant portion of the lung parenchyma, mediastinal area and soft tissue and bony structures in the thoracic region are included in abdominal CT studies. Data belonging to these regions can be stored and evaluated thanks to permanent storage. For example, the abdominal CT images of a patient obtained 6 months ago due to right upper abdominal pain was viewed when they visited the Pulmonology clinic with the complaint of hemoptysis for the first time and pulmonary nodules in the right lower lobe were observed. A new thorax CT imaging allowed comparison of their sizes and properties.

It is of great importance to know and evaluate the prevalence of incidental findings detected on CT images. This study aimed to determine the incidental findings detected in thoracic sections included in abdominal CT images in a tertiary center.

Materials and methods

Patient selection

This descriptive study includes 1133 patients who were admitted to Adıyaman Training and Research Hospital for abdominal pain, diarrhea, vomiting, weight loss, constipation, and recurrent urinary tract infection between 2017-2020. The necessary local ethics committee approval was obtained for the study (2020 / 9-12). This study was carried out in accordance with the Declaration of Helsinki.

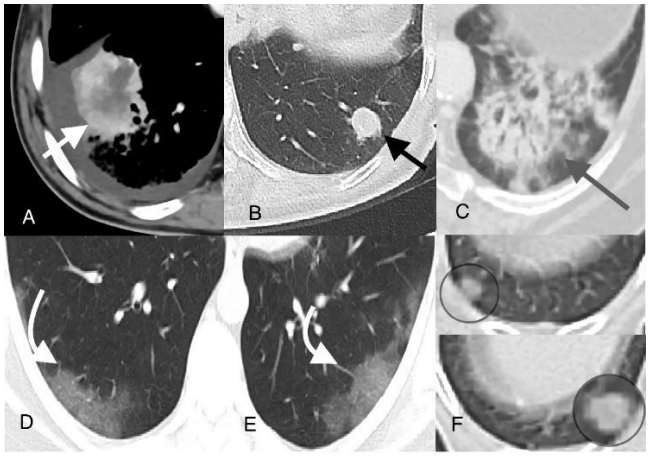
Imaging protocol and evaluation

Imaging was performed on a 64-slice computed tomography device (Toshiba Medical Systems), with or without contrast, while holding the breath after a deep inspiration in the supine position. The scanning parameters were as follows: 120 kV, 80 mAs, 0.35 second spin time, pitch: 1.5. Images were obtained by intravenous (i.v.) bolus contrast agent injection in 421 of the patients included and reconstructed at a slice thickness of 1 mm using a high frequency reconstruction algorithm.

Data collecting

Images of 1133 patients who underwent abdominal CT imaging were retrospectively analyzed. Inclusion criteria in the study were being between the ages of 18-60 years and having had an abdominal CT scan with suspicion of an abdominal pathology. Patients with a known history of malignancy, lung infection in the last 6 months, those admitted with a history of trauma, and a history of degenerative bone pathology were excluded from the study. Thorax, inferior mediastinal area, and mediastinal structures (descending aorta, heart, pulmonary arteries, paratracheal, pretracheal, precarinal areas and mediastinal lymph nodes), adjacent bone structures (costae, thoracic vertebrae), subcutaneous fatty tissue and soft tissues were evaluated. Results were classified as mediastinal findings, infectious findings, pulmonary lesions, pleural findings, pulmonary parenchymal findings, and pleural findings. Mediastinal findings included increased cardiothoracic ratio, atherosclerotic changes in vascular structures, mediastinal lymphadenopathies, and pericardial effusion. Infectious findings comprised an infiltration suggestive of acute bacterial pneumonia, or interstitial pneumonia caused by SARS-CoV-2 virus, pleural effusion, and bronchiectasis (Figure 1). Among lung lesions, air cysts were classified as pulmonary nodules smaller or equal to or larger than 1 cm. Pulmonary parenchymal findings and pleural findings included interstitial lung diseases, atelectatic changes, emphysematous lung disease findings, pleural plaques suggesting asbestosis and acute pulmonary edema. The images were evaluated by two radiologists with 4 and 10 years of experience.

Figure 1: A: A mass lesion with cystic necrotic areas, contoured to the spicule, located peripherally in the posterolateral segment of the right lower lobe of the right lung and adjacent pleural effusion (white arrow). B: Peripherally located solid nodule with irregular contours in the posterolateral segment of the left lower lobe of the left lung (black arrow). C: Consolidated lung areas with air bronchograms and peribronchial thickening are observed in the anterior, posterior and lateral segments of the left lower lobe of the lung. These findings are associated with infective lung diseases (black arrow). D: In the lower lobe posterolateral segment of the right lung, there is a peripheral geographic interlobular septal thickening and ground glass density (white arrow). E: In the left lung lower lobe, posterolaterally and peripherally located ground glass density areas are observed (white arrow). F: Small pulmonary nodules with lobulated contours, irregular borders, located in the basal segments of the lower lobes in the right and left lungs



Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc. Chicago, IL, version 22.0). Data were expressed as numbers and percentages.

Results

The mean age of the patients was 43.8 (18.7) years. Among them, 582 (51.4%) patients were female and 551 (48.6%) were male. Incidental findings were detected in 49.2% of the patients (Table 1).

Table 1: Findings found incidentally in chest sections included in abdominal computed tomography

Incidental finding	Number	%
Mediastinal findings		
Cardiothoracic rate increase	33	2.9%
Vascular atherosclerotic changes	71	6.2%
Mediastinal lymphadenopathies	8	0.7%
Pericardial effusion	9	0.8%
Infectious findings		
Pulmonary infiltration	31	2.7%
COVID-19 pneumonia	17	1.5%
Pleural effusion	59	5.2%
Bronchiectasis	9	0.8%
Pulmonary lesions		
Pulmonary nodule	57	5%
≥ 1 cm pulmonary nodule	17	1.6%
Air cyst	14	1.2%
Pulmonary parenchymal diseases and pleural involvement		
Atelectatic changes	113	9.9%
Asbestosis	79	6.9%
Acute pulmonary edema	19	1.7%
Emphysematous changes	17	1.6%
Interstitial lung disease	7	0.6%

Mediastinal findings were detected in 118 (10.4%) patients, of which 33 (2.9%) had increased cardiothoracic ratio, 71 (6.2%) had vascular atherosclerotic changes, 8 (0.7%) had mediastinal lymphadenopathies and 8 (0.6%) had pericardial effusion.

Infectious findings were present in 116 (10.2%) of the patients. Infection findings suggestive of bacterial pneumonia were present in 31 (2.7%) of these patients, findings of interstitial pneumonia due to SARS-CoV2 virus were observed in 17 (1.5%), pleural effusion, in 59 (5.2%), bronchiectasis was observed in 9 patients (0.8%).

There were lung lesions in 88 (7.8%) of the patients. Of these lesions, 14 (1.2%) were air cysts, 57 (5%) were pulmonary nodules smaller than 1 cm, and 17 (1.6%) were pulmonary nodules larger than 1 cm. Patients with pulmonary nodules ≥1 cm were diagnosed with lung malignancy after necessary clinical examination and evaluation.

There were pulmonary parenchymal findings and pleural involvement in 235 (20.7%) of the patients. Atelectatic changes were present in 113 (9.9%) of these patients, pleural plaques secondary to asbestosis were seen in 79 (6.9%), findings of acute pulmonary edema were observed in 19 (1.7%), and emphysematous lung disease was present in 17 (1.6%). Seven patients (0.6%) had findings of interstitial lung diseases.

Discussion

In this study, we investigated the rate of incidental imaging findings detected in chest structures included in ACT images, which was 49.1%, similar to the rate of chest findings found incidentally in trauma patients recently [9]. The most common incidental finding in our patients was atelectatic changes (9.9%). Suspicious pulmonary nodules were detected in 1.6%. This data in our study was quite low compared to other studies investigating the incidental detection of suspicious pulmonary nodules [10, 11].

In another study investigating the presence of incidentally detected pulmonary nodules in ACT, the incidental detection rate of pulmonary nodules was reported as 3% [12]. This rate was higher in our study. According to studies conducted in previous years, thorax CT scans have increased today. This increase can be attributed to reasons such as easy access to technological devices and malpractice [13]. In addition, it has facilitated the detection of incidental chest findings in thorax CT, which is used as a diagnostic tool in COVID 19 pneumonia. Therefore, the incidental rate of pulmonary nodules detected in our study may be lower.

In whole-body CT studies investigating traumatic pathologies due to blunt trauma, the most common incidental chest finding is pulmonary nodules, followed by atherosclerosis [14]. Detection of infection, infiltration, and pleural findings was also very low in other publications [2, 15, 16].

In our study, unlike other studies, lung parenchymal findings suggesting infective infiltration were the most common. In addition, pneumonic infiltration due to COVID 19 infection were detected in 1.7% of the patients. The high rate of infective pathology in our study may be due to the Coronavirus pandemic. In a case series published at the onset of the pandemic, patients who presented with complaints of lower abdominal pain, fever, nausea, persistent vomiting and weakness and who underwent ACT showed signs of pneumonic infiltration in both lungs' lower zones [17]. Incidental detection of COVID-19 pneumonia is not surprising in this study, in which ACT images of patients presenting with symptoms such as abdominal pain, vomiting, nausea, and diarrhea were included. According to these results, COVID 19 pneumonia should also be considered in the pre-diagnosis of individuals without underlying health problems.

Frequent and convenient access to CT and many imaging methods increases the number of patients viewed and the images obtained. Not only the image capturing methods, but also the development of data evaluation and storage technology increase the importance of the requested imaging area as well as the neighboring structures. Misinterpreting images, failure, or lack of evaluation of non-symptomatic findings may cause important findings to be overlooked and lead to false/incomplete diagnosis. At this point, it is very important for radiologists to identify and categorize these non-clinical findings and convey them to other clinicians.

Limitations

This study has some limitations. First, there may be a bias since the study was carried out retrospectively. Although the data were obtained from the hospital database, unnoted symptoms and anamnesis may cause bias in the study results. Second, the patient age range included in the study is wide. Therefore, it may not be possible to evaluate age-related pathologies with increasing frequency. For this reason, prospective studies can be conducted with large patient groups divided according to their age to generalize the results.

Conclusion

Examination of chest structures entering the imaging field in ACT may be useful in the early diagnosis and treatment of pulmonary infections and pulmonary nodules that are

precursors of malignancy. Cross-sectional imaging methods are important diagnostic tools that are used in the evaluation of patients and offer a wide examination area. Independent of clinical information and symptoms, evaluation of every structure in the imaging field plays a role in the early diagnosis of many pathologies.

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Evaluation of the relationship between polysomnography parameters, physical examination findings and oxidative stress parameters in patients with obstructive sleep apnea syndrome

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Ethics Committee Approval
Necmettin Erbakan University, Ethic Committee of Meram, Number: 2013/32
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Oxidative stress status in obstructive sleep apnea syndrome (OSAS) is well discussed in the literature. Oxidative stress levels increase, and antioxidant system activity decreases in OSAS patients. However, the change in oxidative stress status in positional (pOSAS) and non-positional (npOSAS) OSAS has not been adequately examined. The aim of this study was to compare OSAS patients' polysomnographic (PSG) parameters and oxidative stress capacities with the structural and functional properties of the upper respiratory tract.

Methods: This study was designed as prospective case-control study and patients were divided into three groups as control, pOSAS and npOSAS according to their PSG findings. Ear nose throat examinations including rhinomanometry test and oxidative stress blood parameter tests were conducted to all patients. Variables among the groups were compared.

Results: All PSG parameters were significantly worse in the OSAS groups than the control group (P<0.05). The mean AHIs of the pOSAS and npOSAS groups were 21.7 (16.5), and 31.2 (21.9), respectively. AHI, desaturation number and minimal SpO_2 values of the pOSAS group were significantly lower compared to the npOSAS group (P=0.043, P=0.017 and P=0.006, respectively). TNF α was significantly lower and adiponectin was significantly higher in the pOSAS group compared to the npOSAS group (P=0.001, P<0.001 respectively). The two groups were similar in terms of rhinomanometry results (P=0.888).

Conclusion: The lack of difference between pOSAS and npOSAS patients in terms of rhinomanometry results may indicate that the nose may not play a decisive role in the differentiation of these groups. Only OSAS severity may not be a determinant factor in oxidative stress balance in patients with pOSAS and np OSAS.

Keywords: Obstructive sleep apnea, Oxidative stress, Rhinomanometry

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Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of apnea during sleep and is one of the most common health problems in the community [1]. Changes in sleep position can affect the occurrence and severity of obstructive sleep apnea. Apnea frequency and duration are affected by body position in approximately 56% to 75% of OSAS patients [2]. For the first time, Cartwright [3] defined positional OSAS (pOSAS) as a 50% or more difference in the hourly apnea index between the supine position and lateral lying positions. Depending on the differences in the diagnostic criteria, it has been reported that 53 to 77.4 % of all OSAS patients may be pOSAS [4].

Changes in blood saturation during sleep in OSAS patients may cause the oxidant-antioxidant balance to deteriorate in favor of oxidant molecules due to recurrent hypoxic periods. Chronic OSAS can result in mitochondrial dysfunction caused by tissue hypoxia, increased regulatory hormones, and altered adipocytokine patterns [5, 6]. Diseases with serious morbidity and mortality risk such as hypertension, diabetes mellitus and obesity have an increasing association with OSAS [1, 7]. It can be said that the relationship between OSAS and metabolic disorders is complex. The reason for this complex relationship is that obesity can be both the cause and effect and a confounding factor in OSAS [5]. In this study, we investigated the polysomnography (PSG) and some biochemical parameters to examine both the role of oxidative stress mechanisms and obesity in OSAS. Therefore, we tried to reveal the distribution of these parameters in OSAS subgroups and their relationship with PSG data, after dividing OSAS patients into pOSAS and non-positional OSAS (npOSAS) groups according to the PSG parameters.

Materials and methods

Patients who visited our hospital's sleep outpatient clinic with complaints of snoring and wanted to participate in our study voluntarily were included in this study. According to the PSG results, the patients were divided into three categories [3]. Those with an apnea-hypopnea index (AHI) <5 were included in the control group. Patients with AHI ≥5 in PSG were considered OSAS patients, who were divided into two groups according to PSG data. If the AHI values of the patients on supine position were 2 times or more than the AHI values on lateral position, the patients were considered to have pOSAS, and if the supine AHI values were less than 2 times the AHI values measured on lateral positions, they were considered to have npOSAS.

First, the body mass index (BMI)(kg/m^2) of the patients was calculated by measuring the height and weight. Neck circumference measurement was recorded from the cricothyroid membrane. Epworth Sleepiness Scale was used to determine the daytime sleepiness status of the patients. After ear nose throat examinations of the patients, anterior rhinomanometry test was performed and 3 tubes of venous blood were obtained in the morning and stored at -80°C.

Polysomnographic evaluation

Standard polysomnography was performed with the digital polysomnographic system (Somnoscreen plus, Somnomedics GmbH, Germany) all night in the sleep laboratory. Four-channel (C1A2, C2A1, O1A2, O2A1) electroencephalography (EEG), 2-channel (right and left) electrooculography (EOG), submental electromyelography (EMG) electrodes were placed on the patients for sleep assessment. Air flow in the mouth and nose were recorded by placing an oro-nasal flow meter and thermistor in the nose for respiratory monitoring, thorax and abdominal movements were recorded by placing a thoraco-abdominal effort sensor. In addition, hemoglobin oxygen saturation and heart rate were monitored by pulse oximetry. Leg movements were recorded with the EMG sensor placed on the anterior tibialis muscle. Sleep stages and respiratory events were scored manually according to AASM scoring criteria.

Anterior rhinomanometry test

Rhinomanometry measurements were made with the Rhino 30 (Lenzkirch / Germany) device after the patient rested in a sitting position for 20 minutes in a quiet environment. Nasal resistance measurements were performed with the active anterior technique in accordance with the International Rhinomanometry Standardization Committee. After the right and left nasal cavity measurements were made separately, the total nasal resistance was obtained. The measurements were evaluated at 150 Pascal, as recommended by the standardization committee.

Evaluation of blood parameters

Blood samples obtained from the patients and control groups into straight tubes were centrifuged in a Hettich centrifuge device at 4000 rpm for 10 minutes, and the serums were separated. Separated serum samples were stored at -80 ° C until the end of the study. Total Antioxidant Status (TAS), Malondialdehyde (MDA), Leptin, Adiponectin and Tumor Necrosis Factor alpha (TNFα) parameters were investigated.

TAS was calculated according to absorbance concentration calibration graphs using Bio-rad Microplate absorbance reader xMark (Bio-rad Laboratories, California, United States) system (Rel Assay Diagnostics, Gaziantep, Turkey). MDA levels were measured using the thiobarbituric acid reactivity method. MDA, a product of fatty acid peroxidation, reacts with thiobarbituric acid in a hot and acidic environment, the absorbance of the reacting colored complex was calculated in micromol/L using the Bio-rad Microplate absorbance reader xMark (Bio-rad Laboratories, California, United States) system at 532 nm. Leptin (Boster, California, United States), Adiponectin (Assaypro, Missouri, United States), and TNF α (Boster, California, United States) levels were calculated with ELISA kits according to absorbance concentration calibration graphs using Biotek (Biotek, Vermont, United States) ELX 50 microplate washer and ELX 800 absorbance reader system.

Statistical analysis

Continuous variables were expressed as mean (SD), and categorical data, as numbers and percentages. In the intergroup analysis of continuous variables, normality analyses were performed using the Kolmogorov-Smirnov goodness of fit test. The One-way Anova test (Post hoc: LSD) was used for comparisons of the data in three groups and above, since the data were suitable for normal distribution. Comparison of categorical data was made using the chi-square test. Analyses were

performed with IBM SPSS version 22. (IBM Corporation, Amonk, NY, USA). Statistical significance level was P <0.05.

Sample size

Based on the case-control study conducted by Ursavas et al. [8] whose purpose was to investigate the relationship between plasma adiponectin, leptin, ghrelin, resistin levels and OSAS, at an alpha error (p value) of 0.05 and 1-beta error (Power) of 0.80, 15 individuals per group would be sufficient for testing the absence hypothesis. G Power Statistics Program version 3.1.9.4 (Universität Düsseldorf, Germany) was used for the analysis [9].

Results

In this study in which 71 patients were included, there were 25 patients in the control group, 24 patients in the pOSAS group and 22 patients in the npOSAS group. Demographic and physical examination data of the patients are shown in Table 1. The BMI, neck circumference and rhinomanometry values of the control group were significantly lower than the OSAS groups (P=0.001, P=0.001 and P<0.001, respectively). In addition, the control group consisted of younger patients than the OSAS group. There was no significant difference between pOSAS and npOSAS groups in terms of examination physical findings except for Epworth scale scores (P>0.05). PSG was sufficient in terms of sleep efficiency in all three groups (> 70%). All PSG parameters were significantly better in the control group than both OSAS groups (P<0.05). AHI, desaturation number and minimal SpO2 values of pOSAS group were significantly lower than npOSAS group (P=0.043, P=0.017 and P=0.006, respectively) (Table 2).

Table 1: Distribution of demographic data and physical examination findings according to the groups

Parameters	Control Mean (SD) (n=25)	pOSAS Mean (SD) (n=24)	npOSAS Mean (SD) (n=22)	*P*-value
Age (years)	37.7 (8.4[a])	45.0 (9.6)	46.4 (10.9)	0.006*
Female/Male	6/19	6/18	5/17	0.984**
BMI (kg/m2)	25.0 (2.33[a])	28.0 (6.68)	30.1 (3.08)	0.001*
Neck Circumference (cm)	37.4 (2.34[a])	39.6 (3.99)	41.3 (3.25)	0.001*
Epworth Scale	4.7 (2.26[a])	6.8 (3.82[a])	9.5 (5.4[a])	0.001*
Rhinomanometry (Pascal)	0.30 (0.11[a])	0.61 (0.09)	0.60 (0.24)	<0.001*

* One-way ANOVA Test (Post hoc: [a] LSD), ** Chi-square Test

Table 2: Distribution of polysomnography parameters according to the groups

Parameters	Control Mean (SD) (n=25)	pOSAS Mean (SD) (n=24)	npOSAS Mean (SD) (n=22)	*P*-value
Total Sleep Time (Second)	331 (29.1[a])	300 (58.0)	288 (82.3)	0.045*
Sleep Efficiency (%)	75.1 (8.0)	74.5 (10.8)	74.9 (13.9)	0.982*
AHI	2.4 (0.9[a])	21.7 (16.5[a])	31.2 (21.9[a])	<0.001*
Desaturation Number	1.2 (0.9[a])	16.6 (16.2[a])	26.3 (17.0[a])	<0.001*
Minimal SpO_2	89.3 (1.4[a])	82.5 (5.5[a])	78.2 (6.6[a])	<0.001*
Average SpO_2	94.0 (1.5[a])	90.7 (2.3)	90.1 (2.2)	<0.001*
SpO_2 <90(%)	0.6 (0.6[a])	26.3 (31.1)	37.1 (28.8)	<0.001*

* One-way ANOVA Test (Post hoc: [a] LSD)

There was no significant difference between the OSAS groups in terms of TAS levels, while the TAS levels of the control group were significantly higher than the pOSAS group (P=0.006). While there was no significant difference between OSAS groups in terms of MDA, MDA levels of the control group were significantly lower than OSAS groups (P=0.058, P<0.001 respectively). TNF α was significantly higher in npOSAS group than the pOSAS and control groups (P<0.001). There was no significant difference in terms of TNF-α between pOSAS and control groups (P=0.319). Adiponectin levels were significantly lower in npOSAS group than pOSAS and control groups (P<0.001). There was no significant difference between OSAS groups in terms of leptin levels (P=0.390). However, the leptin levels of the control group were significantly lower than the OSAS groups (P<0.001) (Table 3).

Table 3: Distribution of blood parameters according to the groups

Parameters	Control Mean (SD) (n=25)	pOSAS Mean (SD) (n=24)	npOSAS Mean (SD) (n=22)	*P*-value
TAS	0.55 (0.33[a])	0.29 (0.18[a])	0.42 (0.17)	0.006*
MDA (TBARS)	7.15 (1.93[a])	13.94 (5.92)	17.07 (7.39)	<0.001*
TNF α	5.12 (2.01)	6.35 (3.06)	10.55 (6.69[a])	<0.001*
Adiponectin	6.03 (1.85)	6.24 (1.25)	3.56 (1.09[a])	<0.001*
Leptin	7.43 (3.87[a])	16.80 (7.08)	15.21 (7.30)	<0.001*

* One-way ANOVA Test (Post hoc: [a] LSD)

A negative correlation was found between AHI and TAS (r=-0.249, P=0.036), BMI and adiponectin (r=-0.345, P=0.003), TAS and MDA (r=-0.236, P=0.048) and leptin and TAS (r=-0.278, P=0.019), while a positive correlation was detected between AHI and MDA (r=0.439, P=0.00), BMI and TNF α (r=0.371, P=0.001) and leptin (r=0.379, P=0.001).

Discussion

pOSAS constitutes an important part of OSAS. pOSAS patients tend to be younger than npOSAS patients, have lower BMI, and shorter neck and waist circumferences. They experience less respiratory anomalies during sleep, most pOSAS patients (70-80%) have mild or moderate OSAS [4,10]. In our study, there was no significant difference between the pOSAS and npOSAS groups in terms of demographic data and physical examination findings except for the Epworth scale scores. Rhinomanometry results were similar in both OSAS groups. There was a significant difference between OSAS groups in terms of some PSG parameters, and AHI, desaturation number and minimal SpO2 values of pOSAS group were significantly lower than npOSAS group. In other words, our pOSAS patients also consisted of mild and moderate OSAS patients.

Many studies have shown that oxidative stress levels increase, and antioxidant system activity decreases in OSAS patients [6, 11-13]. As we have already mentioned, OSAS can be seen with various clinical conditions that have a devastating effect on vascular reactivity such as hypertension, cardiovascular diseases, metabolic syndrome, and insulin resistance. This makes it difficult to evaluate the oxidant-antioxidant status because these disorders accompanying OSAS have the potential to reduce antioxidant capacity and increase oxidant load [6]. Cofta et al. [14] stated that the increase in OSAS severity correlated with the increase in total antioxidant status and thiobarbituric acid-reacting substances plasma levels, and these markers may play important roles in the classification of the metabolic properties of OSAS. In our study, there was no significant difference between pOSAS and npOSAS groups in terms of TAS and MDA levels. In addition, as expected, a positive correlation was found between AHI and MDA and a negative correlation was detected between AHI and TAS. While there was a significant difference between pOSAS and npOSAS groups in terms of some PSG parameters, the TAS and MDA levels of the two groups were similar, suggesting that these blood parameters may have been affected by metabolism factors other than OSAS. However, there was no correlation between BMI, neck circumference and these blood parameters.

OSAS is a chronic inflammatory disorder and can cause increased production of certain inflammatory mediators in

circulation, including TNF α. In OSAS patients, proinflammatory cytokine levels increase and the level of anti-inflammatory factors decreases, causing endothelial dysfunction [15, 16]. TNF-α regulates the immune system, induces inflammation and participates in the regulation of fat metabolism. TNF-α levels in the blood of OSAS patients are generally higher than those of healthy controls [17, 18]. In a meta-analysis, TNF-α levels in circulation were higher in OSAS patients than in the control group, and this difference was more evident with increased OSAS severity. The authors claimed that TNF-α could be a promising circulatory biomarker for OSAS development [15]. However, it is controversial whether the high circulating TNF-α levels in these patients are the cause or the result of OSAS. In this study, the TNF α value of the npOSAS group was significantly higher than the pOSAS and control groups. In addition, while there was no correlation between TNF α and AHI, a positive correlation was found between BMI and neck circumference. In this study, it can be said that TNF α levels are affected by physical examination findings rather than the severity of OSAS.

There is a strong relationship between OSAS, obesity and inflammation. Leptin and adiponectin are major adipocytokines indicating the clinical and metabolic effects of obesity. Serum leptin levels increase in response to the degree of obesity, insulin resistance and hypoxia, while adiponectin levels are inversely related to the degree of obesity and insulin resistance [5]. Leptin is a potent pro-inflammatory agent, while adiponectin reduces inflammatory cytokine production and activity [8]. There are publications reporting that leptin levels are increased in OSAS patients, as well as articles reporting otherwise [8, 19, 20]. However, the number of articles reporting paradoxical results in this area are not small. Mutairi et al. [5] reported that adiponectin levels decreased with OSAS severity, and leptin levels decreased paradoxically with increasing OSAS severity. Therefore, they stated that adiponectin may be an independent marker of disease severity in OSAS patients. In our study, there was no significant difference between OSAS groups in terms of leptin levels. While leptin was not correlated with AHI, it negatively correlated with TAS, and positively correlated with MDA. Adiponectin was significantly lower in the npOSAS group compared to the other two groups. In addition, as expected, there was a negative correlation between adiponectin and BMI.

Limitations

The main limitation of this study is the small number of patients. In addition, since it was a double-blind study, the patient groups became clear at the end of the study, which can explain why the patients in the control group consisted of younger patients.

Conclusion

The lack of a homogeneous correlation between AHI and other PSG and blood parameters indicates that these blood values may have been affected by more than one factor in this patient group. Also, the lack of difference between pOSAS and npOSAS patients in terms of rhinomanometry results may indicate that the nose may not play a decisive role in the differentiation of these groups. Other upper respiratory tract sections can also be examined in the determination of positional dependence of OSAS patients.

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Evaluation of third-trimester neutrophil-lymphocyte and platelet-lymphocyte ratios and their correlation with birth weight

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Abstract

Background/Aim: Fetal development is affected by the maternal environment and one of the environment determinants is inflammation. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) have been used as markers of inflammation in many disciplines. The aim of this study is to evaluate the relationship between the value of these easily accessible markers in the 3rd trimester and birth weight, which is the result of fetal development.

Methods: This retrospective cohort study comprised 442 pregnant women who delivered within the last 2 years and met the inclusion criteria. As a result of a percentile adjustment made according to the Alexander growth curves, pregnant women were grouped according to the birth weight of their neonates, as normal birth weight (AGA) and large birth weight (LGA). Statistical analyses were conducted using the birth weights and hemogram parameters between the groups.

Results: There was no significant difference in hemoglobin, neutrophil, platelet, NLR and PLR levels ($P>0.05$ for each) between the groups; however, a negative correlation was observed between lymphocyte and gestational weight ($P=0.014$). When comparing hemogram parameters between the groups, hemoglobin, neutrophil, platelet, NLR, and PLR counts were similar ($P>0.05$ for each). We observed that the lymphocyte counts were lower in the LGA group ($P=0.019$). There was no significant relationship between birth weight, and NLR and PLR counts during the third trimester ($P=0.100$, $P=0.997$, respectively).

Conclusion: NLR and PLR counts are used in many disciplines as indicators of inflammation and have been used to predict many perinatal complications during pregnancy. In the present study, no relationship was found between fetal weight and third trimester NLR and PLR counts.

Keywords: Neutrophil lymphocyte ratio, NLR, Platelet lymphocyte ratio, PLR, Birth weight

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Introduction

The maternal environment during pregnancy affects fetal development. Although there is an increase in systemic inflammation during normal pregnancy, when there is abnormal maternal inflammation, blood flow to the uterus is impaired, and so is fetal development, secondary to the vascular dysfunction in the placenta [1]. The ratio of neutrophils to lymphocytes (NLR) and the ratio of platelets to lymphocytes (PLR) are used as inflammation markers and can be easily calculated using a simple blood test. These parameters, which show the inflammatory response, have been used under many conditions and for many complications.

There are several studies on NLR and PLR that have address gynecological diseases, such as ovarian hyperstimulation syndrome [2], premature ovarian failure [3], endometriosis [4], tubular ovarian abscess [5], adenomyosis and leiomyoma [6], and even gynecological cancers [7]. In addition, perinatal complications, such as hyperemesis gravidarum [8], gestational diabetes [9], intrahepatic cholestasis resulting from pregnancy [10], preeclampsia [11], and preterm labor [12] were also studied. NLR and PLR values are used not only in obstetric and gynecological practice but also in internal and surgical disciplines [13-16]. NLR increases in neutrophil count during acute inflammation and lymphopenia resulting from physiological stress. PLR indicates platelet activation, lymphocyte function, and immune response [17]. Previous studies have shown that using NLR and PLR to predict birth weight can help determine related neonatal morbidities [18]. The aim of the present study was to investigate the effect of inflammation markers, NLR and PLR, on fetal birth weight, which reflects fetal development.

Materials and methods

This was a retrospective study that comprised 442 pregnant women who delivered at Tuzla Government Hospital, Turkey, between 01/01/2019 and 12/31/2020. Permission for this study was granted by the Ethics Committee of Marmara University Faculty of Medicine (Decision number: 09.2021.99). The study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria were as follows: 1) Pregnant women between the ages of 18 and 45 years, 2) singleton and noncomplicated term pregnancies, and 3) a hemogram value at routine follow-up during the third trimester before labor began. The exclusion criteria were as follows: 1) Preeclampsia, 2) hemolysis, elevated liver enzymes, low platelet count syndrome, 3) gestational diabetes, 4) cholestasis resulting from pregnancy, 5) chronic systemic disease, 6) hematologic disease, or 7) no hemogram value measured in the third trimester. In addition, immigrants were excluded from the study because of their different races that would have affected the study set and perinatal results. Gravida, parity, abortion, fetal sex, gestational week, delivery type, and birth weights were recorded. The Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) was used for hemogram analyses. The hemogram parameters were hemoglobin (g/dL), neutrophil (*10³/µL), lymphocyte (*10³/µL), and platelet counts (*10³/µL). The pregnant women were classified according to their birthweights of their neonates using Alexander growth curves, as large for gestational age (LGA) (>90th percentile), and appropriate for gestational age (AGA) (10th-89th percentiles) [19].

Statistical analysis

Statistical analyses were conducted using SPSS v 22.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2019 (https://www.microsoft.com/en-us/). Categorical variables, such as birth weight, gravida, parity, number of abortions and survivors, gestational week, mode of delivery, and sex, were expressed as numbers and percentages. The Shapiro–Wilk test was used to analyze normally distributed data, including age, fetal weight and neutrophil, lymphocyte, platelet, hemoglobin, NLR, and PLR counts. Descriptive data for these variables are expressed as mean, standard deviation, median, and interquartile range. The nonparametric Kruskal–Wallis test was used to analyze statistical differences among NLR, PLR, hemoglobin, platelet, neutrophil, and lymphocyte counts in terms of birth weight. The Mann–Whitney U test was used to evaluate the statistical differences of NLR, PLR hemoglobin, thrombocyte, neutrophil, and lymphocyte counts between AGA and LGA according to their grouped percentiles. Box-plot graphs were drawn for variables showing statistical significance. *P*-value <0.05 was considered statistically significant.

Results

The present study evaluated 442 pregnant women with an average age of 29.50 (5.17) years. The average birth week at delivery was 38.67 (0.77), of which 65 (14.7%) were normal vaginal deliveries, and 377 (85.3%) were cesarean deliveries. Of the newborns, 198 (44.8%) were female and 244 (55.2%) were male. The demographic characteristics of the pregnant women are presented in Table 1.

The mean hemoglobin count was 11.40 (1.22) g/dL, mean neutrophil count was 6.58 (1.38) x10^3/µL, mean lymphocyte count was 1.95 (0.47) x10^3/µL, and the mean platelet count was 237.57 (69.44) x10^3/µL. The mean NLR was 3.50 (0.93), and the mean PLR was 126.63 (42.70) (Table 2).

Table 1: Demographic characteristics of the pregnant women

		Mean (SD)	Min–Max
Age		29.50 (5.17)	18–43
Gravidity		2.69 (1.25)	1–11
Parity		1.38 (0.81)	0–4
Abortions		0.32 (0.85)	0–7
Live births		1.36 (0.78)	0–4
Birth week		38.67 (0.77)	37–42
Birth weight (g)		3407.98 (397.31)	2550–4650
Sex (n (%))	Female	198 (44.8)	
	Male	244 (55.2)	
Type of birth (n (%))	Normal vaginal delivery	65 (14.7)	
	Cesarean section	377 (85.3)	
Percentile (n (%))	AGA	381 (86.2)	
	LGA	61 (13.8)	

SD: Standard Deviation, AGA: appropriate for gestational age, LGA: large for gestational age

Table 2: Hemogram parameters of the pregnant women

Parameter	Mean (SD)	Min–Max
Hemoglobin (g/dL)	11.40 (1.22)	7.60–14.40
Neutrophils (*10³/µL)	6.58 (1.38)	3.10–10.10
Lymphocytes (*10³/µL)	1.95 (0.47)	1.00–4.40
Platelets (*10³/µL)	237.57 (69.44)	92–608
NLR	3.50 (0.93)	1.15–7.27
PLR	126.63 (42.70)	36.80–345.71

SD: Standard Deviation, NLR: neutrophil/lymphocyte ratio, PLR: platelet lymphocyte ratio

The result of the parameter measurements did not provide a definite conclusion on a correlation between hemoglobin, neutrophil, platelet, NLR, and PLR (*P*=0.524,

P=0.970, *P*=0.063, *P*=0.100, *P*=0.997, respectively) and birth weight; however, a negative correlation was observed between lymphocyte count and gestational weight (*P*=0.014) (Table 3).

After adjusting the percentile according to the Alexander growth curves, the babies of 381 (86.2%) pregnant women were grouped as AGA and those of 61 (13.8%), as LGA. The distribution of demographic characteristics and hemogram parameters in the two groups is given in Table 3. When comparing hemogram parameters between the groups, the hemoglobin, neutrophil, platelet, NLR, and PLR values were similar (*P*=0.849, *P*=0.350, *P*=0.053, *P*=0.238; and *P*=0.959 respectively). We also observed that the lymphocyte values were lower in the LGA group (*P*=0.019) (Table 4).

Table 3: Correlation between hemogram parameters and birth weight

Parameter	Weight	
	R	*P*-value
Hemoglobin (g/dL)	-0.030	0.524
Neutrophils (*10³/µL)	0.002	0.970
Lymphocytes (*10³/µL)	-0.117	0.014
Platelets (*10³/µL)	-0.088	0.063
NLR	0.078	0.100
PLR	0.000	0.997

NLR: neutrophil/lymphocyte ratio, PLR: platelet lymphocyte ratio

Table 4: Comparison of groups according to birth weight

Parameter	AGA	LGA	Z	*P*-value
Age	29.25 (5.19)	31.07 (4.80)	-2.524	0.120
Hemoglobin (g/dL)	11.40 (1.21)	11.43 (1.26)	0.000	1.000
Neutrophils (*10³/µL)	6.60 (1.39)	6.43 (1.32)	-0.714	0.475
Lymphocytes (*10³/µL)	1.97 (0.48)	1.82 (0.37)	-2.616	0.009
Platelets (*10³/µL)	240.13 (71.09)	221.59 (55.91)	-1.740	0.082
NLR	3.48 (0.92)	3.63 (0.95)	-1.124	0.261
PLR	126.67 (42.85)	126.36 (42.13)	-0.046	0.963

AGA: appropriate for gestational age, LGA: large for gestational age, NLR: neutrophil/lymphocyte ratio, PLR: platelet lymphocyte ratio

Discussion

Fetal growth can be affected by many factors, such as race, the environment, vitamins used during pregnancy, nutrition, maternal age and weight, and inflammation. The purpose of the present study was to investigate the effect of inflammation markers NLR and PLR on fetal weight, which is a result of fetal development.

Several studies have shown that NLR and PLR can be used as markers of inflammation in cardiology [13], surgery [14], gastroenterology [15], and oncology [16]. These inflammation markers are also beginning to be used for obstetrics and gynecological conditions [2, 7-11, 20, 21]. In several previous studies on pregnancy and inflammation, maternal serum C-reactive protein (CRP) was used to characterize fetal exposure to inflammation [1, 22, 23]. In recent studies, NLR and PLR, which are new parameters that can be measured using a simple blood test, have begun to be used as indicators of inflammation. In a study comparing NLR and CRP in pregnancy, İlhan et al. [20] have found that NLR has a better diagnostic value than maternal serum CRP in cases of acute pancreatitis associated with pregnancy. Another study found that high NLR and normal CRP used to show the placental inflammatory response indicate that preterm delivery is approaching [24]. These studies emphasize that NLR can help to diagnose pregnancy difficulties.

No relationship was observed between birth weight and NLR and PLR counts in the third trimester. However, the lymphocyte count was lower in the group with LGA. Christoforaki et al. [25] have compared first trimester NLR and PLR rates with pregnancy outcomes and found no relationship between those parameters and birth weights; however, Akgün et al. [26] have found a negative correlation between PLR and birth weight. They reported that NLR was not related with birth weight. Several studies have investigated the use of NLR and PLR for predicting perinatal complications; however, results have been inconsistent when comparing complications with NLR and PLR. Although Yücel et al. [27] could not find NLR to be a predictor for pregnancy-related hypertension, Serin et al. [11] have shown that NLR increases significantly in patients with preeclampsia. Similarly, contradictory results have been reported from studies testing NLR and PLR in pregnant women with gestational diabetes. Although Sargin et al. [9] have reported that NLR and PLR significantly increase in gestational diabetes, Aktulay et al. [28] have reported no evidence of NLR and PLR being predictors of gestational diabetes in their retrospective study. In a study that included nonpregnant volunteers during their reproductive period, the mean NLR and PLR values were 1.73 (1.55) and 133.7 (85.6), respectively [29]. Kırbas et al. [10] have found in their trimester-based NLR and PLR study that the mean NLR and PLR values were 2.6 (1.0) and 136.3 (44.3) during the first trimester, 4.0 (1.4) and 144.6 (47.1) during the second trimester, and 3.5 (1.2) and 118.1 (42) during the third trimester, respectively.

Limitations

There were some limitations to the present study. First, not all factors that may affect birth weight, such as vitamins, nutrition, maternal body weight, smoking, alcohol and substance use, and environmental conditions, were evaluated. Second, because the number of normal vaginal deliveries was high among those who were not followed up in the clinic but only applied for birth, the number of births with cesarean sections appeared to be high among the delivery types. Additional larger studies are needed that can assess the correlation between NLR, PLR and birth weight. It would be more appropriate to establish a relationship between hemogram values and birth weight by comparing baseline values at the beginning of the pregnancy with the those obtained at the end of the third trimester.

Conclusion

In the present study, we investigated the relationship between NLR and PLR, which were used as inflammation markers during the third trimester of pregnancy, and birth weight in uncomplicated pregnant women. We found no relationship between NLR and PLR measured only in the third trimester and birth weight.

We noted from previous studies that NLR and PLR do not stably progress from pre-pregnancy to pregnancy because of the effect that pregnancy has on physiology. These values can predict pregnancy complications in some cases in which reference intervals are constantly changing and not in others. Because pregnancy is a dynamic process, hemogram parameters differ on a trimester basis.

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Comparison of sedoanalgesia versus general anesthesia in surgical resection of carotid body tumors: A retrospective cohort study

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Ethics Committee Approval
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Carotid body tumors (CBTs) are very rare. There is no uniform agreement on the method of anesthesia according to the Shamblin classification. The aim of this study was to report and compare outcomes and complications of different anesthesia methods according to the Shamblin classification in patients operated for CBTs.
Methods: The data of 52 patients (40 males, 12 females) diagnosed with CBT Shamblin Type 1 or Type 2 and surgically treated were enrolled. General anesthesia (Group G) and sedoanalgesia (Group S) were administered in 35 and 17 patients, respectively. We retrospectively compared the surgical outcomes and complications between the groups to evaluate which anesthetic approach was more appropriate for early recognition of complications, hemodynamic stability, and surgical satisfaction in CBT surgeries.
Results Group S patients were more stable hemodynamically. Hypertension, tachycardia, hypotension were significantly more frequent in Group G ($P<0.001$). Intraoperative blood loss was significantly less in the Group S ($P=0.024$). Both patient and surgeon satisfaction scores were significantly higher in Group S ($P=0.071$). In Group G, transient ischemic attack developed in 1 patient, postoperative dysphagia developed in 4 patients due to possible nerve injury during resection. Deviation and ptosis of the tongue due to facial nerve damage developed in 3 patients in Group G and in 2 patients in Group S ($P=0.028$).
Conclusions: Sedoanalgesia may be more helpful for patients compared to general anesthesia in tumor surgery of patients with CBT classified as Shamblin Type 1 and 2.

Keywords: Carotid body tumors, General anesthesia, Sedoanalgesia

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Introduction

Carotid body tumors (CBTs) are primary tumors of chemoreceptor tissue and were first described by Von Haller in 1743 [1]. CBTs are malignant at a ratio of 5-6% and require surgical intervention. While benign tumors occur later in life (between 40 and 70 years), malignant tumors occur at earlier ages [2]. CBT is classified according to growth patterns by Shamblin et al. Type 1 tumors are regional masses and easily excised, while type 2 tumors surround the carotid arteries. Type 3 tumors are adherent, completely incarcerate the carotid arteries, and can be excised by a challenging surgery that requires graft replacement of the internal carotid artery. Type 3 tumors represent 25% of the cases and most of the CBTs are non-functional [3]. Resection of the tumor is the most recommended treatment approach [4]. Although literature suggests that the carotid body gland is localized in the adventitia near the carotid artery bifurcation, most surgeons experienced in carotid body dissection indicate that it is more peripherally located within the peri-adventitial tissue. This is critical because dissections in the deeper planes of the carotid artery are associated with complications related to vascular injury [5]. Removal of the tumor requires surgical experience due to cranial nerves, close proximity to the arterial structures, and complex anatomy of the head and neck region. The most important complications of surgery are hemiplegia and cranial nerve injury at the surgical region. Surgical excision should be performed as soon as possible due to the risk of airway obstruction and pulmonary aspiration, hemorrhage, and the possibility of metastasis [6]. Digital subtraction angiography is considered the golden standard for the final diagnosis of CBT. Magnetic resonance imaging (MRI), arteriogram and embolization, lower extremity ultrasonography for possible femoral graft, urinary catecholamines due to the rare risk of adrenal pheochromocytoma, vanillylmandelic acid, and metanephrine test are other methods used in diagnosis [5].

Although general anesthesia is a commonly used method, it has some disadvantages in CBT surgery. Since there is no cooperation of the patient during the operation, possible ischemic events and nerve injuries often go unnoticed.

In this study, we compared patients that underwent general anesthesia or sedoanalgesia during CBT surgeries. We evaluated which anesthetic approach was more appropriate for early recognition of complications, hemodynamic stability, and surgical satisfaction in CBT surgeries.

Materials and methods

We investigated the data of 52 patients who were diagnosed with CBT and operated by single cardiovascular surgeon (YK) between March 2012 and January 2021 in the Department of Cardiovascular Surgery. Thirty-five patients were operated under general anesthesia (Group G) and 17 patients were operated with sedoanalgesia (Group S), respectively. Data from the patients were retrospectively reviewed and included in the study. While carotid body surgery was previously performed under general anesthesia, it is recently being performed with sedoanalgesia. Thus, the patients were enrolled in the study according to the date of surgery. Patient characteristics were similar in both groups. Patients, assessed as Shamblin classification Type 1 and Type 2, were included. Type 3 patients were excluded from the study since sedoanalgesia is insufficient in these types. We excluded patients that underwent carotid artery surgery due to reasons other than CBT or whose histological examination of specimens revealed that the final diagnosis was not CBT. The patients' electronic and paper records were used to gather data. All patients in the study were operated by the same cardiovascular surgeon (YK). All patients that underwent anesthesia were managed and followed by anesthesiology department professionals.

Demographic data and characteristics of the patients

Patients' age, gender, ASA score (American Society of Anesthesiologists), Mallampati score, comorbid diseases, side of tumor, duration of operation, changes in intraoperative blood pressure and heart rhythm (bradycardia, tachycardia), the amount of blood loss, the amount of used blood or blood products, intraoperative inotropic drug use, duration of hospital stay and intensive care unit stay, type and characteristics of tumor, Shamblin classification, and complications associated with cranial nerve and vascular structures were recorded. Also, Pain score (VAS: Visual analogue scale) was measured postoperatively in recovery room and at the 1st hour after surgery.

Systolic blood pressure over 140 mmHg was considered hypertension. Heart rhythm over 100 per minute was considered tachycardia, and under 50 was considered bradycardia. Patient and surgeon satisfaction scores were assessed with a 5-point scale (1: very satisfied, 2: satisfied, 3: average, 4: poor, 5: very poor). Demographic and clinical characteristics of patients are shown in Table 1.

Table 1: Demographic and clinical characteristics of 52 patients

	Patients
Age, years mean (SD)	54 (10.3)
Sex, M / F	40/12
Comorbidities, n(%)	
HT	40 (77)
DM	35 (67)
CODP	20 (38)
CAD	20 (38)
PAD	2 (4)
Tumor characteristics, n(%)	
Mean Tumor diameter	3.56 (1.24)
Unilateral / Bilateral	47 / 5
Benign / Malign	52 /-
Functional /Nonfunctional	- / 52

HT: Hypertension; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; PAD: Peripheral artery disease

Anesthetic management

Complete blood count (CBC), electrolytes, liver and renal function tests, and chest-X-ray examination were conducted preoperatively in all patients of both groups. Color Doppler sonography were performed in all cases. CT scans of the mediastinum and retroperitoneal sonography were performed in patients with multifocal tumors and family history to determine whether there was a spread. MRI was used in some cases; in addition, patients with 2-year disease history were evaluated with Spiral CT angiography (SCTA).

The patients were given 0.05 mg / kg i.v. midazolam for premedication purposes and all patients in both groups were in the supine position during the surgery. At least two large-caliber IV cannulas were placed. Ringer's lactate was typically administered at a rate of 100 ml/hour through an intravenous cannula of 18G (Range 14-22G). The patients were monitored

and pulse oximetry, 3-channel electrocardiography, continuous heart rate (HR), and noninvasive blood pressure (NIBP) were measured when they were taken to the operation room. Nasopharyngeal temperature monitoring was performed. A total of 10 patients underwent invasive BP through left radial artery and central venous pressure (CVP) via left subclavian vein due to elderly ages and coronary artery disease. Intravenous fluid was adjusted to maintain an average arterial blood pressure of 55-60 mmHg and CVP of 10-12 mmHg. Ephedrine was administered at a 5 mg bolus dose for decreases in blood pressure. Inotropic support infusions were initiated in cases of insufficient blood pressure despite the use of adequate fluid replacement and ephedrine. For systemic medication purposes, 10 mg of Dexamethasone i.v. was used. Cerebral oxymeter (Masimo RDS7A, Masimo Corp., Irvine, California, USA) was used for intraoperative cerebral monitoring in the required cases.

Group G: Patients in general anesthesia group were preoxygenated for 3 minutes at the beginning of the operation. Then, induction was initiated in most patients with Thiopentone 2.5 % (4-6 mg/kg), while 1% propofol (2-3 mg/kg) was needed in 6 patients. All patients undergoing general anesthesia were intubated using Atracurium (10 mg/ml) as muscle relaxant. Cuffed Portex oral 7.5-8 mm endotracheal tubes were used and the transoral intubation tube was taped to the contralateral side of the surgical area. The administration of general anesthesia was mainly achieved by applying volume-controlled ventilation using oxygen and nitrous oxide (1:1) and volatile anesthetic agents (isoflurane, sevoflurane). In addition, total intravenous anesthesia (TIVA) was achieved in 6 patients with propofol. Fentanyl (2 mcg/kg) and remifentanil infusion (0.2 mcg/kg/min) were administered for analgesia. Intraoperative fluid replacement was performed with the Hartmann's solution at an average of 1500 ml (range: 1000-2500 ml). Bridion (Sugammadex; 2 mg/kg i.v.) in 10 patients and a combination of atropine (0.5 mg) and neostigmine (2.5 mg i.v.) in 7 patients were used as reversal agents at the end of surgery. Conscious patients that met the extubation criteria, responded to verbal commands, and had adequate spontaneous breathing were extubated in operation room. patients in general anesthesia group were extubated in the operating room at the end of the surgery.

Paracetamol (1 gr i.v.) was used for analgesia in postoperative recovery room and Tramadol (100 mg i.v.) was given to patients whose Visual Analogue Score (VAS) was 5 or greater. The patients were followed up for one day mostly in the high dependency unit (HDU) after the operation. A total of 4 patients were followed up in the postoperative ICU among Group G. The mean duration of hospital stay was 4 (3-6) days. There was no mortality in patients undergoing CBT surgery.

Group S: Patients in the sedoanalgesia group were given Midazolam (0.05 mg/kg i.v.) for premedication purposes. In patients in the operation room, sedation and anxiolysis was achieved using Midazolam (0.05 mg / kg i.v.) and analgesia was achieved using Fentanyl (1 mcg/kg i.v.) with the administration by an experienced anesthesiologist. When a patient was uncomfortable, it was interpreted as pain and 2-5 ml of 1% lidocaine (100-200 mg) was infiltrated by surgeons during the operation. If the pain could not be well controlled by local anesthetic, then additional fentanyl (25 mcg i.v.) was administered. In cases where the desired sedation effect could not be achieved during the procedure, midazolam was added intravenously. The patients were conscious during surgery. Blood pressure and heart rate changes, duration of operation, pain score/discomfort, amount of hemorrhage, cranial and facial nerve function, and cerebral ischemia development were recorded during surgery. Patients were followed in the recovery room during the postoperative period. Paracetamol (1 gr i.v.) was administered to patients requiring analgesia. Tramadol (100 mg i.v.) was administered if the pain was more severe. None of the patients in Group S needed hospitalization in the ICU. All patients were followed up for one day in the high dependency unit (HDU). After an average of 3 days of (2-4) hospital stay, patients were discharged with oral antibiotics. All patients were followed up for 3 months regularly in the cardiovascular surgery outpatient department. Any complications in the postoperative period were noted and dealt with accordingly.

Surgical technique

Horizontal incisions were made lateral to the anterior border of the sternocleidomastoid (SCM) muscle to explore the cervical region. SCM and jugular vein were identified to make the tumor and adjacent cranial nerves visible posteriorly. Special attention was paid to protect cranial nerves, X, XI, XII, superior laryngeal nerve and sympathetic trunk during surgery. After common carotid artery, the internal carotid vein, the cranial nerves X, XI, XII, Superior laryngeal nerve, the accessory nerve, and sympathetic trunk were made clearly visible. The proximal (3 to 4 cm) and distal (2 cm) portions of vessels (common and internal carotid, and multiple branches of the external carotid) were sufficiently liberated with a good separation. If there were vessel loops around the common and internal carotid arteries, unnecessary tension was avoided. The proximal end of the tumor artery and the common carotid artery were blocked by blood vessel blocking bands to control blood flow. Then, vessels feeding the tumor were separated throughout the tumor mass so they could be completely excised. Tumor mass was incised in a Y-shape through the tumor tissue from the anterior region to the carotid artery media layer using a loupe or microscopic magnification. Dissection was performed beginning from the region between the adventitia and carotid media layer toward the mass using bipolar cautery. The dissection was initiated slowly and carefully approximately 0.5 cm from the distal margin of the unaffected side of the tumor's end point. A manual saline irrigation was used during bipolar activation. Finally, the excision of carotid body tumor, progressing throughout the region between the adventitia and media layers of the carotid artery, was performed with a careful dissection. Hemorrhage observed during the dissection phase was sutured with 6/0 polypropylene. At the end of the procedure, a 10 mm flat Jackson Pratt drain was placed in the surgical site and antibiotic ointment was ordered. After surgery, the patients were followed for blood pressure, hemorrhage, or late stroke. All patients included in our study were Shamblin classification type 1 and type 2. No graft or bypass was used for any patient in either group.

Statistical analysis

In the power analysis based on the data of previous studies, a sample size of 32 patients were needed at 95% power

(1-β err prob=0.95) and 5% error margin (α err prob=0.05). Available 52 patients were enrolled in the study after taking possible loss of data into consideration.

The statistical analysis of the data were performed using the Statistical Package for the Social Sciences (SPSS version 21.0, SPSS Inc., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages. Continuous variables were presented as mean (standard deviation). Kolmogorov–Smirnov test was used to check the normality of data. When normality was rejected, a nonparametric test was used. A *P*-value of less than 0.05 was considered statistically significant.

Results

Of the 52 patients included in the study, most were males**.** The majority of patients in each group consisted of the elderly population. There was no mortality in both groups during hospital stay or within 6 months after surgery. In the preoperative evaluation, it was determined that patients in each group with hypertension generally use beta blockers, calcium channel blockers, ACE inhibitors and angiotensin receptor blockers. CBT was more common on right side of the neck (n=30), while 22 were in the left side. Tumor characteristics of the groups are given in Table 2.

Table 2: Clinical features and tumor characteristics of the groups

	General anesthesia (n=35)	Sedoanalgesia (n=17)	*P*-value
Age, years (SD)	53.2 (9.2)	54.32 (10.3)	0.708*
ASA scores, n (%)			
1	2 (5.7)	1 (5.9)	0.043**
2	29 (82.9)	15 (88.2)	
3	4 (11.4)	1 (5.9)	
Shamblin, n (%)			
Type 1	5 (14.2)	7 (41)	0.021**
Type 2	30 (85.7)	10 (59)	
Surgery duration, min	105 (19	72 (22	0.034*
Intraoperative conditions, n (%)			
Hypertension	20 (57.1)	5 (29.4)	<0.001**
Tachycardia	20 (57.1)	2 (11.7)	<0.001**
Hypotension	15 (42.8)	2 (11.7)	<0.001**
Blood transfusions	4 (11.4)	2 (11.7)	0.024**
VAS for pain			
At the end of surgery	3 (0.7)	1 (0.6)	0.013*
At the 1st hour after surgery	2 (0.6)		
Satisfaction score			
Patient	3 (0.7)	2 (0.5)	0.071*
Surgeon	4 (0.7)	1	<0.001*
Length of hospital stay	4.1 (0.8)	2.6 (0.5)	0.001*
Postoperative complications			
Dysphagia (10. CN injury)	4 (11.4)		0.028**
Facial nerve injury	3 (8.5)	2 (11.7)	
Hypoglossal nerve injury	2 (5.7)		

* Mann Witney U test, ** Chi-Square test

Radiological imaging associated with the Carotid Body Tumors are shown in Figures 1-4.

Figure 1: 45-year-old female patient with right sided glomus tumor (white arrow) located at the carotid bifurcation represented on 3D computed tomography angiography (CTA) image.

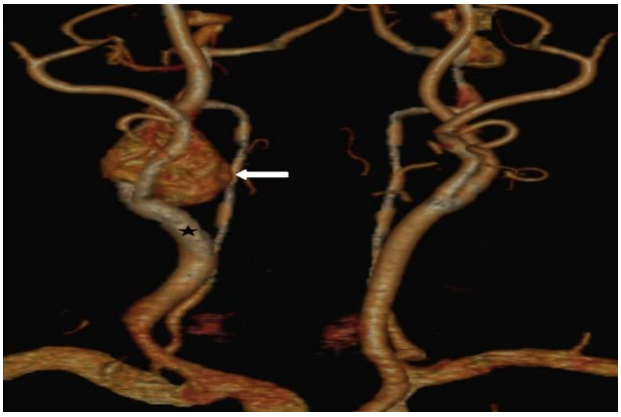


Figure 2: Axial Ce CT image demonstrates the enhanced glomus tumor (white arrow) located between internal carotid artery (ICA) and external carotid artery (ECA).

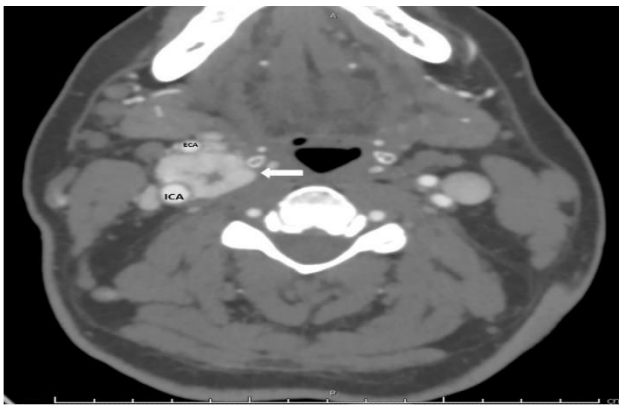


Figure 3: There is no residual mass or lesion recurrence on postoperative control 3D CTA image (white arrow).

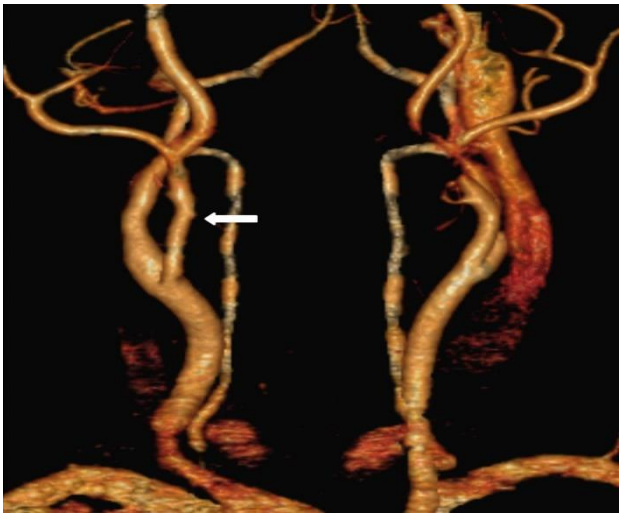
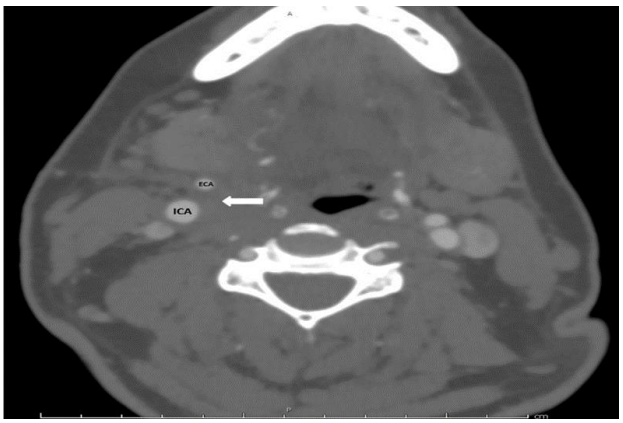


Figure 4: Axial Ce CT image demonstrates normal structures (white arrow) between internal carotid artery (ICA) and external carotid artery (ECA).



Group S patients were more stable hemodynamically and their vital findings were more regular, while almost 50% hemodynamic instability and irregularities in vital findings were observed in group G. Average arterial blood pressure in General anesthesia group (Group G) was 81 (4) whereas average arterial blood pressure in Sedoanalgesia group (Group S) was 78 (3).

In Group G, intraoperative blood pressure was more labile and change in arterial pressure, especially during induction phase and surgical manipulation, was more prominent. During tumoral excision, hypertension and tachycardia developed in 20 patients in group G whereas hypertension developed in 5 patients and tachycardia developed in 2 patients in group S. Esmolol (40 mg IV) and Glycerol trinitrate (Perlinganid) were used for hypertension, and Labetolol (5 mg) was used for tachycardia. A decrease in systolic arterial pressure below 80 mmHg was considered hypotension. When hypotension developed in both

groups, bolus dose ephedrine 5-10 mg i.v. was administered. Fluid replacement was increased, and inotropic support infusion was initiated in cases in which adequate levels of arterial pressure could not be achieved with ephedrine. Bradycardia developed in 5 patients in group G and in 2 patients in group S. Patients with bradycardia were administered atropine (0.5 mg IV). Patients were asked to cough and atropine was needed in 2 patients in group G. The median heart rate in bradycardia attacks was 46 per minute (range: 40 - 48/min).

Intraoperative blood loss was less in Group S than in Group G (585ml (162) vs 303 (213), respectively*).* This was associated with the fact that arterial pressure was more stable than the other group. Erythrocyte suspensions were transfused in 4 patients in Group G and in 2 patients in Group S. Cerebral oximetry values did not decrease more than 25% of pre-induction baseline values after tumor excision and at the end of surgery. However, the decrease was more prominent in Group G.

Postoperative pain was assessed using visual analogue scale (VAS). In the postoperative period, the need for additional analgesic agents was lower in Group S.

In Group G, 1 patient was followed up closely for first postoperative day in the surgical intensive care unit (SICU) due to transient ischemic attack (TIA). The patient's neurological status improved after 1 day. All the other patients were monitored in the high dependency ward. No cerebral infarct developed in any patient except one transient ischemic attack. There were no aphasia or epileptic sequelae.

In Group G, postoperative dysphagia developed in 4 patients due to possible injury of N. Vagus and Recurrent laryngeal nerve during resection. In Group S, dysphagia and related nerve injury were not observed. Mild tongue deviation and left eye ptosis due to facial nerve injury developed in 3 patients in the Group G and in 2 patients in Group S. In Group S, facial nerve weakness was less pronounced, only a slight deviation of the tongue was observed, and it recovered early in the postoperative period. In addition, hypoglossal nerve injury developed in 2 patients in Group G. Within postoperative 6 months, the findings improved in 3 patients with vagal nerve injury, in 1 patient with facial nerve injury, and in all patients with hypoglossal injury, but sequelae were permanent in others. Postoperative baroreceptor failure and loss of reflex respiratory stimulation did not develop in any of the patients in both groups. Finally, there was no mortality during intraoperative and postoperative follow-up period in patients that underwent CBT surgery in both groups in this study.

Discussion

CBTs are very rare tumors that occur at the bifurcation of carotid artery, sensitive to carbon dioxide and partial pressure of oxygen, and originate from chemoreceptor cells playing an important role in the control of ventilation during acidosis, hypoxia and hypercapnia [7]. Although CBT has been reported to be more common in females compared to males in the literature [8], there were 40 males and 12 females in the 52-patient cohort in our study.

Genetic factors and hypoxic conditions seem to play an important role in the pathogenesis of the disease. Living in high altitudes or chronic hypoxia conditions such as sleep apnea syndrome seem to trigger hyperplasia in the carotid body. In genetically predisposed individuals with a family history, the disease has been observed to occur at earlier ages [9]. Digital subtraction angiography (DSA) is the gold standard for the final diagnosis of CBT [10]. The advantage of DSA is that it allows the evaluation of Shamblin classification and intracranial-extracranial blood circulation, as well as the embolization of blood vessels. These tumors may be confused with neuroendocrine carcinoma, thyroid medullary carcinoma, middle ear adenoma, schwannoma, and meningioma [11]. Rarely, these tumors may be associated with phaeochromocytomas and may secrete catecholamines and serotine etc. This may be symptomized by excessive sweating, uncontrolled hypertension, tachycardia, and facial flushing. We did not observe inappropriate catecholamine secretion-induced symptoms suggesting phaeochromocytomas in any of our patients.

Shamblin classification groups CBTs as Type 1, 2, and 3 according to the relationship between tumor mass and the carotid artery wall. For Shamblin type 2 and 3, extensive surgery may be required [12]. During CBT type 2 and Type 3 surgery, neuronal and vascular damage is more likely to develop, and the amount of bleeding is greater, and the duration of operation is longer [13]. Sukanya et al. [14] emphasized the possibility of intraoperative rapid blood loss due to involvement of the carotid artery and jugular veins in Type 2 and Type 3. Rapid blood loss of 1 liter has been reported in the literature [15]. If there is a risk of rapid blood loss, a blood vessel ligation band and atraumatic hemostatic forceps should be prepared before surgical separation. Especially in Shamblin Type 3, cross-clamping can be performed to prevent possible bleeding during tumor resection [16]. If there is stenosis in the contralateral carotid artery, a shunt can be used during clamping. In literature, embolism or carotid artery dissection during shunting has been reported as 1-3% [17]. Only one of the patients included in our study had a transient ischemic attack and the patient's findings improved after 24 hours. This clinical finding was thought to be associated with embolism due to its close proximity to the vascular structures of the surgical site.

For Shamblin classification type 3, more extensive surgical resection may be needed. For this reason, unwanted complications related to neurological and vascular structures are encountered more frequently [12]. Radiotherapy may be a more appropriate treatment approach in patients diagnosed with CBT type 3, elderly patients, or patients with chronic diseases due to intraoperative crucial vascular and neurologic injuries and stroke associated with operation [18]. We did not include patients with type 3 CBTs in this study, because they required more complicated surgeries and management of sedoanalgesia with anesthesia was difficult. In a total of 52 patients undergoing CBT surgery in this study, tumor type was Shamblin classification type 2 in 44 cases and Shamblin classification type 1 in 8 cases.

Sedoanalgesia does not appear to be sufficient because the surgical operation of Type 3 tumors is difficult. However, we started with sedoanalgesia in the last 10 cases of Type 3 where the carotid artery had to be taken under control. We continued with general anesthesia after test clamping to minimize the risk of stroke.

Presently, there has been no consensus on anesthetic management in CBT surgery. However, general anesthesia has been observed to be mostly preferred in these surgeries when the literature was reviewed. It has been reported that these surgeries were performed with local anesthesia and cervical plexus block instead of general anesthesia in some centers. In a high-risk patient due to Eisenmenger syndrome, a case of successful tumor resection without any complication using continuous cervical plexus block was reported in the literature [19]. Although the cervical plexus block is a more appropriate method for carotid artery surgery, there are some risks associated with needle use in block surgery in CBT surgery [20]. The hypervascularity of these tumors and their localization at the carotid bifurcation may cause bleeding and unwanted punctures of the tumoral mass [21]. This unwanted condition may cause instability in the hemodynamic state of patient due to catecholamine release from the tumoral mass.

The main goal of anesthesia management in CBT surgery is to maintain stable hemodynamic circulation, optimal cerebral perfusion, minimal blood loss, early detection and management of complications that may arise due to anatomical closeness of vital structures such as cranial nerves and vessels to tumor, and better operating conditions for surgeon and patient satisfaction.

We used general anesthesia in 35 patients and sedoanalgesia in 17 patients among a total of 52 patients that underwent CBT surgery. In the majority of 35 patients that underwent tumor surgery with general anesthesia, we used thiopentone 2.5%, which has been shown to provide neuroprotection at an infusion rate of 3-5 mg / kg / h by Bilotta et al. [22]. In 6 patients, propofol 1% was used for induction. The most important goal in anesthesia management is to prevent cerebral focal ischemia development by providing optimal cerebral perfusion. There have been studies in literature about the protective effects of barbiturates against possible ischemia during the surgical procedure by protecting tissues against focal ischemia and positively contributing to redistribution [16]. An ischemic event leads to brain edema and the use of mannitol may be beneficial in reducing this [23]. In this type of tumor surgeries, temperature management is also very important since cerebral metabolic rate decreases by 7% at each 1°C decrease in body temperature.

In our study, we observed that the arterial pressure was more labile during both the induction and resection phases in patients in Group G, whereas hemodynamics was more stable in Group S.

In a study of 100 patient series, Birch et al. [24] found that sedoanalgesia is a safe, effective, and acceptable anesthesia management method unrelated to preoperative accompanying diseases. In our study, patient's consciousness provided an important advantage in CBT surgeries with sedoanalgesia, as cooperation with patient continued and early detection of unwanted complications related to possible cranial nerves or other cerebral infarcts was possible. Comparing with general anesthesia, hemodynamic stability was better in the sedoanalgesia group. This made cerebral perfusion more optimal and also provided benefit by resulting in less hemorrhage.

Comparing both groups in this study in terms of neurological and cranial nerve involvement, complications related to neurological and cranial nerve involvement were less frequent in the Sedoanalgesia group. One patient underwent transient ischemic attack (TIA) in the general anesthesia group and recovered at the first postoperative day without sequelae. None of the patients in the groups developed cerebral infarct except this patient with TIA. There was no neurological incident requiring surgery such as decompressive craniectomy or frontal-temporoparietal lobectomy. In addition, no patient developed Aphasia or epileptic sequelae.

In Group G, 4 patients developed postoperative dysphagia associated with possible injury of N. Vagus and recurrent laryngeal nerve. In Group S, there was no dysphagia or related nerve injury. Again, hypoglossal nerve injury developed in 2 patients in the general anesthesia group. During 6 months of follow-up after surgery, findings completely improved in 3 patients with vagal nerve injury and in one patient with hypoglossal nerve injury. Conversely, sequela was permanent in one patient. Mild tongue deviation and left eye ptosis due to facial nerve injury developed in 3 patients in Group G. One of these patients improved, while sequela was permanent in others. Despite the findings of facial nerve involvement in 5 patients in Group S, facial nerve weakness was less pronounced, and only a slight deviation of the tongue was observed, which recovered early in the postoperative period. There were no patients with permanent sequela in this group. Postoperative baroreceptor failure and loss of reflex respiratory stimulation did not develop in any of the patients from both groups.

Conclusions

We showed that anesthetic management in CBT patients is important during and after surgery. Surgery of CBTs requires vigilance for an anesthesiologist during the removal of CBT. The success of the surgery depends on basic objectives in anesthesia management such as maintaining optimal cerebral perfusion, sustaining stability of intraoperative blood pressure levels, detecting neurological and vascular complications early, taking precautions for possible hemorrhage, and providing optimal surgical field.

The present study shows that tumor surgery of patients with CBT, especially those classified as Shamblin classification Type 1 and Type 2, can be accomplished successfully under sedoanalgesia by infiltrating a local anesthetic agent of 1% lidocaine (100-200 mg) in necessary cases. Comparing sedoanalgesia method with general anesthesia in surgeries of Type 1 and Type 2 tumors revealed that there are significant advantages directly affecting surgical success such as intraoperative well-oriented patient, constant consciousness control, less neurological and vascular injuries, more stable hemodynamic conditions, lower risk of hemorrhage, more comfortable surgical environment, higher patient and surgeon satisfaction, less postoperative pain in patients, and shorter duration of surgery and hospital stay.

The sedoanalgesia method may be more helpful for the patients compared to general anesthesia in certain CBT surgeries, especially in tumors evaluated as Shamblin classification Type 1 and Type 2.

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The effect of covid-19 pandemic on emergency general surgery cases: A single-center observational study

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Ethics Committee Approval
This study received approval from Yozgat Bozok University Clinical Research Ethics Committee (Approval date: 14/10/2020. Number: 2017-KAEK-189_2020.10.14_15).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Many people around the world have been affected by the COVID-19 pandemic. Some of them were directly affected as patients. However, even if some did not suffer from the disease, they may have been indirectly affected. The aim of this study was to investigate whether the COVID-19 pandemic has an impact on emergency general surgery admission volume and operations.

Methods: In this retrospective case-control study, all patients referred from the emergency department to our emergency general surgery unit between April 1 - May 31,2020 were evaluated. Patients over 18 years of age, who were hospitalized for longer than 24 hours and required evaluation and treatment by a general surgeon were included in the study. Patients with similar characteristics that were treated in our clinic in the same periods in 2018 and 2019 were evaluated as the control group.

Results: During the pandemic, a total of 208 patients were hospitalized in the emergency general surgery service. The number of admissions to the emergency general surgery service in 2020 was 25.9% less than that in 2018 and 30.8% less than that in 2019. During the pandemic, while there was a decrease in cases of non-specific abdominal pain and trauma (P=0.003, P=0.015, respectively), there was a significant increase in cases of gastrointestinal obstruction and perforation (P=0.001, P<0.001, respectively). The rate of surgery during the pandemic was 65.9%, which was significantly higher than the previous years (P<0.001). The rate of laparoscopic procedures decreased significantly during this period (P<0.001). The complication and mortality rates were significantly higher (P=0.004, P=0.025, respectively).

Conclusion: We observed that while emergency general surgery case applications, surgery rates, and hospital stay decreased during the COVID-19 pandemic, there was an increase in the rate of more serious diagnoses, complications, and mortality.

Keywords: Covid-19, Pandemic, Emergency, General surgery, Outbreak

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Introduction

Coronavirus Disease 2019 (COVID-19) caused by the new SARS-COV-2 virus first appeared in Wuhan, China, in December 2019 [1]. Due to its rapid spread throughout the world, the World Health Organization declared COVID-19 a pandemic on March 11, 2020 [2].

In our country, the first COVID-19 case was detected on March 11, 2020. Immediately after the detection of the first case, the government took a series of gradual measures to prevent the spread of the virus. First, schools at all levels, all restaurants, as well as all non-essential businesses and workplaces were temporarily closed [3]. People with chronic diseases and pregnant women who worked in public institutions were allowed to go on administrative leave. Following the increase in cases, the transition to remote working model in public institutions, intercity travel restriction, curfew for citizens over 65 and under 18 years were implemented. Moreover, in some cities where COVID-19 cases were more widespread, more stringent curfews, where all citizens were asked to stay at home unless needing medical attention, were enacted during the weekends [4-6]. In addition, it was emphasized on many platforms that citizens should stay home and apply to the emergency rooms only when necessary in order to keep the capacity of the emergency services at the maximum. The Ministry of Health took some measures by designating pandemic hospitals in each province and recommending postponing all elective surgical operations to a later date [7, 8].

Our hospital is one of two medium-sized hospitals located in the area with approximate population of 400,000. During the pandemic, our hospital served non-COVID-19 patients, while the other hospital was designated as a pandemic hospital. This was done in order not to alleviate the pressure on the healthcare system and to minimize hospital transmission. Some studies have reported that hospital admissions were gradually decreasing during the pandemic and these late admissions have caused negative outcomes [9, 10]. We have not come across a study evaluating emergency general surgery cases during the pandemic in our country. The aim of this study was to investigate whether the COVID-19 pandemic had an impact on emergency general surgery admission volume and operations. The findings presented here are intended to shed light on the management of emergency general surgery cases in future similar pandemic situations.

Materials and methods

Study design and participants

All patients referred from the emergency department to our emergency general surgery unit between April 1, 2020 and May 31, 2020, which was the time of the strictest measures taken to prevent the spread of the epidemic in our country, were analyzed retrospectively. Before the COVID-19 outbreak, emergency room doctors first evaluated all patients admitted to the emergency room, and patients thought to have general surgery pathologies were referred to the emergency general surgery unit. During the COVID-19 pandemic, this practice was revised and patients who were thought to have emergency general surgery pathology and did not have COVID-19 symptoms were directed to our emergency general surgery unit. Patients who had emergency general surgery pathology and were positive for COVID-19 were referred to the pandemic hospital in our city.

The main inclusion criteria in our study were requiring the evaluation and treatment of a general surgeon and hospitalization that lasted >24 hours. The exclusion criteria were referral to the pandemic hospital, being under the age of 18 years, and a hospital stay of <24 hours.

All patients who had similar inclusion and exclusion criteria with the pandemic group and were treated in the emergency general surgery unit during the same time period (April 1 - May 31) in the last two years (2018 and 2019) were included as the control group.

Data collection

Electronic medical records of patients treated in our institution were examined. Demographic characteristics, diagnoses, operation status, open or laparoscopic operation status, complications, intensive care unit stay, and hospital stay were evaluated. Complications were defined according to Clavien-Dindo Classification [11].

Statistical analysis

For the purpose of statistical analysis, patients were grouped by year of admission. SPSS 22.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) was used for statistical analysis of the data. Chi-square or Fisher's exact tests were used to compare groups of categorical variables. One-way analysis of variance (ANOVA) and Student's t-test were used to determine statistical difference in parametric data. p values <0.05 were considered significant.

Results

A total of 208 patients were hospitalized to the emergency general surgery service between April 1, 2020 and May 31, 2020. The number of admissions to the emergency general surgery service in 2020 was 25.9% less than that in 2018 and 30.8% less than that in 2019. The mean age of the patients in 2020 was higher than those of the patients in 2018 and 2019 (P<0.001). On the other hand, no difference was found between the groups in terms of gender (P=0.236). The demographic data of the patients are given in Table 1.

The distribution of diagnoses of appendicitis, biliary pathology, pancreatitis, diverticulitis, and hernia were similar between the groups. However, the number of patients hospitalized due to non-specific abdominal pain was significantly less in 2020 (P=0.003). On the other hand, in 2020, 31 patients were treated due to gastrointestinal (GI) obstruction, which was more than in 2018 and 2019 (P=0.001). Similarly, the number of patients treated for GI perforation was significantly higher in 2020 (P<0.001). On the contrary, 41 (14.6%) patients in 2018, 36 (12.7%) patients in 2019, and 13 (6.2%) patients in 2020 were treated for trauma, and this decrease in 2020 was significant (P=0.015). Data on patient diagnoses are shown in Table 1.

While 45.9% of the patients hospitalized in the emergency general surgery service were operated in 2018, this rate was 47.2% in 2019. In 2020, the operation rate was higher (65.9%) compared to other years (P<0.001). Laparoscopic

procedure was performed in 55.8% of the patients operated in 2018 and 57.7% in 2019. In 2020, this rate was relatively low with 32.1% (P<0.001). The data on the treatment approach are given in Table 2.

Table 1: Patients' diagnosis and demographic characteristics

	2018	2019	2020	*P*-value
Total admission	281	301	208	
Age †	47.60 (16.54)	50.09 (17.07)	54.06 (17.31)	<0.001*
Gender				
Female‡	126 (44.8)	156 (51.8)	99 (47.6)	0.236**
Male‡	155 (55.2)	145 (48.2)	109 (52.4)	
Diagnosis				
Non-specific abdominal pain‡	41 (14.6)	49 (16.3)	13 (6.2)	0.003**
Appendicitis‡	68 (24.2)	64 (21.3)	68 (24.2)	0.087**
Biliary pathology‡	55 (19.6)	67 (22.3)	37 (17.8)	0.447**
Pancreatitis‡	21 (7.5)	25 (8.3)	14 (6.7)	0.801**
GI obstruction‡	16 (5.7)	21 (7.0)	31 (14.9)	0.001**
GI perforation‡	9 (3.2)	13 (4.3)	27 (13.0)	<0.001**
Diverticulitis‡	14 (5.0)	11 (3.7)	5 (2.4)	0.332**
Hernia‡	16 (5.7)	15 (5.0)	6 (2.9)	0.331**
Trauma‡	41 (14.6)	36 (12.7)	13 (6.2)	0.015**

†mean (SD). ‡n (%). *One-way analysis of variance (ANOVA) was used to determine statistical difference. **Chi-square or Fisher's exact tests were used to determine statistical difference. GI: Gastrointestinal

Table 2: Patients' perioperative data

	2018	2019	2020	*P*-value
Treatment approach				
Non-interventional†	152 (54.1)	159 (52.8)	71 (34.1)	<0.001*
Operative†	129 (45.9)	142 (47.2)	137 (65.9)	
Operation type				
Open†	57 (44.2)	60 (42.3)	93 (67.9)	<0.001*
Laparoscopic†	72 (55.8)	82 (57.7)	44 (32.1)	
Clavien-Dindo Complication: ≥Grade III†	-	-	2 (11.8)	0.530*
ICU admission (day) †	8 (2.8)	12 (4.0)	11 (5.3)	0.389**
Hospital LOS (day) ‡	4.46 (3.03)	4.78 (2.99)	3.70 (2.82)	<0.001**
Mortality†	1 (0.4)	1 (0.3)	5 (2.4)	0.025*

*n (%),‡mean (SD), *Chi-square or Fisher's exact tests were used to determine statistical difference. **One-way analysis of variance (ANOVA) was used to determine statistical difference. ICU: intensive care unit, LOS: length of stay

In general, the rate of complications among the operated patients was 3.9% in 2018, 3.5% in 2019, and 12.4% in 2020. This increase in 2020 was significant (P=0.004). However, the ratio of grade III and above complications according to Clavien-Dindo classification system was similar between the groups (P=0.530). While mortality rates were 0.4% and 0.3% in 2018 and 2019, respectively, this rate was 2.4% in 2020 (P=0.025). Complication status and data on mortality are given in Table 2.

Finally, while the intensive care admission rates were similar between the groups (P=0.388), the mean length of stay in the hospital was significantly lower in 2020 (P<0.001).

Discussion

During the pandemic, the number of patients admitted to the emergency general surgery unit was 25.9% and 30.8% less compared to the same periods in 2018 and 2019, respectively. Similar results were reported in studies conducted in different countries during the pandemic [12, 13]. However, while 2 hospitals were serving the emergency general surgery patients in our city before the pandemic, only our hospital served non-COVID-19 patients during the pandemic (the other hospital was designated as a pandemic hospital). With this in mind, it can be concluded that the decrease in number of patients treated during the pandemic may actually be even greater. However, to be able to make a definite decision on this issue, it is necessary to reach other hospital's date from previous years.

Many factors might have caused the decrease in patient acceptance during the pandemic. The most important factor might be the fear of hospital-related COVID-19 transmission. Indeed, a study has shown that during the first phase of the pandemic, a significant proportion of patients were reluctant to seek access to healthcare services for non-COVID-19 diseases [14].

According to the results of our study, there have been significant changes in diagnoses at the time of patient admission during the pandemic compared to previous years. For example, a significant decrease in hospitalizations due to non-specific abdominal pain during the pandemic is noteworthy. The most important reason for this might have been the desire to avoid COVID-19 transmission. Although there were studies that reported similar results to ours, there was also a study showing that hospitalizations due to non-specific abdominal pain did not change [13, 15]. Moreover, in our study, hospitalizations due to GI obstruction and perforation during the pandemic were higher than in previous years. In fact, this result might indicate patients' late arrival to the hospital. In other words, patients did not come to the hospital when they had non-specific abdominal pain but presented only after the GI perforation had developed. We also found a significant decrease in trauma cases during the pandemic compared to previous years. The decrease in trauma cases is not surprising in this period when human mobility was minimized due to curfews, restrictions on intercity travel, and stay-at-home orders that were enacted to control the spread of the virus.

Although the American and UK Surgical Colleges recommended reducing operational interventions during the pandemic, in our study, the surgery rates were higher during the pandemic, while non-interventional methods were predominant in the past years [16, 17]. It might have been because there were many patients hospitalized with the diagnosis of non-specific abdominal pain in the past and most of them were treated with non-interventional methods. Another reason may have been that the patients waited for their illness to become more severe (if they had received medical treatment earlier, perhaps they would have been treated without surgery) and only then applied to the hospital. The studies on this subject have not reached a consensus. While McLean et al. reported similar surgery rates before and during the pandemic, McGuinness et al. reported that the surgery rates decreased during the pandemic [12, 15]. In addition, in our study, the rate of laparoscopic cases was lower during the pandemic. The underlying reason for the low rates of laparoscopic cases is the recommendation from guidelines to perform open surgery instead of laparoscopic surgery in order to minimize the risk of transmission [16, 17].

The examination of complication status showed that the general complication rate, which was below 4% in the past years, increased to 12.4% during the pandemic. Fortunately, serious complication rates during this period were similar to previous years. The fact that more patients with severe diagnoses such as GI obstruction and GI perforation were operated during the pandemic may explain the higher rate of general complications during the pandemic.

Interestingly, although our rate of surgery and complications was higher during the pandemic, the duration of hospital stay was shorter. Despite the general complication rate being high, the rate of serious complications was similar to previous years, and thus we believe that the effect of complications on the duration of stay was minimal. In addition, the shorter hospital stay can be explained by the effort to keep the hospital bed capacity at maximum and to minimize the

spread of infection. Based on this, it can be concluded that patients' length of stay in the general surgery service and the reasons behind it should be analyzed even further.

In our study, the rate of hospitalization of emergency general surgery patients during the pandemic was similar to the rate from previous years. We think that the effort to keep the ICU occupancy rate as low as possible had an impact on this outcome. Another result of our study indicated that the mortality rate during the pandemic was higher than in previous periods. Facing a more severe disease group during the pandemic may have resulted in a higher mortality rate. In addition, our patient group during the pandemic had higher mean age, which might have led to more comorbidities and thus might have caused higher mortality.

We believe that the main reason for high rates of GI obstruction and perforation diagnoses, as well as high complication and mortality rates seen during the pandemic in our study was the late admission to the hospital. Use of telemedicine during public health emergencies such as COVID-19 pandemic can prevent this trend. Telemedicine can help determine patients that need early admission to the hospital due to severe diagnosis and can help with follow-up of patients treated at home with oral antibiotics, or patients that are followed with "watch and wait" strategy due to non-specific abdominal pain [18]. We believe that with necessary regulations telemedicine is an ideal tool that can be actively used in future public health emergencies.

The fact that our study was conducted in a single center can be considered as a limitation as it prevents generalization throughout the country. Another limitation of our study was that the data of the patients after discharge were not evaluated.

Conclusion

To the best of our knowledge, this is the first study evaluating emergency general surgery cases in our country during the COVID-19 pandemic. We observed a decrease in emergency general surgery case applications, surgery rates, and hospital stay, and an increase in the rate of more serious diagnoses, complications, and mortality during the COVID-19 pandemic. The reason behind these results is probably multifactorial. However, we think that the most important of these are late hospital admissions due to the concern of transmission and the effort of physicians to discharge the patients as soon as possible. Therefore, we emphasize that telemedicine should be developed and used widely as soon as possible.

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Electrocardiographic findings in non-critical patients with coronavirus disease-2019

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Ethics Committee Approval
The study protocol was approved by Kanuni Sultan Suleyman Training and Research Hospital's Ethical Committee (Number: KAEK/2020.05.57)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Cardiovascular involvement in patients with coronavirus disease 2019 (COVID-19) is closely related to the course of the disease; however, this issue has not been adequately studied in Turkey. Thus, we aimed to investigate the electrocardiography (ECG) findings in noncritical patients with COVID-19 in Turkey.

Methods: This retrospective cohort study was conducted on non-critical patients with COVID-19 with no history of any cardiac disease. The laboratory parameters and ECG findings of the patients at the time of admission were analyzed.

Results: In total, 100 patients with a mean age of 56.8 (16.7) years were included in the study, among which 54 were males. The rate of patients having at least one abnormal ECG finding, ST segment pathology, and elevated troponin level were 58%, 26%, and 48%, respectively. The respiratory rate and mean troponin level were higher and the mean lymphocyte count was lower in patients with ST segment pathology than in patients without. The respiratory rate, fibrinogen level, and incidence of T negativity and abnormal ECG findings were higher, and the lymphocyte count was lower in patients with elevated troponin levels than in patients with normal troponin levels ($P<0.05$ for all). Troponin level was significantly negatively correlated with lymphocyte count and significantly positively correlated with respiratory rate and C-reactive protein ($P=0.003$, $r = -0.298$; $P=0.031$, $r = 0.215$; and $P=0.02$, $r = 0.233$, respectively). In the receiver operating characteristic analysis, it was found that ST segment pathologies were more common in patients with a troponin level >0.03 mg/mL ($P<0.001$, area under the curve: 0.763, sensitivity: 61.5%, and specificity: 90.5%).

Conclusion: Cardiac involvement is very common in patients with COVID-19, and elevated cardiac troponin levels and pathological ECG findings are observed.

Keywords: Electrocardiography, Troponin, ST segment pathology, COVID-19

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Introduction

Coronavirus disease 2019 (COVID-19) is an infection that emerged as atypical cases of pneumonia in the Hubei province of China in December 2019 and later became a pandemic [1]. According to the reports of the World Health Organization, as of February 12, 2021, >107 million cases and >2 million deaths were reported worldwide, with a mortality rate of approximately 2.1% [2].

Although pulmonary findings constitute the basic clinical presentation of the disease in patients with COVID-19, cardiac involvement is also common and has an impact on mortality rate in this patient group. In patients presenting with cardiac involvement, the possibility of severe disease progression, need for intensive care, and mortality are higher [3-5]. The mechanisms affecting the occurrence of cardiac symptoms in COVID-19 are uncertain, and various pathophysiological mechanisms have been reported as explanations. According to one hypothesis, the virus can bind to the angiotensin converting enzyme-2 receptor, an aminopeptidase that is highly expressed in the heart and lungs, causing alterations in angiotensin converting enzyme-2 signaling pathways and myocardial damage [6, 7]. Another mechanism could be the occurrence of acute systemic inflammatory response and cytokine storm in severe cases, causing multiorgan failure and cardiac damage due to an increase in circulating proinflammatory cytokine levels [8, 9]. In addition, it is considered that hypoxia and systemic inflammation, which affect myocardial oxygen requirement, increase the risk of plaque rupture due to elevated coronary blood flow rate and that the presence of various electrolyte imbalances that facilitate the occurrence of arrhythmias might cause cardiac damage in this patient group [3, 10]. In addition to the effects of the disease itself, drugs such as chloroquine, hydroxychloroquine, and azithromycin, which are used for its treatment, are known to have various cardiac side effects.

In this study, we aimed to identify any pathological findings detected by electrocardiogram (ECG) analysis at admission before treatment in patients with COVID-19 and examine the relationship of these findings with the severity of the disease and its associated parameters.

Materials and methods

In this retrospective study, we examined patients who were hospitalized in isolation wards with the diagnosis of COVID-19 at a tertiary training and research hospital between January 4, 2020 and May 31, 2020. Individuals younger than 18 years of age and pregnant and breastfeeding women were not included in the study. In addition, patients with any cardiovascular diseases, history of arrhythmia, or anti arrhythmic drug use in the period before the diagnosis of COVID-19 or those who had previously undergone coronary imaging for any reason were excluded from the study. The data of 156 patients were obtained, but 56 were excluded because of the following criteria: Having cardiovascular disease (n = 42), using anti arrhythmic drugs (n = 9), and verbally expressing a history of arrhythmia despite not using anti arrhythmic drugs (n = 7). Demographic data, vital signs, laboratory analysis results, ECG images, and pulmonary imaging findings were obtained through the data stored in the online system. The demographic data of the patients (age, sex, complaints at presentation, and presence of comorbid diseases) and their vital signs at presentation (blood pressure, heart rate, percentage of oxygen saturation at room air, and respiratory rate per minute) were recorded. The results of complete blood count analysis and C-reactive protein (CRP), procalcitonin, cardiac troponin, creatine kinase (CK), ferritin, fibrinogen, D-dimer, and electrolyte levels were recorded from the laboratory tests performed at the time of admission. The patients were grouped as mild, moderate, and severe cases according to the severity of the disease. The clinical presentation was considered severe in the presence of at least one of the following conditions: Respiratory rate ≥30/min, mean oxygen saturation at room air ≤90%, >50% pneumonia involvement detected on imaging and severe respiratory distress symptoms. Patients with a respiratory rate of <24/min, a mean oxygen saturation at room air of >93%, and normal lung imaging were included in the mild disease group. Patients who did not match the criteria for any of the two groups were defined as those with moderate disease.

ECG data of the patients were obtained from the results of 12-lead ECG analysis performed at a speed of 25 mm/s and saved in the system. There were small squares of 1 × 1 mm and large squares of 5 × 5 mm on the electrocardiography sheet, and each small square was considered to represent 0.04 s. In the vertical plane, a 0.1-mV stimulus was adjusted to create a 1-mm deflection. The following parameters were calculated and recorded using ECG:

Heart rate: It was calculated with the formulas of the number of large squares between R-R as 300/R-R, or the number of small squares between R-R, as 1500/R-R. The reference range is between 60–100/min, and a heart rate of <60/min was defined as bradycardia, whereas HR >100/min was defined as tachycardia.

ST segment: The area from the end of the QRS complex to the beginning of the T wave was evaluated. An ST elevation of ≥0.1 mV (1 small square) relative to the point J, where the S wave ends, and an ST depression of ≥0.05 mV (1/2 small square) in two consecutive anatomical leads were considered significant. A T-wave depression of ≥0.1 mV in two consecutive anatomical leads was accepted as T negativity and the presence of sharp T waves, as T sharpness.

P wave: It was obtained by measuring the distance from the beginning to the end of the P wave.

PR range: It was obtained by measuring the segment between the beginning of the P wave and the beginning of the QRS complex. Its normal value was 0.12–0.20 s, and values of >20 s were defined as PR prolongation.

QRS range: It was calculated as the time between the beginning of the Q wave and the end of the S wave.

QT interval: It was obtained by measuring the time from the beginning of the QRS complex to the end of the T wave. The heart rate-corrected QT interval (QTc) was calculated by dividing the QT distance by the square root of R-R interval (Bazett formula). It was defined as long QT for values greater than 460 ms in women and 440 ms in men.

Pathological Q wave: It was considered pathological if the Q wave was wider than 1 mm (0.04 s) or deeper than 2 mm, or if it was greater than one-fourth of the R wave in the same lead.

Axis: The electrical axis of the heart was obtained by measuring the QRS wave amplitudes. The vector was considered normal if the cardiac axis was between 30° and 90°, as right axis deviation if it was between 90° and 180°, and as left axis deviation if it was between −30° and −90°.

In addition to these measurements, ECG was evaluated as a whole, and if there was any specific ECG finding (left bundle-branch block, right bundle-branch block, and atrial fibrillation), it was noted.

Statistical analysis

SPSS version 15.0 for Windows (IBM Corporation, Chicago, IL, USA) was used for statistical analyses. Categorical variables were presented as numbers and percentages and numerical variables, as mean ± standard deviation. The Shapiro–Wilk test was used to determine how the variables were distributed. The Chi-square test was used to compare categorical data between groups. In the comparison of numerical variables, the student's T test was used when the variables showed normal distribution, and the Mann–Whitney U test was used when they showed non-normal distribution. When a numerical variable was compared among more than two groups, analysis of variance test was used for parameters with a normal distribution and the Kruskal–Wallis test was used for parameters with a non-normal distribution. Pearson and Spearman correlation analysis were performed for variables with normal and non-normal distribution, respectively. Multivariate binary regression analysis was performed to analyze whether certain variables had a role in the presence of pathological findings on ECG and whether ECG findings had a role in mortality. *P*-values of <0.05 were considered significant.

Ethical approval: This study was approved by the Turkish Ministry of Health Scientific Research Platform (İskender Ekinci-2020-05-06T18_35_20) and the Clinical Research Ethics Committee of Health Sciences University, Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey (Number: KAEK/2020.05.57). Study procedures were performed in accordance with the 2009 Helsinki Declaration.

Results

A total of 100 patients, 54 of which were male, diagnosed with COVID-19, were included in the study. The mean age of the patients was 56.8(16.7) (20–92) years, and 63 were over 50 years old. Among presentation complaints, 66% of the patients had cough, 52% had weakness, 50% had shortness of breath, and 45% had high fever, followed by myalgia, sore throat, and headache, which were less common. Signs of pneumonia were detected in 89 patients on imaging, whereas 11 had no pneumonia. Fifty-two patients had at least one comorbid disease, and the most common among these were hypertension (n = 32) and type-2 diabetes mellitus (n = 24). The mean hospitalization period of the patients was 8.19 (3.5) (3–19) days, the mean systolic and diastolic blood pressures were 117.8 (10.9) mmHg (100–150), and 71.9 (8.1) (50–95) mmHg, respectively. The mean oxygen saturation rate at room air was 93.7 (4.2) % (75–98), and the mean respiratory rate per minute was 19.2 (2.1) (14–28). Twenty-five patients had mild, 53 had moderate, and 22 had severe disease. Six of the patients included in the study died, and the mortality rate was 6% within the study group.

The number of patients with at least one abnormal ECG finding was 58, and the number of patients with ST segment pathology was 26. Patients were grouped as those with and without ST segment pathology, and their results were compared (Table 1). Findings of sex distribution, incidence of pneumonia, distribution of patients according to disease severity, prevalence of type-2 diabetes mellitus and hypertension, and mean systolic and diastolic blood pressures were similar in patients with and without ST segment pathology (*P*>0.05). The respiratory rate, mean troponin value, and proportion of patients with elevated troponin value were higher, whereas mean lymphocyte count was lower in the group with ST segment pathology than in the group without (Table 1).

Table 1: Laboratory parameters in patients with ST segment pathology and those without ST segment pathology

	All patients	Patients with ST segment pathology	Patients without ST segment pathology	*P*-value
n	100	26	74	
Age, year	56.8(16.7)	54.69(19.10)	57.64(15.89)	0.441
Respiration rate, min	19.2(2.1)	20.03(2.47)	19.01(2.01)	0.038
Saturation, %	93.7(4.2)	91.5(6.66)	94.55(2.59)	0.128
Heart rate, bpm	82(13.2)	81.38(15.06)	82.32(12.62)	0.757
Hemoglobin, g/dL	12.71(1.69)	12.72(1.74)	12.71(1.69)	0.975
Leukocyte, 10^3µ/L	6.74(2.44)	6.48(2.29)	6.83(2.5)	0.621
Lymphocyte, 10^3µ/L	1.52(0.79)	1.18(0.65)	1.63(0.81)	0.004
C-reactive protein, mg/L	52.5(58.93)	67.07(80.16)	47.39(49.06)	0.527
Procalcitonin, mg/mL	0.18(0.63)	0.16(0.2)	0.19(0.73)	0.078
Troponin, mg/mL	0.64(1.94)	2.33(3.27)	0.05(0.24)	<0.001
Creatine kinase, U/L	109.14(165.79)	167.88(285.71)	87.89(86.6)9	0.933
D-dimer, mg/L	1.68(4.73)	3.15(8.82)	1.17(1.63)	0.305
Calcium, mg/dL	8.9(0.81)	8.63(1.42)	8.99(0.45)	0.756
Potassium, mg/dL	4.36(0.58)	4.26(0.49)	4.4(0.61)	0.435
Magnesium, mg/dL	2.14(0.47)	2.09(0.43)	2.16(0.48)	0.936
Ferritin, mg/mL	443.79(671.76)	427.05(511.06)	449.67(722.78)	0.747
Fibrinogen, mg/dL	400.41(168.93)	429(155.12	390.36(173.40)	0.318
Elevated troponin, n	48	19 (%73)	29 (%39)	0.003

ST segment pathology was detected in 16%, 22.6%, and 45.4% of patients with mild, moderate, and severe disease, respectively (*P*>0.05). Other pathological ECG findings were similar between the groups (*P*>0.05). Five of the six patients with mortality had ST segment pathology, and the incidence of ST segment pathology was higher than that among survivors (*P*=0.004).

The troponin level was elevated in approximately half of the patients (48%). Sex distribution, incidence of pneumonia, distribution of patients according to disease severity, prevalence of type-2 diabetes mellitus and hypertension, and mean systolic and diastolic blood pressure were similar in patients with elevated and normal troponin levels (*P*>0.05). In patients with elevated troponin levels, the lymphocyte count was lower (*P*=0.014), fibrinogen level was higher (*P*=0.021), and other laboratory parameters were similar compared to those with normal serum troponin (*P*>0.05). Patients with elevated troponin

levels were compared with those with normal troponin levels in terms of ECG findings, and the results obtained are presented in Table 2. The respiratory rate per minute, incidence of T negativity, and abnormal ECG findings were higher in patients with elevated troponin levels than in those with normal troponin levels. Furthermore, troponin levels were above the normal range in all six patients who died.

Table 2: Electrocardiography findings in patients with elevated troponin level and those with normal troponin level

	All patients	Patients with elevated troponin level	Patients with normal troponin level	*P*-value
n	100	48	52	
Age, year	56.8(16.7)	56.3(19.3)	57.3(14)	0.764
Respiration rate, min	19.2(2.1)	19.7(2.2)	18.8(2)	0.03
Saturation, %	93.7(4.2)	93.5(4.9)	93.9(3.4)	0.626
Heart rate, bpm	82(13.2)	83.1(14.8)	81.1(11.6)	0.451
Tachycardia, n	12	7	5	0.544
ST depression, n	7	5	2	0.256
ST elevation, n	4	2	2	1
T wave negativity, n	24	17	7	0.018
T wave sharpness, n	2	2	0	0.228
Long QT, n	24	13	11	0.640
LBBB, n	3	0	3	0.244
RBBB, n	4	1	5	0.207
Atrial fibrillation, n	3	3	0	0.107
Pathologic Q wave, n	7	3	4	1
Normal axis, n	86	41	45	
Left axis deviation, n	9	6	3	0.243
Right axis deviation, n	5	1	4	
Abnormal ECG findings, n	58	33	25	0.044
P duration, s	0.081(0.022)	0.082(0.024)	0.080(0.021)	0.620
PR duration, s	0.168(0.031)	0.171(0.034)	0.166(0.027)	0.515
QRS duration, s	0.08(0.022)	0.079(0.016)	0.081(0.027)	0.679
QT duration, s	0.366(0.044)	0.365(0.047)	0.367(0.042)	0.793
QTc duration, ms	422.51(41.12)	422.68(43.19)	422.34(39.54)	0.788

The troponin level was significantly negatively correlated with lymphocyte count (r: −0.298, *P*=0.003) and significantly positively correlated with respiratory rate (r: 0.215, *P*=0.031) and CRP level (r: 0.233, *P*=0.02). The troponin level did not have any significant correlation with other laboratory parameters (leukocyte count, levels of hemoglobin, procalcitonin, CK, calcium, magnesium, D-dimer, ferritin, and fibrinogen levels) and distances measured on the ECG (P duration, PR duration, QRS duration, QT duration, and QTc).

Respiratory rate, mean oxygen saturation at room air, lymphocyte count, serum troponin level, and elevated troponin level in the univariate regression analysis and only the mean oxygen saturation value in multivariate regression analysis were found to play significant roles in ST segment pathology (Table 3). Similarly, in the univariate regression analyses in which the role of ECG pathologies in the development of mortality was analyzed, ST depression, T negativity, T-wave sharpness, and ST segment pathology were significant parameters (Table 4).

Based on Receiver Operating Characteristics analysis, the cut-off level for serum troponin in showing ST segment pathology was 0.03. As observed in Figure 1, ST segment pathology was significantly more common in patients with troponin value >0.03 mg/mL (*P*<0.001, area under the curve: 0.763, sensitivity: 61.5%, and specificity: 90.5%).

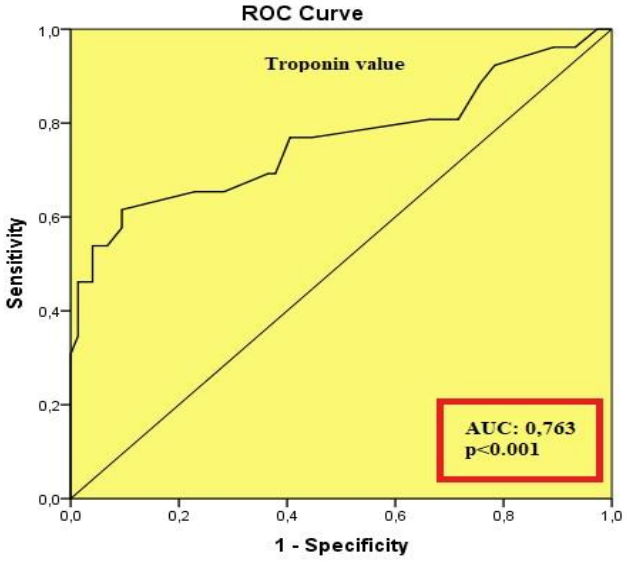
Table 3: Univariate and multivariate logistic regression analysis on the presence of ST segment pathology in patients with Covid-19

Variable	Univariate OR	Univariate 95% Cl (Lower-Upper)	Univariate *P*-value	Multivariate OR	Multivariate 95% Cl (Lower-Upper)	Multivariate *P*-value
Age	1.011	0.984-1.038	0.437	1.030	0.989-1.074	0.157
Male gender	1.242	0.508-3.041	0.635	1.960	0.567-6.769	0.287
Presence of pneumonia	1.076	0.263-4.404	0.919			
Respiratory rate, min	0.796	0.635-0.997	0.047	0.882	0.636-1.224	0.454
Saturation, %	1.175	1.048-1.316	0.006	1.198	1.011-1.419	0.037
Lymphocyte, 10^3µ/L	2.668	1.201-5.924	0.016	1.666	0.656-4.231	0.283
C-reactive protein, mg/mL	0.995	0.988-1.002	0.152			
D-dimer, mg/L	0.924	0.834-1.025	0.136			
Ferritin, mg/mL	1	0.999-1.001	0.882	1.001	0.999-1.003	0.230
Troponin, mg/mL	0.183	0.055-0.609	0.006	0.295	0.099-0.878	0.028
Elevated troponin	0.237	0.089-0.635	0.004			

Table 4: Univariate and multivariate logistic regression analysis on the mortality by electrocardiographic findings in patients with Covid-19

Variable	Univariate OR	Univariate 95% Cl (Lower-Upper)	Univariate *P*-value	Multivariate OR	Multivariate 95% Cl (Lower-Upper)	Multivariate *P*-value
Tachycardia	0.238	0.039-1.469	0.122			
ST depression	8.9	1.303-60.8	0.026	1.635	0.165-16.214	0.674
ST elevation	0	0 -	0.999			
T wave negativity	7.4	1.263-43.348	0.026	0.296	0.008-10.937	0.509
ST pathology	17.381	1.924-157	0.011	39.027	0.592-2573.7	0.086
T wave sharpness	18.6	1-342.9	0.049	2.255	0.054-93.314	0.669
Pathologic Q wave	2.93	0.294-29.28	0.359	1.497	0.064-35.23	0.802
PR duration	7.80	0.013-4.54	0.09			
Prolonged PR	6.067	0.531-69.3	0.147			
QT duration	0	0-6.837	0.073			
QTc duration	0.983	0.960-1.006	0.140			

Figure 1: Receiver operating characteristic analysis for serum troponin level on occurrence ST segment pathology



Discussion

In this study, ECG pathologies were analyzed in patients with COVID-19 and more than half of the patients had at least one pathological finding on ECG and approximately quarter of the patients had ST segment pathologies. In addition, the serum troponin level was elevated as a marker of cardiac damage in approximately half of the patients. Furthermore, we found that respiratory rate, mean oxygen saturation, troponin levels, and lymphocyte count were significant predictors of ST segment pathologies detected on ECG, whereas ST depression, T negativity, T sharpness, and ST segment pathology were significant predictors of mortality. The data of six non-survivor patients revealed that troponin levels were elevated in all, and five patients had ST segment pathology.

In the present study, the most common ECG pathologies were T-wave negativity and long QT (24%), followed by tachycardia (12%), left axis deviation (9%), ST depression (7%), pathological Q wave (7%), short QT (6%), right axis deviation (5%), ST elevation (4%), right bundle branch block (4%), left bundle branch block (3%), atrial fibrillation (3%), and T sharpness (2%), respectively. In a similar study, abnormal ECG findings were reported in 63% of the cases, including ST–T changes (32.6%), sinus tachycardia (12.5%), atrial fibrillation (6.6%), abnormal Q wave (5.6%), right bundle branch block (9.7%), left bundle branch block (0.9%), sinus bradycardia (6%), and long QT (1.3%) [11]. In another study, most patients had ECG pathology, including atrial fibrillation / flutter (5.6%), AV block (2.6%), premature atrial contractions (7.7%), premature ventricular contractions (3.4%), left-axis deviation (13.8%), right-axis deviation (5.5%), right-bundle branch block (7.8%), left-bundle branch block (1.5%), left ventricular hypertrophy (15.5%), right ventricular hypertrophy (4%), pathological Q wave (13.9%), localized ST elevation (0.7%), and localized T wave inversion (10.5%) [12]. In a study conducted in our country, tachycardia was found in 31%, ST segment pathology in 28%, T negativity in 22%, ST depression in 20%, and long QT in 5% of the patients [13]. In yet another study, ST–T abnormalities were reported in 30% and left ventricular hypertrophy, in 33% of the patients [14]. Considering both our own study and previous similar studies, although pathological ECG findings vary, these pathologies are very common in patients with COVID-19.

In the present study, the incidence of ST segment pathologies detected on ECG increased in parallel with the worsening of the disease presentation and led to a difference between the groups. The incidence of ST segment pathology was 45% in patients with severe disease and 16% in patients with mild disease. Other pathological ECG findings in the present study were similar among the groups in terms of disease severity. Deng Q et al. reported that myocarditis, segmental wall motion abnormality on ECG, pulmonary hypertension, and pericardial effusion were more common and the mean ejection fraction was lower in patients with severe disease; however, tachycardia and ST segment pathologies were not different between patients with and without severe disease [15]. McCullugh et al. reported that many pathological ECG findings were more common in non-surviving patients, and in a study conducted in Turkey, ST segment pathologies, ST depression, and T negativity were reported more commonly in patients with severe disease [12, 13]. In a COVID-19 case series of 18 patients with ST elevation, this ECG pathology occurred at the time of admission in 10 patients, and the outcome was mortality in 13 patients [16]. In the present study, five of 26 patients with ST segment pathology died.

In our study, the respiratory rate, troponin value, percentage of patients with elevated troponin value, and mortality rate were higher, and the lymphocyte count was lower in patients with ST segment pathology than in those without. The respiratory rate, mean oxygen saturation, lymphocyte count, and troponin level were significant predictors for the development of ST segment pathology. In a study by Wang et al., troponin and N-terminal pro-brain natriuretic peptide levels, and in a study by Barman et al., presence of hypertension, severe disease presentation, myocardial damage, and elevated D-dimer levels were reported as the parameters that play a role in the emergence of ST segment changes on ECG [11, 13].

In this study, approximately half of the patients had elevated cardiac troponin levels. The respiratory rate was higher and T negativity and abnormal ECG findings were more common in patients with elevated troponin levels. Elevated cardiac troponin level in all patients with mortality was another remarkable finding. In many previous studies, similar to the present study, the cardiac troponin level was higher in patients with severe disease, which required intensive care unit follow-up, or resulted in mortality [9, 13, 17]. Deng Q et al. reported that troponin levels were comparatively higher in patients with severe disease, whereas the respiratory rate was higher and saturation was lower in patients with elevated troponin levels [15]. Zhou et al. found the rate of patients with elevated troponin levels to be 17%, which increased to 46% in a subgroup with mortality: They suggested that cardiac troponin level was a significant marker for mortality rate [9]. In different studies of a similar nature, the rate of cardiac involvement varied between 7.2% to 27.8% in patients with COVID-19 disease [11, 15, 17, 18]. Barman et al. demonstrated that QRS segment duration was longer and long QRS, long QT, ST depression, T negativity, and ST segment pathologies were more common in patients with cardiac damage than in those without [13]. In the present study, only the incidence of T negativity was different, whereas other ECG pathologies were similar in patients with elevated and normal troponin levels. In addition, PR, QRS, QT, and QTc distances were not different between the two groups in the present study.

Studies have shown that patients with cardiac damage have older age, a longer period of hospitalization, more comorbid diseases such as type 2 diabetes mellitus and hypertension, need mechanical ventilation more often, have more disease-related complications, and higher mortality rates than patients without cardiac damage [5, 18]. In these studies, higher leukocyte and neutrophil counts as well as higher CRP, procalcitonin, CK myocardial band, troponin, and D-dimer levels and lower lymphocyte count and calcium levels were reported in patients with cardiac damage. In addition, it has been reported in a case series that cardiac damage markers are closely associated with inflammation parameters [16]. In the present study, the lymphocyte count was lower and the fibrinogen level was higher in patients with elevated troponin levels, whereas age, sex distribution, prevalence of comorbid diseases, mean blood pressure, and incidence of pneumonia were similar. We also observed that the troponin level had a significant negative correlation with lymphocyte count and a significant positive correlation with respiratory rate and CRP level.

Limitations

The limitations of this study include the relatively smaller sample size, especially in terms on non-surviving patients, and the fact that only basal ECG and laboratory data were analyzed. The reason for this is that cardiac pathologies that may arise secondary to the drugs used were intended to be excluded from the scope of this study. This is because our aim in this study was to examine only the cardiac pathologies caused by the presentation of COVID-19. Another limitation is that we did not have former ECG records of these patients before COVID-19

infection. We tried to eliminate this limitation by excluding patients with any known cardiac disease, history of arrhythmia or anti arrhythmic drug use, and those who had previously undergone coronary imaging due to cardiac complaints. Moreover, we believe that prospective studies in which surviving patients who develop cardiac damage are followed up periodically in terms of cardiac signs and symptoms will shed light on the long-term consequences of cardiac involvement.

Conclusions

Considering both findings of the present study and the results of previously published articles, it can be concluded that cardiac involvement is very common in patients with COVID-19 and manifests as both elevated cardiac troponin levels and pathological ECG findings. Moreover, the mortality rate is higher in patients with cardiac damage. Pre-existing cardiac history as well as cardiac involvement during the COVID-19 disease period are important factors for assessing the course of the disease. At this point, we think the present study results are remarkable. In the light of this information, we believe that close monitoring of patients with COVID-19 in terms of the development of cardiac damage will be an appropriate approach, both at an early stage during diagnosis of the disease and while being followed up under treatment.

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The role of vitamin D deficiency and thyroid dysfunction on blood glucose regulation in patients with type 2 diabetes mellitus: A retrospective cohort study

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Ethics Committee Approval
The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Date: 4.3.2020, Decision No:2020/4-2011 KAEK-2) and carried out in accordance with the Helsinki Declaration. This study was produced from Bedriye Açıkgöz Yıldız's Medical Specialty Thesis.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: In patients with diabetes mellitus (DM), complications due to hyperglycemia decrease the quality of life and increase mortality. Vitamin D deficiency and thyroid dysfunction negatively affect blood glucose regulation. We aimed to demonstrate effects of treatment of vitamin D deficiency and thyroid dysfunction on blood glucose regulation. This study aimed to reduce the complications that may develop due to hyperglycemia.

Methods: In this retrospective cohort study, Type 2 DM patients admitted to our clinic between 2015-2018 were reviewed from hospital registry. Patients who did not attend to their control visits for DM at the 0th, 3rd and 6th months and those with the exclusion criteria were not included. Patients who regularly attended diabetes controls at the 0th, 3rd and 6th months were determined. Among them, those with 25-hydroxy (OH) vitamin D, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial blood glucose (PPG), free T4, free T3, thyroid stimulating hormone (TSH) values in the hospital registry were sought. Patients with vitamin D deficiencies and thyroid disorders who began treatment at the 0th month were finally included in the study, and the effects of vitamin D replacement treatment and thyroid dysfunction treatment on blood glucose regulation parameters at the 3rd and 6th months were examined.

Results: HbA1c levels significantly decreased in Type 2 DM patients whose vitamin D levels were within normal limits at the 3rd month after receiving vitamin D replacement therapy (P=0.023). Vitamin D and HbA1c levels at the 3rd month controls were negatively correlated (r=-0.23, P=0.016, respectively). There were no significant differences in FBG and PPG levels at the 3rd month (P=0.063, P=0.361, respectively). In type 2 DM patients with hypothyroidism at the 0th month who were euthyroid at the 3rd month, there were no statistically significant differences in HbA1c, FBG and PPG (P=0.202, P=0.14, P=0.40, respectively). Six type 2 DM patients became euthyroid at the 3rd and 6th months after beginning levothyroxine treatment at the 0th month, and six patients became euthyroid at the 3rd and 6th months after hyperthyroidism treatment. Two patients had their FBG, and PPG values measured. Due to the insufficient sample size, statistical significance of differences in HbA1c, FBG and PPG levels could not be determined.

Conclusion: Vitamin D replacement treatment had positive effects on blood glucose regulation in DM patients with vitamin D deficiency. The effects of vitamin D on blood glucose regulation should be evaluated by HbA1c. Thyroid dysfunctions were not sufficiently questioned during the three-month follow-up of DM patients, so its effects on blood glucose regulation could not be evaluated. Thyroid dysfunction should be questioned in the 3-month follow-up of DM patients and thyroid function tests should be requested.

Keywords: 25 hydroxy Vitamin D, Thyroid dysfunction, Type 2 diabetes mellitus, Blood glucose regulation

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Introduction

Type 2 diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia, insulin resistance, and impairment of insulin secretion [1]. It is thought that insulin resistance, involved in the pathogenesis of type 2 DM, is reduced by the anti-inflammatory and immunomodulatory activity of vitamin D. Also, vitamin D may predict the progression of insulin resistance to type 2 DM [2,3]. Vitamin D acts on insulin receptor gene regulation through calcium metabolism and vitamin D receptors. It has been shown that adequate levels of vitamin D are effective in the release of insulin from pancreatic beta cells [4]. The main form of circulating vitamin D is 25-hydroxy (OH) vitamin D. The most important parameter that shows the amount of vitamin D in our body is 25 OH vitamin D [5]. Type 2 DM patients often have low 25 OH vitamin D levels, which could be associated with high fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) levels [6].

Type 2 DM and thyroid dysfunction are two often concomitant endocrinopathies. Both hyperthyroidism and hypothyroidism are more common in type 2 DM patients compared to those without diabetes. Thyroid hormones affect the lipid and glucose metabolisms [7]. By effect of thyroid hormones, phosphoenolpyruvate carboxykinase enzyme, which increases gluconeogenesis in the liver, is activated. Increased gluconeogenesis causes peripheral insulin resistance by inducing hyperinsulinemia [8]. Hyperthyroidism, subclinical hyperthyroidism, and hypothyroidism impair glycemic control in type 2 DM patients [7]. In addition, antithyroid drugs may worsen glycemic control [8].

In this retrospective cohort study, vitamin D replacement treatments were given to patients with Type 2 DM and 25 OH vitamin D deficiency, and thyroid dysfunction treatments were administered in patients with Type 2 DM as necessary. We aimed to demonstrate the effects of both treatments on diabetes regulation.

Materials and methods

Research method and study population

In this retrospective cohort study, patients diagnosed with Type 2 DM who were admitted to the Internal Medicine Outpatient Clinic of Afyonkarahisar Health Sciences University Medical Faculty Hospital between 2015 and 2018 were scanned from the hospital file system. A total of 4488 files with a diagnosis of DM were accessed. The exclusion criteria were as follows: Patients with chronic renal failure (GFR<60 ml/min), short bowel syndrome, chronic diarrhea, inflammatory bowel disease, history of gastrectomy, history of chronic pancreatitis, celiac disease diagnosis, bone metabolism disorders (rickets, osteomalacia, osteogenesis imperfecta), malignancy, osteoporosis, receiving oral/ intravenous/subcutaneous osteoporosis treatment, primary hyperparathyroidism, and being pregnant. The inclusion criteria were as follows: Type 2 DM patients who attended the regular control visits at the 0^{th}, 3^{rd} and 6^{th} months and were tested for 25 OH vitamin D, HbA1c, FBG, postprandial blood glucose (PPG), free T4, free T3, thyroid stimulating hormone (TSH) levels. Among variables, FBG, PPG and HbA1c parameters, which are the most related to blood glucose regulation, were selected. Patients with type 2 DM who met the exclusion criteria (n=896) and did not attend regular control visits (n=3329) were excluded from the study. Patients with both vitamin D deficiency and thyroid dysfunctions were not included to find out which treatment affected blood glucose regulation parameters. A total of 263 patients with 25 OH vitamin D, HbA1c, FBG, PPG, free T4, free T3, TSH levels at the 0^{th} month were included. Among them, the number of patients with vitamin D deficiency and thyroid dysfunction at the 0^{th} month were 168 and 53, respectively.

According to Turkish Endocrinology and Metabolism Society (TEMS) guideline, serum 25 OH vitamin D levels >20 ng/ml were considered normal, serum 25 OH vitamin D levels between 10-20 ng/ml were considered deficient, and serum 25 OH vitamin D levels <10 ng/ml were considered severely deficient [9, 10].

Patients with vitamin D deficiency at 0^{th} month who received vitamin D replacement therapy, those with thyroid disorders who received relevant treatment and whose Hba1c, FBG, PPG levels were examined at the 3^{rd} and 6^{th} months were determined. The effects of vitamin D replacement and thyroid dysfunction treatment on blood glucose regulation parameters were examined.

Statistical analysis

When evaluating the findings obtained in the study, IBM SPSS Statistics 26 (SPSS IBM, Turkey) program was used. Pearson- Fisher Chi-Square test and Fisher Exact test were used for comparison of categorical data. Descriptive data were presented as frequencies and percentages. The compliance of continuous variables to normal distribution was checked with the Shapiro Wilk test. Study data were presented as mean (standard deviation). Paired Sample T test was used for pre-post comparison of normally distributed continuous variables and Friedman test was used for multiple repeat comparisons. The Wilcoxon test was used for the pre-post comparison of continuous variables that did not show normal distribution. All data were evaluated at 95% confidence interval and values of $P<0.05$ were considered statistically significant.

Results

Among these 263 patients, the number of patients with vitamin D deficiency at baseline was 168 (63.8%). 72.6% (n=122) of the patients with vitamin D deficiency were female and 27.4% (n=46) were male. Severe vitamin D deficiency was found in 65.6% (n=80) of the female and 54.3% (n=25) of the male patients, and vitamin D deficiency was found in 34.4% (n=42) of females and 45.7% (n=21) of males. Severe vitamin D deficiency was significantly more common in females compared to males ($P=0.002$) (Table 1).

Severe vitamin D deficiency and vitamin D deficiency occurred most frequently between the ages of 50-70 years in type 2 DM patients.

One hundred and six patients had vitamin D deficiency at admission, received replacement therapy and had their HbA1c levels along with their vitamin D levels tested at the 3^{rd} month. The vitamin D levels of these patients returned to normal, and the mean HbA1c levels decreased from 7.19 (1.90) % at the 0^{th} month to 6.97 (1.81) % at the 3^{rd} month ($P=0.023$). Vitamin D

and HbA1c levels at 3rd month were weakly negatively correlated (r=-0.23, *P*=0.016) (Table 2).

Table 1: Distribution of vitamin D levels and gender of patients with type 2 diabetes mellitus and vitamin D deficiency at first admission

	25 OH vitamin D		
	Deficiency (10-20 ng/mL)	Severe Deficiency (<10 ng/mL)	Total
Female	42	80	122 (% 72.6)
Male	21	25*	46 (%27.4)
Total	63	105	168

* Female and male were compared in terms of severe 25 OH vitamin D deficiency, it was statistically significant (*P*=0.002).

Table 2. Laboratory parameters of patients who received vitamin D replacement therapy at 0 months and had normal vitamin D levels at 3th month

		0th month			3rd month					
	n	mean (SD)	Median	Min-max	mean (SD)	Median	Min-max	*P*-value[1]	r^2	*P*-value[2]
HbA1c (%)	106	7.19 (1.90)	6.73	4.45-15.5	6.97 (1.81)	6.39	4.35-13.1	0.023*	-0.23	0.016*
FBG (mg/dl)	93	161.5 (100)	109.2	42-654	147.4 (75)	106.4	81.5-578	0.063	- 0.353	<0.001*
PPG (mg/dl)	27	217 (106.74)	204	77.9-576	198.54 (89.43)	200	52.4-441	0.361	-	-

[1] Comparison of 0th and 3rd month laboratory parameters, [2] Correlation between 3rd month vitamin D level and laboratory parameters, * It is statistically significant (*P*<0.05). HbA1c: glycated hemoglobin, FBG: fasting blood glucose, PPG: postprandial blood glucose

Thirty-one patients had vitamin D deficiency at admission, received replacement therapy and had their HbA1c levels along with their vitamin D levels tested at the 3rd and 6th months. The vitamin D levels of these patients returned to normal, and the mean HbA1c levels did not change significantly. There was no correlation between vitamin D and HbA1c levels at the 6th month (Table 3).

Table 3: Laboratory parameters of patients who received vitamin D replacement therapy at 0th month and had normal vitamin D levels at 3rd and 6th months

		0th month			3rd month			6th month					
	n	mean (SD)	Median	Min-max	mean (SD)	Median	Min-max	mean (SD)	Median	Min-max	*P*-value[1]	r^2	*P*-value[2]
HbA1c (%)	31	6.71 (1.02)	6.86	4.19-11.4	6.78 (1.29)	6.75	4.17-9.7	6.79 (1.36)	6.79	4.16-9.95	0.053	0.147	0.430
FBG (mg/dl)	27	163.9 (70.65)	131	82.2-573	142.8 (51.25)	129	74.8-306	152.5 (65.70)	137	78.7-335	0.496	- 0.157	0.408
PPG (mg/dl)	6	219.94 (106.74)	256	217-334	194.54 (89.4)	205	112-361	214.73 (101.21)	228	54-351	-	-	-

[1] Comparison of 0th, 3rd and 6th month laboratory parameters, [2] Correlation between 36th month vitamin D level and laboratory parameters, HbA1c: glycated hemoglobin, FBG: fasting blood glucose, PPG: postprandial blood glucose

Ninety-three patients had vitamin D deficiency at admission, received replacement therapy and had their FBG levels along with their vitamin D levels tested at the 3rd month. The vitamin D levels of these patients returned to normal, but FBG levels did not differ significantly within that time (*P*=0.063) (Table 2). A low but significantly negative correlation was found between the 3rd month vitamin D and FBG levels after vitamin D replacement treatment (r=-0.353, *P*<0.001).

The FBG levels of patients who were given vitamin D replacement treatment at admission and had their vitamin D levels return to normal at the 3rd and 6th months (n=27) are shown in Table 3. No statistically significant difference was found between FBG levels (*P*=0.496), (Table 3).

The PPG levels of patients who were given vitamin D replacement treatment at baseline and had their vitamin D levels return to normal at the 3rd month (n=27) are shown in Table 2. There was no statistically significant difference between PPG levels (*P*=0.361). No correlation was found between 3rd month PPG and vitamin D levels (Table 2). The mean PPG levels of 6 patients who received vitamin D replacement therapy and had their vitamin D levels return to normal at the 3rd and 6th months after vitamin D replacement treatment were examined, but statistical significance could not be determined due to the insufficient sample size.

In our study, 53 type 2 DM patients had thyroid dysfunction at admission. The number of patients with newly diagnosed thyrotoxicosis and over hypothyroidism at baseline were 1 and 1, respectively. These two patients were not included in the study because of the small sample size. The number of patients diagnosed with type 2 DM and hypothyroidism at baseline, who became euthyroid at the 3rd month after receiving levothyroxine replacement treatment was 40. The mean HbA1c level of these 40 patients at baseline was 6.61 (1.26) %, which increased to 6.91 (1.76)% at the 3rd month (*P*=0.202). FBG levels were examined at baseline and the 3rd months in 37 patients. The mean FBG levels at baseline and the 3rd month were 129.3 (33.7) mg/dl and 150 (64.6) mg/dl, respectively (*P*=0.14). PPG levels at baseline and at the 3rd month were examined in 17 patients, with mean PPG levels of 173 (50.3) mg/dl, and 182 (69.6) mg/dl, respectively (*P*=0.40).

The number of patients diagnosed with type 2 DM and hypothyroidism, who received levothyroxine replacement treatment and became euthyroid at 3rd month and were followed up as euthyroid at 6th month was 6. The statistical significance of differences among the HbA1c, FBG and PPG levels of these patients could not be determined due to the insufficient sample size.

The number of patients diagnosed with type 2 DM and hyperthyroidism who received treatment and had their HbA1c levels tested at the 3rd and 6th months were 6. Among hyperthyroidism patients, the number of patients who were tested for FBG and PPG levels at baseline, 3rd, and 6th months were 2. Statistical significance of differences could not be determined in terms of HbA1c, FBG and PPG levels in these patients due to insufficient sample size.

Discussion

Type 2 DM is one of the leading causes of early morbidity and mortality worldwide. Type 2 DM's micro- and macrovascular complications have negative effects on quality of life and increase health expenditures [11]. In addition to its effects on the musculoskeletal system, vitamin D has various other important roles, such as the secretion of insulin from pancreatic beta cells and decreasing insulin resistance in type 2 DM [3, 12].

In the National Health & Nutrition Examination Survey (NHANES) study conducted on 4495 adult participants, the vitamin D deficiency rate was 41.6% [13]. In a study of 2488 patients conducted in Turkey, vitamin D deficiency rate was 24% [14]. However, in these studies, patients were not divided into groups according to DM presence.

Bayani et al. [15] included 120 diabetic and 120 non-diabetic patients in their study and found vitamin D deficiency in 64.2% of diabetic patients and 36.6% of non-diabetic patients. Parallel to this study, vitamin D deficiency was 63.8% among diabetic patients in our study. This rate was similar to that reported in the literature. Holick et al. [16] determined that 25 OH vitamin D levels were below 15 ng/ml in 28% of 242 patients. In their study, the presence of diabetes and female gender constituted higher risk for vitamin D deficiency. Similar to the study of Holick, in our study, vitamin D deficiency was more common in women with DM.

In a meta-analysis of 11 prospective studies, 3612 type 2 DM and 55.713 healthy participants were examined, and a

negative correlation was found between 25 OH vitamin D levels and the presence of type 2 DM [17]. In the NHANES study conducted between 2003 and 2006, Kositsawat et al. [16] examined the relationship between 25 OH vitamin D and HbA1c levels in 9773 adults and found that they were negatively correlated among DM patients. In another meta-analysis conducted by Mirhosseni et al. [18], 24 clinical studies (n=1528) were evaluated and the effects of vitamin D replacement in type 2 DM patients were examined. Although the duration of vitamin D administration varies in studies, the average is three months. In 10 studies, significant decreases in HbA1c levels were detected with vitamin D replacement compared to placebo. However, no significant differences were found in FBG levels. In the meta-analysis conducted by Wu et al. [19], HbA1c levels were examined in 24 studies and FBG levels, in 18 studies. When vitamin D replacement was given to type 2 DM patients for more than three months, Hba1c levels were found to decrease significantly (P=0.001), but FBG levels remained similar. The review of Lee et al. [20] evaluated HbA1c levels in 19 studies and FBG levels in 16 studies and stated that vitamin D replacement decreased HbA1C, but no changes were seen in FBG levels.

Similar to these studies, in our study, we found that after vitamin D replacement treatment, HbA1c levels found to decrease at the 3rd month, which shows the positive effect of vitamin D on blood glucose regulation in patients with DM. In addition, negative correlations found between HbA1c and 25 OH vitamin D levels at the 3rd month supports our thesis.

After vitamin D replacement treatment for three months, there were no significant decreases in FBG and PPG levels. FBG and PPG levels may be affected by many factors such as increase or decrease in the patient's fasting time, waiting time in the outpatient clinic, white coat syndrome, and hospital stress. FBG and PPG levels show blood glucose levels obtained at the time, but HbA1c levels show the 3-month average glucose levels. Therefore, we think that it would be more accurate to evaluate the effect of vitamin D replacement treatment with HbA1c levels.

Krul-Poel et al. [21] included type 2 DM patients in a double-blind, randomized, placebo-controlled study. Of these DM patients, 129 received a monthly vitamin D replacement treatment while 132 received placebo. After 6 months, no differences were found in HbA1c levels. Like Krul-Poel, we found that vitamin D replacement treatment did not affect HbA1c levels at the 6th month. The reason why Vitamin D replacement treatments have no effect on HbA1c levels at the 6th month may be attributed to the fact that vitamin D levels change seasonally (summer-winter). We think that long-term studies should cover at least 1 year, so that factors that affect vitamin D levels such as the duration of sun exposure can be considered. Type 2 DM and thyroid dysfunction are two endocrinopathies that are frequently seen together. Many studies have compared diabetic patients with a control group and more thyroid dysfunctions were observed in diabetic patients [7]. Elgazar et al. [4] investigated thyroid dysfunctions in 200 diabetic patients and 200 healthy controls. They found hypothyroidism in 7%, subclinical hypothyroidism in 13%, hyperthyroidism in 3%, and subclinical hyperthyroidism in 6% of the diabetic patients. Thyroid dysfunctions were detected in 5% of the control group. They stated that thyroid dysfunctions, especially subclinical hypothyroidism, were more common in diabetic patients. In their study of 713 type 2 DM patients, Jali et al. [22] found that thyroid dysfunction was more common among females. Similar to these studies, we observed that thyroid dysfunctions are common in DM patients and most of the DM patients with thyroid dysfunction are females.

Some studies have shown worsening of glycemic control in diabetic patients with thyroid dysfunction. Hage et al. [23] stated that glycemic controls were worse in the population of patients with thyrotoxicosis. In the study conducted by Ogbonna et al. [24], 354 type 2 DM patients were examined, and HbA1c levels were higher in patients with thyroid dysfunction. Bilic-Komerica et al. [25] examined 100 patients with subclinical hypothyroidism, 38 of which were found to be diabetic. After 6 months of levothyroxine treatment, HbA1c and FBG levels of these patients decreased significantly.

In our study, HbA1c levels of the hypothyroid patients at the 3rd month whose levothyroxine doses were increased at admission were similar. This may be due to the small sample size. The reason for the small sample size is that diabetic patients are not questioned in detail in terms of thyroid dysfunction in outpatient settings. When we wanted to examine the relationship between DM and thyroid dysfunctions at 0, 3, and 6 months of follow-up, we found that the number of patients who were followed up regularly for DM at 3-month intervals and whose thyroid hormone parameters were examined was insufficient. Insufficient parameters show that DM patients are not sufficiently questioned in terms of thyroid dysfunctions during their control examinations. Another reason for this may be that HbA1c levels can be requested at 3-month periods, but there is no such restriction in thyroid function tests. In other words, it may be caused by the fact that DM patients were examined at different times for diabetes and thyroid functions. Therefore, we could not evaluate the relationship between DM and thyroid dysfunctions at the 6th month of follow-up. More comprehensive studies are needed in larger populations to reveal the relationship between the two.

Limitations

The results obtained from the study are limited mainly because of the retrospective nature of this study, and the lack of DM patients who attended their 3-month check-ups regularly. We were unable to access patient information before 2015 due to the change in the hospital file system. Also, the number of cases of hypothyroidism and hyperthyroidism were relatively low. Finally, FPG and PPG levels were not examined together in each follow-up visit of the patients with thyroid dysfunction.

Conclusion

Considering the increase in the number of patients diagnosed with DM, attention should be paid to vitamin D and thyroid dysfunction, which may affect blood glucose regulation. Vitamin D replacement treatment had positive effects on blood glucose regulation. The effect of vitamin D replacement treatment on blood glucose regulation should be evaluated by HbA1c. While evaluating the effects of vitamin D levels on blood glucose regulation in the long term, it should be noted that the normal ranges of vitamin D vary seasonally (summer-

winter). Therefore, we think that the studies should cover at least 1 year if the effects of vitamin D replacement treatment on blood glucose regulation were to be evaluated.

Although thyroid dysfunction frequently accompanies DM, we found that thyroid function tests were not examined in the 3-month follow-up of DM patients. In this context, the history of thyroid dysfunctions should be questioned in all DM patients and thyroid function tests should be obtained.

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Comparison of ovarian striation and ovarian fragmentation in a rat model of ovarian insufficiency

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Primary ovarian insufficiency (POI) is defined as the depletion of the primordial follicle pool in women under the age of 40. New methods for stimulating ovarian follicle cells are being investigated in order to ensure the continuity of the menstrual cycle and fertility. The present study aimed to compare follicle reserves after ovarian striation or ovarian fragmentation in rats with ovarian insufficiency.

Methods: Thirty adult female rats in the estrus phase were randomized into three groups. Group 1 and Group 2 were medicated with intraperitoneal 7.5 mg/kg paclitaxel to create ovarian insufficiency. Group 3 was the control group, and intraperitoneal 3 mL 0.9% sterile saline solution was administered. The first laparotomy was performed to evaluate ovarian insufficiency 1 week after chemotherapy. In Group 1, the right ovarian cortex was striated using an insulin injector. In Group 2, the right ovary was divided into five parts. These five pieces were transferred to the pocket created under the right pelvic peritoneum. In Group 3, only laparotomy was performed. After 1 month, all rats underwent a second laparotomy, and the number of ovarian follicles (primordial, primary, secondary, antral) were compared, as were their serum follicle-stimulating hormone (FSH) and estradiol (E2) levels.

Results: There was a significant difference in the number of follicles among all three groups ($P<0.05$). The number of follicles (primordial, primary, secondary, antral) was significantly higher in the striated group than in the fragmented group ($P<0.001$). There were no statistically significant differences between the three groups in terms of mean serum FSH and E2 values measured at the second laparotomy ($P>0.05$).

Conclusion: Ovarian striation on the ovary cortex may be a new method for the treatment of ovarian insufficiency.

Keywords: Follicle count, Fragmentation, Ovarian insufficiency, Ovarian striation, Rats

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Introduction

Primary ovarian insufficiency (POI) is defined as the depletion of the primordial follicle pool and the permanent seizure of menstruation in women under the age of 40 years [1]. Usually, when the number of follicles declines below 1000 (considered the threshold value) follicular development and/or activation do not occur [2]. The prevalence of POI is reported to be approximately 1–3.7% and chemotherapy has been shown to cause increased risk [3, 4]. Patients with POI show symptoms of estrogen deficiency at an early age and they experience infertility problems due to impaired follicular development and ovulation. The probability of spontaneous pregnancy in patients after the diagnosis of POI can be 5–10% [5]. In patients with POI whose oocytes cannot be obtained, oocyte donation is recommended as an effective treatment [3].

Ovarian transplantation has been the subject of research for more than half a century. The first orthotopic transplantation of ovaries and cryopreservation in mice was reported by Parrott in 1960 [6]. The first live birth with ovarian cryopreservation in a human was reported by Donnez et al [7]. However, other methods of follicle stimulation have been explored in other studies. Recently, Kawamura et al. reported that follicle development can be stimulated by fragmentation and in vitro activation (IVA) [8].

In addition to ovarian fragmentation, new methods for stimulating ovarian follicle cells are being investigated. Several authors have explored the possibility of activating dormant cells via physical manipulation on the ovary, such as causing damage with an oocyte pick up needle, laparoscopic grasper, or scissor [9, 10]. These studies have reported promising results, but it is apparent that current evidence is insufficient to determine the comparative efficacy of such methods.

In the current study, we used a model of ovarian insufficiency in rats and applied striation and fragmentation to compare these two methods in terms of the changes in ovarian follicle reserves and the levels of follicle stimulating hormone (FSH) and estradiol (E2).

Materials and methods

Animals

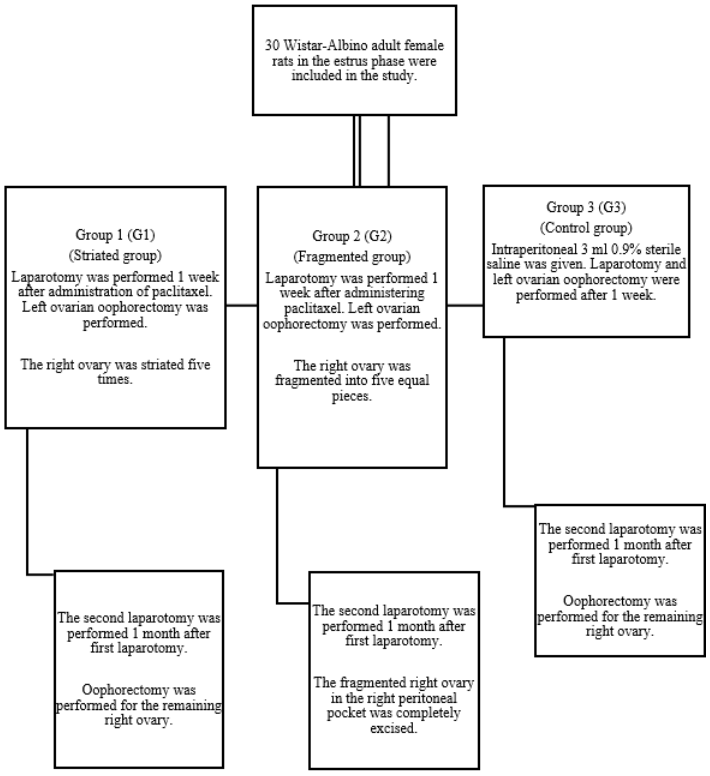
Ethics committee approval was obtained from the University of Health Sciences Experimental Application and Research Center (HSEARC) Ethics Committee (Date:5.3.2019/No:4). Thirty adult female Wistar-Albino rats (16 weeks old, 200–250 grams) in the estrus phase were included in the study. The study was conducted at the HSEARC in accordance with the National Institutes of Health guidelines (NIH Publications No. 8023, revised 1978) for the care and use of animals. The rats were kept in a wire cage with a maximum of four rats per cage, under controlled light (12 hours light/12 hours dark), at 22–24°C, with a humidity level of 45–55%. Food (standard rodent chow) and water (tap water) were provided ad libitum.

All animals were followed daily by research staff for pain-related behavioral changes in addition to the routine controls performed by veterinary staff at the research center. Weight was measured on a weekly basis and recorded. Any need for urgent interventions were immediately reported by veterinary staff or researchers after daily checks, and the principle investigator responsible for animals was contacted to decide a course of action (intervening or euthanizing for humane purposes).

Experimental Design

The 30 adult female Wistar-Albino rats (in the estrus phase) were divided into three groups. Group 1 (G1) (n=10) and Group 2 (G2) (n=10) were administered intraperitoneal 7.5 mg/kg paclitaxel (Taxol, Bristol Myers Squibb, New York, USA) in the estrus phase to create ovarian insufficiency [11]. Group 3 (G3) (n=10) was the control group and received intraperitoneal 3 mL 0.9% sterile saline solution in the estrus phase. One rat from each of the G1 and G2 groups died on the third day after chemotherapy administration. Ovarian insufficiency was evaluated after 1 week, since the average estrous cycle is 4 days in rats. Before laparotomy was performed under anesthesia, all rats in the G1 (n=9), G2 (n=9), and G3 (n=10) groups were administered intraperitoneal ketamine (40 mg/kg; Ketalar, Pfizer, New York, USA) and xylazine (10 mg/kg; Rompun, Bayer, Leverkusen, Germany). The schematic representation of the study design is shown in Figure 1.

Figure 1: Flow chart of the study design



The primary outcome assessed in this study was follicle count after the fragmentation and striation procedures in rats with ovarian insufficiency, and the comparison of groups in terms of this result. Secondarily, we also aimed to determine whether there were hormonal changes associated with these procedures.

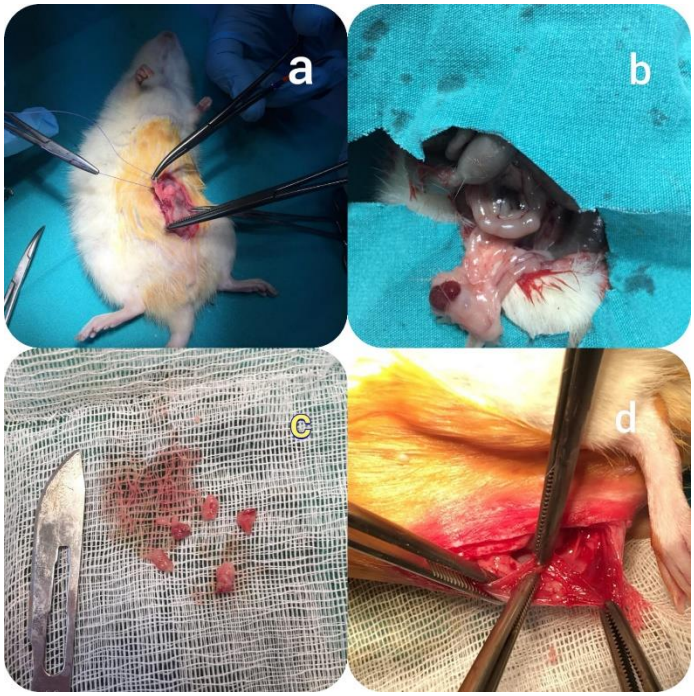
First laparotomy

The abdomen was aseptically prepared and a 3-cm vertical incision was made with a no. 11 scalpel, providing access through the midline. The surgical field was irrigated at regular intervals to reduce fluid loss. Left ovarian oophorectomy was performed in all rats. In the G1 (striated) group (n=9), the right ovarian cortex was striated five times with an insulin

injector at a width and depth of 1 mm. To increase consistency, all procedures were performed by the same operator. In the G2 (fragmented) group (n=9), the same operator performed all fragmentation procedures using a sterile ruler to divide the right ovary into five equal parts. These were kept in 0.9% sterile saline solution for about 15 minutes and were then transferred to the pocket created under the right pelvic peritoneum with the help of a cannula (Figure 2). In the G3 (control) group (n=10), laparotomy was performed, and the abdomen was closed after the completion of oophorectomy (left ovary). However, one rat in this group died after administration of anesthesia, reducing the number of rats in the control group to 9. A blood sample (1.5 ml) was taken from the tails of all rats to study serum levels of follicle stimulating hormone (FSH) and estradiol (E2).

After procedures and blood withdrawal, the rats were administered 3-5 ml of saline (0.9% NaCl) to compensate for fluid loss.

Figure 2: Images of the procedures; a) The right ovary after the striation procedure; b) The aspect of the striated right ovary during the second laparotomy; c) A fragmented ovary; d) The pocket created under the right pelvic peritoneum to transfer the fragmented ovary.



Second laparotomy

The second laparotomy of each animal was performed 1 month after the first via the same approach. However, during the second procedures, one rat from the G3 group died after the administration of anesthesia. At this point, there were a total of 26 rats left (G1=9, G2=9, G3=8). In the striated group (G1), oophorectomy was performed in the remaining right ovary. In the fragmented group (G2), the pocket containing the fragmented ovary (right pelvic peritoneum) was completely excised. In the control group (G3), oophorectomy was performed in the remaining right ovary. Following the respective procedures, the abdomen was closed. In all groups, 1.5-ml blood samples were obtained from the vena cava inferior to study serum FSH and E2 levels.

At the end of the experimental procedures, all 26 rats were euthanized. Cervical dislocation was performed under anesthesia using ketamine (75 mg/kg) and xylazine (10 mg/kg). The results of any animals that had died prior to intended sacrification were excluded from the analyses.

Hormone analysis

All blood samples taken from the tail veins of rats were drawn into Becton Dickinson vacutainer gel tubes. Centrifugation was performed at 2000g for 8 minutes and sera were obtained. The serum FSH and E2 levels were measured with ELISA kits according to the manufacturer's guidelines (Wuhan USCN Business Co., Wuhan, China). Briefly, the procedure was as follows: 50 µL of samples and standards were added to each well, followed by the immediate addition of 50 µL of prepared Detection Reagent A. The plate was mixed by shaking, and incubated for 1 hour at 37°C. After aspirating and washing three times, 100µL of the prepared Detection Reagent B was added to the wells. The tubes were then incubated 30 minutes at 37°C. After aspirating and washing five times, 90 µL of Substrate Solution was added. The final incubation was performed for 10–20 minutes at 37°C, followed by the addition of Stop Solution (50 µL) and immediate measurement at 450 nm wavelength on a Biotech ELx800 device. In the second laparotomy, the serum FSH and E2 levels were studied twice, from samples obtained after the first and second laparotomy procedures.

Follicle count and morphological analysis

The G1, G2, and G3 oophorectomy materials and the fragmented ovary in G2 were fixed with 10% formaldehyde for pathological examination. The tissues were embedded in paraffin blocks for 24 hours, and serial sections of 4 µm thickness were obtained. The entire ovarian surface was sectioned for follicle count and morphological analysis. The sections were stained with hematoxylin and eosin (H&E). All preparations were evaluated at x400 magnification under light microscopy (Leica, Wetzlar, Germany) by the same histopathologist (Ö.K.), who was blinded to the study. The follicles were classified as primordial, primary, secondary, early antral, antral, and atretic according to the definitions in the study by Myer et al., as follows:

1. Primordial follicle: Including an oocyte encircled by a partial or full squamous layer.

2. Primary follicle: Including a single layer of cuboidal granulosa cells.

3. Secondary follicle: Including multiple layers of granulosa cells and no detectable antrum.

4. Early antral follicle: Including one or two small follicular fluid sites; Antral follicle: including one large antral space.

5. Atretic follicle: Including a degenerate oocyte because of apoptosis [12].

Follicles containing prominent nuclei were counted. After the first laparotomy, the oophorectomy materials were used to demonstrate whether ovarian insufficiency occurred in G1 and G2. The oophorectomy performed in the second laparotomy was used to investigate whether there was a difference in the number of ovarian primordial, primary, secondary, and antral follicles between the three groups (G1, G2, and G3).

Statistical analysis

SPSS 20 (SPSS Inc, Chicago, IL, USA) software was used for the statistical analysis. The nonparametric Kruskal-Wallis test was used to assess the differences between the continuous dependent variables and the Bonferroni correction

was utilized to determine pairwise differences. The results are expressed as median and minimum-maximum values, if not stated otherwise. Box-plot graphical presentation was used to visualize group comparisons. Statistical significance was defined as *P*-value <0.05.

Results

Ovarian hormone profile

The mean serum FSH value from the samples taken at the first laparotomy (G1, G2, G3) was significantly higher in G3 (the controls) than in G1 and G2 (P=0.002) (Table 1). There were no significant differences between the groups (G1, G2, G3) in terms of first laparotomy serum E2 values, and the serum FSH and E2 values from samples taken at the second laparotomy (P>0.05) (Table 1).

Table 1: Mean serum FSH and estradiol levels

Initial samples	Control (n=9) Median (Min-Max)	Striated (n=9) Median (Min-Max)	Fragmented (n=8) Median (Min-Max)	*P*-value
FSH (mIU/mL) †	7.25 (3.7-8.6)	3.96 (2.9-5.4)[a]	4.91 (3.9-5.7)[a]	0.002
E2 (pg/mL) †	107.9 (58-311)	84.84 (51-176)	78.30 (44-163)	0.599
Final samples				
FSH (mIU/mL) †	7.04 (4.1-10.0)	5.15 (3.8-6.7)	5.12 (3.8-5.5)	0.379
E2 (pg/mL) †	119.8 (44-310)	89.69 (47-435)	80.20 (52-138)	0.296

Same letter denotes the lack of statistically significant difference in pairwise comparison of the two groups (Bonferroni correction after >2-group comparison reveals significance). FSH: follicle stimulating hormone; E2: estradiol.

Evaluation of the number of follicles and histological analysis

When the left oophorectomy materials (initial samples obtained 1 week after chemotherapy) were examined, the number of primordial follicles, secondary follicles, antral follicles, and total follicle count were significantly higher in G3 (the control group) (P<0.005) compared to the other groups. Therefore, the chemotherapy treatment was successful in creating ovarian insufficiency in the G1 and G2 groups.

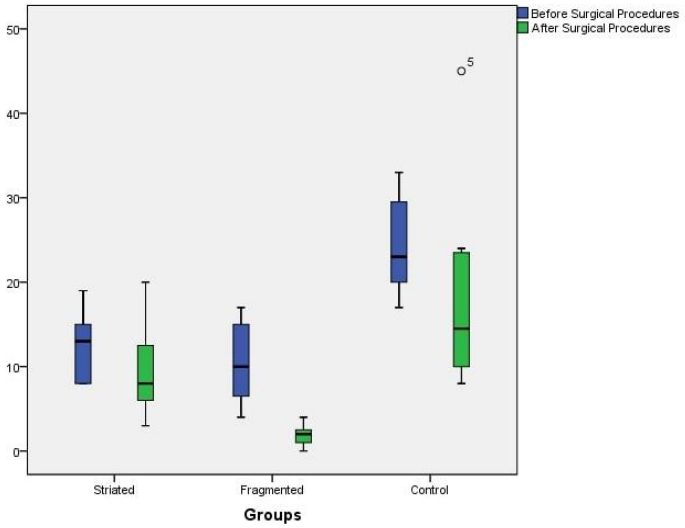
Evaluation of ovarian tissues after the second laparotomy (laparotomy + striation in G1, laparotomy + fragmentation in G2, and laparotomy in G3) demonstrated that there was a statistically significant difference in the number of follicles (primordial, primary, secondary, antral, and total follicle number) in the comparison of the three groups (P<0.05) (Table 2). The number of follicles (primordial, primary, secondary, antral follicles, and total follicle count) were significantly higher in G1 (Striated group) compared to G2 (Fragmented group) (P<0.001) (Table 2). The number of follicles after the striation and fragmentation procedures are depicted in box-plot graphical analysis (Figure 3).

Table 2: Follicle counts in the studied groups

Initial specimens	Control (n=9) Median (Min-Max)	Striated (n=9) Median (Min-Max)	Fragmented (n=8) Median (Min-Max)	*P*-value
Primordial follicles†	7 (3-10)[a]	5 (1-8)[a,b]	2 (1-6)[b]	0.003
Primary follicles†	3 (1-8)	3 (1-4)	2.5 (2-5)	0.477
Secondary follicles†	9 (5-13)	4 (2-9)[a]	3 (1-9)[a]	0.001
Antral follicles†	4 (3-10)	2 (0-5)[a]	1 (0-3)[a]	<0.001
Total number of follicles†	22* (17-33)	14 (8-21)[a]	10 (4-17)[a]	<0.001
Final specimens				
Primordial follicles†	4 (1-16)[a]	2 (1-5)[a,b]	1 (0-1)[b]	0.025
Primary follicles†	3 (1-7)[a]	1.5 (0-4)[a,b]	0.5 (0-2)[b]	0.004
Secondary follicles†	6.5 (3-17)[a]	3 (110)[a,b]	0.5 (0-1)[b]	0.003
Antral follicles†	2.5 (0-7)	2 (0-3)	0	0.002
Total number of follicles†	14.5 (8-45)[a]	8 (3-20)[a,b]	2 (0-4)[b]	<0.001

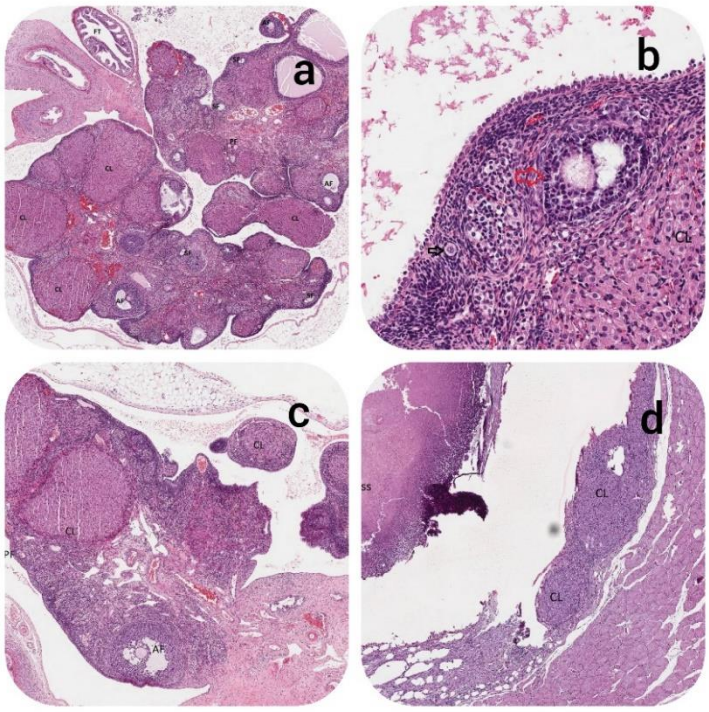
Same letter denotes the lack of statistically significant difference in pairwise comparison (Bonferroni correction after >2-group comparisons have revealed significant difference). FSH: follicle stimulating hormone; E2: estradiol.

Figure 3: Box-plot graphical analysis of the total number of follicles for the three groups.



Cellular degeneration and follicular atresia were more frequent after chemotherapy (G1 and G2) compared to controls (G3). Abscess and fibrosis had developed in the ovarian tissue of three rats in G2 which had undergone fragmentation (Figure 4). An increase in the size of the right ovary was observed in the striated group (G1), as determined by macroscopic examination during the second laparotomy (Figure 2).

Figure 4: Ovarian tissue samples; a) General ovarian morphology in control ovary [H&E staining, x20]; b) Primordial follicle and secondary follicle in control group [H&E staining, x200]; c) Minimal fibrosis secondary to paclitaxel administration in striated group [H&E staining, x40]; d) Abscess areas and corpus luteum in the fragmented ovary group [H&E staining, x40] CL: Corpora lutea; PF: Primary follicle; SF: Secondary follicle; AF: Antral follicle; FT: Fallopian tube



Apart from the deaths that were detailed in the previous section, no adverse events were recorded throughout the study.

Discussion

Chemotherapy agents used for cancer treatment in women can impair ovarian function, which may result in reversible or irreversible amenorrhea and infertility [13]. Permanent ovarian insufficiency after chemotherapy is more common in women >35-years-of-age. This is thought to occur due to age-related deterioration of the primordial follicle reserve [14]. Paclitaxel is a chemotherapeutic agent commonly used in the reproductive period for the treatment of epithelial cancer

[15]. In their study with mice, Gucer et al. [16] reported that paclitaxel reduced the number of primordial follicles in a dose dependent manner. In the study by Yucebilgin et al. [11], which utilized 7.5 mg/kg paclitaxel and 5 mg/kg cisplatin to create a model of ovarian insufficiency, it was reported that both agents were equally effective in causing ovarian insufficiency. Thus, we used paclitaxel to create ovarian insufficiency. Our results show that a 50% reduction was found in the number of follicles (primordial, secondary, antral, total) 1 week after chemotherapy.

Kawamura et al. reported that ovary fragmentation stimulated follicle development and mature oocyte formation via the Hippo signal mechanism [8]. They also noted stimulation of follicles and mature oocyte development with the use of AKT stimulators. In a remarkable study on mice by Li et al., the ovaries of animals were resected and placebo and activating treatments were administered. After the administration of treatments, both ovaries were placed under the kidney capsule of a host mice to stimulate the release of gonadotropin [17]. With this in vitro activation protocol, ovarian weight was reported to increase 3.4-times, and the number of antral follicles increased between 1.8- and 6-times in comparison to controls.

Polycystic ovary syndrome is a gynecological disease that causes anovulation. Ovary wedge resection or ovarian drilling methods have been used as surgical approaches to stimulate follicular development and achieve ovulation [18,19]. The mechanism of action of the ovarian drilling method is unclear [20]. In the oocyte pick-up procedure applied during in vitro fertilization, follicular aspiration, leads to follicle collapse. The remaining follicle cells are thought to undergo atresia after aspiration, but there are not enough studies on this subject to confirm this finding [10]. Ginther et al. hypothesized that the follicle content is filled after aspiration and that the follicle active components may not be completely damaged [21]. The appearance of the remaining ovarian tissue on ultrasonography 12–24 hours after follicle aspiration was suggested to demonstrate that steroidogenic activity continues in the residual follicle cells [22]. Furthermore, Viana et al. questioned whether residual follicular cells have a stimulating effect on follicular development before undergoing complete atresia [10]. Drawing from these studies, we investigated whether forming striation on the ovary cortex would be more effective than ovarian fragmentation in terms of stimulating follicles in the presence of ovarian insufficiency. In our study, there was no significant increase in the number of follicles after the striation procedure. However, the decrease in the number of follicles in the ovarian fragmentation group was significantly higher than in the striation group. Moreover, we observed that abscess and fibrosis developed in three rats whose ovarian pieces were placed under the parietal peritoneum. This finding indicates that blood supply may be impaired after relocation of ovaries. Interestingly, in a case report by Stern et al., it was found that ovarian pieces placed in the right pelvic peritoneum, left pelvic side wall, and in the atrophic left ovary showed activity in all three regions after cryopreservation [23]. However, in another study, it was reported that ischemia/reperfusion injuries may occur during cryopreservation, which may reduce the number of follicles [24]. C

Considering the varying results and conflicting findings, it is apparent that many factors could have an impact on the outcome, including technique, operator experience, and the blood supply potential of the inserted tissue. In addition, it should be noted that fragmentation is more invasive than striation. Furthermore, we did not apply stimulator therapy or vitrification in our study. Therefore, the effect of stimulator therapy on the ovaries must be investigated in further research.

We used paclitaxel chemotherapy to successfully induce ovarian insufficiency within one week. As such, the possibility of ongoing effects (of chemotherapy) on ovaries in the G1 and G2 groups should be considered as a cause of continued reduction in follicle count. The findings reported in previous studies support this view. In a study in which patients underwent chemotherapy for cancer (mean age: 34), the researchers found that mean anti-Mullerian hormone levels were 0.4 ng/mL 1 year after chemotherapy [14]. In agreement, a study by Decanter et al. reported that AMH levels continued to decline until 6 months after seizing chemotherapy [13]. Moreover, ovarian surgery itself may also have a negative effect on ovarian reserve. In a meta-analysis investigating the effect of oophorectomy on ovarian reserve, it was reported that ovarian reserve decreased after unilateral oophorectomy [25]. This may have affected the lower number of follicles observed after the second laparotomy in the control group.

We believe that utilizing the same operator in all interventions prevented inter-operator differences, which is an important advantage. We also attempted to ensure standardization by using a sterile ruler when applying treatments. To the best of our knowledge, this is the first study to compare ovary striation and ovarian fragmentation methods for the stimulation of follicles in the presence of ovarian insufficiency.

Limitations

Since rat ovaries are small, an insulin injector was used to striate the cortex of the ovaries; thus, the manual creation of striation and fragmentation methods can be considered the limitations of the current study. Additionally, the species-related differences may also cause significant differences in the results of these procedures; thus, future studies should investigate whether the results would be similar when these procedures are performed on humans.

Conclusion

Trying to stimulate the follicles by creating striation on the ovary cortex may be a new method for the treatment of ovarian insufficiency. There is a need for additional studies to elucidate whether performing striation on the ovary capsule and using stimulating agents can be utilized to achieve follicle stimulation in the presence of ovarian insufficiency.

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Research article

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Ideal plate screw configuration in femoral shaft fractures: 3D finite element analysis

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The study protocol does not need ethics approval since it describes mechanical work.
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Abstract

Background/Aim: Plate screw fixation is an important method in femoral shaft fractures. Although there are many studies on plate screw fixation, the ideal plate screw configuration has not yet been determined. In our study, we investigated the optimal plate-screw configuration in femoral shaft fractures using the 3D finite element analysis method.

Methods: A fracture model was created by removing the segment from the femur model obtained from 3D computed tomography scanning. Five different fixation models were designed using a 4.5 mm diameter steel locked femoral shaft plate and different screw configurations. Screws with double cortex locks of 4.5 mm in width were used in different configurations. To evaluate the effect of screw diameter, a 5.5 mm diameter screw with a double cortex lock was used in one model. Static linear analyses of these prepared Finite Element models were performed using Ansys Workbench 2020 R2 Finite Elements software.

Results: The maximum stresses on the plate at the fracture sites were 156 MPa at 200 N, and 546 MPa at 700 N in model 1, 274 MPa at 200 N, and 784 MPa at 700 N in Model 2, 274 MPa at 200 N, and 959 MPa at 700 N in Model 3, 389 MPa at 200 N, and 1118 MPa at 700 N in Model 4, and 200 N is 274 MPa, and 961 MPa at 700 N in Model 5.

Conclusion: The stress on the plate in the fracture area increases in parallel with the increase in screw diameter, plate length and plate working distance. Filling all screw holes does not alter the stress on the plate at the fracture line level.

Keywords: Femoral fractures, Plate fixation, Screw configuration, Finite element study

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Introduction

Femoral shaft fractures are one of the most common fractures treated by orthopedists [1]. Its incidence is 0.01% [2]. It often occurs because of high-energy traumas, and is associated with polytrauma, open fractures, and multiple fractures [3]. In young patients, it is frequently caused by traffic accidents, falling from a height, gunshot injuries, and in elderly osteoporotic patients due to falling from same heights [1, 2]. Skeletal traction, plate and screw, intramedullary nail and external fixator are used in the treatment of femoral shaft fractures [4-6]. Intramedullary nailing is the gold standard in treatment [2, 3]. Plate fixation is recommended for fractures where intramedullary fixation is not suitable [7, 8].

In the follow-ups performed after fixation with the plate, the plate was broken at a rate of approximately 3.5% - 13.3% [9, 10]. It has been stated that most of the causes of failure of internal fixation materials are related to material fatigue [11]. There are many studies about the plate screw configuration [12-14]. However, there is still no consensus on the optimal plate screw configuration.

In this study, we aimed to investigate the best plate screw configuration in femoral shaft fractures using 3D finite element analysis method and contribute to the literature.

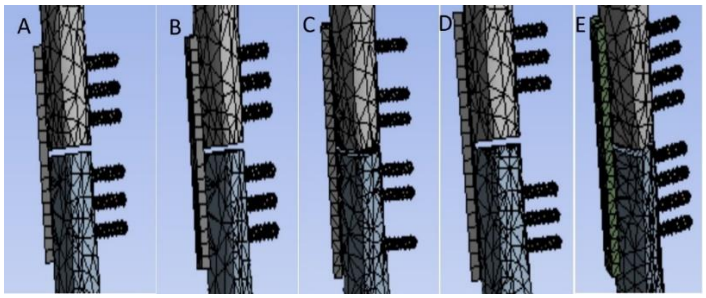
Materials and methods

Finite Element Method (FEM) is a mathematics-based calculation technique used in solving complex analytical structural problems. When creating a model resembling the human body, solid modeling programs such as Solid Works is utilized. This model is obtained from real CT scans using real computed tomography (CT) images. Modified solid models are produced in a problem-based solid modeling program, then transferred to a Finite Element Analysis software such as Ansys Workbench, a useful tool specifically for engineers [15].

In this study, 3-dimensional (3D) plates of different sizes, thicknesses and holes were created in Space Claim to be used in analysis. The femur model was obtained from 3D computed tomography scans used in previous studies in the literature [16,17]. In the 3D femur model, a fracture was created by removing the segment in the transverse plan from the femur diaphysis area. Plates were placed on the models and prepared for Finite Element Analysis under real loading conditions.

Five different fixation models were designed using a 4.5 mm diameter femoral shaft plate with steel lock and different screw configurations. Screws with double cortex locks of 4.5 mm in width were used in different configurations. To evaluate the effect of the screw diameter, a 5.5 mm diameter screw with double cortex lock was used in one model. In the first model, a 6-hole plate was used, and 3 screws of 4.5 mm diameter were placed the proximal and distal to the fracture. In the second model, a 6-hole plate and three screws with 5.5 mm diameter were placed proximal and distal to the fracture. In the third model, an 8-hole plate and 3 screws with locks placed with 4.5 mm between them were used. In the fourth model, an 8-hole plate and 3 screws were used. In this model, the working length was increased by leaving the screw holes closest to the fracture empty. In the fifth model, 8-hole plates and 4 screws were used (Figure 1).

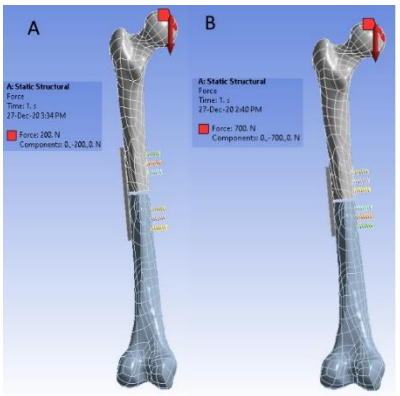
Figure 1: Schematic representation of the loads applied to the models. A: 200 N loading. B: 700 N loading



In this study, the following materials and properties were taken for the parts used in the model. Bone properties for femur: Modulus of Elasticity (E): 16.8 GPa, Poisson's Ratio (u): 0.47. Steel material was used for the plate, and the Modulus of Elasticity (E) was calculated as 200 GPa and Poisson's Ratio (u) as 0.3.

In the analyses, 200 N partial loading and 700 N full loading cases were used to test different loading cases, which were applied vertically to the proximal surface [12] (Figure 2).

Figure 2: Schematic representation of models. A:Model 1. B: Model 2. C: Model 3. D: Model 4. E. Model 5- MISSING PARTS



The connections between the plate, screws and femur were designed in the most realistic way, and the screws and femur connection were realized at the screw thread level. Thus, the distributions in the screw threads could also be obtained. In addition, the femur was fixed from the lowest part so that it could not displace in any direction. Static linear analyses were performed by importing these Finite Element models into Ansys Workbench 2020 R2 Finite Elements software.

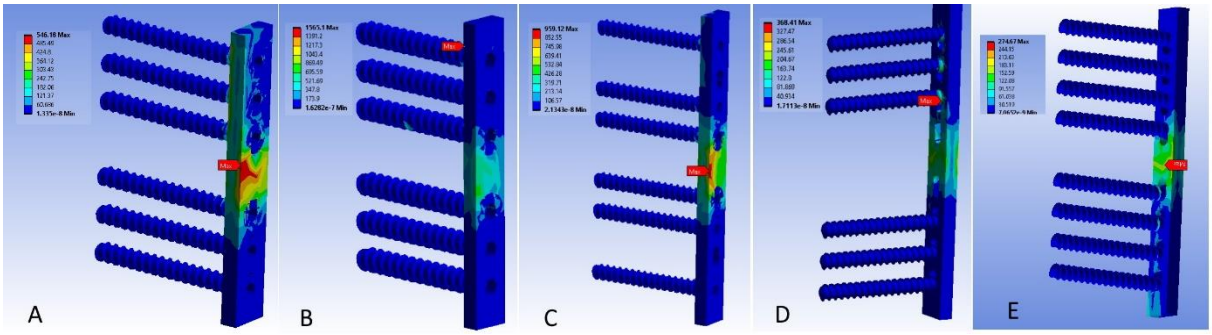
Results

As a result of the evaluation, we found that when the working length increased (the length between the two screws closest to the fracture), the load on the plate was higher in the fracture area. The maximum stress on the plate at the fracture site was 274 MPa at 200 N, and 961 MPa at 700 N in Model 5, and 389 MPa at 200 N, and 1118 MPa at 700 N in Model 4.

Comparing the filling of all screw holes in the 8-hole plate with spaced screws, we found that the stress on the plate was similar in both models. The maximum stress on the plate at 200 N was 274 MPa, and 959 MPa at 700 N in Model 3.

When the use of screws with a diameter of 5.5 and 4.5 mm was compared, it was observed that the stress on the plate at the fracture site was higher in the screws with 5.5 mm width.

Figure 3: Representation of finite element analysis. A:Model 1. B: Model 2. C: Model 3. D: Model 4. E. Model 5



We found that the stress on the plate at the fracture site increased with the plate length. The maximum stress on the plate at the fracture site was 156 MPa at 200 N, and 546 MPa at 700 N in Model 1, and 274 MPa at 200 N, and 784 MPa at 700 N in Model 2. (Figure 3) (Table 1).

Table 1: Stress distribution in models at different loads

	Model 1	Model 2	Model 3	Model 4	Model 5
200 N	156	274	274	389	274
700 N	546	784	959	1118	961

Discussion

Plate selection and screw configuration are important in solving implant failure and reducing complications in plate and screw osteosynthesis.

Plate working length is one of the most important mechanical parameters of plate systems and has a major impact on the mechanical environment and structural stability of the fracture site [18, 19]. Studies on plate systems with locks have revealed conflicting results. While some studies suggest increasing the length of the plate, there are opposing views in some others [20-25]. In our study, we found that increasing the working length increased the stress on the plate in the fracture site. Ellis T. et al. [25] found that increasing the working length in case of a gap in the fracture area correspondingly increased the stress on the plate, but if there was no gap in the fracture area, increasing the working length decreased the stress on the plate. In our study, we found a positive correlation between working length and stress on the plate.

Another important mechanical parameter in plate screw systems is plate length. Jianzhao Wang et al. [12] found that the increase in the length of the plate increased the stress on the plate but reduced the stress on the bone. In our study, we found that the increase in the length of the plate increased the stress load on the plate in the fracture area.

The location and configuration of the screws in the plate is another important parameter in plate and screw osteosynthesis. In a study they conducted, Wei Sheng et al. [13] found that the stress loads on the plate in nine different plate screw configurations of the same length were similar. They also found that the stress on the plate and femur increased significantly in the first and second screw holes near the fracture. In previous studies, it was stated that the use of screw holes near the fracture site had a great effect on the stress distribution in the plate fixation system [26, 27]. In our study, we observed that when we compared the filling of all screw holes and spaced screw placement in an 8-hole plate, the stress on the plate in the fracture line was similar in both groups.

Screw diameter also plays an important role in the mechanics of internal fixation [28, 29]. In their study comparing the screw diameters of 4 mm, 4.5 mm, 5 mm, Wei Sheng et al. [13] revealed that the highest stress on the plate was on the 4 mm screws. They showed that the most suitable screws were those with 5mm diameter. In our study, when the use of a 5.5 mm diameter screw was compared with the use of 4.5 mm, we found that the stress on the plate in the fracture line was higher in the model using 5.5 mm screws. This result was not in line with the study of Wei Sheng et al.

Limitations

Our study is a computer-aided biomechanical study, and biomechanical studies can be performed on cadavers related to the subject. Secondly, in our study, we examined plate screw fixation in two different lengths and five different configurations. Further studies on more models of different lengths and configurations could better demonstrate the biomechanical effects of plate and screw osteosynthesis. More comprehensive biomechanical studies are needed to determine the most appropriate screw plate configuration in plate-screw osteosynthesis.

Conclusion

As the plate's working length, screw diameter, and plate length are increased, the stress on the plate in the fracture area also increases. The reduction of the screws, provided that the screws were placed in the closest and furthest holes to the fracture, did not change the stress on the plate at the level of the fracture line.

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Outcome measures used in lower extremity amputation: Review of clinical use and psychometric properties

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Abstract

Decreased mobility and negative effects of poor functional status (FS) significantly reduce the quality of life in individuals with lower extremity amputation (LEA). These parameters should be evaluated in detail, and FS should be revealed. Measuring the results is important in terms of enabling clinicians to evaluate the quality of care and the effectiveness of treatment. The fact that the measurements are not purposeful makes the obtained results (evidence) and consecutively treatments unreliable. To obtain valid and reliable results, it is important to use measurement tools that are valid and reliable. Considering all these, the current FS should be evaluated using valid and reliable outcome measures (OMs). Numerous OMs are used to evaluate the FS of individuals with LEA. The multiplicity of available criteria, when coupled with the concept of multidimensional FS, complicates the selection of appropriate OMs for use with this population. Resources providing information about OMs used in the domain of LEA are limited in the literature. Many of the commonly used OMs are not included in the available sources. This review is designed to provide up-to-date information on clinical suitability and psychometric properties of OMs used in individuals with LEA. We believe that this study will help healthcare professionals serving in the field of LEA and prosthetics to learn about and choose the appropriate OMs.

Keywords: Amputation, Lower extremity, Outcome assessment, Health care, Psychometrics

Introduction

With the increased prevalence of vascular disease and increased life expectancy, lower extremity amputation (LEA) has become a prominent issue. In Australia, 3.400 LEAs are performed every year due to diabetes mellitus, which amounts to 12 amputations per 100,000 people [1]. If the increases in vascular disease and obesity continue, this rate is expected to increase further. Vascular dysfunction is responsible for 80-90% of LEAs in developed countries. Other causes of amputation include trauma, cancer, and congenital anomalies [2]. The need to evaluate the results of rehabilitation in LEA has become critical in healthcare centers. However, the use of outcome measures (OMs) by clinicians is limited due to insufficient knowledge of valid and reliable OMs. Clinicians not only determine the effectiveness of their interventions using the OMs but also show the positive effects of the intervention to the patient and third parties [3].

Since the decrease in mobility and negative effects of poor functional status (FS) in individuals with LEA will significantly affect the quality of life of the individual, these parameters should be evaluated in detail and FS should be revealed. Given all this, the current FS needs to be evaluated using valid and reliable measures. There are many OMs to evaluate the FS of individuals with LEA. The abundance of existing measures complicates the selection of appropriate OMs used in this population [4].

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In the literature, the sources that provide information about the OMs used in the LEA field are limited, and many of the commonly used OMs are not included in the available sources. However, it is worth noting the need for a study that provides up-to-date and detailed information on the clinical usefulness and psychometric properties of these OMs. This review was designed to provide up-to-date information on clinical use suitability and psychometric properties of OMs used in LEA. The reviewed OMs in this study indicate the most common clinical measures that can be used for assessing the functional abilities and the quality of life in individuals with LEA during the treatment process. This study also describes OMs that are simple to administer and require restricted resources, and, for this reason, could be easily applied in a clinic. This study will help healthcare professionals serving in the field of LEA and prosthetics to learn about and choose the appropriate OMs.

Functional status

Health professions have become responsible not only for the treatment of acute diseases but also for the management of chronic diseases and disability. The World Health Organization (WHO) has developed classification systems to ensure the integrity of concepts and standardize measurement within the healthcare profession following this paradigm shift. The International Classification of Functioning, Disability and Health (ICF) was approved by WHO member states in 2001. In ICF, there are concepts of capacity, ability and performance. FS covers a range of functional areas including individual's thoughts, feelings and overall health-related quality of life, including physical functions such as step activities and walking, the ability to work and maintain a job, psychosocial and emotional functions [5]. Evaluation of FS is important in clinical and scientific research. The clinician records his practices, decides on the choice of treatment and prepares a report on the effects of the selected treatments. The need to record changes in the FS when combined with the complexity and diversity of the FS has led to the development of numerous OMs [6].

Outcome measure types

The way the result measure is applied determines the type of information obtained. The capacity, capability, and performance parameters existing in ICF provide important information about the FS of the individual. Self-report measures such as surveys evaluate capacity, while performance-based measures evaluate also real-world performance along with capacity. Ease of application and the low cost is effective in the widespread use of self-report measures in the clinic. Self-reporting measures include surveys and interviews and do not require extensive additional training for practitioners. The weaknesses of the self-report measures are that they are subjective. Patients may show their capacity more or less than they are. Therefore, the data obtained from the self-report measures may not be a true reflection of the FS. Factors such as culture, language, educational background, cognitive impairment, and depression affect the person's responses to self-report measures [7]. Performance-based measures enable more objective data to be obtained and have the potential to provide quantitative data that enable quantitative analysis as well as evaluating the change in FS [8].

Psychometric properties of outcome measures

Psychometric properties should be taken into account when choosing the outcome measure [9]. The scales and assessment methods used in clinical and academic studies must be valid and reliable to obtain accurate results. Reliability, defined as the consistency of repetitive measurements, is the feature of obtaining similar results from repeated measurements in the same sample. High reliability means that the standard error is low. Reliability types are test-retest, parallel forms, split half, intra-rater and inter-rater reliability, and Cronbach alpha. Evaluation in intra-rater reliability is done by looking at the intraclass correlation coefficient (ICC) if the measurement values are numeric, and by looking at the kappa coefficient of Cohen if the measurement values are categorical. The ICC value ranges from 0 (no consistency) to 1 (full consistency). In inter-rater reliability, the measurement values are evaluated by looking at the ICC if they are numerical, while in categorical terms, the alignment between the evaluators' measurements is expressed as a percentage. Evaluation in test-retest reliability is done by looking at the ICC. Validity is whether the measurement tool can measure the variable to be measured, and if it measures, to what extent it measures the structure it is designed to measure. Validity types are content validity, construct validity, predictive/criterion validity, face validity, and concurrent validity [10].

Outcome measures used in lower extremity amputation

1. Self-report outcome measures

Activities-specific balance confidence scale (ABC)

ABC is a 16-item scale that measures the ability to perform various daily life activities without falling. During the 16 increasingly difficult functional activities, the individual is asked to score the level of confidence felt between 0-100. The scale score is calculated by dividing the total score otained by 16. A higher score indicates a higher balance of confidence. It has been found reliable in individuals with transtibial and transfemoral LEA (ICC for test-retest reliability: 0.91, Cronbach alpha for internal consistency: 0.95). Convergent validity of the scale was supported by 2-Minute Walk Test (2MWT) (r: 0.72) and Timed Up and Go Test (TUG) (r: 0.70). It has been reported to be valid in evaluating balance confidence in individuals with LEA and its use has been proposed [11-13]. The scale, which has high test-retest reliability, internal consistency, and validity, has been reported as suitable for clinical use [14].

Amputee body image scale (ABIS)

ABIS evaluates the situations and experiences that the individual with amputation feels and perceives about her body and consists of 20 items. In the scale, in which the items are scored between 1 and 5 points, the total score varies between 20 and 100, and a high score indicates that body image distortion is high. It is valid and reliable in evaluating body image in individuals with LEA [15]. The internal consistency (Cronbach alfa: 0.834-0.842) and test-retest reliability (ICC: 0.94) of the scale were excellent [16].

Hospital anxiety and depression scale (HADS)

HADS evaluates symptoms of anxiety and depression. It consists of two separate sections that measure the cognitive and emotional aspects of depression (HADS-D) and anxiety (HADS-

A). It has a four-point (0-3 points) Likert scoring scale. High scores from the sections indicate that the risk is high in terms of depression and anxiety. It has been reported that its internal consistency is high (Cronbach alfa; HADS-D: 0.67-0.90, HADS-A: 0.68-0.93), its validity is supported by other scales, and it has sufficient sensitivity and specificity [17]. Its usage is available in individuals with LEA [18].

Socket comfort score (SCS)

It has been reported that 50% of transfemoral amputees and 70% of transtibial amputees use their prosthesis at least seven hours a day. Considering this, it is important to evaluate the comfort with the prosthesis. SCS evaluates the perceived comfort within the prosthetic socket between 0 (uncomfortable) and 10 (most comfortable) point. The use of SCS is suggested because it is easy and simple [11].

Special interest group for amputee medicine (SIGAM)

It is a scale consisting of 21 items used to evaluate mobility level in individuals with LEA. Mobility level is determined by six functional levels (A, B, C, D, E, F). Progress from A to F indicates that the mobility level has increased. It has been reported that internal consistency (Cronbach alfa: 0.67) and test-retest reliability (ICC: 0.82) are high, and external construct validity, convergent and discriminant validity are supported by other scales. It is valid and reliable for use in individuals with LEA [19].

Prothesis evaluation questionnaire-mobility scale (PEQ-MS)

Mobility Scale (PEQ-MS) is a combination of PEQ's ambulation and transfer subscales. It consists of thirteen items with an 11-level numeric rating scale. It evaluates the capacity including transfer and ambulation with a prosthesis for the past four weeks. A high score indicates that the individual has high mobility with the prosthesis. Internal consistency (Cronbach alpha: 0.95) and test-retest reliability (ICC: 0.77) were high in individuals with LEA. Validity based on correlations between PEQ-MS and TUG (r: 0.50), 2MWT (r: 0.50) and ABC Scale (r: 0.85) was confirmed. It has been reported to have excellent reliability and validity for use in individuals with LEA [14, 20-22].

Houghton score (HS)

It evaluates the use of prosthesis and mobility with the prosthesis in individuals with LEA. It consists of four items with a 4-level numeric rating scale. The maximum scale score is 12, and the high score indicates that mobility level and confidence are high. According to the scale score, gait ability is classified into three categories. The test-retest reliability, concurrent validity and internal consistency of the scale were high. The predictive validity of the scale was examined and found to have a high correlation with PEQ-MS (r: 0.73), ABC (r: 0.76), TUG (r: 0.67) and 2MWT (r: 0.73) [14].

Locomotor capability index (LCI)

It evaluates locomotor skills and level of independence in individuals with LEA. Items are scored between 0-3 points on the scale consisting of fourteen items. The highest score is 42, and the higher score indicates higher locomotor capacity and independence [9]. It has a version using a five-point rating scale (LCI-5). It has been reported that both LCI and LCI-5 exhibit sufficient internal consistency, test-retest reliability and construct validity [23]. In different studies, ICC and Croncbach alpha values of the scale were found between 0.95-0.96. Its validity and reliability have been confirmed and it is stated to be correlated with HS [9, 24].

Trinity amputation and prosthesis experiences scales (TAPES)

It is used to determine the level of prosthesis compatibility and evaluate the functional level. In the two-part scale, the first part consists of psychosocial accordance, activity limitation and satisfaction with the prosthesis. The second part consists of eight items that evaluate daily prosthesis use time, general health, physical capacity, phantom limb pain, and residual limb pain [25]. It has been reported that the scale has minimum floor and ceiling effect, high internal consistency (Cronbach alpha: 0.72-0.86), high reliability and validity [9, 25, 26].

Orthotics prosthetics users survey (OPUS)

OPUS consists of four components. The lower extremity FS component is assessed with 20 substances with a five-point rating, while the quality-of-life component is assessed with 23 substances with a five-point rating. The prosthetic satisfaction and prosthetic service satisfaction components are evaluated with 10 and 11 items, respectively, with a four-point rating [27]. The scale can distinguish between different levels of FS, quality of life and level of satisfaction. The test-retest reliability (ICC: 0.50-0.85) and internal consistency (Cronbach alpha: 0.78-0.98) scale is suitable for use in individuals with LEA [9].

Satisfaction with the prosthesis questionnaire (SATPRO)

SATPRO consists of 15 items with triple Likert scale that evaluate the satisfaction of the individuals with the prosthesis. The scores of the 6^{th}, 12^{th} and 14^{th} items, which are asked negatively, are reversed. While calculating the survey score, the total score obtained is divided by the highest score that can be taken from the marked questions, and the result obtained is multiplied by 100. The highest score (45 points) that can be obtained in the survey shows 100% satisfaction and the lowest score (0 points) shows the minimum satisfaction [28]. Internal consistency (Cronbach alpha: 0.90), test-retest reliability (ICC: 0.97) are reported to be high, valid and reliable [28, 29].

Mobility questionnaire for lower extremity prosthesis users (PLUS-M)

PLUS-M is a 44-item mobility scale developed for individuals with LEA and using prosthesis. Each item on the scale which evaluates mobility with prosthesis has a five-point rating. High score gaining from the scale indicates better mobility. The activities on the scale are linked to the two main forms of movement. The first form reports repetitive or continuous movements and the second form shows postural transitions such as moving from one activity or position to another activity or position. The items in the scale evaluate the achievement degree of activity and strain rather than the performance of the person during the activity. There is also a twelve-item short form. In the study where the construct validity of the short form was examined, there was a strong correlation between PLUS-M and PEQ-MS score (r: 0.81); a medium

correlation was found between AMP scores (r: 0.54) and TUG time (r: 0.56). PLUS-M has been reported to be structurally valid and suitable for clinical use [30].

2. Performance-based outcome measures

Amputee mobility predictor (AMP)

The scale, which evaluates the ambulatory potential of individuals with AEA, is available in two versions, with a prosthesis (AMP-Pro) and prosthesis-free (AMP-noPRO) use. However, published psychometric studies are only available for AMP-Pro. AMP-Pro consist of 21 items that evaluate transfers, sitting, standing balance and walking skills. Items in the scale are scored between 0-2 points, and the total scale score is 42. Higher scores indicate better functional ability. AMP-Pro has been reported to have excellent inter-rater (ICC: 0.99) and intra-rater (ICC: 0.96-0.98) reliability [31]. The scale, which has high construct validity and concurrent validity with the 6-Minute Walk Test (6MWT), has been reported as valid and reliable for the evaluation of functional ambulation in individuals with LEA. Taking into account the AMP-pro score, at which K group level the individual is determined according to Medicare Functional Classification Levels [9, 31]. K group levels range from K0 (the lowest) to K4 (the highest) and are used to identify the potential for functional mobility in individuals with AEA [31].

Comprehensive high activity mobility predictor (CHAMP)

CHAMP is a performance-based outcome measure improved for evaluating high-level mobility capacity. It consists of One-Leg Stand Test, Edgren Side Step Test, T-test, and Illinois Agility Test, which measure physical performance parameters such as balance, postural stability, coordination, strength, speed, and agility. Each of these four tests score between 0-10 points. The scores achieved from the four tests are collected and a scale score ranging from 0-40 is obtained. Higher scores indicate higher mobility capacities. In the study in which construct validity was examined, it was found that it had a strong correlation with 6MWT (r: 0.80) and AMP score (r: 0.87). It has been reported that inter-rater reliability (ICC: 1.0) and test-retest reliability (ICC: 0.97) are excellent [32]. It has been reported to be safe, valid and reliable in assessing high-level mobility in individuals with LEA [32, 33].

Berg balance scale

It consists of 14 tests that measure different positions, postural changes and the ability to maintain balance during movement. On the scale, the ability to perform each test independently at a specific time or distance is measured. Fourteen tests involve daily activities that include sitting, standing, lying down, and balance along with transfers, turning and taking an object off the ground. Each test is rated between 0 (the lowest function level) and 4 (the highest function level) points. The total score is between 0 (dependent) and 56 (independent), and higher scores indicate a better balance. 0-20 points indicate balance impairment (high risk of falling), 21-40 points indicate acceptable balance presence (moderate risk of falling) and 41-56 points indicate good balance. Inter-rater reliability (ICC: 0.94) and internal consistency (Cronbach Alpha: 0.82) were high in individuals with LEA. The scale has high convergent validity with the ABC scale (r: 0.63), PEQ-MS scale (r: 0.58), 2MWT (r: 0.68) and L Functional Mobility Test (L Test) (r: -0.80). [34]. It has been reported that the scale has high validity and reliability in evaluating balance in individuals with LEA [14, 34].

3. Evaluation of cardiovascular functions

Cardiovascular capacity is classified as aerobic and anaerobic capacity. Energy consumption during walking can be measured as oxygen consumption per minute. The amount of oxygen consumed per minute per kilo during maximum exertion is called maximum oxygen consumption capacity (VO2max). VO2max is considered the best outcome measure in the measurement of aerobic capacity. The tests used to evaluate aerobic capacity are divided into indirect and direct tests. Direct tests include maximal tests such as the Treadmill Test, Arm Ergometer Test, and Single-Leg Bicycle Ergometer Test. As indirect tests, submaximal field tests such as the Harvard Step Test, 12-minute Run-Walk Test, and 6MWT are used. Anaerobic capacity is assessed by the Wingate Test and The Vertical Jump Test, which includes submaximal loading [35]. In the evaluation of exercise capacity in individuals with AEA, Single-Leg Bicycle Ergometer Test, Arm Ergometer Test, Combined Arm and Leg Ergometer Test and Treadmill Test are used. Single-Leg Bicycle Ergometer Test and Treadmill Test are the most common laboratory tests used to measure VO2max. VO2max measured in these tests is expressed in milliliters/kilograms/minute (ml/kg/min) [36]. Laboratory tests that require expensive equipment and special training are time-consuming and difficult to implement. However, it has been reported that functional walking tests may be advantageous in assessing cardiovascular capacity [37].

Functional walking tests evaluate gait and exercise performance at a given time or distance. These tests that don't require expensive equipment and are easy to implement are divided into two as time-based tests (2MWT, 6MWT, 12-Minute Walk Test-12MWT) and distance-based tests (10-Meter Walking Test-10MWT). Time-based tests, in which energy expenditure can be assessed during walking, provide a submaximal measurement of functional capacity. Energy expenditure is determined by measuring oxygen consumption and its cost during gait. A strong correlation between time-based tests and VO2max was found in individuals with LEA. Measuring oxygen consumption with laboratory tests is time-consuming, difficult and costly, which is effective in carrying out the measurement together with walking tests [38]. 2MWT is suitable for clinical use with the advantages of short application time, less fatiguing, high reliability (ICC: 0.90-0.96) [39] and sensitive to changes [21]. 6MWT has been defined as a reliable measure of functional capacity [37] and indicator of energy expenditure [38] in individuals with LEA. 6MWT has been reported to have high reliability (ICC: 0.97) [21] and a strong correlation with 2MWT (r: 0.89) and 12MWT (r: 0.95) [40]. With advances in technology, portable tools such as pulse oximeter, which measures blood pressure, heart rate and oxygen saturation, and telemetry electrocardiography, which monitors heart rhythms, can be used during walking tests. Thus, it is possible to measure the basic OMs such as heart rate, oxygen consumption and oxygen cost, which are used to evaluate energy expenditure [37, 38].

4. Evaluation of gait

In the case of amputation, part of both the sensory and motor system is lost. With the loss of receptors that provide proprioceptive information from joints and other structures, the amount of proprioceptive input that provides information about the movement and position of the prosthetic limb in space decreases. Loss of motor control of the extremity occurs, and balance strategies are negatively affected. The musculoskeletal system performs more activity to maintain balance. This increases energy consumption and causes fatigue [41,42]. The ability of the individual to gait is adversely affected if he is unable to adequately perceive the position of his prosthesis in space. As a result of abnormal gait, functional capacity decreases and energy consumption increases. However, the economy of the gait declines. Assessment of gait is of great importance in the determination of deviations from normal walking, planning and implementation of appropriate treatment approaches and determining the effectiveness of treatment [42]. Different tests and measurements such as observational gait analysis, footprint method, kinematic and kinetic analysis, electromyographic analysis (dynamic EMG), 2MWT, 6MWT, 10MWT, TUG and L Test are used to evaluate gait in individuals with LEA. With the data obtained from these evaluations, information about the spatiotemporal parameters of gait (stance phase symmetry, single/double stride length, stride width) and functional gait performance (gait velocity, cadence, maximum gait velocity) is obtained [43].

Observational gait analysis

Gait is observed from the front, back and side with a specific sequence. Deviations and compensations from normal gait are noted. It is widely used in the clinic with the advantages of its application in a short time, no need for expensive equipment and specialized laboratories. However, the subjective side (depend on the evaluator's experience), the inability to quantify the results, the difficulty in identifying the primary causes of gait disorder are the weaknesses of this method. In observational analyses, the analysis can be done in conjunction with video recording, as it is difficult to simultaneously study moving body segments during gait. During gait, short video recordings are obtained from the front, back and both sides with the video camera placed at the height of the pelvis. The differences between evaluations can be examined by repeating video recordings. Joint angles can also be measured using special software [44].

Gait analysis by footprint method

In this analysis, the participant is asked to walk at his or her walking speed on a flat 10-meter tracer ground to determine the time-distance characteristics of gait. The two-meter section at the start and end is removed. The analysis is conducted through step marks in the six-meter area in the middle. With this method, step length, stride length, support surface, step width and foot angle can be determined on the amputee and non-amputee extremity. It is widely used in the clinic with the advantages of its application in a short time, its low cost, and not requiring private laboratories and training [41, 43].

Kinematic and kinetic analysis

The inability of the human eye to detect movements taking place within milliseconds has been instrumental in the development of computer-aided analysis methods that provide objective and numerical information. Using these methods, the components of gait (joint angle, strength, moment) that cannot be perceived with the eye can be recorded, converted to numerical data, and the resulting data can be compared in repeated evaluations. In the kinematic analysis, which examines the movements of the body in space, the joint angles, angular, linear velocity and acceleration of the body, pelvis, legs, and feet in three planes are measured and the results are recorded as numerical data. Thus, changes in joint angle, speed and acceleration can be calculated in addition to temporal and spatial characteristics during gait. In the kinetic analysis, the ground reaction force, moment, and force parameters affecting the joint are evaluated using special force platforms [44]. When force platforms are used together with kinematic analysis, moment and forces acting on the hip, knee, and ankle in three planes can be calculated. The use of these analysis methods is available for individuals with LEA [45].

Electromyographic analysis (Dynamic EMG)

The muscle activity that occurs during gait is recorded through surface electrodes. In dynamic EMG, EMG signals from electrodes are transmitted to the computer via wired or wireless systems. These signals are processed with special software and converted into numerical data that provide information about the timing and duration of contraction of muscles. In gait analysis, when dynamic EMG is used in conjunction with kinematic data, it can be determined which muscles show how much activity in which phase of the gait cycle. In this way, the pathological activity can be distinguished from compensatory activity. When used in conjunction with kinetic data, it can be determined which muscle has how much activity in the force and moments acting on joints by muscles [43, 44].

Timed up and go test (TUG)

The TUG test is a numerical measure of the maneuvers required for basic mobility, such as walking, balance, transfers and turning while walking. It is easy to use and interpret in the clinic, where the many maneuvers and gait capacity required for mobility can be measured numerically in individuals with unilateral LEA. The time to complete the test is recorded in seconds. Shorter completion time indicates higher capacity. The decrease in completion time can be interpreted as an improvement in basic mobility [22,46]. It has been reported to have high intra-rater (r: 93) and inter-rater (r: 96) reliability and convergent and divergent validity in individuals with LEA [22]. It is a valid and reliable test in assessing physical mobility in individuals with LEA [46].

L functional mobility test (L Test)

The L test, which assesses basic mobility skills in individuals with a unilateral LEA, is a modified version of the TUG. It is designed to reduce the TUG's ceiling effect. The distance covered in the test, which includes two transfers and four turns, is 20 meters. Completion time is recorded in seconds, and the decrease in completion time indicates an improvement in basic mobility. The distance covered in the L Test is longer than 10MWT and TUG, making the sensitivity of the test higher than these tests. It is more suitable for individuals with high activity levels of LEA. It is reported to have high inter-rater (r: 0.96) and intra-rater (r: 0.97) reliability. It was found to have a high

correlation with TUG (r: 0.93), 2MWT (r: 0.86) and 10MWT (r: 0.97), whose concurrent validity was examined [47].

Conclusions

Amputation is a permanent state of incapacity that restricts an individual's daily life activities and participation. The main goal of health professionals involved in the treatment and rehabilitation of amputees is to minimize the negative effects of inadequacy caused by amputation through appropriate prosthetic design and treatment methods. Thus, the quality of life of the individual can be improved. To achieve this goal effectively, the results of treatment, rehabilitation and prosthetic applications must be measured with appropriate methods. The need to measure treatment and rehabilitation outcomes has become critical in the current health environment. Measuring the outcomes is important in terms of enabling clinicians to evaluate the quality of care and the effectiveness of treatment. It is of great importance to use valid and reliable result criteria with which the necessary adaptations have been made to accurately measure the results. Clinicians not only determine the effectiveness of their interventions using the reliable and valid OMs, but they can also determine the cause of the problem, provide ideas on therapeutic interventions and potential solutions and show the positive effects of the intervention to the patient and third parties. By utilizing the suitable OMs, clinicians may obtain an overall idea of the health outcomes in individuals with LEA, increase satisfaction and prosthetic performance and reduce the cost of treatment. When clinicians incorporate OMs in daily practice, they may be able to evaluate various aspects of clinical care such as socket comfort, functional level, level of confidence with the prosthesis and quality of life with the prosthesis.

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Apoptotic colopathy in a pediatric autologous bone marrow transplantation patient with spontaneous colonic cast excretion: Is it due to GVHD or rotavirus infection?

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The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

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Abstract

Spontaneous colonic cast excretion per anus is a very rare entity. Colonic ischemia and severe infections are the most common etiologic factors. It is mostly seen in adults. Only one pediatric patient with colonic cast excretion was reported in the literature. We present a three-year-old male patient with the diagnosis of neuroblastoma who had undergone autologous BMT. After suffering a prolonged rotavirus infection, on the 25th the post-transplantation day, he presented with nausea, vomiting, abdominal pain, and spontaneous excretion of colonic mucosa-like material via defecation. The histopathological interpretation of the excreted material revealed acellular material composed of fibrin and neutrophils. The patient's colonoscopic biopsy specimen revealed crypt distortion, regeneration, and numerous apoptotic bodies within the crypt epithelium. Apoptotic colopathy and colonic cast excretion per anus is a sign of ischemia, which may be caused by severe intestinal infections or rarely, graft-versus-host disease. Therefore, a clinicopathological correlation was performed to reach a definitive diagnosis. The patient's symptoms were attributed to severe, prolonged rotavirus infection.

Keywords: Allogeneic, Bone marrow transplantation, Colonic cast, Rotavirus, GvHD

Introduction

Passage of intestinal casts per anus is an extremely rare entity. Severe ischemia, inflammation, bacterial and viral infections, and graft-versus-host disease are the etiological factors reported in the literature [1, 2]. Apoptotic bodies in crypt epithelium may be a sign of ischemic crypt damage, viral infections (mostly CMV), chemotherapy, and/or radiation exposure. It is also the characteristic form of cell death in gastrointestinal GVHD [3].

Although CMV is the most common microorganism associated with enterocyte apoptosis, other viral or bacterial infections may also be involved. We present an exceedingly rare entity of colonic cast excretion per anus in a pediatric bone marrow transplantation (BMT) patient with a review of the literature, discussing the differential diagnoses, and stressing the importance of clinicopathological correlation in reaching a definitive diagnosis.

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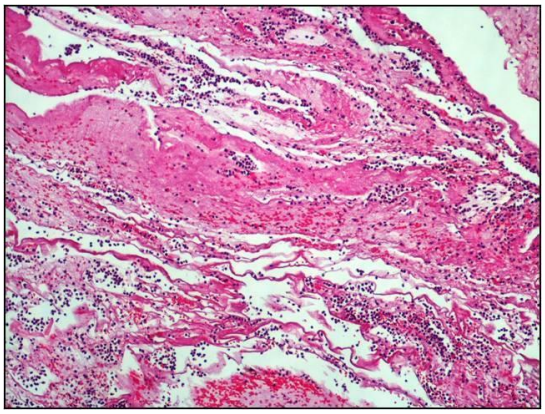
Case presentation

A three-year-old male neuroblastoma patient who had undergone autologous BMT 25 days prior presented with nausea, vomiting, abdominal pain, and spontaneous excretion of colonic mucosa-like material via defecation (Figure 1). His stool culture was positive for rotavirus one month ago when diarrhea began, and negative for clostridium difficile. The macroscopic pathological interpretation of the material was compatible with a colonic cast. The microscopic evaluation revealed casts composed of fibrin, neutrophils, sparse histiocytes, and mucus. Normal intestinal mucosal tissue was not observed (Figure 2). As the patient continued to excrete similar colonic casts, a colonoscopy was performed. Colonoscopic examination revealed edematous, granular, and hyperemic mucosa in the distal and prominent exudates and hyperemia in the proximal colonic segments. Endoscopic diagnosis was compatible with widespread colitis. The differential diagnoses included infectious, pseudomembranous, and ischemic colitis.

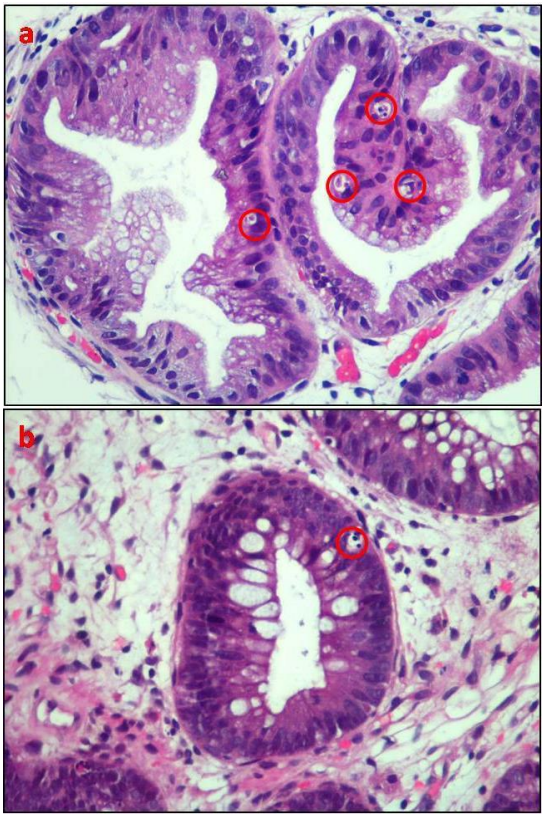
Figure 1: Spontaneously excreted colonic mucosa-like material

Figure 2: Casts composed of fibrin, numerous neutrophils, sparse histiocytes and mucus. Note that there is no normal intestinal mucosal tissue, (H&E, 200X).



The histopathological examination of the colonoscopic biopsy revealed crypt distortion, regeneration, and numerous apoptotic bodies within the crypt epithelium (Figure 3). Viral inclusions were not present and anti-CMV immunohistochemical antibody revealed negative immunoreaction. The pathological diagnosis was compatible with an “apoptotic colopathy.” GVHD and infections were included in the differential diagnoses. To avoid any potential diagnostic bias, we performed a clinicopathological correlation. Since the patient had received autologous BMT and the clinical symptoms were not compatible with GVHD, the patient’s prolonged rotavirus infection was considered the etiological factor.

Figure 3: Numerous apoptotic bodies within the distorted crypt epithelium (circles), (H&E, 400 X).



The patient received fluid and electrolyte therapy. A diarrhea diet was started, and intravenous immunoglobulin was administered every 10 days. The patient's complaints improved during the follow-ups.

Informed consent was received from the primary caregivers of the patient.

Discussion

Only 26 cases of colonic cast excretion per anus were reported in the literature. Most patients with colonic cast excretion (88%) were diagnosed with ischemic colitis.

In most cases (50%), the cause of colonic cast passage is colorectal cancer surgery or surgery for an abdominal aortic aneurysm. Ischemia secondary to operations was attributed to ligation of the inferior mesenteric artery or other bowel arteries [4]. The remaining patients developed colonic ischemia due to prior circulatory disorders.

Most previously reported cases were adult patients. In 2017, Nambu et al. [5] reported a 6-year-old pediatric patient with colonic cast excretion who had a fever, abdominal pain, and refractory diarrhea. The patient had neutropenia (<100 neutrophils/μl), as did our patient. The authors assumed that the patient might have had an autoimmune disorder mimicking inflammatory bowel disease but the exact etiological factor causing colonic cast excretion was not determined [5].

Similarly, Samee et al. reported a neutropenic adult patient with enteropathy and sepsis presenting with the excretion of intestinal casts. The casts contained numerous fungal elements that pointed out a fungal infection [1].

In the literature, the casts excreted by patients with ischemic colitis were composed of necrotic colonic mucosa, sometimes including the muscularis propria and serosal layers. In the present case, the casts were not histopathologically

compatible with colonic tissue or necrosis. They were composed solely of fibrin, large amounts of neutrophils, and scattered histiocytes, i.e., "fibrinopurulent casts."

In one of the reported cases, gastrointestinal GVHD was considered the etiological factor associated with excretion of the colonic casts [6].

GVHD is an immune-mediated complication of allogeneic BMT where graft T lymphocytes attack the tissues of the host [7]. Clinical symptoms of gastrointestinal GVHD are diarrhea, nausea, vomiting, and abdominal pain. Since many of these symptoms are nonspecific, confirmation by an endoscopic biopsy is often needed for both evaluation of the endoscopic findings and a clinicopathological correlation.

Although GVHD is considered a disease of allogeneic BMT patients, GVHD after autologous BMT has also been reported very rarely [7]. It has been reported after cyclosporine administration to patients who have received autologous BMT [8].

Because of the preceding prolonged rotavirus infection, the lack of GVHD findings in gastroscopy, and the fact that the patient was an autologous BMT recipient, apoptotic colopathy due to severe rotavirus infection was considered the pathological mechanism in the formation of colonic casts.

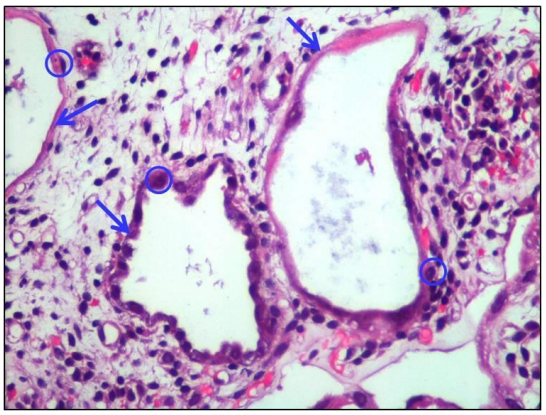
Acute diarrhea after BMT is generally due to GVHD or infection. The incidence of infection-related diarrhea in BMT patients is 40%-50%, mostly occurring in allogeneic BMT patients [9]. Viruses are the most common etiological factor of enteritis [10]. Rotavirus displays prominent tropism for the intestinal enterocytes and is accepted to be the major cause of viral gastroenteritis in pediatric patients [11]. The incidence of rotavirus in stool samples of BMT patients has been reported as high as 10%. In a series of 94 BMT patients with diarrhea, adenovirus, rotavirus, and echovirus were isolated from 20% of the BMT patients. In other case reports and smaller series, severe enteritis in BMT patients due to rotavirus have also been reported [10].

The mechanism of apoptosis due to rotavirus infection has been explained in many studies. The pathophysiology underlying apoptosis is explained by the increase in the concentration of intracellular calcium caused by the rotaviral enterotoxin nonstructural protein-4. Calcium induces the transition in mitochondrial permeability, leading to the release of cytochrome C from the mitochondria, an important condition during apoptosis [12]. SA-11 strain of rotavirus was reported to induce apoptosis in numerous cell types. Chaibi et al. [12] demonstrated that rotavirus infection caused apoptosis in intestinal caco-2 cells via an immune assay. In the present case, we also detected apoptotic bodies in the epithelial cells of cystically dilated and distorted crypts.

Alfajaro et al. [13] demonstrated villous epithelial desquamation, villus atrophy, and crypt hyperplasia in the later stages of rotavirus infections. Boshuizen et al. [14] described irregular nuclei in the enterocytes of the patients infected by rotavirus.

In the present case, histopathological findings other than apoptotic bodies included crypt hyperplasia, crypt distortion, dilatation, and irregularly located nuclei in the crypt epithelium, in line with the literature (Figure 4). In the literature, apoptotic colopathy cases due to mycophenolate use were also reported.

Figure 4: Irregularly located nuclei (circle) in the epithelium of the distorted and dilated crypts (arrows), (H&E, 400 X).



Patients with mycophenolate-related gastrointestinal toxicity typically present with afebrile, watery diarrhea with mostly insignificant or mild endoscopic findings. The histopathological changes in crypt epithelium in patients with a history of mycophenolate use included apoptosis in crypt bases, cystically dilated atrophic crypts, surface epithelium erosion, crypt architectural distortion, and eosinophils in lamina propria [15]. Our patient did not have a history of mycophenolate use.

Conclusion

We present the case of the first pediatric autologous BMT patient with apoptotic colopathy following prolonged diarrhea and resulting in the excretion of fibrinopurulent colonic casts per anus. This is a rare complication of colonic ischemia, severe enteritis, and very rarely, GVHD. In the present case, the etiological factor was a severe and prolonged rotavirus infection. The histopathological findings in the present case coincide with the findings described in the previous studies and case reports. If diarrhea is present in BMT patients, it is crucial to make a clinicopathological correlation and differentiate GVHD, because it requires a completely different treatment regimen, and if left untreated, it may result in mortality.

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A rare cause of hyperamylasemia: A case with pneumothorax and subcutaneous emphysema around the parotid gland in a trauma patient

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Abstract

Amylase is a common laboratory test in emergency departments, especially in trauma patients. Although hyperamylasemia is mostly caused by injury to the pancreas in trauma patients, non-pancreatic causes of hyperamylasemia are not rare. Being aware of these causes may prevent unnecessary diagnostic tests. In this study, we presented a trauma patient with hyperamylasemia of non-pancreatic origin. Possible mechanisms of hyperamylasemia in our case are acute hypoxia-induced hyperamylasemia because of left lung pneumothorax and massage-like activity of subcutaneous emphysema around the parotid gland.

Keywords: Hyperamylasemia, Acute pancreatitis, Pneumothorax, Subcutaneous emphysema, Parotitis

Introduction

Amylase is a common laboratory test in emergency departments and other clinics, especially during the examination of patients presenting with abdominal pain. Although serum amylase levels are used in the diagnosis of salivary gland and pancreatic disorders, they have been observed to increase in many diseases [1]. One of the most common causes of amylase elevation other than pancreatic diseases is salivary gland diseases such as acute parotitis, but it may rarely be due to the release of intracellular amylase of the lung tissue because of hypoxia [2]. In this case report, we aimed to discuss the etiology of hyperamylasemia that may be caused by pneumothorax and periparotid subcutaneous emphysema in light of the literature and raise awareness that hyperamylasemia may also be a result of non-pancreatic problems, especially in patients presenting with trauma.

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Case presentation

A 52-year-old male patient was brought to the emergency department after an in-car traffic accident. The general condition of the patient was moderate, he could not cooperate due to mental retardation. Head and neck, and abdominal examinations were initially normal. Pelvis fracture was present. There was no edema, laceration, or hematoma in the head and neck region. Cranial and abdominal computed tomography imaging were normal. Computed tomography of the thorax was consistent with minimal pneumothorax of the left lung. The laboratory findings of the patient on admission were as follows: WBC: 12.95 (4.4-11 $10^3/\mu l$), AST: 198 (0-40 IU/L), ALT: 167 (0-41 IU/L), amylase: 249 (28-100 U/L), lipase: 102 (0-60 U/L). The patient was admitted to the intensive care unit for close follow-up due to a pelvic fracture and minimal pneumothorax in the left lung. One day after hospitalization, abdominal examination was normal, breath sounds were decreased in the left hemithorax, and crepitus was detected in the left side extending from the lumbar region up to the neck and periparotid region that was consistent with subcutaneous emphysema. Control computed tomography of the thorax was consistent with extended pneumothorax of the left lung and subcutaneous emphysema from the lumbar region up to the parotid gland (Figures 1 and 2). The pancreas gland was normal on control abdominal computed tomography examination (Figure 3).

Figure 1: Coronal computed tomography scan, left pneumothorax and left sided subcutaneous emphysema extending form the lumbar region up to the neck

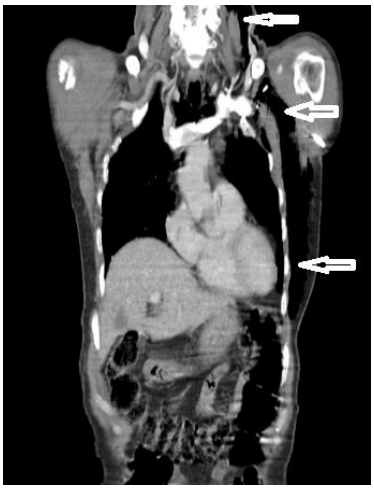


Figure 2: Axial computed tomography scan, subcutaneous emphysema around the parotid gland

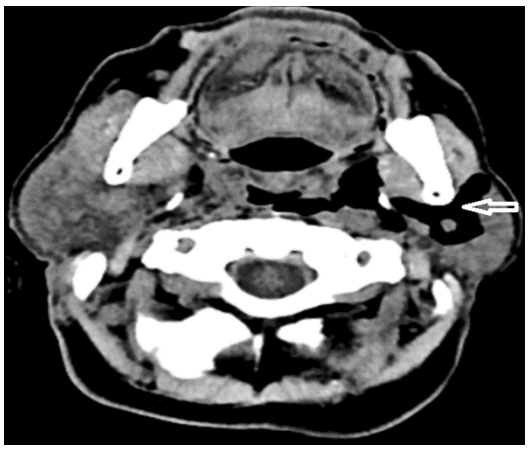
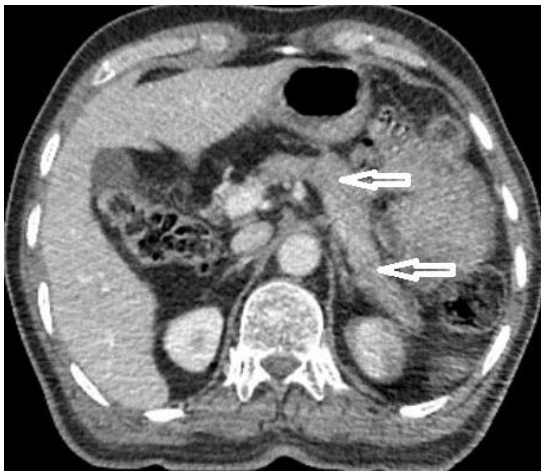


Figure 3: Axial computed tomography scan, normal looking pancreas gland with no pathology (White arrows)



There was no parenchymal abnormality in the parotid gland on ultrasonographic examination. After one day of hospitalization, control laboratory tests were as follows: WBC: 17.08 (4.4-11 $10^3/\mu l$), AST: 66 (0-40 IU/L), ALT: 92 (0-41 IU/L), amylase 753 (28-100 U/L), lipase 11 (0-60 U/L). The patient underwent a tube thoracostomy. On the first day of tube thoracostomy, amylase decreased from 753 to 471 U/L, and on the third day, it was 65 U/L. All biochemical laboratory findings returned to normal and subcutaneous emphysema completely regressed. The patient was discharged on the 9^{th} day of hospitalization. Informed consent was obtained from the patient.

Discussion

Hyperamylasemia can occasionally cause diagnostic confusion. Amylase is mostly released from the pancreas and salivary glands. Its serum level increases mostly in acute pancreatitis and salivary gland inflammation. Therefore, the pancreatic disease is usually suspected in cases of hyperamylasemia. However, amylase may be elevated in many other clinical conditions, such as salivary gland, gynecological, cardiovascular, neurological, renal, and gastrointestinal diseases [3]. Acute pancreatitis is diagnosed if two of the three following criteria are present: Abdominal pain, serum amylase-lipase levels three-fold of the upper reference range and accompanying imaging findings [4]. Elevated amylase levels without abdominal pain or imaging abnormality in the pancreas made us consider etiologic factors other than acute pancreatitis. Several studies have shown that lipase levels have higher sensitivity and specificity than amylase levels in the diagnosis of acute pancreatitis. The sensitivity and specificity of lipase elevation in patients with acute pancreatitis are between 85–100% and 84.7–99.0%, respectively [5]. In our case, although the level of amylase persisted above normal value, the lipase level was normal. Because of these reasons, acute pancreatitis was not considered in our patient and non-pancreatic causes of amylase elevation were investigated. Inflammatory diseases of the salivary gland are the leading non-pancreatic causes of elevated serum amylase. In our patient, no parenchymal damage was detected in the parotid gland. Pneumothorax in the left lung and emphysema around the parotid gland was thought to be two possible causes of amylase elevation. It was reported that the lung might serve as the site of origin for serum amylase activity under hypoxia [2]. Although its exact mechanism is unclear, it

may be due to the disturbance in cellular metabolism with a release of intracellular amylase. Jam et al. [2] reported that acute hypoxemia may raise serum amylase activity through ischemic injury to the pancreas or salivary glands. Li et al. [6] reported that acute respiratory failure increases serum amylase level of lung origin independent of parenchymal damage. Pneumothorax causing acute hypoxemia is one of the possible causes of hyperamylasemia in our patient. Evcimik et al. [7] found that massaging the parotid gland increases serum amylase activity in patients with acute parotitis, and not in patients with normal parotid parenchyma. Regardless, we thought that periparotid long-standing emphysema may cause an increase in amylase level despite normal parotid parenchymal architecture. This may be the second possible mechanism of hyperamylasemia in our case.

Conclusion

In trauma patients with elevated amylase levels, non-pancreatic etiology should be kept in mind. Acute hypoxemia because of left lung pneumothorax and subcutaneous emphysema around the parotid gland are the two possible causes of elevation in serum amylase levels in our patient. It is not known to what extent these two etiologic factors contribute to the increase in serum amylase. Although the role of acute hypoxemia is more well known, long-standing pressure on the parotid gland may have a massage-like activity that increases serum amylase. To the best of our knowledge, there is no study to investigate the relationship between subcutaneous emphysema around the parotid gland and serum amylase levels. A study on patients with subcutaneous emphysema around the parotid gland without pneumothorax will help us learn the effect of emphysema on serum amylase.

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Understanding Sjogren's syndrome through the neurologist's eye

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Abstract

Sjögren’s syndrome (SS) is an autoimmune disease characterized by mononuclear cell infiltration and destruction of the lacrimal and salivary glands, which causes dryness of the eyes and mouth. It has a wide clinical spectrum. It can manifest as focal lesions, including focal or motor deficits, stroke, or cerebellar syndromes. Central nervous system involvement should be kept in mind in patients with SS, as it may have serious consequences. Herein, we report a 60-year-old female patient who was misdiagnosed with cerebrovascular disease in the emergency department.

Keywords: Sjögren’s syndrome, Autoimmune disorder, Stroke

Introduction

Sjögren’s syndrome (SS) is a chronic autoimmune disorder that involves exocrine glands, such as the lacrimal and salivary glands. Its prevalence is estimated to vary from 0.5% to 5.0%. In SS patients, central or peripheral neurological involvement may occur with a frequency ranging from 10% to 60%. Neurological presentations may develop in a large spectrum, including optic neuritis, multiple cranial neuropathies, transverse myelitis, aseptic meningitis, encephalomyelitis, epilepsy, stroke, polyneuropathy, and cognitive involvement. In SS, the central nervous system (CNS) may be affected at a rate of 1.5-20.0%, while the peripheral nervous system (PNS) is estimated to be affected at a rate of 10%. The disease may present with neurological findings in 39% of cases [1-3]. In SS, neurological involvement is more common among women (4- to 30-fold) [4]. In this case report, we discuss a patient who presented with weakness and numbness in the left arm and leg and left half of the face who had diffusion restriction on magnetic resonance imaging (MRI) and was diagnosed with SS based on a detailed history and test results.

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Case presentation

A previously healthy 60-year-old right-handed female was admitted to the hospital with complaints of weakness and numbness in the left arm and leg and in the right half of face. The patient's complaints of weakness and numbness started 6 hours before her hospital admission. Her blood pressure was 200/95 mmHg in the emergency department. The patient had no additional neurological complaints, such as speech disorder or loss of consciousness. The patient had normal results from a brain computerized tomography (CT). However, diffusion MRI revealed diffusion restriction in the corresponding Apparent Diffusion Coefficients (ADC) in the left thalamic region, periatrial region, and at the level of left basal ganglia (Figure 1). Based on these findings, the patient was considered to have ischemic cerebrovascular disease and oral clopidogrel (300 mg) and acetylsalicylic acid (100 mg) were administered. The patient was then consulted with our neurological department. She did not have any autonomic symptoms. Her initial neurological examination revealed normal mental status. However, she had right central facial paralysis, right hemi-hypoesthesia involving the right half of face, and her muscle strength was 4/5 in the right upper and lower extremities. Deep tendon reflexes as well as the Hoffman and Babinski signs were negative. Cerebral MR angiography (MRA) was within the normal range. The lesions located in the left periatrial region and at the basal ganglia level showed a hyperintense signal increase on the T2W and FLAIR images (Figure 2, 3). Unenhanced T1W image lesions had an iso-hypointense signal, while contrast-enhanced T1W image lesions showed no enhancement (Figure 4, 5). P100 latency was prolonged (128 ms and 118 ms in the left and right eyes, respectively), on visual evoked potential test. Nerve conduction studies were normal. The patient had normal hepatic and renal function tests, hepatic panel, anti-HIV test, complete blood count, chest radiography, electrocardiogram, and Doppler evaluation of the carotid-vertebral arteries. Protein C, protein S, anti-thrombin III, homocysteine, lupus anticoagulant, anti-cardiolipin antibody, and erythrocyte sedimentation rate were also normal. Factor V Leiden mutation was negative. The ANA test was positive (titer: >1/1000 - <1/3200; granular, spotted pattern), while her anti-Ro (SS-A) and anti-La (SS-B) antibodies were 2+. Rheumatoid factor was elevated (287 IU/ml), and C3 and C4 were decreased (0.38 and 0.08 g/L, respectively). Oligoclonal bands (OCB) assay in cerebrospinal fluid (CSF) was negative. IgG index was normal (0.46). Schirmer test was positive (bilateral < 5 mm). Vitamin B level was 176 pg/ml, and therefore, intramuscular cyanocobalamin was prescribed. A rheumatology consultation was requested with the preliminary diagnosis of SS. No other suggestions were made by the rheumatologists. Since the patient received steroid therapy and fulfilled the SS diagnostic criteria, a salivary gland biopsy was not performed. Thus, treatment with methylprednisolone (1000 mg/day, IV, for 7 days) and azathioprine (2.5 mg/kg/day) was started. Methylprednisolone was maintained at an oral dose of 1 mg/kg/day after day 7. On the 10th day after admission, the patient had nearly a complete recovery in right facial paralysis, muscle weakness at the right upper and lower extremities, and right hemi-hypoesthesia. The patient consented to participate in the study.

Figure 1: Diffusion-Weighted Imaging (DWI) showing lesions located in the left thalamic region, periatrial region, and at the level of left basal ganglia. These lesions revealed restriction in corresponding Apparent Diffusion Coefficients (ADC).

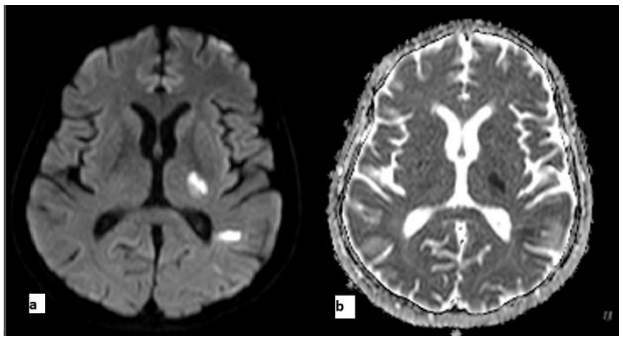


Figure 2, 3: The lesions located in the left periatrial region and at the basal ganglia level showed a hyperintense signal increase on the T2W and FLAIR images.

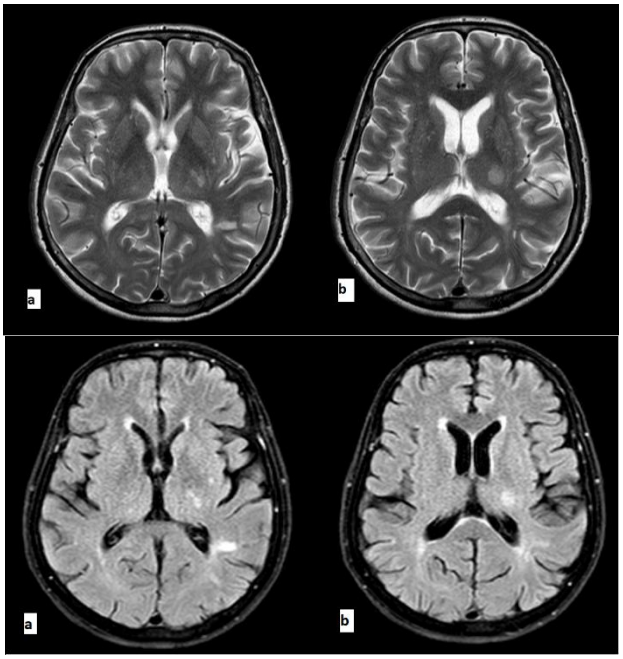
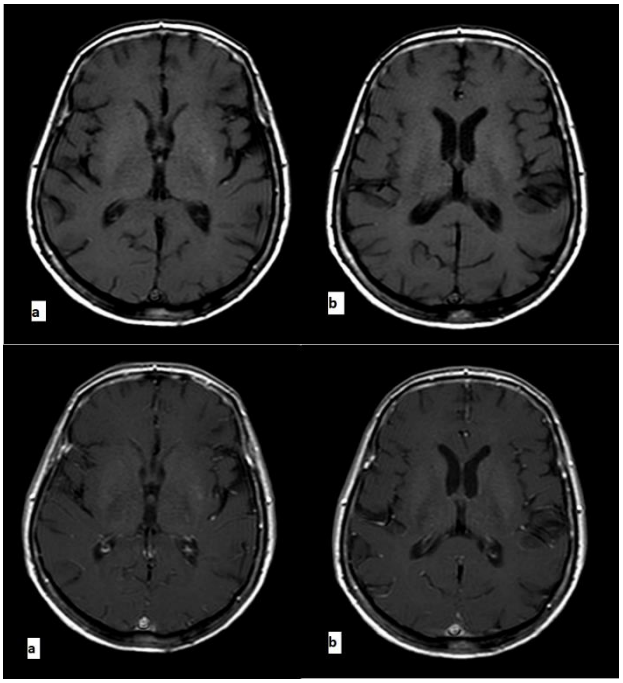


Figure 4, 5: Unenhanced T1 W image lesions show iso-hypointense signal, while contrast-enhanced T1W image lesions show no enhancement.



Discussion

SS is an autoimmune disorder with a gradual course [5]. Neurological signs comprise a wide spectrum. Herein, we report a 60-year-old female patient who had left hemiparesis and paresis in the right half of the face with hypoesthesia. The patient was misdiagnosed with cerebrovascular disease in the emergency department. Although projections about diagnostic criteria for SS vary, in recent years, a consensus was reached in using a revised version of European criteria, also known as American-European criteria [6]. These criteria include: 1) Xerophthalmia, 2) Xerostomia, 3) Positive Schirmer test or Rose Bengal test, 4) Presence of diagnostic histopathological findings in salivary gland biopsy, 5) Other specific salivary gland abnormalities (salivary gland scintigraphy, parotid scintigraphy), and 6) Presence of anti-Ro (SS-A) antibodies [7,8]. The presence of 4 of 6 of these criteria without any other related disease indicates primary SS. Based on the classification system, a diagnosis of SS should be made in cases with a weighted score ≥4. Salivary gland biopsy and anti-SS-A Ro, La appear as factors with the highest weighted values [9].

Our case met 4 of the diagnostic criteria, therefore, she was diagnosed with primary SS. Cranial nerves, PNS, and CNS can be involved in SS [10-12]. Although this patient had signs of CNS involvement, there were no signs indicating PNS involvement. In primary SS, type A (Ro) and type B (La) autoantibodies are elevated in the plasma. They are positive in 20-30% of cases in the early phase and in 62-80% of cases in the late phase. These auto-antibodies can be positive in other auto-immune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, primary systemic sclerosis, and primary biliary cirrhosis [13]. In the diagnosis of SS, the presence of periductal lymphocytic infiltration is a histopathological sign in patients with Sicca syndrome. It is important to note that standard serological tests are less sensitive than salivary gland biopsy.

Salivary gland biopsy should be performed prior to steroid use and the onset of advanced atrophic changes [14]. In the case presented herein, no salivary gland biopsy was performed since the patient previously received steroid therapy. Although CNS involvement rate was comparable in seropositive and seronegative patients in previous studies, it has been reported that more severe complications are associated with anti-Ro positivity, and that individuals with HLA-DR3 and DR4 are more vulnerable to more severe involvement of CNS in a genetic manner [15,16]. Such complications have considerable effects on both the treatment and prognosis of SS.

It remains controversial whether CNS involvement is associated with generalized vasculitis or an organ-specific antibody reaction. MRI is highly sensitive in showing cerebral dysfunction in SS patients. Periventricular or subcortical white matter lesions at T2-weighted images are the most observed findings (70-80%). In addition, hyper-intensity compatible with demyelination suggesting multiple sclerosis (MS), dilated sulci, ventricular dilatation and, in rare instances, corpus callosum lesions can also be seen. Such MRI findings are observed in 80% of primary SS patients with CNS involvement, including focal neurological signs [17,18]. In our case, lesions were detected at the left thalamic and periatrial regions and left basal ganglia in MRI. Although it was first thought that cerebral lesions may be compatible with lesions defined in SS, these lesions may also be related to risk factors, including age and hypertension. In addition, similar lesions can be found in vasculitic lesions and ischemic cerebrovascular diseases. In the patient described herein, vasculitis markers and factors other than anti-SS-A and anti-SS-B, which may predispose the patient to thrombosis, were normal. Since lesions with characteristics similar to those in the case presented herein can also be observed in vasculitic lesions and ischemic cerebrovascular diseases, the lesion in this patient was classified as an ischemic cerebrovascular occlusion secondary to SS hyper-intense signal increase at the left thalamic region on T2-FLAIR sequences. This classification was made even though the patient's vasculitis markers and factors other than anti-SS-A and anti-SS-B (enhancing predisposition to thrombosis) were normal. Moreover, the presence of lesions at the thalamus and basal ganglia excluded MS. The fact that the symptoms of SS were prominent suggested that these lesions were associated with SS.

There are few studies on the risk of ischemic stroke after a diagnosis of primary SS. Although patients with autoimmune disorders, such as inflammatory, systemic vasculitis, rheumatoid arthritis, and systemic lupus erythematosus tend to develop atherosclerosis, this is not the case in primary SS. Although SS does not increase the risk for ischemic stroke [19], anti-phospholipids and lupus anticoagulants are positive more frequently, which increase stroke risk [20]. When considered together, the case presented herein had normal carotid-vertebral CT angiography, normal echocardiography, and normal 24-hour Holter monitoring, and therefore, the patient was considered to have a stroke with neurological involvement of SS. There is no consensus regarding the best treatment of SS cases with CNS involvement. However, a conservative approach is recommended in cases with mild CNS involvement, while intravenous pulse corticosteroid and cyclophosphamide are used in patients with progressive neurological dysfunction and in those with active CNS disorder [21]. In our case, intravenous pulse steroid therapy was given over 7 days, and the patient had almost a complete clinical recovery. For maintenance, therapy continued with 1 mg/kg/day oral steroid and 2.5 mg/kg/day azathioprine. In the current case, clinical and cerebral MRI findings suggest MS in differential diagnosis. However, the patient may have an association of SS and MS. In SS, MS-like clinical and radiological manifestations can be seen, although it is rare. In the current case, CNS involvement of SS was considered based on a negative OCB test, the presence of xerostomia and xerophthalmia, positive ANA and anti-Ro antibodies, and a positive Schirmer test.

Conclusions

Based on the current case, we recommend careful assessment of patients presenting with clinical pictures suggesting ischemic cerebrovascular disease by MRI, blood tests, and additional imaging modalities. Early diagnosis in such cases is important to initiate treatment, direct SS prognosis, and prevent unnecessary treatments and costs.

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A fabricated chimeric SCIP flap with end-to-side anastomosis: A case report

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Informed Consent
The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

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

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Abstract

Superficial circumflex iliac artery perforator flap (SCIP) is one of the most convenient flaps to cover distal extremity defects because it conceals the scar of the donor area well and can be raised as a thin or super-thin flap. In recent years, various chimeric SCIP flaps were reported, including the sartorius muscle, the lateral femoral cutaneous nerve, and the iliac bone. However, chimeric SCIP flap is sometimes difficult to be raised on one pedicle, because of the absence of communication between a skin branch and a branch to a chimeric tissue. We present a case in which end-side anastomosis of a sartorius muscle perforator to a SCIP flap pedicle is made to form a fabricated chimeric SCIP flap due to variation in the pedicle. This design aims to fill cavitary spaces and supply better perfusion for infection control.

Keywords: SCIP flap, Fabricated chimeric flap, Supermicrosurgery

Introduction

The heel and dorsum of the foot are vital in ambulation. Reconstruction of the tissue defects in these areas includes critical difficulties owing to the insufficiency of local tissue, the requirement of three-dimensional reconstruction, the presence of weight-bearing areas, and poor skin blood flow. Among the etiologies of the defects are trauma, vascular diseases, tumor excision, and osteomyelitis. Skin graft, medial plantar artery perforator flap, reverse sural artery flap and free flaps are among the alternatives of heel reconstruction. Free flaps can cope with the limitations caused by pedicled flaps [1]. Koshima et al. [2] described the superficial circumflex iliac artery-based perforator flap (SCIP) in 2004. SCIP flap has become popular in various reconstructive approaches due to a longer pedicle compared to the free groin flap and concealable donor flap. Particularly, it is one of the most beneficial flaps in the reconstruction of distal extremity soft tissue defects. In the literature, there are certain variations of the SCIP flap, such as the super-thin SCIP flap, SCIP flap sensitized by the 12th intercostal nerve, supercharge SCIP flap using intercostal artery perforator flaps, vascularized iliac bone use with SCIP flap, and vascularized inguinal lymph nodes combined with SCIP flap [3, 4]. We present the fabricated chimeric SCIP flap that is used in the reconstruction of heel defects. The end-to-side anastomosis of the free sartorius muscle flap perforator to the SCIP flap pedicle by super microsurgical technique makes this case unique.

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Case presentation

A fourteen-year-old male patient who was paraplegic due to meningomyelocele was admitted to our clinic for a tissue defect because of an atonic wound. Written consent was obtained from the patient's parents. Laboratory studies revealed the following values: Hemoglobin: 10.4 mg/dl, WBC:12960, CRP:75.2. There was a tissue defect of 3x2 cm on the calcaneus bone, which could also be seen in the inspection (Figure 1). MR imaging showed osteomyelitis in the talus, tarsal bones, and tenosynovitis in the tibialis posterior and flexor digitorum longus muscles (Figure 2). Doppler USG revealed normal arterial and venous blood systems. Reconstruction with SCIP flap was scheduled due to the absence of infection signs in the bone and soft tissue, which were seen during the last tissue debridement.

Surgical technique

The first surgical marking was done from the pubic tubercle to the ASIS. The second marking was made parallel to this line and 2.5 cm long. Afterward, the superficial circumflex iliac artery (SCIA) perforators were marked on the skin with 8 MHz hand Doppler USG. First, the superficial branch of SCIA and its accompanying branch were dissected by a medial skin incision. Then a deep branch of SCIA, located below the deep fascia, and the accompanying vein were dissected until the sartorius muscle, guided by the previous medial skin incision. A 5x3cm muscle segment was elevated by keeping the perforator in the middle. A 6x4cm SCIP skin flap was dissected from lateral to medial and superior to inferior above the fascia. Deep branch-based sartorius muscle flap SCIA and superficial branch-based skin flap SCIA were elevated separately due to shortness of the common trunk (less than 2 mm) in the dissection of both the deep and superficial branches until the femoral artery (Figure 3). The diameter of the superficial and deep branches of SCIA were about 2 mm and 0.4 mm, respectively. The end-to-side anastomosis of the deep branch to the superficial branch was performed by 10/0 polypropylene sutures (Figure 4). The superficial branch of SCIA, which was the pedicle of the chimeric flap, was sutured with the medial plantar artery and vein with 9/0 polypropylene sutures. The anastomosis line was covered with STSG above to prevent vascular suppression which could occur postoperatively due to flap congestion. Leech treatment was performed for the venous congestion that occurred on the first postoperative day. On the third postoperative day, the venous congestion had completely regressed. In the third and fourth postoperative weeks, full weight-bearing, and ambulation were allowed, respectively (Figure 5).

Figure 1: Preoperative view. A 14-year-old male patient sustained a 4x3 cm^2 soft tissue defect over his right heel

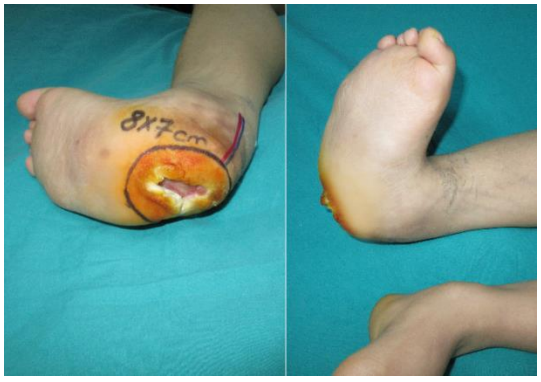


Figure 2: MR imaging which shows osteomyelitis in the talus, tarsal bones, and tenosynovitis in tibialis posterior and flexor digitorum longus muscles

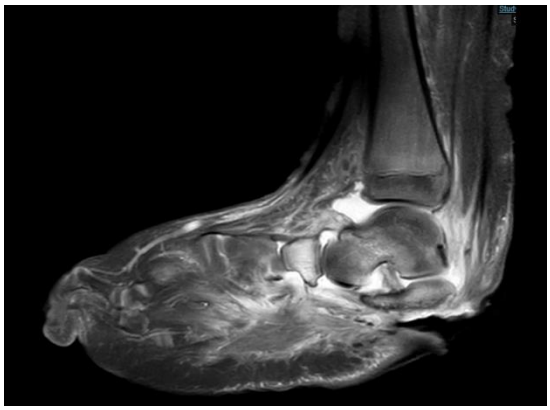


Figure 3: A schematic illustration of the intraoperative vascular variation (left), A schematic illustration of the anastomoses (right)

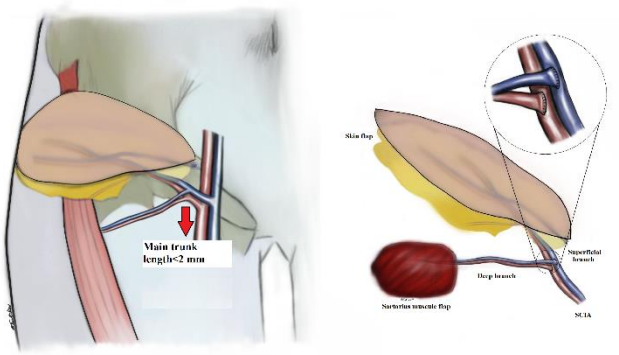


Figure 4: An intraoperative view showing the end-to-side anastomosis

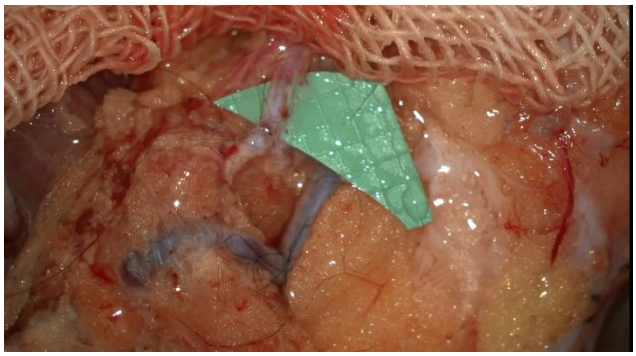
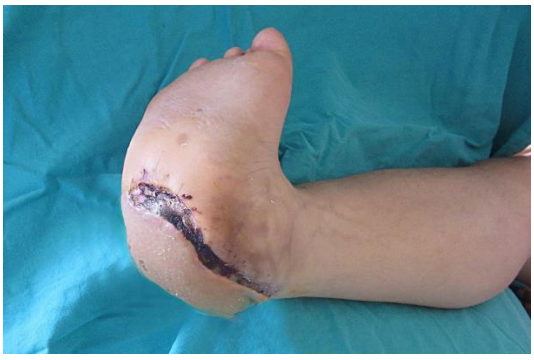


Figure 5: View of the right heel reconstructed by fabricated chimeric SCIP flap in the 3rd postoperative week



Discussion

The aim in the reconstruction of the weight-bearing areas like the heel is to restore normal foot outline, provide a sufficient amount of soft tissue, and choose an appropriate donor area. Free flaps are the best choices for defects of more than 3 cm and when local flaps cannot be used [1].

Free muscle flaps performed on the defects that originated after osteomyelitis are resistant to infections. Buona et

al. [5] have shown that fasciocutaneous flaps have provided 84.6% recovery in infection markers whereas this rate was 90.9% in muscle flaps. Also, muscle flaps minimize the risk of nonunion of fractures within the defects that occur after fractures. Another advantage of muscle flaps is that they prevent ulceration that can occur afterward by increasing the volume in the weight-bearing areas. Free muscle flaps that are used in heel reconstruction are rectus abdominis muscle skin flap, latissimus dorsi muscle skin flap, chimeric anterolateral thigh flap, and chimeric SCIP flap [1,4]. In this case, we aimed to treat osteomyelitis damage with the muscle flap. The most significant factor in choosing free flaps in the pediatric population is the growth retardation that flaps can cause rather than the donor site morbidity. For instance, the use of rectus abdominis and latissimus dorsi muscle flap in the pediatric population can cause scoliosis in the future. Therefore, perforator flaps are more preferable in pediatric patients. However, muscle atrophy and nonfunction may occur during the intramuscular dissection of the perforator [6]. SCIP flap is safer in the pediatric population because intramuscular dissection is not performed, and scar tissue is in an area that does not impede the growth of extremity. In the chimeric SCIP flap in our case, the use of sartorius muscle with the skin island caused minimal functional morbidity. Although a SCIP flap has many advantages, its pedicle often has variations. Berish et al. [7] have indicated that the superficial branch of SCIA may be occasionally hypoplastic or aplastic. However, the deep branch is almost always present. In their study on ten cadavers, Yoshimatsu et al. [8] have shown that the distance between the origin and bifurcation of the SCIA was 2 mm in four cadavers. If the distance between the origin and bifurcation points of SCIA is less than 2 mm, flaps should be transferred separately not to risk the safety of the anastomosis. In recent years, the difficulties in reconstruction are surpassed by the novel techniques in super microsurgery. Anastomosis in vessels below 0.8 mm in diameter, such as perforator-perforator anastomosis, can be performed. As in this case, super microsurgical anastomosis techniques are used in cases where anatomic fabricated chimeric flaps will be created. Chimeric flaps are divided into four types defined by Kim et al. [9] Type 1: Classical Chimerism, Type 2: Anastomosis Chimerism, Type 3: Perforator Chimerism and Type 4: Mixed Chimerism. The advantages of chimeric flaps include three-dimensional reconstruction, acceptable aesthetical appearance, and diminished donor area morbidity. The disadvantages are an increased number of anastomoses, variations in the perforators, and second venous drainage need. Type 2 chimeric flap studies are limited in the literature. Kim et al. [10] described jejunum and Latissimus Dorsi flap, jejunum and ALT flap, ALT and lateral arm flap. Huang et al. have formed a chimeric medial femoral condyle with an end-side anastomosis. In our case, classic chimerism was planned first, then the type 2 chimeric flap was decided on intraoperatively due to the pedicular variation.

Conclusion

Anatomic variations which may be encountered during the creation of chimeric flaps can be managed by super microsurgical methods. This case is essential because it presents a new technique with the use of perforator-to-perforator end-side anastomosis.

Acknowledgments

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The effects of 6 weeks home rehabilitation program for non-ventilated COVID-19 patients after discharge: A case report

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Abstract

COVID-19 disease is a pandemic that affects the cardio-respiratory system and causes other systemic problems. The effect of pulmonary rehabilitation (PR) programs for COVID-19 disease sequelae is not clear. The aim of this study was to investigate the effects of PR on COVID-19 sequelae. A 52-year-old patient was hospitalized for 8 days, and the complaints of fatigue and dyspnea continued after being discharged. For this reason, an exercise program was recommended. The patient underwent a 6-week PR that consisted of breathing, aerobic, and resistance exercises under supervision. After 6 weeks of the PR, complaints of dyspnea and fatigue decreased. There were also improvements in aerobic capacity and quality of life scores. The PR caused improvements in cardiorespiratory system complaints on a non-ventilated COVID-19 patient.

Keywords: Coronavirus, COVID-19, Pulmonary rehabilitation, Dyspnea, Aerobic capacity

Introduction

Coronavirus disease 2019 (COVID-19) has entered the world's agenda from Wuhan city in December 2019. The disease was noticed rapidly after increased unknown pneumonia complaints [1]. Today, it has become a pandemic and spread all over the world. The total number of cases in the world had approached 7 million in June 2020. On the same date, the official number of cases in Turkey was 169K. While worldwide death rate was 5.90%, it was 2.75% in Turkey.

COVID-19 is transmitted from person to person through secretions and has a broad-spectrum chain of symptoms after transmission [2]. Some of these symptoms include dyspnea, headache, weakness, fatigue, shortness of breath, dry cough, chills, fever, myalgia, anosmia, and diarrhea [3]. The most prominent symptom which causes mortality is dyspnea. Also, respiratory capacity loss, seen in diseases such as pneumonia and acute respiratory distress syndrome, can be observed in COVID-19 patients [4].

Reducing the symptoms of the respiratory system and strengthening the immune system is possible with physiotherapy and rehabilitation programs [2, 4]. Especially aerobic and respiratory exercise programs are recommended because of the healing and protective effect of exercise against COVID-19 comorbidity and risk factors [5]. However, the long-term effects of COVID-19 pandemic are not clear. For this reason, there are no specific pulmonary rehabilitation protocols for COVID-19 disease.

The purpose of this case study is to examine the effects of pulmonary rehabilitation programs on non-ventilated COVID-19 patients' symptoms and compliance.

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Case presentation

The patient was informed about the rehabilitation program, and he agreed to participate in the study. Written consent was obtained.

The participant was a 52-year-old male patient diagnosed with COVID-19. He was admitted to the hospital with fever, shortness of breath, dry cough, anorexia, and fatigue symptoms and diagnosed with COVID-19. He was hospitalized for 8 days at the ward, and administered anti-malaria, anti-influenza drugs, antibiotics, antipyretics, and gastroprotective medication during hospitalization. After the symptoms decreased and the diagnostic test result was negative, discharge procedures were started. Azithromycin dehydrates and terbutaline sulfate agents were prescribed to protect against upper respiratory tract infections and relax the bronchial muscles during discharge. The internal medicine specialist recommended the patient to exercise at a level that would not increase shortness of breath to improve the cardiorespiratory situation.

Rehabilitation phases were divided into two main parts, as respiratory exercise that consisted of thoracic expansion exercise (5 min/day), diaphragmatic breathing, pursed-lip breathing, coughing training and general exercise that consisted of aerobic and resistance training. Breathing exercises were supervised by the physiotherapist with 10 repetitions and 3 sets performed every day for six weeks. We used a 6-minute walking test for aerobic capacity estimation.

Aerobic exercise was performed with 50-60% HRmax. HRmax was calculated with the Karvonen formula. For resistance training, the patient used a yellow iso flex band with bare hands for upper and lower extremity big muscle groups for 10 min/day. Also, the patient performed mini-squats (10x3 repetition) and sit-to-stands for 30 sec/day. All these exercises were performed at home under the supervision of a physiotherapist for 6 weeks. Approval was obtained from the patient for the presentation of this case.

The demographics, weight, comorbidity, the presence of other illnesses during the last 6 months, onset complaints of disease, the existing complaints before the exercise program and the hospital process of the patient was questioned. 6-Minute-Walking Test (6-MWT), EuroQol (EQ-5D), sit to stand test, chest circumference length test (CCLT) and Breathing Frequency (BF) were performed.

During his hospitalization period, the patient, who is military personnel, lost 3 kilograms of weight, and his BMI decreased from 24.17 to 23.17. He had no chronic illness and no history of any diseases such as the flu, colds, chronic cough, fever, or others in the past 6 months. Before a hospitalization, he had weakness, fatigue, shortness of breath, anorexia, dry cough, and sore throat complaints. His anorexia, and runny nose complaints continued after discharge, but had completely regressed at the end of the exercise program. No adverse effects were observed throughout the exercise program.

Dyspnea and fatigue were evaluated on a 10-category scale. The results of dyspnea and fatigue scores before the exercise program were 4/10 and 5/10, respectively. Both scores decreased to 1/10 after the intervention. The patient increased the walking distance by 189 meters in 6 minutes and increased repetition of the sit-to-stand test by 8 cycles compared to baseline. Also, quality of life scores improved 3 points, and the result of the patient's self-reported general health status reached 80% of the pre-disease normal. Other results are shown in Table 1.

Table 1: All Assessment Results of the COVID-19 Patient

Parameter	Subtitle	Before Intervention	After Intervention
Dyspnea		4	1
Fatigue		5	1
6-MWT	Distance (m)	390	579
EQ-5D	Total	8	5
	General Health Status	50	80
STS		9	17
BF		26	19
CCLT	Inspiration (cm)	94	101
	Expiration (cm)	85	78

6-MWT: 6-minutes walking test, EQ-5D: EuroQol-5D, STS: Sit-to-Stand test, BF: Breathing Frequency, CCLT: Chest circumference length test

Discussion

COVID-19, which starts with atypical pneumonia, mostly affects the respiratory and cardiac systems. PR has great importance for multi-systemic disease. In this study, PR caused improvements in dyspnea, aerobic capacity, muscle endurance, and quality of life scores.

Physiotherapy programs should be administered both during hospitalization after the patient has stabilized and after discharge to compensate for multi-systemic losses. However, according to some studies, the PR process should not start very early. Deep and slow breathing, thoracic expansion, diaphragmatic breathing, airway cleaning techniques, sitting up, active extremity exercises, walking, and cycling exercises should be started to the COVID-19 patients in the post-acute phase [6].

While the aim of short-term PR in COVID-19 should be to reduce dyspnea as much as possible, the long-term goal is to increase functions. The rehabilitation programs should be organized for these purposes.

The main aim of the PR for the non-ventilated and discharged COVID-19 patients is to reduce dyspnea and disability, as well as improve pulmonary capacity, and quality of life [7]. Especially patients with dyspnea should be carefully examined before the exercise program because the results of studies on rehabilitation practices in COVID-19 disease are not clear yet.

EQ-5D is one of the quality-of-life questionnaires used in lung diseases. Meta-analysis revealed that PR has the same positive effect in patients with idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease (COPD) in terms of dyspnea and quality of life parameters. Also, it was highlighted that breathing exercises added to aerobic programs are a complementary method to improve dyspnea [8]. The pulmonary rehabilitation programs are an effective treatment method for improving the cardiorespiratory functions and quality of life in moderate to severe COPD [9]. The 4-month aerobic and breathing exercise program administered to COPD patients resulted in both statistically and clinically significant improvements in aerobic capacity and quality of life [10].

COPD is a common disease affecting many people all over the world. It is also commonly characterized by dyspnea and a decrease in quality of life. PR is widely used in the

treatment of COPD as it is an effective non-pharmacological treatment for dyspnea. A study showed that PR caused an improvement in dyspnea, tidal volumes, and quality of life. It has been reported that this increase in tidal volume contributes to the improvement of the respiratory pattern and improves dyspnea and quality of life [11].

Reduced exercise capacity and fatigue are two of the main physiological symptoms of sarcoidosis. Improvements can be seen in these two main symptoms with a 4-week PR [12]. Another study showed that 8-week respiratory rehabilitation improves dyspnea, exercise tolerance, and quality of life parameters [13].

A study found no difference in terms of aerobic capacity and quality of life between an 8-week home-based and hospital-based PR program. The lack of a significant difference in aerobic capacity was attributed to the fact that the 6-minute walk test was insufficient to evaluate the patients. However, in almost all respiratory system studies, 6 MWT was used to assess exercise capacity without disadvantages [14].

Postural, motor, and cardiorespiratory losses can be observed due to long-term rest during COVID-19 disease. PR applied to prevent these adverse effects improves exercise tolerance, respiratory muscle functions, and skeletal muscle functions in chronic pulmonary disease patients. A total of 2504 patients with COPD were included in a study and muscle strength, mass, and endurance of the patients increased after the exercise program. The mechanism of action of training in the rehabilitation of diseases with an obstructive pattern is based on the increase in ventilation and gas exchange, and cardiovascular, and limb muscle functions [15]. We think that the likely reason for the decrease in dyspnea is due to the improvements in the cardiorespiratory system.

The new type of coronavirus involves respiratory epithelial cells, leading to respiratory system problems. The 6-week pulmonary rehabilitation program administered to prevent respiratory involvement increased the quality of life of patients. In this study, the exercise program consisted of breathing, stretching, and home exercise programs performed two days a week, and a significant increase was noted in the quality of life of patients [15]. Many studies in the literature report that PR increases the quality of life in lung diseases. Similarly, in our study, the quality of life of the patient increased. We think that the psychological effect of exercise, decreased dyspnea, and increased aerobic capacity makes the patient more active in daily life activities.

Conclusion

Our pulmonary rehabilitation program improved dyspnea, fatigue, aerobic and functional capacity, quality of life, and respiratory parameters in non-ventilated COVID-19 patients. The pulmonary rehabilitation program is used in cardiorespiratory system diseases and related complications as an evidence-based intervention. However, its effects on COVID-19 disease are still under investigation. We examined the effect of an exercise program administered to a clinically stable non-ventilated COVID-19 patient in this study. We know that COVID-19 disease adversely affects different systems of the body, especially the respiratory system. Supervised and planned exercise is an effective treatment method that can eliminate these negative effects. Therefore, pulmonary rehabilitation has had positive effects on the parameters mentioned above.

This was a case report; hence, our results cannot be generalized to the public. There is a need for more randomized controlled studies with large samples to prove the effect of pulmonary rehabilitation in both discharged and inpatient COVID-19 patients, like those performed in other respiratory system diseases. In addition, evaluating the patients with more objective assessment methods is important to prove the effect of the treatment program. This study can be a reference to future studies and can serve as an example for both the clinicians and academicians.

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A case report of the breast tubular adenoma in the perimenopausal age group

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Abstract

Tubular adenoma is a rare benign breast tumor that makes up 1.7% of all breast tumors. Clinically and radiologically, it cannot be distinguished from fibroadenomas. It is rarely seen after 40 years of age. It usually presents in the form of painless masses, and preoperative radiological and pathological diagnosis is challenging. We herein present a case of tubular adenoma diagnosed at the age of 46 years with clinical, radiological, and histopathological examinations. The patient presented with atypical features, and a doppler ultrasonography signal was observed. The diagnosis was made via tru-cut biopsy.

Keywords: Tubular adenoma, Breast, Ultrasonography

Introduction

Tubular adenoma is one of the rare breast lesions. It makes up 4% of benign breast tumors and 0.13 - 1.7% of all breast tumors [1]. Clinical features and radiological findings of tubular adenoma are mostly similar to those of fibroadenoma [2]. Preoperative diagnosis remains difficult [3]. According to literature, tubular adenomas are rare after 40 years of age, and very rare in the postmenopausal period [4]. They are usually seen as a painless, well-circumscribed mass [1-5]. We present the case of a 46-year-old patient with a tubular adenoma which developed during the perimenopausal period, in light of ultrasound (USG) results and histopathological examinations.

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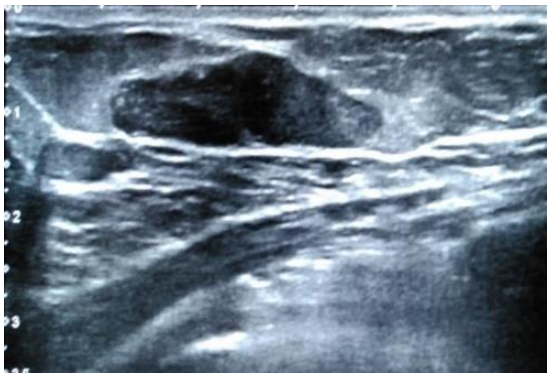
Case presentation

A 46-year-old female patient was admitted to our hospital with a palpable mass under the clavicle and pain in the lower outer quadrant of her right breast. The patient was in reproductive period, but her menstrual cycle was irregular. She had no family history of breast cancer and no notion of drug use. No prior consultation by a surgeon or a radiologist was carried out. The lesion under the clavicle was thought to be a lipoma due to its consistency and flat contour; however, a solid mass lesion was detected in the right lower outer quadrant. The patient was referred to the radiology outpatient clinic with the request of USG.

Radiology

Ultrasonography, performed with Toshiba S 300 device using a high resolution 14 MHz probe, revealed that the lesion under the right clavicle was a lipoma. Bilateral breasts were ACR type C pattern. Both axillae were normal. However, a 28x14 mm solid mass lesion was found in the lower inner quadrant of the left breast at 8 o'clock in the upper medial section, parallel to the pectoral axis. It was hypoechogenic, and internally homogenous with a smooth contour and a superficial location (Figure 1). The mass' sonographic features were similar to fibroadenoma, but Doppler ultrasonography showed intensive blood supply. Tru-cut biopsy was performed at the request of the patient and because of the size of the solid mass (exceeding 2.5 cm). Two preparations were obtained from the lesion.

Figure 1: A well-circumscribed, ovoid, hypoechoic solid mass lesion on sonography



Histopathology

Tru-cut biopsy material consisted of two 1.3 cm-long, cream-colored tissues. The material was fixed in 10% formalin and sampled into tissue cassettes. After routine tissue follow-up, paraffin blocks were formed. 5 µm thick sections were obtained from the blocks and stained with hematoxylin-eosin. Slides were examined by a light microscope.

The lesion was characterized by proliferation of tubular structures with rounded-oval shaped two-layer cell layers close to each other, where stroma was almost non-observable (Figure 2). Immunohistochemically, the myoepithelial layer in the tubules stained positive for CD10 (Figure 3). The lesion without cellular atypia was diagnosed as 'Tubular Adenoma'.

Figure 2: Hematoxylin-eosin (HE) staining x 200. Round-oval glands/tubules in close proximity. Fibrotic stroma can be observed in the narrow spaces. Tubules are lined with two rows of cells.

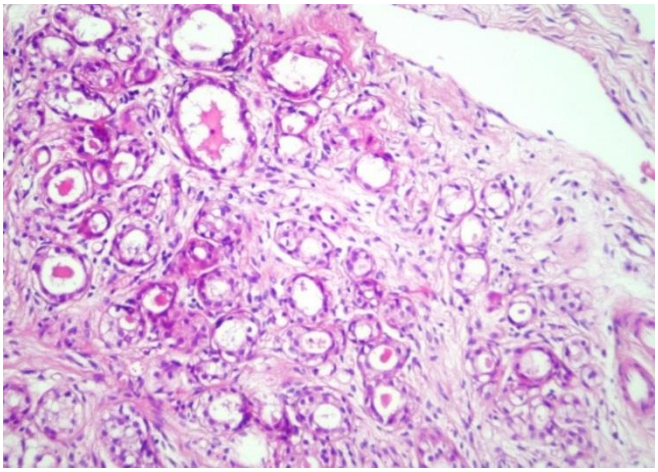
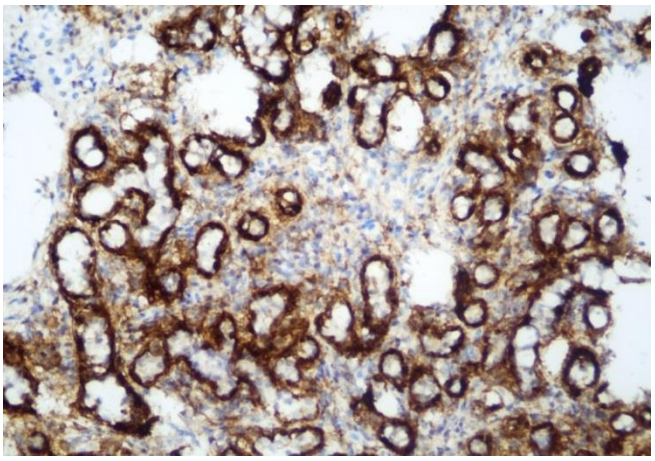


Figure 3: CD10 x 200. Immunohistochemically positive for CD10, all round cells with myoepithelial layers of preserved tubules



Follow-up

The patient did not consent to operation. Two follow-up ultrasounds were performed after three months and one year, along with a mammography after one year. The lesion was entirely stable in shape and size. Annual follow-up was suggested in the last ultrasound examination.

Discussion

Tubular adenoma, a rare breast tumor, is a subclass of breast tumors similar to pericanalicular fibroadenoma. Radiological findings resemble those of fibroadenomas [6]. It is a homogeneous, iso or hypo-echogenic mass lesion with a uniform margin [7]. In our case, B mode USG images were in accordance with the general criteria. Generally, preoperative radiological and pathological diagnosis is rare [8]. Our patient was diagnosed by tru-cut biopsy.

In the literature [9], biopsy indications for fibroadenoma-like lesions are as follows:

- Growing lesion
- Suspicious USG findings in terms of malignancy
- Non-traced lesion of 2.5-3 cm in size
- Patient request

The lesion of our patient was in accordance with the biopsy criteria of fibroadenoma-like lesions; hence, a tru-cut biopsy was performed, and tubular adenoma was diagnosed.

A tubular adenoma is seen in patients under 40 years of age in more than 90% of the cases. Our patient was still in

reproductive period but close to menopause. This is very rare in that age group.

Size of the lesion varies between 1 cm and 7.5 cm at the time of diagnosis and may occur 2-12 months before the diagnosis. The dimensions we measured were consistent with the literature.

Tubular adenomas present as mobile, painless, well-circumscribed masses that do not show skin and nipple changes and are clinically similar to fibroadenomas [1].

Malignant transformation was rarely reported in the literature. In elderly patients, the lesion may contain microcalcifications which can be confused with malignancy (6). According to Lee et al., 77.3% of malignant masses and 16.7% of benign masses showed signals in doppler USG [10]. In our case, the lesion showed a signal on color Doppler US.

Conclusion

Tubular adenoma, one of the rare forms of fibroadenoma-like lesions, is exceptional in the perimenopausal and postmenopausal age group. Although it is usually painless, it may present with different clinical manifestations. It is usually in the form of a well-defined solid mass lesion. Doppler USG features are similar to other benign solid breast lesions.

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Primary T-cell non-Hodgkin's lymphoma of the larynx: A case report

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Abstract

Lymphoma is a malignant disease of lymphatic cells. Despite numerous sub-types, the disease is generally divided into two main groups: Hodgkin and non-Hodgkin lymphoma. Primary laryngeal non-Hodgkin lymphoma accounts for less than 1% of all laryngeal tumors. We herein present a 43-year-old male patient with difficulty swallowing due to a laryngeal mass. Morphological and immunohistochemical examination revealed T cell lymphoma according to the World Health Organization classification. The patient was referred for chemo-radiotherapy. Primary lymphoma of the larynx is a rare, and primary T-cell laryngeal lymphoma is an even rarer tumor.

Keywords: Larynx, Lymphoma, Non-Hodgkin, T-cell

Introduction

Lymphomas are malignant diseases originating from lymph nodes and other lymphatic tissues. Despite numerous sub-types, the disease is generally divided into two main groups: Hodgkin and non-Hodgkin lymphoma. NHL can also be seen in extranodal regions, with the head and neck (salivary gland, larynx, nose and paranasal region, etc.) being the second most NHL involvement area. Less than 1% of laryngeal tumors are non-Hodgkin lymphoma. It is more common in males compared to females [1, 2]. Laryngeal involvement is usually found in the supraglottic area (aryepiglottic folds or epiglottis). There are also a few cases with primary subglottic involvement in the literature [3].

We aimed to present this rare disease and review the literature.

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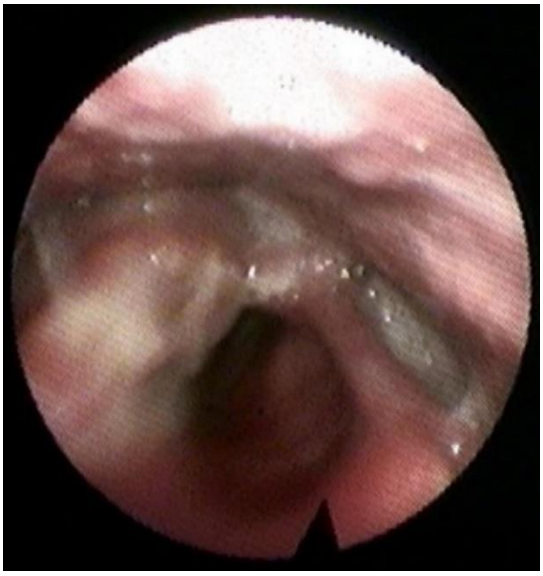
Case presentation

A 43-year-old male patient was admitted to our clinic with a feeling of something stuck and pain on the right side of the throat. The patient had had a swelling in the neck before presentation, which had spontaneously resolved. He had no smoking history. He had hoarseness, and no fever, weight loss and night sweats. In indirect laryngoscopy, a lesion was seen to extend from the right arytenoid to the epiglottis (Figure 1).

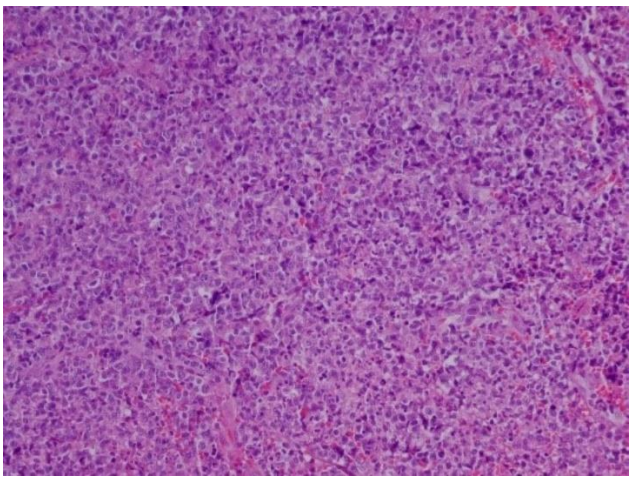
Figure 1: Flexible fiberoptic view of the larynx



After obtaining patient consent, direct laryngoscopy was performed under general anesthesia. On the laryngeal face of the epiglottis, there was a mass extending from the right epiglottic fold to the root of the tongue. A biopsy was obtained.

In histopathological examination, neoplastic cells stained positive for CD3, CD5, CD4, focally positive for CD30 and negative for pancytokeratin, CD20, CD8, Alk-1, Bcl-2, Bcl-6, CD10, CyclinD1, CD79a and CD2. The proliferative index was 70% with Ki-67. The tumor was consistent with T cell lymphoma according to the World Health Organization classification system (Figure 2).

Figure 2: Staining with Hematoxylin eosin (200)



After consultation with medical oncology, the patient was referred for chemo-radiotherapy. He died two years after the diagnosis. Written consent was obtained from the relative of the patient presented in the study.

Discussion

If there is no smoking history, non-SCC laryngeal cancers may be the cause of hoarseness and difficulty in swallowing. In such patients, adenocarcinoma, sarcomas, lymphoma are the first malignancies that come to mind. If there are systemic complaints (fever, night sweats, weight loss etc.), lymphoma is considered first.

Laryngeal lymphomas tend to remain localized and asymptomatic for a long time. Classical laryngeal lymphoma symptoms include lymphadenopathy, dysphagia, dyspnea, and hoarseness. Systemic symptoms are less common [4]. In a retrospective cohort study of 200 cases with laryngeal lymphoma, Scott et al. found the mean age to be 64.2 years (range: 4-82 years) [2]. Other publications in the literature state that laryngeal lymphoma occurs more frequently in 7th decade of life [5,6]. The patient in our case report was 43 years old.

Laryngeal lymphomas are extremely rare malignancies since the larynx contains a relatively small amount of lymphoid tissue compared to other tissues. Most laryngeal lymphomas were detected in the supraglottic region, because this area contains relatively more follicular lymphoid tissue than other parts of the larynx [7]. In his epidemiological study, Scott et al. reported that the tumor was supraglottic in 51.5% of cases [2].

The majority of extranodal lymphomas in the head and neck region are NHLs [8]. Among the cases of NHL affecting the larynx, the most common classifications described in the literature include mucosa-associated lymphoid tissue (MALT) lymphoma, plasmacytoma, and diffuse large B cell lymphoma [9].

In the literature, approximately 70% of laryngeal lymphomas are B-cell non-Hodgkin lymphoma [2, 3, 6]. The diagnosis of primary NHL with peripheral T cells is very rare [10].

Radiologically, primary laryngeal lymphomas are defined as soft submucosal masses, and ulceration occurs vary rarely. [3].

Macroscopically, these tumors typically appear as flat or non-polypoid ulcer masses in endoscopy [3, 4]. Histopathological examination is required for definitive diagnosis. According to the literature, more than one biopsy may be required to make an accurate diagnosis [11].

Chemotherapy and radiotherapy are the most common treatment strategies advocated worldwide in the treatment of laryngeal lymphoma. Laryngeal lymphomas are highly radiosensitive [12].

Although supraglottic lymphomas are more common than lymphomas originating from the glottic or subglottic regions of the larynx, they do not have a better or worse prognosis. It was concluded that survival in laryngeal lymphoma patients is not significantly affected by the primary site of the tumor [2]. Patients with T cell NHL and lymph node involvement show poor prognosis [1]. Primary laryngeal peripheral T cell lymphoma appears to be worse than its nodal counterparts [13].

Conclusion

Laryngeal lymphomas are rare, and T-cell lymphomas are even rarer than other types. Laryngeal lymphomas are usually limited to the larynx, so they remain asymptomatic for a long time. There may be difficulties in diagnosis due to its atypical

clinical presentation. This case report and presentations of other laryngeal lymphomas in the literature can help create a database.

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A case of an acute coronary syndrome associated with anomalous origin of the left main coronary artery, with a right coronary sinus origin

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

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Abstract

We present a case whose left main coronary artery (LMCA) arose from the right sinus of Valsalva, which is a very rare congenital anomaly. In a 48-year-old male, coronary angiographic (CAG) examination revealed LMCA arising from the right sinus of Valsalva. Although this kind of anomaly has generally been accepted to have a benign course, it may cause sudden death. In this case report, we present a patient who was admitted to our clinic with Acute Coronary Syndrome (ACS) and was found to have LMCA originating from the right sinus of Valsalva in the CAG. A percutaneous coronary angioplasty was performed with stent placement in the critical stenosis in the left anterior descending (LAD) coronary artery.

Keywords: Congenital coronary anomaly, Left main coronary artery, Acute coronary syndrome

Introduction

Anomalies of the coronary arteries (CAA) are found incidentally in 0.6% to 1.5% of patients undergoing CAG. Ectopic outlet anomalies, in which coronary arteries originate from a part of the aorta or pulmonary artery other than the sinus Valsalva, are the most common anomalies in CAA [1]. It is exceedingly rare for the LMCA to originate from the right sinus Valsalva and its incidence is about 1-3%. It may be completely asymptomatic or present with angina pectoris, acute coronary syndrome, and even sudden cardiac death [2].

In this case report, we present a patient who was admitted to our clinic with the diagnosis of acute coronary syndrome and found to have the LMCA originating from the right sinus Valsalva in coronary angiography. A percutaneous coronary angioplasty was performed with stent placement in the critical stenosis in the left anterior descending (LAD) coronary artery.

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Case presentation

A 48-year-old male patient was admitted to the emergency department with a complaint of chest pain which began 3 hours ago. There were no risk factors for coronary artery disease. In physical examination, his blood pressure was 150/90 mmHg and his heart rate was 87/min. There were no pathological findings in his electrocardiography and telegraphy. In the echocardiographic examination of the patient, no pathology was observed except hypokinesia in the left ventricular anterolateral wall apical segment and mild tricuspid regurgitation. Left ventricular ejection fraction (LVEF) was 50%. In laboratory parameters, troponin values were high (82 ng/mL), while other parameters were normal. The patient was hospitalized with acute coronary syndrome and coronary angiography was performed.

CAG was performed via a percutaneous approach from the right femoral artery using the Judkins technique. First, imaging the left coronary system was tried, but when the left coronary system could not be visualized, a right coronary artery injection was performed. It was observed that the LMCA and the right coronary artery (RCA) originated from the right sinus Valsalva with separate ostia. LMCA was viewed with the left Amplatz II catheter. An eccentric lesion causing 70-90% occlusion was observed in the middle segment, and another one causing 70-90% was detected in the LAD. RCA and circumflex (Cx) arteries were normal (Figure 1). Then, with the consent of the patient, a 2.75x24 mm stent was placed in the mid-LAD lesion, and the distal stenosis was treated with a 2.5x16 mm stent, resulting in good TIMI3 flow (Figure 2).

Figure 1: Conventional Angiography A: RCA emerging from the right coronary cusp B: LMCA emerging from the right coronary cusp, Amplatz 2 catheter (red arrow), LAD lesions (yellow arrow)

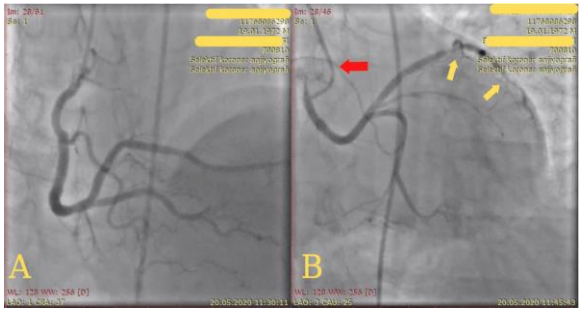
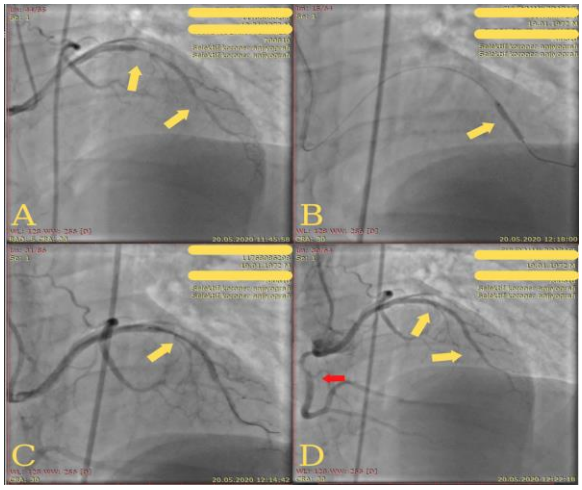
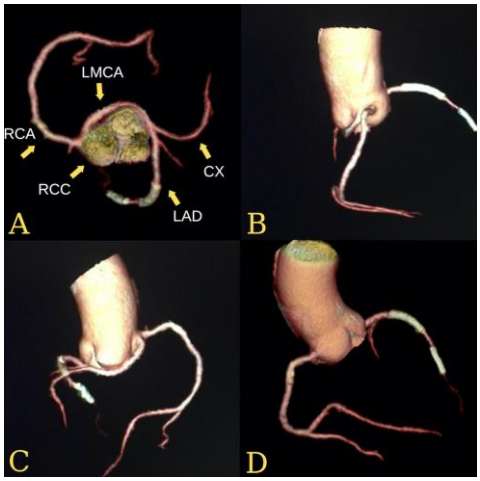


Figure 2: A: LAD lesions (yellow arrow), B: Successful stent procedure to LAD distal lesion (yellow arrow), C: Successful stent procedure to LAD proximal lesion (yellow arrow), D: Final view of RCA, CX, and LAD.



In our case, multi-slice computed tomography (CT) angiography was performed for a more detailed examination to determine the course of the left main body and whether there was any other accompanying cardiac anomaly. No other congenital coronary anomalies were detected in the multi-slice CT and the LMCA was observed to pass posterior to the aorta (Figure 3). The patient was in good condition in the post-interventional period, followed up for 3 days, and discharged without complications. He had an uneventful 6-month follow-up period.

Figure 3: Coronary multi-slice tomography image A: LMCA and RCA originating from the right cusp B: LMCA and RCA originating from separate ostia C: The course of LMCA from posterior to the aorta D: Anterior view of the aorta



Discussion

CCAs are extremely rare and usually detected incidentally in the autopsies of healthy individuals, with CAG, during surgical operations, or CT angiography [3].

The incidence of the LMCA arising from the right coronary sinus Valsalva was 0.17% in the study of Yamanaka and Hobbs on 126.595 patients, 0.15% in the study of Angelini et al. [4], and 0.03% in the Turkish population. Although it is one of the rare congenital CAA, it is a potentially serious anomaly of origin because of its association with sudden death.

Anomalous origin of LMCA from right sinus Valsalva is divided into 5 subgroups and classified according to its relationship with aortic root, pulmonary truncus, and course towards the left. 1-Posterior: LMCA courses posterior to the aorta, 2-Anterior: LMCA courses anterior to the pulmonary artery, 3-Intraseptal: LMCA courses through the interventricular septum, 4- Interarterial: LMCA courses between the aorta and pulmonary artery, 5-Combined: The anterior and septal types or posterior and septal types are seen together. Although the first three types are generally benign, cases with angina, effort-induced syncope, and myocardial infarction have been reported. Type 4 is the most dangerous. The presence of coronary artery disease with an abnormal course of LMCA is important in determining the treatment strategy, and there is no specific treatment modality. Prophylactic surgery is recommended in type 4 cases [2]. In our case, the LMCA originated from the right sinus Valsalva and coursed from the posterior of the aorta (type 1), which is generally considered benign.

Other congenital coronary anomalies are found in 10.1% of those with CCA. Among these, mitral valve prolapses, bicuspid aorta, and great artery transposition are the most common [5]. Multi-slice CT angiography can be useful in

identifying congenital coronary anatomy in addition to CAA, better defining coronary anatomy, and if necessary, guiding the treatment strategy [6].

Although the anomalous origin of LMCA from the right sinus Valsalva is an exceedingly rare coronary anomaly, it can lead to serious clinical consequences depending on its type. In these cases, multi-slice CT angiography can be used in addition to CAG, because type 4 can cause sudden cardiac death.

Conclusion

We presented a case of acute coronary syndrome in which the left coronary system originated from the right sinus Valsalva with an ostium separate from RCA. The retro-aortic course of LMCA is generally a benign variant. Although there is no presentation with sudden cardiac death, it may present with atherosclerosis which develops with age.

PCI is the preferred strategy in patients with acute coronary syndrome, but it should be kept in mind that tomographic identification of the origin is vital in patients with anomalous origin of coronary arteries.

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Unusual primary manifestations of multiple sclerosis: A case report

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Informed Consent
The authors stated that the written consent was obtained from the patient and the parents of the patient presented with images in the study.

Conflict of Interest
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Abstract

Isolated cranial nerve involvement is rarely seen in multiple sclerosis patients. A 17-year-old female patient presented with complaints of numbness in the right half of her face, difficulty in chewing with the right jaw, having the right corner of her mouth drooping to the right, and blurring in both eyes. She had loss of sensation, left central facial paralysis, and frust monoparesis in the left arm in the right trigeminal nerve dermatome. Following systemic steroid treatment, her left central facial paralysis and chewing difficulties regressed, and loss of sensation improved. As in this case, MS may present with multiple instances of cranial nerve paralysis in addition to the involvement in the extremities. The association of the fifth and seventh nerve palsy in MS is rarely seen in the literature.

Keywords: Multiple sclerosis, Facial paralysis, Cranial nerve neuropathy

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating disease of the central nervous system (CNS) [1]. Although brain stem involvement is common at the onset of MS and during the course of the disease, MS patients rarely have isolated cranial nerve involvement. In fact, of all MS patients, isolated cranial nerve palsy appeared as the first finding in only 1.6% to 5.2% [2]. Although some report that brain stem demyelination is one mechanism, isolated cranial nerve palsy is insufficient to explain MS pathogenesis [3]. Recently, the first clinical picture of recurrent MS has been described as “clinical isolated syndrome” (CIS) [4]. Therefore, isolated cranial nerve palsy with characteristic imaging patterns is now in this category. It is likely that, diplopia follows a partial sixth nerve lesion, while mild facial paralysis is observed in the partial seventh nerve lesion. As a result, the sixth nerve lesion is likely to be more prominent than the seventh nerve lesion. In the literature, there are case reports of MS patients with facial paralysis [5-7]. In the early stages of multiple sclerosis, facial hypoesthesia is observed as a result of the fifth nerve lesion, but it usually does not cripple the patient. However, magnetic resonance imaging (MRI) may miss some brainstem lesions. In patients with MS, the third and fourth nerve palsy (internuclear ophthalmoplegia and convergence disorder) show up without brainstem lesions. In one study, 19.6% of Japanese patients with MS had facial paralysis during the course of the disease [6]. However, in a Croatian cohort, the prevalence of facial paralysis was reported as 3.7% [8]. In a recent study conducted in Turkey, 5.3% of MS patients reported peripheral facial paralysis during the attack period [9].

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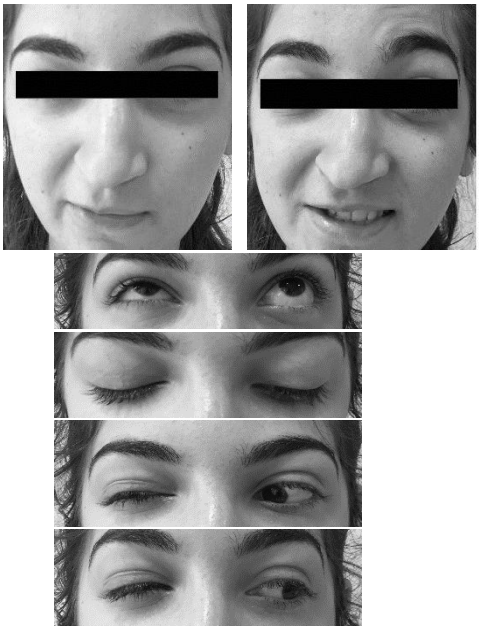
Case presentation

A 17-year-old previously healthy female was admitted to hospital with complaints of numbness in the right half of the face, difficulty chewing on the right side, dropping in the right mouth corner, and blurring in both eyes. She did not complain of any limb weakness, imbalance tendency to fall, but she did have weakness in the left arm. Her complaints started suddenly about two days prior to seeking treatment, and when the symptoms did not pass, she went to the hospital. The patient did not describe any complaints of diplopia, painful eye movements, hearing impairment, facial rash, dysphagia, or dysarthria. The patient had no history of traveling to a foreign country. Her neurological examination revealed normal orientation of place, person, and time. Although facial asymmetry was uncertain at first glance, when the patient was asked to show her teeth, there was retraction in the right mouth corner and indistinctness in the left nasolabial sulcus. She could lift her left eyebrow but not her right (Figure 1).

Figure 1: The first examination of the patient revealed that although facial asymmetry due to seventh nerve paralysis was uncertain at first glance, when the patient was asked to show her teeth, there was drooping in the right mouth corner, indistinctness in the left nasolabial sulcus, and she could not move her left eyebrow.



As a result of the current clinical findings, the patient was considered to have right trigeminal and left central facial paralysis. There was no saliva secretion or facial rashes. There was no weakness in the temporal and masseter muscles with palpation. Sensory examination revealed hypoesthesia on the right side of the face, characteristically matching the distribution of the trigeminal nerve in the skin, including the maxillary and mandibular parts of the trigeminal nerve. Other cranial nerve examinations were normal. Ophthalmoscopic examination revealed no optic atrophy or papillitis. Reflex examinations revealed no demonstrable pathological involvement affecting the extremities in the corticospinal, spinothalamic, and posterior colon pathways. Cerebellar tests were normal. Brain and spinal MRI were performed (Figure 2, 3).

Figure 2: T2 FLAIR images show multiple hyperintense plaques in the periventricular deep white matter, the juxtacortical area, and in the plaque lesion located in the corpus callosum.

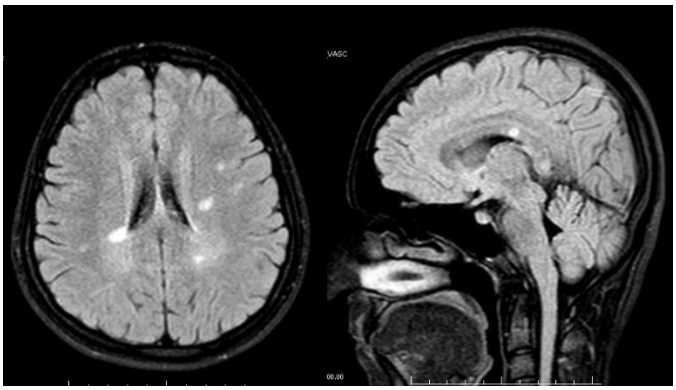
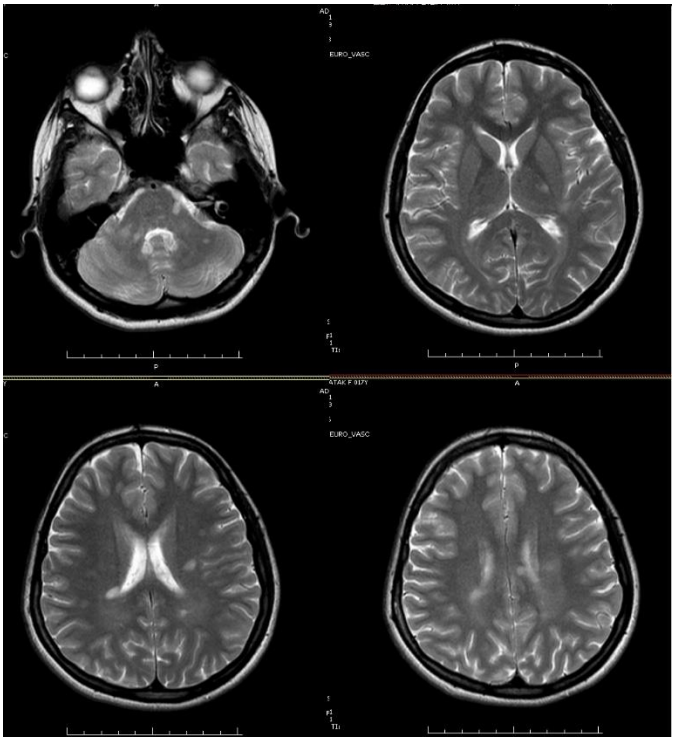
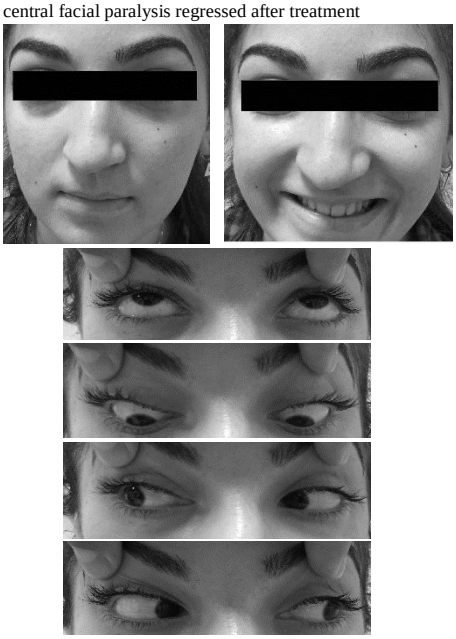


Figure 3: T2 A images are negative for plaque formation in the left pontobulbar junction, right inferior cerebellar peduncle level, left periatrial, callosal, and both periventricular deep white matter and juxta cortical placement.



There was no lesion in the spinal cord. Cerebrospinal fluid (CSF) analysis revealed normal protein levels without cells. Oligoclonal band (OCB) type 2 (three bands) was positive. Anti-myelin oligodendrocyte glycoprotein (MOG) and neuromyelitis optica (NMO) antibodies were negative. VEP, tibial, and median SEP of evoked potentials were within normal limits. All other basic biochemistry results were normal, including inflammatory markers. The patient was HLA B27 (-) and HLA B51 (+). The patient was treated with intravenous methylprednisolone (1000 mg / day) for 7 days. On the seventh day of hospitalization, the patient's left facial paralysis and chewing difficulties regressed and loss of sensation improved (Figure 4). The patient consented to participate in this study.

Figure 4: The left central facial paralysis regressed after treatment



Discussion

Isolated cranial nerve strokes can result from many diseases, including vasculitis, basal meningitis, and many other inflammatory conditions of the brain stem. The pathogenesis of isolated cranial nerve paralysis in multiple sclerosis is uncertain. Some reports suggested that brain stem demyelination plays a role [3], and the case presented herein had a brain stem lesion on MRI. Isolated cranial nerve paralysis is rarely seen in demyelinating diseases, including MS [10, 11].

While brain stem involvement is common in MS, isolated cranial nerve palsy is rare. In their retrospective study, Thömke et al. [12] reported that isolated cranial nerve palsy is a rare clinical finding in MS, affecting only 1.6% of patients in their series. Trigeminal neuralgia was reported as the first sign of MS in 0.3% and 1.9% of cases during the disease [3, 13, 14]. The case presented herein was admitted with motor and sensory symptoms due to trigeminal nerve involvement. The pathogenetic mechanism of trigeminal sensory neuralgia in MS patients is usually caused by demyelinating lesions affecting the pontine trigeminal pathways. Trigeminal sensory neuropathy secondary to MS preferably affects the second and third division of the trigeminal nerve, and in our case, there was hypoesthesia in the second and third branch of the trigeminal nerve. However, she did not have trigeminal neuralgia. In the literature, MS patients with facial paralysis have mostly been reported as case reports [5, 6]. In a case presented by Critchley, the first sign of MS disease was facial nerve paralysis [7]. Another study reported facial paralysis in 21 (19.6%) of 107 MS patients [6]. Zadro et al. [8] reported that 2.7% of patients presenting with seventh cranial nerve paralysis and 3.5% presented with trigeminal nerve paralysis as the first clinical symptoms. In the study of Thömke et al. [12] facial paralysis was the first finding of admission in three patients. Yetimalar et al. [15] reported peripheral facial paralysis in one of 21 MS patients who began having with unusual symptoms. The case presented herein was admitted with left central facial paralysis.

Conclusion

Since MS is characterized by multiple neurological symptoms, early diagnosis and treatment are critical to its prognosis and course. Therefore, MS should be considered in the differential diagnosis of young adult patients presenting with isolated cranial nerve palsy.

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