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The assessment of etiology and risk factors of urinary tract infections in geriatric patients admitted to emergency department

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The study was approved by the Scientific Research Ethics Committee of Kahramanmaras Sütçü İmam University (decision date: 11/7/2018, decision no: 06, session: 2018/20).
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: A urinary tract infection (UTI) is one of the most common bacterial infections in the elderly population. This study aimed to evaluate the etiology and risk factors of UTI among patients aged 65 and over who were admitted to the emergency department and then hospitalized.
Methods: This study was designed as a descriptive epidemiological study. Data of patients aged 65 and over, who were admitted to the adult emergency department of Kahramanmaraş Sütçü İmam University Medical Faculty and hospitalized between October 2015 and October 2018 with a diagnosis of UTI, were included in the study. Study data were collected through a retrospective scan of the patient files from the automated hospital system.
Results: Of the patients, 51% (n = 50) were female, and 49% (n = 48) were male. Of the patients diagnosed with UTI, 68.4% were aged 75 years or older. Fever, flank pain, and dysuria were found to be among the main reasons for patients with UTI to present to the emergency department. The most common risk factors for UTI were found to be the presence of diabetes mellitus and immunosuppression. Benign prostatic hyperplasia and nephrolithiasis were found to be the most common risk factors in males. In 83.7% of the patients, urine cultures were obtained at the initial presentation, and *Escherichia coli* was found to be the most common microorganism in patients with positive urine cultures.
Conclusion: The presence of UTI causes an increase in the risk of mortality in geriatric patients. Therefore, UTI should be considered in the differential diagnosis when the general condition has deteriorated in the geriatric patient even if the patient is asymptomatic. Urine culture samples should be obtained in cases of suspected infection, and antibiotic therapy should be started immediately to decrease mortality and increase recovery rates when the urine results indicate infection.

Keywords: Emergency department, Geriatrics, Urinary tract infection

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Introduction

The World Health Organization (WHO) defines the elderly as the chronological age, namely the calendar age, of 65 years and older. Although the concept of old age has many biological, psychological, and social dimensions, the definition proposed by WHO is accepted worldwide [1]. According to data from WHO, 12% (900 million) of the world's population consisted of elderly people as of 2015. According to the estimates made by WHO, the elderly population will double in 2050, and individuals aged 65 and over will account for 22% (two billion) of the world's population [2]. The elderly population in Turkey is 8.8% (seven million) as of 2018, and this ratio continues to increase rapidly. Over the last four years, the proportion of the elderly population in Turkey has increased by 16% [3]. Prolongation of the median lifespan has led to an increase in the problems related to old age in the last century, particularly in developed countries, and thus, to the development of geriatrics, a specialized medical science that treats the elderly population [4]. The estimates made by WHO show that a further increase in the elderly population and the medical needs of this population will also increase in the upcoming years [2].

Older age-related weakening of the immune system and decrease in physiological functions, such as cough reflexes, circulation, and wound healing increases the susceptibility to infection. Urinary tract infection (UTI) is among the most commonly diagnosed infections in the elderly population and is the most common reason for antibiotic use in this population [5, 6]. Particularly in individuals over 65 years of age, the incidence of UTI in both sexes increases with advancing age [7]. Since clinical symptoms are generally atypical, diagnosis and treatment can be quite difficult, particularly in elderly patients living in a nursing home. While the incidence of UTI in the community-dwelling elderly population is 25%, this rate can vary between 25% and 50% and 15% and 40% in elderly women and men, respectively, who are nursing home residents. The incidence of UTI also varies in the geriatric age groups with a female-to-male ratio of 2:1 and even 1:1 [8, 9]. Bladder outlet obstruction resulting from benign prostatic hyperplasia is an important risk factor leading to UTI in elderly men. A relative decrease in UTI can be seen due to decreased sexual activity in elderly women. Since anatomical and pathophysiological factors, such as uterine prolapse, urolithiasis, and genitourinary malignancies are more common in the elderly, recurrent and complicated UTI infections are encountered more frequently in this population. Furthermore, catheter-related UTI is common in these age groups and carries an increased risk in terms of complications and morbidity.

In light of current information, this study aimed to evaluate the etiology and risk factors of UTI among patients aged 65 and over who were admitted to the emergency department and then hospitalized.

Materials and methods

This study was a retrospective cohort study. Data of patients aged 65 and over, who were admitted to the adult emergency department of Kahramanmaras Sütçü İmam University Medical Faculty and hospitalized between October 2015 and October 2018 with a diagnosis of UTI, were included in the study. One-hundred ninety-six patients were identified for the study, and 98 of these cases fulfilled the inclusion criteria. Study data were collected through a retrospective scan of the patient files from the hospital automation system. Patients under 65 years of age, those who presented to the emergency department for reasons other than a UTI, and those who were not hospitalized were excluded from the study. The study was approved by the Scientific Research Ethics Committee of Kahramanmaras Sütçü İmam University (decision date: 11/7/2018, decision no: 06, session: 2018/20). The research was performed in agreement with the Helsinki Declaration. Informed consent was not taken from patients due to the retrospective nature of the study.

The following parameters were recorded in an Excel table prepared for the study: (1) sociodemographic data, such as age and sex of the patient, (2) complaints at the time of admission, (3) complete urinalysis (CU) parameters (leukocyte, erythrocyte, bacteria, nitrite, crystal), (4) venous blood test parameters (leukocytes, hemoglobin levels, neutrophils, lymphocytes, platelets (PLT), mean platelet volume (MPV), C-reactive protein (CRP)); and (5) imaging techniques (abdominal ultrasonography (USG), abdominal computed tomography (CT)), urine culture results, antibiotics administered during the treatment, and prognosis of the patient. Presence of a urinary catheter, genitourinary system anomaly (vesicoureteral reflux (VUR), ureter stenosis, and others), neurogenic bladder, fecal incontinence, benign prostatic hypertrophy (BPH), diabetes mellitus (DM), immunosuppressed conditions (use of chemotherapy, exposure to radiotherapy, drugs causing immunosuppression), malignancy, and the presence of nephrolithiasis, all of which have been defined as risk factors, were also evaluated and recorded.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 software (SPSS Inc, Chicago, Illinois, USA). Descriptive data were expressed as frequency and percentage for qualitative data and as frequency, mean (standard deviation (SD)) for numerical data. Visual (histogram) and analytical (Kolmogorov–Smirnov, Shapiro–Wilk tests) methods were used to determine whether the parameters followed a normal distribution. In the comparison of quantitative data, the Student's t-test was used to compare the parameters between the two groups, and one-way analysis of variance (ANOVA) was used for the comparisons between more than two groups in cases in which parametric assumptions were met. If parametric assumptions could not be met, the Mann–Whitney U test was used for comparisons between two groups, and the Kruskal–Wallis test was used for comparisons between more than two groups. Correlation tests were used to compare two sets of quantitative data. In cases in which two sets of quantitative data followed a normal distribution, correlation coefficients and statistical significance were calculated using Pearson's correlation coefficient. Correlation coefficients and statistical significance were calculated using Spearman's rank correlation coefficient for relationships between variables, at least one of which did not follow a normal distribution or was ordinal. A chi-square test was used to compare qualitative data. A P-value of < 0.05 was considered statistically significant.

Results

Of the patients included in the study, 51% (n = 50) were female, and 49% (n = 48) were male. Of the patients, 40.8% (n = 40) were between 75 and 85 years of age (middle-old), and the main complaints at the time of admission were fever in 63.3% (n = 62). the most common risk factors for UTI were found to be DM or immunosuppression in 37.8% (n = 37) of the patients. Demographic outcomes are presented in the Table 1.

Table 2 examines the relationship between gender and both complete urinalysis and blood count. When gender and complete blood count were evaluated together, it was found that only the lymphocyte count was statistically significantly higher in women (P = 0.024). Other values are presented in Table 2.

The mean duration of antibiotic use was 11.1 (7.8) days in men and 9.2 (6.6) days in women. This difference also did not create a statistically significant difference between the sexes. All parameters are summarized in Table 2.

Table 1: Sociodemographic characteristics of the patients

	Sex					
	Female		Male		Total	
	n	%	n	%	n	%
Age						
65–75 years	12	24.0	19	39.6	31	31.6
75–85 years	26	52.0	14	29.2	40	40.8
85 and above	12	24.0	15	31.2	27	27.6
Total	50	51.0	48	49	98	100
Complaint at the time of admission						
Fever	30	60	32	66.7	62	63.3
Dysuria	10	20	5	10.4	15	15.3
Polyuria	0	0.0	1	2.1	1	1.0
Pollakiuria	2	4.0	0	0.0	2	2.0
Flank pain	8	16.0	10	20.8	18	18.4
Risk factors						
No risk factor	17	34.0	16	33.4	33	33.7
Kidney Stone	3	6.0	4	8.3	7	7.1
Neurogenic bladder	0	0.0	1	2.1	1	1.0
Benign prostatic hyperplasia	0	0.0	11	22.9	11	11.2
Prostate cancer	0	0.0	5	10.4	5	5.1
Diabetes mellitus/immunosuppression	29	58.0	8	16.7	37	37.8
Presence of a catheter	1	2.0	3	6.2	4	4.1

Table 2: Urine and venous blood analysis values and mean duration of antibiotic use of the patients by sex

	Sex				
	Female		Male		
	n	Mean (SD)	n	Mean (SD)	P-value
Complete urinalysis					
Leukocyte	48	2.5 (0.9)	47	2.3 (1.1)	0.51[a]
Erythrocyte	48	2.0 (1.2)	47	1.7 (1.2)	0.24 [a]
Bacterium	48	0.0 (0.0)	47	0.0 (0.0)	---
Nitrite positivity	48	0.3 (0.5)	47	0.2 (0.4)	0.15
Crystal	48	0.0 (0.0)	47	0.0 (0.0)	---
Complete blood count					
Leukocyte	50	12.8 (5.2)	48	12.9 (7.8)	0.72[a]
Hemoglobin	50	11.6 (2.4)	48	12.1 (2.5)	0.27[b]
Neutrophil	50	10.1 (4.9)	48	10.7 (7.2)	0.64[b]
Lymphocyte	50	1.6 (1.0)	48	1.2 (1.0)	0.024[a]
PLT	50	252.4 (130.6)	48	225.7 (132.9)	0.21[a]
MPV (μm^3)	50	10.9 (12.8)	47	10.5 (8.8)	0.78[a]
CRP (mg/L)	50	100.1 (89.5)	47	120.2 (86.3)	0.18[a]
Mean duration of antibiotic use (day)	50	9.2 (6.6)	40	11.1 (7.8)	0.28[a]

PLT: Platelet, MPV: Mean platelet volume, CRP: C-reactive protein, [a] p value found using the Mann–Whitney U test, [b] p value found using Student's t-test , SD: standard deviation

Urine cultures were obtained in 83.7% of the patients (n = 82) at the first visit, and urine culture was positive in 52.3% of female patients (n = 23) and 39.5% of male patients (n = 15). *E. coli* was found to be the most frequently reproducing microorganism (52.7%, n=20) in both sexes. No statistically significant difference in terms of *Escherichia coli* growth in the culture between both sexes was found (Table 3).

A control urine culture was obtained in 58.2% (n = 57) of the patients, and the result of control urine culture was positive in 48.3% (n = 14) of females and 21.4% (n = 6) of males. *E. coli* was found to be the most frequently reproducing microorganism in patients with positive control urine culture (55%; n = 11) in both sexes. Control urine culture positivity was statistically significantly higher in women than in men (P = 0.034) as shown in Table 4.

Table 3: Urine culture data of patients at the time of first admission according to sex

	Sex						
	Female		Male		Total		
	n	%	n	%	n	%	P-value
Urine culture at the time of the first admission							0.24
Yes	44	88.0	38	79.2	82	83.7	
No	6	12.0	10	20.8	16	16.3	
Initial urine culture result							0.25
Positive	23	52.3	15	39.5	38	46.3	
Negative	21	47.7	33	60.5	44	53.7	
Microorganisms reproducing in the first urine culture							
Escherichia coli	13	56.5	7	46.6	20	52.7	0.16 *
Klebsiella spp.	2	8.7	1	6.7	3	7.9	
Pseudomonas spp.	0	0.0	1	6.7	1	2.6	
Enterococcus spp.	3	13.0	0	0.0	3	7.9	
Streptococcus spp.	1	4.4	2	13.2	3	7.9	
Candida spp.	3	13.0	1	6.7	4	10.6	
Candida melibiosica	0	0.0	1	6.7	1	2.6	
Trichosporon spp.	1	4.4	0	0.0	1	2.6	
Corynebacterium amycolatum	0	0.0	1	6.7	1	2.6	
Contamination	0	0.0	1	6.7	1	2.6	

** Only the relationship of *Escherichia coli* and growth status with sex was examined.

Table 4: Control urine culture data of patients according to sex

	Sex						
	Female		Male		Total		
	n	%	n	%	n	%	P-value
Control urine culture							0.97
Yes	29	58.0	28	58.3	57	58.2	
No	21	42.0	20	41.7	41	41.8	
Control urine culture result							0.034
Positive	14	48.3	6	21.4	20	35.1	
Negative	15	51.7	22	78.6	37	64.9	
Microorganisms reproducing in control urine culture							
Escherichia coli	8	57.1	3	50.2	11	55.0	
Klebsiella spp.	1	7.1	0	0.0	1	5.0	
Pseudomonas spp.	1	7.1	0	0.0	1	5.0	
Candida spp.	4	28.7	1	16.6	5	25.0	
Staphylococcus epidermidis	0	0.0	1	16.6	1	5.0	
Contamination	0	0.0	1	16.6	1	5.0	

Of the patients, 27.6% (n = 27) underwent abdominal USG and 18.4% (n = 18) underwent abdominal CT. When the patients were evaluated in terms of prognosis, 84.7% (n = 83) were discharged with full recovery, whereas 2.0% (n = 2) refused treatment, and 13.3% (n=13) died. No statistically significant difference between sexes in terms of imaging and prognosis was found (P > 0.05).

The relationship of the mean duration of antibiotic use with the age, CU, and venous blood analysis was examined. Only a statistically significant positive correlation between blood CRP level and the mean duration of antibiotic use was found (r = 0.330; P = 0.001) as shown in Table 5.

The duration of antibiotic use was evaluated according to the age groups of the patients, sex distribution, positive/negative urine culture at the time of admission, and prognosis. Age, sex, urine culture results, and prognosis of the patients did not yield statistically significant differences in the mean duration of antibiotic use (Table 6).

Table 5: Correlation of the mean duration of antibiotic use with the age, complete urine analysis (CU), and venous blood analysis

	Duration of antibiotic use		
	n	r	*P*-value
Age	94	−0.021	0.84
Complete urinalysis			
Leukocyte	95	−0.174	0.09
Erythrocyte	95	−0.132	0.21
Bacterium	95	---	---
Nitrite positivity	95	−0.117	0.27
Crystal	95	---	---
Complete blood count			
Leukocyte	98	0.093	0.37
Hemoglobin	98	0.043	0.68
Neutrophil	98	0.094	0.37
Lymphocyte	98	−0.080	0.44
PLT	98	0.009	0.93
MPV (μm^3)	98	0.077	0.46
CRP (mg/L)	98	0.330	0.001

PLT: Platelet, MPV: Mean platelet volume, CRP: C-reactive protein, * Since at least one of the variables was not normally distributed or ordinal, correlation coefficients and statistical significances were calculated using the Spearman's rank correlation coefficient for all relationships between variables.

Table 6: The relationship between the demographic characteristics of patients and the mean duration of antibiotic use

	Duration of antibiotic use		
	n	Mean (SD)	*P*-value
Age			0.52[a]
65–74 years	29	11.0 (8.3)	
75–84 years	38	9.4 (7.6)	
85 years and older	27	10.0 (5.2)	
Sex			0.28[b]
Female	50	9.2 (6.6)	
Male	44	11.1 (7.8)	
Urine culture at the time of the first admission			0.31[b]
Positive	36	11.1 (8.2)	
Negative	58	9.5 (6.5)	
Control urine culture			0.60[b]
Positive	20	10.4 (6.5)	
Negative	74	10.0 (7.4)	
Endpoint*			0.42[b]
Discharged	79	9.5 (5.6)	
Death (Exitus)	13	14.6 (12.9)	

[a] *P*-value found using Kruskall–Wallis test, [b] *P*-value found using the Mann–Whitney U test, * Analysis was performed by excluding those who refused treatment, SD: standard deviation

Discussion

The incidence of UTI increases in elderly patients over the age of 65 [7]. Bacteremia is associated with higher mortality rates in elderly patients. Deficiencies in the immune system and increased incidence of comorbidities (pulmonary, neoplastic, cardiovascular diseases, and others) can cause an increase in the risk of morbidity and mortality. In geriatric patients, UTI can be controlled with antibiotics since UTI can result in bacteremia, sepsis, and death [10]. A study published in the literature reported that the incidence of UTI is 25% among the community-dwelling elderly population and this rate increases with advancing age. In a similar study, this rate has been reported to be similar and the incidence of UTI in both sexes is almost equal in the advanced ages [8, 9]. The results obtained from the present study support these literature data, and it was a particularly remarkable finding that more than 2/3 of the patients were aged 75 years and older. Furthermore, the incidence of UTI among the sexes was almost equal to each other in the present study.

Tanyel et al. [10] reported in their study that typical UTI symptoms (dysuria, polyuria, fever) may be rarer in elderly patients compared to younger individuals and these elderly patients may be even asymptomatic. In the present study, most patients presented typical complaints at the time of admission. The presence of underlying comorbidities has been reported as an important risk factor for UTI in elderly patients [7, 10]. Similarly, in the present study, risk factors for UTI were present in about two-thirds of patients, and DM and immunosuppression were the most common ones.

Blood tests, CU, urine culture, and imaging tests are performed to diagnose suspected UTI in geriatric patients. The microscopic examination of urine is important in the diagnosis of UTI. The presence of bacteria and leukocytes in the urine is called bacteriuria and pyuria, respectively. The presence of one or more leukocytes in each field or 10 or more white blood cells per mm^3 in a urine specimen at x 40 magnification is considered compatible with UTI [11]. Leucocyte cylinder in the urine is identified with leukocytosis, sedimentation, and CRP elevation in patients with pyelonephritis. Imaging techniques are recommended in cases in which a complicated UTI or structural anomaly is suspected and in the presence of recurrent infections. Direct radiography can show urinary tract stones. Urinary tract USG or abdominal CT may be performed to detect abscesses and other pathologies. Pyuria (presence of 10 or more leukocytes per mm^3 in the urine) is also seen in more than 90% of men and women with bacteriuria [12]. The results obtained from the present study support these data in the literature. Although the increases were not statistically significant, the mean number of leukocytes and erythrocytes per µL and leukocyte and neutrophil count in addition to CRP levels have been observed to increase.

The detection of the growth of the active microorganism in urine culture ensures the definitive diagnosis of UTI [11]. Ginde et al. [13] reported that *E. coli* (32.4%) is the most frequently reproducing microorganism in urine culture in patients with UTI. In a study by Uluğ et al. [14], *E. coli* was isolated in 262 (64.5%) of the patients. The results in the present study are compatible with the literature; *E. coli* was detected in urine culture examination in most patients.

Patients with complaints of UTI are diagnosed based on the history of the patient, physical examination, blood test, and urinalysis and empirical antibiotic treatment is applied without waiting for urinalysis results in general. The main objectives of UTI treatment are to provide effective and rapid responses to treatment, prevent recurrence in the recovered patients, and prevent rapidly increasing resistance by microorganisms to antimicrobials. Determining the type of UTI is important in treatment selection. The initial treatment preference is empirical. Treatment should be planned taking into account the presence of complicating factors and the antimicrobial resistance pattern. Several factors regarding the antibiotic to be selected should be taken into consideration in the treatment: (1) active in the urine, (2) reaching an adequate urine concentration in the renal parenchyma and bladder, (3) long-term steady concentration effective against possible different microorganisms, (4) resistance of uropathogens, (5) bactericidal activity, (6) patient compliance, (7) possible side effects, and (8) cost [11]. Empirical antibiotic selection should be made based on the most likely cause of infection. A broad-spectrum antibiotic may be preferred at the beginning of the treatment but a more specific, less toxic, and more appropriate effective antibiotic should be started depending on the antibiogram results [15].

In a study by Tüzün et al. [16], the duration of antibiotic treatment may vary depending on the sex and clinical condition of the patient. The recovery rate in short-term treatment has been reported to be low and the seven-day treatment will be more suitable in older women. It has been reported that the duration of symptomatic lower UTI treatment should be 10–14 days in older

men, and that the treatment may need to be extended up to 6 to 12 weeks in recurrent infections [12, 16]. Compatible with the literature, the duration of antibiotic use was longer in male patients than in female patients in the present study. The correlation of the mean antibiotic use with complete blood count parameters and CRP levels was further investigated. A statistically significant correlation was found between the duration of antibiotic use and increased CRP levels.

It has been reported that low mortality rates are achieved by initiating appropriate antibiotic treatment in patients with UTI-induced urosepsis [10]. In the present study, mortality has been observed in 13.3% of the patients although antibiotic treatment has been initiated in the early period. This mortality rate may have occurred because patients are in the geriatric age group, and underlying comorbidities can worsen the condition.

Limitations

As a limitation in our study, the study was retrospective, and some data (antibiotic dose) could not be completely recovered.

Conclusion

The presence of UTI in geriatric patients increases the risk of mortality. Comorbidities, advanced age, and late diagnosis are among the important causes of mortality. Early diagnosis and treatment play an important role in producing a reduction in mortality rates. Therefore, UTI should be considered in the differential diagnosis when the general condition is deteriorated in the geriatric population even in cases in which patients are asymptomatic. Urine culture samples should be obtained in cases of suspected infection, and antibiotic therapy should be started immediately to decrease mortality and increase recovery rates when the urine results indicate infection.

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The effect of type 2 diabetes mellitus on early postoperative cognitive functions

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Abstract

Background/Aim: Postoperative cognitive dysfunction (POCD) is an important problem that is encountered perioperatively and has a complex pathophysiology. Diabetes mellitus (DM) can cause adverse effects on cognitive functions, such as memory dysfunctions, psychomotor retardation, slower information processing, impairment of complex motor functions, deterioration of verbal rationality, and attention deficit. We assume that DM will have a triggering effect on POCD. Mild cognitive dysfunction caused by diabetes mellitus may increase the risk of POCD. For this purpose, we aimed to investigate the effect of type 2 DM on early POCD.

Methods: Fifty literate patients who ranked 1-2 on the American Society of Anesthesiologists (ASA) scale were included in our prospective case-control study. They ranged in age from 35 to 70. All were scheduled for elective laparoscopic cholecystectomy at the İstanbul Training and Research Hospital. Patients were divided into two groups: the diabetes mellitus group and the control group. The DM group consisted of 25 patients who had been diagnosed with type 2 DM and had been on regular oral antidiabetic medication or insulin for at least five years. To examine the patients neuropsychologically, the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) Test were conducted one day before the surgery. The MMSE and MoCA were repeated at the 4^{th} and 24^{th} hours postoperatively. The patients were monitored to record their depth of anesthesia, peak heart rate, mean arterial pressure, oxygen saturation, end-tidal carbon dioxide value, and expiratory sevoflurane concentration prior to perioperative intubation and every five minutes after intubation until the end of the operation. The state of postoperative pain and total analgesic dose used for the patients were also recorded.

Results: Demographic data in both groups were similar in terms of age, gender, body mass index, and duration of surgery ($P > 0.05$ for each). Perioperative depth of anesthesia, hemodynamic data, and postoperative pain scores were similar in both groups ($P > 0.05$ for each). While there was initially no significant difference between the groups in terms of preoperative cognitive function, compared with the control group, the DM group had significantly lower values of MMSE and MoCA at the postoperative 4^{th} ($P = 0.014$ and $P = 0.014$) and 24^{th} hour ($P = 0.026$ and $P = 0.01$) .

Conclusion: Our study shows that the early postoperative cognitive functions of diabetic patients are affected more than non-diabetic patients in laparoscopic surgery. MMSE and MoCA tests are appropriate for screening type 2 diabetic patients. Thus, complications can be prevented in diabetic surgical patients by detecting cognitive dysfunction in the early stages, so that appropriate treatment can be initiated.

Keywords: Cognitive dysfunction, Postoperative cognitive complications, Diabetes mellitus type 2

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Introduction

Postoperative cognitive dysfunction (POCD) has become one of the most important problems of the perioperative period, with the increasing population of elderly patients [1, 2]. For the first time in 1955, Bedford et al. [3] drew attention to the development of cognitive dysfunction in the perioperative period. The independent variables that play a role in the etiology and pathogenesis of POCD vary. Clinical studies on this subject have concluded that anesthesia and anesthetic agent selection [4], postoperative pain treatment agents used, postoperative pain [5], sleep disorders in the perioperative period [6], perioperative hypoperfusion, and adverse events, such as stress response and inflammation [7, 8], play multifactorial roles in the etiopathogenesis of POCD. The effect of comorbidities, such as cerebrovascular events, hypertension, and obesity in the development of POCD has not yet been clarified [9].

Diabetes mellitus (DM) is a multisystemic disease [10, 11]. As approaches to prevent and treat the microvascular and macrovascular damage of DM advance, the life expectancy with this disease increases. As a result, new complications such as impaired cognitive functions can be observed. DM can cause adverse effects on cognitive functions such as memory dysfunctions, psychomotor retardation, slower information processing, impairment of complex motor functions, deterioration of verbal rationality, and attention deficit [12].

We assume that DM will have a triggering effect on POCD. For this purpose, we aimed to investigate the effect of type 2 DM on early POCD.

Materials and methods

This prospective case-control study was conducted in the Istanbul Training and Research Hospital between March 2016 and December 2016.

The study included 50 literate patients with perfect vision and hearing in the age group from 35 to 70 years. All participants had scored 1-2 on the pre-anesthesia assessment of the American Society of Anesthesiologists (ASA). All patients were scheduled for elective laparoscopic cholecystectomy. The DM group included 25 patients who had been diagnosed with type 2 DM and had been on regular oral antidiabetic medication or insulin for at least five years. Preoperative blood glucose control had been achieved in these patients. The control group included 25 randomly selected patients who underwent laparoscopic cholecystectomy without a diagnosis of DM. Those over the age of 70 years, with a score of ASA III and above, who were known to be allergic to anesthetic drugs, had liver or kidney dysfunction, alcohol and/or substance addiction, or psychiatric symptoms and diagnosis were excluded from the study. Also excluded were patients who were on psychiatric drugs, had central nervous system disorders, dementia, permanent deficits caused by cerebrovascular events, or had received general anesthesia in the last three months. Patients with a body mass index (BMI) over 40, those diagnosed with hyperthyroidism or hypothyroidism, or scheduled for emergency surgery did not meet the inclusion criteria. Patients whose operation was started by laparoscopic method and completed using open surgery and who were administered intraoperative blood products, vasopressor drugs, antihypertensive drugs, or glucocorticoids were also excluded from the study.

In the preoperative period, age, gender, ASA score, BMI, and the presence and duration of DM diagnosis were recorded. A funduscopic examination was performed in the DM group, and the presence of diabetic retinopathy was recorded. Premedication was not given to the patients. Anesthesia was induced with 2 mg/kg propofol, 1 mcg/kg fentanyl, and 0.6 mg/kg rocuronium. Sevoflurane was used as a volatile anesthetic for anesthesia maintenance. Necessary adjustments were made in the sevoflurane concentration to maintain the depth of anesthesia in each patient so that the Bispectral Index (BIS) value was between 40 and 60. The BIS, peak heart rate (PHR), mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO_2), end-tidal carbon dioxide concentration, and the end-expiratory sevoflurane concentration (EX-SEVO) were recorded before intubation and every five minutes thereafter until the end of the operation. As analgesics, 1 gram of paracetamol was administered peroperatively, and tramadol HCL was started intravenously using a patient-controlled analgesia device. The pain status of the patients was evaluated using the Visual Analog Scale (VAS) score at the postoperative 1st, 2nd, 4th, 8th, 12th, and 18th hour.

The Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) Test were used one day before surgery to examine the patient's neuropsychology. The tests were repeated at the postoperative 4th and 24th hour. Consisting of 11 questions, the MMSE is a test that examines orientation, memory, attention, calculation, recall, language, motor function, and perception abilities and whose validity and reliability in Turkish was confirmed by Güngen et al. [13, 14]. MoCA is a psychomotor test with a maximum score of 30 that assesses attention, concentration, executive functions, memory, language, visual-spatial skills, abstract thinking, evaluating calculation, and orientation functions and whose validity and reliability in Turkish was confirmed by Selekler et al. [15, 16].

Power analysis

Group sample sizes of 25 and 25 achieved 85% power, detecting a difference of -3.0 from the null hypothesis; both group means were 21.0. The alternative hypothesis for the mean of Group 2 was 24.0 with known group standard deviations of 3.6 and 3.2 and with a significance level (alpha) of 0.05000 using a two-sided Mann-Whitney test assuming that the actual distribution is normal.

Statistical analysis

In the statistical analysis, the descriptive statistics of the data were presented as mean values (standard deviation), median lowest, median highest, frequency, and ratio values. The distribution of variables was measured with the Kolmogorov–Smirnov test. To analyze quantitative independent data, the Independent Samples t-test and Mann–Whitney U test were used. The Chi-squared test was used for analyzing the qualitative independent data, and SPSS 22.0 program was used for statistical analysis.

Results

The age, gender distribution, and BMI of the patients in the DM group and the control group did not show any statistically significant difference ($P > 0.05$ for each). The surgical duration of the patients in the DM group and the control group did not differ significantly ($P > 0.05$) (Table 1).

Table 1: Comparison of the DM and control groups by demographic data

	DM group	Control group	*P*-value
Age	55.8 (7.2)	51.7 (9.9)	0.1
Gender:			0.156
Female	16 (64)	11 (44)	
Male	9 (36)	14 (56)	
BMI	30 (3.7)	30.7 (4.6)	0.539
ASA I	0 (0)	12 (48)	< 0.001
II	25 (100)	13 (52)	
Surgery time	48.4 (12.7)	52.2 (14.7)	0.383

Values are given as mean (standard deviation) and n (%); BMI: body mass index; ASA: American Society of Anesthesiology Physical Status Classification System; DM: diabetes mellitus

Of the 25 patients included in the DM group, 3 were found to have retinopathy in the preoperative funduscopic examination, whereas the mean duration of diabetes was 9.16 (3.7) years.

Measured preoperatively and every five minutes during the peroperative period, the values of BIS, HR, MAP, SPO_2, $ETCO_2$, EX-SEVO did not show a statistically significant difference between the two groups, and their pain status in the postoperative period was found to be similar ($P > 0.05$ for each).

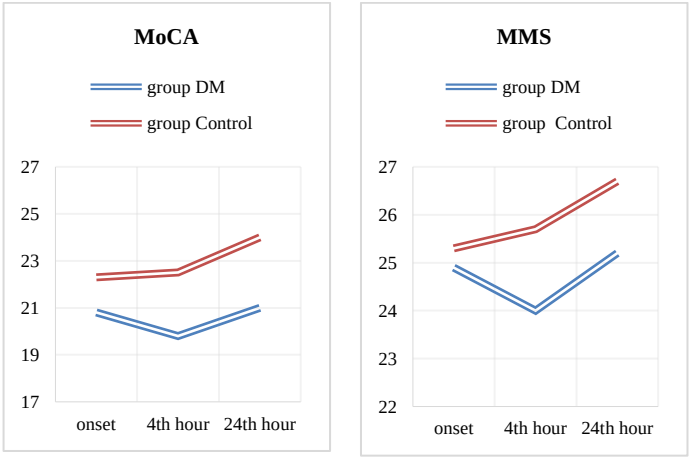
The baseline MoCA score did not differ significantly in both groups. The DM group had significantly lower MoCA scores at the 4th and 24th hours compared with those in the control group ($P = 0.014$ and $P = 0.010$). The baseline MMSE score did not differ significantly in both groups. The DM group had significantly lower MMSE scores at the 4th and 24th hours compared with those in the control group ($P = 0.014$ and $P = 0.026$) (Table 2 and Figure 1).

Table 2: Comparison of the DM and control groups by MoCA and MMSE scores

	DM group	Control group	*P*-value
Preoperative MoCA	20.8 (3.1)	22.3 (3.1)	0.20
Postoperative 4th hour MoCA	19.8 (3.6)	22.5 (3.4)	0.014
Postoperative 24th hour MoCA	21.0 (3.6)	24.0 (3.2)	0.010
Preoperative MMSE	24.9 (1.7)	25.3 (2.4)	0.47
Postoperative 4th hour MMSE	24.0 (2.1)	25.7 (2.5)	0.014
Postoperative 24th hour MMSE	25.2 (2.1)	26.7 (2.3)	0.026

Values are given as mean (standard deviation). MoCA: Montreal Cognitive Assessment; MMSE: Mini-Mental State Exam; DM: diabetes mellitus,

Figure 1: a) Comparison of the MoCA Scores in the DM and Control Groups, b) Comparison of the MMS Scores in the DM and Control Groups



Discussion

In our study, although there was no statistically significant difference between the two groups in terms of preoperative cognitive function, the DM group had significantly lower scores of MMSE and MoCA at the postoperative 4th and 24th hours compared with those in the control group.

Age was the main risk factor in POCD [17]. A study by Monk et al. [18] reports the prevalence of POCD to be 36.6% in the age group of 18–39 years, 30.4% in the age group of 40–59 years, and 41.4% in the age group of over 60 years. These patients were those who had undergone major non-cardiac surgery, and three months later, this rate was found to be 5.7% in the young patient group, 5.6% in the middle-aged group, and 12.7% in the elderly group over the age of 60. In the study by Fodale et al. [19], the increase in amyloid beta peptide level in the elderly brain and its association with Alzheimer's disease should be taken into account, and considering that anesthetics would interact with this substance in cases of long-duration anesthesia administration, it was evaluated as an expected increase in the prevalence of POCD in elderly patients. To reduce age-related cognitive dysfunction, we included individuals aged under 70 herein. In addition, the mean age was 55.8 years in the DM group and 51.7 in the control group, and there were no statistically significant differences between the two groups.

The development of POCD is affected by factors, such as the type of surgery [20, 21], the anesthesia method applied [22, 23], the duration of anesthesia [24], and the depth of anesthesia [25]. The patients included in our study were those who underwent laparoscopic cholecystectomy under general anesthesia and the mean anesthesia duration was less than 75 minutes. The depth of anesthesia in both groups was monitored peroperatively by BIS monitoring to ensure a BIS value between 40 and 60. According to our results, surgical time, BIS follow-ups, and respiratory sevoflurane concentrations were similar in both groups. According to the literature, studies have shown that peroperative hypoxia and hypotension are risk factors for POCD [5, 25]. In our study, SpO_2 was not observed to be below 90 in any patient, and the levels of PHR, MAP and SpO_2 in both groups were similar in the peroperative follow-up. It has been shown in many studies that postoperative pain is one of the important risk factors in the development of POCD [5, 26]. In our study, no statistically significant difference was observed between the DM and control groups in terms of their VAS values at the postoperative 1st, 2nd, 4th, 8th, 12th, and 18th hour.

Cognitive values can be expected to worsen in the preoperative period in diabetic patients [27-29], and it is known that the risk for postoperative cognitive dysfunction is increased in patients with impaired preoperative cognitive functions [18]; however, no significant difference was found in preoperative cognitive tests between diabetic patients and non-diabetic patients in our study.

Type 2 diabetes has been associated with reduced frontal lobe executive function, psychomotor speed, verbal memory, processing speed, complex motor speed, recall, delayed recall, verbal fluency, visual memory, and attention [12]. The underlying pathophysiology of the development of cognitive dysfunction in DM patients has not been fully elucidated. There

are many hypotheses including hypoglycemia, insulin resistance, vascular damage, and amyloid accumulation [30, 31]. In the peroperative period, imbalances in the neurotransmitter system, such as acetylcholine and serotonin, increase in inflammatory mediators, and disruption of the blood–brain barrier due to cytokine release are the primary mechanisms responsible for the development of postoperative cognitive function [7, 8]. Considering these factors, it is expected that diabetic patients will experience a greater decrease in cognitive functions during the peroperative period.

Cognitive dysfunction is more common in cardiac surgery compared with non-cardiac surgery, and extracorporeal circulation-related micro-embolism, non-pulsatile flow, hypotension, and hypoxia contribute to its etiology. In these patients, cerebral perfusion impairment plays a major role in postoperative neuropsychological outcomes [32]. In a prospective study by Nötzold et al. [33], 14 diabetic and 20 non-diabetic patients who underwent coronary artery bypass graft operation were studied. Both groups were operated on by the same surgeon under standard intraoperative and perioperative conditions. Cognitive changes were evaluated daily at a 2–5-day interval postoperatively. Their results demonstrated that all patients had postoperative cognitive deterioration, and compared with the non-diabetic group, this deterioration was found to be significantly higher in the diabetic group. A study by Tang et al. [34] included a total of 131 patients undergoing valve replacement with cardiopulmonary bypass in the study group, along with the control group that included 40 healthy volunteers. Their cognitive functions were measured preoperatively one day before the surgery and on the seventh day postoperatively through neuropsychological testing, and the prevalence of POCD was found to be 43.8% seven days after the surgery.

Insulin resistance was significantly higher in the POCD patients than in the non-POCD patients. Insulin resistance was demonstrated to be correlated with incidence of POCD and increased proinflammatory cytokines. The meta-analysis conducted by Feinkohl et al. [35] in 2017 investigated the relationship between diabetes and POCD, and the risk of POCD after cardiovascular surgery was found to be 1.26 times higher in diabetic patients compared with non-diabetic patients. In the study conducted by Kadoi et al. [36] in 180 patients who underwent elective coronary artery bypass graft surgery, POCD was at 68% in the diabetic group and 55% in the control group on postoperative day 7. Age, presence of hypertension, jugular venous oxygen saturation, presence of atherosclerosis in the ascending aorta, diabetic retinopathy, and insulin treatment have been associated with short-term cognitive dysfunction. In the postoperative sixth month, POCD was detected in 28% of the diabetics and in 11% in the control group. Insulin therapy, diabetic retinopathy, and hemoglobin A1c levels have been associated with long-term cognitive dysfunction.

There are also studies showing a relation between the presence of diabetic retinopathy and cognitive dysfunction in non-cardiac surgery [37]. In our study, three patients had retinopathy, which we think is due to the short duration of diabetes (9.16 (3.7) years). Therefore, we could not make a significant comparison. We also indicated that elevated HbA1c levels and cognitive dysfunction were correlated [38, 39]. Yaffe et al. [40] showed that those with an HbA1c of over 7% have a four times higher risk of developing mild cognitive dysfunction. We did not measure HbA1C levels, because we included patients with close follow-up in our study, whose blood glucose was regulated in the preoperative period, and who received regular oral antidiabetic medication or insulin therapy.

There are only a few studies that have investigated the relation between DM and POCD in non-cardiac surgeries. Three studies including cardiac and non-cardiac surgery were examined in a meta-analysis conducted in 2018. After adjustments on age, gender, type of surgery, randomization, obesity, and hypertension, diabetes was associated with a 1.84-fold increased risk of POCD (OR 1.84; 95% CI 1.14, 2.97; $P = 0.01$). Obesity, BMI, hypertension and baseline blood pressure were not found to be associated with POCD [9]. Seventy-seven patients aged 65–75 years were included in the study by Zhang et al. [41] in patients who had undergone colorectal surgery, and cognitive dysfunction was demonstrated in 29 patients on postoperative day 7. As a result of multivariate logistic regression analysis, diabetes history (OR = 8.391 [2.208–31.882]; $P = 0.012$) was shown to be an independent risk factor for early cognitive dysfunction in elderly patients who underwent colorectal surgery. Therefore, the POCD-triggering effect of DM, especially in the elderly, should be considered to result in prolonged duration of hospital stay, decreased functional independence, increased risk of dementia, burden for the caregiver, increased healthcare costs, morbidity, and mortality [42, 43].

Limitations

This was a monocentric study and our patients were selected from a specific group. Cognitive dysfunctions that developed in the first 24 hours in both groups were evaluated, and the lack of follow-up of patients in the long term is our main limitation.

Conclusion

Today, as in laparoscopic cholecystectomy, outpatient surgeries are preferred more frequently and early postoperative discharge is emphasized. Our study has shown that the early postoperative cognitive functions of diabetic patients are affected more than non-diabetic patients. We believe that patients with DM should be evaluated in terms of POCD especially in the early postoperative period after outpatient surgery before deciding on their discharge.

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Do myometrial lesions affect the discrepancy of pathological findings in women with endometrial hyperplasia?

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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.

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Abstract

Background/Aim: Benign myometrial lesions are frequently found in pathologic specimens of hysterectomies. High rates of coexistence of these lesions with endometrial cancer have also been reported. Our aim was to evaluate the effect of myometrial lesions on the consistency of diagnoses between endometrial sampling results and final hysterectomy findings in patients with endometrial hyperplasia (EH) before hysterectomy.

Methods: Two hundred seventeen patients who were diagnosed as having EH via endometrial sampling and underwent hysterectomy within three months were included in this retrospective cohort study. The patients' preoperative and postoperative pathologic findings were compared, and discordant results were defined to be either overdiagnosed or underdiagnosed.

Results: The overall diagnostic concordance between the endometrial sampling results and the final hysterectomy pathologic findings was 32.2%. The rate of concurrent endometrial carcinoma (EC) among all EH was 22.1%. The discordance between preoperative endometrial sampling and final hysterectomy specimen results was evaluated, and patients with underdiagnosis were older (60.5 years, $P < 0.001$), had a higher BMI (30.84 kg/m^2, $P < 0.001$), were mostly postmenopausal ($P < 0.001$), had lower parity numbers (median = 2, $P = 0.002$), and had a lower rate of co-existing adenomyosis ($P = 0.009$). The rates of co-existing leiomyoma between the groups were not different. No effect of other demographic characteristics was observed in the multivariate regression analysis; however, the presence of adenomyosis was a significant independent risk factor affecting a 5.8-fold increase in overdiagnosis (-1.50; OR: 0.17 (0.05-0.50) $P = 0.002$) and 4.5-fold increase in underdiagnosis (-1.50; $P = 0.005$).

Conclusion: Co-existing adenomyosis could lead to discordance of the pathologic findings in women with EH diagnoses before hysterectomy.

Keywords: Adenomyosis, Endometrial hyperplasia, Leiomyoma, Diagnosis

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Introduction

Endometrial hyperplasia (EH) is an abnormal proliferation of the endometrial glands and stroma [1]. In 1994, the World Health Organization (WHO) divided EH into four groups according to cytologic nuclear atypia and glandular complexity: simple hyperplasia without atypia, complex hyperplasia without atypia, simple hyperplasia with atypia, and complex hyperplasia with atypia [2]. In 2014, the WHO revised the EH classification into two groups based on only nuclear atypia: non-atypical EHs (NAEH) are defined as benign, and atypical EHs (AEH), which are similar to endometrial intraepithelial neoplasia (EIN), and considered as precursors of endometrial carcinoma (EC) [3]. The clinical significance of atypical hyperplasia, in particular, is that these patients have an up to 40% probability of having concomitant EC detected in the final pathologic examination of hysterectomy specimens [4, 5].

It may not be easy to distinguish EC precursor AEH from well-differentiated EC [6]. Therefore, studies have focused on identifying patients with concurrent EC and evaluating factors that contribute to the discrepancy between endometrial sampling results and final pathologic findings of hysterectomy specimens. The most studied subject has been the effect of different endometrial sampling methods. The effect of patient-related factors, such as age, body mass index (BMI), chronic diseases, and nulliparity on the coexistence of EC with AEH was also evaluated [7-9].

Adenomyosis and leiomyoma, which are benign myometrial lesions, are frequently found in pathologic specimens of hysterectomies performed with benign indications at rates of 20-30% and 40-60%, respectively [10, 11]. High rates of coexistence of these benign myometrial lesions with EC have also been reported (adenomyosis 18.9-22.6%; leiomyoma 27%) [12-14].

Therefore, in this study, we aimed to evaluate the effect of myometrial lesions, such as adenomyosis and leiomyoma, on the discordance of pathologic findings in patients who were diagnosed as having any type of EH before undergoing hysterectomy.

Materials and methods

This retrospective observational study was performed in a university-affiliated hospital. Institutional review board approval was obtained (2011 KAEK 25 2021/04-09). The study complied with the principles of the Declaration of Helsinki. All patients signed informed consent forms before undergoing surgery, allowing their medical records to be used for research purposes.

Patients who were diagnosed as having EH through endometrial sampling and had undergone hysterectomy within three months following the diagnosis between May 2016 and May 2021 were reviewed. The medical records of 288 patients were evaluated. Women, whose endometrial sampling results classified according to the WHO 2014 EH classification and who underwent hysterectomy as first-line therapy were included [3]. Additionally, patients with full medical records were included to avoid recall and diagnostic suspicion biases. In order to avoid observer bias, patients whose pathology specimens were evaluated in another center were excluded (n = 9). In addition, patients who received progestin treatment before hysterectomy, using tamoxifen or hormone replacement therapy, whose duration between EH diagnosis and hysterectomy was longer than three months, and those with missing medical records were excluded (n = 62) . A total of 217 patients remained in the study. Endometrial sampling was performed under local anesthesia using an Endosampler® device. Endometrial sampling and hysterectomy specimens of patients were reviewed by gynecologic pathologists in our institution.

The presence of myometrial lesion was concluded according to preoperative ultrasonography reports and pathologic examination results after hysterectomy. Final hysterectomy histopathology results for endometrium, which were reported as ‘secretory’ or ‘proliferative’ were considered normal.

The patients were evaluated in three groups according to the consistency of endometrial sampling and final hysterectomy pathology results: overdiagnosis, underdiagnosis, and concordance. Among patients with preoperative diagnosis of NAEH (n = 105), those diagnosed as normal according to hysterectomy were defined as overdiagnosed. Those with AEH and EC in final pathologic examinations were defined as underdiagnosed, and patients with NAEH in the hysterectomy examination were defined as concordant. Among patients with preoperative diagnoses of AEH (n = 112), those who were normal and had NAEH in the final pathologic examination were defined as overdiagnosed; those with EC in the final pathological examination were defined as underdiagnosed, and patients with AEH in the final examination were defined as concordant. Patients with EC were staged according to the revised *2009 International Federation of Gynecology and Obstetrics* (FIGO) staging system [15].

Statistical analysis

The SPSS version 20.0 software package (SPSS Inc., Chicago, IL, USA) was used for data storage and statistical analysis. The descriptive statistics of the data were presented as mean (standard deviation). The Shapiro-Wilk test was used for detecting the distribution pattern of variables. The Mann-Whitney U test, Kruskal-Wallis and Chi-squared tests were used for comparing continuous and categorical variables among groups. Multivariate logistic regression was performed to detect the independent effects of variables on discordant results. *P*-values of < 0.05 were considered statistically significant.

Results

A total of 217 patients who were diagnosed as having EH before undergoing hysterectomy and met the inclusion criteria were retrospectively evaluated regarding their hysterectomy histopathology results.

The histopathologic results of endometrial samples and final hysterectomy specimens are shown in Table 1. The overall diagnostic concordance between the endometrial sampling results and the final hysterectomy pathologic findings was 32.2%; 26.7% of patients were underdiagnosed and 41.0% were overdiagnosed. Concurrent EC was observed in 22.1% of all patients.

According to the endometrial sampling results among the EH groups, the patients in the AEH group had a higher BMI

than NAEH (29.6 kg/m^2 vs 27.5 kg/m^2, P = 0.005). There was no difference between the groups in terms of other demographic data (Table 2).

Table 1: Endometrial sampling and final hysterectomy histopathology results

Endometrial sampling results	Final Hysterectomy findings				
	Normal	NAEH	AEH	EC	Total
NAEH	60 (57.1)	28 (26.7)	10 (9.5)	7(6.7)	105 (48.3)
AEH	21(18.8)	8(7.1)	42(37.5)	41 (36.6)	112 (51.7)
Total	81 (37.3)	36 (16.6)	52 (24.0)	48 (22.1)	217 (100)

NAEH: Non-atypical endometrial hyperplasia, AEH: atypical endometrial hyperplasia, EC: endometrial carcinoma. Values are given in percentages.

Table 2: Demographic characteristics of the groups according to the endometrial sampling results

	NAEH n = 105	AEH n = 112	*P*-value
Age (years)	52 (40-79)	53.5 (36-84)	0.664
BMI (kg/m^2)	27.5 (21.8-35.1)	29.6 (21.5- 39.1)	0.005
Parity	3 (0-10)	3 (0-7)	0.112
Menopause status, n (%)			
Premenopausal (n = 88)	48 (45.7)	40 (35.7)	0.167*
Postmenopausal (n = 129)	57 (54.3)	72 (64.3)	
Myometrial lesions, n (%)			
Adenomyosis (n = 64)	32 (29.5)	34 (30.4)	0.459*
Leiomyoma (n = 98)	60(57.1)	38 (33.9)	0.001*

BMI: Body Mass Index, NAEH: Non-atypical endometrial hyperplasia, AEH: atypical endometrial hyperplasia. Values are given as median (range) unless stated. The Mann-Whitney U test was performed. *Chi-squared test was used.

Those with underdiagnosis had significantly higher BMI (30.4 kg/m^2, P = 0.001) and were older (60 years, P < 0.001) than the other groups. The rate of patients in the postmenopausal period was also high in the underdiagnosis group (75.9%, P < 0.001). Co-existing adenomyosis was lowest in the underdiagnosis group and significantly different from the others (P = 0.004) (Table 3). There was no difference between groups in terms of co-existing leiomyoma rates (Table 3).

Table 3: Comparison of groups according to endometrial sampling and final hysterectomy pathological results compatibility

	Overdiagnosis (n = 89)	Underdiagnosis (n = 58)	Concordance (n = 70)	*P*-value
Age (years)	51 (38-72)	60 (37-79)[b]	52 (36-84)	< 0.001
BMI (kg/m^2)	27.5 (21.8-35.1)	30.4 (21.5-38.0)[b]	27.5 (21.9-39.1)	0.001
Parity	3 (0-10)	3 (0-6)[b]	3 (1-7)	0.04
Menopause status[a]				
Pre- (n = 88)	46 (51.7)	14 (24.1)[b]	28(40.0)	0.004
Post- (n = 129)	43 (48.3)	44(75.9)[b]	42 (60.0)	
EH diagnosis to surgery interval (days)	45 (16-82)	39 (18-88)	42 (20-81)	0.301
Adenomyosis[a]				
Yes (n = 65)	34 (38.2)	8 (13.8)[b]	23 (32.9)	0.004
No (n = 152)	55 (61.8)	50 (86.2)[b]	47 (67.1)	
Leiomyoma[a]				
Yes (n = 98)	46 (51.7)	25 (43.1)	27 (38.6)	0.245
No (n = 119)	43 (48.3)	33 (56.9)	43 (61.4)	

BMI: Body mass index, EH: endometrial hyperplasia. Values are given as median (range); The Kruskal-Wallis test was used unless stated otherwise. [a] Chi-squared test was used. Values are given n (%). [b] The group that differs from others.

The rate of co-existing adenomyosis was 29.9% among all EH cases, and the rate of co-existing adenomyosis was 13% in patients with a preoperative diagnosis of AEH and a final pathologic diagnosis of EC. In a multivariate logistic regression model, in which factors identified as potential risk factors (P < 0.05) in univariate analyses were included, no significant independent effects of age, BMI, parity, menopausal status, or presence of fibroids on discordant results were observed. The presence of adenomyosis was found to be a significant independent risk factor in obtaining discordant pathologic results. Overdiagnosis was found to be 5.8 times more likely in the presence of adenomyosis, regardless of age (B = -1.76; OR: 0.17 (0.05-0.50) P = 0.002). The presence of adenomyosis was also found to increase the probability of underdiagnosis by 4.5 times (B = -1.50; OR: 0.22 (0.07-0.63), P = 0.005).

Discussion

To the best of our knowledge, the current study is the first to report the effect of myometrial lesions, such as adenomyosis and leiomyoma, on the discordance of pathologic findings in patients who were diagnosed as having EH before undergoing hysterectomy. We retrospectively evaluated patients who underwent hysterectomy and their endometrial pathology results. We calculated the discordance rate of these results as 67.7%; 26.75% of patients were underdiagnosed and 41.0% were overdiagnosed. Patients who were classified as underdiagnosed were found to be older and had higher BMI than the others. It was also concluded that discordance rates were higher in patients with adenomyosis.

Adenomyosis is described as the presence of the endometrial glands and stroma within the myometrium. Microscopically, adenomyosis consists of non-neoplastic ectopic endometrial stroma and glands surrounded by hypertophic and hyperplastic myometrium [16]. Although traditionally the diagnosis is made through histopathologic examination, preoperative diagnosis can be made using transvaginal ultrasonography (TVUSG) or magnetic resonance imaging (MRI) due to the developments in imaging techniques [17]. Adenomyosis is found incidentally in 20-25% of benign hysterectomy specimens [18]. The relation between the diagnosis of EH and adenomyosis cannot be demonstrated with the available data. Existing literature has focused on EC developing in the presence of adenomyosis. Although the results of studies related to the co-existence of adenomyosis with EC are contradictory, a 22.6% pooled prevalence of adenomyosis in EC has been reported in recent studies, and it has been shown that this rate is not different from co-existence in benign conditions [13]. In our data, the co-existence rate of adenomyosis and EC was 12.5% (6 of 48). Although the underlying disorder is hyperestrogenism, the known etiologic factors of EC and adenomyosis are incompatible. While multiparity and use of oral contraceptives increase the risk of adenomyosis, they also reduce the risk of EC [14]. The reason for the coexistence of these two pathologies may be a coincidental association rather than a common etiology due to the high incidence of adenomyosis in peri/postmenopausal patients.

In the current study, none of the concurrent ECs originated from adenomyotic foci. Thirty-nine of the ECs were stage 1, and nine were stage 2. None of the stage 2 ECs had co-existing adenomyosis. Although the adenomyosis co-existence rate did not differ between EH subtypes, it was observed that adenomyosis accompanied fewer cases in those who were underdiagnosed in the final pathologic evaluation.

When the presence of myometrial lesions is not taken into account, several studies identify patients with EH who are likely to be underdiagnosed to avoid possible suboptimal surgery, especially in AEH cases in which concurrent EC rates are reported up to 40% [4]. Vetter et al. [19] evaluated 169 patients with complex AEH and reported that the concurrent EC rate was 48.5% and that the risk of concurrent EC increased in patients with a preoperative endometrial thickness of more than 2 cm and those aged over 65 years. Erdem et al. [9] reported that over the age of 50, diabetes mellitus, hypertension, and nulliparity were independent risk factors for concurrent EC in

AEH. In our study, we found that underdiagnosed patients were significantly older and postmenopausal. In the underdiagnosis group, patients had higher BMI and lower parity. Consistent with our results, Hui et al. [20] examined occult AEH and EC risk factors in NAEH cases and stated that patients with higher grades in the final pathology had significantly lower median parity and higher BMI. A recent study that evaluated risk factors for occult AEH and EC in women diagnosed as having NAEH in an endometrial biopsy found that patients over 51 years with complex NAEH subtype had a high risk for underdiagnosis [21]. According to the results of the mentioned studies [20, 21] and our research, it could be concluded that although NAEH was considered as benign by the WHO and the first-line treatment option was conservative, hysterectomy may be an option in the presence of risk factors for underdiagnosis in patients with NAEH.

In addition to the aforementioned risk factors regarding concurrent EC risk, the preferred endometrial sampling method is also relevant. Endometrial aspiration biopsy using a pipelle or Endosampler is the most preferred sampling method because it can be performed easily in an outpatient setting, does not require general anesthesia, and is as accurate as a D&C in the diagnosis of endometrial pathologies [8, 22]. In the current study, the Endosampler was preferred for preoperative diagnosis.

Studies of overdiagnosis in EH are limited. In one study, no characteristic features could be identified that distinguished the overestimated group from the other groups among the clinical parameters and imaging findings [23]. In our research, although the preoperative characteristics of patients with overdiagnosis did not differ from those of concordant patients, we found that the presence of leiomyoma did not affect the results, but the presence of adenomyosis increased the rates of overdiagnosis.

This novel study investigating the relationship between endometrial pathology discordance and myometrial lesions has a large sample size. Other strengths of this study include the use of the same endometrial sampling method in all patients and the evaluation of both pre- and postoperative pathology results by the same gynecologic pathologists in the same center. On the other hand, the retrospective design and conducting the study in a referral center might increase the incidence of occult EC, and this could be considered as a limitation of the study. Other limitations include the fact that the size of the preoperative lesion is not clear in the overdiagnosis group, and the possibility that the entire lesion was removed by biopsy before hysterectomy.

Conclusion

In conclusion, adenomyosis, which is an incidental and common benign pathology, can cause both overdiagnosis and underdiagnosis in patients with EH. For appropriate diagnostic and therapeutic management of EH, it should be highlighted that the possibility of discordant results in the presence of adenomyosis should be considered, and those patients should be carefully evaluated together with their clinical features for treatment options.

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Simulation-based clinical learning for final year medical students about Focused Assessment Sonography for Trauma

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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.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Point-of-care ultrasound is a focused exam. It is a method that can be easily repeated by clinicians, especially as it aims for answering specific questions. The current study aimed to evaluate how successfully the students could learn Focused Assessment with Sonography for Trauma (FAST) and the permanence of the education after the simulation-based training.

Methods: This study was conducted with final year medical students in Acibadem Mehmet Ali Aydinlar University Hospital Emergency Department and Acibadem University Center of Advanced Simulation and Education. The FAST course was taught by emergency physician specialists. After 2 h of theoretical training, a 3-h hands-on small group practical session was held face-to-face in which the students performed FAST scans with a CAE Vimedix high-fidelity simulator. After ultrasound training, the participants were separated into three groups of 20 each. One group was considered a control group in which they did not perform FAST on any real patient during the emergency medicine rotation (Group A). Group B performed FAST on 20 real patients, and Group C performed the technique on 40 real patients in the emergency department. A re-evaluation exam was done six months later.

Results: This study included 60 participants. At the end of the first evaluation, the mean scores of Groups A (Control Group), B, and C were 6.05 (1.72), 6.05 (1.27), and 5.55 (13.2), respectively. The second evaluation results were 2.51 (0.51) with $P < 0.001$) and 8.84 (0.73) with a $P < 0.001$, and 9.71 (0.27) with $P < 0.001$, respectively.

Conclusion: The long-term memory retention of the training presented in the simulation alone may be controversial. In our study, the take-home point is that for 2 h of theoretical lectures and 3 h of simulation training to be permanently retained, practicing the technique with at least 20 patients is needed.

Keywords: Simulation, FAST, Education, Bedside ultrasound, Emergency medicine

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Introduction

Healthcare providers still use the same old instruments for physical examination. An ophthalmoscope, otoscope, and stethoscope are components of the traditional physician's black bag. Educators and students are increasingly using visual systems, simulation, tridimensional (3D) images, and schematic patterns which are all based on computer processing. Ultrasound is becoming increasingly popular in medicine for a variety of reasons: (1) it does not emit potentially harmful ionizing radiation, (2) it is inexpensive and portable, (3) tests can be easily repeated, and (4) it provides speedy answers to clinically significant problems [1]. A bedside ultrasound is a focused exam that can be performed at a patient's bedside by the clinician caring for the patient to answer specific questions. This method is now standard practice for screening of abdominal aortic aneurysms, vascular access, critical care, rheumatology, and emergency cardiac function testing [2].

Focused Abdominal Sonography for Trauma (FAST) scanning has been adopted by emergency physicians to evaluate the presence of free fluid in the abdomen, pelvis, or pericardium with the aim of guiding further assessment using computed tomography or to speed surgical investigation. The evaluation for the detection of free intraperitoneal fluid has been shown to be both sensitive and specific [3]. Physicians practicing emergency medical services have been using FAST in many facilities worldwide for those reasons. FAST produced an increase in diagnostic accuracy, a drop in trauma mortality, a shorter time to surgery, and a reduction in hospital stay and expenditures. To obtain the necessary proficiency, the traditional training model requires significant practice on patients. Training novices in FAST during the acute resuscitation phase of a critically sick patient with trauma may not be acceptable or possible. Medical picture simulation is a growing topic of study that allows researchers to artificially replicate clinical scenarios with crucial and/or aberrant events in a safe environment [4]. According to consensus guidelines, such simulators should be validated before clinical teaching [5].

The study's major aim was to assess medical students' capacities to incorporate themselves into the practical teaching of fundamental components of clinical ultrasonography using simulation in addition to assessing their effectiveness and whether memory of these techniques was retained six months later.

Materials and methods

This study was designed prospectively at Acibadem Mehmet Ali Aydinlar (MAA) University Hospital Emergency Department and Acibadem MAA University Center of Advanced Simulation and Education (CASE). Approval for the study was obtained from the Acibadem University and Acibadem Healthcare Institutions Medical Research Ethics Committee (ATADEK; Approval number: 2015-6/12 and Approval date: 05/05/2015). When the post-hoc power analysis with 57 participants was performed using the G*power software 3.1.9.7 version, it was found that the power = 0.75, the effect size (odds ratio [OR]) = 0.4, and alpha error = 0.05. Sixty participants were included in the study, and written informed consent was obtained from 60 medical students at Acibadem University. The inclusion criteria for the study included several parameters: (1) final year medical student (FYMS), (2) never having taken any seminars/courses/training modules on ultrasonography, and (3) also fulfilling the same criteria after six months for the second evaluation in terms of no other training other than the one on their emergency medicine (EM) rotation. Potential participants were informed that they would be excluded if they underwent any educational experience concerning ultrasonography. Informed consent was obtained. Potential participants who did not meet these criteria were excluded from the study.

A pilot course was designed to teach FAST scanning to final year medical students in the Simulation laboratory at the start of the EM rotation. All participants had no prior experience with FAST. The course consisted of seminars on introductory ultrasound physics and the principles of FAST scanning in addition to the role of ultrasound in surgical decision-making. The course was taught over a period of 2 h by EM specialists qualified for ultrasound and simulation training. Teaching methods included a formal seminar, practical demonstrations, and problem-solving exercises using a constructivist, learner-centered approach. These activities were followed by a 3-h hands-on small group practical sessions face-to-face for which students performed FAST scans with CAE Vimedix high-fidelity simulator. The students calibrate the probe according to its position on the mannequin on the monitor, and as he/she moves the probe, the ultrasound image obtained from a real patient on the monitor moves correlated with the hand movements of the student. In this way, the students tried to catch the site to be visualized by moving the probe to the desired direction and free fluid.

A complete FAST scan was defined as an assessment of the splenorenal recess, hepatorenal recess (Morrison's pouch), 4-chamber view of the heart and pericardium, in addition to a transverse and longitudinal view of the bladder and pelvis. At first, normal findings were taught followed by the method for searching for free fluid in these areas was taught. At the end of the training, the course concluded with a one-on-one FAST performed on 10 cases by each student. The program included 10 FAST cases consisting of a wide range of issues ranging from those with no free fluid to those with a large amount of fluid. When the participant performed FAST on different cases, two emergency physicians evaluated them. Both emergency physicians were blinded to each other's evaluation. The evaluation rubric was influenced by a study by Shaukat et al. [6] (Table 1). Based on the rubric, participants who scored 5 or higher were classified as adequate, and those who scored 4 or lower were classified as inadequate. In each question, the average of two raters was taken. Each of the essential assessment views involved in the FAST examination, and their interpretation is described in Table 1. For each case, five evaluation items were found, and for each evaluation item, points (such as 0, 1, and 2) were assigned.

The participants were separated into three groups after FAST training in the CASE and after that the first evaluation was done. After the first assessment, participants began their emergency rotation of seven weeks in emergency service. Participants in Group A (Control Group) never performed FAST

on any patients in their EM rotation, Group B performed FAST on 20 patients during their EM rotation, and Group C performed FAST on at least 40 patients. During the EM rotation, the students used ACUSON X150 Ultrasound System to perform FAST on real patients. Six months after the first evaluation, participants were invited to the simulation unit. The same exam (10 cases) was used each time. The flow chart is provided in Figure 1. Two independent emergency physicians re-evaluated them. After the second evaluation, 40 students who were in Groups B and C were asked to give points to with respect to comparing FAST on a simulator versus the real patient for all the regions separately: (1) suprarenal recess, (2) subxiphoid approach, (3) hepatorenal recess, and (4) pelvic approach. They assigned points based on a 5-point Likert scale to the ultrasound experience on the simulated patient versus the real patient under four topics.

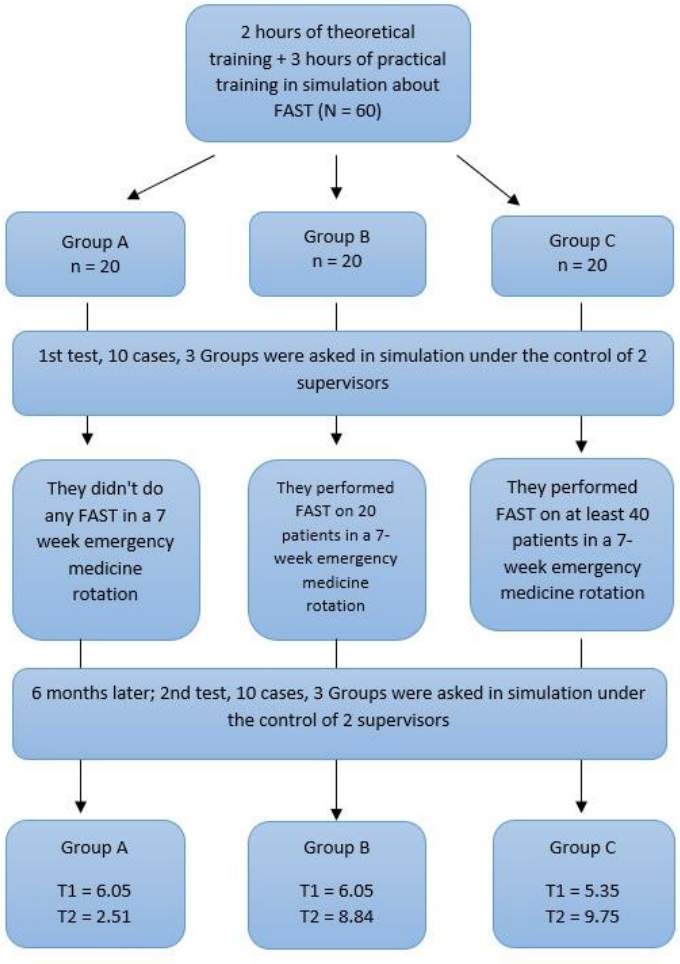
Students were blinded to both the correct answers and their previous scores. However, asking the same questions in the first and second evaluation could develop a bias in terms of the participants' ability to remember the cases. However, this method underwent standardization. Between the two evaluation processes, the participants were not followed closely on whether they were trained again (or not) about FAST. Therefore, prior to the second evaluation, consent was obtained from all the participants indicating that they had not received any other ultrasound training.

Table 1: Assessment and scoring Checklist for Performance of Focused Assessment with Sonography for Trauma (FAST) Examination

	0 Point (Fail)	1 Point (Sufficient)	2 Point (Sufficient)
1- Overall FAST rating, contrast, brightness, focus adjustment. placement of the transducer in the appropriate anatomical location, transducer angles	Transducer misplacement, inappropriate anatomical image, missing 1 or more of the 4 areas to be viewed. inability to detect pathology or detect pathology in a healthy place.	Detecting pathology but needs guidance to obtain better images.	Detailed view of the region and obtaining a quality image. being able to clearly indicate whether there is free fluid or not.
2- Hepatorenal recess or Morison's pouch (RUQ)	Transducer misplacement, inability to detect pathology or detect pathology in a healthy place.	Detecting pathology, but needs guidance to obtain better images.	Detailed view of the region and obtaining a quality image. Being able to clearly indicate whether there is free fluid or not.
3- Splenorenal or perisplenic view (LUQ)	Transducer misplacement, cannot detect pathology or detect pathology in a healthy place.	Detecting pathology but needs guidance to obtain better images.	Detailed view of the region and obtaining a quality image. Being able to clearly indicate whether there is free fluid or not.
4- Pelvic view	Transducer misplacement, inability to detect pathology or detect pathology in a healthy place.	Detecting pathology but needs guidance to obtain better images.	Detailed view of the region and obtaining a quality image. Being able to clearly indicate whether there is free fluid or not.
5- Pericardial or subxiphoid view	Transducer misplacement, inability to detect pathology or detect pathology in a healthy place.	Detecting pathology but needs guidance to obtain better images.	Detailed view of the region and obtaining a quality image. Being able to clearly indicate whether there is free fluid or not.

For each question, students can get a minimum of 0 and a maximum of 10 points. Successful for Focused Assessment with Sonography for Trauma (FAST) 5 points and above

Figure 1: Flowchart of the study



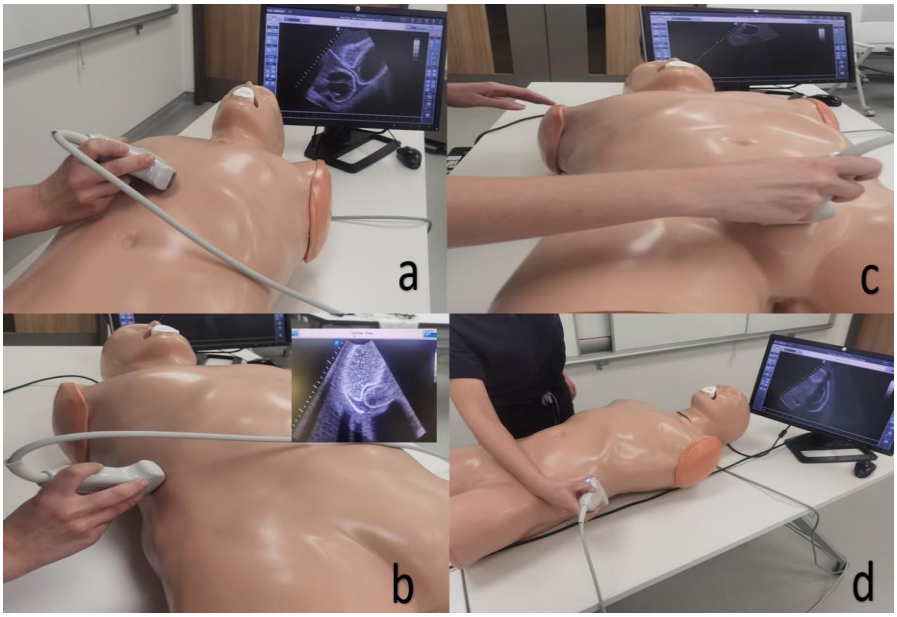
T1: 1st exam average score, T2: 2nd exam average score
FAST: Focused assessment with sonography in trauma

The workshop was conducted using the CAE Vimedix high-fidelity simulator. An integrated ultrasound simulator consists of a human mannequin, a probe, and a computer. The probe is directly attached to a monitor, which displays an ultrasound image based on the position and movements of the probe. The position of the probe in this simulator is defined by electromagnetic tracking technologies. A 3D sensor, capable of capturing virtual location data in real time, is frequently included in the probe. This simulator is mostly used to teach both EM students and residents the fundamental skills of doing a FAST assessment (Figure 2).

Statistical analysis

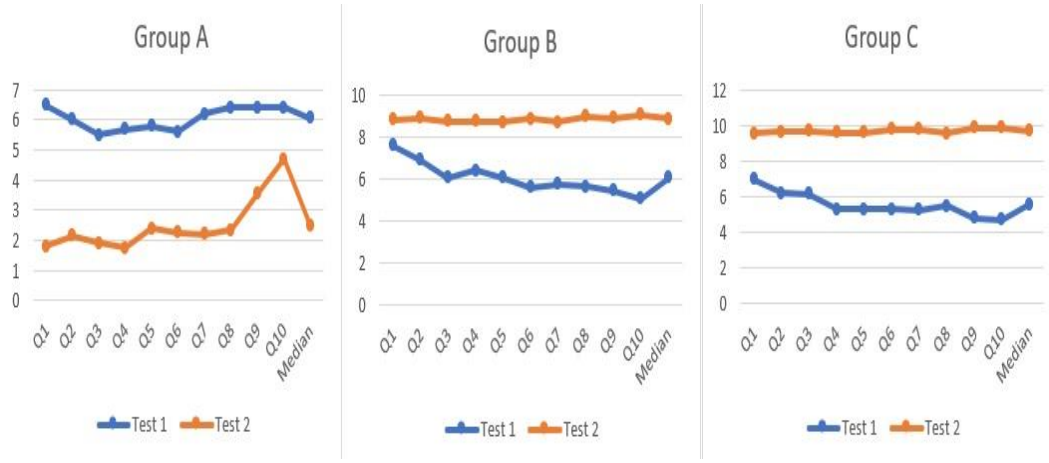
The data were collected based on descriptive statistics, such as frequency, percentage, and mean (standard deviation). The result of evaluations obtained by the attendees for the images obtained and diagnosing were compared between Group sA, B and C. Construct validity was assessed using Kruskal–Wallis test and Mann–Whitney U test as appropriate. A *P*-value of < 0.05 was accepted as statistically significant. In the comparison of categorical variables between the groups, Fisher's Exact and chi-squared tests were used. The statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA).

Figure 2: Student's FAST practice on simulator



a: Pericardial or subxiphoid view, b: Hepatorenal recess or Morison's pouch, c: Pelvic view, d: Splenorenal or perisplenic view

Figure 3: The differences between groups after the first and second evaluations



Q: Question; Median: Proficiency rate in the test, T1: First Evaluation; T2: Second Evaluation

Table 2: First evaluation and second evaluation in groups and distribution of points in each question and in society

	Group A			Group B			Group C		
	T1 Mean (SD)	T2 Mean (SD)	*P*-value	T1 Mean (SD)	T2 Mean (SD)	*P*-value	T1 Mean (SD)	T2 Mean (SD)	*P*-value
Q-1	6.5 (1.82)	1.85 (1.14)	< 0.001	7.6 (2.16)	8.8 (1.2)	0.055	6.95 (2.33)	9.55 (0.69)	< 0.001
Q-2	6.0 (1.86)	2.15 (1.27)	< 0.001	6.9 (1.86)	8.9 (0.85)	< 0.001	6.2 (2.33)	9.65 (0.67)	< 0.001
Q-3	5.5 (1.88)	1.9 (1.12)	< 0.001	6.05 (1.93)	8.75 (1.16)	< 0.001	6.15 (1.95)	9.7 (0.57)	< 0.001
Q-4	5.7 (1.98)	1.75 (1.21)	< 0.001	6.4 (1.76)	8.75 (1.37)	< 0.001	5.3 (1.59)	9.6 (0.5)	< 0.001
Q-5	5.8 (1.94)	2.4 (1.57)	< 0.001	6.05 (1.96)	8.7 (1.34)	< 0.001	5.3 (1.63)	9.8 (0.41)	< 0.001
Q-6	5.6 (1.96)	2.25 (1.07)	< 0.001	5.6 (1.73)	8.85 (1.27)	< 0.001	5.3 (1.53)	9.75 (0.55)	< 0.001
Q-7	6.2 (2.12)	2.2 (1.06)	< 0.001	5.75 (1.59)	8.7 (1.03)	< 0.001	5.25 (1.07)	9.8 (0.41)	< 0.001
Q-8	6.4 (2.37)	2.35 (1.04)	< 0.001	5.65 (1.6)	8.95 (0.76)	< 0.001	5.5 (1.36)	9.55 (0.76)	< 0.001
Q-9	6.4 (2.23)	3.55 (1.05)	< 0.001	5.45 (1.67)	8.9 (0.91)	< 0.001	4.8 (1.4)	9.85 (0.49)	< 0.001
Q-10	6.4 (2.16)	4.7 (1.38)	0.023	5.05 (1.79)	9.05 (0.89)	< 0.001	4.7 (1.56)	9.85 (0.37)	< 0.001
Result of evaluation	6.05 (1.72)	2.51 (0.51)	< 0.001	6.05 (1.27)	8.84 (0.73)	< 0.001	5.55 (1.32)	9.71 (0.27)	< 0.001

Wilcoxon Signed Ranks analysis, Q: Question; T1: First Evaluation; T2: Second Evaluation; SD: Standard Deviation

Results

Sixty participants were included in the study. None of the FYMS had any knowledge concerning FAST. The average age of the participants was 26 (minimum 22–maximum 29). The study group consisted of 36 female and 24 male participants. The distributions of the average scores on the first and second evaluations are provided in Table 2. In the first evaluation, all three groups were found to be adequate when performing FAST. Table 3 shows in which cases the participants scored 5 or higher on the first and the second evaluations. In the first evaluation, differences in the adequacy of the groups in all cases were not found to be statistically significant (P = 0.1). In the second evaluation, the difference in the adequacy of the groups in all cases were found to be statistically significant (P < 0.001). The distribution of the first and the second evaluation results were shown in Figure 3. According to the similarity scores given by 40 students who performed ultrasound both with simulation and on real patients, the right upper quadrant view mean value was 4.5 (90%), left upper quadrant view mean value was 4.42 (88.5%), subxiphoid view mean value was 4.72 (94.5%), and pelvic view mean value was 4.3 (86%) with respect to similarity. FAST similarity mean value was 89.75%.

Table 3: Numbers of Student qualified for FAST at first evaluation and second evaluation

	Group A		Group B		Group C		*P*-value
	n	(%)	n	(%)	n	(%)	
T1							
Q-1	17	(85)	17	(85)	16	(80)	1.000
Q-2	15	(75)	18	(90)	15	(75)	0.440
Q-3	16	(80)	13	(65)	15	(75)	0.551
Q-4	15	(75)	17	(85)	15	(75)	0.789
Q-5	16	(80)	16	(80)	14	(70)	0.797
Q-6	15	(75)	14	(70)	13	(65)	0.788
Q-7	16	(80)	15	(75)	14	(70)	0.766
Q-8	16	(80)	14	(70)	15	(75)	0.766
Q-9	17	(85)	15	(75)	11	(55)	0.100
Q-10	17	(85)	13	(65)	11	(55)	0.116
Q_T	17	(85)	15	(75)	11	(55)	0.100
T2							
Q-1	0	(0)	20	(100)	20	(100)	< 0.001
Q-2	0	(0)	20	(100)	20	(100)	< 0.001
Q-3	0	(0)	20	(100)	20	(100)	< 0.001
Q-4	0	(0)	20	(100)	20	(100)	< 0.001
Q-5	2	(10)	20	(100)	20	(100)	< 0.001
Q-6	0	(0)	20	(100)	20	(100)	< 0.001
Q-7	0	(0)	20	(100)	20	(100)	< 0.001
Q-8	1	(5)	20	(100)	20	(100)	< 0.001
Q-9	3	(15)	20	(100)	20	(100)	< 0.001
Q-10	12	(60)	20	(100)	20	(100)	< 0.001
Q_T	0	(0)	20	(100)	20	(100)	< 0.001

Pearson Chi-Squared, Fisher's Exact test, Q: Question; QT: Proficiency rate in the test, T1: First Evaluation; T2: Second Evaluation

Discussion

In light of this study, it was found that participants have a critical increment in their capacity to interpret ultrasound images and coordinate them into clinical decision-making after a brief period of simulation education. The literature reflects general enthusiasm for ultrasound simulation-based medical education with reported instances of meaningful learning [7]. This finding demonstrates that ultrasound can be integrated as a curriculum topic in medical school training and provides students with focused diagnostic skills. [8]. Some universities worldwide have ultrasonography training in their curriculum, and the number of these universities is increasing [9].

Students have reported that after performing FAST on the simulated patient, performing FAST in the emergency department on real patients was not challenging for them. Simulation training before encountering a real patient appears to have provided some level of confidence to the student. Moreover, the students were acquainted with the display that they were going to view on the ultrasound screen and the points they were going to examine. This simulation training is favorable in terms of being both time- and cost-effective. Not having the capability of simulating pathological images is a dramatic shortcoming of using human models. The use of simulators eliminates the need for human models thereby also eliminating added costs for additional ultrasound machines for training purposes. Medical imaging simulation for detecting pathological processes in an unstable patient under stressful situations is an ongoing field of study field. In abnormal situations, it allows clinical scenarios to be artificially altered in a controlled environment without any risks to patient safety or confidentiality [10]. The total view of an ultrasonography image (including artefacts, anatomical region, detecting pathological conditions) and anatomical presentation in the simulation when compared with their real counterparts may be listed as the reason why students find understanding the principles of and performing FAST on a real patient to be undemanding.

EM physicians are expected to promptly detect any intra-abdominal hemorrhages, particularly in critical trauma patients, ask for appropriate consultations, and begin immediate resuscitation thus consequently decreasing the rate of mortality and morbidity in patients. The students in this study were all found to be adequate when performing FAST in the first evaluation. In the second evaluation, which occurred six months later, the adequacy ratio of Group A (control group), which did not perform FAST on any real patients, was insufficient, whereas Group B, which performed FAST on 20 real patients throughout their EM rotation, was same as the first evaluation, and Group C, which performed FAST on at least 40 patients, was found to be above 90%. These findings are consistent with previous studies previously concerning the adequacy of medical student training in ultrasonography [11–13]. Practice appears to be the best method for a given training to be retained in the long-term. The number of practice opportunities are directly proportional to the sustainability of the given training.

Ultrasound training provided to residents differs not only between countries, but even between universities in the same country. Residents are given ultrasound training according to their specialty [14]. Ultrasound is known for its many advantages; however, the most important drawback of ultrasound is that it is highly operator-dependent. The training level and the amount of practice with ultrasound equipment determines how easily an accurate diagnosis will be obtained [15]. Certain ultrasound trainings are included in the residency programs in most countries. Having obtained basic ultrasound skills in medical school would be a beneficent skillset for performing ultrasound to a higher standard [16]. As in every aspect of medicine, a need for continuing education in EM exists. It is necessary for the assistants in the clinic to practice the training they receive in sufficient numbers. It is important to keep up-to-date [17].

The use of ultrasound has dramatically increased in gastroenterology, general surgery, and EM as the use of ultrasound has been added to the algorithms on diagnosis, screening, and follow-up stages [1]. Addition of ultrasound to the medical school curriculum may assist the students with future residency program when residents need to evaluate patients with ultrasound or when there is ultrasound training [4, 18]. In a research study carried out with third year medical students, the efficacy of an hour long extended FAST training provided during general surgery rotation was assessed, and medical students were found to be successful in performing extended FAST in the evaluation done afterwards [19]. In the current study, the first evaluation adequacy rate also was high; however, in the second evaluation, which was done six months later, the group without practice opportunities were found to be inadequate when performing FAST.

FAST trainers utilize different models for training physicians to perform FAST on trauma patients. Models, including didactic imaginary presentation, video presentation of actual patients, animal models, simulator models, cadavers, normal healthy individuals, and/or peritoneal dialysis models have been utilized in training [19]. Having said that, simulation has been increasing in popularity in the recent years. One of the major determinants of the success of simulation training is the closeness of the images on anatomical features, pathologic conditions, and artifacts. Companies have been working on obtaining more realistic images with new ultrasound simulator

models. The former ultrasound stimulators used for training were problematic because the images did not resemble the original ones [10]. In addition to the image on the screen, image changes with probe manipulation should be realistic, and the image needs to mimic a real patient. In this study, students reported a likeness ratio above 89.75%.

Limitations

The number of evaluated students could be higher. This study is a single-centered study with a single simulation model. Competency in FAST long after the 6-month period is not known. All students had similar backgrounds in terms of curriculum, and even though students with no previous ultrasound training were included, it does not eliminate the fact that some students may have been more prone to performing ultrasound individually. Although the simulation model cannot replace a real patient, evaluations were done using the simulation model (another limitation).

Conclusions

The role of medical simulation in ultrasound training has been expanding nowadays. It will be highly beneficial for students to learn ultrasound training in simulation during different rotations according to the proper topics before graduating from medical school. Medical simulation has gained importance for students or residents to be educated about ultrasound in simulation before performing ultrasound scans on real patients. FAST training, which is given only in simulation, does not provide long-term retention for students. After simulation training, the number of practice sessions on real patients is important so that students do not forget the training. In our study, the take-home point is that for two hours of theoretic lecture and three hours of simulation training to be permanent, practicing with at least 20 patients is needed.

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Evaluation of acromion morphology and subacromial distance in patients with shoulder pain

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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: Acromion morphology is not always considered when examining pathologies that may cause shoulder pain in patients who are undergoing physical therapy. However, acromion morphology and the changes caused by these morphological variations in the subacromial distance may cause serious shoulder problems during physical therapy. In this study, the effects of acromion morphology and subacromial distance measurements on shoulder pain were investigated, and the effects of various factors on acromion types were examined.

Methods: Our study was a cross-sectional design, and in total, 240 patients had shoulder magnetic resonance images (MRIs) were included in the study. The study included patients with shoulder pain persisting for at least eight weeks and excluded patients with a history of fractures, peripheral nerve damage, osteogenesis imperfecta, and severe osteoporosis. Acromial morphology and subacromial distance were examined on MRIs. Acromial morphology was examined in four subgroups according to the classification by Vanarthos and Monu (1995). Furthermore, the patients were divided into three age groups (18–30, 31–45, and 46–60), and acromion types were examined based on these age groups. In addition, patients' demographic data were collected, and patients were questioned about painful extremities, dominant extremity, and pain status based on the visual analogue scale (VAS).

Results: Subacromial space was measured by determining acromion types using MRIs, and mean subacromial distance was 7.91 mm. Acromion types had significant differences in terms of subacromial distance values ($P < 0.001$). Pairwise comparisons revealed that the subacromial distance values of Type 3 patients were lower than that of Types 1, 2, and 4 patients ($P < 0.001$, $P = 0.001$, and $P < 0.001$, respectively).

Conclusion: The study results revealed that injury of the rotator cuff muscles may occur more frequently in Type 3 acromion than in other acromion types because of the low subacromial distance value. Acromion types, especially the subacromial distance, must be considered in patients with shoulder pain.

Keywords: Acromion shape, Shoulder pain, Rotator cuff pathologies, Subacromial distance, Acromion types

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Introduction

The shoulder joint has a wide range of motion and poor joint contact. It is the most complex joint of the body with support for this joint contact provided by cartilage and ligaments that secure the range of motion. Injuries of the shoulder joint, a structure that acts as a link between the upper extremity and the trunk, severely affects the quality of life in individuals [1].

The rotator cuff muscles act as a compressor of the humeral head against the glenoid cavity and provide shoulder movements on different spatial planes. Rotator cuff pathologies lead to disruption of this balance and may cause more advanced injuries with the elevation of the humeral head. This assessment, called subacromial space, is determined by measuring the distance from the humerus to the acromion [2–7]. Clinically, this measurement can be used to evaluate the function of the rotator cuff and to help select the type of therapy to be used. An acromiohumeral distance ≤ 7 mm measured on an anteroposterior radiograph suggests the presence of a large rotator cuff tear and reduced likelihood of successful outcome after surgical treatment [3, 8–10].

Shoulder pain is the most common musculoskeletal problem after low back and neck pain [11–13]. A literature review has shown that the causes of shoulder pain are classified in 91% of the articles. In this classification, 52% is classified as subacromial pain, 17% instability, 9% adhesive capsulitis, and 4% other diagnoses [12]. Another study found that rotator cuff lesions accounted for 65% of shoulder pain cases, whereas the pathology of art. acromioclavicularis accounted for 10% of the cases [14]. Studies have found many risk factors, such as sex, obesity, advanced age, trauma, and anatomical, neurological, and psychological problems. Furthermore, shoulder pain is reportedly more common in employed people than in unemployed people. In addition, sports that require repetitive motion and sports that require throwing have been found to carry a higher risk for shoulder pain than other sports [15–18].

Acromion morphology is not always considered when examining pathologies that may cause shoulder pain in patients who are undergoing physical therapy. However, acromion morphology and the changes caused by these morphological variations in the subacromial space may cause serious shoulder problems during physical therapy. The effect of acromion morphology and subacromial space measurements on shoulder pain were investigated and the effects of various factors on acromion types were examined.

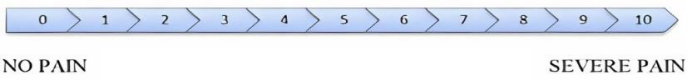
Materials and methods

Our study is a cross-sectional study, and in total, 240 patients (120 males and 120 females; age, 18–60 years) who presented to Adana Private Yaşam Medical Center Physical Therapy Unit in 2019 and to the Health Sciences University Gaziosmanpaşa Training and Research Hospital in 2020 and had shoulder magnetic resonance images (MRIs) were included in the study. The study included patients with shoulder pain persisting for at least eight weeks and excluded patients with a history of fracture, peripheral nerve damage, osteogenesis imperfecta, and severe osteoporosis. Approval for the study was obtained from the Non-Invasive Clinical Research Ethics Committee of Çukurova University (approval number: 91/12, date: 04.09.2019) and permission from the participating the healthcare institutions was granted before performing measurements on the existing MRIs of the patients. The patients who were diagnosed based on MRIs were asked to sign an informed consent form when they started physical therapy. Furthermore, the patients were divided into three age groups (18–30, 31–45, and 46–60), and acromion types were examined by these age groups. In addition, patients' demographic data (body weight, height, and body mass index [BMI]) were collected, and patients were questioned about painful extremities, dominant extremity, and pain status based on the visual analogue scale (VAS). Examinations of the MRIs were performed on the data obtained from the 1.5 Tesla GE SIGNA EXPLORER device.

VAS

To determine the severity of the pain status of patients with shoulder pain, the VAS, a measurement tool, was used to measure values that could not be measured directly (Figure 1). Usually, a 10-cm line is drawn and extreme limit definitions are written on both ends of the parameter to be evaluated, and the patient is then asked to indicate the location on this line that applies to their condition by drawing a line, placing a dot, or pointing.

Figure 1: Visual Analogue Scale



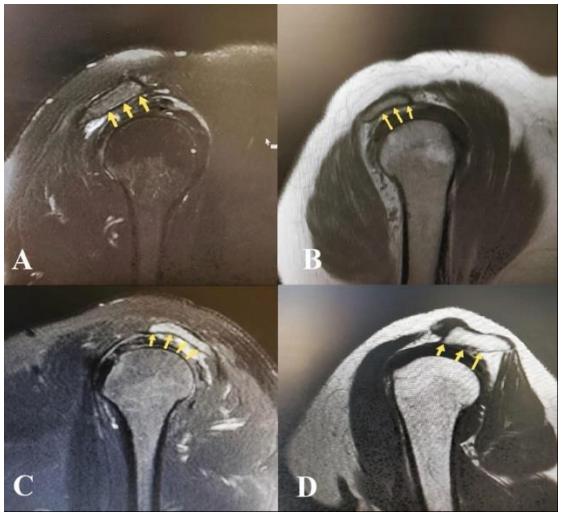
The numbers used in Figure 1 are indicated in cm.

MRI image measurements

Acromial morphology was classified into three different types by Bigliani (1986) [19]. In addition, Vanarthos and Monu (1995) defined Type 4 acromion with a convex undersurface [20]. In our study, acromial morphology was examined in four subgroups according to the classification by Vanarthos and Monu (1995) as shown in Figure 2:

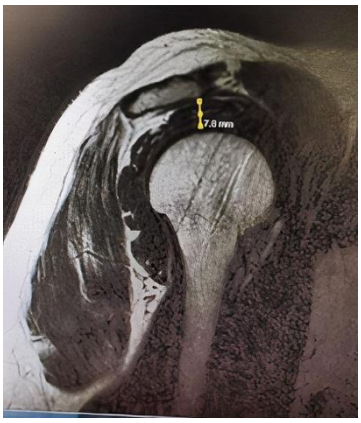
a) Type 1 acromion: It has a flat undersurface.
b) Type 2 acromion: It has a smooth, curved lower surface that is almost parallel to the superior caput humeri on the sagittal oblique plane.
c) Type 3 acromion: It has a hook shape in the anterior portion and is greatly predisposed to rotator cuff tears.
d) Type 4 acromion: It has a convex undersurface.

Figure 2: Type 1 acromion (A), Type 2 acromion (B), Type 3 acromion (C), and Type 4 acromion (D) on sagittal oblique T1 SE images



Subacromial distance was measured from the caput humeri to the distal end of the acromion (Figure 3).

Figure 3: Subacromial Distance Measurement



The evaluation of MRIs was performed under supervision of a specialist radiologist, and the measurements were repeated twice by a single author. Intraclass correlation coefficients ([ICC] with 95% confidence intervals [CI]) were used for reliability testing. When the intra-observer reliability was examined in all measurements, the ICC value was found between 0.93 and 0.96. All MRIs were measured by using axial proton density fast spin echo (PD FSE), coronal oblique T1 SE, coronal oblique PD FSE, and sagittal oblique T1 SE sequences. Acromion types were established on sagittal oblique T1 SE images. Subacromial distance measurements were made on sagittal oblique T1 SE images. Measurements were recorded in "mm". MR measurements were performed electronically on the computer using ExtremePacs Pacs Software 4.3 (Çankaya, Ankara).

Statistical analysis

Sample size was determined using G*Power (v3.1.9) software based on the subacromial distance values in a previously published study by Duymuş et al. [21]. Effect size was calculated as d = 0.508, assuming a power of 80% and alpha of 0.05, and the minimum required sample size was 62 patients per gender.

R version 2.15.3 program (R Core Team, 2013) was used for statistical analysis. Study data were reported by using mean, standard deviation, median, first quartile, third quartile, frequency, and percentage. The conformity of the quantitative data to the normal distribution was evaluated with the Shapiro–Wilk test and graphic reviews. Independent sample t-tests were used for evaluating normally distributed variables between two groups. The Kruskal–Wallis test was used in the intergroup evaluations of non-normally distributed variables, and the Dunn–Bonferroni test was used to identify the source of significance in cases in which significance was found. Pearson's chi-square, Fisher's exact, and Fisher–Freeman–Halton exact tests were used for comparisons between qualitative variables. Pearson's correlation coefficient was used to determine the level of relationship between quantitative variables. Statistical significance was set at $P < 0.05$.

Results

Demographic data of the patients included in the study are given in Table 1. The patients' ages ranged from 19 to 60 years with an average of 44.39 (10.01) years. No statistically significant difference in patient ages according to sex ($P > 0.05$) was found. While the male's height, weight, BMI, and subacromial distance values were higher than the female's, their VAS scores were lower ($P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.015$, respectively).

Table 1: Minimum, maximum and mean (standard deviation) values of the patients' demographic data

Parameters	FEMALE		MALE		TOTAL		[a] *P*-value
	Min–Max	Mean (SD)	Min-Max	Mean (SD)	Min-Max	Mean (SD)	
Age (years)	22–60	45.25 (9.04)	19–60	43.53 (10.86)	19–60	44.39 (10.01)	0.185
Height (cm)	157–175	163.82 (3.10)	163–190	178.67 (3.60)	157–190	171.24 (8.16)	<0.001
Weight (kg)	54–81	67.62 (6.30)	68–105	86.15 (7.11)	54–105	76.9 (11.46)	<0.001
BMI (kg/m^2)	19.61–31.64	25.23 (2.59)	21.46–32.87	27.01 (2.07)	19.61–32.87	26.12 (2.51)	<0.001
VAS	5–7	5.60 (0.64)	4–8	5.40 (0.63)	4–8	5.5 (0.64)	0.015
Subacromial distance (mm)	4.40–11.70	7.50 (1.29)	5.50–11.27	8.32 (1.22)	4.4–11.7	7.92 (1.32)	<0.001

[a] Independent samples t-test, BMI: Body mass index, VAS: Visual analogue scale

The number of patients, VAS scores, and subacromial distance based on acromion types are shown in Table 2. A statistically significant difference was found in acromion types ($P < 0.001$). A statistically significant difference was found in subacromial distance values according to acromion types ($P < 0.001$). The pairwise comparisons performed using the Dunn–Bonferroni test showed that subacromial distance values were lower in Type 3 patients than in Types 1, 2, and 4 patients ($P < 0.001$, $P = 0.001$, and $P < 0.001$, respectively). Type 2 patients were also found to have lower values than Type 1 patients ($P < 0.001$). No statistically significant difference between other acromion types ($P > 0.05$) was found. In addition, statistical evaluations could not demonstrate any significant difference in VAS scores in terms of acromion types ($P > 0.05$).

Table 2: Number of patients, VAS scores, and subacromial distance by acromion types

	Acromion Type				*P*-value
	Type 1 Median (Q1; Q3)	Type 2 Median (Q1; Q3)	Type 3 Median (Q1; Q3)	Type 4 Median (Q1; Q3)	
n (%)	71 (29.6)	154 (64.2)	11 (4.6)	4 (1.7)	[a] <0.001*
VAS	5 (5; 6)	5 (5; 6)	6 (5; 6)	5 (5; 5.5)	[b] 0.317
Subacromial distance (mm)	8.6 (7.9; 9.9)	7.5 (6.8; 8.2)	5.8 (5.1; 6.9)	9.35 (8.35; 10.55)	[b] <0.001*

[a] One-sample chi-square test, [b] Kruskal-Wallis test, *$P < 0.05$, VAS: Visual analogue scale. The results are presented as median (first quartile; third quartile).

Acromion type comparison by age, BMI, painful extremity, and sex are shown in Table 3. No statistically significant difference was found in the analysis of the acromion types of the patients by BMI groups ($P > 0.05$). The patients were divided into three age groups, and acromion types were examined based on this classification. No statistically significant difference was found in the distribution of acromion types within age groups ($P > 0.05$). When the acromion types were examined according to the painful extremity side, no statistically significant difference was found ($P > 0.05$). When the acromion types of the patients were examined regardless of sex, a statistically significant difference was found ($p < 0.05$). However, no statistically significant difference was found in the distribution of acromion types by sex ($P > 0.05$).

Many studies have concluded that the critical value for the subacromial distance is 7 mm, and subacromial impingement syndrome is more common in patients with a distance of < 7 mm, and these patients had a considerable degree of shoulder pain. In our study, subacromial distance was divided into two

groups: (1) ≤ 7 mm and (2) > 7 mm. The comparison of age, BMI, and VAS values by subacromial distance groups is shown in Table 4. No statistically significant difference was found in the comparison of age, BMI and VAS scores between subacromial distance groups ($P > 0.05$).

Table 3: Acromion type comparison by age, BMI, painful extremity, and sex

	Acromion type				*P*-value
	Type 1 (n=71) n (%)	Type 2 (n=154) n (%)	Type 3 (n=11) n (%)	Type 4 (n=4) n (%)	
Age					[a] 0.222
18–30	11 (37.9)	14 (48.3)	2 (6.9)	2 (6.9)	
31–45	26 (27.4)	65 (68.4)	3 (3.2)	1 (1.1)	
46–60	34 (29.3)	75 (64.7)	6 (5.2)	1 (0.9)	
BMI (kg/m^2)					[a] 0.266
< 20	1 (100)	0 (0)	0 (0)	0 (0)	
20–24.9	26 (36.1)	39 (54.2)	6 (8.3)	1 (1.4)	
25–29.9	41 (26.3)	107 (68.6)	5 (3.2)	3 (1.9)	
30–34.9	3 (27.3)	8 (72.7)	0 (0)	0 (0)	
Painful extremity					[a] 0.448
Right	43 (32.6)	79 (59.8)	7 (5.3)	3 (2.3)	
Left	28 (25.9)	75 (69.4)	4 (3.7)	1 (0.9)	
Sex					[a] 0.388
Female	32 (26.7)	78 (65)	8 (6.7)	2 (1.7)	
Male	39 (32.5)	76 (63.3)	3 (2.5)	2 (1.7)	

[a] Fisher-Freeman-Halton exact test, * $P < 0.05$

Table 4: Comparison of age, BMI, and VAS values by subacromial distance groups

Parameters	Subacromial distance		[a] *P*-value
	≤ 7 mm (n=63) Mean (SD)	> 7 mm (n=177) Mean (SD)	
Age (years)	45.24 (9.51)	44.09 (10.20)	0.436
BMI (kg/m^2)	25.62 (2.53)	26.29 (2.49)	0.068
VAS	5.54 (0.67)	5.49 (0.63)	0.568

[a] Independent groups t-test, *$P < 0.05$, BMI: Body mass index, VAS: Visual analogue scale

The evaluation of sex, acromion type, and painful extremity by subacromial distance groups is shown in Table 5. Furthermore, examination of the distribution of males and females in the subacromial distance groups revealed that the percentage of men was higher in the group of patients with a subacromial distance of > 7 mm than in the group of patients with a subacromial distance ≤ 7 mm ($P < 0.001$). A statistically significant difference was found in the percentage of acromion types between patients with a subacromial distance value of > 7 mm and that of ≤ 7 mm ($P < 0.001$). Although the percentage of Type 1 acromion was higher in patients with a subacromial distance > 7 mm, the percentages of Types 2 and 3 were lower ($P < 0.001$, $P = 0.012$, and $P < 0.001$, respectively). No statistically significant differences in the percentages of painful extremity side between the subacromial distance groups were found ($P > 0.05$).

Table 5: Evaluation of gender, acromion type, and painful extremity by subacromial distance groups

	Subacromial distance		*P*-value
	≤ 7 mm (n = 63) n (%)	> 7 mm (n = 177) n (%)	
Sex			[b] < 0.001*
Female	45 (71.4)	75 (42.4)	
Male	18 (28.6)	102 (57.6)	
Acromion type			[a] < 0.001*
Type 1	2 (3.2)	69 (39)	
Type 2	50 (79.4)	104 (58.8)	
Type 3	11 (17.5)	0 (0)	
Type 4	0 (0)	4 (2.3)	
Painful extremity			[b] 0.323
Right	38 (60.3)	94 (53.1)	
Left	25 (39.7)	83 (46.9)	

[a] Fisher-Freeman-Halton exact test, [b] Pearson'S chi-square test, * $P < 0.05$, BMI: Body mass index, VAS: Visual analogue scale

A correlation analysis was performed between the subacromial distance and patients' ages, heights, weights, BMIs, and VAS scores (Table 6). A statistically significant positive correlation was found between subacromial distance and height (r = 0.282; $P < 0.001$), weight (r = 0.276; $P < 0.001$), and BMI (r = 0.147; $P = 0.023$). However, no statistically significant correlation was found between subacromial distance, patient age, and VAS scores ($P > 0.05$).

Table 6: Analysis of correlation between subacromial distance and age, height, weight, BMI, VAS, and frequency of exercise

Parameters	Subacromial distance	
	r	*P*-value
Age	−0.026	0.686
Height	0.282	< 0.001 *
Weight	0.276	< 0.001 *
BMI	0.147	0.023 *
VAS	0.030	0.638

Pearson correlation analysis, * $P < 0.05$, BMI: Body mass index, VAS: Visual analogue scale

Discussion

Most patients presenting with shoulder pain are diagnosed with subacromial impingement syndrome. It may be difficult to diagnose the cause of shoulder pain in these patients. Therefore, diagnosis can be established more easily and accurately using radiological methods. In many studies, except for those on cadavers, shoulder MRI or X-ray images are used [22–24].

In their study with 70 cadavers, Bigliani et al. [19] divided the acromion in three morphological classes according to undersurfaces. They found 17% Type 1, 43% Type 2, and 40% Type 3 acromion. In addition, they detected full-thickness rotator cuff tears in 33% of the subjects' studies and reported that Type 3 acromion is dangerous and associated with rotator cuff rupture. Subsequently, Vanarthos and Monu [20] defined Type 4 acromion as having a convex undersurface in 1995. In a study of 102 cases, Ekin et al. [25] reported the incidence of Type 1 acromion at 18%, Type 2 acromion at 61%, Type 3 acromion at 13%, and Type 4 acromion at 8%. In addition, this study reported that acromial bone spurs and sclerotic changes appeared to be significantly more common in Type 3 acromion. In another study, Coşkun et al. [26] reported the rates of acromion types as 10%, 73%, and 17% for Types 1, 2, and 3, respectively. They also reported that Type 4 acromion was not detected in either the bones or during radiological examinations. Vanarthos and Monu [20] found the percentage of Type 4 acromion as 13% in their study of 30 shoulders. Yazici et al. [27] found in their study of 80 shoulders that the percentage of Type 1 acromion was 22.5%, Type 2 acromion 70%, Type 3 acromion 5%, and Type 4 acromion 2.5%. In a study of 423 scapulae, Natsis et al. [28] found that percentage of Type 1 acromion was 12.1% (51 scapulae), Type 2 was 56.5% (239 scapulae), Type 3 was 28.8% (122 scapulae), and Type 4 was 2.6% (11 scapulae), whereas Gagey et al. [29] found 27.5% Type 1 acromion, 58.8% Type 2 acromion, 12.1% Type 3 acromion, and 1.6% Type 4 acromion. Our study examined patients with shoulder pain. Type 1 acromion was found to be 29.6%, Type 2 acromion 64.2%, Type 3 acromion 4.6% and Type 4 acromion 1.7%. The presence of significant differences between the acromion types was noted.

Although many studies have been carried out on the effect of age and acromion morphology, this issue has not been fully elucidated [23, 27, 30]. However, Edelson and Taitz [30] reported that they detected 22% Type 1, 62% Type 2, and 16% Type 3 acromions and underlined that the incidence of Type 3 acromion increased after the age of 30 years. In their study, Botanlioğlu et al. [23] could not detect a difference in acromion types based on age. They found that no transition from Type 1 acromion to Type 3 acromion or from Type 3 acromion to Type

1 acromion occurred and did not correspond to increasing age. They also reported a weak relationship between age and acromion type. In a study conducted on 154 scapulae in 2007, Type 2 acromion was found to be significantly more common in both sexes. In addition, the rates of acromion types did not differ significantly by sex or age groups [31]. Nicholson et al. [32] studied 420 scapulae and found 32% Type 1, 42% Type 2, and 26% Type 3 acromion. According to the results of this study, they emphasized that the acromion morphology did not change with age. In another study, Edelson [33] examined 750 scapulae and 80 cadavers and reported that they did not find Type 3 acromion in individuals under the age of 30 years. Some of the patients > 40 years had a protrusion at the tip of the acromion, but this protrusion was a newly formed bone at the site of attachment of the coracoacromiale ligament to the acromion. Edelson argued that Type 3 acromion is an acquired feature and occurs as a result of degenerative changes. In their study using MRI and computed tomography (CT) scans of 132 symptomatic shoulders, Macgillivray et al. [34] found that the acromion developed a downward angulation morphology with increasing age in most patients. However, Büyükbebeci et al. [35] found that Type 2 acromion was the most common type, and also Type 1 acromion is more common in people in their 30s, Type 2 acromion in 40s, and Type 3 acromion in 50s and older with an increase in acromion curve corresponding to increasing age. In their study analyzing 272 cases, Wang and Shapiro [36] stated that they observed a statistically significant increase in the incidence of Type 3 acromion and a statistically significant decrease in the incidence of Type 1 acromion in patients aged ≥ 50 years. In our study, no significant difference was found between acromion types and age groups.

Many studies have been conducted on the relationship between acromion morphology and rotator cuff tear. Nyffeler and Meyer [37] examined the acromion morphology of patients with degenerative rotator cuff tears and those without rotator cuff tears and reported significant intergroup differences. They stated that patients with rotator cuff tears had severe shoulder pain, so acromion morphology was an important parameter for understanding the pathomechanism of the rotator cuff. Additionally, in another study, Balke et al. [22] evaluated 126 patients who underwent arthroscopic rotator cuff repair in two groups as degenerative with supraspinatus tendon rupture and traumatic with supraspinatus tendon rupture. They stated that Type 2 acromion was equally distributed in both groups, whereas Type 1 acromion was more common in traumatic cases and Type 3 acromion morphology was more common in degenerative cases.

Narrowing of the subacromial space was first described by Golding [16] in 1962 using direct radiography of patients with rotator cuff tears. He stated that subacromial distance in healthy individuals is in the range of 7–13 mm. In a study conducted in 1968, Cotton and Rideout [15] measured the subacromial distance in patients with and without full-thickness rotator cuff tears. They stated that subacromial distance was 1–4 mm in patients with full-thickness tears and 6–14 mm in patients without tears. In another study, Yao et al. [18] reviewed the shoulder MRIs of 58 patients. From these images, they measured the distance between the upper edge of the cavitas glenoidalis and the lower point of the acromion closest to the acromioclavicularis from the coronal oblique plane and found that narrowing of this distance was associated with subacromial impingement. In a study, Saupe et al. [6] examined the anteroposterior radiography and MRI results of the patients and found the mean subacromial distance to be 5.9 mm (range, 1.2−9.8 mm). In addition, in that study, they reported that 7 mm was the critical threshold for the subacromial distance, and rotator cuff tears increased statistically significantly when subacromial distance was less than 7 mm. França et al. [3] evaluated the sagittal plane MRIs of the shoulders of 160 patients who were older than 45 years and reported that mean subacromial distance was 6.99 and 7.71 mm in the group with degeneration of the rotator cuff muscles and the control group, respectively, and subacromial distance decreased significantly according to the comparison of the two groups. Jost et al. [8] and Norwood et al. [9] reported that in clinical settings, subacromial distance measurement would help to evaluate the function of the rotator cuff muscles and to choose the treatment to be applied. Petersson and Redlund-Johnell [10] and Jost et al. [8] stated that an acromiohumeral distance of ≤ 7 mm measured on anteroposterior radiographs triggered significant damage to the rotator cuff muscles and reduced the likelihood of successful surgery. Park et al. [38] found a significant difference between VAS and subacromial distance values in the study they conducted in the general population aged 29–74 whose pain persisted for > 3 months. In our study, similar to the literature, 7 mm was set as the critical value for the subacromial distance and identified the changes above and below this threshold. No statistically significant difference was found when comparing patient age, BMI, and VAS scores between subacromial distance groups. A statistically significant difference was found in the percentages of acromion types in patients with a subacromial distance > 7 mm. Low subacromial distance values in Type 3 acromion has led us to think that the injury of the rotator cuff muscles in this group may occur more frequently than in other acromion types.

Limitations

The most important limitation of our study was the retrospective nature, and the number of patients was low due to the strict inclusion criteria.

Conclusion

Shoulder pain severely limits activities of daily living in patients who have shoulder impingement syndrome. For this reason, the treatment processes of these patients are extremely important. The morphological characteristics of the acromion and the changes that are caused by these morphology in the sub-acromial distance lay the ground for the formation of rotator cuff tears. Similar to data reported in the literature, a significant decrease was detected in the subacromial distance, especially in Type 3 acromion with hook appearance. Although a significant relationship was detected between the sub-acromial distance and VAS in the studies reported in the literature, the change in the sub-acromial distance may not be the factor that causes the pain in patients with shoulder pain as discussed in the present study. Aside from the acromion morphology, other factors that may cause changes in the subacromial distance must be examined, and the actual source of the pain should be investigated. In

addition, in line with the data obtained from our study and comparison of these data with similar studies in the literature, acromion types, especially subacromial distance, should be considered in patients with shoulder pain.

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Clinical significance of pathologically detected lesions in reduction mammoplasty

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Abstract

Background/Aim: Breast reduction surgery is performed for various reasons, especially macromastia. Although the mammoplasty material obtained after surgery is generally accepted as normal breast tissue, incidental breast cancer or precursor lesions of breast cancer are also observed in these materials. Detection of these lesions will provide important information both for the risk developing breast cancer in the normal population and for the early treatment of these lesions. Our study aimed to investigate the rate of occurrence of high-risk lesions, such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and carcinoma *in situ* (DCIS, LCIS) and the relationship of these lesions with patient age and weight of the resected material.

Methods: This study was a retrospective cohort study examining incidentally detected pathological lesions after examining reduction mammoplasty materials after breast reduction in our pathology department between 2011 and 2021. None of the cases had been previously diagnosed with breast cancer. The cases were pathologically classified as benign lesions, high-risk lesions with atypia, and *in situ* carcinoma. The association of atypical high-risk lesions with age (> 40 and ≤ 40 years) and resection weight was evaluated.

Results: The surgical materials of 288 breasts were evaluated in a total of 144 women. The mean age of the patients was 38.9 years. Atypical high-risk lesions, such as ADH, ALH, and DCIS were detected in seven patients (4.8%). İnvasive cancer was not observed. The mean age of the patients with risky lesions was 45.98 years, and the mean weight of these lesions was 2,045 grams. Cases with high-risk lesions were older (P = 0.041) and had a higher resection weight (P = 0.003).

Conclusion: The findings in our study reveal the necessity for mandatory histopathological examination of reduction mammoplasty materials. This examination is even more important in terms of high-risk lesion detection, especially in patients over 40 years and those with a high resection weight. In these cases, taking more tissue samples than used for the other situation for examination is recommended.

Keywords: Mammoplasty, Atypical hyperplasia, DCIS, Breast carcinoma

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Introduction

Breast reduction operations are performed for various reasons, especially macromastia. The pathological examination of surgical materials is important for the detection of risky proliferative lesions that may be a precursor to breast cancer. The pathological examination of reduction mammoplasty materials is more important in terms of detection of these lesions and incidental carcinomas, especially among patients in their 40s with an increased risk for developing breast cancer and those with a family history of this cancer [1].

Reduction mammoplasty materials are usually reported as benign proliferations, such as normal breast tissue, fibrocystic changes, fibroadenoma, flat epithelial changes, usual ductal hyperplasia, apocrine metaplasia, intraductal papilloma, adenosis or risky proliferative lesions, such as and atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), flat epithelial atypia (FEA), intraductal papilloma with atypia, and ductal and lobular carcinoma *in situ* (DCIS, LCIS). These atypical lesions are known to carry a higher risk of developing breast cancer than normal lesions [1, 2].

Among the common screening programs to determine the risk and rate of breast cancer development in the population, general breast examinations, mammography scans, and autopsy evaluations have an important place [3]. However, some of these practices may contain a slight age-related bias. Regardless of age, family history, and previous breast cancer history, high-risk lesions and cancer prevalence detected incidentally in reduction mammoplasty materials can provide important information concerning the overall risk of developing breast cancer [4]. On the other hand, data obtained from examination of these materials can guide screening and prevention strategies. In other words, high-risk lesions detected incidentally in materials removed during breast reduction may represent the most real-life data in terms of detecting the prevalence of breast cancer development in the general population.

Many studies examining lesions in breast reduction materials have been conducted. These studies have reported different risky lesions and cancer detection rates. Mammoplasty studies conducted evaluating cases without a previous history of breast carcinoma indicate that the incidence of incidental cancer and high-risk lesions generally ranges from 1.5% to 8.9% [5–7].

In a study including 2,498 reduction mammoplasty cases, Desouki et al. found 4.3% high-risk lesions, 0.16% DCIS lesions, and 0.08% invasive carcinomas [8]. In a recent study, it was reported that the rate of invasive carcinoma and carcinoma *in situ* increased to 2.3% and the rate of proliferative risky lesions to 13.8% [9].

This study aimed to evaluate the relationship between the detection rate of lesions carrying a particularly high risk for breast cancer development that were found in the materials removed during reduction mammoplasty operations performed for reconstructive reasons and patient ages, and weights of resected tissues.

Materials and methods

A total of 144 patients who underwent mammoplasty at Atatürk University Medical Faculty Research and Application Center between January 1, 2011, and December 31, 2021 were included in the study. None of the cases had previously been diagnosed with breast cancer or had undergone breast surgery for any reason, and all underwent surgical reduction mammoplasty for reconstructive purposes for reasons such as macromastia. At least three paraffin blocks were taken from the resected tissues for each breast, and the diagnosis was made by examining the hematoxylin and eosin (H&E)-stained sections. Some tissues were sampled more than others. The pathology reports of the patients were screened from the hospital information system. The diagnoses obtained from the reports were classified in terms of patient age, weight of resected tissue, and risk status according to the lesion type. Furthermore, data obtained by evaluating the relationship of high-risk lesions with patient age and weight of resected tissue are discussed in light of studies in the literature.

Statistical analysis

The cases included in the study were divided into two groups according to the diagnostic risk of lesions (high-risk ADH, ALH, DCIS, and other atypical lesions), two groups according to age (≤ 40 years and > 40 years), and three groups according to resected tissue weights (1,000 grams, 1,000–3,000 grams, and > 3,000 grams). The Pearson/Spearman correlation test was used to determine the correlation between all the groups. A *P*-value of < 0.05 was accepted as statistically significant. Data analysis was performed using IBM SPSS statistics v. 20.

Results

The surgical materials from 288 breasts (144 patients) were evaluated. The pathology results were generally reported as normal breast tissue, fibrocystic changes, (fibrosis, adenosis, macro cyst, micro cyst apocrine metaplasia) ductal ectasia, usual ductal hyperplasia, FEA, fibroadenoma, intraductal papilloma, ADH, ALH, and DCIS. The majority (95.2%) of the cases received a diagnosis of normal breast tissue or benign and benign proliferative lesions. High-risk lesions were detected in seven individuals (4.8%). The general distribution of the cases is summarized in Table 1.

Table 1: General distribution of pathological lesions

Lesion group	Lesion type	Mean weight of resected tissue (g)	Mean age	n	%
Benign Lesions	Fibrocystic changes (fibrosis, adenosis, macro-microcyst and apocrine metaplasia, etc.)	1,366.88	39.2	68	47.2
	Fibroadenoma	1,475.25	33.1	10	6.9
	Ductal ectasia	1,208.31	41.2	7	4.9
	Intraductal papilloma	1,375.25	37.3	7	4.9
	Usual ductal hyperplasia	1,854.10	43.9	14	9.7
	Other	993.75	36.5	31	21.5
Atypical High-Risk Lesions	Atypical ductal hyperplasia	2,075.78	46.7	3	2.1
	Atypical lobular hyperplasia	2,045.00	48	1	0.7
	Flat epithelial atypia	1,910.00	46	1	0.7
	Apocrine atypia	2,150.00	38	1	0.7
In situ	Ductal carcinoma in situ	1,875.00	51	1	0.7
Carcinomas	Lobular carcinoma in situ	0	0	0	0.0
Invasive Carcinom	Ductal, lobular, other	0	0	0	0.0
Total			38.9	144	100

The mean age of the patients was 38.9 years, and 75 (52.08%) were ≤ 40 years old and 69 (47.91%) were > 40 years old. The youngest patient was 17 years old, and the oldest was 64 years. The mean age of the patients with risky lesions was 45.98 years, and six of these patients were in the > 40 years group, while one was under 40. The incidence of high-risk lesions was

higher and statistically significant over 40 years than under 40 years (P = 0.041). The weight of resected tissue was < 1,000 grams in 60 (41.7%) cases, between 1,000 and 3,000 grams in 68 (47.2%), and > 3,000 grams in 16 (11.1%). The lowest weight of resected tissue was 110 g, and the highest weight was 3,410 g with the average weight per breast being measured as 1180 g. The mean weight of high-risk lesions was 2,045 g with one weighing < 1,000 grams, two weighing between 1,000 and 3,000 g, and four weighing > 3,000 g. The incidence of high-risk lesions with atypia was higher in cases with high resection weights (P = 0.003).

Discussion

The breast is very important for a woman's physical and mental health. However, women may need to undergo breast surgery at any time during their lives for a wide variety of reasons related to various disorders. Malignant and benign lesions of the breast are among the most important causes of the need for breast surgery. On the other hand, breast reduction operations are frequently performed due to macromastia, a condition that causes back pain and spinal and balance disorders. In addition, women with cancer in one breast usually undergo mammoplasty on the other breast to correct the asymmetry between the two breasts. The pathological examination of tissues removed after these operations is very important. Breast cancer is the most common cancer in women and is a major cause of mortality and morbidity in women. It is stated that in 2021, 284,200 new breast cancers will be detected in the United States, and 43,600 deaths will result from this diagnosis [10].

Pathological examinations of breast tissues obtained after reduction mammoplasty offer very important opportunities for the detection of lesions observed in the breasts or that are likely to be seen later. It is known that many lesions are associated with an increase in the risk of developing breast cancer in the future. In this regard, the detection of proliferative atypical breast lesions is very important in terms of the possibility of subsequent breast carcinoma development. In a study by Hartmann et al., it was reported that the increase in the risk for cancer development was 1.3 times for non-proliferative lesions, 1.9 times for proliferative lesions without atypia, and 4.2 times for atypical proliferative lesions [10, 11]. In addition, Wang et al. reported that the risk of breast cancer significantly increased even when benign breast lesions were found and was independent of other risk factors for breast cancer [12].

Mammoplasty studies evaluating cases with no prior history of breast carcinoma have shown that overall incidence of incidental cancer or high-risk lesions ranged from 1.5% to 13.8%. In many studies, it has been reported that the risk of proliferative lesions and carcinoma is higher in patients of advanced age and those with a family history of breast cancer [9]. In a cohort of 2,498 cases, Desouki et al. found that invasive carcinoma occurred at a rate of 0.08% and DCIS at 0.16%. The authors reported the prevalence of high-risk lesions as 4.3% [8]. In a study by Cook et al. with 1,289 patients, lesions with uncertain malignant potential were detected in 2.0% of reduction mammoplasty materials, DCIS in 0.3%, and invasive carcinoma in 0.1% [13]. In another study, including a total of 595 patients, significant pathological findings were detected in 9.8% of the patients, and the rate of carcinoma *in situ* was reported as 2.4%. The authors emphasized that increasing the sampling number would have resulted in detection of a higher number of lesions [14].

In a review by Uson et al., it was stated that the incidence of pre-malignant and malignant lesions was around 5%, and the rate of invasive carcinoma was 0.3% in breast reduction surgery samples. This risk was reported to be significantly higher in patients older than 40 years of age. In the same study, it was noted that taking at least four paraffin block samples would have significantly increased the lesion detection rate [6]. Acevedo et al., who evaluated a total of 4,775 cases, found pathological findings in 7.06% and detected high-risk lesions at a rate of 6.26%. The incidental detection rates were determined as 0.48% for DCIS and 0.31% for invasive carcinoma. It was also concluded that atypia and cancer rates increased with age [15].

Pitanguy et al. found the rate of carcinoma *in situ* as 0.5% in a total of 2,488 cases over a 45-year period and emphasized the importance of the histopathological examination of reduction mammoplasty materials [7]. In an autopsy study, Nielsen et al. determined that the total rate of ADH, ALH, and DCIS was 7% [3]. In a meta-analysis evaluating a total of 13 studies, Thomas et al. stated that the rate of invasive cancer was 0.85%, and the incidence of carcinoma *in situ* and ductal and lobular atypical hyperplasia was 8.9% on average [4].

In the review of Ambaye et al. [16], it was stated that since mammoplasty materials were randomly sampled from breast tissue, data obtained from the literature studies showed the minimum rates and the lesion detection rates would increase by increasing the number of samples. On the other hand, the authors found no relationship between large resection weight and positive pathologies.

In another study, Fisher et al. [17] suggested that careful histological examinations of breast reduction specimens were required. In that study, patients with a family history of breast cancer, previous breast surgery, and more breast tissue resected exhibited a greater risk of having proliferative or cancerous lesions. The authors stated that as the weight of the resected breast tissue increased, the probability of positive pathologies also increased; therefore, patients with larger breasts would likely have greater resection weights and thus, present a higher tendency to have positive pathologies. On the other hand, studies supporting the idea that breast volume is a risk factor for breast cancer recurrence and mortality have been published [18] in contrast to others indicating no relationship between breast weight and atypical lesion detection [16].

Tadler et al. [19] reported that the rate of breast cancer-related lesions was 2.8%, and the rate of carcinoma *in situ* was 0.9%. The authors found the rate of *in situ* carcinoma to be 5.5% higher among the materials resected during asymmetry correction mastectomy performed in patients with a history of cancer in the contralateral breast. Another analysis reported that the presence of positive pathologies was associated with advanced age, higher body mass index, and history of cancer, and a positive association between larger resection weight and positive pathologies was described [9].

In our study, high-risk lesions were detected in 4.1% of the cases and carcinoma *in situ* in 0.07%. Our findings are consistent with those in the literature. In addition, hyperplasia with atypia was observed in older patients and in cases with more breast mass. Our findings are valuable in terms of indicating the importance of a more careful examination of tissue samples in patients over 40 years and those with larger amounts of resected materials. Taking a higher number of samples and performing a meticulous microscopic examination of the above-mentioned groups can increase the probability of detecting important pathological findings.

Limitations

Although the number of cases in our study and the number of blocks taken from the tissues were acceptable for evaluation, these factors may still limit our ability to generalize them to the rest of the population. Therefore, analytical studies with more variables in larger patient groups in the future should be performed.

Conclusion

The findings in our study reveal the necessity of mandatory histopathological examination of reduction mammoplasty materials. This examination is even more important in terms of high-risk lesion detection, especially in patients over 40 years of age and with a high resection weight. In these cases, taking more tissue samples than for other cases for examination is recommended. On the other hand, careful follow-up of the pathology reports of these cases by clinicians is important for the management of atypical cases with atypia.

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Comparison of the luteal phase estradiol priming stimulation and standard antagonist protocols in patients with diminished ovarian reserve undergoing ICSI

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Ethics Committee Approval
The study protocol was approved by the Etlik Zubeyde Hanim Women's Health Training and Research Hospital Local Ethics Committee (2019/209).
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: No consensus on the optimal stimulation protocol for increasing *in vitro* fertilization (IVF) treatment's success rate in patients with diminished ovarian reserve is available. This study aimed to compare IVF outcomes in patients with diminished ovarian reserve (DOR) stimulated with a luteal phase estradiol (E2) priming protocol versus the standard antagonist protocol.
Methods: This retrospective cohort study included 603 patients who underwent intracytoplasmic sperm injection cycles (ICSI) after the diagnosis of DOR and who were stimulated with the luteal E2 priming protocol (E2 priming group; n = 181) or the standard antagonist protocol (antagonist group; n = 422). Groups were compared in terms of demographic characteristics, ovarian stimulation results, ICSI cycle outcomes, clinical pregnancy, and live birth rates per embryo transfer.
Results: The duration of ovarian stimulation was longer, and the total gonadotropin dose used was significantly higher (P = 0.001) in the E2 priming group than in the antagonist group. The number of embryos transferred was higher in the antagonist group when compared with E2 priming group (0.87 (0.75) versus 0.64 (0.49); P = 0.01), but no statistically significant difference in terms of embryo quality between groups was found (P > 0.05). The cycle cancellation rate, clinical pregnancy, and live birth rates per embryo transfer were similar in both groups.
Conclusions: No difference between IVF outcomes in the patients diagnosed with DOR who were stimulated with the antagonist protocol and the luteal E2 priming protocol was detected. The antagonist protocol might be considered more advantageous because of the shorter treatment duration and lower doses of gonadotropin. This protocol also allows more embryos to be transferred. Additional randomized controlled trials are needed to verify these findings.

Keywords: Luteal phase estradiol priming, Antagonist protocol, Diminished ovarian reserve, Intracytoplasmic sperm injection

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Introduction

Diminished ovarian reserve (DOR) refers to the patients with decreased number and quality of oocytes. The number of patients with the diagnosis of DOR who present for *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment cycles with the has increased markedly in recent years. No standard definition for DOR has been put forth to date, and the incidence among IVF patients is reported to be 10% [1, 2]. A decrease in antral follicle count, decrease in number of oocytes retrieved, higher cycle cancellation rates, and lower fertilization, implantation, clinical pregnancy, and live birth rates are still significant problems in DOR patients.

Controlled ovarian hyperstimulation (COS) is essential for multi-follicular development and is the main step in the IVF protocol. The optimal number of retrieved oocytes is important for development of an increased number of embryos available for transfer and higher pregnancy rates in IVF cycles [3]. The most appropriate ovarian hyperstimulation protocol for DOR patients is controversial [4]. Several strategies are recommended for IVF patients with DOR to increase the outcomes. These strategies include increasing the gonadotropin dose administered during controlled ovarian stimulation [5], using multiple types of gonadotropins, estradiol priming [6], antagonist protocol, and alternative supplementation of dehydroepiandrosterone (DHEA), growth hormone [7] and oral L-arginine [8]. Nonetheless, no consensus on the optimal stimulation method for increasing IVF treatment's success rate in DOR patients has been reached [9].

The present study aimed to compare the IVF outcomes (the number of retrieved oocytes, cycle cancellation and clinical pregnancy rates, live birth rate per embryo transferred in DOR patients treated with the standard antagonist protocol and the luteal estradiol (E2) priming protocol).

Materials and methods

This retrospective study included 603 DOR patients who underwent ICSI treatment cycles according to the standard antagonist (antagonist group) and luteal E2 priming antagonist protocols (E2 priming group) between January 2007 and July 2019. A total of 5236 patients were treated during this period at the Etlik Zubeyde Hanim Women's Health Training and Research Hospital's IVF center. The electronic records from 753 patients diagnosed with DOR were screened. After excluding patients who underwent different treatment protocols and who had insufficient medical records, 603 patients were examined.

The study protocol was approved by the Etlik Zubeyde Hanim Women's Health Training and Research Hospital Local Ethics Committee (2019/209). In reproductive period, FSH level < 12 IU/L and E2 level < 80 pg/ml are considered as normal levels of these hormones. Patients with at least two of three criteria were considered to have DOR: 1) basal serum follicle-stimulating hormone (FSH) level ≥ 12 IU/L and E2 level > 80 pg/ml measured within the last three months of the IVF cycle, 2) antral follicle count (AFC) < 7.3, and/or (3) serum Antimullerian hormone (AMH) level < 1.1 ng/ml measured over six months. Several factors, including infertility, indication for pre-implantation genetic diagnosis (PGD), freeze–thawed embryo cycles, presence of chromosomal and/or autoimmune disorders, and/or endocrine or metabolic disorders (such as diabetes, hypo/hyperthyroidism, and hyperprolactinemia) were considered exclusion criteria.

Demographic characteristics, such as age, body mass index (BMI), number of previous IVF cycles, duration of infertility, and basal characteristics (AFC, AMH measurement, and serum basal FSH, E2, and luteinizing hormone (LH) levels) were recorded. Groups were compared in terms of duration of ovulation induction, total gonadotropin dose used, E2 and progesterone (P) levels, and endometrial thickness on hCG (conception) day, the number of retrieved oocytes, mature oocytes, and fertilized oocytes. The number of embryos (good or poor quality) transferred, E2 and P levels, and endometrial thickness on the transfer day were also analyzed. The number of embryo transfer (ET) cycles, the number of canceled cycles, day of embryo transfer (day 3 or 5), biochemical pregnancy, clinical pregnancy, and live birth rates per ET were compared between the groups.

Antagonist protocol

In the standard flexible GnRH antagonist protocol, gonadotropin was initiated on day 3 of the menstrual cycle. The patients received gonadotropin at a starting dose of 225 to 450 IU/day using recombinant FSH (recFSH; Gonal-F, Merck-Serono, Istanbul, Turkey or Puregon; Organon, Istanbul, Turkey) with human menopausal gonadotropin (hMG; Menagon; Ferring, Istanbul, Turkey or Merional; IBSA, Istanbul, Turkey). The dose was determined based on age, BMI, and AFC and tailored according to follicular development. When the mean diameter of ≥ two follicles reached 13–14 mm during stimulation, the antagonist was initiated (Cetrotide, Merk-Serono, Istanbul, Turkey) and was continued until the day of recombinant human chorionic gonadotrophin (rechCG) administration.

Luteal phase estradiol priming protocol

The patients in the luteal E2 priming protocol group received oral E2 hemihydrate (Estrofem, Novo-Nordisk, Istanbul, Turkey) twice a day, beginning on day 21 of the previous cycle until the first day of menses. The gonadotropins (recFSH and hMG) were initiated on day 3 of menstruation similar to the standard antagonist protocol and when ≥ two follicles reached 13–14 mm in diameter, the antagonist, Cetrotide, was initiated and continued until the day of rechCG administration.

Ovarian response was monitored by serial transvaginal ultrasound and serum estradiol and LH assessments. Rec hCG of 250 mg (Ovitrelle, Merck-Serono, Poland) was administered to all subjects for the final oocyte maturation when at least three follicles reached a diameter of 18 mm. Transvaginal oocyte retrieval (OPU) was performed 35.5–36 hours after hCG administration, and intracytoplasmic sperm injection (ICSI) was performed for all mature oocytes. The presence of two pronuclei 18–20 hours following ICSI confirmed fertilization. The absence of fertilization was defined as total fertilization failure (TFF). Embryo development was assessed daily, and a development arrest for 24 h or the presence of an embryo with degenerated or lysed cells was accepted as embryo development arrest (EDA). For assessment of embryonic quality, embryos were graded using an embryo scoring system as described by Baczkowski et al. [10].

Cycle cancellation was classified as no follicular development with ovarian hyperstimulation, no oocytes retrieved in OPU, and/or presence of TFF and EDA.

Embryo transfer was performed on either day 3 or 5 under ultrasonography guidance. Luteal phase support was provided to all patients with the combination of intramuscular (Progestan amp, Koçak Farma, Turkey) and vaginal progesterone (Crinone 8% gel, Merck-Serono, UK). A positive pregnancy test was diagnosed by blood β-hCG levels obtained 14 days after OPU. Clinical pregnancy was defined by the presence of an intrauterine gestational sac with detectable fetal cardiac activity as assessed by transvaginal ultrasonography. Spontaneous abortion was defined as the loss of a nonviable fetus/pregnancy up to 20 weeks. Live birth was defined as the delivery of a viable fetus after 24 weeks of gestation.

The primary outcomes were clinical pregnancy rate per ET, live birth rate per ET, and the cycle cancellation rate. The secondary outcomes were the number of retrieved oocytes, mature oocytes and the number of embryos transferred.

Statistical analysis

Statistical analyses were performed using the SPSS Windows version 23.0 (SPSS Inc., Chicago, IL). The distribution of the continuous variables, coefficients of skewness, and kurtosis were checked using the Kolmogorov–Smirnov test and histograms. Continuous variables were defined as mean (standard deviation (SD)), and categorical variables were defined as frequencies and numbers (%). The Mann–Whitney U test was used to evaluate comparison between non-normally distributed continuous variables and two-level variables. The chi-squared test was used to evaluate categorical variables. A value of $P < 0.05$ was accepted as statistically significant.

Results

A total of 603 patients (422 (70.0%) stimulated with the standard antagonist protocol, and 181 (30.0%) stimulated with luteal E2 antagonist protocol) were included. Mean age, duration of infertility, number of IVF cycles, basal FSH, LH, and E2 levels, and AFC did not differ significantly between the two protocol groups ($P > 0.05$) as shown in Table 1. The BMI of patients who were stimulated with the standard antagonist protocol was significantly higher than in patients who were stimulated with luteal E2 antagonist protocol ($P = 0.02$). Serum AMH levels were higher in the antagonist group than in the E2 priming group [0.53 (0.22) versus 0.26 (0.06)] ($P = 0.001$) as shown in Table 1.

Duration of ovulation induction was significantly longer in the E2 priming group versus the standard antagonist group [9.7 (2.2) versus 9.2 (2.0) days; $P = 0.001$]. The total gonadotropin dose was also significantly higher in the E2 priming group [3141.76 (948.06) IU versus 2734.66 (1038.49) IU; $P = 0.001$]. Serum E2 and P levels on hCG day, endometrial thickness on hCG day, and the number of retrieved oocytes, mature oocytes, fertilized oocytes did not differ significantly between these two groups ($P > 0.05$). The number of embryos transferred was higher in the antagonist group than the E2 priming group [0.87 (0.75), 0.64 (0.49)], but the number of good or poor-quality embryos that were transferred did not differ between the groups ($P > 0.05$). Serum E2 levels on transfer day was lower, whereas serum P levels and the endometrial thickness on transfer day was higher in the E2 priming group compared with the antagonist group ($P > 0.05$).

The rate of embryo transfer cycles (53.1% versus 47.5%) and the cycle cancellation rate (46.9% versus 52.5%) didn't differ between the groups (Table 2). Day of ET, biochemical pregnancy rate per ET (6.3% versus 10.7%), clinical pregnancy rate per ET (31.5% versus 25%), spontaneous abortion rate per ET (12.1% versus 10.5%), and live birth rate per ET (19.2% versus 14%) also did not differ between groups ($P < 0.05$) as shown in Table 2.

Table 1: Demographic characteristics and COS parameters of patients stimulated with antagonist protocol and luteal E2 antagonist protocol

	Antagonist group n = 422	E2 priming group n = 181	*P*-value
Maternal age, years	35.20 (5.24)	35.34 (4.89)	0.865
Body mass index, kg/m^2	26.90 (4.71)	25.60 (4.83)	0.002
Duration of infertility, months	63.9 (56.1)	59.9 (56.3)	0.291
Number of IVF cycle	1.84 (1.26)	1.85 (1.28)	0.951
Basal FSH level, IU/L	11.77 (6.98)	12.97 (7.26)	0.012
Basal LH level, IU/L	5.52 (2.98)	5.68 (4.00)	0.941
Basal E2 level, pg/ml	51.33 (48.80)	52.30 (34.41)	0.321
AMH, ng/ml	0.53 (0.22)	0.26 (0.06)	0.001
Antral follicul count	5.27 (3.03)	5.09 (3.01)	0.315
Cos Parameters			
Duration of ovulation induction, days	9.21 (2.05)	9.71 (2.20)	0.001
Total gonadotrophin dose, IU	2734.66 (1038.49)	3141.76 (948.06)	0.001
E2 level on hCG day, pg/ml	1029.61 (581.70)	1040.32 (560.98)	0.008
P level on hCG day, ng/ml	0.59 (0.60)	0.75 (0.24)	0.001
The endometrial thickness on hCG day, mm	9.37 (1.64)	9.41 (1.50)	0.213
Number of retrieved oocytes	4.40 (2.51)	4.33 (2.54)	0.941
Number of mature oocytes	3.30 (2.04)	3.14 (1.95)	0.566
Number of fertilized oocytes	1.57 (1.53)	1.77 (1.49)	0.378
Number of embryos transferred	0.87 (0.75)	0.64 (0.49)	0.001
Good quality	1.05 (0.52)	1.06 (0.38)	0.683
Poor quality	0.17 (0.41)	0.14 (0.36)	0.522
E2 level on transfer day, pg/ml	584.94 (310.18)	507.28 (232.13)	0.001
P level on transfer day, ng/ml	42.82 (14.76)	50.81 (15.35)	0.001
The endometrial thickness on transfer day	9.90 (1.78)	10.15 (1.26)	0.001

FSH: follicle-stimulating hormone, LH: luteinizing hormone, E2: Estradiol, P: Progesterone, AMH: antimullerian hormone, COS: Controlled ovarian stimulation, hCG: human chorionic gonadotrophin, IVF: *In vitro* fertilization. Data are presented as mean (SD).

Table 2: IVF outcomes of patients stimulated with antagonist protocol and luteal E2 antagonist protocol

	Antagonist group n = 422	E2 priming group n = 181	*P*-value
Number of embryo transferred cycles	224 (53.1)	86 (47.5)	0.210
Number of canceled cycles	198 (46.9)	95 (52.5)	0.870
No folliculer development	41 (21.1)	21 (21.3)	
No oocytes in OPU	32 (16.1)	12 (12.8)	
TFF	52 (26.1)	24 (25.5)	
EDA	73 (36.7)	38 (40.4)	
Day of ET			0.130
Day 3	180 (80.7)	75 (87.2)	
Day 5	44 (19.6)	11 (12.8)	
IVF outcome per ET			0.287
Biochemical pregnancy	14 (6.3)	9 (10.7)	
Clinical pregnancy	70 (31.5)	21 (25)	
Pregnancy outcome per ET			0.725
Spontaneous abortion	27 (12.1)	9 (10.5)	
Live birth	43 (19.2)	12 (14)	

OPU: oocyte pick up, TFF: total fertilization failure, EDA: embryo development arrest, ET: embryo transfer, IVF: *In vitro* fertilization. Data are presented as n (%).

Discussion

The present study compared the standard antagonist and luteal E2 priming protocols in terms of IVF outcomes in DOR patients. Although ovulation induction duration and the total gonadotropin dose were significantly higher in the E2 priming group, cycle cancellation, and clinical pregnancy, and live birth rates per ET were similar in both stimulation groups.

The definition of DOR varies across studies [11–13]. Baseline FSH, AMH, and AFC were recently used to predict the ovarian reserve [14], and the present study used these four parameters to define DOR (baseline values for FSH, E2, AMH, and AFC).

Many different methods are used to treat DOR, but no one method is better than another one [9]. The use of the combined E2 priming and antagonist protocols was first described by Dragisic et al. [15]. Studies have shown that E2 administration during the luteal phase of the previous cycle causes suppression of the early elevation of FSH and results in homogenous growth in early antral follicles preventing follicular asynchrony [16,17]. Additionally, lower cycle cancellation rates, higher number of ETs, and higher pregnancy rates were noted in patients treated with the luteal E2 priming protocol [18,19]. Oral estradiol valerate, transdermal estradiol hemihydrate patches, and an estradiol pump were used for E2 priming and when compared to the other groups, it was stated that pregnancy rates were not different between the three groups [20].

Most of the studies comparing the luteal E2 priming protocol with the standard antagonist protocol have been published in poor ovarian response (POR) patients [6, 21, 22]. In two of these studies, the total gonadotropin dose administered during stimulation was found to be significantly higher in patients in the E2 priming protocol arm [21, 22] than in the other arms. Another study reported that no difference was found in the total gonadotropin dose between the E2 priming and antagonist protocol groups [6]. In the present study, the total gonadotropin dose was significantly higher in the E2 priming protocol group.

Mutlu et al. [21] compared the luteal E2 priming and the standard antagonist protocols, reporting that the number of oocytes retrieved, the number of mature oocytes, and the number of embryos transferred did not differ significantly between the groups. A retrospective study that included 86 patients who had been primed with oral E2 valerate and the antagonist protocol observed that the number of oocytes retrieved, the number of fertilized oocytes, and the percentage of good quality embryos were higher in the E2 priming group [6]. More recently, Lee et al. [22] compared the IVF outcomes in 65 POR patients treated with luteal oral E2 valerate and the antagonist protocol, noting that the number of oocytes retrieved and the number of mature oocytes in the E2 priming protocol group were significantly higher than in the antagonist group. The number of retrieved, mature, and fertilized oocytes did not differ between groups in the present study.

Chang et al. [6] reported that the pregnancy rate per ET was higher, and the cycle cancellation rate was significantly lower in the E2 priming protocol group than in the antagonist protocol group in poor responders. Lee et al. [22] reported that clinical pregnancy and live birth rates were significantly higher in the E2 priming group than in the antagonist group. In contrast, Mutlu et al. [21] noted that the clinical pregnancy rate and the live birth rate per ET did not differ between the luteal E2 priming and antagonist protocol groups. They also observed that no significant differences between the cycle cancellation rates between the two protocols existed, similar to the results in the present study. Recently, the luteal E2 priming protocol with the small number of patients with 4 mg oral E2 was prospectively compared with standard antagonist group, and no difference in IVF outcomes was noted [23]. One retrospective observational study was published in the literature that compared luteal E2 priming using E2 hemihydrate and antagonist protocol groups in normo-responders and poor responders. In normo-responders, no difference between the groups in terms of IVF outcomes was found. However, in the poor responder group, pregnancy and live birth rates per ET were higher in the luteal E2 priming group [24]. The heterogeneity of the findings might be due to the small number of relevant studies, differences in the type of estradiol administered, and/or small patient populations.

Limitations

The limitation of the present study is the retrospective design; however, its strength is the sizeable number of patients included in the study.

Conclusion

Although no difference between the antagonist protocol and luteal E2 priming protocol groups in terms of IVF outcomes in the DOR patients was found, it seems that the antagonist protocol is the better choice as it allows administration of small doses of gonadotropins, and the duration of ovulation induction is short. Additional prospective and randomized clinical trials are needed to verify the present study's findings.

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Evaluation of electrocardiographic parameters in patients who had lung resections

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Abstract

Background/Aim: The anatomic location of the heart in the mediastinal space may change and significant electrophysiological changes may appear after pneumonectomy, lobectomy, and segmentectomy. The aim of the present study was to perform a comprehensive investigation of electrocardiographic alterations after lung resection.
Methods: In this retrospective cohort study, sixty-six patients (9 females, 57 males) who had lung resections were enrolled. Electrocardiograms of preoperative (24 hours before operation) and postoperative periods (after operation 7 (2) days) were analyzed.
Result: Postoperative mean Pmin and QRS duration levels were lower than the respective preoperative values. In comparison with preoperative values, postoperative mean P dispersion, QTmax, QTmin, QT mean, QTd, QTc, QTc dispersion, JT, JTc, mean Tpe/QTmean, mean Tpe/QTc ratio (%), and mean Tpe/JT ratio (%) levels were found to be significantly higher. Postoperative mean pulse, mean Pmax, mean PR interval, mean RR, and mean Tpe/JTc ratio were not significantly different when compared with preoperative levels.
Conclusion: Alterations in electrocardiography parameters reflecting the electrophysiology of the heart since heart position basically changes after lung resection may appear.

Keywords: Electrocardiography, Pneumonectomy, QRS, P dispersion

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Introduction

Electrophysiological alterations may appear as a result of a change in the physiological position of the heart in the mediastinum [1]. These electrophysiological changes may appear as life-threatening arrhythmias [2]. This usually occurs as a result of lung resection, which impacts a significant part of the mediastinal space [3, 4]. The anatomic location of the heart in the mediastinal space may change after pneumonectomy, lobectomy, and segmentectomy because of lung tumors, infiltrative pulmonary diseases, chronic obstructive lung disease, emphysema, chronic pulmonary infections, and bronchiectasis [5–7]. Moreover, local infection may occur in the neural structures, pericardium, and atrium after such a significant surgical procedure [8].

It has been known since 1940 that supraventricular arrhythmias such as atrial fibrillation (AF) and atrial flutter, as well as cardiac failure, may develop after clinical practice and lung resection procedures [9, 10]. However, there is no comprehensive study on possible electrocardiography (ECG) changes after lung resection. A limited number of studies focused on the PR distance, QT distance, and QRS complex superficially as ECG changes in a limited number of resection types with fewer cases [3, 8, 9].

Therefore, the aim of the present study was to perform a comprehensive investigation on electrocardiographic alterations in multiple cases after lung resection.

Materials and methods

This retrospective cohort study was conducted in the Cardiology and Thoracic Surgery Clinics of Istanbul Yedikule Training and Research Hospital between February 2019 and August 2019. The study was designed in compliance with the 2013 Declaration of Helsinki and good clinical practices. Approval of the SBU Istanbul Research and Training Hospital Ethics Committee (registration number 2019/1660 and date 01/02/2019) was obtained for the study. Written and verbal consent of the participants was also obtained before the beginning of the study.

Study population

Sixty-six patients (9 females, 57 males) who had lung resections due to malignancy, non-specific infections, or trauma were enrolled in the study. Assuming an alpha of 0.05, a power of 0.80, and 30% change after resection in terms of degree of QRS axis consistent with previous reports, the estimated sample size was at least 40 patients in total.

Patients with previous coronary artery disease, cardiac failure, congenital heart disease, history of pulmonary embolism, chronic obstructive lung disease, history of asthma, or use of anti-arrhythmic drugs were excluded.

Clinical (resection type, ECG findings) and demographic (age, gender) data of all patients were recorded from their files via the hospital's electronic information system.

Electrocardiography

For all participants, a 12-lead ECG recording was performed at preoperative (24 hours before operation) and predischarge (postoperative 7 (2) days) period in the supine position at 50 mm/s paper speed (Nihon Kohden, Tokyo, Japan). ECG measurements were performed by two cardiologists who were blinded to the patient data. Heart rate (HR), maximum P wave duration (Pmax), minimum P wave duration (Pmin), P wave dispersion (Pdisp), PR distance, maximum QT wave duration (QTmax), minimum QT wave duration (QTmin), QT dispersion (QTd), corrected QT interval (QTc), QRS interval, Tpeak to Tend (Tpe), mean QT value (QTmean), QTdc, QTdc dispersion, JT, JT interval (JTc), RR interval, Tpe/Qtmean (%), Tpe/QTc (%), Tpe/JT (%), and Tpe/JTc (%) were measured in all derivations and their means were calculated.

The onset of the P-wave was defined as the junction between the isoelectric line and the beginning of the P-wave deflection. The offset of the P-wave was defined as the junction of the isoelectric line and the end of the P-wave deflection. Maximum P-wave duration was accepted as the longest P-wave and the longest atrial conduction time. The difference between the longest and the shortest P-wave duration was accepted as P-wave dispersion. The QT interval was defined as the distance between the onset of the Q-wave and the offset of the T-wave. Heart rate-corrected QT interval (QT_c) was calculated using Bazett's formula. The JT interval was defined as the distance between the onset of the J-wave and the end of the T-wave and was calculated by subtracting the QRS duration from the QT interval. JT_c was calculated by subtracting the QRS duration from the QT_c interval [11, 12].

Statistical analysis

Statistical evaluation was performed using SPSS 20 for Windows (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate whether the data were normally distributed. Numerical variables were determined as mean (standard deviation), whereas categorical changes were presented as number and percentage. The changes in ECG findings after the procedure were analyzed by paired samples test and Kruskal-Wallis H test for numerical variables with normal distribution. The effect of resection type on ECG findings was assessed by repeated measures mixed model analysis. Values of $P < 0.05$ were accepted as statistically significant.

Results

The research population consisted of 66 patients including 57 (86.4%) males and 9 (13.6%) females. The average age of the patients was 58.5(10.2) years. At baseline, sixty-five patients (98.5%) had normal sinus rhythm, whereas 1 (1.5%) patient had atrial fibrillation. Right bundle branch block was detected in 3% (n=2) of the patients, left bundle branch block was detected in 1.5% (n=1), and left incomplete block was detected in 3% (n=2). Distributions of demographic findings and operation types are shown in Table 1.

The postoperative changes in ECG findings are shown in Table 2. In brief, postoperative mean Pmin and QRS duration levels were lower than the respective preoperative values. In comparison with preoperative values, postoperative mean P dispersion, QTmax, QTmin, QT mean, QTd, QTc, QTc dispersion, JT, JTc, mean Tpe/QTmean, mean Tpe/QTc ratio (%), and mean Tpe/JT ratio (%) levels were found to be significantly higher. Postoperative mean pulse, mean Pmax, mean PR interval, mean RR, and mean Tpe/JTc ratio were not significantly different when compared with preoperative levels.

Table 1: Baseline demographic and clinical findings of the study population

Variables	n=66
Age, years	58.5(10.2)
Gender, n (%)	
Female	9 (13.6)
Male	57 (86.4)
Rhythm, n (%)	
NSR	65 (98.5)
AF	1 (1.5)
Branch blocks, n (%)	
No	61 (92.4)
Right bundle branch block	2 (3.0)
Left bundle branch block	1 (1.5)
Left incomplete block	2 (3.0)
Resection type, n (%)	
Left pneumonectomy	16 (24.2)
Left upper pneumonectomy	14 (21.2)
Left lower pneumonectomy	9 (13.6)
Right pneumonectomy	2 (3.0)
Right upper pneumonectomy	4 (6.1)
Right lower pneumonectomy	13 (19.7)
Double pneumonectomy	3 (4.5)
Right lower lobectomy	5 (7.6)

The values are expressed as mean (standard deviation), NSR: normal sinus rhythm, AF: atrial fibrillation

Table 2: Changes in ECG findings before and after the operation

Variables	Preoperative n=66	Postoperative n=66	*P*-value
HR, beats/min	85.3(16.7)	85.2(15.7)	0.943
Pmax, ms	110.2(16.7)	110.6(19.6)	0.890
Pmin, ms	86.3(16.3)	82.0(21.3)	0.029*
P disp, ms	23.9(12.9)	28.6(12.6)	0.011*
PR, ms	152.2(22.1)	148.1(24.9)	0.117
QTmax, ms	354.2(30.2)	372.0(33.2)	< 0.001*
QTmin, ms	335.7(30.3)	348.2(31.2)	0.001*
QT disp, ms	18.5(12.1)	23.8(11.7)	0.004*
QTc, ms	406.9(25.7)	424.6(26.8)	< 0.001*
QRS, ms	90.2(17.3)	86.5(19.1)	0.025*
Tpe, ms	68.5(7.8)	74.1(11)	< 0.001*
QTmean, ms	344.9(29.6)	360.1(31.7)	< 0.001*
QTc disp,ms	21.7(13.9)	28.1(13.7)	0.003*
JT, ms	289.3(22.8)	306.5(24.9)	< 0.001*
JTc, ms	342.6(36.7)	362.8(37.2)	< 0.001*
RR	0.7(0.1)	0.7(0.1)	0.994
Tpe/QTmean ratio, (%)	19.9(2.4)	20.7(3.2)	0.029*
Tpe/QTc ratio, (%)	16.9(2.2)	17.5(2.7)	0.013*
Tpe/JT ratio, (%)	23.8(3.5)	24.5(4.9)	0.045*
Tpe/JTc ratio, (%)	20.3(3.6)	20.8(4.6)	0.072

The values are expressed as mean (standard deviation), HR: heart rate, max: maximum, min: minimum, disp: dispersion, min: minutes, ms: milliseconds

Discussion

Lung resection was found to be associated with some postoperative thoracic anatomic changes and hemodynamic changes that may cause significant electrocardiographic changes. Depending on the reason for the pulmonary resection, the procedure may vary from a small segmental resection to the resection of a whole lobe or the lung itself. This clinically means that possibly fatal arrhythmias may appear during the postoperative period. So, in the present study, we investigated preoperative and postoperative ECG changes of patients who had lung resections as a result of different causes.

In our study, QRS duration and Pdisp were found to be decreased in the postoperative period when compared with the preoperative period. The QRS complex reflects ventricle depolarization. QRS duration changes depending on the vertical or horizontal position of the heart in slim and overweight individuals. The position of the heart changes after pneumonectomy, and the axis slides. Therefore, the duration of ventricle depolarization changes. Apart from that, decreased QRS durations, or namely narrow QRS complexes, may be associated with aberrant conduction of supraventricular complexes. This is related to pneumonectomy [13–15]. Pmin indicates the minimum P wave duration. Increased preload, presence of right and left atrial dilatation, and external pressure of the heart may cause an increase in the duration of Pmin. The possible cause of the decrease in Pmin level after lung resection may be associated with the elimination of previous pathologies of the lung by the procedure, along with the change of the heart's position. Guntekin et al. [16] reviewed P wave duration according to the altitude level of subjects' places of residence. The Pmin level was found to be higher in people living at higher altitudes than those living at sea level.

The increase of the postoperative Pdisp level may have been caused by the following factors: (a) significant perioperative fluid losses that contribute to increased atrial strain, (b) atrial pressure increased due to postoperative ventricular stunning, (c) increased sympathetic stimulus increased just after the surgery, and (d) mediastinal or cardiac dislocation [8]. Tukek et al. [17] conducted a study of patients with chronic obstructive pulmonary disease and considered an association between newly developed atrial fibrillation and prolonged Pdisp. Senen et al. [18] reviewed P wave duration and Pdisp in patients with dilated cardiomyopathy. They reported that Pdisp was higher in the dilated cardiomyopathy group than the healthy control group. Supraventricular tachycardia, i.e., atrial fibrillation frequency, increases in both situations stated above. We know that the incidence of supraventricular tachycardia increases after lung resection. Therefore, we believe that increased Pdisp durations may be associated with arrhythmia [9].

In the present study, we found that postoperative QTmax, mean QTmin, mean QTd, mean QTc, mean Tpe, mean QTort, and mean QTdc increased after surgery. General mean QRS vector and QRS vector shift presented a quantitative correlation in the majority of the patients for each subtype of lung resection. The most likely cause of the change in mean QRS axis shift towards a mediastinal shift after lung resection is the rapid wave nature of QRS and the appearance of a left ventricle-dependent vector pattern [8]. Dispersion of the QT interval shows regional heterogeneity in myocardial repolarization. An increase is accepted as a non-invasive indicator of the risk of increased ventricular arrhythmia [19]. Because the incidence of arrhythmia may increase after lung resection, increases in QTc, QTd, QTmin, and QT max levels are acceptable.

It is known that the JT interval indicates ventricle repolarization in ECG. Some previous studies reported that the JT interval indicated ventricle repolarization better than the QT interval [20]. An increased JT interval after lung resection indicates the increase of ventricle repolarization. A difference in excitability may appear along with the change in the location of the heart. This may contribute to changes of depolarization and repolarization phases.

Limitations

The primary limitation of the present study is its retrospective cohort design. The retrospective design does not make it possible to provide sufficient information about hemodynamic changes, electrolyte imbalance, or medical therapies used. The second limitation is the relatively small number of patients. Therefore, study population could not be grouped according to the etiology of pneumonectomy. Therefore, there is a need for studies with a larger number of patients and with a prospective design.

Conclusion

Before evaluating the ECG, the clinician should keep in mind that some alterations in electrocardiography parameters reflecting the electrophysiology of the heart may occur because

the heart's position can change after lung resection. According to this study analysis, a decrease was detected in Pmin and QRS durations after lung resection. Furthermore, the mean Pdisp, QTmax, QTmin, QTd, QTc, Tpe, QTort, QTdc, and JT were detected to be increased postoperatively.

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Research article

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Diagnostic use of CA 125 values measured on the 2nd and 14th days of the menstrual cycle in endometriosis

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Ethics Committee Approval
The study was approved by the Ethics Committee of Dokuz Eylul University (protocol number: 3686-GOA, 07.12.2017).
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Abstract

Background/Aim: This study examines the difference of serum CRP and CA 125 levels between the menstrual and non-menstrual phases of the menstrual cycle (days 2 and 14) and aims to investigate the diagnostic value of these markers for the early diagnosis of endometriosis.
Methods: There were 36 patients in the study group and 30 patients in the control group (n = 66) in this prospective case-control study. The patients in the study group, who were prediagnosed with endometriosis, were tested for serum CA 125 and CRP on the 2nd and 14th days of menstrual cycle preoperatively (during menstruation and non-menstrual phase) and underwent surgery. The women in the control group were patients who visited the outpatient clinic for a regular checkup without any gynecological complaints.
Results: The CA 125 levels were significantly higher on the 2nd day of the menstrual cycle than the 14th day in the study group [108.15 (90.33) U/mL and 58.60 (39.53) U/mL, respectively, $P < 0.001$]. In the control group, the CA 125 levels were also significantly higher on the 2nd day than the 14th day [22.97 (15.42) U/mL and 13.82 (6.82) U/mL, respectively, $P < 0.001$]. When the comparison was made between the CRP levels on the 2nd and 14th day for the study group [4.52 (4.45) mg/L and 2.82 (3.79) mg/L, respectively], the levels were significantly higher on the 2nd day ($P < 0.001$). The difference of CA 125 and CRP levels between the days [for the study group: ΔCA 125 = 49.55(56.89) U/mL, ΔCRP = 1.69(3.45) mg/L and for the control group ΔCA 125 = 9.14 (11.95) U/mL, ΔCRP = 1.42 (4.74) mg/L] were higher for both markers in the study group, and the differences with the control group were statistically significant ($P < 0.001$ for ΔCA 125 and $P = 0.033$ for ΔCRP).
Conclusion: Our data indicates that it may be possible to support the diagnosis with the evaluation of CA 125 levels during different phases of menstruation separately.

Keywords: Endometriosis, CA 125, CRP, Menstrual cycle

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Introduction

Endometriosis is an estrogen-dependent benign gynecological disease, which affects 10% of women in the reproductive period, and is characterized by endometrial glands and stroma outside the uterine cavity. Typical implantation sites of endometriosis are pelvic organs and the peritoneum. It can cause widespread adhesions in the pelvic region, including the intestines, bladder, and ureters. Less frequently, this can be observed in extrapelvic areas, such as incision sites, eyes, or brain [1].

The definitive diagnosis is made by histopathological examination after surgical excision of lesions. Symptoms that best predict the diagnosis are infertility, dysmenorrhea, and chronic pelvic pain [2]. Among these, the most frequently reported symptom is dysmenorrhea.

Endometriosis foci may be observed as widespread or scarcely distributed in the peritoneum during laparoscopy. Nowadays, endometriosis is examined under three categories: peritoneal endometriosis, ovarian endometriosis, and deep adenomyotic nodular endometriosis [3].

Many serum markers have been studied for the noninvasive early diagnosis of endometriosis. However, no indicator with sufficient sensitivity and specificity has been found yet. These include cytokines, such as VEGF, GM-CSF, IL-2, IL-8, IL-15, IL-6, monochemotactic protein-1, interferon-gamma (IF-γ), and tumor necrosis factor (TNF) [4].

In endometriosis, there is a pelvic inflammatory process with the deterioration of immune cell function in the peritoneal region [5]. For this purpose, C-reactive protein (CRP) is a marker that is investigated in the diagnostic approach of endometriosis, similar to other cytokines.

CA 125 is a well-studied marker and is often increased in women with advanced endometriosis. Serum CA 125 values fluctuate during the menstrual cycle; levels are usually highest in the menstrual phase and lowest in the mid-follicular and periovulatory phases [6].

Clinical rectovaginal examinations and imaging modalities, such as USG, MRI, and CT, have diagnostic value only in patients with advanced endometriosis. The limited diagnostic value of imaging modalities in early-stage endometriosis increases the importance of markers to predict early diagnosis.

In patients with endometriosis, the intraperitoneal inflammatory process is expected to reactivate during the menstruation phase of the cycle. Accordingly, CA 125 and CRP values are expected to increase more during the menstrual phase than the rest of the cycle and the difference between the two measurements is expected to increase. The study aims to determine the difference in CRP and CA 125 levels between the menstrual and non-menstrual phases (days 2 and 14) of the cycle and to investigate the diagnostic value of these markers for the early diagnosis of endometriosis.

Materials and methods

This study was a prospective case–control study. The patients were admitted to the Obstetrics and Gynecology Clinic of Dokuz Eylul University School of Medicine between October 2017 and September 2018. The study was approved by The Ethics Committee of Dokuz Eylul University (protocol number: 3686-GOA, 07.12.2017). The case group consisted of patients, who were previously diagnosed with endometrioma and were studied for CA 125 and CRP levels on the 2nd and 14th days of the preoperative menstrual cycle and underwent an operation. The control group consisted of patients without active gynecological complaints or pathologies and who had visited for a routine checkup. These patients were also tested for CA 125 and CRP on the 2nd and 14th days of the cycle as in the case group. Preoperative diagnoses of the case group were confirmed histopathologically in the postoperative period. Patients who had not been diagnosed with endometriosis histopathologically or who had been previously diagnosed with medical treatment were excluded.

The inclusion criteria for the case group required being 15–49 years of age, being in the reproductive period, and a confirmation of the preoperative diagnosis by postoperative histopathology. For the control group, no gynecological pathology was detected among the patients. In this study, 36 patients in the case group and 30 patients in the control group were included.

Signed informed consent forms were obtained from all participants. Necessary measurements were made for all patients on the 2nd and 14th days of the cycle. In addition, another measurement was made after the surgical procedure in the case group. All findings were recorded in the data record form.

CA 125 analysis was performed on Siemens ADVIA Centaur CP (Siemens Healthineers AG, Erlangen, Germany) with original kits (CA 125 II, cat. No. 09427226) using the chemiluminescent immunoassay method. The sensitivity of the test was 2 U/mL and the measuring range of the test was 2–600 U/mL according to the original documentation.

CRP analysis was performed by Beckman Coulter Olympus AU5800 autoanalyzer (Beckman Coulter, Inc. Diagnostics Division, Brea, CA, United States) with original kits (CRP Latex, cat. No: OSR6199, OSR6299) using the immunoturbidimetric method. According to the original documentation, the sensitivity of the test was 0.2 mg/L and the measuring range of the test was 0.2–480 mg/L.

Statistical analysis

The research was not based on a previous study and, therefore, the sample size calculation was not made according to another research. For a medium effect size, in order to reach 80% power with alpha value set as 0.05, each group required at least 30 participants according to our sample size calculations.

Data, such as age, CA 125, and CRP levels of all patients in the case and control groups were evaluated with the Kolmogorov–Smirnov normality test for normal distribution. For non-normal distributed population, non-parametric Mann–Whitney U and Wilcoxon tests were used to compare both groups between each other and within each other, respectively. Without comparing case and control groups, repeated measurements were analyzed (initial and latter measurements of the same serum marker) with variance analysis to detect any statistical difference between measurements. In this study, the ROC curve and the area under the curve (AUC) was calculated to determine the diagnostic performance in endometriosis of CA 125 and CRP levels on the 2nd and 14th day as well as the level

difference between the two phases. Accordingly, sensitivity and specificity were calculated for the tests with appropriate values.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 24.0) (IBM, Armonk, NY, United States), and $P < 0.05$ was considered statistically significant.

Results

A total of 66 patients, 36 with endometriosis and 30 controls, were included in the study. The mean age of the patients was 33.06 (7.37) years in the endometriosis group and 27.90 (7.34) years in the control group. The age range of the patients in the endometriosis group was 21–45 years; in the control group, it was 18–45 years.

In the study, the mean CA 125 level measured on the second day of the menstrual cycle in the endometriosis group was calculated as 108.15 (90.33) U/mL, and 22.97 (15.42) U/mL for the control group. The mean CA 125 level measured on the 14th day in the endometriosis group was calculated as 58.60 (39.53) U/mL, while it was 13.82 (6.82) U/mL for the control group (Table 1).

The mean serum CRP level measured on the 2nd day in the endometriosis group was 4.52 (4.45) mg/L and it was 3.44 (5.17) mg/L for the control group. The mean value for the CRP level measured on the 14th day was 2.82 (3.79) mg/L in the endometriosis group and 2.02 (2.27) mg/L in the control group.

Differences in CA 125 and CRP values measured on the 2nd and 14th day of the cycle in both groups were also calculated in the study. This difference was named delta CA 125 (ΔCA 125) and delta CRP (ΔCRP) in our study.

The mean value for ΔCA 125 in the endometriosis group was 49.55 (56.89) U/mL. The mean value for ΔCA 125 in the control group was 9.14 (11.95) U/mL. The mean value for ΔCRP in the endometriosis group and the control group were 1.69 (3.45) mg/L and 1.42 (4.74) mg/L respectively (Table 1).

Table 1: Comparison of CA 125 and CRP levels between the case and control groups on the 2nd and 14th day of the menstrual cycle

CA 125/CRP/ day of menstrual cycle	Cases (n = 36)	Control (n = 30)	*P*-value
CA 125 (day 2)	108.15(90.33)U/mL	22.97(15.42) U/Ml	< 0.001
CA 125 (day 14)	58.60(39.53) U/mL	13.82(6.82) U/mL	< 0.001
CA 125 (delta)	49.55 (56.89) U/mL	9.14 (11.95) U/mL	< 0.001
CRP (day 2)	4.52 (4.45) mg/L	3.44 (5.17) mg/L	0.064
CRP (day 14)	2.82 (3.79) mg/L	2.02(2.27) mg/L	0.571
CRP (delta)	1.69 (3.45) mg/L	1.42(4.74) mg/L	0.033

The Mann–Whitney U test was used to compare CA 125 (day 2 and day 14), CRP (day 2 and day 14), ΔCA 125, and ΔCRP between both groups. In the analysis performed using the Mann–Whitney U test, the values of CA 125 measured on the 2nd and 14th day of the menstrual cycle ($P < 0.001$ and $P < 0.001$, respectively), ΔCA 125, and ΔCRP ($P < 0.001$ and $P = 0.033$, respectively). The differences were found to be statistically significant between both groups. There was no significant difference between the two groups in CRP values measured on the 2nd and 14th days ($P = 0.064$ and 0.571, respectively) (Table 1).

When CA 125 values on day 2 and day 14 were compared in the study and control groups, the level of day 2 was found to be statistically significantly higher ($P < 0.001$) compared to the 14th day. The difference between the 2nd and 14th day CRP measurements in the case group was statistically significant ($P < 0.001$). There was no significant difference ($P = 0.054$) in the CRP measurements of the control group (Tables 2 and 3).

Table 2: Comparison of CA 125 and CRP values on the 2nd and 14th days in the case group (n = 36)

Variables	2nd day	14th day	*P*-value
CA 125	108.15(90.33) U/mL	58.60 (39.53) U/mL	< 0.001
CRP	4.52(4.45) mg/L	2.82 (3.79) mg/L	< 0.001

Table 3: Comparison of CA 125 and CRP values on the 2nd and 14th days in the control group (n = 30)

Variables	2nd day	14th day	*P*-value
CA 125	22.97 (15.42) U/mL	13.82 (6.82) U/mL	< 0.001
CRP	3.44 (5.17) mg/L	2.02 (2.27) mg/L	0.054

In our study, variance analysis was also performed in repeated measurements (blood values on the 2nd and 14th days of the cycle) without discriminating between the case or control groups. According to the analysis, the serum CA 125 level was found to be significantly higher on the 2nd day of the cycle compared to the 14th day in the study sample ($P < 0.001$). Serum CRP levels were higher on day 2 than on day 14, but the difference was not statistically significant ($P = 0.787$) (Table 4).

Table 4: Comparison of CA 125 and CRP values on day 2 and 14 in the whole sample (n = 66)

Variables	2nd day	14th day	*P*-value
CA 125	69.44(79.54) U/mL	38.25(36.97) U/mL	< 0.001
CRP	4.03(4.79) mg/L	2.46(3.19) mg/L	0.787

When the cut-off for the CA 125 level on the 2nd day was set as 35 U/mL, the false positive rate of the test was 13.1%. The false negative rate was 10.7%;the positive predictive value was 91.6%; and the negative predictive value was 83.3% for endometriosis. When the cut-off for the CA 125 level on the 14th day was set as 35 U / mL, the false positivity rate of the test was 0%. The false negative rate was 25%; the positive predictive value was 72.2%; and the negative predictive value was 100% for endometriosis.

According to the ROC curve analysis, the optimal cut-off value for ΔCA 125 was 14.85 U/mL with 80.6% positive predictive value and 80% negative predictive value (AUC: 0.85, $P = 0.047$). The ratio of two values was also evaluated (the ratio of levels on the second and fourteenth days of the cycle, for each parameter). The ROC curve analysis was unable to provide a statistically significant value ($P > 0.05$); therefore, a cut-off was not set (Figure 1 and Table 5). On the other hand, the ROC curve analysis for CRP-related values could not yield a cut-off value with sufficient positive and negative predictive value either ($P > 0.05$) (Figure 2 and Table 6).

Figure 1: ROC curve for CA 125 values

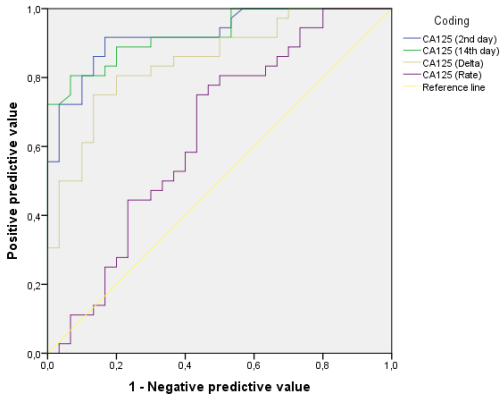

Table 5: Areas under the curve (AUC) on the ROC curve for values using CA 125

CA 125	AUC	95% confidence interval
2nd day	0.93	0.86-0.99
14th day	0.93	0.87-0.99
Delta (Δ)	0.85	0.76-0.94
Rate	0.64	0.50-0.78

Figure 2: ROC curve for CRP values

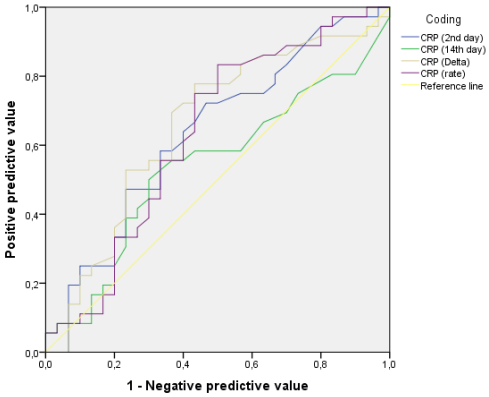

Table 6: Areas under the curve (AUC) on the ROC curve for values using CRP

CRP	AUC	95% confidence interval
2nd day	0.63	0.50-0.77
14th day	0.54	0.40-0.68
Delta (Δ)	0.65	0.20-0.79
Rate	0.63	0.49-0.77

Discussion

Early diagnosis of endometriosis is important. Long-term delays are experienced in diagnosis. In studies conducted for the diagnosis of endometriosis, it was shown that the sensitivity of CA 125 can reach 80% at best, and its benefit in the diagnosis of the disease is limited [7]. According to Oliveira et al. [8], it is possible to increase the sensitivity and specificity of CA 125 in patients with endometriosis when measurements are performed in different periods of the menstrual cycle. In our study, it was determined that the average time between the onset of nonspecific complaints, such as dysmenorrhea and chronic pelvic pain symptoms that may indicate the disease and the diagnosis of endometriosis patients, was four years on average. Even in developed centers, delays of more than six years may occur [9]. Despite the existence of advanced imaging methods, such as transvaginal ultrasonography and MRI, the success in diagnosis is still far from the ideal level because the methods depend on the operator [10, 11].

An effective serum indicator would be useful, as it can easily be standardized and potentially makes screening more accessible. CA 125 is a widely studied serum marker in the diagnosis of endometriosis. According to various comparative studies, other markers have no advantages over CA 125 in the diagnosis of endometriosis. Due to their low sensitivity and specificity, none of the serum markers are accepted as noninvasive diagnostic tests [12, 13].

Menstruation is the most prominent inflammatory phase of the cycle. The measurement of CA 125 during the menstrual period is preferred since the marker is expected to be at its highest level. The reason for fluctuations seen at CA 125 levels during menstruation is thought to be due to endometrial desquamation during menstruation and subsequent short-term deterioration in the tissue blood barrier [14]. By making two measurements, it is possible to evaluate the performance of CA 125 on the 2nd and 14th days and to calculate the difference between these two phases of the cycle.

Some authors have published data on serum CA 125 concentration in spontaneous and stimulated menstrual cycles, revealing that the levels of the marker fluctuate throughout the cycle [15, 16]. In our study, the 2nd day CA 125 levels were significantly higher than the 14th day CA 125 levels in both the case and control groups. This finding supports the belief that CA 125 fluctuates throughout the cycle.

Koninckx et al. [17] evaluated the ratio between two consecutive cycles by studying blood samples taken at the time of menstruation and seven days after (mid-follicular phase). The median value of CA 125 for endometriosis patients was 84 IU/mL in the menstrual phase and 55 IU/mL in the mid-follicular phase. Although the average difference was high (29 IU/mL), the researchers evaluated the menstrual phase/mid-follicular phase ratio to improve the diagnostic power of CA 125, and it was determined that it had no diagnostic potential. In the analysis we performed to measure the diagnostic performance of CA 125 values in our study, we found that the ratio of CA 125 values on the 2nd day and the 14th day did not have a diagnostic function.

In a meta-analysis evaluating CA 125 in the diagnosis of endometriosis, its sensitivity was shown as 28% and specificity as 90% [18]. Our study data gave better results in terms of positive predictive value (91.6%) on the 2nd-day measurement of CA 125, and negative predictive value (100%) on the 14th-day measurement. The diagnostic performance of the difference between the two measurements was not superior. Taking two measurements in different phases of the menstrual cycle raises doubts in terms of cost effectiveness. However, when two measurements in different phases are evaluated separately, it is seen that CA 125 distinguishes sick and healthy people at a higher rate. Thus, better results in terms of cost effectiveness may be obtained by avoiding unnecessary diagnostic procedures.

There are studies on serum CRP levels in patients with endometriosis. In one of these studies, it was shown that CRP was significantly higher in women with advanced-stage (stage 3-4) endometriosis [10]. In another study, no significant difference was found in terms of CRP levels in healthy women with endometriosis [11].

The CRP level measured on the 2nd day in endometriosis patients was found to be significantly higher than on the 14th day. In our study, it was found that the ΔCRP value was statistically significantly different between the two groups. This result shows that CRP may support the diagnosis in endometriosis, but none of the CRP-related values had diagnostic performance for endometriosis.

Limitations

The limitation of the study is that the presence or absence of any pathology was not demonstrated by the diagnostic operation in the patients of the control group.

Conclusion

Our study could not provide any findings that could suggest the use of CRP as a practical parameter for the diagnosis of endometriosis. On the other hand, our research supports the trend in the literature that promotes CA 125 as a valuable parameter for the diagnosis. ΔCA 125 seems to be a potentially helpful marker and future research is expected to further define its use and reliability for both diagnosing the disease and reducing the need for diagnostic surgical interventions.

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Anesthesia management in a pregnant patient with neurofibromatosis

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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
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Abstract

Neurofibromatosis (NF) is a genetic and multisystemic disease with autosomal dominant transition. It can affect anesthesia applications by affecting more than one system. In the presence of neurofibromas in the airway, it can cause airway obstruction and difficulties in respiratory delivery during general anesthesia. The presence of tumors affecting the central nervous system makes spinal anesthesia risky. Anesthesiologists should act with awareness of each multisystemic complication when evaluating and managing patients. This case report aims to present our general anesthesia practice in an elective cesarean operation in a pregnant patient with neurofibromatosis type 1.

Keywords: Neurofibromatosis, Pregnant, General anesthesia

Introduction

Neurofibromatosis is an autosomal dominant disease and is divided into two groups: neurofibromatosis type-1 (NF-1) and neurofibromatosis type-2 (NF-2) [1]. Type 1 neurofibromatosis, also known as von Recklinghausen disease, is the most common type and is characterized by café-au-lait spots and benign skin neurofibromas. Type 2 neurofibromatosis affects the central nervous system due to spinal cord tumors and bilateral vestibular schwannomas [2, 3]. In NF-1, neurofibromas in the tongue, pharynx, and larynx can prevent intubation by making the airway more constricted. For this reason, in pregnant women with NF-1, difficult airway has been the main cause of anesthesia-related deaths. In these cases, it is important for anesthesiologists to perform airway examinations carefully [4]. Increasing the risk of bleeding while applying regional anesthesia, there is an increased risk of hematoma and intracranial pressure. However, successful computer spinal anesthesia has been reported in patients by excluding the presence of spinal neurofibroma by brain computer tomography (CT) and magnetic resonance imaging (MRI) [5]. We present our anesthetic approach to cesarean surgery performed under elective conditions in a pregnant patient diagnosed with NF-1.

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Case presentation

A 38-year-old pregnant woman weighing 72 kg was brought into the operation room after receiving a confirmation form due to cesarean surgery. In the preoperative evaluation, it was determined that she had hypothyroidism for which she used drugs; she smoked two cigarettes per day. It was determined that she had been operated on ten years ago for a cesarean birth. In the physical examination performed in the preoperative period, it was determined that there were diffuse neurofibromas and café-au-lait spots on the body (Figures 1, 2). Patient consent was obtained for the images presented in the study. No mass was observed in the oral examination and this was evaluated as Mallampati II. Respiratory, cardiovascular, and neurological system examinations of the patient were normal. There were no restrictions in the mouth opening or neck movement. Apart from the high TSH, no abnormal results were found in the preoperative laboratory tests. In terms of hypothyroidism, an internal medicine doctor was consulted preoperatively and his recommendations were followed. Operational risk was determined as ASA 2 according to the classification of the Association of Anesthesiologists (ASA).

Figure 1: Diffuse neurofibromas

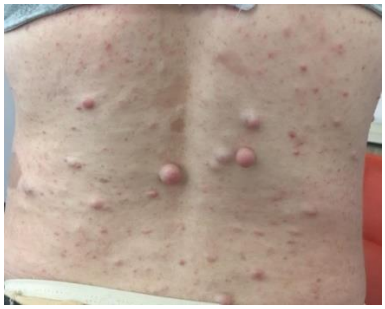
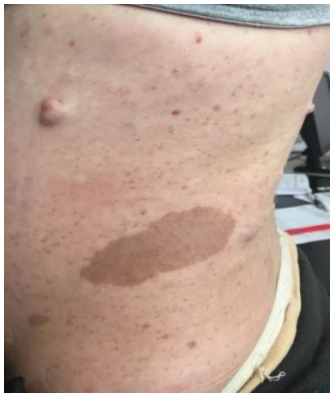


Figure 2: Café-au-lait spot



When she entered the operating room, first, her heart rate (HR), noninvasive blood pressure (TA), and peripheral oxygen saturation (SpO2) were monitored. Her TA value was 130/85 mmHg, HR 90 / min, SpO2 97. Vascular access was opened with 18 G and 20 G cannula from both hand ridge veins, preop 500 mL isotonic sodium chloride was given, and fluid infusion continued during the operation. Due to the absence of preoperative computed tomography or magnetic resonance imaging, we chose general anesthesia because we could not rule out spinal cord neurofibroma. We made the necessary preparations for the possibility of difficult intubation preoperatively. We applied 2 mg/kg propofol, 0.6 mg/kg rocuronium in anesthesia induction and used sevoflurane in maintenance. By ensuring sufficient preoxygenation, we intubated the patient without any problems with an endotracheal tube with an internal diameter of 7 mm. No hemodynamic problem was detected during the operation. At the end of the operation, the patient was sent to recovery, where she was followed up without any problems.

Discussion

Neurofibromatosis is an inherited disease with an autosomal dominant transition and is classified in 2 types. NF1 (von Recklinghausen disease) is the more common type and is characterized by benign neurofibromas (cutaneous neurofibroma) of the skin and brown skin patches (café-au-lait spots) [2, 3, 6, 7]. NF-2 occupies the central nervous system. The bilateral vestibular schwannomas leading to gradual hearing loss are characteristic [8]. Features, such as meningioma of the brain, cranial, spinal or peripheral nerve schwannoma and juvenile cortical cataracts, may also be present [9].

In NF-1 patients, neurofibromas pressing on the tracheobronchial system and located in the lung parenchyma, chest wall deformities with severe scoliosis and kyphosis are commonly detected [10, 11]. In NF-1, pheochromocytoma or hypertension associated with renal artery stenosis can be seen [8, 9]. Neurofibromas can also affect the gastrointestinal tract and can be carcinoid tumors in the duodenum [12, 13]. The presence of cervical neurofibroma, laryngoscopy, and tracheal intubation can cause spinal cord injury, and, therefore, radiographic examination of the neck is recommended prior to anesthesia application [14]. In NF-1, urethral obstruction of retroperitoneal neurofibromas can be seen, and genitourinary system disorders such as hydronephrosis are also common. This may cause difficulty in bladder catheterization [15]. In addition, it has been reported that NF-1 patients have increased sensitivity to nondepolarizing neuromuscular blocking drugs [16, 17].

In neurofibromatosis, macroglossia, abnormal formations in the tongue, presence of plexiform fibromas in the pharynx, larynx, and supraglottic region can prevent endotracheal intubation and cause upper airway obstruction during anesthetic induction [2, 4, 18]. For this reason, in the patient, dysphagia, dysarthria, presence of stridor, and voice changes should be questioned and these lesions should be questioned [2]. The involvement that causes facial malformations can cause facial asymmetry, and may contribute to facial mask and difficult ventilation [19].

General anesthesia is considered safer since the presence of intracranial neuromas or unknown spinal neuromas in neurofibromatosis may cause destructive complications, such as hematoma and stroke [20-22]. Gliomas, meningiomas, hydrocephalus, spinal tumors, and spina bifida have been identified in NF-1, and these findings prevent the use of regional anesthesia [18]. Esler et al. [23] reported that an undiagnosed NF-1 patient had difficulty in analgesia after an epidural block application and an epidural hematoma occurred in the patient. In addition, the presence of skeletal anomalies, such as kyphosis and kyphoscoliosis, in patients with neurofibromatosis may cause difficulties in regional anesthesia application [21]. There is consensus that it is correct to put on a regional anesthetic indication after proving that there are no neurofibromas in the central nervous system by using imaging methods such as computed tomography and magnetic resonance in patients with NF [5]. In addition, successful neuroaxial anesthesia applications have been reported [22-24].

In our patient, findings of upper respiratory obstruction and facial malformation were not available. CT can be used to detect upper airway neurofibromas. However, the CT imaging

method could not be performed in the preoperative period due to the pregnancy of the patient. Despite these risks, we preferred to perform general anesthesia because our patient had a history of uneventful operation. Her mallampati score was 2, and there was no central nervous system image of the patient. However, we took the necessary precautions against the possibility of difficult airway. Our patient remained peroperatively hemodynamically stable.

Due to airway management, respiratory and cardiovascular problems, central nervous system structure, and vertebral anomalies, it may be difficult to choose an anesthesia method in neurofibromatosis patients [22]. A careful systemic evaluation is required to decide the appropriate anesthetic method.

Conclusion

When deciding on the anesthesia method to be applied in a pregnant patient with neurofibromatosis, we should thoroughly evaluate the patient preoperatively, perform the physical examination completely, and use imaging methods if possible. Necessary precautions should be taken by taking into consideration the possibility of difficult airway, problems encountered in regional anesthesia, and multisystem complications that may develop.

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A case of insulinoma confused with dumping syndrome after total gastrectomy

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Abstract

We present the case of a 70-year-old female patient with persistent hypoglycemia after total gastrectomy due to gastrointestinal stromal tumors. She was thought to have late dumping syndrome but was diagnosed with insulinoma after further examination. Dumping syndrome is mainly seen after stomach or esophageal surgery. It is divided into early dumping and late dumping syndrome. Late dumping syndrome is initially manifested by an exaggerated insulin response and reactive hypoglycemia after glucagon-like peptide-1 release. Diagnosis is based on clinical findings. Treatment mainly consists of reducing carbohydrate intake and not ingesting solid and liquid foods together. In cases where diet alone is not sufficient, acarbose, an α-glucosidase inhibitor that slows the digestion of carbohydrates, may be beneficial for late dumping. Octreotide can be used in resistant cases. However, the diagnosis of insulinoma, which leads to a similar clinical presentation in resistant dumping cases, should be kept in mind. Our patient who showed clinical signs of dumping syndrome after gastrectomy, and treatment-resistant hypoglycemia was diagnosed with insulinoma on the basis of further investigations. The patient's symptoms resolved after surgery for insulinoma.

Keywords: Dumping syndrome, Gastrectomy, Hypoglycemia, Insulinoma

Introduction

Gastrointestinal stromal tumors (GISTs) are the most widely occurring mesenchymal tumors affecting the gastrointestinal tract. They are generally frequently observed in the stomach and proximal small intestine. However, albeit rarely, they can be seen anywhere in the gastrointestinal tract [1]. Gastrointestinal bleeding is a common clinical finding. However, small asymptomatic lesions are frequently detected incidentally. Treatment is planned using a multidisciplinary approach. Surgery is the only curative treatment particularly for resectable masses [2].

Dumping syndrome is a common complication in patients following gastric surgery. It is seen in approximately 25%–50% of patients after surgery, and 5%–10% of these patients exhibit marked clinical symptoms. The severity of dumping syndrome varies depending on the type of surgery. The syndrome occurs in 75% of patients in the early period following gastric bypass surgery. The condition persists for approximately 12–18 months, while recovery occurs subsequently in most patients [3].

Insulinoma is a rare neuroendocrine tumor characterized by hyperinsulinism-related hypoglycemic episodes. It is generally detected as a benign solitary tumor and can also be seen together with multiple endocrine neoplasias (MEN) [4].

We describe the case of a patient who had undergone total gastrectomy due to GIST approximately 1 year previously and who was followed-up with a diagnosis of dumping syndrome throughout the previous 2 months. Insulinoma was detected using advanced tests that were performed due to continuous worsening of the patient's symptoms. This case will contribute to the existing literature as a case of insulinoma presenting as dumping syndrome following gastrectomy due to GIST.

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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Case presentation

A 70-year-old woman presented with occasional malaise, palpitations, and sweating over the previous 2 months. The patient had presented twice to the emergency department with her current symptoms, and we were consulted when low blood sugar was determined.

The patient had undergone a right mastectomy due to breast cancer 13 years previously and total gastrectomy due to GIST 1 year earlier. The patient was receiving regular imatinib therapy. The patient had a history of total gastrectomy, and her symptoms were initially thought to be possibly associated with dumping syndrome. Hypoglycemia symptoms together with low blood sugar were observed at least twice a day, approximately 2 h after eating. The patient's blood sugar during hypoglycemia was 45 mg/dL, insulin was 2.6 mIU/L, and c-peptide was 1.4 μU/mL. Adrenal reserve evaluation was requested to investigate a potential tyrosine kinase side effect in this patient using imatinib. Adrenal failure was excluded when the patient's cortisol levels at the time of hypoglycemia were 34 mg/dL. Late dumping syndrome was then suspected. The interval between the patient's meals was reduced to 4 h, and pre-meal acarbose therapy was initiated. However, low blood sugar values persisted at follow-up. The prolonged fasting test was performed. Blood sugar at hour 5 was 40 mg/dL, insulin was 3.7 μU/mL, and c-peptide 1.7 ng/mL. Magnetic resonance imaging of the pancreas was performed with a preliminary diagnosis of insulinoma. Galyum-68 DOTA TATE PET/B (DOTAPET) was also performed, and these results revealed a 12-mm lesion in the pancreas. The case was evaluated as insulinoma on the basis of these results (Figure 1, 2). The patient was referred to the general surgery clinic, and the mass was removed with enucleation. The patient's pathology report indicated a "well-differentiated neuroendocrine tumor, insulinoma".

Figure 1: MR imaging revealed pancreatic insulinoma

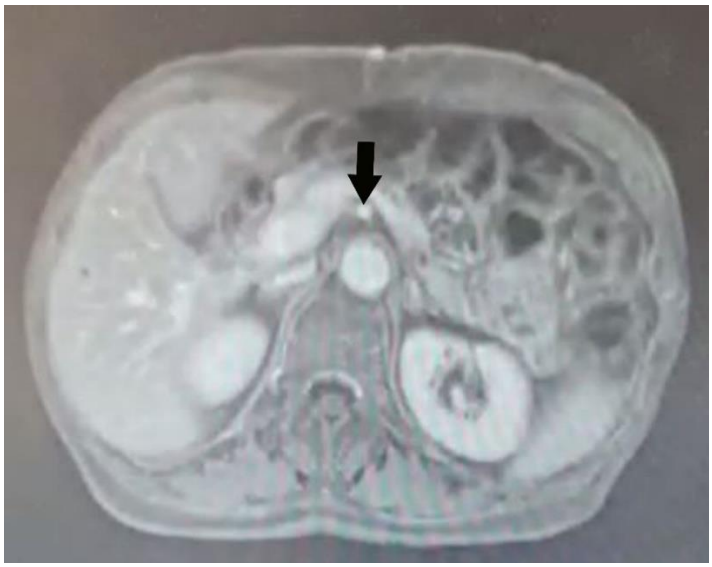
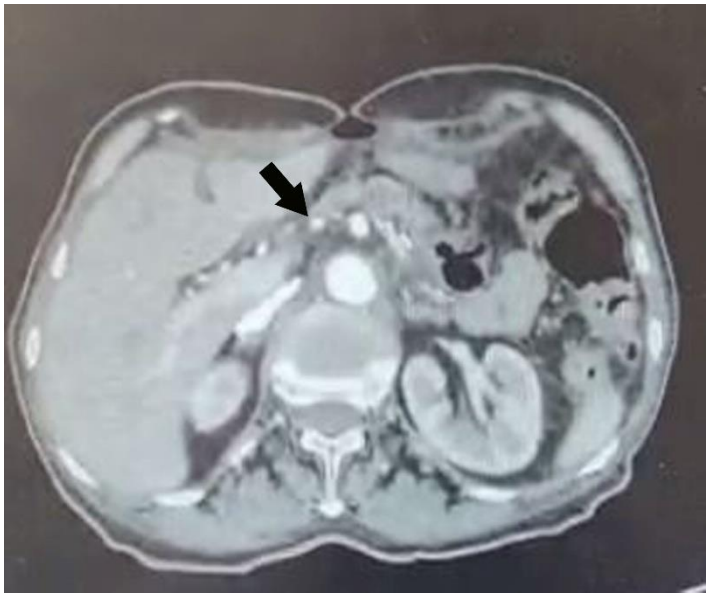


Figure 2: PET imaging revealed pancreatic insulinoma



Discussion

The present case is important in terms of insulinoma being diagnosed in a patient presenting with dumping syndrome-like symptoms following gastric surgery and in terms of diagnosing an neuroendocrine tumor in a patient previously diagnosed with GIST and breast cancer. This is the only case to date of insulinoma that was diagnosed in a patient who underwent surgery for GIST and breast cancer.

There are two types of dumping syndrome. Early dumping syndrome emerges 15 min after food intake. This results from the rapid emptying of foods into the small intestine. Symptoms of colic-type abdominal pain, nausea, tachycardia, and diarrhea are generally present. Precautionary measures such as reducing the amount of carbohydrate in meals and increasing the patient's fiber intake, shortening the interval between meals, and fluid intake 30 min after solid food intake are generally sufficient. Patients generally tend to recover 3 months after surgery [5].

Late dumping syndrome is rare after gastric surgery. It is seen in 0.1%–0.3% of patients, and generally in Roux-en Y gastric bypass patients. Symptoms emerge approximately 1–3 hours after carbohydrate-rich meals in particular, and the basic cause is hyperinsulinemic hypoglycemia. The etiology is not fully understood. Similar to early dumping syndrome, dietary changes are recommended. Medical treatment can also be considered in non-responsive patients (such as nifedipine, acarbose, and diazoxide). If medical treatment is unsuccessful, invasive procedures such as feeding by inserting a tube into the residual stomach and re-operation can also be applied [5, 6].

Insulinoma is a rare neuroendocrine tumor, and the etiology of solitary adenomas is not fully understood. It can be seen as a component of MEN type 1 (MEN1) syndrome. Hypoglycemia develops with high insulin concentrations. Insulin is normally released from pancreatic cells with high blood glucose. For insulinoma, however, insulin production continues although blood glucose is low. When intracellular insulin storage pools are full, insulin is released into the blood. Hyperinsulinemia increases glycogen synthesis while reducing gluconeogenesis and glycogenolysis [7].

The reported annual incidence of insulinoma is 1–4 per million. Insulinoma generally appears as a solitary benign tumor, although 5.8% of cases have been shown to be malignant. Other benign tumors may be co-present in 7% of cases, and a relationship with MEN1 syndrome has been shown in 6%–7.6% of cases. Patients are diagnosed on average between 40 and 50 years of age [8].

GIST represents approximately 20% of soft tissue sarcomas. The annual incidence is approximately 10 per million. Micro-GISTs less than 1 cm in size and with low mitotic activity and mild clinical symptoms are more common in middle or more advanced age. Micro-GISTs constitute 10%–35% of all GISTs. They are most frequently located in the stomach and proximal small intestine, although they can be present anywhere in the gastrointestinal tract. Fewer than 5% are present outside the gastrointestinal tract, and these are known as extra-GISTs [9].

Hypoglycemia can occur following gastric bypass surgery, although cases of severe hypoglycemia are rare. The pathophysiology remains unclear. Patients must be closely followed-up, and insulinoma, although rare, must be ruled out. Dietary adjustment is important in patients with suspected dumping syndrome in particular. However, as in our patient, diet modification may not always be effective, especially in individuals experiencing severe neuroglycopenic symptoms. Interventional procedures should also be considered, particularly in patients developing pancreatic islet cell hypertrophy [10].

Endogenous hyperinsulinemic hypoglycemia may rarely be seen, particularly following Roux-en-Y gastric bypass surgery. If this condition is observed, the most common cause is islet cell hyperplasia (nesidioblastosis). A rare cause of endogenous hyperinsulinemic hypoglycemia is an insulinoma. Thirty-six patients undergoing pancreatic surgery due to nesidioblastosis over approximately 13 years were evaluated in one study. A previous history of gastric bypass surgery was present in 27 patients [11].

GISTs can occur together with several malignancies. Comorbidity with neuroendocrine tumors may be determined in the presence of neurofibromatosis. However, co-existent neuroendocrine tumor and GIST in the absence of neurofibromatosis is rare, with only one case having been reported. Insulinoma was diagnosed in a patient who was followed-up due to hypoglycemia, and concomitant GIST was detected [12].

GIST and insulinoma without neurofibromatosis were present in our patient. However, because the patient had undergone surgery due to GIST approximately 1 year previously, she was followed-up with a diagnosis of dumping syndrome for 2 months. Insulinoma was diagnosed after tests were performed due to worsening of the patient's symptoms. The present case is important as the first in which a neuroendocrine tumor was detected in a patient diagnosed with GIST who had undergone gastric bypass surgery with a dumping syndrome-like presentation.

Conclusion

Despite its rarity, patients should be examined for possible insulinoma, especially in the presence of severe hypoglycemia and dumping syndrome after gastric bypass surgery.

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Case report

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Pneumopericardium due to blunt trauma

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Abstract

Pneumopericardium is the presence of gas in the pericardial sac. Its etiology includes chest trauma, iatrogenic causes, thoracic surgery, and mechanical ventilation, and it is mostly asymptomatic. However, pneumopericardium can also be fatal because it can cause cardiac tamponade. All surgeons dealing with thoracic trauma should be aware of this pathology. A case of a 30-year-old patient presenting with pneumopericardium due to blunt trauma who was evaluated in the emergency department at our hospital is presented.

Keywords: Pneumopericardium, Blunt chest trauma, Cardiac tamponade

Introduction

Pneumopericardium is the presence of gas in the pericardial sac. The main etiology is often blunt chest trauma [1]. Pneumopericardium is divided into simple and tension forms [2]. Simple pneumopericardium is usually asymptomatic. If the pneumopericardium is of the tension form, symptoms related to cardiac tamponade appear [1]. Oxygen therapy is usually sufficient in asymptomatic cases [3]; however; it should be kept in mind that such cases may progress to pericardial tamponade. Therefore, their follow-up should be done carefully [4]. In tension pneumopericardium, pericardial air should be immediately decompressed [2]. A case of pneumopericardium after blunt trauma is presented, and the possible follow-up outcomes are based on other literature studies.

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Case presentation

A 30-year-old male patient was evaluated in the emergency department after a motorcycle accident. The patient's oxygen saturation was 85%, pulse: 105 beats/min, and blood pressure 110/60 mmHg. On palpation, extensive subcutaneous emphysema in the thorax and neck was found. Bilateral crepitation in the chest wall and sternum was noted. Respiratory sounds were decreased bilaterally. Laboratory parameters indicated a hemoglobin value of 12 g/dl, platelet: count of 350,000 /mm^3 (reference value: 150,000 - 450,000 /mm^3), and leukocyte count of 12,000 /mm^3 (reference value: 4,000 - 10,000 /mm^3). Fractures on the right spine 1–9, left spine 1–2, sternum, and thorax were seen on computed tomography (thorax CT). Bilateral hemopneumothorax, bilateral lung contusion, and pneumopericardium could also be observed (Figure 1). Bilateral tube thoracostomy was immediately performed because the patient had severe dyspnea. It was observed that dyspnea regressed after performing a tube thoracostomy. Chest radiography was taken after tube thoracostomy (Figure 2). Cardiac compression was not detected during electrocardiography (ECHO), which was performed for detecting a pneumopericardium. It was decided to follow the patient for the occurrence of pneumopericardium. Thoracic drains were removed on the eighth post-operative day. On the control chest radiograph, regression of the pneumopericardium was observed. Written informed consent was obtained from the patient for the study.

Figure 1: Computed tomography (CT) of the thorax (Arrow: shows pneumopericardium)

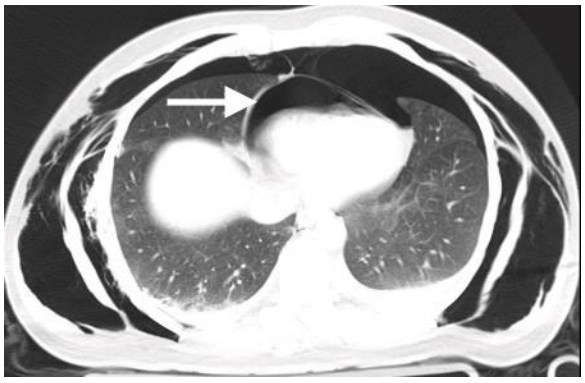
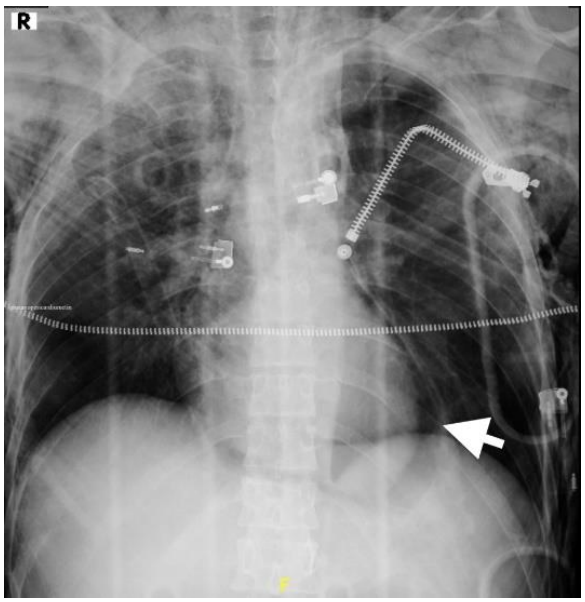


Figure 2: Lung X-ray (Arrow: shows pneumopericardium)



Discussion

Pneumopericardium was first described by Bricheteau in 1844 [2]. Pneumopericardium is defined as a collection of air in the pericardial space. Its etiology includes chest trauma, cardiothoracic surgery, mechanical ventilation (especially in children), infection, and pericardiocentesis [5]. Pneumopericardium is usually asymptomatic. It is found incidentally in trauma patients. Symptoms, such as dyspnea and pericardial chest pain, may present; however, these are not necessarily specific symptoms [6]. In our case, pneumothorax was considered during the preliminary diagnosis. Pneumopericardium was diagnosed incidentally on thoracic CT.

Hamman's sign is typical on physical examination. In addition, a murmur in the form of "bruit de moulin" could be heard on auscultation [4]. It is mandatory to evaluate hemodynamic stability at the first examination. In a hemodynamically unstable patient, the clinical staff should be alerted to cardiac tamponade. Cardiac tamponade can be diagnosed using ECHO [7]. Loss of a systolic echo signal in pneumopericardium was first shown in 1983 and termed as air gap sign. Air bubbles can be seen in the pericardial cavity (swirling bubbles sign) [8]. Radiological findings are diagnostic. An air image surrounding the heart could be seen on the chest radiograph. Pericardial air seen on thorax CT is diagnostic [4]. Severe dyspnea was noted in our case. Bilateral tube thoracostomy was performed on the patient after which the dyspnea regressed. An ECHO was then performed for pneumopericardium. It was observed that there was no cardiac compression in ECHO. Pneumopericardium was treated medically (Nasal oxygen therapy).

The presence of pneumopericardium indicates that a significant force is transferred during injury [9]. In the pathophysiology of pneumopericardium, several factors should be considered:

(1) With an increase in intra-alveolar pressure, alveoli rupture occurs. However, rupture in the pericardium also occurs. Thus, air enters the pericardial sac.

(2) With the increase in intra-alveolar pressure, alveolar wall rupture occurs. Infiltrated air flows through the peribronchial and vascular sheaths into the pericardial sac.

(3) This passage of air into the pericardial sac occurs with congenital pleuro-pericardial defect [9, 10].

The clinical signs of pneumopericardium are variable. The main determinants of clinical severity are the rate of occurrence of pneumopericardium and the underlying etiology. This situation guides the treatment strategy [11]. Pneumopericardium is often asymptomatic. However, it can cause serious events, such as cardiac tamponade and can sometimes be confused with hemorrhagic shock in trauma patients [10]. Cardiac tamponade caused by pneumopericardium is reported to be associated with mechanical ventilation [12]. In another study, it was reported that 37% of simple pneumopericardium can progress to tension pneumopericardium. In these cases, the mortality rate is 57% [2]. Our case was hemodynamically stable. Cardiac tamponade was not found during the ECHO process. Therefore, no surgical procedure was performed for pneumopericardium. It regressed spontaneously during follow-up.

Conclusion

Pneumopericardium should be suspected in a patient presenting with chest trauma if there is hypotension without bleeding, and the patient does not improve even with fluid support. Diagnosis and treatment procedures should be started immediately. Pneumopericardium usually regresses spontaneously, and it rarely causes cardiac tamponade and endangers a patient's life.

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ERRATUM

On page 1122, the date is written as the ethics committee number and the study time interval is indicated differently in the material method section. "This cross-sectional study was conducted in a private university hospital between April-June 2021." and the Ethics part has been changed to (Date: 08.04.2021 Number: 16). These errors only appear in the printed version of the article. The online version has already been corrected.

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