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Research Article

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Diagnostic and prognostic value of Nesfatin-1 in sepsis and septic shock

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Abstract

Nesfatin-1 is an anorectic protein, and we expect it to decrease during sepsis and septic shock. We aimed to analyze it and determine the relationship between Nesfatin-1 levels and quick Sequential Organ Failure Assessment(qSOFA) score, renal Sequential Organ Failure Assessment (SOFA) score, and mortality in patients with sepsis and septic shock. Sixty-nine hospitalized adult patients diagnosed with sepsis and septic shock in the internal medicine department, were included in the study after approval of the Clinical Research Ethics Committee. Sepsis diagnosis was based on the detected focus of infection, positive blood cultures, and response to antibiotics. Twenty-one healthy controls matched for age and sex with these patients were also included in the study. Sixty-nine septic patients and twenty-one healthy volunteers were included in the study. Nesfatin-1 levels were compared with covariates. Nesfatin-1 levels in septic patients were lower than that of healthy controls. There was no significant difference in Nesfatin-1 between diabetic and non-diabetic subgroups. Patients with quick Sequential Organ Failure Assessment (qSOFA) score of three had a statistically significantly lower Nesfatin-1 level than those of patients with the score of zero, one, and two. Nesfatin-1 was correlated negatively with C reactive protein. We found a statistically significant difference in 1-month mortality between Nesfatin-1 levels below and over 80pg/mL. In order to use Nesfatin-1 as a biomarker in differentiating sepsis from healthy population, more comprehensive and more studies are needed. If supported by new studies, Nesfatin-1 levels below 80 pg / mL at first admission in septic patients may direct the clinician to broad-spectrum antibiotic therapy and earlier intensive care follow-up.

Keywords: Nesfatin-1, sepsis, septic shock, biomarker

1. Introduction

Nesfatin-1, which was first detected in the hypothalamus of mice, is a recently discovered peptide with a half-life of 23.5 minutes derived from a precursor protein, nucleobindin 2 (NUCB2), (1, 2). In particular, its anorectic effect has been demonstrated in many studies. In this respect, intracerebroventricular injection has been shown to dose-dependently reduce food intake in newborn chicks and to have an anorectic effect (3) and to reduce food intake after central injection (4) in animals. It is important to note that it is co-localized with ghrelin in gastric X / A-like cells in mice and in P / D1 cells of humans, which creates the hypothesis that peptide products are stimulated by insulin in X / A-like cells: so, food intake is either stimulated by ghrelin or via nesfatin-1. is inhibited (5). Administration of Nesfatin-1 in renal ischemic mice has been found to cause a significant decrease in creatinine levels, indicating the future therapeutic effect of Nesfatin-1 (6). It has been shown to cross the blood-brain barrier and it has an opposite effect on food intake with Ghrelin (7). Recently, a large number of studies were published investigating the effects of Nesfatin-1.

On the other hand, sepsis is an inflammatory process in which appetite decreases. Studies in the current literature analyzed the course of Nesfatin-1 in chronic events such as malignancy and diabetes mellitus (8, 9). Still, the literature data is insufficient in acute conditions like sepsis. In order to correct this deficiency and in line with the knowledge that Nesfatin-1 protein is anorectic, we expect its level to decrease in sepsis and septic shock.

In accordance with the knowledge that Nesfatin-1 is an anorectic protein, we expect it to decrease during sepsis and septic shock and we aimed to analyze this condition. Another

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aim of our study was to determine the relationship of Nesfatin-1 levels and quick Sequential Organ Failure Assessment (qSOFA) score, C reactive protein (CRP), procalcitonin, lactate and creatinine levels, hourly urine output, renal Sequential Organ Failure Assessment (SOFA) score, leukocyte count, and mortality in patients with sepsis and septic shock.

2. Materials and methods

2.1. Patients and clinical data collection

Based on the results of the published generation, we aimed to determine the difference in 1 unit Nesfatin 1 with 80% power. A sample size of at least 17 diseases per group is required to predict the impact measurement of 1 (alfa: 0,05)

Sixty-nine hospitalized adult patients diagnosed with sepsis and septic shock in the internal medicine department, were included in the study after approval of the Clinical Research Ethics Committee (date: 21.01.2016 no: 48670771). Sepsis diagnosis was based on the detected focus of infection, positive blood cultures, and response to antibiotics. Twenty-one healthy controls matched for age and sex with these patients were also included in the study. Patients who were under 18 years of age, did not give consent to participate in the study, had malignancy, were obese (Body Mass Index >35), or were diagnosed with schizophrenia/anorexia nervosa were excluded from the study.

2.2. Measurement of serum Nesfatin-1 levels

The nesfatin-1 level was determined in all patients and control samples. Venous blood samples were centrifuged at 1000xg for 20 min. Blood was collected in Eppendorf tubes and plasma samples were saved at –80C. All stored blood samples were dissolved only once on the analysis day and serum Nesfatin-1 levels were measured by using Enzyme-Linked Immune Sorbent Assay (ELISA) kits. The linear measurement range was: 1.5ng/ml-300ng/ml. The reported intraassay and intraassay CV's were <10% and <12%. The minimum detectable dose of Nesfatin-1 is typically less than 234.2pg/mL.

2.3. Data analysis

Serum CRP, procalcitonin, lactate, leukocyte counts, creatinine levels, and hourly urine output were recorded. In terms of leukocyte counts, patients were divided into three groups as follows:<4000 leukopenia, 4000-12000 normal, and > 12000 leukocytosis.

Renal SOFA score of each patient was calculated and patients were divided into 5 groups according to their creatinine values and urine outputs: creatinine: <1.2 mg/dL (0 point), creatinine: 1.2-1.9 mg/dL (1 points), creatinine: 2-3.4 mg/dL (2 points), creatinine: 3.5-4.9 mg/dLorurine output 200-500 ml/day (3 points), creatinine: > 5 mg/dLorurine output <200 mL/day (4 points) (6-8). The outcomes of the patients hospitalized in the internal medicine service were evaluated (discharge, referral to the intensive care unit, death). The mortality rates of the patients were also analyzed.

2.4. Statistics

The Statistical Package for Social Sciences (SPSS) version 20 was used to analyze the data. It has been determined by the Kolmogorov-Smirnov test that gender, Nesfatin-1, lactate and creatinine levels and hourly urine output differ significantly from normal distribution. Therefore, non-parametric methods have been used in the analysis of these data. For non-normally distributed data we reported interquartile range. Significant differences were calculated using the Mann–Whitney U test and Kruskal Wallis test for continuous variables. Spearman's rank correlation was used to examine the relationship between two continuous variables. Age, CRP, procalcitonin values were normally distributed and parametric tests were used to analyze the data on these values (one-way ANOVA, independent samples t-test). Descriptive statistics (frequency, mean, standard deviation, and minimum, maximum, median) of the variables were calculated. P values of less than 0.05 were considered statistically significant.

3. Results

Sixty-nine septic patients and twenty-one healthy controls were included in our study. The demographic and clinical characteristics of our patients are presented in Table 1. There was no statistically significant difference between patients and healthy individuals regarding age or gender (Table 1).

Table 1. Characteristics of patients and healthy controls

	Septic patients (n:69)	Control group (n:21)	P
Gender (male/female)	39/30	8/13	0.139*
Age (year)	62.3 ± 17.6	50.8 ± 10.9	0.114*

*analyzed by independent Sample t test

As shown in Table 2, Nesfatin-1 levels were significantly lower in patients with sepsis and septic shock (median: 674.70 pg/ml, IQR: 169.60 – 1010.90pg/ml) compared to healthy controls (median: 902.10 pg/mL, IQR: 724.95 - 1370 pg/mL) (p=0.005). There was also statistically significant difference in CRP levels (p<0.001) (Table 2).

Table 2. Median Nesfatin-1 levels and mean CRP levels of patients and control group

	Sepsis (n:69)	Control (n:21)	P
Nesfatin-1 (pg/mL)	674.70 (169.60-1010.9)	902.10 (725-1370)	**0.005***
CRP (mg/L)	220.52±140.77	2.99±1.9	**<0.001****

*analyzed by Mann-Whitney-U test; ** analyzed by independent Sample t test

In our study, a negative correlation was found between Nesfatin-1 and CRP levels (p: 0.007, r: -0.250) (Fig. 1). When Nesfatin-1 levels were compared between the groups with and without diabetes mellitus, the difference was statistically non-significant. However, CRP values were statistically significantly different between diabetic sepsis (287.63 mg/L±162.98) and nondiabetic sepsis (189.9 mg/L ±118.35) patients (p: 0.038) (Table 3).

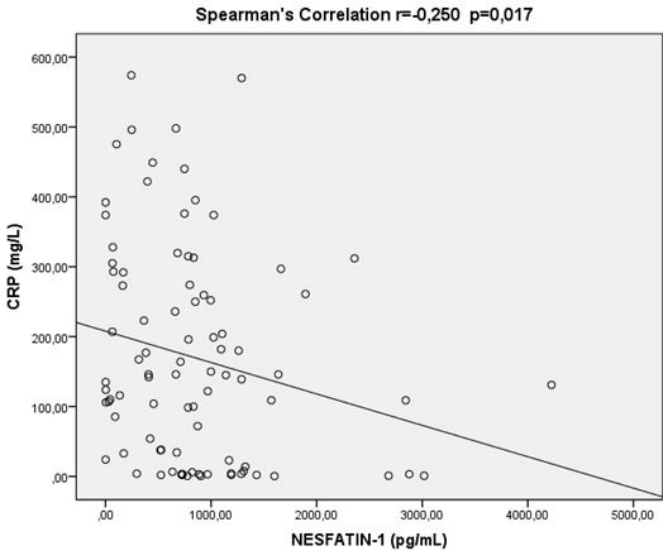

Fig. 1. The scotter plot of nesfatin and C-reactive protein

Table 3. Median Nesfatin-1 levels and mean CRP levels of patients with or without diabetes mellitus

	Sepsis with diabetes (n=22)	Sepsis without diabetes (n=47)	p
Nesfatin-1 (pg/mL)	764.80 (246.95 - 1045)	666.80 (90.90-998.80)	0.435*
CRP (mg/L)	287.63±162.98	189.1±118.35	**0.038****

*analyzed by Mann-Whitney-U test; ** analyzed by independent Sample t test. CRP: C-Reactive Protein

There were no significant differences in procalcitonin, creatinine or lactate levels, hourly urine output, qSOFA score, renal SOFA score, or leukocyte count (for all of them p > 0.05).

In contrast to CRP, there was no correlation between Nesfatin-1 levels and qSOFA score, procalcitonin, lactate, and creatinine levels or hourly urine output (p> 0.05 for all) (Table 4).

Table 4. Correlation between Nesfatin-1 levels and other parameters

	Nesfatin-1 (r)*	Nesfatin-1 (p)*
CRP	-0.250	0.017
Procalcitonin	0.128	0.294
qSOFA	-0.230	0.058
Lactate	-0.093	0.446
Creatinine	-0.42	0.733
Hourly Urine Output	0.016	0.896

*analyzed with Spearman's Correlation, CRP: C-Reactive Protein, qSOFA: quick Sequential Organ Failure Assessment

Nesfatin-1 levels did not differ significantly in different renal SOFA scores (p: 0.853). When the outcomes of 69 septic patients were assessed; 33 patients were discharged from the internal medicine department (19 patients over 65 years of age, 13 of whom were diabetic), 4 patients died (2 patients over 65 years of age, no diabetic patients), and 32 patients were referred to ICU (21 patients over 65 years of age, 9 were diabetic). Of the 32 patients referred to the ICU, seven were discharged (six were older than 65 years of age, three were diabetic) and 25 died (15 were older than 65 years of age; six were diabetic). Of the 42 septic patients over the age of 65 years, 19 died in the outcome assessment of their internal medicine hospitalization. Mortality rates of patients with sepsis were found to be independent of diabetes and age (over 65 years of age and below 65 years of age) (p: 0.722).

There was no statistically significant difference in terms of Nesfatin-1 levels in septic patients who were discharged, and patients referred to ICU during the hospitalization or compared with patients who died during the 1-month follow-up (p: 0,694; p: 0,821, respectively).

Also, when we evaluated 1-month mortality, we found that 35 of 69 patients died (50.72% mortality) and 34 of them were alive. Of 12 septic patients with Nesfatin-1 levels below 80 pg / mL, 10 (83.33% mortality) died while among nine patients with Nesfatin-1 levels above 1300 pg / mL, only 2 (22.22% mortality) died.

In our study, we can say that the mortality increased below 80 pg / mL Nesfatin-1 (arbitrary cut off) and the mortality decreased above the 1300 pg / mL Nesfatin-1 (arbitrary cut off) level. In other words, 10 (28.57%) of 35 patients who died during 1-month follow-up had a Nesfatin-1 value below 80. On this result, we divided the patients into two subgroups as patients with Nesfatin-1 values below 80 and over 80, and we found statistically significant differences in the 1-month mortality of patients (p: 0.013). Table 5 shows the distribution of Nesfatin-1 levels in 1-month mortality assessment on the survivors and non-survivors.

Table 5. Distribution of Nesfatin-1 in death and survivor patients in 1-month mortality assessment

Nesfatin-1 Levels (pg/mL)	Patients (n=69)	Control (n=21)
0-80 n (%) [Death(n)/ survivor (n)]	12 (17.4) (10/2)	0(0) (0/0)
80-500 n (%) [Death(n)/ survivor (n)]	17 (24.6) (8/9)	1 (4.7) (0/1)
500-1300 n (%) [Death(n)/ survivor (n)]	31 (44.9) (15-17)	11 (52.4) (0/11)
1300-4224 n (%) [Death(n)/ survivor (n)]	9 (13.1) (2-7)	9 (42.9) (0/9)

There was not any significant association between 1-month mortality and procalcitonin (p: 0.398), lactate (p: 0.606), and creatinine (p: 0.408) levels, hourly urine output (p: 0.104), renal SOFA score, qSOFA score, or leukocyte count (p: 0.714). However, there was a significant difference between the survivors and non-survivors in terms of CRP levels (p <0.05). The mean value of CRP was 186.5 mg / L in patients who died, and it was 255.4 mg / L in survivors.

4. Discussion

Sepsis is an inflammatory process in which appetite decreases. In sepsis, a clinical diagnosis, there is still no strong laboratory parameter to predict mortality today. A biomarker that predicts early mortality in septic patients will

be invaluable to clinicians.

Nesfatin-1 is a multifunctional, anorectic-acting peptide hormone with a half-life of 23.5 minutes (2). Studies conducted until this time investigated the course of Nesfatin-1 in chronic conditions such as malignancy, Polycystic Ovary Syndrome or Diabetes Mellitus. Nesfatin-1 level was reported to be significantly decreased in lung cancer (11). However, the data about the alterations in Nesfatin-1 levels in acute conditions is limited.

In our study, we compared the Nesfatin-1 levels in septic patients and healthy volunteers, and we found that Nesfatin-1 levels were significantly lower in septic patients. Our study was the first in the literature evaluating the Nesfatin-1 levels in sepsis and septic shock.

We further grouped septic patients as diabetic and nondiabetic and Nesfatin-1 levels did not differ between these two subgroups. However, in previous studies, serum Nesfatin-1 levels were found to be higher in patients with prediabetes and Type 2 Diabetes Mellitus (8,9). This information suggests that the Nesfatin-1 level is high in diabetic patients when there is no septic event, but it seems to be low in septic patients like non-diabetic patients. The fact that the Nesfatin-1 protein can be used as a marker in the diagnosis of sepsis; it is a promising result that Nesfatin-1 levels are not affected by the presence of diabetes. In addition, in this study, a negative correlation was found between Nesfatin-1 levels and CRP. These data suggest that Nesfatin-1 may be as reliable as CRP in the diagnosis of infection but may be superior to CRP due to the lack of affected results in diabetic patients because the CRP value was significantly different between diabetic and nondiabetic septic patients in our study. In rats with renal ischemia, the administration of Nesfatin-1 caused a significant decrease in creatinine levels and this was thought to indicate the future therapeutic effects of Nesfatin-1 (12). However, in a study in which Saldanha et al compared hemodialysis patients and healthy controls, Nesfatin-1 levels did not show a significant difference between the two groups (13). Similarly, in our study, there was no correlation between creatinine levels, hourly urine output or renal SOFA score, and Nesfatin-1 levels. Our study differs from the study performed with mice, since there was no relationship between kidney damage and Nesfatin-1 levels in our study performed with patients equally distributed according to renal SOFA score. In this respect, our study is the second human study showing that there is no relationship between Nesfatin-1 levels and kidney damage.

In addition, we did not find any correlation between Nesfatin-1 levels and procalcitonin, or lactate levels or leucocyte counts.

Nesfatin-1 values did not differ significantly in different qSOFA scores. However, when we combined the patients with qSOFA scores zero, one and two in a single group and three in a separate group, and compared these two groups, a statistically significant difference was observed in terms of Nesfatin-1 levels. Although more studies are warranted, this result suggests that Nesfatin-1 protein such as qSOFA, can be used for rapid evaluation of sepsis and may provide us an objective data in clinical practice.

There was not any significant difference between the patients who survived or died in the 1-month follow-up. However, the median Nesfatin-1 levels of the patients who died in the early period and who did not need to be followed up in the ICU at early periods (discharged from the service) were 54.03 pg / mL and 674.70 pg / mL, respectively. However, this difference did not reach a statistically significant level most probably due to the small number of septic patients who died at early periods (n: 4). If larger studies with more patients would be performed, it may be suggested that early ICU follow-up would be more appropriate in patients with lower Nesfatin-1 levels and a more aggressive treatment decision may be taken. Thus, this protein will be an important source of light for clinicians in the follow-up of patients, in the decision of treatment and in the unit to be followed.

When we evaluated 1-month mortality, 50.72% of the patients died. Previous studies have reported that in-hospital mortality rates due to sepsis are between 10 and 52% (14-17). In our study, the mortality rate in internal diseases wards was 5.7%, while in-hospital mortality rate was 42% that was in parallel with the current literature. Although most deaths are seen within the first six months, it is known that the risk continues for two years (18-22). In our study, 40 patients were discharged after hospitalization due to sepsis but six of them died within 1 month. This data supports the increase in mortality after hospitalization due to sepsis. One point we would like to draw attention to here is that the sensitivity and specificity of the cut off value for the Nesfatin-1 levels were too low for clinical use. However, 83.33% of patients with Nesfatin-1 levels below 80 pg / mL and 22.22% of patients with more than 1300 pg / mL died. Based on this information, we found that the mortality rate increased below the value of 80 pg / mL, which we determined as arbitrary cut off in our study, and we can still say that the mortality rate was lower in patients with Nesfatin-1levels higher than 1300 pg / mL, which was again determined as an arbitrary cut-off.

In the same way, the lowest Nesfatin-1 level in our control group was 296 pg / mL. Although larger studies with a higher number of patients and the control cases are required, we would like to note that we had Nesfatin-1 levels lower than 296 pg / mL only in the septic patient group. This value can serve as a valuable parameter in evaluating patients as sepsis and it may be associated with poor prognosis. However, it is obvious that more studies are warranted.

Furthermore, supporting our findings, as indicated in the kit procedure it was noted that the value of the Nesfatin-1

protein at a concentration close to zero was indicated to be at a sensitivity of 234.2 pg / mL. In parallel with this information, there was no value less than 234.2 pg / mL in the control group, but it was below the value specified in three of four patients who were expired during their hospitalization. This suggests that Nesfatin-1 protein is too low to be detected in early-onset sepsis.

We did not find any association between 1-month mortality and procalcitonin, lactate or creatinine levels, hourly urine output, renal SOFA score, qSOFA score, or leukocyte count. However, there was a significant difference in terms of CRP levels among survivors and expired patients within 1 month. The mean value of CRP was 186.5 mg / L in the expired group, and it was 255.4 mg / L in survivors. However, since both values were clinically high, we think that this result has no clinical significance.

In previous studies, it has been emphasized that low procalcitonin levels in septic patients would negatively affect prognosis since it may cause misdiagnosis (23-28). In our study, we did not find a correlation between procalcitonin levels and in-hospital or 1-month mortality. Therefore, we believe that procalcitonin should not be used in the clinical prognostic approach.

In our study, we did not find a relationship between qSOFA score and in-hospital or 1-month mortality. However, mortality is estimated to be more than 10% in patients who meet all of the qSOFA criteria in the literature (29). The fact that the qSOFA score, which has been in use since 2016, has not predicted mortality in our study shows that more studies are required in this regard.

In past publications, the anti-inflammatory and antiapoptotic properties of Nesfatin 1 have been emphasized (30). It is known to inhibit neutrophil infiltration. Due to this effect, it is an expected finding that the level of Nesfatin 1 decreases, as the anti-inflammatory effect may need to be suppressed in a situation where inflammation is intense such as sepsis and septic shock. In our study, a result in this direction was obtained.

Our study has some limited aspects. The first is the limited number of patients. The sensitivity and specificity of some markers may not have reached statistical significance. The area we want to mention in this regard is the comparison with the patients who were mortal in the early period. The second restricted aspect of our study was that all samples were not taken before the first antibiotic dose, which weakened the results and may showed higher Nesfatin-1 values in the septic group. Thirdly, since we did not report the infection focus and type of infection (microbial agent) of septic patients, we were unable to group accordingly and could not evaluate its effects on prognosis. Fourthly, we did not evaluate the level of NUCB2 protein or NUCB2 gene expression. Fifthly, Sepsis has many prognostic factors including early recognition and management of sepsis, appropriate antibiotic treatment initiation time, antibiotic resistance profile of infectious agent, APACHE scores, co-morbidities and age, etc. Therefore, evaluation of prognostic value of any test requires analysis of the test value together with confounder factors. We could not analyze the confounder factors. Finally, we did not state the causes of death.

Nesfatin-1 level was lower in septic patients compared to healthy controls and had a negative correlation with CRP. This does not differ in diabetic and nondiabetic septic patients in contrast to CRP. Nesfatin-1 can be used as a biomarker for differentiation of healthy population with sepsis. In patients with qSOFA score 3, the fact that Nesfatin-1 protein was lower than those with qSOFA score of 0, 1 and 2 indicates that this protein can be used in the rapid evaluation of sepsis and it may give us clinical benefit as an objective data.

Furthermore, Nesfatin-1 levels below 80 pg / mL in septic patients at the time of admission to the hospital may lead the clinician to early ICU follow-up with antibiotic therapy, with a broader spectrum and less resistance.

It is evident that prospective randomized controlled trials with a greater number of cases are warranted for the use of serum Nesfatin-1 levels in the diagnosis of sepsis and the prediction of mortality.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Evaluation of Covid-19 cases that applied to the hospital at the first peak of the pandemic

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Abstract

Early diagnosis in COVID-19 is essential in terms of treatment and prevention of contagiousness. In this study, we aimed to find an alternative diagnosis method by using fewer laboratory parameters in the early diagnosis of COVID-19 disease by creating a fast, easily accessible, cost-effective index and has a diagnostic accuracy rate of over 90%. All patients over the age of 18 who applied to Hitit University Erol Olçok Training and Research Hospital Emergency COVID Outpatient Clinic with a pre-diagnosis of COVID-19 between March and April 2020 were evaluated retrospectively. Patients were divided into two groups as COVID-19 positive and COVID-19 negative. It was aimed to create a HITIT-19 index by evaluating the cases according to the clinical and laboratory results. Between March and April 2020 (in the first peak of the pandemic), 1586 patients were applied to the Emergency COVID-19 outpatient clinic with a pre-diagnosis of COVID-19. According to COVID-19 RT-PCR, card test, and CT involvement, 285 (13%) patients were diagnosed with COVID-19. PCR was positive in 285 (18%) of 1586 patients, and PCR was negative in 1301 (82%). While 153 (53.7%) of the patients diagnosed with COVID-19 were male and the median age was 45 (28-62.75), 883 (55.7%) of the patients not diagnosed with COVID-19 were male, and the median age was 43 (31-65). Hypertension (HT) was the most common underlying disease in 10.5% of patients applied to the emergency room with a diagnosis of COVID-19, while 38.9% dyspnea and 35.1% fever were the most common symptoms. While 76% of Plaquenil and 58% azithromycin were the most frequently started treatments, 31.4% (28.4% of them were hospitalized in the service, 3% in the intensive care unit) of them hospitalized. It was to create a HITIT-19 index that is fast, easily accessible, cost-effective, and has a diagnostic accuracy rate of over 90% by using laboratory tests. However, we could not achieve this goal due to the low accuracy of the diagnostic tests and the lack of significant change in the laboratory levels of the patients at admission. Considering that the pandemic is continuing rapidly, there is still a need to develop practical diagnostic methods that are easier and cheaper in diagnosis. In this sense, we believe that our study will be a guiding study for other studies that will be designed for diagnostic index studies.

Keywords: Covid-19, early diagnosis, RT-PCR, HITIT-19 index

1. Introduction

SARS-CoV-2 is the cause of a serious pandemic that started in Wuhan City of China in early December 2019 and still has an ongoing impact, affecting the whole world. As of January 9, 2021, 87,589,206 patients and 1,906,606 deaths were reported with laboratory approval, affecting 218 countries worldwide (1, 2).

SARS-CoV-2 is a member of the β coronavirus family and is an enveloped positive strand RNA virus. SARS-CoV-2 acts by attaching to the angiotensin converting enzyme 2 (ACE2) receptor. Since this receptor is found in tissues such as the digestive system, the neurological system and the liver as well as the respiratory system, it also acts by attaching to these tissues (3).

Tang et al. identified two main types, L and S, based on analysis of 103 genomes of SARS-CoV-2. While the L type is more aggressive and can spread more rapidly, the S type may cause a relatively mild clinical course. L-type is more common and has more mutations (3).

Although the duration of contagion is not known exactly, it can start 1-2 days before the symptomatic period and last up to 14 days following the onset of symptoms. The incubation period is approximately 2-14 days, on average 4-5 days (4). Common symptoms of COVID-19 infection are fever, cough, and dyspnea. In more severe cases, pneumonia, severe acute respiratory infection, kidney failure, and even death may develop. Pneumonia is the most common serious finding of

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the disease. According to the World Health Organization (WHO), COVID-19 clinic is divided into five categories; asymptomatic (test positive, no symptom), mildly symptomatic (difficulty breathing, shortness of breath, or any signs and symptoms without abnormal chest imaging), moderate cases (mild lung involvement detected by clinical evaluation or imaging and> 93% oxygen saturation) severe illness (> 30 respiratory rate / minute, 93% oxygen saturation, partial arterial oxygen pressure to inspired oxygen <300 or lung infiltration> 50%) and critical illness (respiratory failure, septic shock and / or multi-organ failure) (5).

In COVID-19 disease, early diagnosis is important in terms of treatment and prevention of contagiousness. With this study, we aimed to evaluate of COVID-19 cases that applied to the hospital at the first peak of the pandemic and to create an alternative diagnosis method by using some laboratory parameters in the early phase of COVID-19 disease. This index should be fast, easily accessible, cost-effective, and have a diagnostic accuracy of over 90%.

2. Material and Methods

All patients over the age of 18 who applied to Hitit University Erol Olçok Education and Research Hospital Emergency Department "COVID-19 Outpatient Clinic" with the symptoms of COVID-19 between March and April 2020 were evaluated retrospectively. Oropharyngeal and nasopharyngeal swab samples were taken into vNAT™ Transfer Tube in our hospital. Manual RNA extraction was performed in the vNAT™ Transfer Tube. Bio-Speedy SARS-CoV-2 Double Gene RT-qPCR Kit and Bio-Rad CFX96 Real-Time PCR automated system were used for detection of SARS-CoV-2. Patients were divided into two groups as COVID-19 positive and COVID-19 negative according to RT-PCR, antibody-based card test and CT results. All cases were evaluated with clinical findings and laboratory results. Laboratory tests results such as complete blood count, coagulation, fibrinogen, routine biochemistry, D-dimer, venous blood gas, troponin, CRP and procalcitonin; which were taken at the emergency admission of cases were used to create the COVID-19 index for use to evaluate patients. Complete blood count, coagulation, routine biochemistry, D-dimer, fibrinogen, venous blood gas, troponin, CRP and procalcitonin test results were obtained from the automation system of our hospital; Data of clinical findings such as cough, shortness of breath, fever, malaise, weakness, and muscle pain were obtained from the patient files. Clinical data of COVID negative cases could not be accessed.

Hitit University licensed SPSS 23.0 package program was used to create the COVID-19 Index. Demographic and biochemical data were classified as continuous or categorical variables. Kolmogorov Smirnov analysis was used for normality test, and data with Gaussian distribution were presented as mean ± standard deviation, and data without Gaussian distribution were presented as median (25-75 quarters). Comparisons between groups were made using Student's t-test or Mann-Whitney U-test, as appropriate. Categorical variables were compared using the Chi-square test. Univariate and multivariate logistic regression analyzes were used to create a new COVID Index. With this new COVID Index, which was planned to be created, ROC analysis was performed to determine the diagnostic accuracies in the differentiation of COVID-19 patients. P <0.05 was considered statistically significant. The study was approved with the decision of the Ethics Committee of our hospital, dated 12.05.2020 and numbered 240.

3. Results

Between March and April 2020, 1586 patients applied to Hitit University Erol Olçok Education and Research Hospital Emergency Department "COVID-19 Outpatient Clinic with suspicion of COVID-19. According to COVID-19 RT-PCR, card test and CT involvement, 285 (13%) patients were diagnosed with COVID. PCR was positive in 285 (18%) of 1586 patients, and PCR was negative in 1301 (82%) patients. While the typical appearance compatible with COVID-19 in thorax CT was present in 189 (11.9%) cases, card test positivity was detected as 27 (1.7%). The median age of COVID-19 patients was 45 (28-62) and 153 (53.7%) were male, while the median age of patients that negative tests results were 43 (31-65) and 883 (55.7%) of them were male. Hypertension (HT) was the most common comorbidities in COVID-19 cases (10.5%). Other comorbidities are summarized in Table 1. Clinical findings of COVID-19 positive and negative cases are shown in the Table 2.

Table 1. Underlying diseases of Covid-19 negative and positive cases

Underlying Disease	Negative Patients (n=1301)	Positive Patients (n=285)	P
DM	211 (1.2%)	14 (4.91%)	<0.001
HT	399 (30.7%)	30 (10.5%)	<0.001
Cancer	55 (4.23%)	3 (1.05%)	0.010
COPD	61 (4.69%)	5 (1.75%)	0.025
Asthma	76 (5.84%)	6 (2.11%)	0.010
Heart Disease	116 (8.92%)	11 (3.85%)	0.004

DM: Diabetes Mellitus, HT: hypertension, COPD: Chronic Obstructive Pulmonary Disease

Table 2. Symptoms and findings of Covid-19 negative and positive cases

Symptoms and Findings	Negative Patients (n=1301)	Positive Patients (n=285)	*P*
Fever	417 (32.1%)	100 (35.1%)	0.322
Dyspnea	439 (33.7%)	111 (38.9%)	0.095
Cough	732 (56.3%)	49 (17.2%)	<0.001
Sore Throat	215 (16.5%)	14 (4.91%)	<0.001
Fatigue	219 (16.8%)	19 (6.67%)	<0.001
Headache	87 (6.69%)	8 (2.81%)	0.012
Vomit	36 (2.77%)	2 (0.70%)	0.039
Myalgia	82 (6.30%)	8 (2.81%)	0.021
Stomach Ache	27 (2.08%)	0 (0%)	0.009

First laboratory tests result of COVID-19 cases which were evaluated in the emergency department, only the CRP result was found above normal. Other tests results were within normal limits. Laboratory findings are summarized in Table 3. The treatments that initiated for COVID-19 are summarized in Table 4. The most used agents in the treatment were plaquenil (76%), azithromycin (58%), low molecular weight heparin LMWH (42%) and oseltamivir (25%). 31.4% (n=689) of the patients were hospitalized. 91% (n=624) of them were hospitalized in COVID services and 3% (65) in intensive care units. We could not create a COVID-19 index due to the lack of significant changes in the laboratory parameters (ROC analysis, Fig. 1).

Table 3. Laboratory information of Covid-19 cases

	Negative Patients (n=1301)	Positive Patients (n=285)	*P*
WBC (10^9/L)	8.45 (6.77-10.48)	5.82 (4.61-7.19)	<0.001
Neutrophil (10^9/L	5.33 (3.93-7.48)	3.42 (2.67-4.53)	<0.001
Lymphocyte (10^9/L)	1.97 (1.31-2.62)	1.45 (1.05-1.96)	<0.001
Platelet (10^9/L)	239 (199-289)	209 (169-255)	<0.001
AST (U/L)	22 (17-30)	23 (18-32)	0.063
ALT (U/L)	21 (14-33)	20 (15-30)	0.285
LDH (U/L)	195 (164-246)	212 (164-280)	0.009
CK (U/L)	90 (63-138)	78 (53-124)	0.004
D.Dimer (ug/mL)	0.26 (0.10-0.62)	0.29 (0.20-0.63)	0.003
PRO-BNP (pg/mL)	39 (12-176)	44 (15-107)	0.631
Fibrinogen (mg/dL)	341 (280-437)	343 (282-460)	0.626
CRP (mg/l)	5.41 (3.14-31.3)	7.91 (3.14-27.3)	0.744
Procalcitonin (ng/ml)	0.05 (0.03-0.1)	0.13 (0.04-4.3)	<0.001
Ph	7.39 (7.36-7.42)	7.40 (7.38-7.4)	0.001
PCO_2 (mmHg)	43 (39-48)	41 (37-46)	<0.001
Lactate (0.5-2 mmol/L)	1.79 (1.41-2.25)	1.73 (1.45-2.2)	0.451
Hematocrit (%40 - 49.4)	41 (38-45)	40 (38-43)	0.021
RDW (%12–13.6)	35 (13-41)	14 (13-32)	<0.001

WBC:White blood cell, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDH: Lactate Dehydrogenase, CK: creatine kinase , PRO-BNP: pro b-type natriuretic peptide, CRP: C-Reactive Protein, PCO2: Partial Carbon Dioxide Pressure, RDW: Red cell distribution width

Table 4. Treatments initiated for COVID-19

Treaments Started	n (%)
Plaquenil	217 (76.1%)
Azithromycin	165 (57.9%)
LMWH	119 (41.8%)
Oseltamivir	72 (25.3%)
Vitamin C	68 (23.9%)
Favipiravir	61 (21.4%)
Ceftriaxone	40 (14.0%)
Steroid	11 (3.86%)
Tosilizumab	4 (1.4%)

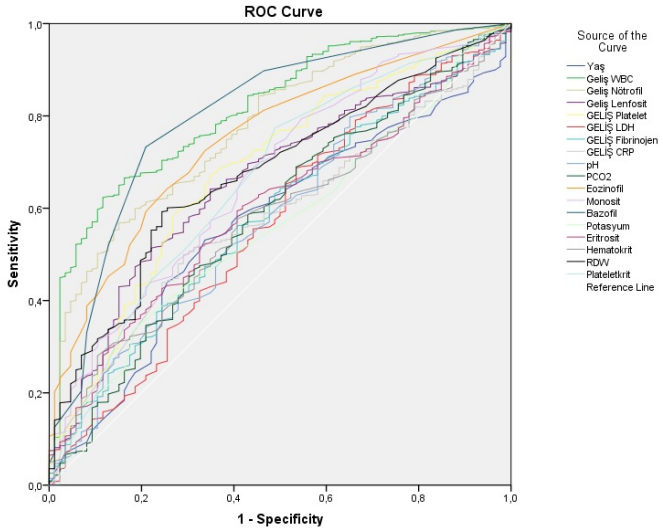

Fig. 1. ROC analysis

4. Discussion

Turkey was also affected by COVID-19, which caused a global public health problem by affecting the whole world. The diagnosis of COVID-19 is based on epidemiological history, clinical symptoms, RT-PCR, thoracic CT and antibody-based card test (6). In our country, according to the Ministry of Health COVID-19 diagnosis and treatment guideline, definitive diagnosis of the COVID- 19 based on real-time reverse transcription polymerase chain reaction (rRT-PCR) positivity (7). It is reported in the literature that the RT-PCR test used in the diagnosis of COVID-19 has high specificity (8) and a low sensitivity rate (9). Although the sensitivity rate of the test is not clear, it is estimated to be around 45–97% (10-12). Because the sample is taken in the early or late period, mutations, low viral load may cause the test to be negative (10). RT-PCR was obtained from all 1586 patients applied to our Emergency Department "COVID-19 Outpatient Clinic". The PCR results of 285 (18%) cases were positive. This was a very low value compared to the literature. It was thought that this result may be caused by the excessive number of applies due to COVID-19 anxiety and panic in both physicians and patients at the beginning of the pandemic.

Typical CT findings are diagnostic in patients until RT-PCR results are available (12). RT-PCR should be repeated to avoid the isolation and misdiagnosis of patients with typical CT findings and negative RT-PCR results. It has been reported that the missed diagnosis of COVID-19 by CT is low (3.9%) (13). CT positivity was reported as 64% in the study of Kostaoğlu et al. (12). In our study, on thoracic CT, typical appearance compatible with COVID-19 was present in 189 (11.9%) cases. This low rate can be explained by the fact that almost all patients were referred to the Emergency Department COVID-19 Outpatient Clinic for both retraction and diagnostic purposes due to the concern of COVID-19, the high rate of thoracic CT scans, and most of the patients presenting to the emergency COVID-19 outpatient clinic with panic.

After a while, antibodies (IgM, IgG, IgA) develop in those who recovering from the disease. Antibody response usually begins to occur after 4-7 days of illness. Since antibody positivity occurs approximately after the 10th day of the disease, serological tests should be performed after this day (14). The sensitivity and specificity of serological tests vary according to the test technique, the specificity of the antibody examined, the duration of symptoms at the time of collection, and the immune competence of the individual (10). Li et al. Reported the sensitivity of these tests as 88.7% and the specificity as 90.6% (15). Similarly, in another study conducted in Thailand, 98% sensitivity and 98-100% specificity rates were reported (16). In our study, card test positivity was detected as 27 (1.7%). The test positivity rate was low because our cases were in the early stages of the diseases.

While Baloch et al. (17) reported that the median age was 56 and 54.3% were male, the median age was reported to be 62 in the study of Jin et al. (18). 59% of the cases were male and the mean age was 52 in the study of Kostakoglu et al. (12). Wan et al. was reported the average age of patients as 47 years (19). In our study, 55.7% of our cases were male and the average age of our cases was 45 and it was like the literature.

In the study of Jin et al., 37% were reported to have at least one comorbidity (18). In the study of Kostaoğlu colleagues, the most common comorbidity was hypertension (12). In a study conducted in Iran, diabetes, chronic respiratory disease, and hypertension were the most common comorbidities (20). Wan et al. reported that 32% of their patients had a comorbidity and the most common of them were hypertension (10%), diabetes (9%), cardiovascular disease (5%) and malignancy (3%) (19). In our study, hypertension (11%), diabetes (5%) and heart disease (4%) were the most common comorbid diseases in patients diagnosed with COVID-19 and were like the literature.

Baloch et al. reported the most common symptoms as 98% fever, 76% cough and 44% myalgia (17). The most common symptoms in the study of Jin et al. were 95% fever and 65% cough (18). In our study, dyspnea (39%) and cough (17%) were the most common symptoms. Since our study consisted of patients applied to the emergency department, that is, it did not include only hospitalized patients, our rates were expected to be lower than in the literature.

Laboratory findings include leukopenia, lymphopenia, thrombocytopenia, transaminases, increased CK, LDH, ferritin, and fibrinogen (7,21). Wan et al. reported the mean leukocyte mean 5.4×10^9 / L, lymphocyte mean 1.1×10^9 / L, platelet mean 158×10^9 / L, coagulation parameters were normal in almost all patients, mean creatine kinase 82.2U / L, mean LDH 320 U / L reported the mean CRP of 10.5 mg / L and the mean procalcitonin as 0.11 ng / Ml (19). In our study, the mean laboratory parameters of the patients who were evaluated in the emergency department were within normal levels, but statistically significant differences were found between two groups.

There are many different approaches and guidelines for effective drug therapy in the treatment of COVID-19 patients in the first peak of pandemic. There is no specific treatment with proven safety and efficacy. Remdesivir, which is one of the agents used in treatment, is licensed for the treatment of COVID-19, while chloroquine phosphate, favipravir, lopinavir / ritonavir, and remdesivir are among the recommended drugs (7,22). LMWH (enoxaparin) is also recommended for prophylaxis due to the predisposition to venous and arterial thromboembolic events by various mechanisms in the course of COVID-19 disease (7). Wan et al. initiated 100% antiviral therapy (catheter and interferon), 44% antibacterial therapy, and 26% corticosteroid therapy (19). Our treatment experience in the first two months was 76% plaquanil, 58% azithromycin, 42% LMWH and 25% oseltamivir.

While planning this study, our aim was to use laboratory tests such as complete blood count, coagulation, routine biochemistry, D-dimer, fibrinogen, venous blood gas, troponin, CRP, and procalcitonin to create a COVID 19 index which is fast, easily accessible, cost-effective, and diagnostic accuracy rate of over 90%. However, we could not achieve this goal due to the low accuracy of diagnostic tests and the lack of significant change in the laboratory values of the patients at admission.

Considering that the pandemic is continuing rapidly, there is still a need to develop practical diagnostic methods that are easier to diagnose. In this sense, we believe that our study will be a guiding study for other studies that will be designed for diagnostic index studies.

Conflict of interest

None to declare.

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None to declare.

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The prevalence of occupational accidents and diseases among 112 emergency medical workers and factors affecting it

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Abstract

Occupational health has been defined by the World Health Organization (WHO) as employees in all professions have complete physical, mental, and social well-being and maintain and develop this well-being. This study aimed to determine the prevalence of work-related risks, work-related diseases, occupational accidents, and diseases faced by 112 emergency medical workers and factors affecting it. This descriptive, cross-sectional study included 415 health personnel working in 112 emergency medical services in Elazig Province. It was found that 74.7%, 21.2%, and 6.3% of participants, throughout their professional life, have experienced at least one of the work-related risks, occupational accidents, and diseases, respectively. Female employees experienced more work-related diseases ($p<0.01$), work-related risks ($p<0.01$), and occupational accidents ($p<0.01$) than males. Being female was identified as a risk factor, and training on occupational health and safety issues was a protective factor.

Keywords: occupational accident, occupational disease, work-related risk, 112 EMW, occupational health

1. Introduction

Occupational health has been defined by the World Health Organization (WHO) as employees in all professions have a complete physical, mental, and social well-being, and also maintenance and development of this well-being (1). When this state cannot be achieved, work accidents and occupational diseases can occur (2). Occupational diseases can be led to exposure to chemical, physical, and biological risk factors. The work environment and condition may also play a role, together with other risk factors in developing these diseases characterized by a multiple etiology which is named work-related disease. In occupational disease, there is a direct cause-effect relationship between hazard and disease. In contrast, in work-related disease, the work environment contributes to developing the disease multifactorial and complex etiology as one of several factors (3). These emergencies are all different from each other because of the unique working environment of each profession. Therefore, healthcare providers need to protect their health while providing health care, one of the main areas of work. "Activities in health institutions where outpatient and/or inpatient diagnosis and treatment are done" have been classified as hazardous works in the world and Turkey (3). This danger reaches its highest level among 112 emergency medical workers (EMWs), and so they have difficulty maintaining their health while providing emergency service (4).

Ambulance services, which are one of the first and emergency services, aim to protect life, taking measures against unexpected dangers, speeding up the treatment, and timing the procedures correctly (5). 112 EMWs consist of a physician, nurse, ambulance and emergency care technician, emergency medical technician (EMT), and health officer in Turkey (6). The guide created by the Turkish Labor and Social Security Institution defined falls, bumps, percutaneous injury, exposure to body fluids, exposure to chemicals, stress, non-ergonomic applications that cause musculoskeletal disorders, traffic accident, violence, and oxygen tube burst as significant risks to 112 EMWs (6). The prevalence of these risks, and work-related diseases caused by them and the prevalence of occupational accidents and diseases and influencing factors should be clarified with further and comprehensive studies.

Therefore, this study was performed to determine the prevalence of work-related risks, work-related diseases, occupational accidents, and diseases encountered by 112 EMWs in Elazıg city center and the factors affecting it.

2. Material and Methods

2.1. Study design and study setting

We included 415 health personnel working in 112 emergency medical service (EMS) in Elazig Province in this descriptive, cross-sectional study. Ethical permission was obtained from Fırat University Rectorate Non-Interventional Research Ethics Committee (06.02.2020/03-01) and administrative approval from Elazig Provincial Health Directorate.

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2.2. Population and sample size

According to the data of Elazig Provincial Health Directorate dated 01.02.2020, 112 EMS employs 464 personnel, consisting of 18 physicians, 147 paramedics, 139 EMT, 23 paramedics, 5 nurses, and 132 ambulance drivers. Due to being on leave (30 persons) and not volunteering (19 persons), 415 (89.4%) health workers could be reached.

2.3. Data collection

The literature-based questionnaire consisted of four parts; the socio-demographic information, training status on occupational health and safety, the status of experiencing occupational accidents and diseases, and protection status from occupational accidents and diseases: socio-demographic part contained fill-in-the-blank and multiple-choice, and other sections optional questions (7-9). In socio-demographic information, age (also grouped as 20-30, 31-40, 41-50, > 50), gender, marital status, the working year, profession, academic education status was interrogated. Occupational accidents and diseases, prevention of those diseases, and the status of receiving training on personal protective equipment (PPE) were asked in the second section (about training on occupational health and safety). The risks leading to occupational accidents and diseases, the position of experiencing them, and work-related diseases were interrogated in the third part of the survey. The fourth part, which is protection status from occupational accidents and diseases, included questions about immunization status (hepatitis A, hepatitis B, influenza vaccine (annual regular), flu shot (not regular/at least once, tetanus), and use of PPE.

2.4. Outcome measures

The protection score (PS) was calculated by evaluating immunization status, and each of the subtitles of PPE usage as 1 point. The prepared survey was submitted online to 112 EMWs' phones in March 2020 via Google Docs. The reply form was then sent to the researcher by mail.

2.5. Data analysis

The data obtained from the study were evaluated with SPSS 22.0. According to the characteristics of the variables, percentage, mean, t-test, Mann Whitney U, Kruskal Wallis, chi-square, and logistic regression tests were used in statistical analysis. Means were given with standard deviation (mean ± SD), and statistical significance was accepted as $p<0.05$.

3. Results

The average age of the 112 EMWs involved in the study was 33.28 ± 8.85 (min: 20, max: 62). Of the participants, 66.0% were male, and 69.2% were married. 33.8% were EMT, 30.5% were nurse/health officers, and 37.8% were high school graduates. 81.9% have received training on occupational accidents and diseases and preventing them and PPE (Table 1). The participants' average working time was 9.15 ± 6.95 (min: 1, max: 31) years. In terms of work-related risk types, 35.2 % experienced fall/bump, 23.4% stress, 22.4% contact with body fluids, 19.3% traffic accident, 21.2% violence (3.9% physical, 17.3% verbal), and 5.1% experienced exposure to chemicals. Whereas 92.7% of violence victims did not apply for white code, 7.0% of those who had a work accident did not notify. Besides, 82.1% of those with occupational diseases were diagnosed with a herniated disc.

Table 1. Socio-demographic information

	n	%
Sex		
Female	141	34.0
Male	274	66.0
Marital Status		
Married	287	69.2
Single	123	29.6
Other	5	1.2
Profession		
EMT	140	33.8
Paramedics	66	15.9
Physicians	12	2.9
Nurse/health officer	126	30.5
Driver	70	16.9
Education Status		
High school	157	37.8
Associate degree	142	34.2
Undergraduate	105	25.3
Postgraduate	11	2.6
Occupational Accident Training		
Yes	340	81.9
No	75	18.1
Work Accident Prevention Training		
Yes	340	81.9
No	75	18.1
PPE Training		
Yes	340	81.9
No	75	18.1
Work related hazard, risk		
Yes	310	74.7
No	105	25,3
Occupational Accident		
Yes	88	21.2
No	327	78.8
Occupational Disease		
Yes	26	6.3
No	389	93.7

Female workers experienced more work-related diseases ($p<0.01$) and risks that will cause occupational accidents and diseases ($p<0,01$) than males. Also, they had more occupational accidents ($p<0.01$), more applied for occupational diseases ($p=0.032$), and were more diagnosed with those diseases ($p=0.027$) than males. No difference was found between female and male workers regarding immunization status ($p=0.533$) and taking any protective measures ($p=0.329$). However, the total protection score of female participants was higher than males ($p=0.008$). Those with the highest work-related risks were singles, and those with the least were married ($p=0.01$). No difference was seen in terms of marital status and the status of experiencing an occupational accident ($p=0.754$). Singles had more work-related diseases than married and divorced ($p=0.003$). When compared according to academic education groups, high

school graduates experienced fewer hazards and risks (p<0.01), work-related diseases (p<0.01), and occupational accidents (p=0.01). The high school graduate group's PS was significantly lower than the other groups (p<0.01).

Those who received training on occupational accidents and diseases took more precautions than those who did not (p<0.01) and had higher PSs (p<0.01). Those who received training on the prevention of occupational accidents and diseases took more precautions than those who did not (p<0.01) and had higher PSs (p<0.01). It was also striking that those who received training on PPE took more precautions (p<0.01) and had higher PSs than those who did not (p=0.01). Participants were grouped as 20-30, 31-40, 41-50, > 50 by age. The 20-30 age group experienced more hazards and risks (p<0.01) and work-related diseases than other age groups (p<0.01). 41-50 age group was the group that took the most precautions (p=0.029). It was found that the PS decreased with increasing age (p=0.02, r=-0.114) but increased with an increasing number of keeping watch (p=0.031, r=0.106). All 112 EMWs with a rate of 21.2%, males 19.0 %, and females 25.5% were exposed to at least one type of violence. Although females were more often subjected to violence, this trend was not statistically significant (p=0.122). Singles have experienced more violence than any other marital status (p=0.02), besides the graduate education group was exposed to more violence compared to other education groups (p=0.01) and the 20-30 age group compared to other age groups (p=0.047). Age, marital status, profession, academic education status, and working year were evaluated by logistic regression analysis to determine risk factors for exposure to work-related risks. Being a female, young age, advanced academic education, and increasing working year were determined as a risk factor, and being a driver as a protective factor (Table 2).

Table 2. Risk factors for exposure to work-related hazards and risks

	B	p	OR	CI
Sex	-0.649	**0.009**	2.261	1.278-4.167
Age	-0.074	**0.006**	0.929	0.882-0.979
Marital Status (Ref=Married)				
Single	-1.696	0.166	0.183	0.017 2.017
Other	-1.229	0.332	0.293	0.024-3.504
Profession (Ref=EMT)				
Paramedics	-0.653	0.192	0.520	0.195-1.389
Physician	-0.879	0.163	0.415	0.121-1.429
Nurse	-1.036	0.253	0.355	0.060-2.098
Driver	-1.608	**<0.001**	0.200	0.094-0.428
Education status	0.703	**<0.001**	2.020	1.439-2.836
Working year	0.065	**0.018**	1.068	1.011-1.127

Risk factors for experiencing work-related diseases were identified as being a female and having higher academic education (Table 3).

Table 3. Risk factors for experiencing work-related diseases

	B	p	OR	CI
Sex	-0.560	**0.003**	2.024	1.379 3.374
Age	-0.023	0.394	0.977	0.926-1.031
Marital Status (Reference =Married)				
Single	0.407	0.735	1.502	0.143-15.800
Other	0.682	0.575	1.977	0.183-21.357
Profession (Ref=EMT)				
Paramedics	0.575	0.181	1.777	0.766-4.120
Physician	0.311	0.534	1.365	0.512-3.637
Nurse	0.505	0.489	1.657	0.396-6.929
Driver	-0.659	0.083	0.517	0.245-1.090
Education status	0.584	**<0.001**	1.793	1.351-2.379
Working year	0.047	0.101	1.048	0.991-1.108

The logistic regression analysis of age, gender, marital status, profession, academic education status, and the working year was assessed to reveal risk factors for occupational accidents. Being a female, advanced academic education status, and increasing working year observed as a risk factor, and being a driver found to be a protective factor (Table 4).

Table 4. Risk factors for experiencing occupational accidents

	B	p	OR	CI
Sex	-1.046	**<0.001**	2.849	0.196-0.629
Age	-0.053	0.134	0.949	0.886-1.016
Marital Status (Ref= Married)				
Single	-0.388	0.747	0.679	0.064-7.148
Other	-0.293	0.810	0.746	0.069-8.120
Profession (Ref=EMT)				
Paramedics	-0.481	0.348	0.618	0.226-1.689
Physician	-0.854	0.159	0.426	0.129-1.399
Nurse	-0.289	0.727	0.749	0.147-3.801
Driver	-0.935	**0.045**	0.393	0.157-0.980
Education status	0.311	0.063	1.365	0.983-1.896
Working year	0.085	0.019	1.088	1.014-1.168

4. Discussion

The prevalence of work-related risks, work-related diseases, occupational accidents, and diseases encountered by 112 EMWs in Elazıg city center and the factors affecting it were evaluated in this study. Most of the EMWs were EMTs and nurses. Being a woman was determined as a risk factor and getting an education as a protective factor. Our participants' average age was 33.28, and in one research to determine the profile of emergency workers in Spain, this was the same decade, like our study results (9). Again, our study revealed in parallel with the same research that most of the workers were male and married (9). This finding has suggested that 112 EMSs are preferred by the younger age group and males due to the massive working conditions.

Most of the 112 EMWs in this study have received informational training about prevention and awareness of occupational accidents and diseases, and PPE's use still leads to occupational accidents and diseases. Some were not reported from occupational accidents. In Onal's recent study that we mentioned above, the rate of having a traffic accident in the ambulance was found like our results (10). Despite the high rate of training at least once in a lifetime, work-related risks and occupational accidents also occurred in this researcher's study group. Therefore, it has been thought that periodic evaluation of EMWs' training and practices, periodically giving the necessary training, identifying difficulties in implementation, encouraging EMWs to implement, and the diligent work of occupational health and safety inspectors in the field is required (11). We, moreover, believe that it would be beneficial to carry out further and comprehensive studies for more effective reporting of work accidents. In the current study, the frequency of verbal violence was higher than physical violence. Females were exposed to at least one type of violence more than males. Most of the violence victims did not apply for the white code. Singles and younger age group were remarkably more exposed to violence. These results revealed the requirement for a detailed investigation of risk factors for violence and taking necessary measures. In a study by Gulen et al., patient-related violence was evaluated, and the frequency of physical violence and verbal violence by health workers was higher than in our study (12). In the literature data, this variation in rates may have resulted from the different regions where the studies were conducted.

The herniated disc was the most common of the work-related diseases found in our study. In another recent study, low back pain was associated with the activity limitation in ambulance workers (8). It has even been reported that the work and physical conditions' seriousness are the most critical stressors (13). Concerns about working conditions have appeared to be a major risk factor for health complaints (14). In a study conducted in the USA, examining occupational health and safety for EMWs, it was found that all workers should be subjected to a special training program according to their position. It was also emphasized that a system operated with trained and experienced human resources positively affected practical work in cooperation in all institutions related to occupational health and safety (7). We think that effective models should be applied by adapting to our country and that this may have beneficial and positive results for our country.

In the current study, female workers experienced approximately two times more work-related diseases and risks causing occupational accidents and diseases than males. They, again, about two times more than males, both applied for occupational diseases and were diagnosed with those diseases. There was no difference between males and females in terms of having any immunization and taking protective measures. However, the total PS of female workers was higher than males. Although females did not act differently regarding implementing at least one of the measures, they had high PSs. This means that women experienced more risk, despite more protection. In the literature, in various studies, it has been mentioned that the increasing female population in health workers changes the psychosocial dynamics, and it increases the danger (2).

In this study, those who received training on occupational accidents and diseases, prevention of them, and PPE took more precautions than those who did not, and their PSs were also higher. Those trained in all subjects were acting more carefully, which showed the positive effect of vocational education. As academic education progressed, rates of exposing to risks and experiencing work-related diseases increased. We have predicted that the self-confidence created by academic education, causing carelessness, yielded these results.

This study found that ambulance drivers experienced fewer risks and occupational accidents than other professions. In another study, being a doctor or other medical worker was riskier for developing occupational or work-related diseases than being a paramedic, EMT, or a driver (10). This finding is like our study results. It may have resulted from the fact that ambulance drivers are at less risk and lack an active healthcare provision role. As the working years increased, the increase of experiencing risks and occupational accidents has been considered the natural effect of time passed away.

This study's limitation is that data included in the present study were obtained by the survey method, so they are based on the study participants' statement. If there were an occupational health and safety file for EMWs and saved in this file, all the situations, personal information, and training received would be completely objective. There was no such data. Therefore, all data were obtained from the participants through questionnaires. Our study's strength is that all the province health workers that can reflect 112 EMWs across Turkey are included regardless of the occupational groups.

In this study to determine the prevalence of work-related risks, work-related diseases, occupational accidents, and diseases, and factors affecting it that 112 EMWs in Elazig Province encountered, it was established that 74.7% of the personnel experienced work-related hazards and risks, 21.2% work accidents, and 6.3% experienced occupational diseases. Being a female was determined as a risk factor and receiving training on occupational health and safety issues as a protective factor. It was observed that there were unreported work accidents and situations of violence. Therefore, efforts to eliminate the hazards and risks encountered should be made, and occupational health and safety training should also be repeated periodically. As the next step, occupational safety inspectors must serve on the field and even make notifications easy for employees.

Conflict of interest

None to declare.

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None to declare.

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The effects of foot reflexology upon pain, anxiety, and patient satisfaction among patients having undergone open-heart surgery

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Abstract

This interventional study was conducted to analyze the effects of foot reflexology intervention upon patients having undergone an open-heart surgery on their pain, anxiety, and satisfaction level. This research was conducted with 70 patients having undergone open-heart surgery in the cardiovascular surgery clinic of a Turkish hospital. Thirty-five patients were assigned to a test group, and 35 patients were assigned to a control group. In this research, patients in the test group were reported to have a statistically significant decrease in the mean scores of the visual analog scale when compared with the scores of patients in the control group ($p<0.05$). Although no statistically significant difference ($p>0.05$) was measured between the mean scores of the state-trait anxiety inventory and the visual analog scale of patient satisfaction completed by patients in the test and control groups, it was also noted that both groups were exceptionally satisfied. The findings of this research can be utilized to alleviate pain, lessen patients' anxiety levels during the post-operation phase, and elevate patient satisfaction levels.

Keywords: anxiety, cardiac surgery procedure, pain, patient satisfaction reflexology, pre-operative nursing

1. Introduction

By the year 2030, the United Nations Sustainable Development Goals aim to reduce premature mortality from non-communicable diseases by a third (1). Cardiovascular diseases are the most common diseases globally (2). Medical and surgical procedures are employed in the treatment of cardiac diseases. Open-heart surgery, as a popular method in the surgical treatment of cardiac disease, has been the fundamental treatment implemented in the case of coronary artery disease, cardiac valve disease, treatment of congenital lesions, and heart transplants (2, 3).

The operation (surgery) process induces an extreme level of anxiety in many patients. In the literature, it has been posited that, among adult patients, the incidence of pre-operative anxiety ranges between 11%-80% and that any increase in pre-operative anxiety level would cause delayed recovery from post-operation scars, extended hospitalization length, a need for anesthesia and post-operation analgesic, and elevated rates of morbidity and mortality (3,4). It has been acknowledged that, in modern health care, there has been increased intervention with complementary therapy methods in coordination with conventional methods to ensure physical and emotional healing as well as relaxation. Non-pharmacological complementary therapy methods have been harnessed to magnify the effects of pharmacological methods, primarily on pain and anxiety. An increasing number of studies indicate that one of these methods, reflexology, has proven to be effective, and its clinical intervention has been highly recommended (4, 5).

In the reflexology method, pressure is applied on reflex points via specific hand and finger techniques to release blocked energy in certain parts of the body, thereby stimulating the self-healing power of the body and leading to physical transformation by alleviating stress (2). Reflexology is a non-pharmacological, non-surgical, and cost-effective method that nurses can safely implement for the management of pain and anxiety after open-heart surgery. A number of studies concluded that, among a variety of patient groups, reflexology proved to be an effective and complementary non-pharmacological method for pain management (5). Hence, it is proposed that reflexology, which is a complementary therapy method that any nurse can apply individually, would contribute to alleviating post-operation pain and lead to a decreased level of anxiety and an increased level of satisfaction among patients who have undergone open-heart surgery (6).

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Despite the existence of several relevant studies in the literature, there is a deficit of research on this subject in Turkey, and there has yet been no study that specifically investigated the effect of reflexology on patients having undergone open heart surgery. It is thus concluded that this study could act as a torchbearer for the future in this field of study.

Based on these data, this research was conducted to analyze the effect of foot reflexology on the pain, anxiety, and satisfaction levels of patients with an open-heart surgery history.

2. Materials and Methods

2.1. Study design

This is an interventional study conducted to analyze the effects of foot reflexology upon the pain, anxiety, and satisfaction levels of patients having undergone open-heart surgery.

2.2. Sample and setting

The research was conducted between the dates of March 1, 2016 and August 31, 2016 in the cardiovascular surgery clinic of a university hospital in Turkey. Seventy patients were detected to be included in the study based on reference studies and by using Open-Epi program in 95% confidence interval and 90% power. Random samples method was used in the study and the study was completed with 70 patients (35 in test group and 35 in control group) who agreed for participation and who met inclusion criteria (7). In order to avoid from the patients' affecting each other, the study was started with control group and continued with the test group). 73 patients in total were approached, but three patients were excluded from the research since one patient was transferred for a second operation and two patients had diabetes.

The inclusion criteria for the research were being age 18 and older; the ability to conduct verbal communication; the capability of recognizing people, place and time; and the willingness to be included in the research. Exclusion criteria for the research were having a previous history of open-heart surgery, having an open foot wound, being suspected of having a fracture or burn, having a pace maker, being visually impaired, being afflicted with a malignity, having a psychiatric-disorder or using a psychiatric drug, having a history of epilepsy, being afflicted with deep vein thrombosis, having insulin-dependent diabetes, having neuropathy, or having used a narcotic drug within four hours of the intervention.

2.3. Data collection method and instruments

In this research, data were collected using a questionnaire form developed by the researchers using the relevant literature, a State-Trait Anxiety Inventory (STAI), a Visual Analog Scale (VAS), and a Visual Analog Scale of Patient Satisfaction (VASPS).

2.4. State-Trait anxiety inventory (STAI)

The State-Trait Anxiety Inventory (STAI) is a self-assessment survey formed by short statements in order to identify state and trait anxiety levels individually. The inventory that was implemented for this study was developed by Spielberger et al. (8) and adapted for Turkey by the validity and reliability analysis of Öner and Le Compte (9). The STAI measures the anxiety level of teenagers over age 14 and adults. As a type of self-assessment, this inventory includes 40 items with short statements. The 20-item State Anxiety Inventory and the 20-item Trait Anxiety Inventory are independent of each other. In the State Anxiety Inventory, each item is scored in four Likert type responses as follows: none: 1, a little: 2, a lot: 3, and completely: 4; in the Trait Anxiety Inventory, each item is scored in four Likert type responses: almost never: 1, sometimes: 2, most of the time: 3, and almost always: 4. Higher scores indicated a higher level of anxiety whereas low scores indicated that the anxiety level was low.

2.5. Visual analog scale (VAS)

This is a 10-cm scale with the response "no pain" at one end and the response "max. pain" at the other end. In this scale, individuals are asked to point at their experienced pain level on a 0 to 10 score line. It had been reported that for measuring pain severity VAS is more precise and reliable than other one-dimensional scales (10).

2.6. Visual analog scale patient satisfaction (VASPS)

Developed by Kılınçer and Zileli (11), VASPS is formed by combining the features of two frequently used and widely recognized scales. One of them is the Visual Analog Pain Scale (a sliding scale version of the Visual Analog Scale of Patient Satisfaction) located on a horizontal axis and formed by a 100-mm straight line with no partitions while the other one is the Wong-Baker Percentage Scale. In this scale there is a vertical straight line, and the patient puts a cross (X) on the point on the vertical line corresponding to the level of satisfaction with the provided medical care provided. On this scale, the score range varies from 1 to 10. Score 1 means "not satisfied at all" and score 10 indicates "extremely satisfied" (11).

2.7. Procedure

Prior to this study, the researcher received a qualification for foot reflexology therapy, the Certificate for Clinical Reflexology. Next, to avoid any interaction among patients, the control group was formed before the test group. To ensure that hemodynamic changes, pain levels, and vein narcotic analgesics would not interfere with the study results, the reflexology intervention was performed on the second post-operative day.

2.8. Control group

On the second day, post-operative patients in the control group were administered the patient information form, the STAI, the VAS, and the VASPS. Next, on the third post-operative day, the VAS was used to measure the level of pain experienced by the patients. On the fourth post-operative day, the STAI, the VAS, and the VASPS were used. Patients in the control group were not administered foot reflexology intervention. Instead, these patients received the standard/routine healthcare provided in the clinic.

2.9. Test group

On the second post-operative day, patients in the test group were administered the patient information form, the STAI, the VAS, and the VASPS. Afterwards, a 20-minute session of foot reflexology therapy was administered, 10 minutes for each patient's foot. At the end of the procedure, the VAS was applied again. On the third post-operative day, prior to the reflexology procedure, the VAS for foot reflexology was applied, and, next, the VAS was administered. On the fourth post-operative day, the VAS was administered before the foot reflexology intervention. At the end of the procedure, the VAS, the STAI, and the VASPS were applied.

2.10. Data analysis

Kolmogorov-Smirnov test was used for normality distribution besides descriptive statistical methods including percent, mean, standard deviation and median (25^{th} -75^{th} percentile). For comparison of non-normally distributed variables, Mann-Whitney U test, Kruskal Wallis variance analysis, Friedman test, Wilcoxon paired samples test and chi-square test were used. A p level of <0.05 was accepted as statistically significant.

2.11. Ethical considerations

Approval for the study was granted by the X University Faculty of Medicine Ethics Committee (date: February 2, 2016, decision no:171). The study was conducted in compliance with the ethical standards specified in the Helsinki Declaration.

3. Results

In this study, it was identified that 91.6% of patients in the test group were male, 40.0% of patients were between 59 to 70 years old, 91.6% of the patients were married, 91.4% of patients were elementary school graduates, 45.8% of patients lived in the city center, 60.0% of the patients were retired, and 88.6% of the patients had coronary artery disease. In the control group, 68.6% of patients were male, 42.8% of patients were between 59 to 70 years old, 100% of the patients were married, 91.4% of the patients were elementary school graduates, 54.4% of patients lived in the city center, 65.8% were retired, and 80.0% of patients had coronary artery disease. A statistically significant difference was not detected between test and control groups with regard to descriptive statistics (p>0.05). Test and control groups were similar (Table 1).

In patients of both the test group (before and after foot reflexology intervention) and the control group, it was observed that a statistically significant difference was measured in the VAS mean scores of the second, third, and fourth post-operative days (p<0.001). Also, in patients in both the test and control groups, a statistically significant difference was measured in the VAS mean scores of the second (p=0.002), the third (p=0.001), and the fourth days (p=0.001) post-operative (Table 2).

Table 1. Socio-demographic features of the patients in test and control groups

Soci-demographic features	Test Group n (35) %		Control Group n (35) %		P
Age Group					
27-58	9	25.6	11	31.4	
59-70	14	40	15	42.8	0.540*
71 and older	12	34.4	9	25.8	
Gender					
Female	3	8.4	11	31.4	0.536**
Male	32	91.6	24	68.6	
Marital status					
Married	32	91.6	35	100	0.309**
Single	3	3	0		
Education level					
Elementary school	32	91.4	32	91.4	
High school	2	5.8	2	5.8	0.337*
University	1	2.8	1	2.8	
Residency					
City	16	45.8	19	54.4	
Town	8	22.2	11	31.4	0.159*
Village	11	31.4	5	14.2	
Job					
Self-employed	3	8.6	3	8.4	
Retired	21	60	23	65.8	0.169*
Employed	7	20	9	25.8	
Unemployed	4	11.4			
Diagnosis					
CAD[a]	31	88.6	28	80	
MI[b]	1	2.8	5	14.2	0.271*
AD[c]	3	8.6	2	5.8	

[a]CAD: Coronary artery disease; [b]MY: Mitral Insufficiency; [c]AD: Aort Dissection; *Kruskal Wallis; **Mann-Whitney U test

Table 2. Second, third and fourth post-operative days for patients in the test and control groups comparison of daily mean scores of the visual analog scale (VAS) (n=70)

	VAS * Mean scores		
Groups	**Days**	**Median (min-max)**	**P**
Test group	**2nd day**		
	Pre-intervention	8.0 (3-10)	***p*<0.001** **
	Post-intervention	5.0 (1-8)	
	3rd day		
	Pre-intervention	6.0 (2-8)	***p*<0.001** **
	Post-intervention	3.0 (1-6)	
	4th day		
	Pre-intervention	3.0 (1-8)	***p*<0.001** **
	Post-intervention	1.0 (0-6)	
Control group	**2nd day**	6.0 (0-10)	
	3rd day	5.0 (0-8)	***p*<0.001** **
	4th day	3.0 (0-7)	
Test and control groups	**2nd day**		***p*=0.002** **
	3rd day		***p*=0.001** **
	4th day		***p*=0.001** **

*VAS: Visual analog scale; **Mann-Whitney U test

A statistically significant difference was detected between test and control groups with regard to Trait Anxiety Mean Score (TAMS) (p=0.028) and State Anxiety Score Means (SAMS) (p=0.001) scores on post-operative day 2, the scores of test group were found to be lower. While a statistically significant difference was not detected between groups with regard to TAMS scores (p=0.630), a significant difference was found in SAMS scores, they were lower in test group (p=0.003). A statistically significant difference was found between TAMS scores on days 2 and 4 following foot reflexology in test group (p=0.000). In control group, there was not a statistically significant difference between TAMS scores on post-operative days 2 and 4 (p=0.084) (Table 3).

Table 3. Comparison of test and control groups patients' mean scores on the state/trait anxiety scale on the second- and fourth-days post-operative (n=70)

	2nd day post-operative		4th day post-operative	
	Test group	Control group	Test group	Control group
	Median (min-max	Median (min-max)	Median (min-max)	Median (min-max)
SAMS*	38.0 (32-52)	41.0 (33-48)	42.0 (36-52)	42.0 (34-52)
P value	***p*=0.028** ***		***p*=0.630** ***	
TAMS**	43.0 (33-49)	47.0 (39-58)	44.0 (34-49)	47.0 (40-58)
P value	***p*=0.001** ***		***p*=0.003** ***	

*SAMS: State Anxiety Mean Score; **TAMS: Trait Anxiety Mean Score; ***Mann-Whitney U test

A statistically significant difference was found between VASPS scores before and after foot reflexology on days 2 and 4 in test group (p=0.004). In control group, there was not a statistically significant difference between VASPS scores on post-operative days 2 and 4 (p=0.163). A statistically significant difference was not found between VASPS scores on post-operative days 2 (p=0.214) and 4 (p=0.479) in test and control groups (p=0.214) (Table 4).

Table 4. Comparison of the mean scores of the visual analog scale of patient satisfaction (vasps) for patients in the test and control groups on the second and fourth post-operative days (n=70)

VASPS* mean scores			
Patient groups	**Days**	**Median (min-max)**	**P**
Test group (*n*=35)	2. day 4. day	9.0 (5-10) 9.1 (5-10)	**0.004****
Control group (*n*=35)	2. day 4. day	9.0 (5-10) 10.0 (6-10)	0.163**
Test and control groups (*n*=70)	2. day 4. day	*	0.214** 0.479*

*VASPS: Visual Analog Scale Patient Satisfaction; **Mann-Whitney U test

Although not included in the table, a statistically significant difference was not found between VAS scores on post-operative days 2 and 4 before and after foot reflexology with regard to age groups, gender and education level in test and control groups (p>0.05). In test group, on post-operative days 2 and 4, a statistically significant difference was found between VAS scores with regard to marital status, VAS scores were higher among the married (p<0.05).

In test and control groups, on days 2 and 4 post-operatively, a statistically significant difference was not detected between state-trait anxiety scores before and after foot reflexology with regard to age, gender and marital status (p>0.05). In test group, before foot reflexology application on post-operative days 2 and 4, a statistically significant difference was not found between state-trait anxiety scores with regard to education status (p>0.05). In control group, the difference in state-trait anxiety scores were found to be statistically significant with regard to education status on post-operative day 4, scores were higher in graduates of elementary school (p<0.05).

The difference between VASPS scores with regard to age, gender, marital status and education status was not statistically significant on days 2 and 4 post-operatively in test and control groups (p>0.05).

4. Discussion

Gender plays a critical role as one of the risk factors of coronary artery disease. It has been acknowledged, that compared to women of the same age, males aged forty and older are at greater risk of developing coronary artery disease. In our study, almost the entire list of patients was male. Echoing our findings, studies of patients with an open-heart surgery history conducted by Kadda et al. (12) (74.0%), Gligor et al. (13) (66.6%), Momeni et al. (14) (61.5%), and Hosseini et al. (6) (57.8%) indicated that the majority of patients were men. Hence, our study is in line with relevant literature.

Coronary artery disease is the most pervasive cardiovascular system disease. As humans live longer, pathologic changes in coronary arteries with the potential to develop coronary artery disease rise correspondingly (13). It was seen that nearly half of the patients in this study were aged from 59 to 70. In our research, the mean age was in line with other studies of patients who had undergone open-heart surgery, particularly those of Babajani et al., (15), Vardanjani et al., (16), Yüksel et al., (17) and Motomatsu et al. (18). In the literature, it has been reported that in males age 45 and above and females age 55 and above have increased risk factors for developing coronary artery disease. Our findings are also in line with these findings in the literature.

Almost all patients in our study were married. In line with our study, Vardanjani et al. (16) in their studies on patients who had undergone open-heart surgery indicated that nearly all of the patients were married. This finding leads to the assumption that since patients in our study were from a culture with a traditional family structure, the number of married patients was higher.

In this study, one fifth of all patients graduated only from elementary school. Unlike in our study, Vardanjani et al. (16), Babajani et al. (15) and Hosseni et al. (6) concluded that patients who had only graduated from elementary school were fewer in number. Since patients in our study were only

elementary school graduates, it is safe to assume that during school age, they lived in villages and had to work at rural chores.

In our study, it was posited that four in five of all participants had coronary artery disease. Findings in the literature echo our findings (4, 14). The literature review indicates that coronary artery disease is the most pervasive cardiovascular system disease. Our findings are in line with relevant literature. It was detected that four in five patients had undergone coronary artery bypass graft surgery within the scope of open-heart surgery. Similarly, in studies of patients who experienced open-heart surgery reported that more than half of all patients had undergone coronary artery bypass graft surgery (17, 18). Unlike our research, in a study among patients who had open-heart surgery, Kadda et al. (12) indicated that more than half of all patients had undergone cardiac valve surgery. These results show that in the surgical treatment of cardiac diseases, both methods are selected for different patient groups.

Another finding of this research was that patients of test group who were administered foot reflexology got lower VAS mean scores on the second, third, and fourth days, and there was a statistically significant difference in the VAS mean scores before and after the intervention. Likewise, it was seen that the difference in the VAS mean scores among control group patients was statistically significant on the second, third-, and fourth-days post-operative. On the other hand, it was found that the VAS mean scores of test group patients were lower than the scores of control group patients. This finding indicates that after foot reflexology intervention on the fourth day, the pain levels of the test group patients were lower than in patients in the control group. In line with this research, in studies conducted by Candy et al. (19), and Babajani et al. (15) on patients having undergone open-heart surgery concluded that reflexology intervention significantly lowered experienced pain levels. Similarly, in studies conducted among different patient groups, it was indicated that foot reflexology intervention substantially lowered pain level (19, 20).

The high risk of complication and a long recovery period are potential anxiety triggers for patients who have undergone open-heart surgery. In patients in both the test and control groups, there was a rise in both state anxiety mean scores and trait anxiety mean scores on the fourth day compared to the second day while it was observed that trait anxiety mean scores for the test group were below the scores of the control group. It was also observed that the state anxiety mean scores of both test and control group patients were identical. In their studies of patients having undergone open-heart surgery, Navaee et al. (4) and Ahmadi et al. (21), concluded that reflexology intervention lowered anxiety levels. In relation to this subject, identical findings were obtained in studies conducted among various groups (20, 22, 23).

The high anxiety levels of the patients in our study signaled that there was need for psychological assistance in tandem with provided medical care.

It was seen in our study that the VASPS mean scores for the test and control group patients were analogous, and their satisfaction levels were high. In parallel with our research, Brent et al. and Lesley et al. in their studies analyzing patients who had undergone open-heart surgery revealed that massage therapy elevated patient satisfaction (24, 25). In the literature, we have found no research on the connection between foot reflexology intervention and patient satisfaction. Thus, our study needs to be contrasted with the findings of studies investigating different types of massage.

Among the patients in the test group having received foot reflexology, it was reported that on the second, third, and fourth days the VAS mean scores lowered with respect to age, gender, marital status, and education level; and the difference between marital status and the VAS mean scores was statistically significant. However, it was also reported that the VAS mean scores of the test group was lower than the scores of the control group. Differing from our study, Özdemir et al. (26) indicated that female patients' pain levels were lower than those of male patients, and yet there was not any statistically significant difference between age groups and pain levels.

Prior to an operation, a patient's anxiety level can be affected by his/her personal traits, age, gender, education level, and the type of operation to be undergone. For the patients in our study, in both test and control groups, there was no statistically significant difference between the mean scores of state anxiety and trait anxiety on the second and fourth days with respect to gender and marital status while, in the patients in the control group, there was a statistically significant difference in the mean scores of trait anxiety. Among patients in the test and control groups, the mean scores of state anxiety increased on the second, third, and fourth days with respect to gender, marital status, and education level; but it was also observed that the mean scores of trait anxiety for patients in the test group were below the scores of the control group. Echoing our findings, Vardanjani's (16) study indicated that there was no statistically significant difference with respect to age, profession, education level, and degree of measured anxiety (16).

In their study investigating the connection between patients' age group and anxiety level, Fekrat et al. (27) observed that younger patients were even more anxious than older ones (27). In the literature, observed differences in mean scores between age groups and the mean scores for levels of anxiety can be attributed to the existence of' family, friends, and other assistive people around the patients and the presence of post-operative complications.

In some studies, it was reported that an increase in education level would elevate the anxiety level while some studies showed that education level had no effect on anxiety level. As in our study, when the mean scores of state anxiety and trait anxiety were compared with respect to education level, it was revealed that, on the fourth post-operative day, the mean scores of trait anxiety for patients in the control group who had only graduated from elementary school were statistically higher than the mean scores of high school and higher educated patients. Kyohara et al. (28) indicated that patients' education level had no effect on their anxiety level. Particularly related to patients having undergone open-heart surgery, being in an older age group, having a deficit of information, not having access to information, having communication with the medical care team, and the presence of risk factors during surgery could be interconnected with the educational level. In light of these factors, it is suggested that previous studies manifested a variety of findings on this particular issue.

In our study, with respect to age, gender, and marital status, the VASPS mean scores of patients in both the test and control groups displayed no statistically significant difference on the second and fourth days. On the second and fourth days, the VASPS mean scores were analogous, and satisfaction levels were high with respect to gender, marital status, and education level. The findings in the literature indicate that an increase in age corresponds to elevated patient satisfaction. The finding of higher satisfaction levels among elderly patients could be attributed to the more tolerant and compassionate character of elderly individuals. Kyohara et al. (28) identified no statistically significant difference between the satisfaction levels of female and male patients. The findings of our study suggest that, irrespective of being in the control or the test group, any interaction between the healthcare team and patients for any reason could increase patient satisfaction level, and, in particular, the white coat of physicians could create a placebo effect in patients.

The findings of our research indicated that patients in the test group having received foot reflexology had, compared to the patients in the control group, had a lower level of experienced pain. Also, while anxiety levels increased in both groups, it was still lower in test group. As for satisfaction level, scores were identical and high in each group. Reflexology is one of the noninvasive and easily applicable complementary therapies in which nurses can become directly involved. Foot reflexology intervention particularly applied to patients who had undergone open-heart surgery would lower the experienced pain and anxiety of patients and speed their recovery process, thereby shortening the length of hospitalization. Taking into account the positive effects of reflexology intervention on patients, it is suggested that nurses be encouraged to perform this intervention on patients with a history of open-heart surgery during the post-operative period.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Prognostic nutritional index predicts perioperative adverse events in patients undergoing hemiarthroplasty after a hip fracture

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Abstract

The relation of the prognostic nutritional index (PNI) with perioperative adverse events (PE) has never been described in hip fracture surgery patients. Therefore, this study aimed to evaluate the impact of preoperative PNI on the outcome of patients undergoing hemiarthroplasty after a hip fracture. A total of 154 adult patients aged ≥ 65 years undergoing hemiarthroplasty after a hip fracture were included in this retrospective study. The outcomes of interest were the length of stay in hospital and PE during hospitalization, defined as death, surgical site infection, major bleeding, cardiopulmonary complications, acute renal failure, pneumonia, cerebrovascular accidents, and sepsis. PNI was calculated from the following formula: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm3). Patients' information, including demographic data, routine preoperative laboratory tests, and PNI, was collected to assess the association between these factors and the PE. Perioperative adverse events occurred in 21 (13.6%) of the patients. Older patients and those with more comorbid conditions such as heart failure, coronary artery disease, diabetes mellitus, cerebrovascular diseases, and chronic obstructive pulmonary diseases were tended to have a higher rate of PE. Patients with PE had lower PNI (45.2±4.2 vs. 51.6±5.4; $p < 0.001$) on admission. Multivariate analysis showed that age (OR: 2.23, 95% CI 1.15-4.45, p=0.042), presence of diabetes (OR: 2.34; 95% CI: 1.74–6.89; p =0.005) and PNI < 47.2 (OR 2.54, 95% CI 1.32-5.72, p = 0.004) were significant and independent predictors of PE. This study is the first to demonstrate that the lower preoperative PNI is associated with PE in patients undergoing hip fracture surgery.

Keywords: prognostic nutritional index, hip fracture, surgery, prognosis, complication

1. Introduction

Hip fracture surgery is not only associated with a high rate of perioperative adverse events (PE), morbidity and mortality but also associated with increased costs (1). The combination of improvements in surgical techniques, extending surgical indications and an aging society with increasing medical comorbidities makes preoperative risk assessment increasingly important to guide patients in the preoperative decision for hip fracture surgery (2, 3). Previous studies have reported that prolonged operative time, older age, duration between injury and surgery, timing of rehabilitation, surgical technique, and presence of significant comorbidities are associated with a higher incidence of complications in hip fracture surgery, such as surgical site infection, delayed wound healing, and cardiovascular adverse events (4-9). These studies showed that the preoperative health condition is an extremely important consideration when deciding whether it is safe to proceed with hip fracture surgery especially in elderly patients.

Nutritional status is also an important preoperative risk factor for PE in patients undergoing surgery for hip fracture (10, 11). While several tools for assessing nutritional status have been evaluated in patients undergoing various surgeries, most of these are difficult to use in daily clinical practice due to their complexity (12). In contrast, the prognostic nutritional index (PNI) can be easily calculated with parameters which are routinely evaluated in laboratory tests during preoperative diagnostic workup and are easy to repeat (13). The PNI, which is based on serum albumin concentration and total peripheral lymphocyte count, was originally proposed to assess the perioperative immunological status and surgical risk in patients undergoing gastrointestinal surgery (14). In recent years, the PNI has been shown to be a prognostic marker in patients with various solid tumors (15, 16), in patients with acute heart failure (17), pulmonary embolism (18) and in patients undergoing cancer surgery (19). However, there is only one study in the literature evaluating the significance of C-reactive protein/PNI ratio for predicting outcomes in hip fracture surgery which revealed that the PNI was not an independent prognostic factor for adverse events in these patients (20). Therefore, the aim of our study was to

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assess the value of preoperative PNI as a predictor of PE in patients undergoing hip fracture surgery.

2. Materials and Methods

2.1. Study design and selection of patients

This is a retrospective and observational study which was approved by the regional ethics committee. The medical records of all patients, aged ≥65 years undergoing hemiarthroplasty after a hip fracture from July 2017 to May 2019 in Muğla Sıtkı Koçman University Hospital were retrospectively analyzed. Patient demographic characteristics, comorbid conditions, and medical history were obtained for all patients from patient medical records. Complete blood count and routine biochemical analyses were measured at admission and before the surgery. Exclusion criteria were as follows: patients with incomplete records, patients with chronic, or infectious diseases or taking immunosuppressive drugs which may influence the status of albumin and lymphocyte counts, patients with high energy trauma, patients with previous same side hip surgery and patients with pathological fracture due to malignancy or metabolic disease.

PNI was calculated using the following formula: 10 × serum albumin value (g/dl) + 0.005 × total lymphocyte count in the peripheral blood (per mm^3).

2.2. Study endpoints

The outcomes of the study were length of stay and PE during hospitalization, which was included death, deep wound infection, major bleeding requiring transfusion, cardiopulmonary complications, thromboembolic events, pulmonary embolism, acute renal failure, pneumonia, cerebrovascular accidents, sepsis.

2.3. Statistical analysis

Statistical Package for Social Sciences (SPSS) for Windows-version 20.0 (SPSS, Chicago, IL, USA) software was used for statistical analyses. The continuous variables are expressed as means (minimum-maximum values), and we compared these variables between patients with and without PE using a 2-tailed Student *t* test. Nonparametric tests (Mann–Whitney *U* test) were performed when appropriate. Fisher exact and χ^2 tests were used to compare categorical variables. Multivariate logistic regression analyses were applied to determine crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the relationship between preoperative variables including PNI and PE. For all analyses, P <0.05 was considered statistically significant.

3. Results

A total of 180 patients aged ≥65 years underwent hemiarthroplasty in our institution during the study period. Twelve patients were excluded due to incomplete data, 6 patients were excluded due to have a chronic, or infectious disease or due to were taking immunosuppressive drugs, 3 patients were excluded due to pathological fracture, and 5 patients were excluded due to high energy trauma mechanism**.** After implementation of exclusion criteria, the final study population consisted of 154 patients (mean age 71.2±9.5 years, and 48% male). Hypertension was the most frequent comorbidity (51.9 %), followed by coronary artery disease (26 %), and diabetes mellitus (20.8 %). Median length of stay was 9 days.

3.1. Perioperative adverse events

PE occurred in 21 (13.6%) patients. Comparison of baseline characteristics, laboratory parameters, length of hospital stay and PNI in patients with and without PE are shown in Table 1. Patients who had PE were older (76.1 ± 7.6 vs 69.5±6.1 years; p< 0.001) and were more likely to have underlying comorbid diseases such as coronary artery disease (52.4 vs 21.8%; p= 0.003), diabetes mellitus (47.6% vs 16.5%; p<0.001), heart failure (19% vs 5.3%; p=0.045), cerebrovascular disease (23.8% vs 8.3%; p=0.046) and chronic obstructive pulmonary disease (38.1% vs 9.8%; p<0.001).

Table 1. Baseline characteristics and length of stay of patients with and without perioperative adverse events undergoing hip fracture surgery

	No Adverse Event (n=133)	Adverse Event (n=21)	P Value
Male	63 (47.4)	11 (52.4)	0.526
Age (years)	69.6 ±6.1	76.1 ± 7.6	<0.001
Systolic blood pressure (mmHg)	125.4 ± 15.3	126.4 ± 13.4	0.785
Diastolic blood pressure (mmHg)	78.1 ± 8.8	78.1 ± 8.3	0.423
Medical History			
Atrial fibrillation	6 (4.5)	3 (14.3)	0.107
Smoking	31 (23.3)	4 (19)	0.785
Diabetes mellitus	22 (16.5)	10 (47.6)	<0.001
Hypertension	66 (49.6)	14 (66.7)	0.146
Coronary artery disease	29 (21.8)	11 (52.4)	0.003
Cerebrovascular disease	11 (8.3)	5 (23.8)	0.046
Heart failure	7 (5.3)	4 (19.0)	0.045
Chronic obstructive pulmonary disease	13 (9.8)	8 (38.1)	<0.001
Laboratory Results			
White blood count (×10³cells/mL)	8.7 ± 3.5	8.40 ± 3.2	0.442
Hemoglobin (g/dL)	12.2 ± 1.9	12.03 ± 1.6	0.228
Albumin (g/dL)	3.91 ± 0.57	3.52 ± 0.33	0.075
Creatinine (mg/dL), median (IQR)	1.0 (0.7-1)	1.0 (0.9-1.2)	0.324
Glucose (mg/dL)	106.8 ± 39.5	111.1 ± 47.3	0.153
Length of stay (median, days)	5.0 (4.0-9.0)	15.0 (10.0-25.0)	<0.001
Prognostic nutritional index	51.6±5.4	45.2±4.2	<0.001

Values are given as mean ± SD or number (%) unless otherwise indicateed

Although the difference did not reach statistical significance, patients who had PE had lower preoperative albumin levels compared to patients without PE (3.52 ± 0.33 vs 3.91 ± 0.57 g/dL respectively; p= 0.075). Patients with PE had lower preoperative PNI levels than those with uncomplicated in-hospital course (45.2 (41-49.4) vs 51.6 (46.2-57); p<0.001). Patients with perioperative complications had longer length of stay (15 vs 5 days, median, respectively; p < 0.001) compared with uncomplicated patients.

3.2. Predictors of perioperative adverse events

Univariate analysis showed that the following variables were associated with PE: heart failure, coronary artery disease, diabetes mellitus, cerebrovascular diseases, chronic obstructive pulmonary diseases, preoperative PNI levels. The parameters that proved to be significant on the univariate analysis were subsequently tested with the multivariate model (Table 2). Multivariate analysis showed that only age (OR: 2.23, 95% CI 1.15-4.45, p=0.042), presence of diabetes (OR: 2.34; 95% CI: 1.74–6.89; p =0.005) and PNI < 47.2 (OR 2.54, 95% CI 1.32-5.72, p = 0.004) were significant and independent predictors of PE.

Table 2. Multivariate analysis for the prediction of perioperative adverse events

	OR	95% CI	P
Age (per 1 y)	2.231	1.152-4.451	0.042
Diabetes mellitus (presence vs absent)	2.341	0.865-4.476	0.005
Coronary artery disease (presence vs absent)	0.788	0.410-0.936	0.236
Prognostic nutritional index < 47.2	2.542	1.321-5.721	0.004
COPD (presence vs absent)	1.125	0.955-3-214	0.065

4. Discussion

Our study investigated the incidence of PE after hip fracture surgery and identified risk factors for these complications. In this single-center, retrospective, and observational study of 154 patients, over the age of 65, the incidence of PE was 13.6%. The results of this study showed that older age, presence of diabetes and lower preoperative PNI were independent prognostic factors for PE. To the best of our knowledge, this is the first study to demonstrate an association between preoperative PNI and PE in hip fracture surgery patients.

Although several clinical and laboratory variables have been established as the predictors of perioperative complications in patients undergoing hip surgery, preoperative nutritional status have not been comprehensively evaluated in these studies (21). Aldebeyan and colleagues analyzed the data of 10,117 patients with hip fractures and showed that hypoalbuminaemia was an independent predictor of postoperative complications and patients with hypoalbuminaemia had a longer hospital length of stay. In a recently published retrospective and observational cohort study, Wilson et al. examined the relationship of nutrition parameters with the modified frailty index and postoperative complications in hip fracture patients (22). Of the 377 patients, 2.6% and 17.5% of patients were malnourished as defined by total lymphocyte count of <1500 cells/ mm^3 and albumin of <3.5 g/dL, respectively. The authors showed that both total lymphocyte count and albumin weakly correlated with frailty but combining malnutrition and frailty revealed an increased predictive synergy for postoperative complications (22).

Malnutrition can be identified using a variety of anthropomorphic measurements, laboratory values, and screening tools. Although, malnutrition is most identified using serum albumin levels, PNI is not only a marker of nutritional status but also reflective immunologic status. To date, several studies showed that the prediction of surgical risk is possible by evaluating preoperative immunonutritional status with PNI in various types of surgeries such as gastrointestinal surgery (23), neurosurgery (24) and lung surgery (25).

However, the prognostic impact of PNI in patients undergoing hip surgery is remained unexplored. In a recent study, Ren and colleagues, prospectively evaluated the significance of C-reactive protein/PNI ratio for predicting the prognosis in eighty patients undergoing hip fracture surgery (20). The results of this study showed that PNI was not an independent prognostic factor but low C-reactive protein /PNI ratio was significantly associated with low one-year mortality rate after hip fracture surgery (20). Nevertheless, our findings showed that preoperative PNI may predict perioperative adverse events in patients undergoing surgery for hip fracture.

This study has several limitations. First, this study included only patients aged ≥65 years undergoing hemiarthroplasty after a hip fracture. Our hospital is a referral hospital, to which patients are referred from peripheral hospitals, which may affect our results. Therefore, caution should be taken in extrapolating these results to other surgical populations. Another important limitation of the current study is the fact that it was a retrospective analysis. Due to its retrospective nature, the study is prone to various forms of bias, such as selection bias and recall bias.

Preoperative PNI measurement can help identify patients at high risk for of PE after hip fracture surgery. The estimation of the PNI is inexpensive and easily available from laboratory data in daily clinical practice. Therefore, we suggest that the PNI should be calculated routinely before surgery, and it could be a useful indicator for pretreatment nutritional management in adult patients undergoing hip fracture surgery.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Nailfold capillaroscopy findings for patients receiving hemodialysis treatment and patients with renal transplant

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Abstract

Cardiovascular diseases are the most common cause of death in hemodialysis patients. Early diagnosis of cardiovascular diseases has vital importance. The aim of our study is to use the NFC method to determine the importance of microcirculatory structure changes for early detection of increased cardiovascular disease risk in hemodialysis patients. The research was performed from april/2017 to july/2017. The study included 15 patients receiving hemodialysis treatment and 15 renal transplant patients followed by the nephrology department and 15 healthy volunteers attending the internal diseases clinic. Every patient were examined by videocapillaroscopy according to procedure and data were recorded. Statistical analyses were evaluated with SPSS 22.0. There was a significant difference in laboratory values between hemodialysis patients and both groups except uric acid ($p<0.05$). There was not a significant difference between the groups in terms of capillary density, capillary hemorrhage rate, tortuous capillary incidence, and giant capillary incidence ($p>0.05$). In conclusion, investigation of nailfold capillaroscopy in hemodialysis and renal transplant patients did not identify a significant disruption in microcirculation compared to the healthy control group. There is a need for nailfold capillaroscopy studies of hemodialysis and renal transplant patients with higher numbers of patients.

Keywords: vasculitis, microvascular changes, nailfold capillaroscopy, renal transplantation

1. Introduction

Hemodialysis (HD) and renal transplantation are frequently applied renal replacement treatment methods for treatment of end-stage renal disease (ESRD). Cardiovascular diseases are the most common cause of death in hemodialysis patients (1). Early diagnosis of cardiovascular diseases has vital importance.

In situations like diabetes mellitus (DM), hypertension and renal failure, initiation of the pathologic cascade involves changes to the microvascular structure and functions of the end organ (2). Functional and structural abnormalities at the microcirculation level may display easy transition to events occurring in larger arteries and coronary arteries (3). These types of changes were identified to correlate with development of cardiovascular disease (4). Measurement of capillary rarefaction, defined as reductions in the numbers of capillary veins in a tissue, allows the possibility for early assessment of microvascular functions and tissue perfusion in a variety of disease situations including chronic kidney disease (CKD) (5). Techniques developed to measure capillary rarefaction in skin were shown to accurately reflect central organ pathology like coronary artery disease and vascular calcification in dialysis patients (6,7). Very little is known about capillary rarefaction in hemodialysis and renal transplant patients and there is no study to date in adults.

Nailfold capillaroscopy (NFC) is an easily accessible, easily applied, inexpensive and non-invasive technique showing skin microcirculation (8). NFC is used to assist in diagnosis of rheumatic diseases like systemic sclerosis, systemic lupus erythematous and rheumatoid arthritis and provides an idea about microcirculation by investigating the vein bed (9).

The aim of our study is to use the NFC method to determine the importance of microcirculatory structure changes for early detection of increased cardiovascular disease risk in hemodialysis patients. At the same time, the aim was to investigate the effect of metabolic disorder, expected to ameliorate after transplant, on microvascular structure in renal transplant patients.

2. Materials and Methods

2.1. Patients

The research was performed from April/2017 to July/2017. The study included 15 patients (group A) receiving hemodialysis treatment and 15 renal transplant patients (group B) followed by the nephrology department. The control group (group C) included 15 individuals comprising

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healthy volunteers attending the internal diseases clinic for any reason. Patients were chosen from young age groups. The aim was to minimize venous abnormalities and structural diversity that may develop with age.

Inclusion in the research was based on volunteering. After patients who met the inclusion criteria were informed about the study, they were invited to participate and those who accepted were included in the study. All cases provided signed informed consent forms.

2.2. Inclusion and exclusion criteria

Inclusion criteria were for group A; patients from 18-65 years, patients receiving hemodialysis treatment, for group B; patients from 18-65 years, patients with renal transplant, for group C; individuals with similar age and sex features to Group A and Group B age from 18-65 years. Exclusion criteria (for groups A, B and C) were; damage to the fingers to be examined in recent times, chemicals which may affect the quality of investigation of the fingers, situations with probability of causing structural changes in microcirculation like DM, hypercholesterolemia, hypertension, rheumatic diseases, and smoking, cardiovascular disease.

2.3. Parameters examined

Individuals included in the study had physical examination and blood pressure measurements performed, with routine blood tests requested (hemogram, albumin, calcium, phosphorus, parathormone, ferritin, transferrin saturation, bicarbonate level, uric acid, blood urea nitrogen and creatinine). Nailfold capillaroscopy was performed by experienced clinician team. Investigations were performed with a VideoCap 3.0 videocapillaroscope.

Necessary permission for the study was obtained from Ankara Numune Education and Research Hospital Clinical Research Ethics Committee.

2.4. Statistical analysis

Normal distribution of continuous variables was examined with the Shapiro Wilk test. Comparisons of the means in three independent groups used the one-way analysis of variance (ANOVA) test, with post hoc Tukey test applied to significant results. Analysis of categoric variables used the chi-square test. For all analyses, statistical significance value was taken as 0.05.

3. Results

3.1. Demographic characteristics

The ages of patients included in Group A were from 18 to 57 years (39.07±11.14; mean ± SD) with 9 males and 6 females. The ages of patients included in Group B were from 20 to 58 years (36.87±11.34) with 7 males and 8 females. The ages of patients included in Group C were from 26 to 61 years (33.27±11.27) with 8 males and 7 females. There was no statistically significant difference between the mean ages in the patient group and control group ($p>0.05$). There was no statistically significant relationship between the groups for gender; the distribution was homogeneous ($p=0.765$) (Table 1).

3.2. Laboratory parameters

There was a significant difference between the groups in terms of mean hemoglobin, creatinine, bicarbonate, albumin, calcium, phosphorus, ferritin, transferrin saturation and parathyroid hormone levels ($p<0.05$). Accordingly, the differences were between the control-hemodialysis ($p<0.05$) and transplant-hemodialysis ($p<0.05$) groups. There was no significant difference between the groups in terms of mean uric acid ($p>0.05$) (Table 2).

3.3. Nailfold video capillaroscopy findings

There was not a significant difference between the groups in terms of capillary density, capillary hemorrhage rate, tortuous capillary incidence, and giant capillary incidence ($p>0.05$) (Table 3).

Table 1. Demographic data

	HD patients N=15	Patients with renal transplantation N=15	Control group N=15	P value
Age (years)	39.07±11.14	36.87±11.34	33.27±11.27	>0.05
Gender: N (%)	Female: 6 (40)	Female: 8 (53.3)	Female: 7 (46.7)	>0.05

Table 2. Laboratory and metabolic parameters

Parameter	HD patients N=15	Patients with renal transplantation N=15	Control group N=15	P value
Hemoglobin (g/dL)	10.85±0.96	13.79±1.48	14.01±1.17	<0.001
Creatinine (mg/dL)	2.78±0.79	0.83±0.20	0.91±0.16	<0.001
Uric acid (mg/dL)	5.25±0.71	4.89±1.02	5.12±1.51	>0.05
Bicarbonate (mEq/L)	20.34±3.47	23.67±2.08	23.73±1.54	<0.001
Albumin (g/dL)	3.76±0.28	4.28±0.43	4.35±0.48	<0.001
Calcium (mg/dL)	8.76±0.86	9.82±0.69	9.53±0.53	<0.001
Phosphorus (mg/dL)	5.00±1.32	3.26±0.63	3.84±0.75	<0.001
Ferritin (ng/mL)	393.80±305.38	100.73±58.52	96.07±71.74	<0.001
Transferrin saturation (%)	29.80±10.09	38.13±8.62	30.73±9.32	<0.05
Parathyroid hormone (mg/dL)	686.53±457.67	38.53±15.99	49.40±16.07	<0.001

Table 3. Nailfold capillaroscopy findings

	HD patients N=15	Patients with renal transplantation N=15	Control group N=15	P value
Giant capillary, n (%)	3 (20)	2 (13.3)	2 (13.3)	>0.05
Tortuous capillary, n (%)	3 (20)	4 (26.7)	2 (13.3)	>0.05
Reduced capillary density, n (%)	3 (20)	3 (20)	0 (0)	>0.05
Capillary hemorrhage, n (%)	3 (20)	3 (20)	4 (26.7)	>0.05

4. Discussion

Hemodialysis is the most frequently performed renal replacement treatment method. The most frequent cause of death among hemodialysis patients is cardiovascular diseases (10). This situation is accepted because of the association between renal and cardiovascular pathologies.

Early detection of cardiovascular diseases has vital importance. Many studies have found a positive correlation between skin microcirculation disorders and other vascular diseases and an increased risk of development of heart disease was identified with disrupted microcirculation (11). Many studies were performed to early assess for cardiovascular system diseases which are not yet clinically significant with identification of changes in microcirculatory structure using the nailfold videocapillaroscopy method (12, 13).

A study of the pediatric age group researched the capillary density, biochemical markers, cardiovascular risk factors and capillary function assessment tests in 19 end-stage hemodialysis patients and 20 healthy controls. Capillary density (capillary/mm^2) of hemodialysis patients was identified to be significantly low compared to the control group. There was an inverse correlation between serum calcium and parathormone levels with capillary density with no correlation found for cardiac risk determinants and serum phosphorus levels (14).

Another study investigated the microcirculatory changes in the upper extremities of hemodialysis patients with arteriovenous fistula. The patient group comprising 43 patients was assessed without a control group and no difference was observed in terms of morphological microcirculation parameters between the shunt arm and contralateral side (13). Due to limitations of the research, the arteriovenous fistula route, most frequently used for the dialysis entry route in hemodialysis patients, was shown not to disrupt capillary morphologic structure and this is important in terms of supporting the measurements in our study from this aspect.

A study compared 17 predialysis patients, 35 ESRD patients (20 HD and 15 PD patients) with 19 healthy controls and found capillary density in predialysis patients and ESRD patients were lower compared to the control group. They identified that the high serum phosphorus and bicarbonate levels associated with advanced CKD caused structural and functional capillary density disruption (12).

In our study, there was no significant difference between the groups in terms of capillary parameters. When both groups are compared with the hemodialysis group, apart from uric acid, all laboratory findings were significantly different. This situation complies with the literature. Our study has limited case numbers in terms of more advanced assessments.

There are a few studies performing videocapillaroscopy assessment of non-rheumatologic cases. A study of migraine patients included 50 participants as a healthy control group. Among these, 26% were identified to have tortuous capillary and 22% were identified to have giant capillary (15). In our study, in 15 healthy volunteers the incidence of tortuous capillary was 13.3% and the incidence of giant capillary was 13.3%.

Another study assessed 82 healthy individuals and mean value for capillary density was 11/mm^2, with capillary hemorrhage incidence 0%, tortuous capillary incidence 4.9% and giant capillary incidence 0% (16). In our study, the mean capillary density value was 10.5/mm^2, the reduction in capillary density was 0%, capillary hemorrhage rate 26.7%, tortuous capillary incidence 13.3% and giant capillary incidence 13.3%.

In all two studies, the capillary values in the control groups were identified to be different. For this reason, it is clear there is a need to perform studies with higher case numbers about this topic.

One of the secondary results of our study is that when both groups are compared with the hemodialysis patient group, apart from uric acid, all laboratory findings were significantly different. This is important in terms of recording the success of the effect on correctable laboratory values of renal transplantation, a renal replacement treatment with definite effect on mortality, in our case group.

In conclusion, investigation of nailfold capillaroscopy in hemodialysis and renal transplant patients did not identify a significant disruption in microcirculation compared to the healthy control group. There is a need for nailfold capillaroscopy studies of hemodialysis and renal transplant patients with higher numbers of patients.

There was not a significant difference between the groups in terms of capillary density, capillary hemorrhage rate, tortuous capillary incidence, and giant capillary incidence.

In our study, in 15 healthy volunteers the mean capillary density value was 10.5/mm^2, the reduction in capillary density was 0%, capillary hemorrhage rate 26.7%, tortuous capillary incidence 13.3% and giant capillary incidence 13.3%.

There is a need for nailfold capillaroscopy studies of hemodialysis and renal transplant patients with higher numbers of patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Research Article

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To determine safety profile of azithromycin in Covid-19 patients

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Abstract

At the end of the year 2019, a novel virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV or COVID-19) first appeared in the Chinese city of Wuhan and the WHO declared the novel coronavirus disease as a global pandemic on March, 11th 2020. Corona Virus is RNA virus, major virus that affects respiratory system and can result in acute respiratory distress syndrome, so there emerged several management strategies to combat the challenge of the disease. Azithromycin is one of those treatment options. Azithromycin have been used widely and generally considered as safe medication. The design of this study is Cross-Sectional Study. The 80 Covid-19 positive in ICU were given Azithromycin along with other standard treatment, Side effects were divided into mild serious and allergic reactions. These were noted down in pre designed proforma. Data analysis was done in SPSS version 25. 80 patients were studied 38 (46.2%) patients experienced side effects, majority of which were mild in nature, Out of 80 patients Abdominal Pain was 37.5%, diarrhea 22.7% nausea 25%, transaminitis 2.5%, anorexia 26.3%, taste perversion 36.3%, dyspepsia 15%, vomiting 17.5%, headache 6.3% and somnolence 1.3%. Only 1 (1.25%) patients had arrhythmia and 1 (1.25%) had urticaria that was successfully treated. After this study this can be concluded that Azithromycin is safe drug as majority of side effects experienced were mild in nature and it can be safely used to treat Covid-19 positive patients.

Keywords: 2019-nCoV, azithromycin, COVID-19, SARS-CoV-2

1. Introduction

The Wuhan City of China experienced Covid-19 virus upsurge for the first time late in December 2019, became a pandemic, it has been treated as pneumonia with unknown etiology (1, 2). One of the major target of corona virus is pulmonary system of the humans (3). It was named as 2019-nCoV by Chinese experts (4) and Later, it was named by the International Committee on Taxonomy of Virus as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (5). Rapid and accurate detection of COVID-19 is crucial to control outbreaks in the community and in hospitals (6). Current diagnostic tests for coronavirus include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (RRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP) (7). The need of an hour is to find effective therapeutic agents for the treatment of COVID-19 whether inpatient or outpatient as the devastating effects of the coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demands an urgent attempt to combat situation. (8) It has been demonstrated by few studies that hydroxychloroquine sulfate (HCQ) inhibits SARS-CoV-2 in vitro (9) and one of study proves that the combination of HCQ and azithromycin (AZ) inhibits SARS-CoV-2 *in vitro*. (10)

Azithromycin is a macrolide antibiotic it has a structure modified from erythromycin. Like other macrolides, azithromycin has activity against Moraxella catarrhalis and Streptococcus pneumoniae and also against atypical microbes (11). It has been showing activity against Zika and Ebola viruses in vitro and has immunomodulatory action as demonstrated by in vivo activity in the prevention of severe respiratory tract involvement in viral infections (12). Azithromycin works by inhibiting protein synthesis and experimentally reduces viral replication and inflammation possibly because viruses and cytokines are both made of proteins and use cellular ribosomes for protein translation. In addition, inhibiting virus production can reduce viral transmission to others, which is an important additional benefit (13).

The COVID-19 pandemic has resulted in over 144 million confirmed cases and over 3.06 million deaths globally. Corona Virus is RNA virus, major virus that affects respiratory system and can result in acute respiratory distress syndrome, so there emerged several management strategies to combat the challenge of the disease. Azithromycin is one of those treatment options. Azithromycin have been used widely and generally considered as safe medication.

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2. Materials and Methods

In Intensive Care Unit of Allied Hospital Faisalabad, from 1 December 2020 to 31 January 2021. Eighty (80) patients were taken through non probability purposive sampling. Patients were taken according to inclusion a criterion that is Covid-19 PCR patients admitted in ICU, Both genders included, Age range was 18 to 85 years, and all grades of severity of disease were included. The patents who has documented known allergy to macrolides. Females who were pregnant, those with prolonged QT interval documented on Baseline ECG. Patients cardiac issue, were excluded from study. After Ethical Committee approval of the proposal of the study, patient according to inclusion and exclusion criteria were recruited. After taking informed consent, all patients received a standardized clinical examination, all baseline and specific investigations according to their clinical condition and Baseline ECG at day 0 and they were regularly followed up daily during their stay in hospital. All of them given Tab Azithromycin 500mg oral daily, they were observed and asked questions regarding side effects of Azithromycin and side effects were noted down on tenth day.

The side effects has been divided in three major groups, Mild Side Effects, Serious Side effects and Allergic Reactions. All findings and self-reported side effects were noted down in pre designed proforma. Data Analysis was done with SPSS version 25.0 that was used to enter and analyzed the data. Quantitative data like age were presented as means and standard deviation and qualitative data like gender, diarrhea was presented as frequency and percentages.

2.1. Ethical approval

This cross-sectional study was conducted at the Allied hospital (Faisalabad Medical University) Pakistan. This study was approved by the Institutional ethics committee of Allied hospital (Faisalabad Medical University) with approved no. AHF-353-FMU-04/15.

3. Results

Eighty (n=80) patients presented to Covid ICU were studied, all of them were given Azithromycin 500mg daily orally. Their demographic profile is shown in Table 1, there were 56 (80%) male and 24(30%) female patients. Mean Age was 54.9 + 11.28 with Minimum 27 and Maximum 85 years, Out of which 11 (13.7%) were in 18-40 year age group, 46 (57.5%) in 41-60 year age group, 22 (27.5%) in 61-80 years age group and 1 (1.25%) in> 81 year group. All patients were Covid PCR positive 80(100%) and only 4(5%) were smokers. (Table1) Out of 80 patients 11(17.5%) were having mild to moderate Disease, 50(62.5%) patients had sever disease and 16 (20%) were critical. (Table 2) Out of 80 patients 38 (46.2%) suffered from Side effects, of which 36 (45%) out of 80 and 94.7% out of 38 had Mild Side effects, 1(1.25%) out of 80 and 2.6% out of 38 patient had Sever Adverse reaction and 1(1.25%) out of 80 and 2.6% out of 38 patient had Allergic reaction (Table 3a).

Table 1. Demographic profile of patients

Total No. Patients (n)		80
Male		56 (70%)
Female		24 (30%)
Age Group	18-40	11 (13.7%)
	41-60	46 (57.5%)
	61-80	22 (27.5%)
	➢ 81	1 (1.25%)
Covid-19 PCR		80 (100%)
Smokers		4 (5%)

Table 2. Clinical severity

Mild To Moderate Disease	14 (17.5%)
Sever Disease	50 (62.5%)
Critical IIIness	16 (20%)

Table 3 (a). Side effects profile of azithromycin in 80 patinets

Occurrence Of Adverse Events	38 (46.2%) out of 80 patinets
Mild Side Effects	36 (45%) out of 80 and 94.7% out of 38
Sever Adverse Events	1 (1.25%) out of 80 and 2.6% out of 38
Allergic Reaction to Azithromycin	1 (1.25%) out of 80 and 2.6% out of 38

Table 3 (b). Side effect profile of azithromycin

	Mild side effects	
1	Abdominal Pain	30 (37.5%) out 80 and 78.9% out of 38
2	Diarrhea	22 (27.5%) out of 80; 57.8% out of 38
3	Nausea	20(25%) out of 80 and 52.6% out of 38
4	Elevated ALT AST	2 (25%) out of 80 and 5.2% out o0f 38
5	Anorexia	21 (26.3%) out of 80; 55.2% out of 38
6	Taste Perversion	29 (36.3%) out of 80; 76.3% out of 38
7	Dyspepsia	12 (15%) out of 80 and 31.5% out of 38
8	Vomiting	14 (17.5%) out of 80 and 36.8 % out of 38
9	Headache	5 (6.3%) out of 80 and 13.1% out of 38
10	Somnolance	1 (1.3%) out of 80 and 2.6% out of 38
	Serious Adverse Reaction	
11	Arrythmia	1 (1.25%) out of 80 and 2.6 out of 38
12	Hypotension	None
13	QT Prolongation	None
14	Torsade's de Point	None
15	Renal and Hepatic Failure	None
16	Convulsions	None
17	Neutropenia, Leeucopenia and Thrombocytopenia	None
	Allergic Reactions to Azithromycin	
18	Arthralgia	None
19	Edema	None
20	Urticaria	1 (1.25%) out of 80; 2.6% out of 38
21	Angioedema	None

Table 4. Co morbid conditions

1	**Co Morbid Conditions**	**38 (47.5%) out of 80**
2	Diabetes	28 (35%) out of 80 and 73.6% out of 38
3	Hypertension	19 (23.7%) out of 80 and 50% out of 38
4	Ischemic Heart Disease	5 (6.25%) out of 80 and 13.1% out of 38

Amongst Patients having mild side effects 30(37.5%) out of 80 and 78.9% out of 38 had Abdominal Pain. 22(27.5%) out of 80 and 57.8% out of 38had Diarrhea, 20(25%) out of 80 and 52.6% out of 38 had Nausea, 2(2.5%) out of 80 and 5.2% out of 38 had Elevated ALT AST, 21(26.3%) out of 80 and 55.2% out of 38 had Anorexia, 29(36.3%) out of 80 and 76.3% out of 38 experienced Taste perversion 12(15%) out of 80 and 31.5% out of 38 had Dyspepsia.14(17.5%) out of 80 and 36.8 % out of 38 had Vomiting. 5(6.3%) out of 80 and 13.1% out of 38 had Headache. 1(1.3%) out of 80 and 2.6% out of 38 had Somnolence. Only 1(1.25%) out of 80 and 2.6% out of 38 had Arrythmia as serious adverse event and 1(1.25%) out of 80 and 2.6% out of 38 had Urticaria, Amongst Allergic reaction. (Table 3b) Out of 80 patients, 38 (47.5%) had Co Morbid Conditions in the form of Diabetes 28 (35%) out of 80 (73.6% out of 38). Hypertension was present in 19 (23.7%) out of 80 (50% out of 38) and 5(6.25%) out of 80 (13.1% out of 38) had Ischemic Heart Disease (Table 4).

Fig. 1 is bar chart showing frequency of occurrence of side effects was more in Age group 41-60 years that is 25 patients. 2 patients from 18-40 years, 10 from 61-80 years and 1 from> 81 years experienced adverse reaction.

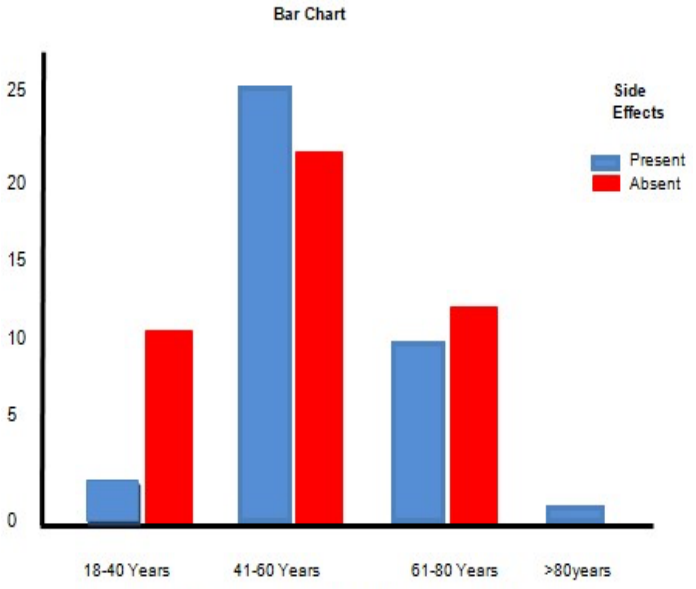

Fig. 1. Showing frequency of side effects according to age groups

4. Discussion

Azithromycin is the prototype of an antimicrobial agent which falls in the class of azalides derived from the macrolides (14). Azithromycin has good tolerance in general, but relatively common adverse effects (1–5 % of patients) include gastrointestinal upset, headache and dizziness (15). Compared to study done by Barbara A. Brown Mean age was 66 years compared to 54.9 in our study. He noted unpropitious event in 32 of 39 patients (84%) while taking Azithromycin compared to 38(46.2%) patients in our study which is quite less. The mostly was GI event (82%) in Barbara's study, GI symptoms included diarrhea (62%) compared to (27.5%) in ours, abdominal pain (41%) compared to (37.5%) in ours, anorexia (33%) compared to (26.3 %) in ours, unusual taste sensation (33%) compared to (36.3%) in ours, nausea (28%) compared to (25%) in ours, vomiting (18%) compared to (17.5%) in ours and abdominal bloating or dyspepsia (~IO%) compared to (15%) in our study (16).

Hence it is demonstrated that generally, Azithromycin remained safe drug option to use in covid positive, ICU admitted patients in Allied hospital (Faisalabad Medical University), majority of side effects were mild and tolerable and resulted in completion of antibiotic course, one patient had episode of arrhythmia, he had multiple co morbid conditions as well, that episode was successfully treated and does not resulted in fatality.

Further research with larger sample size however will definitely enable us to better manage this potentially fatal Novel Corona Virus. We concluded that Azithromycin is a safe drug as demonstrated by results only 38 (46.2%) out of 80 patients experienced side effects, majority of which were mild in nature. Only 1 (1.25%) patients had arrhythmia and one (1.25%) has allergic reaction that was successfully treated.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Effects of curcumin on arginase enzyme activity, ornithine and nitric oxide levels in experimental breast cancer model

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Abstract

Breast cancer accounts for almost 30% of all cancer types, making it the most common type of tumor among women in the world. Arginase, an essential enzyme of the urea cycle, leads to the formation of urea and ornithine from L-arginine using the same substrate as nitric oxide synthase (NOS). Arginase has been reported to be higher in cancer patients and can be used as a useful biomarker. In this study, we aimed to investigate the effects of curcumin, an anticarcinogenic agent, on arginase enzyme activity, ornithine, and nitric oxide (NO) levels in experimental breast cancer model in mice. 43 male Balb/c mice were used, and Erhlich acid tumor model was created in the study. Mice were divided into five groups as healthy control group, curcumin treatment before tumor formation, curcumin treatment after tumor formation and cancer control groups. 100 mg/kg curcumin were given orally. Serum and tissue arginase enzyme activities, NO levels and tissue ornithine levels were determined spectrophotometrically. Increased serum arginase activity decreased with curcumin treatment, but this difference was not statistically significant. On the other hand, decreased NO levels were increased with curcumin treatment. In tumor tissue, arginase activity and ornithine levels decreased significantly with curcumin treatment and tissue NO levels increased significantly with curcumin treatment. In our study, we show that curcumin may have a protective effect on the development of breast cancer by inhibiting arginase enzyme activity and ornithine levels, which are the precursors of polyamines, as well as inducing NO production via NOS. As a promising anticancer agent, the net effects of curcumin in this mechanism should be supported by more advanced studies and new parameters.

Keywords: arginase, breast cancer, curcumin, nitric oxide, ornithine

1. Introduction

Breast cancer is one of the leading causes of cancer and cancer death, which is the most common diagnosis among women who constitute 23% of all cancer cases and 14% of cancer deaths (1). Therefore, it is very important to continue to develop the diagnostic and treatment methods currently used and to identify new prognostic variables (2). Arginase, (L-arginine amidinohydrolase; E.C.3.5.3.1) catalyzes the hydrolysis of L-arginine, urea and ornithine as the key enzyme (3) responsible for nitrogen metabolism (4). Nitric oxide synthase is the enzyme responsible for the catalysis of L-arginine, nitric oxide and L-citrulline oxidation (3).

Arginase enzyme has two isoforms, AI and AII. AI (hepatic arginase) is a cytosolic enzyme and is involved in the liver. AII (extrahepatic arginase) was localized to the mitochondrial matrix. While AI is mainly related to urea synthesis and detoxification of ammonia, AII is thought to be related to biosynthetic functions such as ornithine, proline, glutamate synthesis (5). Arginase can induce nitric oxide synthase (NOS) activity (6) and plays a role in wound healing, immune response, tumor biology and inflammation regulation in conjunction with NOS (7). Serum arginase activity is low in healthy individuals (8). The arginase enzyme is a potent immune inhibitor and is present in the cytoplasm of cancer cells in a much larger amount than in normal cells (9). It was found that serum arginase level was 4 times higher in breast cancer than healthy women in the preoperative period (10). Because of the polyamines, which are very important for cell proliferation, it is possible that high ornithine level due to increased arginase activity will lead to cancer development. Many different studies on serum and tissue arginase levels in various types of cancer indicate that arginase enzyme activity is related to cancer (8, 10). It was also stated that arginase enzyme activity might be an important determinant in breast cancer patients (11). Arginine is catalyzed by NOS and nitric oxide (NO) and citrullin are synthesized. Three types of NOS are mentioned: neuronal (nNOS or NOS1), inducible (iNOS or NOS2) and endothelial (eNOS or NOS3). eNOS and nNOS are thought to be constitutive (cNOS) (11). Numerous studies have shown that NO is associated with both tumor-inducing and tumor

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suppressing functions. Today, the contradiction continues (2). In addition to that, NO and NO metabolites have been shown to have an inhibitory effect on tumor tissue metastasis and cell development (12). Curcumin is a yellow-colored hydrophobic polyphenol extracted from the *Curcuma longa* roots. Experimental studies show that curcumin inhibits breast cancer cell growth through the nuclear factor kappa B (NF-κB) signaling pathway and induces breast cancer apoptosis by regulating the expression of apoptosis-related genes (13, 14). The aim of this study is to investigate the effects of curcumin on serum and cancer tissue arginase enzyme activities, NO levels and tissue ornithine levels for the first time in this study.

2. Materials and Methods

2.1. Animals and tumor cells

This study was performed in the Experimental Animal Breeding and Research Unit of the Trakya University upon approval by the local animal ethics committee. 43 male Balb / c mice with a mean weight of 25-30 grams (mean 27 grams) were used. Ehrlich ascites tumour cells which were derived from a spontaneous murine mammary adenocarcinoma were used obtaining the breast carcinoma (11).

2.2. Experimental design

In the eighth week, five groups were formed. The first group was healthy controls (Cont.). The other groups were breast cancer. To induce the formation of tumours, subcutaneous inoculation of Ehrlich ascites cells into the mice's left footpath was performed. Tumor growth was visible, and mice had difficulty walking. 7 days after injection of Ehrlich acid cells, the thickness of the footpad was measured and assessed. Group 2 (tumor cont. 1) received 100 µl of ethyl alcohol orally 5 days prior to the injection of Ehrlich acid tumor, which continued for 23 days. Group 3 (tumour cont. 2) One week after the injection of Ehrlich acid tumor, 100 µl of ethyl alcohol was given orally every other day for the whole experiment. Group 4 (Treatment 1), treatment was started 5 days before the injection of Ehrlich acid tumor and 100 mg/kg curcumin dissolved in 100 µl of ethyl alcohol and administered orally over the course of the entire experiment. Group 5 (Treatment 2) treatment was started 1 week after the Ehrlich acid tumor was injected and 100 mg/kg curcumin dissolved in 100 µl of ethyl alcohol and administered orally over the course of the entire experiment. At the end of the experimental studies, the animals were sacrificed under anaesthesia. Serum and cancer tissue samples were stored at -80 °C. Determination of Arginase enzyme activity in serum and cancer tissue Cancer tissue Arginase activity; The amount of urea produced as a result of the hydrolysis of arginine with arginase in the sample was determined by spectrophotometric determination with TDMU (Thiosemicarbazide-Diacetyl Monoxime Urea) method (15). Breast tissue ornithine Levels were measured colorimetrically with Chinard's Method (16). Breast tissue protein levels were determined by Lowry method (17). Serum arginase activity was determined by spectrophotometric determination with Munder method with some modifications (18). NO was measured spectrophotometrically using Cartos and Wakid method (19).

2.3. Statistical analysis

The statistical analysis of the data provided in our study was performed using STATISCA statistical program. The differences between arginase enzyme activity, ornithine and NO levels between tumor control and treatment groups were evaluated by Kruskal Wallis test and compared with Mann-Whitney U test. In addition, correlations between the groups were evaluated using Spearman's rank correlation coefficient analysis. P values below 0.05 were accepted to be statistically significant.

3. Results

Serum means and standard deviation values arginase enzyme activities and NO levels as well as tissue arginase enzyme activities, ornithine and NO levels were shown in Table 1. Serum arginase enzyme activities were significantly higher in tumor groups than healthy control groups. When treatment groups and tumor groups were compared, serum NO levels were significantly increased in treatment groups. Although there was a decrease in the serum arginase enzyme activity after treatment, this decrease was not statistically significant. It was found that arginase enzyme activity decreased significantly with curcumin treatment in tumor tissue samples. As a result of curcumin treatment, both decreasing arginase activity and ornithine levels were significantly decreased. On the other hand, curcumin treatment increased NO levels significantly. The effects of curcumin on cancer, arginase enzyme activity, ornithine and NO levels were found to be more effective than cancer after curcumin (Fig. 1-5). Also, Spearman's rank correlation coefficient analysis was performed and a significant difference was found between tissue arginase enzyme activities and ornithine levels only in the third group. The p value was determined to be 0.047.

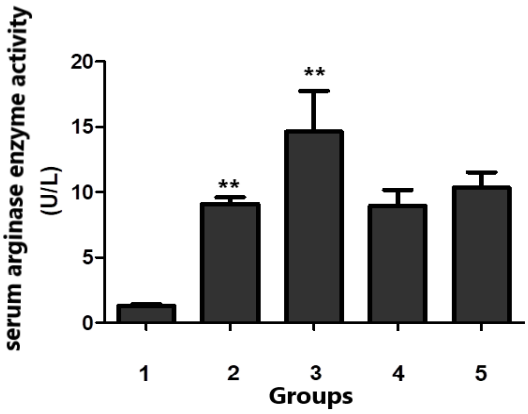

Fig. 1. Serum arginase enzyme activity, *: p<0.05, ** : p<0.001

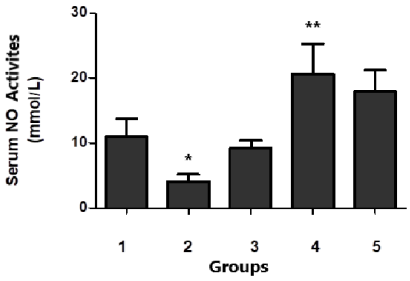

Fig. 2. Serum NO activity

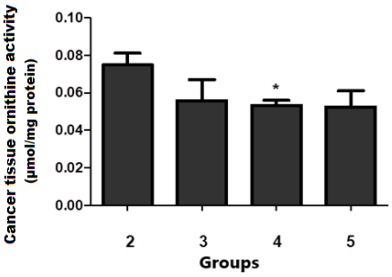

Fig. 4. Cancer tissue ornithine activity

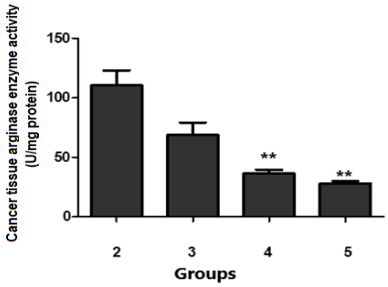

Fig. 3. Cancer tissue arginase enzyme activity

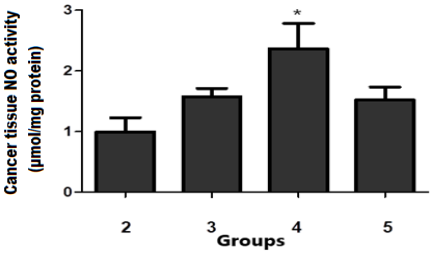

Fig. 5. Cancer tissue NO activity

Table 1. Arginase enzyme activity and NO levels of serum samples and arginase enzyme activity, ornithine and NO levels mean and standard deviation values of the tissue samples

	Cont. (Group 1)	Tumor cont. 1 (Group 2)	Tumor cont. 2 (Group 3)	Treatment 1 (Group 4)	Treatment 2 (Group 5)
Serum Arginase (U/L)	1.31±0.24	9.10±1.40c**	14.63±8.84c**	8.96±3.42	10.36±3.45
Serum NO (mmol/L)	10.95±7.39	4.06±3.19a*	9.27±3.13	20.62±13.14b**	17.96±9.79
Tissue Arginase (U/mg protein)		110.48±35.66	68.98±28.40	36.28±9.09d**	27.65±6.94e**
Tissue Ornithine (µmol/mg protein)		0.074±0.018	0.056±0.031	0.053±0.079f*	0.056±0.026
Tissue NO (µmol/mg protein)		0.99±0.65	1.57±0.39	2.36±1.17g*	1.52±0.63

a: Comparison of serum NO levels between Group 1 and 2.
b: Comparison of serum NO levels between Group 2 and 4.
c: Comparison of serum arginase levels between Group 1, 2 and 3.
d: Comparison of tissue arginase levels between group 2 and 4.
e: Comparison of tissue arginase levels between group 3 and 5.
f: Comparison of ornithine levels between group 2 and 4.
g: Comparison of tissue NO levels between group 2 and 4.
* : p<0.05, ** : p<0.001.

4. Discussion

Curcumin may have a beneficial effect on cancer by inhibition of arginase enzyme. In addition to reducing arginase enzyme activity with curcumin, it is also possible to reduce ornithine levels, which are precursors of carcinogens and polyamines. The inclusion of NO in this mechanism and the demonstration that NO has anti-carcinogenic effect suggests that this system may be an important part of the non-carcinogenic curcumin mechanism. Both arginase and nitric oxide synthases enzymes competed for their common substrate; L-arginine. This relationship between the two enzymes represents one of the important factors in the regulation of NO production. Increased arginase activity may limit NO synthesis by reducing the availability of L-arginine for NOS (11). The arginase enzyme has a Vmax value at physiological pH, 1000 times more than the NOS enzyme Km value of arginase enzyme for L-arginine is 2-20 mM and it is 1-20 mM for NO (20, 21). Therefore, these two enzymes, even at low concentrations of L arginine are capable of using this substrate easily (5). It is stated that NO and NO metabolites inhibit cell growth and metastases in tumor tissues, inhibit tumor growth at high concentrations of NO and induce apoptosis of tumor cells in this way (12, 21, 22). At the same time, there are studies suggesting that NO can be used as an agent with chemical sensitivity and immune sensitivity and may be effective in immunotherapy or chemotherapy in cancer treatment by showing a synergistic effect (23). Up on constridation of serum NO levels in our study, NO values were decreased significantly in the tumor groups compared to the healthy group. This result gives us a meaningful understanding of the relationship between NO and cancer. In patients with breast cancer, significantly increased tissue ornithine levels and serum arginase enzyme activities were observed. These finding

will result in increased polyamine biosynthesis. In several studies, this is introduced as the triggering the mechanism for cancer development (3, 10, 24). In addition to this case, the decrease in NO level, which has been reported to play a protective role in the development of cancer, due to increased arginase enzyme activity, can be shown as a complement to the mechanism on the development of cancer (3, 23). In this study, the decreased NO level in the group of cancer patients against increased arginase enzyme activity supports this theory. In recent years, studies on the anticarcinogenic properties of curcumin have increased. In animal models, curcumin has been shown to be a potent antioxidant, anti-inflammatory molecule. It has been shown that it fights agonist carcinogenic DNA damage and inhibits tumorigenesis (25). Curcumin is one of the molecules used in the treatment of various diseases as an ethnic drug. Especially, curcumin has been acknowledged as an effective anticancer agent that regulates multiple intracellular signaling pathways, including transcription factors (e.g., STAT3, NF-κB, and AP-1), receptors (e.g., IL-8, HER2, and CXCR4), kinases (e.g., EGFR, ERK, and JAK), cytokines (e.g., TNF, IL, and MIP), enzymes (e.g., MMP, iNOS, and GST), and growth factors (e.g., EGF, NGF, and HGF) (13). Curcumin, p53, Ras, phosphatidylinositol-3-kinase, protein kinase B are targeted at numerous signaling pathways associated with cancer therapy and curcumin cell cycle regulation is closely related to PI3K / AKT / mTOR, a signaling pathway associated with cellular silence, proliferation, cancer and longevity. In addition, curcumin has been shown to cause anticancer effects by activating apoptotic pathways in cancer cells, inhibiting pre-cancerous processes including inflammation, angiogenesis and metastasis (26, 27, 28). Another study reveals the anti-metastatic and apoptosis-inducing potential of curcumin with increased Bax levels, decreased MMP-2, MMP-9 and Bcl-2 levels in breast cancer cells and erlich acid tumor cells (29). While curcumin treatment applied to breast cancer animals was found to increase serum NO levels significantly, a decrease in the same rate was not detected on arginase enzyme activity. However, even increasing the NO levels of curcumin can be considered as a positive effect in preventing cancer formation. Therefore, curcumin is an anticarcinogenic agent the action mechanism(s) as outlined above, due to inhibitory effects an arginase enzyme stimulatory effect on NO, as well as it suppressive effects on ornithine and polyamine levels. There is no study investigating the effects of curcumin on arginase enzyme activity which is reported to be associated with cancer and increased in cancer patients. In our study, interesting results were obtained in evaluating the effectiveness of time to start treatment of curcumin. Two different treatments were performed for this purpose. Although curcumin was administered to a group of animals (treatment group 1) before cancer cell injection, the second group (treatment group 2) was given curcumin after the cancer tissue was formed in the animal body. When these two groups were evaluated in terms of arginase enzyme activity, ornithine and NO levels; the curcumin intake was found to be much more effective before the cancer cell was given in the body. For this reason, curcumin, which is already used as a spice, can be considered as a factor that prevents the formation of cancer with daily diets. Unfortunately, we could not determine NOS levels in this study, and that was one of our study's limitations. As a result, curcumin, which is shown as an anticarcinogenic agent, exhibits this effect by inhibiting serum and tissue arginase enzyme activity in breast cancer patients and shifting the pathway towards from NO formation. This positive effect of curcumin can be more clearly shown by the fact that it starts to take a long time before the formation of cancer. Curcumin, a promising agent in cancer treatment, should be supported by further studies and new parameters.

Ethics Committee Approval

Ethics committee approval was received for this study from the ethics committee of Trakya University Animal Ethics Committee.

Informed Consent: N/A.

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

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Effects of psychological predictors on hospital discharge duration after total knee arthroplasty

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Abstract

This study aims to evaluate the effects of somatosensorial amplification, kinesiofobia, health anxiety and depression on hospital discharge durations after knee arthroplasty. 193 patients with total knee arthroplasty were included in the study. Patients were divided into two groups due to discharge durations. Group 1 included patients who were discharged in 1 to 4 days; Group 2 included patients who were discharged in 5 to 7 days. Functional outcome was measured with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). For psychiatric evalution; a Sociodemographic form, Somatosensory Amplification Scale, Health Anxiety Inventory, Hospital Anxiety and Depression Scale and The Tampa Scale of Kinesiophobia were used. There wasn't any significant difference in terms of WOMAC scores between Group 1 and 2 postoperatively. (Pain; p=0.666, Stiffness; p=0.349, Functionality; p= 0.145). There was a significant difference in terms of Health Anxiety Inventory and Somatosensorial Amplification scores between Group 1 and 2 (p=0.006; p=0.031). In correlation analysis Somatosensorial Amplification score was positively correlated with hospital discharge duration. There was a significant difference in terms of Tampa kinesiophobia scores between Group 1 and 2 (p<0.001). In correlation analysis there was a positive correlation between Tampa kinesiaphobia score and hospital discharge durations (r: 0.618; p: 0.000). Multiple regression analysis indicated that Tampa Scale of Kinesisophobia was the major predictive factor for hospital discharge durations. Health anxiety, Somatosensory amplification and mostly Kinesiophobia were related with longer hospitalization periods due to worse functional outcomes after total knee arthroplasty. Maladaptive psychological strategies about false bodily sensations lead a worse outcome for knee arthroplasty patients. Therapeutic programs aiming false cognitive factors would result with improved functional recovery.

Keywords: somatosensory amplification, kinesiophobia, health anxiety, total knee arthroplasty, WOMAC

1. Introduction

As the life expectancy of the population continues to rise, the frequency of operations such as knee arthroplasty is becoming more prevalent. When conservative management strategies fail and the quality of life continues to decline for patients, knee arthroplasty may be the surgical treatment of choice to decrease pain and joint destruction to improve quality of life (1, 2). It's known that over 2% of individuals in the United States were living with a total hip or total knee replacement in 2010 which corresponds to an estimated seven million people (3). Another study conducted in US in 2013, represented an increasing prevalence that 4.2 % of the population had total knee replacement in fifty years of age or older patients (4). Although there are not many studies about the prevalence of knee arthroplasty in our country, in a recent study Ceyhan et al. indicated that a total of 283,400 primary and 9900 revision knee arthroplasty operations were applied in Turkey between 2010 and 2014, and also showed an increase in prevalence of knee arthroplasties (5).

There are many factors about a better outcome of a knee artroplasty; like type of surgery, age, gender, body mass index, comorbidities, duration of symptoms, home environment variables, baseline caregiver assistance, preoperative ambulation status; among those one of the most important predicting risk factor for worse outcome is shown as postsurgical pain and postoperative ambulation status (6, 7, 8). It has been shown that most patients have pain relief after approximately three months after total knee arthroplasty; but unfortunately despite surgical and radiological success, 8-34% patients still experience chronic postsurgical pain which effects patients' functional status and quality of life (9, 11). Also, pain after knee arthroplasty has been shown to be one of the most important predictive factor for prolonged use of opioids and postoperative dissatisfaction (11, 12).

Researchers have been suggested many preoperative and postoperative risk factors for postoperative pain in patients undergoing knee arthroplasty like genomics, functional status, clinical characteristics, medical comorbidities, socioeconomic status. But among all risk factors preoperative pain and psychological status especially anxiety, depression and pain catastrophizing were shown to have the strongest association

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with chronic postsurgical pain following total knee arthroplasty which cause delayed postoperative ambulation and complications (11, 13). In this context findings suggest that there may be differences in pain perception and somatization among patients. Previous studies showed a positive correlation between somatosensory amplification (SSA), pain perception and pain-related fear of movement called as Kinesiophobia (14, 17).

Somatosensory amplification is defined as the tendency to experience strong bodily sensations, to the extent that they become harmful and troublesome. In other words, SSA is a tendency to experience bodily sensations as intense, noxious and disturbing. There are many reports about SSA in terms of increased somatic symptoms in various medical conditions like rheumatoid arthritis, drug sensitivities, pseudocoronary symptoms of patients with normal coronary arteries and specifically reports mostly suggest that patients who have higher SSA scores are more vulnerable about higher pain perception (15, 18-22).

SSA is associated with a tendency to catastrophize bodily sensations that patients may have disease-avoidance behaviors such as delayed postoperative ambulation. We therefore carried out a longitudinal investigation and determined the knee arthroplasty patients for delayed postambulation in terms of psychological factors; kinesiophobia, anxiety, depression and SSA. It's hypothesized that patients' functional status and discharge from the hospital would relate to psychological factors, somatosensorial amplification, or kinesiophobia.

2. Materials and Methods

2.1. Subjects

The study was approved by the University Ethics Committee. All patients signed a written informed consent form. 193 patients with total knee arthroplasty who were operated between August 2018-August 2019 were included in the study. A total of 193 of the 212 patients were included in the study. The patients whose BMI were above 40, who had a chronic joint disease like rheumatoid arthritis, who were not able to answer the scale questions, who had secondary surgery and who had a serious psychiatric disease like dementia, delirium were excluded from the study. They were determined and operated by the same orthopedic surgeon and a psychiatrist before and after the surgery. Patients who had cognitive inability, diagnosis of another chronic disease that may impair joint functions were excluded from the study. Also patients with severe obesity (BMI>40kg/m^2) were excluded. Patients were divided into two groups due to their discharge durations. Group 1 included patients who were discharged in 1 to 4 days; Group 2 included patients who were discharged in 5 to 7 days. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to determine functional outcomes of patients postoperatively while discharge. A sociodemographic form including age, gender, body mass index (BMI) were applied to all participants. Patients were determined with Somatosensory Amplification Scale (SAS), Health Anxiety Inventory (Short Form) (HAI), The Hospital Anxiety and Depression Scale (HADS) and The Tampa Scale of Kinesiophobia (Tampa Scale) before the surgery.

2.2. Measures

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC osteoarthritis index is a generalized scoring system for osteoarthritis, including three parts as pain, stiffness and functionality with a total score ranging from 0 to 96 (a low score indicates a better result) (23).

2.3. Somatosensory Amplification Scale (SAS)

The scale has 10 items describing the tendency to experience harmless bodily sensations as intense, noxious or disturbing. Participants rate each item on a 5-point likert type scale from 1 ("not at all") to 5 ("extremely"). A higher total score suggests greater symptom amplification with the scores ranging between 10 and 50. Turkish version of the scale was used to determine all patients (24, 25).

2.4. Health Anxiety Inventory (Short Form) (HAI)

The short form of Health Anxiety Inventory is a measure designed to assess the spectrum of health anxiety and to discriminate between individuals with exaggerated health anxiety from those without it, also in samples of somatically ill patients. This scale is comprised of 18 items highly correlated with the full scale (26, 27).

2.5. The Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) which measures anxiety and depression in physically ill adults was used to determine all patients. The scale comprises 14 items, 7 items screen for anxiety, 7 for depression. Each item takes four possible response options [0−3] making the possible sum scores range from 0 to 21 for each of the subscales, HADS-A and HADS-D. Higher values indicate greater symptom severity. A score≥8, has been proposed for the identification of for both depression and anxiety. In accordance with the original HADS, we defined respondents with a score below 8 as "no cases/low", respondents with a score between 8 and 10 as "suspicious cases/moderate" and respondents with a score higher than 10 as "definite cases/high". Turkish version of the scale was used for all patients (28, 29).

2.6. The Tampa Scale of Kinesiophobia (Tampa Scale)

The Tampa Scale is a 17-item questionnaire to determine fear of movement and re-injury due to movement and physical activity on a scale of 0-68, where 68 indicates greater fear of re-injury due to movement. Turkish validated version was used for all patients (30, 31).

2.7. Surgical method

Total knee arthroplasty was applied to all patients with mid-vastus approach under general or spinal anesthesia. Cemented

prosthesis was used for all patients under tourniquet. All patients were given systematic prophylactic antibiotics and anticoagulants to decrease deep venous thrombosis risk after the surgery. Patients were given analgesics for 24-hours to control pain due to the same analgesic procedure.

2.8. Hospital Discharge Criteria's

The hospital discharge decision was due to the pain and knee flexion ROM. Patients whose pain is under 5 in the 10 –point visual analog scale and patients who can flex their knee to 90 degrees were discharged from the hospital. Also patients were able to walk with walkers and had no need any intravenous analgesics.

2.9. Statistical analysis

SPSS v.18 is used for statistical analysis. Kolmogorov-Smirnov test is used to determine whether the variables have normal distribution or not. Variables were expressed as mean± standard deviation. Chi-square test was performed for qualitative variables. Continuous variables between two groups were compared with Independent-t test. Pearson correlation test is used to determine correlation between SAS, HAI, HADS, Tampa Scale and hospital discharge status in knee arthroplasty patients. Multiple linear regression analysis was used to determine independent associations between variables. The threshold of statistical significance was $p<0.05$.

3. Results

A total of 193 patients were included in the study. Sociodemographic variables were shown on Table 1. A total of 145 (57.1%) female patients and 48 (18.9%) male patients participated in the study. The mean age of the participants was 66.97±7.41. The mean body mass index (BMI) score was 28.29±3.69. There were no significant difference between Group 1 and Group 2 in terms of age, gender and BMI (Table 1). In terms of WOMAC scores, there wasn't any significant difference in discharge durations postoperatively for pain, stiffness and functionality (p=0.666; p=0.349; p= 0.145)

3.1. Comparison of HAI and HADS scores

The mean HAI score in female was 21.30±6.97, the mean HAI score in male was 21.30±6.97 (p=0.865). In correlation analysis, age was not correlated with HAI scores (p=0.530). The mean HAI score for Group 1 was 20.72±6.91; the mean score for Group 2 was 24.84±6.90. There was a significant difference in terms of HAI scores between Group 1 and Group 2 (p=0.006). In correlation analysis HAI scores were positively correlated with hospital discharge durations (r: 0.197; p: 0.006).

The mean HADS anxiety scale score in female was 8.88±4.56, the mean hospital anxiety score in male was 7.81±4.22 (p=0.153). In correlation analysis, there wasn't any correlation between age and HAI scores (r: 0.016; p=0.822). The mean HADS anxiety scale score in Group 1 was 8.45±4.01; the mean HADS anxiety scale score in Group 2 was 9.68±6.95 There wasn't any significant difference in terms of HADS anxiety scores between Group 1 and Group 2 (p=0.205). The patients whose HADS anxiety scale scores were above 8 were determined as anxiety, that 79(47.02%) patients in Group 1 and 17 (68%) in Group 2 had anxiety diagnosis (p=0.050).

The mean HADS depression scale score in female was 8.67±2.90, the mean hospital depression score in male was 8.72±2.76 (p=0.902). In correlation analysis, age was not correlated with HADS depression scale scores (r: 0.006; p=0.931). The mean HADS depression scale score in Group 1 was 8.98±2.76; the mean HADS anxiety scale score was 8.88±2.26. There wasn't any significant difference in terms of HADS depression scores between Group 1 and Group 2 (p=0.852). The patients whose HADS depression scale scores were above 8 were determined as depression, that 92(54.76%) patients in Group 1 and 9 (36%) in Group 2 had depression diagnosis (p=0.080).

Table 1. Sociodemographic characteristics of the patients

	Group 1 (N=168) Mean±SD	Group 2 (N=25) Mean±SD	p
Age (years)	66.95±7.38	67.16±7.77	0.893*
Gender (F/M)	130/38	15/10	0.061**
BMI (kg/m²)	28.27±3.65	28.39±4.08	0.873*

*Independent sample *t* test ** Chi-square test SD: Standard deviation BMI: Body Mass Index

3.2. Comparison of Somatosensory Amplification Scale (SAS) and The Tampa Scale of Kinesiophobia (TSK) scores

The mean SAS score in female was 32.54±8.92, the mean SAS score in male was 31.71±9.07 (p=0.579). In correlation analysis, there wasn't any correlation between age and SAS scores (r: 0.061; p=0.400). The mean SAS score in Group 1 was 31.80±9.08; the mean SAS score in Group 2 was 9.68±6.95. There was a significant difference in terms of SAS scores between Group 1 and Group 2 (p=0.031). In correlation analysis SA score was positively correlated with hospital discharge duration times (r: 0.155, p: 0.031).

The mean Tampa scale score in female was 41.06±7.00, the mean Tampa scale score in male was 41.50±5.16 (p=0.646). In correlation analysis, there wasn't any correlation between age and Tampa scale scores (p=0.539). The mean Tampa scale score in Group 1 was 40.04±4.72; the mean SAS score in Group 2 was 50.44±1.76. There was a significant difference in terms of Tampa scale scores between Group 1 and Group 2 (p<0.001). In correlation analysis there was a positive correlation between Tampa scale score and hospital discharge durations (r: 0.618; p: 0.000).

3.3. Correlation analysis of SAS, TSK, HAI and HADS anxiety

Correlation analyses of all scales are shown in Table 2. According to the analysis all scales are positively correlated with each other and the strongest relation was between TSK and HAI scores (Table 2).

Table 2. Correlation coefficients between SAS, TSK, HAI and HADS anxiety scores

	SAS (r-value)	TSK (r-value)	HADS-Anxiety (r-value)
HAI	*0.496	*0.531	*0.507
SAS	-	*0.348	*0.453
TSK	*0.348	-	*0.323

3.4. Multiple linear regression analysis of variables

Heath anxiety, SAS and Tampa Scale scores, which were statistically correlated to hospital discharge durations mentioned as Group 1 and Group 2 were considered to multiple regression analysis. Multiple regression analysis indicated that Tampa Scale of Kinesisophobia was the major predictive factor for hospital discharge durations (Table 3).

Table 3. Multiple lineer regression analyses associated with Hospital discharge duration in knee arthroplasty patients

Independent variables	Standard regression coefficients (ß)
	Hospital Discharge Duration
HAI	0.013
SAS	0.049*
Tampa Scale of Kinesiophobia	0.176*

R^2 (Multiple coefficient of 0.611 determination) * $p<0.001$

4. Discussion

The main findings of this study was higher health anxiety, somatosensory amplification and kinesiophobia scores were correlated with longer hospital discharge durations independent of age, gender and BMI in knee arthroplasty patients.

First of all, we determined both health anxiety, and general anxiety in both groups and found higher anxiety scores in patients those have longer hospital durations. Health anxiety is defined to discriminate individuals with exaggerated health concerns from those without it. In our study patients who had longer hospital durations were found as more concerned about their health and disabilities. Although most of the studies determining anxiety levels and clinical outcomes in knee arthroplasty patients mention that higher anxiety levels are related with worse clinical outcomes, to our knowledge our study was the first investigating both anxiety and health concerns in knee arthroplasty patients using health anxiety inventory (32, 33). In literature, health anxiety is mostly found related with chronic pain that our study findings about longer discharge durations might be due to heath anxiety and prolonged pain (34-36). Also anxiety was found associated with a negative effect on muscle tone causing a reduced local blood flow due to hyperplasia of sympathetic ganglia, which results with symptom increases (37). In a study conducted in Turkey revealed better functional outcomes and less analgesic use with an anxiolytic agent Alprazolam after total knee arthroplasty (38). Alattas et al mentioned that greater pre-operative anxiety, pain and poorer function predict a worse outcome of a total knee arthroplasty consistent with our findings (32).

In our study, we suggested that somatosensory amplification (SSA) may explain inter-individual differences for functional outcomes and effects to discharge durations in knee arthroplasty patients (39). SSA is defined as a tendency to experience bodily sensations as disturbing and SSA is found associated with increased somatic sensations which was defined before in various medical conditions (22). In non-psychiatric patients it was hypothesized that SSA could explain inter-individual differences in symptom reporting. And although the exact mechanisms and determinants of SSA are still unknown, Nakao et al. reported a significant relationship between the event-related potentials (P300) amplitude and SSA which may cause ‘hypervigilance’ to body sensations (39). Higher levels of SSA are assumed to turn body sensations into symptoms and increase the severity of already body sensations into symptoms (41). In literature, chronic pain and lower back pain was found associated with higher SSA (42, 43). In our study, we firstly reported the negative effects of higher SSA in knee arthroplasty patients consistent with previous findings.

Kinesiophobia was another important term investigated in our study. We found that kinesiophobia was the most significant factor for prolonged hospital discharge durations. Kinesiophobia is defined with fear avoidance model. In fear avoidance model, patients feel pain as harmful (pain catastrophizing) leading an avoidance of movement or touch. According to fear-avoidance model kinesiophobia can be a risk factor for persistent pain and disability (44). If patients don’t have kinesiophobia they are more likely to confront daily activities resulting with fast recovery. In a study conducted with 89 total knee artroplasty patients, authors reported that during six-minute walk test, patients without kinesiophobia walked significantly farther than patients with kinesiophobia and consistent with our findings the effect of kinesiophobia on functional results was independent of age, gender and BMI (45). But Monticone et al. didn’t find any difference for knee flexion ROM of knee arthroplasty in terms of kinesiophobia (45). However, in another study conducted in Turkey reported that, in early functioning, higher kinesiophobia levels were related with lower flexion of knee after total knee arthroplasties as indicated in our study (46). Also Brown et al. found a negative correlation between kinesiophobia levels and knee flexion ROM in total knee arthroplasty patients (47).

Another important point of our study was all psychological parameters were interacting with each other positively. In other words health anxiety and somatosensory amplification was increasing kinesiophobia mutually. Maladaptive psychological, behavioral and cognitive strategies like health anxiety were increasing kinesiophobia. It’s known that somatosensorial amplification may be reduced

with psychoeducational programs by applying techniques that aim to prevent catastrophic thoughts about bodily sensations (37). Hence, such techniques including therapies or agents to reduce anxiety and also cognitive restructuring for somatosensoriel amplification would lower kinesiophobia resulting with a better outcome for total knee arthroplasty patients in early functioning.

The main limitation of our study was the short follow up that makes it difficult for us to comment on long-term results. Also the psychological measures were self-report questionnaires. Furthermore this study didn't include obese patients that may change the outcomes.

In conclusion we found health anxiety, somatosensory amplification and mostly kinesiophobia were related with longer hospital discharge periods due to worse functional outcomes after total knee arthroplasty in early periods. The strength of our study was we evaluated health anxiety and somatosensory amplification function with the relation of kinesiophobia for the first time in literature. We highlight that maladaptive psychological strategies about false bodily sensations lead a worse outcome for knee arthroplasty patients. Total knee arthroplasty in patients is particularly challenging for orthopedic surgeons and requires close interdisciplinary cooperation. We suggest therapeutic programs aiming false cognitive factors that contribute to activity avoidance would result with improved functional recovery after total knee arthroplasty.

Conflict of interest

The authors have no conflict of interest.

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The relationship between disease severity and GDF-15 in individuals diagnosed with obstructive sleep apnea syndrome

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Abstract

Obstructive sleep apnea syndrome (OSAS) is characterized with interruption of sleep with apnea attacks and is associated with various diseases such as metabolic syndrome. GDF-15 (Growth differentiation factor 15) is a cytokine belonging to the transforming growth factor – β superfamily and it has been found to be associated with chronic heart failure, acute pulmonary embolism, and acute attacks of chronic obstructive pulmonary disease (COPD). It was aimed to evaluate the relationship between disease severity and mean GDF-15 in patients diagnosed with OSAS. Our study was carried out with 75 patients with OSAS. GDF-15 levels were checked by in the morning fasting blood test. Among the 75 patients, 27 constituted the mild, 22 constituted the moderate and 26 constituted the severe OSAS groups. The mean ages of the patients were not significantly different between groups (53.17±10, 54.61±10.2 and 53.5±11.6 respectively; p>0,05). GDF-15 levels were not significantly different between groups separately (p>0.05). There was only a weak positive relationship between GDF-15 and NREM and REM (p<0.05). In our study, it was revealed that there was no significant relationship between the OSAS severity groups and GDF-15. Our determination of a positive relationship with NREM and REM may have been related to reduction of minute ventilation experienced in OSAS-diagnosed patients, tachycardic fluctuations, their more severe nature and increased right ventricular pressure. Consequently, our current knowledge indicates that GDF-15 is not much guiding in the prediction and monitoring of OSAS severity.

Keywords: sleep apnea syndrome, OSAS, GDF-15, REM, NREM, apnea

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by recurrent partial or complete upper respiratory airway obstructions ending in hypoxia/reoxygenation and arousals during sleep (1). While its etiology and pathophysiological mechanisms have not been completely understood, it is a complex, polygenic, and multifactorial disease accompanied by some predisposing factors such as age, sex, obesity, anatomic and mechanical factors and neuromuscular function (2, 3). OSAS may lead to some complications such as cardiovascular complications, malignancy and diabetes while studies have shown that these complications may be associated with endothelial dysfunction, excess oxidative stress, increased systemic inflammation and sympathetic stimulation (4-7). GDF-15 (Growth differentiation factor 15) is a cytokine belonging to the transforming growth factor – β superfamily, and it plays a role in cellular growth and differentiation. It has been found to be associated with acute coronary syndrome, chronic heart failure, acute pulmonary embolism, idiopathic pulmonary hypertension and acute attacks of chronic obstructive pulmonary disease (COPD) (7-9). A study where OSAS patients were compared to a control group did not find a GDF-related difference. However, in the study, the OSAS group was assessed without separation into sub-groups based on severity (mild-moderate-severe) (10).

In difference to previous studies on this topic, in this study, it was aimed to assess the relationship between disease severity and mean GDF-15 in patients diagnosed with OSAS.

2. Materials and Methods

The ethics board approval for the study was obtained from the Kirsehir Ahi Evran University Faculty of Medicine Clinical Studies Ethics Board with the Decision No:2020-02/11 with date of 11-02-2020. Written consent was obtained from the patients who volunteered to participate in the study. The costs of the kits that were used in the study were covered by the researchers.

2.1. Population

Our study was carried out with 75 patients who visited the Pulmonology and Cardiology clinic of our hospital, pre-diagnosed with OSAS, were of the ages of 18-80, had newly diagnosed OSAS and not started positive airway pressure (PAP) treatment. Patients with a diagnosis of central type sleep apnea, neurological diseases such as history of

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cerebrovascular disease and recent head trauma and those who had cardiovascular diseases that could lead to increased GDF-15, diagnoses like heart failure, acute coronary syndrome or history of idiopathic pulmonary hypertension were excluded from the study. The included patients did not have a history of any medication usage. The patients meeting the exclusion and inclusion criteria and volunteering to participate were hosted at the sleep clinic for a night for polysomnography (PSG), and after fasting overnight, their venous blood samples were taken into plain and K2EDTA-containing tubes. The blood samples were transferred to the biochemistry laboratory without waiting. The samples that were taken into plain tubes were centrifuged at 1500g for 10 minutes after waiting for them to coagulate. From a part of the serum that formed, routine biochemical parameters were studies by standard methods by using a Cobas 8000 (Roche Diagnostics®, Germany) autoanalyzer. The remaining serum was kept at -80 °C until the time it would be studied for GDF-15 levels. Serum GDF-15 was measured with the ELISA method by using a commercial kit (www.relassay.com, Gaziantep, Turkey). Validation of performance parameters of ELISA kits as were:

1) Within-batch difference: CV<10%,

2) Batch-batch difference: CV<12%,

3) Sensitivity: 5.09 ng/L,

4) Period of validity: Twelve months.

In the blood samples taken into K2EDTA tubes, complete blood count tests were carried out with a Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) automated blood count device.

2.2. Polysomnography (PSG)

The diagnosis of OSAS is made by polysomnography (PSG). In the examination that was made for an entire night, using a Philips Respironics Polysomnography device (1001 Murry Ridge Lane Murrysville, PA 15668 USA Respironics Deutschland Gewerbestrasse 17 82211 Herrsching, Germany), four-channel electroencephalogram (EEG) and two-channel electrooculography (EOG), submental electromyography (EMG), pulse-oximetry, thoracic and abdominal movements, electrocardiogram (ECG), tracheal sounds and oronasal air flow were recorded. In PSG, measurements of respiratory decrease (H=hypopnea) and complete stoppage of respiration (A=apnea) are made, and the hourly Apnea (A)- Hypopnea (H) counts (I=index) are determining. OSAS diagnosis is made as AHI: (apnea-hypopnea index): 5-15/hour: Mild; AHI: 16-30: Moderate, and AHI: > 30: Severe OSAS. A stoppage of air flow for more than 10 seconds was defined as apnea, and a reduction of 4% in oxygen saturation and a >30% reduction in air flow for more than 10 seconds were defined as hypopnea. For OSAS severity, based on the apnea and hypopnea counts per hour determined during sleep, the apnea-hypopnea index (AHI) was calculated. All patients were grouped based on their AHI scores as mild (AHI: 5-15), moderate (AHI: 15-30) and severe (AHI> 30) OSAS (11).

The PSG recordings of the patients were reported by the same doctor and on the same day.

2.3. Reproducibility and validation

To calculate the intraobserver and interobserver coefficients of variation for measurements of PSG recording and GDF-15 results, 20 random selected patients among severe group were assessed by repeating the measurements under the same baseline conditions. To test the interobserver variability, we performed the measurements offline from video recordings by a second observer. The intraobserver and interobserver coefficients of variation for PSG and HGI measurements were found to be <5% and nonsignificant.

2.4. Statistical analysis

This study aimed to test the relationships of the AHI group variable with other variables. Considering the observation numbers based on groups, parametric and non-parametric hypothesis tests were applied for tests towards quantitative data. For comparison of quantitative medical parameters among the AHI groups, ANOVA and Kruskal Wallis tests were applied based on the suitability of the data for normal distribution. Shapiro-Wilk test was used to test normal distribution. For the categorical data, to test the relationships between the AHI groups based on sexes, chi-squared test was used. The findings of the statistical analyses were obtained by using the IBM SPSS 20 package software. Values of $p<0.05$ was accepted as statistically significant.

Table 1. Comparison of the GDF-15 values of the AHI ratio index groups

Variables	AHI ratio index groups			p¥
	5-15 Mild OSAS	16-30 Moderate OSAS	>30 Severe OSAS	
Age	53.62± 10.01	54.93± 9.63	54.48± 11.05	0.231
GDF-15	389.84± 147.54	506.48± 239.23	429.76± 175.39	0.350

¥: Kruskal Wallis Test. GDF-15 levels were not found to be different between groups

3. Results

The study included 75 patients satisfying the inclusion criteria. Among these, 27 constituted the mild, 22 constituted the moderate, 26 constituted the severe OSAS groups.

The mean ages of the patients who were included in the study based on the mild, moderate and severe groups were respectively 53.17±10, 54.61±10.2 and 53.5±11.6, while there was no statistically significant age difference among the groups. Again, respectively 25%, 36.4% and 40.9% were male, 75%, 63.6% and 59.1% were female.

According to the age and GDF-15 mean comparisons of the AHI ratio index groups, there was no significant difference in these variables ($p>0.05$). The relationships of

GDF-15 with several parameters that are shown in Table 2 were assessed, and only a weak positive relationship was found between GFT-15 and the parameters of NREM and REM ($p<0.05$). GDF-15 also did not have a significant relationship with the inflammation markers of C-reactive protein (CRP) and platelet counts.

Table 2. Correlations between GDF-15 and other parameters

Parameters	GDF-15	
	r	pβ
Age	0.038	0.760
Height-meter	0.072	0.554
Hba1c (%)	0.102	0.402
Hgb (g/dL)	-0.156	0.201
Glucose	0.027	0.827
Platelet (10^3/mm^3)	0.073	0.549
Monocyte (%)	0.008	0.945
Eosinophil (%)	-0.055	0.654
Basophil (%)	-0.021	0.863
MVC (µm3)	0.040	0.742
MCH (pg)	-0.057	0.642
MCHC (g/dL)	-0.217	0.073
RDW (%)	-0.109	0.372
MPW (µm^3)	0.110	0.369
CRP (mg/dL)	-0.003	0.983
Creatinine (mg/dL)	0.099	0.416
Total-Cholesterol (mg/dL)	0.074	0.556
LDL-Cholesterol (mg/dL)	-0.035	0.783
HDL-Cholesterol (mg/dL)	0.128	0.306
Triglyceride (mg/dL)	-0.077	0.553
Total Sleep Duration (minute)	0.056	0.648
Activity/Sleep	-0.042	0.732
Apnea-count	-0.022	0.860
Hypopnea-count	0.029	0.812
Apnea + Hypopnea Total count	0.005	0.967
Central apnea-count	0.005	0.971
Obstructive apnea-count	-0.048	0.693
Mixed apnea-count	0.025	0.840
NONREM/ratio	0.267	**0.027 β**
Non-REM-Stage-1-ratio	-0.161	0.187
Non-REM-Stage-2-ratio	0.122	0.318
Non-REM-Stage-3-ratio	-0.075	0.543
REM-ratio	0.270	**0.025 β**
NONREM-AHI	0.092	0.454
REM-AHI	0.073	0.549
Apnea-index	-0.055	0.655
Hypopnea-index	0.010	0.938
Left-side-AHI	0.003	0.983
Supine-AHI	0.052	0.670
Right-Side-AHI	-0.046	0.707
Left-Side-Sleep-Duration	0.078	0.534
Left-Side-Deep-Sleep-Duration	-0.007	0.956
Supine-Sleep-Duration	0.086	0.483
Supine-Total- Sleep-Duration	0.036	0.768

β: Spearman Correlation Analysis. Only Non-REM and REM-ration were found to be correlated with GDF-15 level but weakly. AHI: Apnea-hypopnea index, REM: Rapid Eye Movement

4. Discussion

In our results, interestingly, it was revealed that there is no significant relationship between OSAS severities and GDF-15. However, studies on GDF-15 have found it associated with many chronic diseases (8-14). Studies have more clearly demonstrated the relationship between cardiac pathologies and GDF-15 (5,12). In other diseases whose relationship to GDF-15 has been more clearly demonstrated especially such as cardiac pathologies, the severity of inflammation might also have affected this situation. More importantly, it is seen that the cardio-specificity of GDF-15 (myocardial, endocardial or pericardial specificity) is strong. We would expect OSAS to have varying rates of significant relationships with GDF-15 based on not only its primary etiopathogenic mechanism but also its accompanying comorbid chronic diseases and the levels and severities of this disease. However, this result of ours showed that there are unknowns in terms of GDF-15 cytokine pathways, effect mechanism and receptor activation-specificity.

As previous studies have found its relationship to many chronic diseases, while planning our study, we also thought that it could be a practical marker regarding its relationship to OSAS severity, therefore, disease severity projection and monitoring (especially in cardiac disease projection). The fact that our results did not constitute significance among the groups showed that, before studies with GDF-15 on chronic diseases, it is needed to follow up on new developments regarding GDF-15. With our current knowledge, it is seen that GDF-15 is not very useful in estimation and monitoring of OSAS severity.

GDF-15 serves as a cardiokine inducible with stress which provides protection against pathological myocardial reshaping as a response to a pressure or volume overload (12). It is known that the circulation levels of GDF-15 are high in acute pulmonary embolism patients and GDF-15 may respond to RV overload in those with idiopathic pulmonary hypertension (13-14). In order to more clearly demonstrate the relationship between GDF-15 and OSAS, we did not include individuals with coronary artery disease in our study. As we excluded the situation of OSAS and myocardial effect this way, in our study, we showed that there is no significant relationship between GDF-15 and isolated OSAS.

In our study, weak positive relationships were found between GDF-15 and the parameters of NREM and REM.

As known, sleep consists of two stages, it starts with NREM and then transitions to the REM stage. The NREM stage also has sub-stages as 1, 2 and 3. The EEG wave frequency decreases, and wavelength increases. The reason for this is increased synchronization. Falling asleep starts with the 1(N1) stage, transition occurs respectively to 2 and 3 (N2, N3), and sleep deepens (15).

It was reported that the minute ventilation at each stage of sleep decreases by 1.6 liters. As the metabolism decreases in sleep, oxygen consumption and carbon dioxide production also decrease. As the decrease in minute ventilation is more effective, the partial carbon dioxide pressure in arterial blood increases, and the partial oxygen pressure and oxygen saturation decrease. The ventilation response to hypercapnia decreases by 20-50% in NREM and even more in REM. It is

thought that this decrease has two reasons. These are a reduction of working medullary respiration neurons in relation to the decrease in the central chemoreceptor sensitivity and an increase in the upper respiratory airway resistance. The lower response in REM sleep was attributed to increased brain blood flow during REM (16).

In sleep, the heart rate changes in relation to sympathetic and parasympathetic system effect changes. The parasympathetic effect is dominant at the NREM stage and bradycardic. Bradycardia also continues at the REM stage, but there are occasional bradycardic and tachycardic fluctuations based on sympathetic activity (17).

Based on these data, we believe our determination of a positive relationship with NREM and REM may have been related to reduction of minute ventilation experienced in sleep physiology in OSAS-diagnosed patients, tachycardic fluctuations, these fluctuations' more severe nature and increased right ventricular pressure, and therefore, increased normal function of the myocardium.

Consequently, our current knowledge indicates that GDF-15 is not much guiding in the prediction and monitoring of OSAS severity. Following molecular-level studies of GDF-15 may perhaps allow us to have a better idea on this issue in the future.

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Conflicts of interest
The authors have no conflicts of interest to declare.

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Demirtas' early renal vascular control technique (DERVACT): A novel technique for open partial nephrectomy

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Abstract

"Demirtas' Early Renal Vascular Control Technique (DERVACT)" is a novel technique for renal pedicle control that aims to achieve rapid and direct access to the renal artery through the retroperitoneal space and then the superior-dorso-lateral aspect of the kidney. In this study, we aimed to introduce DERVACT and to present the initial outcomes of this technique. This retrospective-observational study compared two groups of patients that were operatively treated by the same surgical team using two different nephron sparing surgery (NSS) procedures. Group I (n=95) underwent standard open NSS and Group II (n=92) underwent open NSS with the DERVACT between Jan 2015 and July 2020. Mean age was 56.42 ± 13.27 years. No significant difference was found between the two groups with regard to age, gender, Body mass index, mass laterality and size, and the Padua and c-index scores (p=0.087, p=0.354, p=0.642, p=0.957, p=0.200, p=0.101, p=0.361, respectively). Similarly, no significant difference was found between the DERVACT group and the other group with regard to ischemia duration (20.0 [15.0-30.0] min *vs.* 18.5 [11.0-27.0] min, respectively, p=0.060) and intraoperative vascular complication rate (6.3% *vs.* 1.1%, respectively. p=0.059). However, non-ischemic operative time was significantly shorter in the DERVACT group than in the standard partial nephrectomy group (64.0 [50.0-75.0] *vs.* 84.0 [61.0-105.0], p<0.001). As a conclusion, DERVACT is a simple, time-saving, and safe procedure for NSS that can be used in clinics with no opportunities for robotic-laparoscopic partial nephrectomy or in open partial nephrectomy.

Keywords: kidney surgery, retroperitoneal approach, vascular anatomy, partial nephrectomy

1. Introduction

Renal cell carcinoma (RCC) is the third most common urological cancer worldwide. Nephron-sparing surgery (NSS) or partial nephrectomy (PN) is a common technique used in the treatment of RCC (1). This technique typically consists of three stages: (i) dissection of renal hilum and vascular clamp, (ii) dissection and complete release of the kidney, and (iii) removal of the mass and renorrhaphy (2). The primary aim in this technique is to achieve renal hilar clamping and vascular control as promptly as possible (3).

In addition to classic PN techniques, numerous other techniques have also been developed to date. These novel techniques have mainly focused on ischemic/non-ischemic PN and its effect on renal functions, differences between the effects of clamping main versus segmental renal arteries, treatment outcomes based on the type and duration of ischemia, and renorrhaphy (4-7). However, to our knowledge, there have been very few studies focusing on vascular control, which is a critical step in PN and has a direct effect on the operative time (8).

Variations in renal arteries account for ~30% of their existence (9). However, renal artery is mostly localized to the posterior renal segment, which complicates renal pedicle control and thereby leads to inadequate control of the arterial system during the standard procedure (Fig. 1A and 1B) (8).

In this study, we aimed to introduce a new technique for open PN that aimed to reduce the duration of vascular control and achieve renal hilar dissection in a safer and faster manner by utilizing the localization of the renal artery, which runs more superiorly and posteriorly compared to the renal vein. The study also aimed to present the initial treatment outcomes of this technique.

2. Matherials and Methods

2.1. Study design and population

The retrospective study compared two groups of patients that were operatively treated by the same surgical team with 10-year experience in PN using two different nephrectomy procedures at Erciyes University, Department of Urology. Group I (n=95) underwent standard open PN and Group II (n=92) underwent PN with the "Demirtas' Early Renal Vascular Control Technique (DERVACT)" between Jan 2015 and July 2020. Patients with a history of renal/adrenal surgery were excluded from the study. Demographic and clinical characteristics including age, gender, body mass index (BMI), laterality and size of the mass, Padua and Cindex scores,

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duration of ischemia, and surgical duration were compared between the two groups. Mass size was calculated based on the histological examination of the specimens.

2.2. Calculation of operative time

Operative time was calculated as the time from first incision to closure of the skin. However, duration of ischemia was excluded from when calculating the operative time in order to rule out the factors associated with mass localization, mass complexity, and renographic variations.

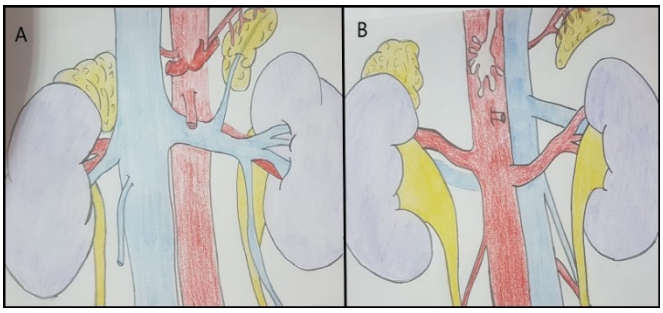

Fig. 1. Standard anatomical view of the kidneys. **A.** Anterior view**. B.** Posterior view

2.3. Anatomical touchstones: DERVACT-Point, DERVACT-Line and DERVACT-Triangle

DERVACT-Point was defined as the anterior-superior-lateral point on the kidney. In accordance with the Padua scoring system, this point was defined as the lateral point on the upper polar line (10).

DERVACT-Line was defined as the line extending from the DERVACT-Point to the posterior-inferior-medial point on the kidney (renal hilus) when the kidney is deviated anteriorly. This line technically indicates the renal artery. DERVACT-Triangle was defined as the space among (i) renal artery (which is exposed by a dissection made along the DERVACT-Line), (ii) medial segment of the upper pole kidney, and (iii) adrenal gland in the anterior-superior segment of the kidney. Renal hilus is normally located in this space and any type of hilar dissection can be performed in this area. Illustrations of the technique are shown in Fig. 2.

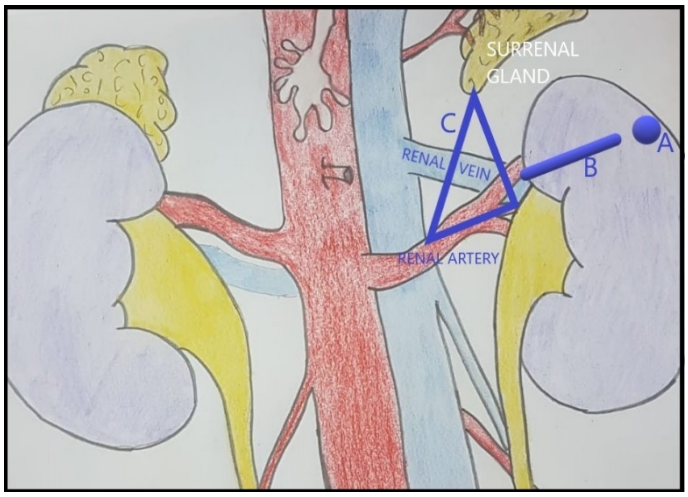

Fig. 2. Illustration for anatomical touchstones of the technique. **A**. DERVACT-Point. **B.** DERVACT-Line. **C.** DERVACT-Triangle

2.4. Novel surgical technique

The patient was placed in a full flank position with the affected kidney side facing upwards. A supra-11th flank incision was made through the skin and underlying subcutaneous tissues and the 11th rib was partially removed (Fig. 3A). The retroperitoneal space was accessed by retracting the peritoneum medially. After dissecting Gerota's fascia laterally, the upper pole of perirenal fat was dissected beginning from the anterior-superior-lateral point (DERVACT-Point) and then the upper pole was separated from the adrenal gland. The superior-lateral-posterior segment of the kidney was dissected and the dissection was continued along the DERVACT-Line towards the posterior-inferior-medial segment (renal hilus) by lifting the kidney anteriorly after it had been freed from the surrounding attachments. At the end of this line, the renal artery was easily accessed and was suspended by a vessel tape. At this stage, a triangle was formed, with the renal artery localized in its floor, the adrenal gland localized on its top, and the medial aspect of the upper pole localized at its lateral wall (DERVACT-Triangle) (Fig. 3B). After this stage, all the other attachments of the kidney were freed completely and the dissection was continued only to the renal hilum. However, renal hilum was not dissected so as not to lose time. Renal artery was subsequently occluded with Bulldog clamp after intravenous administration of 150 ml of 20% mannitol solution. Warm or cold ischemia was applied based on the clinical characteristics of the renal mass. In cases that were administered cold ischemia, the renal capsule around the mass was drawn after renal artery occlusion with Bulldog clamp and 10 min of cold ischemia, and then the mass was removed by enucleation. Surgical margin and frozen section specimens obtained from the mass base were sent for histological examination. Bleeding foci and resected portions of the collecting duct system (if any) were repaired with 3-0 absorbable sutures. Renorrhaphy was completed after the placement of Surgicel in the surgical site. PN was completed after the removal of the Bulldog clamp.

2.5. Standard nephron sparing surgery with anterior approach

The steps up to the Gerota's fascia are similar to those of DERVACT. In the standard technique, after the Gerota's fascia was parted, the psoas muscle and ureter were found. By following the ureter, kidney parenchyma and renal hilum were reached. Careful dissection was conducted to isolate the ureter, renal vein, and renal artery, each of which is surrounded by a different colored vessel loop. It should be remembered that the renal vein was usually located anteriorly in the renal hilum and this was the first vessel encountered. In order to reach the renal artery, the renal vein should be completely dissected and lateralized at the first step. Then the renal artery was dissected enough to put a bulldog clamp. The kidney was completely dissected starting from the lower pole and separated from the surrounding adipose tissue after hilum dissection. Dissections were made between the adrenal gland and the parenchyma in the upper pole. After the entire kidney was completely free, the

applied renal artery was brought into a state to be clamped. The methods applied from this stage are similar to DERVACT.

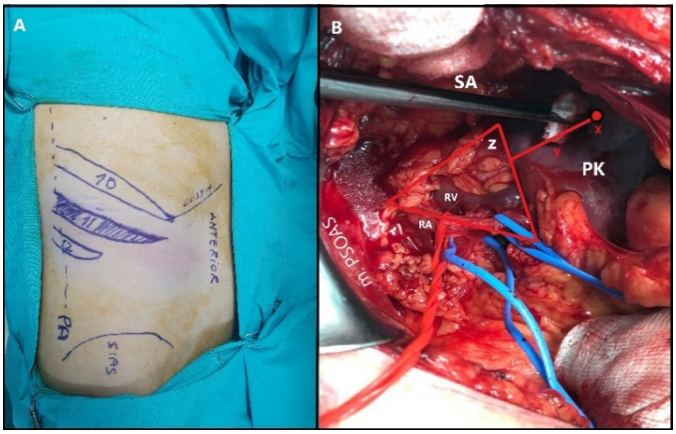

Fig. 3. Operation view for anatomical touchstones of the technique. **A.** Patient position and incision area. An incision is made on the 11th rib. PA: Posterior axillar line. **B.** Anatomical definitions of the technique. The DERVACT point is located in the posterior and upper pole of the kidney (x). The line extending from the DERVACT point to the posterior hilus-posterior renal lodge axis is the DERVAT-line (y), DERVACT-Triangle is defined as the space among renal artery-medial segment of the upper pole kidney, and adrenal area (z). Red vessel strip shows the main renal artery. Blue vessel strips show the segmental arteries. PK: posterior wall of the kidney, SA: Surrenal area, RV: Renal vein, RA: Renal artery

2.6. Statistical analysis

Data were analyzed using SPSS 22.0 for Windows (IBM Corp. Released 2013, Armonk, USA). Normal distribution of quantitative data was assessed using Shapiro-Wilk test and Histogram plots. Quantitative data with normal distribution were expressed as mean ± standard deviation (SD) and data with non-normal distribution were expressed as median (1st-3rd quartile). Categorical data were expressed as percentages (%). Continuous variables in independent groups were compared using independent samples t-test or Mann-Whitney U test based on their distribution pattern. Categorical variables were compared using chi-square test (Pearson's Chi-square test or Fisher's Exact test). A *p* value of less than 0.05 was considered significant.

2.7. Ethical approval

This study was approved by the Erciyes University Clinical Research Ethics Committee (Approval number: 2020/246). All participants were informed verbally and in writing before the operations and a written consent was obtained from each of them.

3. RESULTS

3.1. Patient characteristics

The 187 patients comprised 110 (58.8%) men and 77 (41.2%) women with a mean age of 56.42 ± 13.27 years and a median BMI value of 29.0 (27.0-33.0) kg/m^2. The mass was located in the right kidney in 102 (54.5%) and in the left kidney in 85 (45.5%) patients. The mass was mostly localized to the lower pole (n=72; 38.5%), followed by upper pole (n=62; 33.1%) and middle pole (n=53; 28.4%). Median mass size was 4.0 (3.0-5.0) cm, median Padua score was 7.0 (6.0-8.0), and median C-Index score was 2.0 (1.0-3.0). Median duration of intraoperative ischemia was 20.0 (12.0-29.5) min and median operative time was 70.0 (55.0-120.0) min. In histological examination, 157 (84.0%) cases were reported as RCC, 20 (10.7%) as oncocytoma, 9 (4.8%) as angiomyolipoma, and 1 (0.5%) as sarcoma.

3.2. Outcomes of the novel technique and comparison of groups

No significant difference was found between the two groups with regard to age, gender, BMI, mass laterality and size, and the Padua and C-Index scores (p=0.087, p=0.354, p=0.642, p=0.957, p=0.200, p=0.101, p=0.361, respectively). However, median operative time was significantly shorter in the DERVACT group (p<0.001) (Table 1).

Table 1. Comparison of the two techniques

Variable	Standard Enucleation Nephrectomy (n=95)	DERVACT Enucleation Nephrectomy (n=92)	*p*
Age (years)	54.79±12.82	58.11± 13.58	0.087
Gender (Female/Male)	40/52	35/60	0.354
Body mass index (kg/m^2)	29.0(27.0-32.0)	29.0(27.0-34.0)	0.642
Laterality (Right/Left)	52/43	50/42	0.957
Mass size (cm)	5.0(4.0-7.0)	6.0(5.0-7.0)	0.200
Padua	6.5(6.0-8.0)	8.0(7.0-9.0)	0.101
C-Index	2.0(1.0-3.0)	3.0(2.0-4.0)	0.361
Duration of ischemia (min)	20.0(15.0-30.0)	18.5(11.0-27.0)	0.060
Operative time (min)	84.0(61.0-105.0)	64.0(50.0-75.0)	<0.001

DERVACT: Demirtaş' Early Renal Vascular Control Technique

3.3. Intraoperative complications

Intraoperative vascular complications occurred in six (6.3%) patients that underwent standard PN and in one (1.1%) patient in the DERVACT group (p=0.059). In the group that underwent standard PN, five (5.3%) patients developed minor vascular injury during renal pedicle control. In the same group, the segmental renal artery branch was injured in one (1.1%) patient and thus required ligation. In the DERVACT group, however, only one patient developed renal venous injury. All these injuries were repaired intraoperatively and PN was completed in all patients. Apart from these complications, no major intraoperative complications occurred in both groups.

4. Discussion

The results indicated DERVACT provided several advantages: (1) safer and faster completion of kidney dissection, (2) avoidance of time loss due to the non-requirement of dissection

of fat tissues in the renal pedicle and renal vein, and (3) reduced operative time. Moreover, the DERVACT group had a similar complication rate to that of other group, which implicates that DERVACT is a safe procedure.

Renal hilar dissection followed by vascular clamping represents the most important and critical step in renal surgery (3). Although there are a limited number of studies conducted on this subject, Porpiglia et al. are known as the precursors of the strategy used for accessing and controlling the renal artery, who proposed that the arterial control can be achieved via direct access to the aorta and renal artery at the level of Treitz ligament (11-13). Based on this technique, Tunc et al. developed modified laparoscopic radical nephrectomy that involved accessing the renal artery and renal pedicle through the Morison space and performing rapid pedicle control via en-bloc ligation of the renal pedicle (14). In 2019, Yang et al. described a renal hilar dissection technique for laparoscopic partial and radical nephrectomy that offered early vascular control. In this technique, renal artery is reached via direct access to the renal hilum through the posterior aspect of the kidney immediately after entering the retroperitoneal space. The researchers named this technique "three-step method" and proposed it as a safe and practical technique (15). Zhang et al. developed a similar technique for retroperitoneal laparoscopic PN, which involved full exposure of the tumor via dissections followed by renal artery access through the ureter and the superior-lateral aspect of the kidney (5). Nouralizadeh et al. argued that by rotating the kidney 180 degrees on the horizontal axis, the renal pedicle can be controlled more easily (16). The common feature of these three techniques and our technique is that all four of them prioritize the control of the renal artery by accessing the renal hilum through the posterior aspect of the kidney. However, our technique, unlike the others, involves accessing the kidney through the superior-dorsal-lateral aspect rather than the lateral or inferior-lateral aspect of the kidney, thus prioritizing direct and prompt access to the renal artery. Accordingly, DERVACT-Line and DERVACT-Triangle, which were introduced within this technique, may allow the implementation of this technique in a more systematic way. Additionally, DERVACT was developed based on open PN by taking into account the clinics with no opportunities for laparoscopic PN or those with no such experience.

In our study, the operative time was calculated by excluding the duration of ischemia in order to reduce the effect of the complexity of the renal mass and the duration of enucleation. As a result, the mean operative time was calculated as 64 min in the DERVACT group as opposed to 84 min in the group that underwent standard PN, which indicates that DERVACT reduced the operative time by approximately 20 min. Yang et al. evaluated patients that underwent laparoscopic PN and reported the mean operative time as 88 min (15). In contrast, Zapala et al. and as 174 min by Pereira et al. reported the mean operative time in patients undergoing open PN as 100-120 min and 174 min, respectively (17, 18). These findings indicate that the mean operative times in our study, even when the durations of ischemia were included, were shorter than those reported in the literature. This difference could be attributed to the fact that all the procedures were performed by the same surgical team that had 10 years of experience in PN.

A previous meta-analysis evaluated the outcomes of three studies and reported the rate of intraoperative complications in patients undergoing open PN as 4.9% (19). Similarly, another study reported this rate as 5.3% (20). In our study, however, intraoperative vascular complications occurred in only 3.7% (n=7) of 187 patients that underwent open PN, including six (6.3%) patients in the standard PN group and one (1.1%) patient in the DERVACT group. However, this difference was statistically insignificant (p=0.059). Considering that only vascular complication rates were calculated in the present study, our complication rates seem to be consistent with those reported in the literature.

Our study had several important limitations. First, the study had a retrospective design and a small patient population. Second, the time interval between skin incision and pedicle control could not be recorded due to the retrospective nature of the study. Finally, the study introduced a technique for open PN, which is used rarely when compared to the laparoscopic or robotic techniques.

In conclusion, DERVACT is a simple, time-saving, and safe procedure that can be used in clinics with no opportunities for robotic-laparoscopic partial nephrectomy or in cases requiring NSS.

Conflict of interest

All authors declare that, there is no conflicts of interest in connection with this paper

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The importance of paracetamol blood levels on the cost and management of patients with paracetamol overdose

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Abstract

We aimed to evaluate the effect of serum paracetamol level measurement on cost and patient management by evaluating the patients with a history of paracetamol overdose in the emergency department. This study was performed by investigating the data of 175 adult patients admitted to the emergency service after ingestion of the paracetamol-containing drug. Patients were divided into main three groups according to the narrative of ingested amount, and ten subgroups according to the serum paracetamol level, antidote treatment and hospitalization. According to the patients' narrative, the ingested paracetamol amount was toxic in 97 (55.4%) patients. Serum levels were non-toxic in 50 (28.6%), and toxic in only 4 (2.3%) patients. In intergroup cost analysis, the highest median cost per patient was in Group 4 ($ 332.9 [332.2 – 335.6]), and the lowest median cost per patient was in Group 3 ($ 98.0 [67.1 – 98.0]). When the patient groups in our study were evaluated in terms of cost per patient, there was a statistically significant difference between the groups ($p < 0.001$). Antidote administration, hospitalization and duration of treatment were independent variables affecting cost in our study. One unit increase in antidote administration, hospitalization, and the length of treatment caused to increase in cost about 67.3 units, 56.1 units, 2.2 units, respectively ($p<0.001$). The treatment cost can be reduced by measuring serum paracetamol levels. For avoiding a potential missed diagnosis of paracetamol overdose the routine measurement of paracetamol level warrants to reduce the cost of the patients who had an ingestion history of unknown paracetamol amount, especially in cases with altered mental status and psychiatric disorder who had suspected/elusive medical anamnesis about drug ingestion.

Keywords: paracetamol, ingestion, level, management, cost, emergency

1. Introduction

Paracetamol (acetaminophen) widely used for its anti-pyretic/analgesic effects is one of the most common medications ingested in overdose (1). It is cheap, easily accessible, and combined with many other drugs and accepted as a harmless medicinal agent by many users. Nevertheless, intentional and unintentional massive paracetamol ingestions are commonly seen in all around the world.

Paracetamol poisoning is a heavy burden on health systems. In a study conducted in the United Kingdom (UK) between 1992 and 1995, the average cost per patient was 181 Euro (€) due to paracetamol overdose. The total annual cost of paracetamol poisoning is approximately € 8 billion in the UK. Therefore, studies have focused on reducing the costs of diagnosis and treatment (2).

The measure of the paracetamol blood level can only reveal the actual risk of toxicity, especially in most of the patients who required the antidote therapy according to the narrative of the ingested amount. Choosing the right patients for hospitalization and antidote treatment may reduce the costs. The cost-effectiveness and correct antidote use can be achieved only by giving it to the patients who are above the treatment line using the Rumack-Matthew nomogram after the serum paracetamol measurement. Then, unnecessary antidote treatment is prevented by measuring serum paracetamol levels. With its serum level measurement, early diagnosis is made, and complications are prevented, particularly in the patients who do not need antidote according to the ingestion, but have a history of unreliable doses with high serum paracetamol levels (especially in suicidal and psychiatric patients). It provides convenience in the management of patients whose ingested amount is unknown, and unnecessary antidote administration can be prevented by measuring serum paracetamol level in patients who do not need antidote and when anamnesis cannot be taken in relation to paracetemol blood concentrations. For all these reasons, we aimed to examine the importance of serum paracetamol measuring on the patient management and cost in the patients with a history of excessive paracetamol ingestion in the emergency department.

2. Materials and Methods

2.1. Study design, setting, and population

This retrospective and descriptive study was conducted with the patients aged 18 years and above who admitted to the

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emergency service after the ingestion of a paracetamol-containing drug. One hundred eighty-six patients met the inclusion criteria in this study. But due to lack of clinic findings, 11 patients were excluded from the study, and totally 175 patients were enrolled. This study was approved by The Clinical Research Ethics Committee of Ondokuz Mayıs University Medical Faculty (OMU CREC protocol no: 2012/172).

The sociodemographic characteristics, the presence of risk factors for liver damage (advanced age, malnutrition, chronic alcohol consumption, combined drug-using [cytochrome p450 inducers] and primary liver disease), vital signs, symptoms of patients on admission, the amount of paracetamol-containing medication (in grams), the other drugs and their amounts, the ingestion time and the medical history (the presence of psychiatric illness and/or suicidal attempt) were recorded. All the patients were evaluated according to a number of data with the results of liver function tests, serum paracetamol level, treatment (hydration, antidote therapy [intravenous and oral n-acetylcysteine], extracorporeal therapy), the requirement of critical care, the length of hospitalization duration, the hospitalized unite, total cost and prognosis (discharge, death).

The diagnosis for paracetamol poisoning was made by using the following definitions: 1) > 10 gr or 200 mg/kg over a 24 hour period, and 2) > 6 gr or 150 mg/kg per 24-hour period at least two consecutive days (3). The distribution of patients was determined with respect to Clinical staging (Stage 1-4) for paracetamol poisoning (3). Patients' prognosis evaluated according to discharge, liver damage, and death. The cut-off level of hepatocellular injury tests (AST, ALT) for hepatotoxicity was defined as 1000 IU / L and above (4,5). Patients were divided into main three groups (A: Ingestion of non-toxic amounts, B: Ingestion of toxic amounts, C: Ingestion of unknown amounts) and also ten subgroups according to the amount of paracetamol ingestion, serum paracetamol level, antidote treatment and hospitalization (Table 1). Due to the differences in fees of medical procedures, inpatient treatment applied to patients over the years, the total cost for each patient was calculated in the United States dollar ($) considering the current costs in 2020.

Table 1. The research groups according to the amount of paracetamol intake

Groups	Number of Patients(n=175)	The ingested amount*	Serum Parasetamol Level**	Antidote Treatment***	Hospitalization Status****
1	74	M_1	P_0	A_1	Y_1
2	18	M_2	P_0	A_2	Y_1
3	25	M_2	P_0	A_2	Y_2
4	4	M_3	P_0	A_1	Y_1
5	4	M_1	P_1	A_1	Y_1
6	7	M_1	P_2	A_2	Y_1
7	12	M_1	P_2	A_2	Y_2
8	10	M_2	P_2	A_2	Y_1
9	15	M_2	P_2	A_2	Y_2
10	6	M_3	P_2	A_2	Y_1

*The amount of paracetamol intake: M_1, Toxic; M_2, Non-toxic; M_3, Unknown. **Serum paracetamol level: P_0, Level cannot be measured; P_1, Toxic; P_2, Nontoxic. ***Antidote treatment: A_1, Antidote given; A_2, Antidote not given. ****The decision of hospitalization: Y_1, Hospitalized; Y_2, Not hospitalized

2.2. Data Analysis

IBM® SPSS® Statistics V21 software was used for statistical analysis of the data. Data were expressed as mean ± standard deviation (SD), median (minimum – maximum), and number (%) after it was determined if the data were parametric or non-parametric. The Kolmogorov-Smirnov/Shapiro-Wilk Test was used to evaluate the conformity of the quantitative data distribution to a normal distribution. It was determined that it would be appropriate to use non-parametric tests for data analysis in this study. Kruskal-Wallis Test was used for the statistical significance of inter-group costs, which were not found to fit the normal distribution. Regression analysis was performed to determine the independent variables affecting the cost. The statistical significance level was accepted as $p < 0.05$ for all tests.

3. Results

In perspective of the patients' narrative, the ingested paracetamol amount was toxic in 97 (55.4%), non-toxic in 68 (38.9%), and unknown in 10 (5.7%) of patients. Serum paracetamol level could not be measured in 121 (69.1%) of patients because of a lack of analysis kit in the emergency laboratory. Serum paracetamol levels in 54 (30.9%) of patients were measured. Serum paracetamol concentrations were non-toxic in 50 (28.6%), and toxic in only 4 (2.3%) of patients. A mild allergic reaction was seen in one patient (0.6%) during intravenous n-acetylcysteine (NAC) antidote therapy. No patient died and also underwent hemodialysis and liver transplantation in the study population. The characteristics of the patients are presented in Table 2. According to the laboratory parameters, hepatocellular damage markers (ALT, AST) in 8 (4.6%) of patients had increased, and also INR value in 3 (1.7%) of patients had elevated. In intergroup cost analysis, the highest median cost per patient was observed in Group 4 ($ 332.9 [332.2 – 335.6]), and the lowest median cost per patient was seen in Group 3 ($ 98.0 [67.1 – 98.0]). In the regression analysis, the independent variables affecting the cost were determined as antidote administration, hospitalization, and duration of treatment. 98.6% of the cost can be explained with these three independent variables. One unit increase in antidote administration, hospitalization, and the length of treatment caused to an increase in the cost about 67.3 units, 56.1 units, 2.2 units, respectively ($p<0.001$).

Table 2. The characteristics of the sample patients studied (n = 175)

Age	24 (18 -56)
Gender n (%)	
Female/Male	112 (64%) / 63 (36%)
Admission Time (hour)	4 (0.5 -12)
Medical History	
No previous history	130 (74.2%)
Depression disorder	32 (18.2%)
Drug intoxication	9 (5.1%)
Bipolar disorder	4 (2.2%)
Suicidal paracetamol intake	170 (97.1%)
Risk factors for Liver Failure	
No risk	78 (44.5%)
Additional drug ingestion	97 (55.4%)
Chronic alcohol user	5 (2.8%)
Primary liver disease	2 (1.1%)
Multidrug ingestion	
Present/Absent	106 (60.6%)/69 (39.4%)
Vital signs	
Systolic blood pressure	110 (70 -180)
Heart rate	80 (60 -116)
Ingested amount	
Toxic	97 (55.4%)
Non-toxic	68 (38.9%)
Unknown	10 (5.7%)
Serum paracetamol level	
Unmeasurable – no kit	121 (69.1%)
Toxic level	4 (2.3%)
Non-toxic level	50 (28.6%)
Clinical stage	
Stage 1/2	172 (98.3%) /3 (1.7%)
Lenght of treatment (hour)	24 (1 -96)
Treatment modalities	
Normal saline	175 (100%)
Normal saline+Decontamination [Gastric lavage, active charcoal]	175 (100%)
Normal saline + Oral NAC therapy	4 (2.2%)
Normal saline + IV NAC therapy	79 (45.1%)
Hospitalization	
Emercency observation room	120 (68.5%)
Intensive care unite	3 (1.7%)
Final status	
Full recovery	149 (85.1%)
Refuse to receive treatment	26 (14.9%)
Cost ($)	161.1(67.1387.9)

Data are presented as number (%) or median (min - max).

Fig. 1 presents the data of antidote therapy, hospitalization, duration of treatment, and cost values in study groups. When the patient groups were evaluated in terms of cost per patient, there was a statistically significant difference between the groups ($p < 0.001$). The cost per patient ($) was significantly lower in Group 6 (M1P2A2Y1) than in Group 1 (M1P0A1Y1) ($p=0.027$). In addition, the cost value was significantly higher in Group 1 compared to Group 7 ($p < 0.001$). However, there was no statistically significant difference between Group 4 (M3P0A1Y1) and Group 10 (M3P2A2Y1) in terms of the cost ($) per patient ($p > 0.05$).

4. Discussion

Paracetamol overdose is the most common etiological cause of acute liver failure (6). The patient management strategies for paracetamol overdoses include the rapid identification of high-risk patients and low-risk patients because of the need of antidote therapy. With accurate and current patient management strategies, avoiding unnecessary examinations and treatments can alleviate the financial burden on health systems.

Paracetamol-induced liver damage is related to the direct effect of paracetamol and its toxic product (NAPQI) produced excessively by the liver. In relation to drug metabolism, glutathione binds NAPQI and then it converts into non-toxic products (7). Thus, paracetamol intoxication lead to decrease in liver's glutathione stores (8). Moreover, it assumes that hepatic glutathione reserves may decrease in a number of conditions such as advanced age, malnutrition, fasting, and chronic liver disease are though to be risk factors for liver injury in paracetamol overdose. Isoniazid, rifampin, phenobarbital, chronic alcohol consumption may affect the cytochrome P-450 enzyme system, and could give rise to liver damage. Non-steroidal anti-inflammatory drugs, fibrates, and statins may cause paracetamol-induced liver damage as a result of unknown mechanisms. Obesity and non-alcoholic fatty liver disease are risk factors for paracetamol-induced liver injury (5,9).

Multidrug use (antiepileptic, antipsychotic, antidepressant drugs most commonly metabolized in the liver) was estimated as a risk factor for liver damage in our study group. However, there were also patients with chronic alcohol consumption, and chronic liver disease (HBV-induced liver disease) along with multiple drug intake. Actually, no significant differences were observed for the development of paracetamol overdose induced hepatotoxicity, the presence of multiple drug intake, chronic alcohol consumption, chronic liver disease, and the other risk factors for liver damage in this study. Hypoprotrombinemia, metabolic acidosis, and renal failure are associated with elevated aminotransferase levels in paracetamol-induced liver injury (10,11). In our study group, the increased levels in ALT, AST and INR were detected in a small number of laboratory parameters used as a marker of hepatotoxicity. Since hepatocellular damage markers were higher than 1000 IU / L, it was associated with toxicity (9); no patients with hepatotoxicity were detected in our study. This situation may be interested in the low number of patients and the absence of severe poisoning.

Litovitz et al. reported that the majority of patients with acute intoxication who applied to the emergency department were not in poor condition (12). In the study of Sorodoc et al., 51.9% of patients with acute intoxication had good general status (13). In our study, 98.3% of patients were asymptomatic (Stage 1 for paracetamol poisoning) when the complaints, symptoms, and physical examination findings of the patients were evaluated, considering that patients are asymptomatic in the early period of paracetamol-induced liver injury.

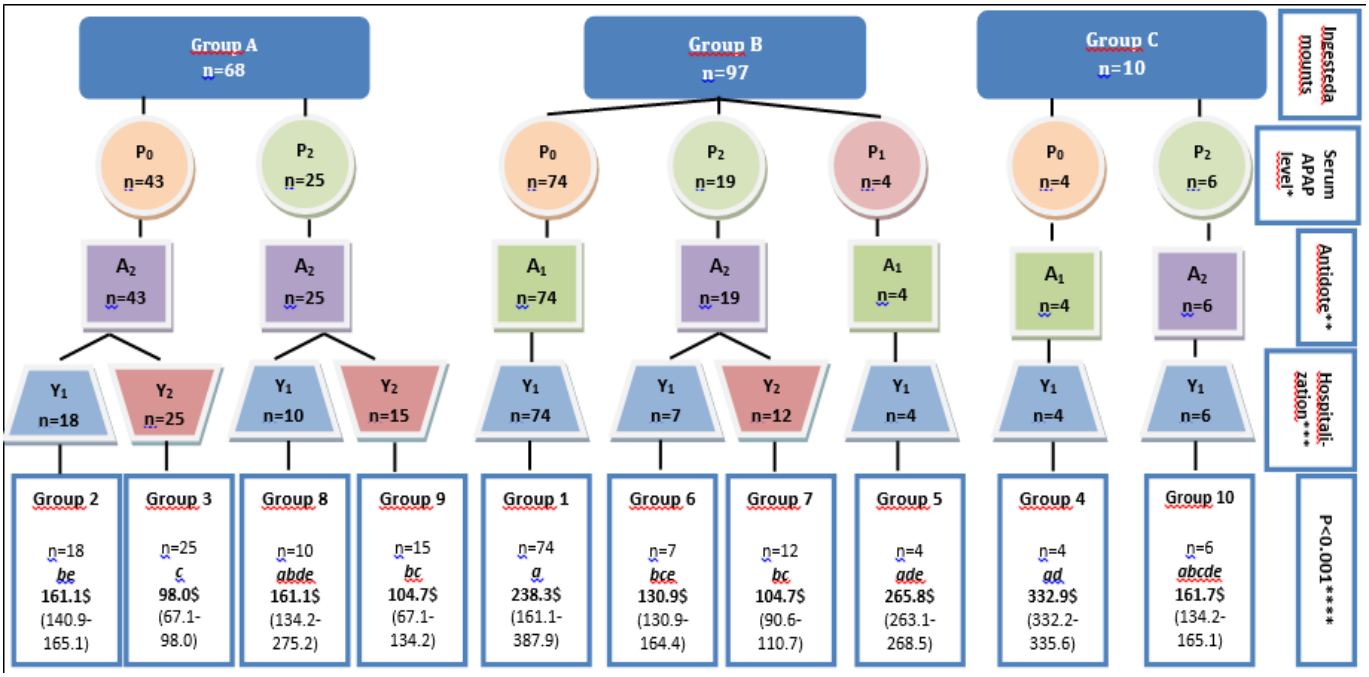

Fig. 1. Analysis of study groups according to ingested amounts, antidote therapy, hospitalization and costs using Kruskal-Wallis Test
Group A: Ingestion of non-toxic amounts, B: Ingestion of toxic amounts, C: Ingestion of unknown amounts.
* According to serum paracetamol level, "P0 = Level cannot be measured, P1 = Toxic, P2 = Nontoxic".
** According to antidote treatment, "A1 = Antidote given, A2 = Antidote not given".
*** According to the decision of hospitalization, "Y1 = Hospitalized, Y2 = Not hospitalized".
****Study groups were identified with the letters "abcde" using Kruskal-Wallis test according to cost differences. The presence of the same letter in the study groups indicates that there was no statistical difference between the groups.

The median value of hospital stay in patients with hepatotoxicity was 3 (1-192) days, and the median value of total hospital expenses was $ 2,123 (342–89,182) in a study (14). In our study, the median value of hospital stay was 24 hours. The patients with high ALT and AST values on admission were hospitalized for three days, and the median cost per patient was $ 94.0 (75.8-131.5). The fact that 14.9% of the patients left the emergency department before the completion of the treatment period could explain the total length of hospital stay and the lower total cost than other studies. The previous study included only patients who developed hepatotoxicity. Thus, the need for organ transplantation, hemodialysis, and the need for prolonged intensive care associated with these conditions increase both the total length of hospital stay and the cost. The absence of hepatotoxicity (ALT and AST ≥ 1000 IU / L) in our study may be another additional factor affecting length of hospital stay and cost. The independent variables affecting total cost and length of hospital stay were age, sex, comorbid diseases, paracetamol-related hepatotoxicity in the previous study (14). In our study, antidote administration, hospitalization, and duration of treatment were found to be independent variables affecting cost, considering that this condition is related to the absence of hepatotoxicity.

Antidote treatment is frequently arranged according to the patient's narrative of ingested amount in emergency departments where serum paracetamol level cannot be measured. Hesitative, low-reliability anamnesis, especially in psychiatric, or unconscious patients are challenging conditions for the emergency physician. However, there were no patients had a toxic serum level of paracetamol in the patient groups who had a non-toxic intake in the anamnesis.

In cases have no additional factor for the indication of hospitalization and follow-up, serum paracetamol measuring facilitates patient management (diagnosis, antidote treatment, hospitalization, and discharge) as long as the ingested amount is toxic according to the patient's anamnesis. When we compared the total costs of Group 1 and 6 in our study, serum paracetamol measuring was cost-effective, especially in patients who received excessive amounts of paracetamol in their medical history.

In cases with the ingestion of unknown amounts of paracetamol or suspected history of intoxication with altered mental status, the routine measurement of paracetamol level should be made to avoid a potential missed diagnosis of paracetamol overdose. Dargan et al. detected 4 (3.5%) patients poisoned with paracetamol among 115 patients presenting with collapse after routine measurement of serum paracetamol level. Based on their results, they suggested that the potential for missed paracetamol poisoning in such patients warrants the routine use of paracetamol screening in all patients presenting to the emergency department with a history of altered mental status (15).

Diagnosis for paracetamol poisoning can be made only by measuring serum paracetamol levels in patients who had no information about ingested amount such as group 10. If the serum paracetamol level could not be measured as in group 4, the patients should be closely monitored using the liver

function tests for paracetamol poisoning. In group 10, paracetamol over-intake was excluded using serum paracetamol level measurement, and antidote treatment was not applied. The fact that the cost per patient in Group 10 is less than Group 4 can be explained by the decrease in the length of hospital stay and laboratory examination costs. Measuring the serum paracetamol level seems to reduce the possible additional costs (hospital stay, follow-up of laboratory tests and antidote treatment). Similarly, serum paracetamol measuring appears to provide cost-effectiveness when the costs between groups 1 and 7 were evaluated. The measurement of serum paracetamol level decreases the cost by shortening the duration of hospital stay and clinical follow-up.

Serum paracetamol levels should be controlled in poisonings with unknown history of drug ingestion. As a result of this, the concomitant paracetamol overdose can be excluded or confirmed. If the determined level is non-toxic, unnecessary antidote treatment decreases, and it results in shortening the hospital stay and reducing the cost. In the view of our findings, we noticed that the routine measurement of serum paracetamol level in patients with paracetamol overdose of unknown ingestion and patients with multiple drug intake of unknown type contributed to patient management (diagnosis, antidote treatment, hospitalization and discharge).

In conclusion, our study aims to contribute to the development of correct diagnosis and treatment strategies in order to reduce the burden of massive paracetamol ingestion among the etiologic factors leading to acute hepatic failure by evaluating the effect of serum paracetamol level on the patient management and cost. Accordingly to our findings, it is suggested that the measuring of serum paracetamol level can permit to reduce patients' cost interested in an ingestion history of unknown paracetamol amount and the number of potential missed paracetamol poisoning in the presence of altered mental status and psychiatric disorder for patients in associated with suspected/elusive medical anamnesis about drug intake.

Although some countries have studies discussing the cumulative costs of paracetamol to their national economies (16,17), our study is the only study that evaluates the effects of paracetamol levels on cost and patient management in detail. The most important limiting factors of our study were retrospective study and absence of hepatotoxicity in the study group. Prospective studies involving more patients are needed to elucidate many factors affecting the cost and length of hospital stay and its relationship with serum paracetamol levels. In our country and other countries in the world, patients who applied to the emergency department due to excessive intake of paracetamol, the number of similar studies on patient management, and cost is not very high. Hence, our study is also essential in terms of shedding light on future studies.

Conflict of interest

None to declare.

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This study was approved by The Clinical Research Ethics Committee of Ondokuz Mayıs University Medical Faculty (OMU CREC protocol no: 2012/172).

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A comparison of the safety of two different enoxaparin doses for thromboprophylaxis following cesarean section

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Abstract

Enoxaparin, from the low molecular weight heparin group, is used as thromboprophylaxis in patients with risk factors following caesarean section. The aim of this study was to investigate the effect of enoxaparin doses on the formation of deep vein thrombosis (DVT), wound site infection (WSI), wound site hematoma (WSH) and hemogram results of patients on the 10th postoperative day. A retrospective examination was made of the files of patients who had undergone a caesarean section operation and been administered enoxaparin as postpartum thromboprophylaxis for 10 days postoperatively. Two groups were formed of 16 patients who received enoxaparin at dose of 60mg/day and 25 patients who received 40mg/day. The groups were compared in respect of age, weight, gravida, gestational week at the time of operation, the leukocyte (Wbc), hemoglobin (Hb), and platelet (Plt) values on postoperative days 1 and 10, and the development of DVT, WSI, and WSH on postoperative day 10. The development of WSI and WSH was determined to be significantly higher in the group that received 60mg/day enoxaparin than in the group that received 40mg/day (p=0.007, p=0.008). With the use of 60mg/day enoxaparin, no change was observed in the Wbc and Hb values on the postoperative 10th day compared to the 1st day (p=0.128, p=0.947), and a significant reduction was determined in Plt values (p=0.014). With an increase in the dose of enoxaparin used as thromboprophylaxis following caesarean section in patients with risk factors, there was seen to be an increase in the formation of WSI and WSH. Compared to a dose of 40mg/day, the use of 60mg/day enoxaparin reduced serum Wbc, did not change Hb, and increased Plt values. Dose adjustment should be made for the drug used as caesarean postoperative thromboprophylaxis in patients with indications, taking the side-effects of enoxaparin into consideration.

Keywords: caesarean, deep vein thrombosis, enoxaparin, hemogram, wound site infection-hematoma

1. Introduction

The likelihood of thromboembolism developing in pregnant females is 4-5-fold greater than in non-pregnant females. Thromboembolic events in pregnancy are venous in 80% of cases, and prevalence is 0.5-2.0 per 1000 pregnancies (1). Deep vein thrombosis (DVT) is seen in 75% of pregnancy-related venous thromboembolism (VTE), and pulmonary embolism (PE) in 20-25% (2). The VTE risk is greater in the postpartum period, and especially in the first two postpartum weeks (3). In a meta-analysis of the relationship between caesarean delivery and VTE, caesarean section delivery was reported to be an independent risk factor for VTE, and the estimated incidence of VTE was 0.003% which was seen to be a 4-fold increase compared with vaginal delivery (4).

While the leading cause of maternal death is hemorrhage in developing countries, thromboembolic diseases are among the leading causes in developed countries (5). Due to the high prevalence of thromboembolism in pregnancy and the postpartum period, and the severity of the outcomes, the treatment and prophylaxis of this disease have a very important place in antenatal care (6, 7). A national guideline has been established in Turkey, based on the RCOG guidelines, for the determination of pregnant patients at moderate-high risk of thromboembolism (8, 9).

Various agents are used in postpartum thromboprophylaxis. The most used drug group is low molecular weight heparin (LMWH), but this may have side-effects such as bleeding and hematoma (10). Enoxaparin is a widely used LMWH (11). The aim of this study was to investigate deep vein thrombosis (DVT), wound site infection (WSI), wound site hematoma (WSH) and hemogram results on the 10th postoperative day of patients administered 40mg/day or 60mg/day enoxaparin according to the risk classification following caesarean section operation.

2. Materials and Methods

This retrospective study included 41 female patients who underwent caesarean delivery and then received postpartum thromboprophylaxis of enoxaparin for 10 days between January 2019 and January 2021 in the Obstetrics and Gynaecology Clinic of Turhal State Hospital. All the patients were aged 18-36 years and had no comorbidities. Two groups were formed of 16 patients who received enoxaparin at a dose of 60mg/day and 25 patients who received 40mg/day.

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Patients were excluded from the study if they had an allergy to heparin or heparin derivatives, liver failure, or any findings of perioperative bleeding (intraabdominal, retroperitoneal, and intracranial). As Turhal State Hospital is a second level healthcare institution, patients with a known high risk of thrombophilia, a history of VTE, a mechanical heart valve, heart failure, active systemic lupus erythematous, or active inflammatory bowel disease, were transferred to a tertiary level healthcare institution. The study was approved by the Local Ethics Committee of Gaziosmanpaşa University with no: 21-KAEK-070.

All the patients underwent caesarean operation by the same surgeon. The operations were conducted under spinal or general anesthesia. The abdomen was entered with a Pfannenstiel caesarean-type incision, and the uterus was opened with a transverse incision. In all the operations, the uterus was sutured in a single layer after the procedure. At mean 8 hours postoperatively, the patients were mobilized and thromboprophylaxis was started at the postoperative 12th hour. In the postnatal period, prophylactic enoxaparin was administered for 10 days to patients with ≥2 points (apart from those with a history of VTE or high-risk thrombophilia) in the VTE risk factors according to the "management guidelines for venous thromboembolism in pregnancy" published by the Republic of Turkey Ministry of Health in 2017 (12) (Fig. 1).

Enoxaparin was administered as a single dose of 40mg/day to patients <90 kg body weight and at 60 mg/day to those weighing >90 kg. A record was made for each patient of age, weight, gravida, gestational week, and postoperative first day hemogram results. The patients were discharged after 48 hours at the earliest and were called for follow up at postoperative 10 days. The development of DVT-PE, the presence of wound site infection or hematoma, and hemogram results were recorded. All these data were compared between the two groups of patients who received 60mg/day enoxaparin and those who received 40 mg/day. The changes in the hemogram from postoperative day 1 to day 10 were also compared between the groups.

Statistical Analysis: Data obtained in the study were analyzed statistically using SPSS vn. 20.0 software (Statistical Package for Social Sciences Chicago, IL, USA). Descriptive statistics were stated as mean ± standard deviation (SD) values for continuous variables and as number (n) and percentage (%) for categorical values. In the paired group comparisons, the Independent Samples t-test, Mann Whitney U-test, or the Chi-Square test were used. A value of $p<0.05$ was accepted as statistically significant.

3. Results

Evaluation was made of a total of 41 females applied with enoxaparin following caesarean section delivery, as 25 patients who received 40mg/day and 16 patients who received 60 mg/day. The mean age of the patients was 27.20±4.76 years in the 40mg/day enoxaparin group and 26.25±4.49 years in the 60mg/day group (p=0.451). No difference was determined between the groups in respect of gestational week at the time of caesarean operation and gravida (p=0.882, p=0.754).

Table 1. Comparison of the groups administered enoxaparin 40 mg/day and enoxaparin 60 mg/day for thromboprophylaxis after cesarean section

	Enoxaparin 40 mg/day (n=25)	Enoxaparin 60 mg/day (n=16)	p
Age (years)	27.20± 4.76	26.25 ± 4.49	0.451
Gravidity	2(1-3)	2(1-3)	0.754
Maternal weight (kg)	77.68 ± 8.47	98.75 ± 7.03	**<0.001***
Gestational week	38 (34-41)	39 (34-40)	0.882
Wbc in po. 1stday(10^3/μL)	8.79 ± 2.96	8.21 ± 3.41	0.385
Wbc in po. 10thday(10^3/μL)	8.29 ± 3.9	9.14 ± 3.21	0.302
Hb in po.1stday(g/dL)	11.79 ± 1.15	11.49 ± 1.67	0.862
Hb in po.10th day(g/dL)	11.04 ± 0.97	11.05 ± 1.43	0.715
Plt in po.1stday(10^3/μL)	259.92 ± 55.34	264.19 ± 58.47	0.904
Plt in po.10th day(10^3/μL)	203.16 ± 61.53	171.75 ± 39.69	0.316
IIS	2 (8)	7 (43.75)	**0.007***
HIS	0	4 (25)	**0.008***
DVT	0	1 (6.25)	0.236

Variables presented as mean ± sd and number (%). Wbc= white blood cell, Hb= hemoglobin, Plt= platelet, po.=postoperative, IIS= Infection in the incision site, HIS= Hematoma under the incision site, DVT= Deep Vein Thrombosis

The development of WSI and WSH was determined to be significantly lower in the group that received 40mg/day enoxaparin than in the group that received 60mg/day (p=0.007, p=0.008). In the comparison of the Wbc, Hb, and Plt values on the postoperative 1st and 10th days, no statistically significant difference was determined between the groups (p=0.385, p=0.302, p=0.864, p=0.715, p=0.904, p=0.316) (Table 1).

From postoperative day 1 to postoperative day 10, there was a decrease of 56.76±55.61 103/μL in the serum Plt value in the 40 mg/day enoxaparin group and a decrease of 92.44 ±48.53 103/μL in the 60 mg/day enoxaparin group. The change in Plt was statistically significant between the groups (p=0.014).

From postoperative day 1 to postoperative day 10, there was a decrease of 0.5±4.04 103/μL in the serum WBC value in the 40 mg/day enoxaparin group and an increase of 0.92±3.27103/μL in the 60 mg/day enoxaparin group, and the difference between the groups was not statistically significant (p=0.128). From postoperative day 1 to postoperative day 10, there was a decrease of 0.75±1.70 g/dL in the serum Hb value in the 40 mg/day enoxaparin group and a decrease of 0.43±2.06 g/dL in the 60 mg/day enoxaparin group. The change in Hb was not statistically significant between the groups (p=0.947) (Table 2).

Table 2. Comparison of the changes in Wbc, Hb and Plt levels of groups from postoperative 1st to postoperative 10th days

	Enoxaparin 40 mg/day (n=25)	Enoxaparin 60 mg/day (n=16)	p value
Wbc (10^3/µL)	0.5± 4.04	-0.92 ±3.27	0.128
Hb(g/dL)	0.75 ± 1.70	0.43 ± 2.06	0.947
Plt(10^3/µL)	56.76 ± 55.61	92.44 ± 48.53	**0.014***

Variables presented as mean ±sd and number (%). Wbc= white blood cell, Hb= hemoglobin, Plt= platelet

4. Discussion

Within a two-year period, 41 patients who had undergone caesarean section operation in the single centre of the Obstetrics and Gynaecology Clinic of Turhal State Hospital received enoxaparin as postpartum thromboprophylaxis according to the "guidelines for the management of venous thromboembolism in pregnancy" published by the Republic of Turkey Ministry of Health in 2017. Of these patients, 16, weighing <90 kg received enoxaparin at a dose of 40mg/day and 25, weighing>90kg received 60 mg/day. The results of this study showed that with an increase in enoxaparin dose, there was an increase in the formation of WSI and WSH. Compared to enoxaparin at a dose of 40mg/day, with the use of 60mg/day, no change was observed in the serum WBC and Hb values, and a reduction was seen in Plt values.

During pregnancy, the risk of DVT or PE is approximately 0.1%, and this rate is 3-4 folds higher than in non-pregnant women of the same age (13). During the pregnancy and for 6-8 weeks postpartum, the DVT risk increases 5-6-fold. The frequency of DVT in pregnancy is 0.05%-1.8% and in pregnant patients who have a caesarean delivery, this rate increases to 2.2%-3% (14). Previous studies in literature have shown the efficacy of postpartum thromboprophylaxis (15). In a review of international guidelines, it was reported that LMWH administered for one week postpartum reduced the likelihood of DVT development by 70% (3). Caesarean section delivery increases the risk of venous thromboembolism2-fold. Nevertheless, this risk for a healthy woman with no risk factors is still low (1/1000) (1). In the current study, PE was not observed in any patient, and DVT developed in only one patient. Due to the low numbers, no significant relationship could be determined between enoxaparin dose and DVT development.

LMWH may have side-effects such as bleeding and hematoma (16). Thrombocytopenia and osteoporosis are rarely seen side-effects caused by heparin (17). In a previous observational study, the likelihood of severe hemorrhage associated with LMWH was reported to be 0.3%-1.1% (18-20). In another study, it was calculated that to prevent each DVT, treatment with LMWH would cause two major hemorrhages, seven wound hematoma, and si transfusion cases (3, 21). In contrast, Watanabe et al. reported that enoxaparin started immediately after caesarean did not increase the incidence of hemorrhagic complications and showed that of 131 cases, there was only one case of potential incision hematoma, and no change was recorded in hemoglobin (22). In the current study, of the 25 patients who received 40mg/day enoxaparin, WSI developed in two patients and no cases of WSH or DVT were observed.

In heparin-related thrombocytopenia, although the risk changes according to the form used, there is a risk of thrombocytopenia associated with all heparin preparations. Therefore, whatever type of heparin is used, the thrombocyte count of all patients using heparin should be monitored closely for at least 5-14 days after starting treatment (5, 23). This causes hypercoagulopathy, which is observed in platelet IgG antibody activation (24). In the current study, a significant reduction was seen in the Plt values from the first to the tenth day.

The selection of an appropriate and safe dose of enoxaparin is clinically important for obese women as this patient population is at high risk of developing DVT and hemorrhage after giving birth (25, 26). Of the 16 patients who received 60mg/day enoxaparin in the current study, WSI developed in 7, WSH in 4, and DVT in 1. The frequent occurrence of WSI was attributed to maternal excess weight.

There were some limitations to this study, primarily the retrospective design, and that patient data were gathered from the available patient follow-up forms and then analyzed. The low number of patients in each group may have been the reason that significant results were not obtained in the comparisons of some parameters. Therefore, there is a need for further prospective studies with a greater number of patients.

In conclusion, the Republic of Turkey Ministry of Health has set a target of the application of postpartum thromboprophylaxis to at least 50% of patients undergoing caesarean section delivery. The administration of enoxaparin at doses of 40mg/day and 60mg/day to pregnant patients at moderate – high risk of thromboembolism is effective and safe, but the side-effects of enoxaparin must not be overlooked. For patients with indications after caesarean delivery, there should be good dose adjustment of enoxaparin to be used as thromboprophylaxis.

Conflict of interest

None to declare.

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Research Article

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Investigation of Epstein-Barr Virus antibodies by ELISA and IFA methods

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Abstract

Epstein-Barr Virus (EBV), play role in etiology of malignancies as Burkitt Lymphoma and Nasopharyngeal Carcinoma alongside very common situation like Infectious Mononucleosis. Also in patients groups, like transplant and oncologic patients whose immune system especially depressed detection of EBV reactivation is important. In this study, investigation of results defined by Immunofluorescent Antibody (IFA) and Enzyme-Linked ImmunoSorbent Assay (ELISA) methods aimed. Between 2017 July and 2020 July in our laboratory, With 7455 samples Anti-VCA IgM results detected by the ELISA method were 3.9% positive, 94.1% negative, and 3% borderline. With 5510 samples Anti-VCA IgG results detected by the ELISA method were 82,3% positive, 16.1% negative, and 1.6% borderline. With 449 samples, 32.9% of Anti-VCA IgM, 96.8% of Anti-VCA IgG,55% of Anti-EA IgG, and 93.5% of Anti-EBNA antibody results detected by the IFA method were positive. Positive Anti-VCA IgM results were 3% by ELISA and 25% by the IFA, positive Anti-VCA IgG results were 96.3% by ELISA and 98% by IFA. ELISA Anti-VCA IgG sensitivity was found to be 96.3% and ELISA Anti-VCA IgM sensitivity was found to be 12.9% in statistical analysis, considering IFA as the gold standard. For serological diagnosis of acute EBV infection or reactivation of latent infection EBV Anti-VCA IgM, Anti-VCA IgG, Anti-EBNA IgG, Anti-EA IgG, and Anti-VCA IgG avidity antibodies should be evaluated together.

Keywords: epstein-barr virus, immunoflourescent antibody, enzyme-linked immunosorbent assay, anti-epstein-barr nuclear antigen

1. Introduction

Epstein-Barr virus (EBV) is a virus from the Herpesviridae family, which can be seen quite frequently in the world, can be transmitted through oropharynx secretions through close contacts such as kissing, blood, and common items. It contains DNA as genetic material. Infectious mononucleosis (IM) is a clinical condition that can occur with symptoms such as lymphadenopathy (LAP), pharyngitis, fever, and splenomegaly in young and adult patients, while pediatric patients often pass without symptoms (1, 2). The virus can cause malignant transformation in B and T lymphocytes, epithelial cells, and smooth muscle cells. It has been shown to be associated with various cancers such as Burkitt's Lymphoma (BL), nasopharyngeal carcinoma (NFC), post-transplant lymphoproliferative disease (PTLD), gastric carcinoma, Hodgkin, and non-Hodgkin lymphoma, and leiomyosarcoma (3). In immunocompromised individuals, EBV reactivation occurs when cytotoxic T lymphocytes, B lymphocytes, as well as latent antigens are affected and cause malignant changes. This system is quite balanced to normal conditions in a healthy individual and causes almost no specific symptoms and signs. In cases where the immune system is weakened, T cell activity is reduced, such as in a solid organ or stem cell transplants, or HIV infection, virus reactivation can cause serious complications (4).

The fact that EBV infections have become an important problem in immunocompromised patients, whose number is increasing, has increased the importance of EBV specific tests (5). It is important to detect and demonstrate the reactivation of latent EBV, especially in immunocompromised patients such as organ and bone marrow recipients or cancer patients (6). In this study, it was aimed to examine the EBV antibody results determined by Enzyme-Linked ImmunoSorbent Assay (ELISA) and Immune Fluorescent Antibody (IFA) test.

2. Materials and Methods

EBV viral capsid antibody Anti- (VCA) IgM in 7455 serum samples sent to our laboratory from various clinics of our university's hospital between July 2017 and July 2020 and Anti-VCA IgG antibodies in 5510 serum samples was investigated by ELISA method (Architect, Abbot, Wiesbaden-Germany). EBV Anti-VCA IgM, Anti-VCA IgG, Anti-EarlyAntigen (EA) IgG, Anti-Epstein-Barr Nuclear Antigen (EBNA) IgG antibodies and Anti-VCA IgG avidity in 449 serum samples with IFA method (Euroimmun, Luebeck-Germany) status has been investigated. In addition, in this study, Anti-VCA IgG and Anti-VCA IgM antibody results determined by IFA and ELISA were compared in 164 samples sent simultaneously from the same patients. The IFA method was accepted as the gold standard and the sensitivity and specificity of the ELISA test were calculated.

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3. Results

Hematology 3534 (47.4%), pediatric hemato-oncology 756 (10.2%), infectious diseases 448 (6.1%), internal diseases 324 (4.3%), pediatric nephrology 289 (3.8%) and 2104 (28.2%) from other clinics among the 7455 anti-VCA IgM antibodies investigated by ELISA, 298 (4.1%) were positive, 7018 (94.1%) were negative, 139 (1.8%) were determined as intermediate values (Table 1). The average age of these patients, whose age range is 1-88, is 46, the gender distribution is 3986 (53.5%) male and 3469 (46.5%) female.

Table 1. EBV Anti-VCA IgM and Anti-VCA IgG antibody results determined by ELISA

	Anti-VCA IgM n (%)	Anti-VCA IgG n (%)
Positive	298 (4.1%)	4539 (82.3%)
Negative	7018 (94.1%)	886(16.1%)
Intermediate	139 (1.8%)	85 (1.6%)
Total	7455 (100%)	5510 (100%)

Hematology 1924 (34.9%), pediatric hemato-oncology 692 (12.6%), internal diseases 536 (9.8%), infectious diseases 327 (5.9%), pediatrics 298 (5.4%) and 1733 (31.4%) samples from other clinics. Of the 5510 samples investigated for anti-VCA IgG antibody, 4539 (82.3%) were positive, 886 (16.1%) were negative, and 85 (1.6%) were determined as intermediate values (Table 1). The average age of these patients, whose age range is 1-79, is 34, the gender distribution is 3101 (56.2%) male and 2409 (43.8%) female.

Hematology 398 (88.6%), pediatrics 29 (6.5%), and 22 (4.9%) from other clinics, 148 (32.9%) of 449 samples investigated by IFA method had Anti-VCA IgM, 435 (96.8%) had Anti -VCA IgG was found to be positive in 247 (55%) Anti-EA IgG, 420 (93.5%) with anti-EBNA antibodies, low avidity in 33 (7.3%) of the samples studied with the IFA test, 416 (92.7%), high avidity was detected (Table 2). The average age of these patients, whose age range is 1-67, is 41, the gender distribution is 237 male (52.7%) and 212 female (47.3%).

Table 2. EBV profile results determined by IFA

	Positive	Negative	Total n (%)
Anti-VCA IgM n(%)	148 (32.9%)	301 (67.1%)	449 (100%)
Anti-VCA IgG n(%)	435 (96.8%)	14 (3.2%)	449 (100%)
Anti-EA IGG	247 (55%)	202 (45%)	449 (100%)
Anti-EBNA IgG	420 (93.5%)	29 (6.5%)	449 (100%)
	High n(%)	**Low n(%)**	**Total n(%)**
Anti-VCA IgG Avidity	416 (92.6%)	33 (7.3%)	449 (100%)

Anti-VCA IgM and Anti-VCA IgG antibodies were studied simultaneously with IFA and ELISA tests in a total of 164 samples, 146 of whom were from the Hematology clinic, in 3% of the patients with the Anti-VCA IgM antibody ELISA, in 25% with IFA, Anti-VCA IgG antibody was detected as positive in 96.3% by ELISA and 98.1% by IFA (Table 3). While ELISA and IFA were consistent, differences were found in Anti-VCA IgM results. ELISA Anti-VCA IgG sensitivity was found to be 96.3%, while ELISA Anti-VCA IgM sensitivity was 12.9% in the statistical analysis performed by accepting IFA as the gold standard. Anti-VCA IgM antibody results, the p-value was <0.00001 ($p < 0.05$), Anti-VCA IgG results were statistically insignificant; the p-value is .310579 ($p < 0.05$) when two methods were compared with Pearson Chi-Square test. EBV other antibody results of these patients are given in Table 4. The average age of these patients, whose age range is 3-77, is 45, the gender distribution is 94 (57.3%) male and 70 (42.7%) female.

Table 3. Comparison of Anti-VCA IgM and Anti-VCA IgG antibody results in patient samples studied with ELISA and IFA method

	Anti-VCA IgM n (%)		Anti-VCA IgG n (%)	
	ELISA	IFA	ELISA	IFA
Positive	5 (3%)	41 (25%)	158 (96.3%)	161 (98.1%)
Negative	159 (97%)	123 (75%)	6 (3.7%)	3 (1.9%)
Total	164 (100%)	164 (100%)	164 (%100)	164 (100%)

Table 4. IFA EBV Profile results of patients compared with ELISA and IFA antibody results

	Positive n (%)	Negative n (%)	Total n (%)
Anti-EA IgG	99 (% 57)	65 (%43)	164 (%100)
Anti-EBNA IgG	134 (%81.4)	30 (%18.6)	164 (%100)
	High avidity n(%)	**Low avidity n(%)**	**Total n (%)**
Anti-VCA IgG Avidity	157 (%94.7)	7 (%5.3)	164 (%100)

4. Discussion

By detecting antibodies produced against four different antigens of EBV, the infection is diagnosed serologically and the infection period is determined. These antigens; VCA is the diffuse component of EA (EA / D), the restrictive component of EA (EA / R), and the nuclear antibody (EBNA). In acute infection, EBV VCA IgG, IgM, and EA antibodies are positive, and EBNA antibodies are negative. Four weeks after the onset of the acute period, VCA IgM disappears, while VCA IgG is detected positive in serum for life. Anti VCA IgG and EBNA are persistent for life and are an indicator of chronic virus carriers (7). Specific serological tests for EBV antigens are used to identify EBV infection and to distinguish between other mononucleosis-causing infections. The diagnosis of primary and past EBV infection can often be made by looking at only 3 parameters: anti-VCA IgM, anti-VCA IgG and anti-EBNA IgG antibodies. Most likely, anti-VCA IgM and anti-VCA IgG positivity as well as anti-EBNA IgG negativity favor acute infection, presence of

anti-VCA IgG and anti-EBNA IgG, absence of anti-VCA IgM past infection (8). In cases where there is only anti-VCA IgG in the absence of anti-VCA IgM and anti-EBNA IgG, or in cases where all three parameters are present, it may be difficult to diagnose infections such as acute, past or reactivation serologically. The presence of isolated anti-EBNA IgG may also raise suspicion. To interpret such profiles, detection of anti-IgM and anti-IgG antibodies by IFA, immunoblot test, detection of anti-VCA IgG avidity and anti-EA / D antibodies, and viral genome determination by molecular methods can be used. These tests can be useful to identify possible infection status and to resolve problems that may arise in routine laboratory practice (6, 8, 9–11).

Table 5. Serological profiles and interpretations in EBV infection

Anti-EBV Antibodies			Evaluation
VCA IgM	**VCA IgG**	**EBNA IgG**	
Negative	**Negative**	**Negative**	Not exposed to EBV infection
Positive	**Negative**	**Negative**	Acute infection early or nonspecific*
Positive	**Positive**	**Negative**	Acute infection
Negative	**Positive**	**Positive**	Past infection
Negative	**Positive**	**Negative**	Acute or past infection *
Positive	**Positive**	**Positive**	Late primary infection or reactivation *
Negative	**Negative**	**Positive**	Past infection or nonspecific *

*: Atypical serological profile

Table 6. Possible causes of atypical ebv serological profiles and further review suggestions

Atypical Profile	Possible Causes	Further Review
Isolated VCA IgG positivity	EBV VCA IgM may not have been produced, can be found in low concentration (false negativity), can occur 1-2 weeks after VCA IgG. In 5% of past infections, EBNA IgG may not be produced or may be produced below the detection limit (False negativity), present in immunocompromised patients may disappear over time.	-Immunoblot -VCA IgG Avidity -EBV DNA Research -Heterophil Antibody Tests -Repetition of tests after 30 days -Anti EA-IgG research
Combination positivity of EBNA IgG, VCA IgM and VCA IgG	VCA IgM may remain positive for several more months after acute infection, may occur in EBV reactivation, may persist from primary infection. Late period of primary infection where EBNA IgG is newly formed. False positivity can be found in VCA IgM during CMV, Parvovirus B19, Toxoplasma gondii, HAV, HIV infections.	-Immunoblot -VCA IgG Avidity -EBV DNA Research -Heterophil Antibody Tests -Repetition of tests after 30 days -Anti EA-IgG research - Parvovirus IgM and CMV IgM analysis
Isolated EBNA IgG positivity	VCA IgG Loss in previous infection	-Immunoblot -Anti EA-IgG research -Heterophil Antibody Tests

After primary infection, EBV can enter the latent phase and then reactivation can be observed depending on the immunological status of the host. In reactivation, virus replication and excretion usually occur asymptomatically. In rare cases, reactivation is associated with clinical manifestations such as EBV-associated lymphoproliferative disorders, mostly in individuals with compromised T-cell immune systems, such as in AIDS patients and transplant recipients. In addition, EBV is also associated with Burkitt's Lymphoma and Nasopharyngeal Carcinoma in individuals with strong immune systems (12). Due to such reasons and its importance in the differential diagnosis, early and correct diagnosis of EBV is very important. Conventionally, antibodies against EBV are measured by IFA. IFA is considered the 'gold standard' in the serological diagnosis of EBV infection (1, 13). The use of IFA in EBV infected cells is the reference method for determining specific EBV antibodies (14). However, the disadvantages of the IFA method are nonspecific immunofluorescent staining, difficulties in standardization, requiring experienced personnel, and subjective interpretation of the results. It is therefore important to determine the sensitivity and specificity of the ELISA method, in which many sera can be evaluated more practically, compared to IFA (15, 16). EBV infections are acquired at different ages in different socioeconomic groups, and this may affect clinical presentation (17). The positivity rates in various age groups in a variety of low seroprevalence studies reported from Turkey at 70%, was reported to be the highest at 99.4% (18-21). In these studies, seroprevalence was investigated using the ELISA method and it is consistent with the results of our study.

Haque et al. (15) found 97% compatibility between IFA and ELISA in a study, while ELISA was found to be less sensitive than IFA. Farber et al. (23), EBV VCA IgG was measured by ELISA and IFA, and the compatibility between the two methods was examined, and ELISA was shown to be 95% compatible with IFA for VCA IgG. According to IFA, the sensitivity of ELISA for EBV VCA IgG was determined as 94% and specificity was 97.8% (23). Michalek et al. (22) emphasized that serology and DNA analysis should be evaluated together in the diagnosis of EBV infections in pediatric oncology patients, and serological tests alone are not sufficient in the diagnosis. Serological profiles that can be obtained by the ELISA method and their interpretations are given in Table 5, and some atypical situations that may be encountered in interpreting the profiles are given in Table 6. In the interpretation of serological profiles, acute or previous infection or reactivation comments cannot always be made clear.

Kaşifoğlu et al. (24), ELISA and IFA compliance rates were found to be 100% for seronegativity, 100% for acute primary infection, 22.2% for late primary infection, and 92.1% for the previous infection. In our study, while ELISA and IFA Anti-VCA IgG results were consistent, differences were found in Anti-VCA IgM results. In the statistical analysis performed by accepting the IFA as the gold standard, ELISA Anti-VCA IgG sensitivity was found 96.3%, while ELISA Anti-VCA IgM sensitivity was found 12.9%.

In our study, when the VCA IgM IFA and ELISA results were compared, a difference was found in the positivity rates. When we examine this result, it is known that the evaluation of IFA test requires experienced personnel. Experienced personnel are employed in our laboratory as well. At the same time, it was found that the VCA IgM antibody positivity evaluation of the kit used in this study was a little more difficult, besides easily detecting other antibodies. We think it is important for the manufacturing company to consider this assessment.

VCA IgM antibodies can persist for months after acute infection (25) and reappear in reactivation situations (26). In some cases, VCA IgM may not be produced or appear in VCA IgG after 1-2 weeks, or they are produced in concentrations too low to be detected by standard methods (8). It may be useful to consult the EA IgG and Anti-VCA IgG results to interpret the VCA IgM antibodies investigated by both IFA and ELISA methods in acute or past infection or reactivation situations.

Especially for Anti-VCA IgM, there is a need to compare IFA and ELISA results in larger patient groups. In the serological diagnosis of acute EBV infection, late primary infection, or reactivation, anti-VCA IgM, Anti-VCA IgG, Anti-EBNA IgG, Anti-EA IgG and Anti-VCA IgG avidity antibodies of EBV antibodies should be evaluated together.

Conflict of interest

None to declare.

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None to declare.

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Determinants for poor perinatal outcome in term pregnancies with umbilical cord prolapse

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Abstract

Umblical cord prolapse is a very rare condition. It is an obstetric emergency that can have unfavourable consequences for the fetus. We aimed to investigate the determinants for poor perinatal outcome following emergency cesarean delivery performed due to umbilical cord prolapse in uncomplicated term pregnancies. Fifty-three term pregnants and their babies born with cesarean section due to umbilical cord prolapse were included in this retrospective study. Newborns who were taken to neonatal intensive care unit were defined as poor perinatal outcome.Eleven of fifty-three newborns needed intensive care. All of them were discharged without any problem after the treatment. The presence of fetal distress detected before or during the umbilical cord prolapse was found to be the only marker associated with poor perinatal outcome. Abnormalities detected in fetal heart rate monitoring before or during umblical cord prolapse increase poor perinatal outcome in uncomplicated term pregnancies.

Keywords: cesarean section, perinatal outcome, umblical cord, newborn

1. Introduction

Umbilical cord prolapse (UCP) is a rare condition in obstetrics practice. Its incidence is generally reported to be between 0.1%-0.6% and increases in non-cephalic presentations, multiple pregnancies, polyhydramnios, or early gestational ages (1, 2). It is classified as an obstetric emergency because it can cause poor neonatal outcomes such as hypoxic encephalopathy and death (2).

Some predictors for perinatal outcome have been identified including location where the prolapse occurred, diagnosis-to-delivery interval (DDI), gestational age/birthweight of the fetus and mode of delivery (3). While when UCP occurs outside the hospital, the mortality rate has been reported as 44% and it has been reported 3% when it occurs inside the hospital (4). Premature and low birth weight infants have less favorable outcomes, and the risk of perinatal mortality was 2-fold higher than in those without UCP (5). In some studies, it has been found that DDI less than 30 minutes is associated with higher Apgar scores (6). And emergency cesarean section (ECS) delivery reduces the risk of perinatal mortality and morbidity compared to vaginal delivery. Nevertheless, poor perinatal outcome may also occur when CS is applied promptly (7).

Umbilical cord prolapse is believed to be as an “all or non event condition’ that causes overwhelming neurological injuries and death. It may cause brain damage to fetus (2, 3). However, there is insufficient information about the factors that may be associated with poor perinatal outcome even when emergency interventions are performed. In our study, we aimed to investigate whether there are any factors that increase the probability of poor perinatal outcome in cesarean delivery which is applied urgently in uncomplicated term pregnancies due to UCP indication.

2. Materials and Methods

This retrospective study included pregnant women who were delivered by cesarean section due to UCP at Zekai Tahir Burak Woman’s Health Education and Research Hospital over a 5-year period. The detection of a segment of the umbilical cord descending through the cervix to the vagina in front of the presenting part of fetus was defined as UCP (3). In our clinics, as soon as UCP is detected, the prolapsed cord is pushed manually from the vagina and an immediate ECS is performed. Pregnant women who were included in the study had term pregnancy and all had singleton vertex presentation fetuses. Pregnant women with complications such as hypertension, diabetes mellitus, intrauterine growth restriction, polyhydramnios was excluded from the study. Multiple pregnancies were also excluded. In addition, pregnant women who had insufficient data about pregnancy follow-up, labor process and perinatal period were excluded from the study. Necessary approval was obtained from the institutional review board of the hospital for the study.

The presence of admission to the neonatal intensive care unit (NICU) of the newborn following cesarean section was defined as poor perinatal outcome. Pregnant women with poor perinatal outcome were classified as case group, while the women with no poor perinatal outcome constituted the

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control group. The data were retrieved from the hospital records and each reviewed with special interest to the demographic parameters and the pregnancy status of the mothers. The gestational age (corrected by the first trimester ultrasonography) and the delivery phase at which the UCP occurred as well as intrapartum fetal well-being determinants (meconium-stained amniotic fluid and fetal heart rate monitoring record), DDI, and the perinatal outcome were also noted. The detection of any recurrent abnormal fetal heartbeat decelerations during fetal heart rate monitoring (FHRM) including prolonged decelerations, moderate-to-severe variable decelerations, late decelerations combined with absent or minimal variability, or bradycardia with a reduction in baseline FHR to less than 70 beats per minute was defined as fetal distress (8).

Statistical analyses were carried out by using the statistical packages for SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine the data distributions. Continuous variables were expressed as mean ± standard deviation, and categorical variables were given as number (percentage). Continuous variables were analyzed using Students' t-test and categorical variables were compared using a $\chi 2$ test. Factors classified as related risk factors for poor perinatal outcome were assessed using multivariate logistic regression model. The p values less than 0.05 were considered statistically significant.

3. Results

UCP was detected in 68 (0.12%) of 56179 term pregnant women delivered in our hospital during the study period. After exclusion criteria, 53 pregnant women were determined to be eligible for the study. Eleven (20.8%) of them constituted the case group, while 42 (79.2%) of them constituted the control group. All newborns in the case group were taken to NICU due to respiratory distress and were discharged from the hospital without any problem after treatment. No perinatal mortality was detected in the newborns of the study.

Table 1. The clinical and demographic characteristics of groups

	Case group (n=11)	Control group (n=42)	p
Woman's age (year)	27.63±1.80	27.90±3.36	0.800
Gestational age (day)	275.37±6.33	275.26±4.90	0.954
Multiparity	6 (54.5)	23 (54.8)	0.990
Labor induction with oxytocin	7 (63.6)	26 (61.9)	0.916
ARMs	10 (90.9)	35 (83.3)	0.532
Early ARM (before 5 cm cervical dilatation)	4 (36.4)	14 (33.3)	0.850
Meconium-stained amniotic fluid	4 (36.4)	6 (14.3)	0.096
Cervical dilatation (cm) during UCP	6.00±1.00	5.14±1.76	0.129
Fetal head engagement	4 (36.4)	11 (26.2)	0.505
Antecedent or coincedent fetal distress	9 (81.8)	12 (28.6)	**0.001**
Diagnosis to delivery interval (min.)	21.95±3.94	20.18±4.38	0.200
Diagnosis to delivery interval >30 min.	1 (9.1)	2 (4.8)	0.580
Diagnosis to delivery interval>20 min.	7 (63.6)	30 (71.4)	0.616
Newborn birth weight (gr)	3740.00±515.93	3721.90±383.63	0.898
Newborn birth weight ≥4000 gr	6 (54.5)	12 (28.6)	**0.046**
Newborn gender ratio (male/female)	7:4	19:23	0.277

Values were presented as mean±standard deviation and number (%). UCP: Umblical cord prolapse; ARM: Artificial rupture of membranes. p<0.05 was considered as statistically significant.

Table 2. Multivariate analysis of possible risk factors for poor perinatal outcome

	Wald	S.E.	p	OR (95% CI)
Cervical dilatation during UCP	2.37	0.34	0.123	0.59 (0.31-1.15)
Antecedent or coincedent fetal distress	9.04	1.34	**0.003**	56.16 (4.07-775.61)
Meconium-stained amniotic fluid	1.33	1.36	0.249	4.81 (0.33-69.52)
Diagnosis to delivery interval	1.13	0.12	0.287	1.14 (0.90-1.44)
Newborn birth weight ≥4000 gr	0.40	1.04	0.228	1.93 (0.25-14.82)
Newborn gender ratio (male/female)	3.07	1.51	0.080	14.14 (0.73-274.38)

UCP: Umblical cord prolapse; SE: Standart error; OR: Odds ratio, CI: Confidence Interval. p<0.05 was considered as statistically significant

The clinical and demographic characteristics of the groups were listed in Table 1. Maternal and gestational age did not reveal any significant differences between the groups (p=0.800 and p=0.954; respectively). In both groups, more than half of the pregnancies were multiparous (p = 0.990) and more than half were administered oxytocin infusion for labor induction (p = 0.916). In each group, almost all of the pregnancies (90.9% vs. 83.3%) had undergone an artificial rupture of membranes (ARMs) (p=0.532), and about a third of these (36.4% vs. 33.3%) were early ARM (p= 0.850). Although the presence of meconium-stained amniotic fluid was detected more frequently in the case group, the difference between the groups was not significant (36.4% vs. 14.3%; p= 0.096). The cervical dilatation measurements when UCP occurred (p=0.129) and the state of engagement of the fetal head (p=0.505) were similar in both groups. DDI duration in the case group was 21.95 ± 3.94 min, and in the control group it was 20.18 ± 4.38 min. and these values did not reveal a

statistical difference (p=0.200). There were also no significant differences between the groups in terms of DDI >30 or >20 frequency (p=0.580 and p=0.616, respectively). Similarly, no significant difference was found between the birth weights of the newborns (3740.00±515.93 gr vs. 3721.90±383.63 gr; p=0.898). In addition, considering the neonatal gender, the male gender in case group and female gender in the control group was higher, but this difference was not statistically significant (p=0.277). On the other hand, the presence of antecedent or coincident fetal distress (81.8% vs. 28.6%) and newborns with ≥4000gr birthweight (54.5% vs. 28.6%) were significantly more frequent in the case group than in the control group (p=0.001 and p=0.046; respectively). Variable decelerations detected during FHRM in 5 (55.6%) pregnant women and absent / minimal variability in 4 (4.4%) pregnant women were defined as fetal distress. In the control group, the number of these pregnant women was 7 (58.3%) and 5 (41.7%), respectively. The multivariate analysis found that the only significant independent risk factor for poor perinatal outcome was the presence of antecedent or coincident fetal distress (Odds Ratio= 56.16 95% Confidence Interval= 4.07-775.61; p=0.003) (Table 2).

4. Discussion

UCP is an obstetric disaster, fortunately its frequency is quite rare, as found in our study. Today, although the rate of perinatal mortality has gradually decreased in the presence of UCP due to scientific and technological developments in obstetric practice, UCP still causes serious health consequences (9). In our study, we did not observe mortality in any newborn. We think that this result is important and shows that we apply the appropriate management in the presence of UCP. It has been previously reported that mechanical occlusion caused by compression of umbilical cord between the presenting part of fetus and surrounding tissues or vasospasm developing in the umbilical cord due to relatively cold environment in the vagina during UCP may disrupt fetal blood supply and the oxygenation. Also, it was shown to cause deep or total acute asphyxia or subacute hypoxia with poor neonatal outcome (10). In our clinical practice, when we detect UCP, we perform the ECS immediately. At the same time, we also elevate the fetal presenting part with digital examination. In this way, the pressure and the risk of occlusion on the umbilical cord is reduced. We also prepare optimal emergency resuscitation conditions that the newborn may need after birth. We think that these management strategies improve neonatal outcome. Indeed, in the literature, it has been reported that perinatal outcomes during UCP have improved with more liberal ECS administration and better and faster neonatal care (3,11).

Considering the risk factors for poor perinatal outcome related to UCP, the only determined factor was the presence of fetal distress identified before or during UCP. In our study, most of the newborns with poor perinatal outcome (81.8%) had signs of distress in their FHR tracing before delivery. On the other hand, in most of the newborns with no poor outcome (71.4%), signs of fetal distress were not identified. Huang et al. reported that fetal distress to be a strong determinant for low apgar score and poor perinatal outcome, and even severe fetal distress accompanying UCP may be associated with fetal death (10). In contrast, Koonings et al. did not observe any fetal death in the presence of variable deceleration or prolonged deceleration that they detected during fetal monitoring in UCP cases (4). In another study, Nizard et al showed that the incidence of adverse neonatal outcomes was low in the presence of normal findings in FHR monitoring, which lasted at least 20 minutes after the diagnosis of UCP (12). All these studies support our study, albeit partially. As a result of our study and the findings of the above studies, it can be said that the severity and duration of the fetal distress are as important as the presence of fetal distress. However, fetal monitoring alone may be insufficient to show the perinatal outcome. Fetuses with low reserves against distress can experience worse outcomes in the presence of UCP. The fact that fetal death was not observed in the UCP cases accompanied by the findings of variable deceleration and variability loss in our study similar to the findings in the study of Koonings et al. suggest that fetuses with these monitoring findings may have relatively sufficient reserves against UCP. However, additional studies are needed regarding which monitoring finding makes UCP more dangerous for the fetus.

UCP can quickly lead to a dangerous condition for the fetus, resulting in long-term disability or death. Therefore, if the fetus is alive when UCP is diagnosed, it is necessary to deliver it quickly. This type of prompt intervention can positively affect the fetal outcome (6). The generally accepted approach is to deliver UCP cases by ECS delivery. For UCP, which occurs in the first stage of the labor, where there is no full dilatation in the cervix, delivery by ECS is inevitable. In the second stage of the labor, when the cervix is completely dilated, an instrumental delivery can be applied, but even in this case, there are studies reporting that perinatal outcomes are better with ECS (3,6). As we have already mentioned, when we diagnose UCP, we perform ECS delivery in our clinical approach. Therefore, no case in our study was delivered vaginally, which led to the inability to compare the effect of vaginal delivery and cesarean delivery on perinatal outcome.

Although DDI is reported as a determining factor for fetal outcome, there is no full consensus on optimal value for this period. While the German Society of Gynecologists and Obstetricians recommends a maximum of 20 minutes for favorable fetal outcome (13), the Royal College of Obstetricians and Gynecologists (14) and the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (15) emphasize that this period should not exceed 30 minutes. On the other hand, poor outcomes can be observed in those born with DDIs that are less than 20 minutes, while it has not always been shown that adverse

outcomes are always present for babies born much longer than 30 minutes (16,17). Such contradictions suggest that other factors besides DDI may also be effective. In our study, the mean DDI values (approximately 20 minutes for both) and >20 and >30 minutes DDI frequency of the groups were similar. The number of newborns delivered within 30 minutes was 3, but 1 of them was in the poor outcome group. All babies were discharged without any problem. Our hospital is a refereed center that is active 24 hours a day and has sufficient equipment regarding all kinds of staff and tools in the obstetric field. Therefore, UCP diagnosis can be made easily during labor follow-up and delivery via ECS can be performed quickly, ensuring that the DDI process is short for patients. Perhaps that we have such equipment and ability to intervene quickly leads to good perinatal results. Thus, DDI has moved away from being a factor that may lead to poor perinatal outcome for our study.

The retrospective character of our study may have caused limitations on the variety and reliability of the data. However, it should be remembered that conducting a controlled prospective study on UCP can be very difficult and force ethical rules. In addition, there are no long-term follow-up results for newborns in our study. As a result of this, the morbidity / mortality assessment of the future periods that UCP may cause could not be investigated completely. Unfortunately, the current literature is still insufficient in this regard. On the other hand, since UCP is a very rare condition, there are limited number of studies on UCP and we think that the studies on this subject are important and valuable for the literature.

In conclusion, although UCP is a rare condition during the labor of uncomplicated term pregnant women, it may cause poor results for the newborn. In particular, abnormalities in FHR monitoring detected before or during UCP increase the need of NICU for newborn. Whereas, when the diagnosis of UCP is made, vaginal elevation of the presented part, performing immediate cesarean delivery in a short time and providing optimal care conditions for the newborn increase the expectation of the specialist and parents about good perinatal outcomes. Therefore, providing adequate medical facilities and staffing is very important to improve perinatal outcome during UCP.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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MRI utilization in pediatric emergency department: An analysis over 5 years

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Abstract

There are concerns on exposure to radiation especially in pediatric population, as magnetic resonance imaging (MRI) can be used in emergency departments and provides an imaging without radiation; its utilization has recently increased. This study aimed to evaluate MRI utilization trends in patients who underwent a MRI in a pediatric emergency department within a period of five years. Examination data of the patients admitted to pediatric emergency department between 2014 and 2018 were obtained from database of the hospital with the approval of Clinical Research Ethical Committee. Rate of MRI utilization in patients admitted to pediatric emergency department was 0.88%. There was a statistically significant increase in MRI utilization within five years ($p<0.001$). The rate of male patients (1.24%) who underwent MRI was significantly higher than that of female patients (0.65%) ($p<0.0001$). There was a statistically significant decrease in MRI utilization by age in all categories ($p<0.0001$). Neuroradiology imaging was the most common. Complaints at presentation and pre-diagnoses were analyzed. The results of MRI were evaluated by radiologists and 53.9% of the results were normal. The highest rate (46.1%) of MRI utilization was between 4 pm and 12 am in a day. The highest rate of MRI utilization was on Friday and the lowest rate was on Sunday. While MRI utilization has increased in pediatric patients, neuroradiology imaging is the most common type. MRI utilization in pediatric emergency department is higher in male patients and in the early ages.

Keywords: pediatrics, pediatric emergency department, magnetic resonance imaging, clinical indication

1. Introduction

Emergency departments are dynamic areas where disorders and injuries of the patients are evaluated as acute or emergent and where the resuscitation, first care, diagnosis and treatment of these emergencies are performed. Pediatric emergency departments consist of 25% of all patients with an emergency (1, 2).

In addition to clinical evaluation, radiological imaging is also needed to diagnose several emergent cases. Although imaging is a guide for disorders, its potential damages should be considered as well (3-6). As there are concerns on exposure to radiation especially in pediatric population, there should be an effort to reduce the radiation dose in imaging for infant and pediatric patients in emergency departments (2, 7). As magnetic resonance imaging (MRI) can be used in emergency departments and provides an imaging without radiation, its utilization has recently increased (2, 8). Although it is hard to obtain an image in MRI for pediatric patients due to the noise, fear, and inability to remain indoors or inactive, it is possible to obtain quality images in some patients with sedation or general anesthesia.

This study aimed to evaluate the frequency of MRI utilization according to age, gender, indication and type of examination in a pediatric emergency department in Turkey between 2014 and 2018.

2. Materials and Methods

This study was performed in a pediatric emergency department which was an 18-bed tertiary care center. Thirty-five thousand patients on average are admitted to this department every year. All age groups under 18 are admitted to the pediatric emergency department. Three MRI scanners are actively used in the Department of Radiology. While 2 MRI scanners were in use from January 2011 to January 2015, 3 MRI scanners have been used since 2015. Technical staffs work in shifts (8am-4pm, 4pm-12am and 12am-8am). This scheme operates 24 hours a day and 7 days a week. Scanners are active for imaging requested for the patients in emergency departments, wards, and outpatient clinics. Physicians who requested MRI examination for these patients are internal, external, or emergency physicians.

The patients who underwent MRI examination after admitted to the pediatric emergency department between January 2014 and January 2019 were accessed from the database of the hospital and included in the study. Data obtained in the study were transferred to IBM SPSS 23 for

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evaluation. For descriptive statistics, continuous data were given as mean and standard deviation while categorical data were given as counts and percentiles in the analysis of the data. Chi-Square test and T-test were used in the comparison of the data. The value of $p<0.05$ was accepted as statistically significant. This study was performed with the approval of the Clinical Research Ethical Committee of Ondokuz Mayıs University.

3. Results

The number of patients who were admitted to the emergency department between 2014 and 2019 was 175,331. While the number of patients admitted to pediatric emergency department was 24,411 in 2014, this number increased to 45,992 in 2018. Within this period of 5 years, 1,551 MRI examinations were performed for 1,233 patients (1.25 imaging per patient). While 1,198 (77.2%) of the patients were admitted to the emergency department, 353 (22.8%) had been followed up for a chronic disease. According to the years, the ratio of the number of MRI requested in pediatric emergency department to the number of patients was 0.86% in 2014 and 1.1% in 2018. There was a statistically significant increase in MRI utilization ($p<0.001$). The average rate of MRI utilization in patients admitted to pediatric emergency department over 5 years was 0.88%.

Out of 1551 patients, 859 (55.4%) were male and 692 (44.6%) were female. The rate of male patients (n=69,308; 1.24% of the patients admitted to the emergency department) who underwent MRI examination was statistically significantly higher than that of female patients (n=106,023; 0.65% of the patients admitted to the emergency department) ($p<0.0001$). While the number of neuroradiology and musculoskeletal imaging was significantly higher in male patients ($p<0.0001$), the number of body imaging was significantly higher in female patients ($p<0.0001$). The rate of male patients who underwent neuroradiology imaging among all MRI examinations was 52.1% (n=809) and that of female patients was 40.1% (n=623). The rate of female patients who underwent body imaging was 3.4% (n=54) and that of male patients was 1.6% (n=25). The rate of musculoskeletal imaging was 1.6% (n=25) in male patients and 0.96% (n=15) in female patients. The ratio of male to female patients in neuroradiology examination was 1.3:1, the ratio in musculoskeletal examinations was 1.6:1, and the ratio in body examinations was 1:2.1.

Among the categories of MRI, neuroradiology was the most requested imaging type with a rate of 92.3% (brain: 82.6%; spine: 3.4%; angiographic: 3.3%; orbit: 1.7%; pituitary: 1%; and MR spectroscopy: 1%). The rate of body imaging (chest, abdomen, and pelvis) was 4.9% and the rate of musculoskeletal imaging was 2%. When the categories of imaging were analysed, a statistically significant increase was found in neuroradiology imaging ($p<0.001$) (Fig. 1a). Complaints of the patients who underwent MRI examination were given in Table 1. The most common complaint in neuroradiology imaging was seizure with a rate of 29.3%. The most common complaint was trauma in musculoskeletal imaging and abdominal pain in body imaging. The most common pre-diagnoses in MRI were cranial pathologies (vascular pathologies such as arteriovenous malformation, bleeding, thrombosis, and stroke, structural brain abnormalities, neurodevelopmental pathologies, etc.) with a rate of 54.9%, suspected infections (meningitis, encephalitis, etc.) with a rate of 18.5% and ventriculoperitoneal shunt dysfunction/infection with a rate of 12.3% for neuroradiology imaging. While the most common pre-diagnoses were acute abdomen (suspected appendicitis, ovarian torsion, etc.: n=28, 1.8%) and ovarian cyst rupture (n=23, 1.5%) in body imaging, they were arthritis/arthralgia (n=23, 1.5%) and mass etiology (n=7, 0.5%) in musculoskeletal imaging. Eight hundred and thirty-six (53.9%) of MRI results were evaluated as normal by radiologists. There was a statistically significant decrease in MRI utilization by age in all categories ($p<0.0001$) (Fig. 1b). The rate of neuroradiology imaging was statistically higher in the age group of 0-6 than in other age groups ($p<0.0001$). And the rate of body imaging was statistically higher in the age groups of 7-12 and 13-18 ($p<0.0001$).

Table 1. Complaints of the patients who underwent MRI

Neurologic System		
Seizure	454	29.3%
Fever / vomiting / seizure with ventriculoperitoneal shunt	195	12.6%
Headache	91	5.9%
Fever, headache, vomiting	83	5.4%
Fever, vomiting, somnolence	60	3.9%
Nausea, vomiting	57	3.7%
Visual impairment	45	2.9%
Somnolence	42	2.7%
Headache, vomiting	41	2.6%
Fever, seizure	40	2.6%
Ataxia	34	2.2%
Inability to walk	31	2%
Muscle weakness	28	1.8%
Fainting	23	1.5%
Neck stiffness	23	1.5%
Speech disorder	21	1.4%
Headache and visual impairment	19	1.2%
Facial paralysis	18	1.2%
Dizziness	13	0.8%
Bulging fontanel	12	0.8%
Numbness	10	0.6%
Other (Incontinence, Otorrhagia, Swollen eye)	13	0.8%
Musculoskeletal System		
Trauma	56	3.6%
Joint swelling	26	1.7%
Cervical swelling	7	0.5%
Soft tissue swelling	6	0.4%
Backache	3	0.2%
General		
Abdominal pain	59	3.8%
Abdominal mass	7	0.5%
Heart failure	4	0.1%
Cough	1	0.1%

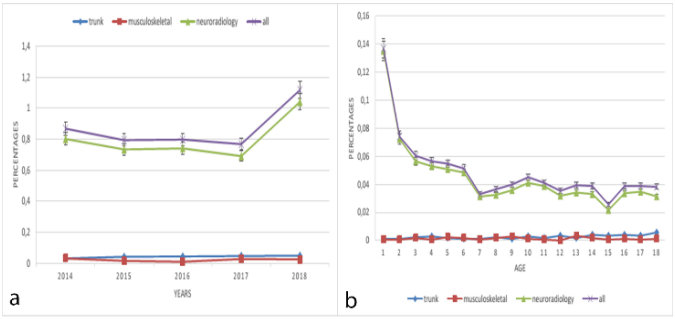

Fig. 1. a. Magnetic resonance imaging (MRI) utilization by year, b. Magnetic resonance imaging (MRI) utilization by age

The rates of MRI utilization within a day were 35.9% between 8am and 4pm, 46.1% between 4pm and 12am and 18% between 12 am and 8 am. In the distribution of MRI utilization days, the highest rate was on Friday with a rate of 15.9% (n=246). The rates in other days were 15.7% (n=243) on Tuesday, 15% (n=232) on Thursday, 14.8% (n=229) on Wednesday, 14.1% (n=218) on Monday and 13.7% (n=213) on Saturday. The lowest rate of MRI utilization was on Sunday with a rate of 11% (n=170). The months when the rate of MRI utilization was the highest were August (n=171, 11%), December (n=162, 10.4%), September (n=151, 9.7%) and October (n=145, 9.3%). The months when the rate of MRI utilization was the lowest were February (n=92, 5.9%) and April (n=91, 5.9%).

4. Discussion

MRI scanner is an imaging device used to evaluate a variety of diseases (9). Neuroradiology exams including brain, head, neck, and spine consisted of 92.3% of the total amount of imaging. MRI utilization especially for brain, head and neck has considerably increased and this increase was predicted in a study performed years ago (10). The rate of neuroradiology imaging was reported as 90% in a former study on a pediatric emergency department and 92.2% in another study on an emergency department in which adult patients were admitted. The rate of body imaging was consistent with those of other pediatric studies; however, the rate of musculoskeletal imaging was lower (11, 12).

Utilization of MRI was more in male patients than in female patients. While the number of male patients was significantly higher especially in neuroradiology and musculoskeletal imaging, the number of female patients was significantly higher in body imaging. Although MRI is not used as a primary care imaging in conditions on pelvic region such as ovarian torsion, it is helpful for the cases that are hard to be diagnosed (13). As in many studies conducted recently, the utilization of MRI with high sensitivity in the presence of free fluid and in intra-abdominal imaging has increased as an alternative of computed tomography (CT) in the diagnosis of appendicitis in conditions in which ultrasonography is insufficient (14, 15). MRI is a type of imaging that gives better results than CT does in the evaluation of appendicitis or adnexal pathologies in pregnant women (16, 17). As pregnant women are admitted to the emergency department for adults even if they are under the age of 18, there were no pregnant women who underwent MRI examination in our study.

The most common complaint in neuroradiology was seizure. Seizures during infancy are different from those during childhood or adulthood and a variety of conditions such as eye misalignment, blinking or rapid eye blinking, sucking, smacking or other buccal movements and swimming or pedaling movements may occur. Moreover, there is generally no loss of consciousness (18). A variety of movements during childhood from simple but unnatural movements to complex motor movements like natural movements in inconvenient environments may be characterized with seizure (19). As several movements are evaluated as seizure by families, they present to the emergency department. The prevalence of lifelong seizure has increased by 4% with pediatric rates ranging from 0.4% to 1.0% (20). This is consistent with our study.

The most common pre-diagnoses established by the clinician working in an emergency department in which the most common complaint was seizure were intracranial pathologies. Pre-diagnoses of the patients who were admitted to the emergency department with seizures and who were considered to have suspected infections such as meningitis and encephalitis or ventriculoperitoneal shunt dysfunction varied according to their conditions. Almost half of the reported MRI results were compatible with the pre-diagnosis. Pre-diagnoses are of great importance in MRI reporting of the radiologist. It is important to establish a strong cooperation between emergency physicians and radiologists in deciding the correct examination according to the clinic of the patient. We could not find any study on pre-diagnoses and their results in literature.

The most common complaint in body imaging was abdominal pain and the most important reason to request abdominopelvic MRI for female patients was abdominal pain symptom of complex adnexal pathologies (13, 14). Although musculoskeletal imaging was generally low in number, the higher rate of male patients who underwent musculoskeletal imaging was associated with more active characters of boys and sports injuries (21). Moreover, the fact that the rate of septic arthritis and osteomyelitis and the prevalence of bone tumors are higher in boys is another factor for that (22, 23).

MRI utilization decreases by age. The rates of imaging increasing by age were reported in two different pediatric studies performed in Orlando and Bronx (11, 24). MRI is used more in younger age group because the young population, especially the population under the age of 5 is high and patients mostly present with seizures that are seen at very young ages. Although MRI utilization in emergency department differed according to the seasons, there was a slight increase during summer and autumn months. There was an increase in similar months in the study of adult emergency

department (8). There were also slight differences among weekdays. The day with the lowest rate of MRI utilization was Sunday and the shift with the lowest rate was 12am-8am. While MRI was not used during the shift of 12 am-8 am on Sundays due to the limited number of technicians two years ago, a single MRI scanner was used during the shift of 12 am-8 am on weekdays. MRI utilization is high during the shift of 4pm-12am. However, MRI utilization was higher in evenings and at nights in most of emergency departments (8, 11). While patients in outpatient clinics and patients admitted to emergency department share MRI scanners during the day, mainly patients admitted to emergency department use them at the evening hours. As our hospital is a tertiary care district hospital, the number of patient transfers from external centers increases at the evening hours and therefore, MRI utilization is more at these hours.

The number of CT examinations per 1000 people increased by 30% and the number of MRI examinations increased by 60% in Turkey between 2008 and 2010, which reveals the rapid increase in the number of demands. The number of MRI examinations per 1000 people was 79.5 by 2010 and nearly two times more than the average MRI examination (44.9) predicted by the Organization for Economic Cooperation and Development (OECD) in the same year (25). Although the date of our study was not similar, it revealed that the rate of MRI increased from 0.86% (2014) to 1.1% (2018) over 5 years. This increase was also seen in other countries such as the USA as well as our country (6, 26). The number of MRI utilization increased after 2014; however, increase in the number of patients was higher (4). Therefore, the increase in MRI utilization in our country was not as much as expected. In a study on pediatric MRI in the USA, this rate increased from 0.23% to 0.49% (11) and while the rate of increase was 113%, it was 27% in our study. The rate of increase in the study of emergency department for adults was 15% as the rate increased from 1.64% to 1.9% (8). In a study performed in Korea, the number of MRI per 1000 people increased from 8.1 to 74.6 within 10 years (12).

Increases in the number of MRI utilization are consistent with the effort of clinicians to establish a final diagnosis due to medical concerns (27). It is an undeniable fact that clinicians perform extra tests, procedures, or imaging in order to decrease their medical malpractice liability to protect themselves from legal actions (28). Moreover, diagnosis with MRI is a great advantage for patients especially with suspected ventriculoperitoneal shunt dysfunction as they are not exposed to ionized radiation on the contrary to computed tomography (29). Thanks to these advantages, MRI utilization is increasing. The cost of MRI is two times higher than that of computed tomography depending on the institution where MRI is used (30). Although its cost is high, this will not matter when a possible risk of cancer is considered in children (31, 32).

Our study had some limitations. The results are related to the approaches we used in our hospital. A broader study can be performed with MRI utilization trends of other centers. Although MRI has a great advantage in terms of exposure to radiation, its effects due to sedation were not considered in this study. Factors such as duration of hospital stays, or the cost of the examination can be analyzed in another study.

The rate of MRI utilization has increased within years. Neuroradiology imaging was used more. The rate of MRI utilization was higher in male patients than in female patients. While trends, approaches, examinations, and treatments change in medical world, more research is needed to understand the factors responsible for these changes and determine the effect of radiology utilization in emergency departments on patient results

Conflict of interest

None to declare.

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None to declare.

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Research Article

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Retrospective evaluation of 16 patients who underwent spinal cord stimulation

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Abstract

The aim of this study was to examine the outcomes of patients who underwent Spinal Cord Stimulation (SCS) in our clinic. In this study, records of 16 patients who underwent SCS in the Algology and Neurosurgery Clinic of the Ministry of Health, Health Sciences University, Samsun Training and Research Hospital between 2015 and 2018 were retrospectively analysed. The pain levels of the patients before and after the procedure were evaluated with the Visual Analogue Scale (VAS). The mean age of the patients was 54.25 ± 11.45 years. After the SCS procedure, it was found that pain levels determined by the VAS decreased significantly ($p < 0.001$). Eleven (68.7%) patients reported that they were quite satisfied or partially satisfied after SCS, and seven patients (43.8%) underwent revision due to hardware malfunctions and post-surgical complications. Based on our study results, we believe that SCS is an effective treatment method that can be used to reduce pain.

Keywords: neuromodulation, spinal cord stimulation, pain, VAS, CSF

1. Introduction

Spinal cord stimulation (SCS) is a reliable, minimally invasive treatment method that is widely used in the treatment of chronic pain. In recent times, it has been successfully used for the management of chronic pain conditions, such as complex regional pain syndrome, failed back surgery syndrome, peripheral vascular disease, chronic refractory angina, and visceral pelvic pain (1, 2).

Studies report that 30%–40% of patients with SCS have device-related malfunctions or post-surgical complications (3). Device-related malfunctions that were reported included lead migration, lead breakage, high or low stimulation, hardware failure, generator failure or failure to connect with the generator. Post-surgical complications that were reported included infection, epidural bleeding, seroma, neurological damage, cerebrospinal fluid (CSF) leakage, pain at the implant site, allergic reactions, and skin erosion (4).

The present study aimed to guide and help clinicians to predict, prevent and manage these complications in the early post-operative period by retrospectively examining the indications for and common complications observed in SCS.

2. Materials and Methods

This study was designed as a retrospective descriptive study. Prior to the study, ethics approval was obtained from the Ministry of Health Samsun Training and Research Hospital Medical Specialization Training Board. Sixteen patients over the age of 18, who were not pregnant nor were planning for pregnancy soon and who applied to the Algology and Neurosurgery Clinic of the Ministry of Health, Health Sciences University, Samsun Training and Research Hospital between 2015 and 2018, were included in the study.

The severity of low back pain and satisfaction levels of the patients before and after the procedure were evaluated using the Visual Analogue Scale (VAS). In addition, complications that occurred after the procedure were recorded. The patients were evaluated during routine polyclinic controls after the procedure. Informed consent was obtained from all patients prior to the procedure.

2.1. Surgical technique

The patients were taken to the operating table in the prone position for the SCS procedure. After surgical asepsis 0.05 mg/kg of midazolam was administered for sedation, whereas fentanyl was titrated at a dose of 1–2 µg/kg for analgesia. A small incision was made in the midline over the intervertebral space at the surgical site where a local anesthetic was injected, and a pocket was created for the connection cables of the electrode over the lateral part of the incision. A 14 G Touhy/16 G R-K needle was used to gain access to the epidural space from the T12–L1 vertebral space through a paramedian approach at an angle of nearly 45°. A guide was sent through the epidural needle to allow easy access to the electrode in the epidural region. Later, the electrode was controlled with fluoroscopy and moved towards the relevant dermatome. By providing stimulation with different

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stimulation modes, the area where the patient felt paranesthesia and painful area were determined and the electrode was fixed. Interconnections of the electrode were passed under the skin and removed from a distant point. After the procedure, patients were followed for three hours, and stimulator settings were adjusted. Detailed information was given to the patients and their relatives about the device usage. In patients with successful results during the trial period, the part placed in the intervertebral space was connected to the permanent electrode so that a permanent system could be placed.

2.2. Statistical analysis

SPSS 22.0 software program was used for statistical analysis. The normality of numerical data was evaluated with the Shapiro–Wilk test. Descriptive statistics were presented in terms of frequency (n), percentage (%), mean ± standard deviation, minimum (min), maximum (max), median (median), 25th percentile and 75th percentile. The Chi-Square test was used to compare categorical variables. The difference between the values before and after SCS placement was analysed using the Wilcoxon test. Statistical significance was accepted as $p < 0.05$.

3. Results

Sixteen patients were evaluated in the present study. Nine (56.3%) of the patients included in the study were female, and seven (43.8%) were male (Fig. 1). The mean age of the patients was 54.25 ± 11.45 years, that of females was 54.33 ± 13.85 and that of males was 54.14 ± 9.48 years. There was no statistically significant difference between males and females in terms of age ($p = 0.976$). The most common location of pain was the waist and leg (43.8%), followed by only leg (31.3%), back (12.5%) and arm–foot pain (6.3%) (Fig. 2).

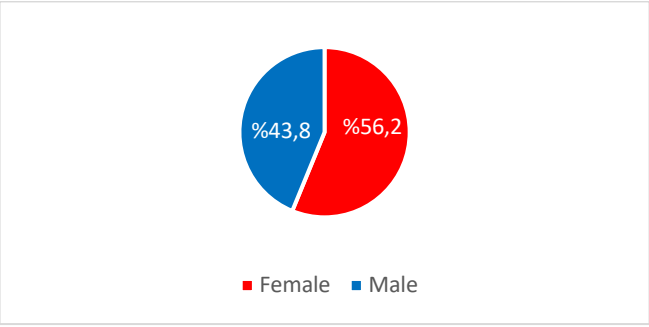

Fig. 1. Distribution of patients by gender

SCS was performed in more than half of the patients (n = 9; 56.25%) due to failed back surgery syndrome (FBSS), also known as post laminectomy syndrome (PLS), in four (n = 4; 20%) patients due to complex regional pain syndrome, in two patients due to spinal tumors (n = 2; 12.5%) and in one patient due to traumatic cauda equina syndrome (n = 1; 6.25%) (Table 1). It was determined that the median VAS score of the patients before the SCS procedure was 8 (min/max = 7/9), and it decreased to 2 (min/max = 1/8) after the procedure, which was statistically significant ($p < 0.001$) (Table 2).

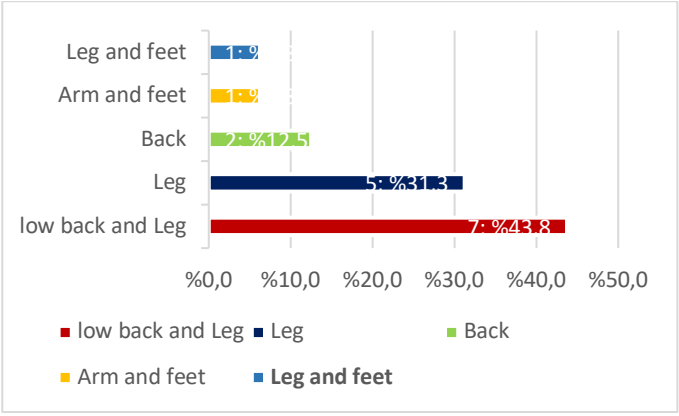

Fig. 2. Distribution of pain location

Table 1. Spinal cord stimulation (SCS) indications

	n (%)
Failed back surgery syndrome	9 (56.25)
Complex regional pain syndrome	4 (20)
Spinal tumour	2 (12.50)
Traumatic cauda equina syndrome	1 (6.25)

n: Number of cases, %: Percentage

When the satisfaction levels of the patients, changes in daily activity and time of return to work after the SCS procedure were examined, it was found that 11 (68.7%) patients were quite satisfied or partially satisfied, whereas the remaining patients reported that they were less satisfied or dissatisfied (Table 3). Within three years after the initial procedure, a revision procedure was performed in seven (43.75%) of 16 patients included in the study due to hardware malfunctions or post-surgical complications. The revision procedure was performed in five (71.43%) cases due to hardware malfunctions and in two (28.57%) cases due to post-surgical complications. It was determined that hardware malfunctions were most frequently caused by lead migration (n = 4, 80%) and due to failure to connect to the generator (n = 1, 20%). Post-surgical complications were observed in three patients. Seroma and infection requiring removal of the generator were observed in two of these patients. In the other patient, a hematoma was observed in the paravertebral tissues. Spontaneous resorption was observed during the controls in the patient who had hematoma in the paravertebral tissues.

Table 2. VAS scores of patients before and after the SCS procedure

Variables	X ± SS	Median (Min/Max)	p
Pre-VAS score	7.9 ± 0.7	8 (7/9)	< 0.001*
Post-VAS score	3.5 ± 2.2	2 (1/8)	

Wilcoxon test, *: $p < 0.05$, X: Mean, SD: Standard deviation, Min: Minimum, Max: Maximum

Table 3. Distribution of patients' satisfaction levels

Satisfaction level	n (%)
Quite satisfied	9 (56.2)
Partially satisfied	2 (12.5)
Neutral	1 (6.3)
Partially dissatisfied	2 (12.5)
Not satisfied at all	2 (12.5)

n: Number of cases, %: Percentage

4. Discussion

In the present study, the records of the patients who applied to our clinic between 2015 and 2018 for SCS were analysed retrospectively. A total of 16 patients were included in the study. Nine (56.3%) of the patients were female and seven (43.8%) were male. More than half of the patient population was female. In a study conducted with 707 patients in 2011, Mekhail et al. reported that 57.7% of the patient population was female (5). In another study conducted in Turkey with 62 patients in 2017, Özdemir et al. reported that 62.9% of patients who underwent SCS procedure were female (6). The results of the present study in terms of gender distribution are consistent with that in literature.

Mekhail et al. reported that the mean age of patients was 46 ± 15 years in their study (5), whereas Özdemir et al. reported that the mean age was 57.95 ± 13.16 years in theirs (6). In the present study, the mean age was calculated as 54.25 ± 11.45 years. Thus, in terms of age, our patient population was like that in the study by Özdemir et al., whereas it was older compared with that in the study by Mekhail et al.

When the indication distribution of SCS, a neuromodulation method applied in the treatment of many chronic pain cases, was examined, it was determined that more than half of the patients in our study underwent this procedure due to FBSS. The second most common indication after FBSS was complex regional pain syndrome. While the most common indication was Complex Regional Pain Syndrome (CRPS) in a study by Mekhail et al., it was followed by FBSS (5). Like the results of the present study, Özdemir et al. reported that FBSS was the most common indication for SCS, followed by angina and CRPS (6, 7).

In a study conducted by Kumar and Toht to determine the effectiveness of SCS, 182 patients who underwent SCS with a diagnosis of FBSS were followed for 8.8 ± 4.5 years, and it was determined that 48% of the patients had a 50% or more reduction in pain intensity. Taylor et al. conducted a systematic review of 63 studies in 2014 to examine the reduction in pain levels of patients who underwent SCS due to chronic low back and leg pain and found that there was a statistically significant pain reduction in 58% of the patients (8).

In a randomized controlled study conducted by North et al. (2005), 50 patients with a diagnosis of PLS who had undergone surgery three years ago were randomly divided into two groups, and while SCS was performed on participants in one group, those in the other group were reoperated. It was reported that opioid use was higher in patients who underwent reoperation compared with that in the SCS group. In addition, they reported that SCS application in patients with persistent radicular pain after spine surgery was more cost-effective than surgery for reducing pain (9). Our study results found that the median VAS score was 8 (min/max = 7/9) before the SCS procedure, and it decreased to 2 (min/max = 1/8) after the procedure; this decrease was statistically significant and consistent with literature.

In a multicenter prospective randomized controlled study conducted by Kumar et al. (2007) to examine the effectiveness of SCS and conventional medical treatment, 100 patients with FBSS were divided into two groups as a conventional treatment group and SCS treatment group and were followed for a year. The study results found a decrease in axial pain intensity, an increase in quality of life and treatment satisfaction in the SCS group (3). In another study conducted by Sanders et al. on 199 patients who underwent SCS between 2001 and 2011, it was reported that 84.27% of the patients were satisfied with the implant (10, 11). In the present study, we found that more than half of the patients (n = 11, 68.7%) were quite satisfied or partially satisfied after the SCS procedure, like that observed in literature.

In literature, complications have been reported in 30%–40% of patients undergoing SCS due to device-related malfunctions, such as lead migration, lead breakage, high or low stimulation, hardware failure, generator failure or failure to connect with the generator, or due to post-surgical factors, such as infection, epidural bleeding, seroma, neurological damage, CSF leakage, pain at the implant site, and allergic reactions (3, 4).

In a 20-year systematic review published by Cameron in 2004, 68 studies and 3679 patients were evaluated. In this review, it was reported that the most common complication after SCS was lead migration seen in 13.2% (n = 361) of the patients (12). In a case series by Mekhail et al., which included 707 patients, it was reported that none of the patients had serious complications, such as permanent neurological deficit or death due to the SCS procedure. Infection was occurred in 32 (4.5%) of 707 patients. Seroma without signs of infection was reported in 1 patient, pain on the generator side was reported in 86 (12%) patients. Lead migration was reported in 119 (22.6%) patients, lead connection failure was reported in 50 (9.5%) patients and lead breakage was reported in 33 (6%) patients out of 527 patients who had IPG implantation. (5). In the study conducted by Özdemir et al., it was reported that complications occurred after the SCS procedure in 14.5% of the patients, and the most common complication was infection with a rate of 33.3% (6). In the present study, it was determined that the most common complication in the three-year period was lead migration (n = 4; 25%), like that observed in Cameron's study (12).

SCS application is an important treatment method that can be used in reducing pain scores and improving the quality of life of patients as it is a minimally invasive method, has lesser side effects compared with pharmacotherapies and is highly cost-effective. To the best of our knowledge, this is the first study in literature reporting results obtained from the Middle Black Sea region regarding the SCS procedure.

Therefore, we believe that this study can significantly contribute to literature. However, the limitations of the present study are that this was a single-center study, which cannot be generalized to the whole population, and the retrospective study design. Therefore, there is a need for future multi-center studies that will contribute to the determination of appropriate treatment strategies by clinicians along with defining the indications for and complications of SCS.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Research Article

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Possible effects of some anaesthetic agents in rat hepatotoxicity: Histological and biochemical study

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Abstract

Selectively steroidal neuromuscular blocking agents, such as rocuronium, are required to maintain surgical procedures. It is a sugammadex γ-cyclodextrin-derived drug that encapsulates these drugs and reverses its effects. In the present study, it was aimed to investigate the effects of sugammadex rocuronium complex on liver and possible toxic effects on hepatocytes using histopathological and biochemical methods. Thirty-two adult Sprague - Dawley male rats were used. Four groups were designed as pure control, control group, sugammadex and sugammadex-rocunorium. Following the experimental procedures, liver tissues extracted from rats were stained after routine histological procedures. The images were taken from the sections for histopathological evaluation. For biochemical analysis, glutathione (GSH) and malondialdehyde (MDA) enzymes were analyzed in the liver tissues. In the group treated with the sugammadex-rocunorium complex, caspase-3 expressions were observed to be higher than in other groups. In addition, while the amount of GSH belonging to sugammadex and sugammadex-rocunorium groups decreased compared to the control group, an increase in MDA amount was found. Sugammadex-rocunorium can lead to oxidative stress in the hepatocytes. However, more studies are needed to reveal the toxic effects of sugammadex and sugammadex and rocunorium complex in the liver.

Keywords: sugammadex, rocuronium, oxidative stress, immunohistochemistry, liver histology, rat

1. Introduction

Most patients who undergo surgical procedures require general anesthesia. For this purpose, in addition to neuromuscular blockers, various analgesic and anesthetic agents are used (1). Muscle relaxants can cause many side effects such as atelectasis, pneumonia, pulmonary complications, hypercapnia, and hypoxemia in the postoperative period (2,3). Rocuronium is one of the muscle relaxants commonly used in general anesthesia and provides neuromuscular junction blockade (4). In general anesthesia applications, neuromuscular blocking agents are used to facilitate airway intubation, to provide mechanical ventilation and to adapt surgical operation conditions (5). In this regard, it is necessary to eliminate the effect of muscle relaxants to improve muscle function in the patient and prevent neuromuscular blockage (6). Steroidal neuromuscular blocking drugs, such as rocuronium, are widely used in clinical anesthesia to facilitate tracheal intubation and to allow surgical access to body cavities. Residual neuromuscular block and subsequent respiratory insufficiency are associated with substantial morbidity and mortality, although the quality of tracheal intubation has significantly improved because of the clinical use of neuromuscular blocking agents (NMBAs), resulting in a reduction of pharyngo-laryngeal lesions. Therefore, many anesthetists routinely reverse neuromuscular block to facilitate rapid and complete recovery after surgery to prevent residual block (7-10).

Sugammadex is a γ-cyclodextrin designed to reverse the effects of steroidal neuromuscular blocking agents such as rocuronium and vecuronium (11). The mechanism of action of sugammadex is different from other reversing agents. Since sugammadex is a molecule-binding agent, it does not act on acetic cholinesterase and other receptor systems (12). The sugammadex-rocuronium complex formed by the binding of a sugammadex molecule target agent rocuronium in plasma, quickly and safely restores the rocuronium-induced deep neuromuscular blockade (13). The complex formed by the pharmacokinetic properties of sugammadex is inactivated and excreted from the body through the kidneys (12). In addition, it has been suggested that this complex remained in circulation for a long time. For this reason, it has been reported that it causes histopathological findings such as skeletal muscle myopathy, vacuolization, pyknotic nuclei clumps, and thus causes disorders such as weakening of muscle fibers and hypertrophy (14). Since sugammadex is excreted from the kidneys and is not metabolized in the liver (15), there are a limited number of studies including its effect on liver morphology and enzymes (16). Clarke et al. (17)

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reported that a cutaneous anaphylaxis effect in patients sensitive to rocuronium was alleviated with sugammadex after two minutes. It has been demonstrated that sugammadex reduces the rocuronium-induced increase in tryptase concentration caused by rocuronium in the rat liver after five minutes (17). In this context, sugammadex is suggested to reduce the activation of mast cells (18). In the light of this information, studies on the role of rocuronium and sugammadex on anaphylaxis-related liver enzymes are limited (17-19). There are no morphological studies hepatopathologically. Based on this point, we aimed to investigate the effects of sugammadex and sugammadex-rocuronium complex on liver morphology in our study by using histopathological, immunohistochemical and biochemical methods. The presented study contributes to the literature in terms of explaining the effect of suggamadex on the liver in detail using immunohistochemical, histopathological and biochemical methods.

2. Material and Methods

2.1. Animals and study design

The experimental procedures of the present study were approved by the Adıyaman University, Animal Experiments Local Ethics Committee with the report of ADYU-HADYEK 2019/032. In our study, 32 adult *Sprague - Dawley* male rats weighing 300-350 g were used (20,21). The rats were monitored daily under favorable conditions (Room temperature: 22-25 °C and humidity: 50-55%) with standard pellet diet and water ad libitum. 12-hour light-dark cycle using cold white fluorescent lamps (06.00-18.00) was provided. The rats were randomly divided into four groups (n=8): Pure control group, control group, sugammadex group, sugammadex-rocuronium group. The pure control group consisted of animals that did not have any surgical treatment and that comply with the routine care rules to obtain basal values. Rats of the control group were given 16 mg / kg intravenous (IV) 0.9% isotonic saline. Rats of the sugammadex group were given 16 mg / kg IV sugammadex (BridionR; Schering - Plow Corporation, Oss, The Netherlands). After three minutes following the administration of 16 mg/kg IV sugammadex (the bridion; Schering - Plow Corporation, Oss, The Netherlands), 1 mg/kg IV rocuronium (ESMERON is, Organon, Istanbul, Turkey) was injected to sugammadex + rocuronium group. All drugs were administered intravenously over the tail vein. Doses administered Bostal et al. (22) and Pühringer et al. (23) was determined by taking the studies conducted as a guide. Following experimental procedures, liver tissues under ketamine/xylazine anesthesia were dissected from animals under ketamine/xylazine anesthesia.

2.2. Tissue processing, sectioning, and staining procedures

Liver samples obtained for the purpose of histopathological examinations were placed in 10% formaldehyde solution in separate groups. After a week-long fixation, paraffin blocks were prepared by routine histological tissue follow-up. 5 µm thick sections were taken from paraffin blocks. The sections taken were stained with hematoxylin-eosin, Masson trichrome and Toluidine blue dyes. Images were obtained from liver slides of each group using a microscope with a digital camera attachment, Axiocam ERc5 model of Carl Zeiss. Histopathological evaluation was performed on the images obtained.

2.3. Immunohistochemical staining

For immunohistochemical analysis, primary antibody Caspase-3 (Thermo Fisher Scientific; cat no: PA5-16335) diluted 1/200 with the commercial kit Termo Scientific ™ TP-015-HA was used. From the blocked tissues, 5 µm thick sections were taken into adhesive slides and deparaffinized. Streptavidin-biotin-peroxidase complex method was used in staining. Positive and negative controls were performed as recommended by the manufacturers. After applying AEC Chromogen, reverse staining was performed with Mayer's hematoxylin. Histopathological evaluation was performed on the images obtained. The degree of staining was determined as 0: no, +0.5: extremely low, +1: low, +2: moderate, +3: severe (24). The removed liver tissues were used for histopathological and biochemical analysis

2.4. Biochemical tests

The dissected liver samples were washed with saline at a temperature of +4°C, placed in ependorphic tubes according to the cold chain principles and kept at -70°C until examination. Tissue homogenates for malondialdehyde (MDA) and reduced glutathione (GSH) measurements were prepared cold using 0.15 M KCl with 10%, (w/v) homogenizer. The Mihara and Uchiyama method used for the determination of lipid peroxidation and MDA, which is a marker of free oxygen radical amount, is based on the reading of the pink colored product from N-butanol phase at 535 and 520 nm because of reacting with the thiobarbituric of the pink colored product at 95 °C (25). Liver tissue was centrifuged by homogenizing in 10% trichloroacetic acid. After the supernatant was mixed with an equal volume of 0.67% thiobutyric acid, it was incubated in boiling water for 15 minutes at 90 ° C. Following incubation, it was centrifuged by cooling. Tissue MDA concentrations were measured in nmol /g tissue under 532 nm absorbance. GSH is an antioxidant enzyme that catalyzes the reduction of harmful peroxides such as lipid peroxide and hydrogen peroxide. During this reduction, reduced glutathione is converted to oxidized glutathione. In the GSH analysis performed by the method described by Elman (26), glutathione in the analysis tube reacts with 5i-dithiobis2-nitrobenzoic acid to give a yellow-greenish color. The light intensity of this color was measured with a spectrophotometer at a wavelength of 410 nm.

2.5. Statistical analysis

In the statistical analysis of the data obtained, the Kolmogorov-Smirnov test was used to determine whether the data was normally distributed. One Way ANOVA test was

used for normally distributed data and Tukey test, post-hoc test for multiple comparisons. The Kruskal-Wallis test was used for non-normally distributed data and the Mann Whitney-U test for multiple comparisons. The results were evaluated within the mean ± standard deviation (SD) of 95% confidence interval. P value <0.05 was considered statistically significant. SPSS program (Chicago, IL, USA; version 22.0) was used for statistical analysis.

3. Results

3.1. Light microscopic findings

When hematoxylin eosin-stained sections of tissues belonging to pure control and control groups were examined, it was observed that hepatocyte cords extending from v. centralis to periphery in the middle of the liver lobule and sinusoids located between these cords were normal (Figs. 1a and 2a). The presence of polygonal shaped liver cells was monitored. It was determined that hepatocyte cytoplasm showed acidophilic staining feature, which varies in density according to the activity status of the cells. The nuclei of these cells were found to be centrally located, large, round and euchromatic, some hepatocytes have bi-nucleus and in normal morphology (Figs. 1b and 2b). In the rat liver tissues belonging to pure control and control group, which was applied by Masson's trichrome staining method to show the connective tissue density, Intense connective tissue was observed around the v. centralis and periportal area (Figs. 1c and 2c). The density of mast cells in the vascular connective tissue was normal (Figs. 1d and 2d). When hematoxylin eosin-stained sections of rat liver tissues belonging to the group treated with sugammadex were examined, hepatocytes that formed the parenchyma in small magnification compared to the group treated with Rocuronium. It was observed that it showed a slightly more regular structure around v. centralis (Fig. 3a). It was noted that the hepatocytes that make up the liver parenchyma are of normal structure and maintain their acidophilic structure in large enlargements of the same group. Among the hepatocytes, it was determined that there were degenerated hepatocytes, and dilatation in sinusoids (Fig. 3b). The connective tissue density was observed to be normal around the v. centralis and periportal areas in the Masson's trichrome staining method (Fig. 3c). Mast cell density was low compared to sugammadex and rocunorium applied group (Fig. 3d). When the sections of rat liver tissues belonging to the group treated with sugammadex and rocunorium were examined with hematoxylin-eosin, at small magnification, a liver structure was observed in which there was a disruption in the arrangement of hepatocyte cords formed by hepatocytes around the v. centralis, and the lobule structure and boundaries were not clearly distinguishable (Fig 4a). It is noteworthy that in the large enlargements of the same group, the cytoplasmic boundaries of the hepatocytes that make up the parenchyma are not clearly distinguished, the polygonal shapes disappear, the size differences and degenerative changes between the cells are broken. These were observed to have a dark pyknotic core in some areas. In addition, in this group, an increase in dilatation was observed in sinusoid structures (Fig. 4b). To show the connective tissue density, Masson's trichrome staining method has been applied in rat liver tissues, compared to other groups around the v. centralis and periportal areas, it was observed that the connective tissue density increased (Fig. 4c). The density of mast cells in the vascular connective tissue was significantly increased compared to the pure control and control groups (Fig. 4d).

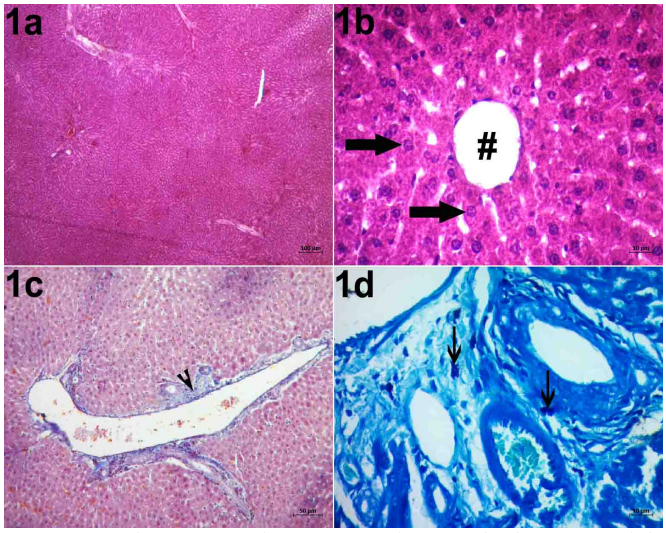

Fig. 1. (1a-1d pure control group) 1a, 1b, 1c and 1d: Images of the group in magnification x4, x40, x10 and x40 respectively; (Hematoxylin-Eosin staining, Masson' trichrome staining and Toluidine blue staining); #, central vein; thin arrow, mast cell; thin arrowhead, connective tissue; thick arrow, healthy hepatocyte

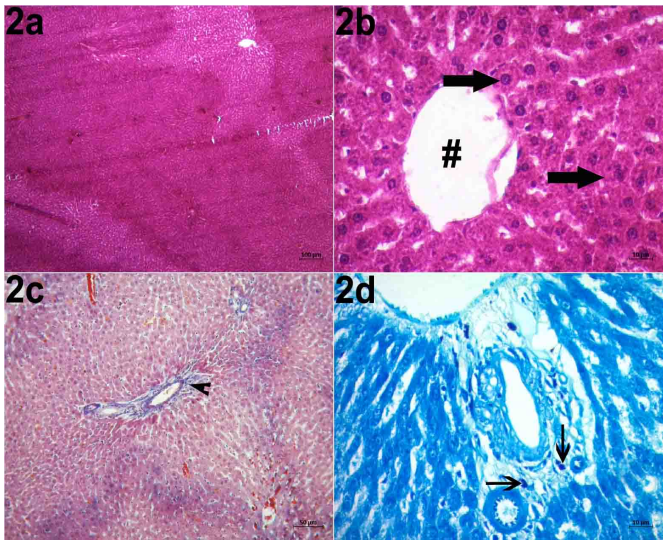

Fig. 2. (2a-2d control group) 2a, 2b, 2c and 2d: Images of the group in magnification x4, x40, x10 and x40 respectively; (Hematoxylin-Eosin staining, Masson' trichrome staining and Toluidine blue staining); #, central vein; thin arrow, mast cell; thin arrowhead, connective tissue; thick arrow, healthy hepatocyte

3.2. Histopathological results

When the cellular degeneration, lobular degeneration, fibrosis, sinusoidal dilation, mast cell density, mast cell density parameters of the sugammadex+rocuronium group were examined by histopathological scoring, it was determined that there was a highly significant increase in the pure control and control groups. Statistical data are given in

Table 1.

3.3. Immunohistochemical findings

Caspase-3 immunoreactivity was extremely low in hepatocytes in the hepatic cords in the pure control and control groups (Figs. 5a and b). The involvement in the sugammadex group increased slightly compared to the control and control groups (Fig. 5c). In the sugammadex + rocuronium group, positively stained cells were higher than in the other groups (Fig. 5d).

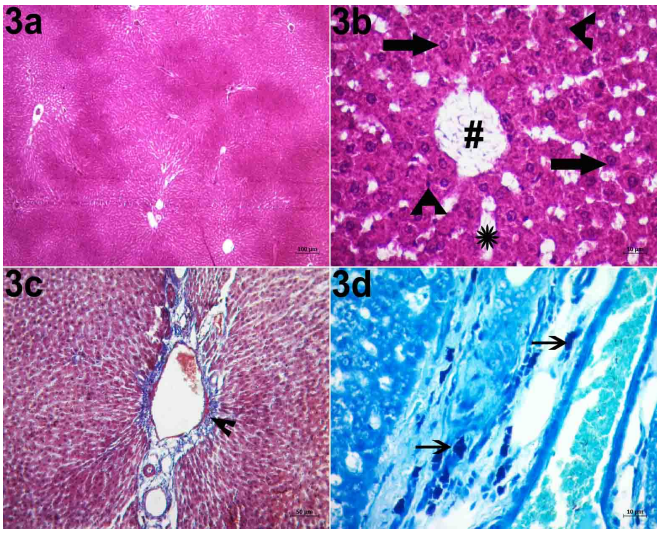

Fig. 3. (3a-3d sugammadex group) 3a, 3b, 3c and 3d: Images of the group in magnification x4, x40, x10 and x40 respectively; (Hematoxylin-Eosin staining, Masson' trichrome staining and Toluidine blue staining); #, central vein; thin arrow, mast cell; thin arrowhead, connective tissue; thick arrow, healthy hepatocyte; thick arrowhead, degenerated hepatocyte cells; star, dilated sinusoid

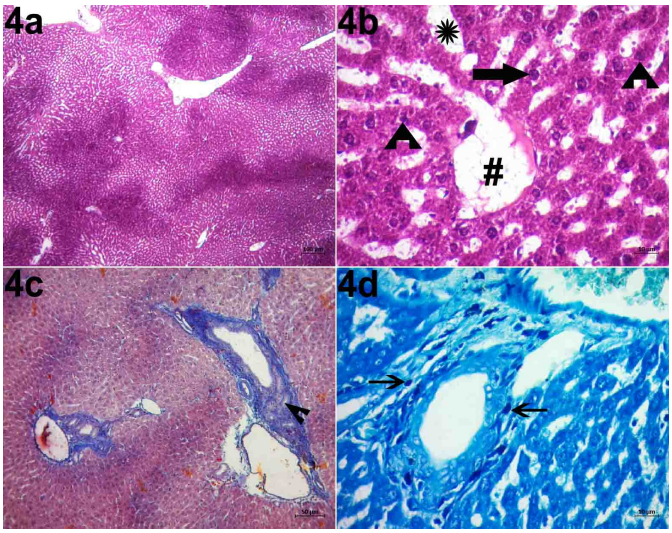

Fig. 4. (4a-4d sugammadex + rocuronium group) 4a, 4b, 4c and 4d: Images of the group in magnification x4, x40, x10 and x40 respectively; (Hematoxylin-Eosin staining, Masson' trichrome staining and Toluidine blue staining); #, central vein; thin arrow, mast cell; thin arrowhead, connective tissue; thick arrow, healthy hepatocyte; thick arrowhead, degenerated hepatocyte cells; star, dilated sinusoid

When the degree of immunostaining of the sugammadex+rocuronium group were examined by histopathological scoring, it was determined that there was a highly significant increase in the pure control and control groups. Statistical data are given in Table 1.

3.4. Biochemical analysis results

There was no statistically significant difference between pure control and control groups at the MDA level, which is defined as the indicator of free radical-induced damage in tissues ($p > 0.05$). However, sugammadex and sugammadex + rocuronium groups showed a significant increase in MDA levels compared to pure control and control groups ($p < 0.01$). The data of the groups are shown in Table 2 and Fig. 6.

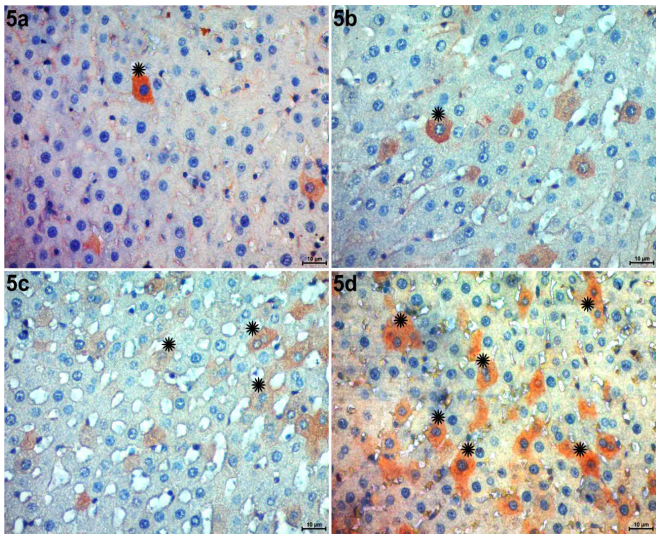

Fig. 5. 5a, 5b, 5c and 5d: Images at x40 magnification of groups (Pure control, control, sugammadex and sugammadex + rocuronium group respectively); * Caspase 3 positive cells exposed to apoptosis

Table 1. Histopathological scoring in all groups

Groups	Pure Control	Control	Sugammadex	Sugammadex + Rocuronium
Cellular degeneration	0.75 ± 0.71	0.50 ± 0.53	1.14 ± 0.70	2.12 ± 0.83*
Fibrosis	0.50 ± 0.75	0.62 ± 0.74	0.71 ± 0.75	2.01 ± 0.78*
Sinusoidal dilation	0.62 ± 0.74	0.65 ± 0.51	1.42 ± 0.78	1.98 ± 1.09*
Lobular degeneration	0.62 ± 0.74	0.50 ± 0.75	0.85 ± 0.69	2.10 ± 1.12*
Mast cell density	0.75 ± 0.70	0.75 ± 0.70	1.57 ± 0.53	2.09 ± 1.24*
The degree of immunostain	0.81 ± 0.65	0.50 ± 0.46	1.21 ± 0.56	2.37 ± 0.91*

It was found that GSH level, which plays a role in preventing free radical-induced damage in tissues, decreased in the group treated with sugammadex + rocunorium compared to other groups ($p < 0.01$). The data of the groups are shown in Table 2 and Fig. 6.

Table 2. Liver biochemical parameters in all groups (n=8)

Groups	Pure Control	Control	Sugammadex	Sugammadex + Rocuronium
MDA (nmol/g)	630.22 ± 70.23	553.09 ± 46.95	889.85 ± 78.77*	901.99 ± 73.09*
GSH (nmol/g)	2277.15 ± 104.72	2999.48 ± 221.66	2358.08 ± 105.59	1721.89 ± 153.51#

Valus are expressed as mean±SE; n=8 for each treatment group, * Statistical significancy compared to the Pure Control and Control groups ($p<0.01$), # Statistical significancy compared to the other groups ($p<0.01$)

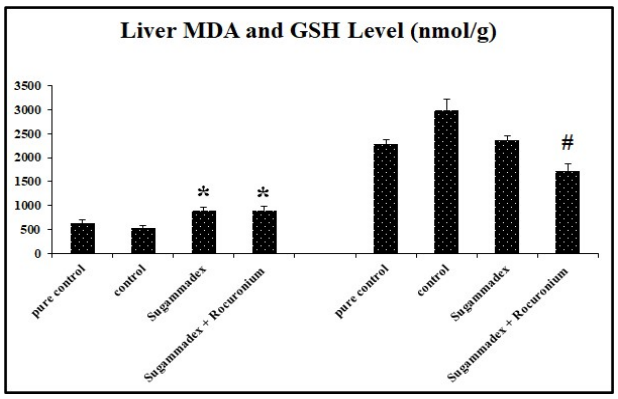

Fig. 6. Biochemical data which resulted from these groups are presented in this graph. Values are expressed as means ± SD; n=8 for each treatment group. Statistical significancy compared to the pure control and control group: *: p<0.01. Statistical significancy compared to the control group: #: p<0.01

4. Discussion

In current anesthesia applications, rocuronium, which is in the aminosteroid structure, is a muscle relaxant that is frequently used before intubation and is safe for surgical maintenance. The return of this neuromuscular blockade is at least as important as its maintenance. In this regard, various agents, such as sugammadex, are needed to restore the patient's airway control. These agents play an important role in reducing mortality and morbidity due to respiratory complications in the postoperative period. Sugammadex-rocuronium complex is eliminated by the kidneys. In this regard, prolonged effect of rocuronium in patients with renal failure is observed (15). As a result, depending on the elimination time of sugammadex-rocuronium complex, it is not recommended for use in patients with severe renal disease, since the decrease in sugammadex in plasma concentration varies (27). Tomak *et al.* (28) observed that the number of mast cells increased in rats treated with sugammadex compared to the control group. In this case, they suggested that treatment with sugammadex increased susceptibility to allergic reactions. However, the susceptibility to rocunorium-induced allergic reaction has been observed to a greater extent than susceptibility to sugammadex in the liver. The results show that sugammadex may inhibit rocuronium-induced mast cell degranulation depending on the dose (28). However, according to Clarke et al. (28), sugammadex is not sufficiently effective in changing the clinical reflection of the allergic reaction caused by rocuronium use (17). In histopathological examination, we found less mast cells in sugammadex group compared to sugammadex-rocunorium group. This finding supports the suppression feature of sugammadex anaphylaxis. There are no adequate studies on the effects of sugammadex on the liver. However, the effects of cyclodextrins on the liver have been studied (29-31). There are three types of cyclodextrin, α, β and γ cyclodextrins consist of six, seven and eight a- (1,4) linked glycosyl units, respectively. Although three types of cyclodextrin have water solubility feature, γ cyclodextrins with the highest water dissolution rate (32). In one study, the oral combination of a β-cyclodextrin group drug with clotrimazole, an antimycotic agent, induces fat accumulation in the liver compared to clotrimazole and can lead to liver hypertrophy. Although the resulting complex is promising in treatment due to its oral bioavailability, the hepatoxicity it causes cannot be excluded (29). On the other hand, in another study, it is noted that β cyclodextrins can affect the hepatoprotective effect positively as carbon tetrachloride-induced acute hepatotoxicity increases the water solubility of the proactive detective hydrophobic flavone compounds (23). In this case, it can be concluded that the β cyclodextrin group may vary depending on the complex it constitutes regarding the hepatoxic activity. Based on this point, we examined the effects of sugammadex alone, γ gamma cyclodextrin, and sugammadex and rocunorium complex on the liver using histopathological and biochemical methods. Redox signal transmission pathways play an important role in the regulation of cell functions. Oxidative stress is an important part of the pathogenic processes that occur in relation to redox homeostasis disorder. In case of cell damage, a high concentration of redox signal is observed by DNA degeneration (33). Pathological processes caused by oxidative stress can be reversible or irreversible (34). In addition, liver is the primary organ sensitive to pathological cascades caused by oxidative stress, and especially parenchymal cells are very vulnerable in the oxidative environment. Abundant reactive oxygen radicals are produced from microsomes in mitochondria and parenchymal cells (35). Simultaneously, the hepatic content of increased MDA, decreased hepatic superoxide dismutase, glutathione peroxidase, GSH indicates hepatic oxidative damage. In addition to these signs, increased caspase 3 mRNA expression in the cell indicates this (36). In this context, the increase in MDA levels in the groups belonging to sugammadex and sugammadex-rocunorium complex in our study proves oxidative stress occurring in liver tissues of both groups. However, the simultaneous decrease in GSH levels in the sugammadex and sugammadex-rocunorium groups is also accompanied. Especially the decrease in GSH level of sugammadex-rocunorium group is higher compared to sugammadex group. Therefore, oxidative stress damage occurring in the group treated with Sugammadex-rocunorium complex is higher compared to sugammadex group. Similarly, Palanca *et al.* (37) examined the neurotoxic effects of sugammadex and suggested that sugammadex-induced changes were associated with oxidative stress and apoptosis activation. sugammadex predominantly causes cell death in neurons, and induced apoptosis induction has been associated with a change in neuronal cholesterol homeostasis (37). The immunohistochemical analyzes also indicated this. Caspase 3 is expressed more in the sugammadex-rocunorium group compared to the sugammadex group. Caspase 3 is considered as an important biomarker in the mitochondrial apoptotic pathway (38). Based on this point, the sugammadex-rocunorium complex can trigger the apoptotic process in

hepatocytes.

In conclusion, sugammadex is γ gamma cyclodextrin group drug that can reverse the effects of rocuronium, a neuromuscular blocker. There are no adequate publications on the effects of suggamadex on the liver. In addition, suggamadex can inhibit rocuronium-induced anaphylaxis by reducing mast cell count. However, its toxic effect on hepatocytes has not been studied. In this context, in the present study, it has been demonstrated by biochemical methods that sugammadex and sugammadex-rocunorium complex cause hepatic oxidative stress. In addition, sugammadex-rocunorium complex was shown to increase induction of apoptosis and increase caspase 3 expression in hepatocytes compared to sugammadex. Furthermore, several morpho-quantitative studies are needed to reveal the toxic effects of the sugammadex-rocunorium complex.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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The risk of tuberculosis bacilli seeding during mediastinoscopy in mediastinal tuberculosis: Is it clinically important?

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Abstract

Mediastinoscopy is the gold standard for diagnosis in the absence of parenchymal lesions in mediastinal tuberculosis lymphadenitis. During mediastinoscopy biopsy, tuberculous bacillus seeding into the mediastinum is a rare complication. This study aimed to test the safety of mediastinoscopy in terms of *Mycobacterium tuberculosis* seeding in the mediastinum by microbiologically evaluating mediastinal lavage samples taken before and after biopsy. Classical cervical mediastinoscopy was performed all of patients and who were reported as granulomatous inflammatory events results of histopathological examinations and who underwent mediastinal lavage before and after biopsy, were included in the study. All the lavage fluids were tested for AFB and subjected to *Mycobacterium tuberculosis* PCR DNA testing and standard tuberculosis culture. The patients were divided into two groups, Group 1: Necrotizing granulomatous inflammation, Group 2: non-necrotizing granulomatous inflammation. The microbiological tests of the patients in Group 1 were negative before biopsy. However, in two patients of Group 1, the results of cultures of lavage fluids that taken from after biopsy were positive for tuberculosis. In all patients in Group 2, all microbiological tests of the lavage fluids were negative (Power of the decision: 99.8%, with 5% error). All of patients in group 1, Antituberculosis treatment was initiated and continued for 6 months. There weren't seen any serius complications due to treatment and recurrence during the follow-up period. Mediastinoscopy can be used safely, with low morbidity and mortality rates and a high success rate for the diagnosis of mediastinal tuberculosis.

Keywords: tuberculosis, mediastinoscopy, biopsy, lavage, culture

1. Introduction

Lymph node tuberculosis is the most common form of extrapulmonary tuberculosis after pleural tuberculosis. Mediastinal lymph node tuberculosis (MLNT)accounts for 5% of tuberculosis lymphadenitis cases (1). In the absence of parenchymal lesions in mediastinal tuberculosis lymphadenitis, obtaining a diagnosis with microbiological examination of sputum and bronchoalveolar lavage fluids is very difficult. Mediastinoscopy is the 'gold standard' method for diagnosis, especially for non-cancerous mediastinal lymphadenopathies such as tuberculous and sarcoidosis (2-5).

Complications during and after mediastinoscopy are rare. Reported morbidity and mortality rates for mediastinoscopy are 0.08% and 0%, respectively. Severe bleeding, tracheobronchial laceration, esophageal perforation, recurrent and phrenic nerve paralysis, thoracic duct injury, mediastinitis, venous air embolism and tumor cell seeding in the mediastinum and along the incision line are major complications that can accompany mediastinoscopy (6). However, there is no available information about the seeding of tuberculosis bacilli in the mediastinum during mediastinoscopy and its effects on the treatment process of tuberculosis. Therefore, this study aimed to test the safety of mediastinoscopy in terms of *Mycobacterium tuberculosis* seeding by microbiologically evaluating mediastinal lavage samples taken before and after biopsy.

2. Materials and Methods

This study was approved by the Medical Research Ethics Committee and Informed consent was obtained from patients who participated in our study. Four hundred and fifty-three patients of our clinic who underwent mediastinoscopy between 2012 and 2019 were included in our study. Mediastinoscopy was performed on 573 patients who had lung cancer or mediastinal mass identified for cancer staging or diagnosis. For diagnostic purposes, mediastinoscopy was also performed on 135 patients who had mediastinal lymphadenopathy. Subsequently, all the patients were further evaluated with chest X-Ray, thorax tomography, bronchoscopy. In addition, positron emission tomography/computed tomography (PET-CT) was applied to patients with suspected malignancy.

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Inclusion criteria for patients were histopathological diagnosis of lymph node biopsy as granulomatous disease, underwent mediastinal lavage before and after biopsy during mediastinoscopy. Exclusion criteria for patients were underwent mediastinoscopy for the staging of lung cancer, underwent mediastinoscopy due to malignant mediastinal mass, granulomatous disease diagnosis by mediastinoscopical biopsy but did not have lavage applied before and after biopsy during mediastinoscopy. Ultimately, 88 patients having mediastinal, pathological sized lymphadenopathy (LAP) and whose results were reported as granulomatous inflammation by mediastinoscopy and who underwent mediastinal lavage before and after biopsy in mediastinoscopy were included in the study. The patients were divided to two groups according to the results of histopathological examination of their lymph node biopsies: Group 1: Necrotizing granulomatous inflammation and Group 2: non-necrotizing granulomatous inflammation.

All patients underwent classical cervical mediastinoscopy. Under general anesthesia, a 3 cm skin incision was performed in the supine position at 2 cm above the jugular notch, over the cervical midline. After the skin and subcutaneous and muscle layers were dissected, the mediastinum was entered from the anterior of the trachea. The subcarinal region was reached with blunt and sharp dissection along the midline without exploring the lymph node stations. Before their exploration with blunt and sharp dissection, 20 cc of serum physiological solution was delivered to the pretracheal area via a 14-gauge feeding tube through a mediastinoscope. This process was repeated three times. Finally, all the laving fluid in the mediastinum was aspirated. Following pre-biopsy, the right-left 2., right-left 4. and 7. mediastinal lymph node stations [upper paratracheal, lower paratracheal and subcarinal] were explored (Fig. 1, Table 1). Samples were taken from all lymph nodes by multiple punch biopsies. After the biopsy procedure, mediastinoscope was advanced into the subcarinal area. The mediastinum was lavage with 20 cc of serum physiological solution again. So, both before and after biopsy, the mediastinum was laved with 20 cc of serum physiological solution. These fluids were collected into different test tubes labelled ‘prebiopsy mediastinal lavage’ and ‘post biopsy mediastinal lavage’. The incision was then closed, and the procedure was terminated. All patients were awakened in the operating room and followed up in our clinic.

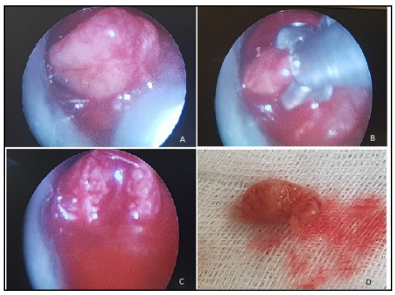

Fig. 1. Peroperative images of a patient whose tuberculosis culture of lavage fluid was positive

Table 1. Statistical results

Station number	Culture		Total n [%]
	Negative n [%]	Positive n [%]	
1	17 [100]	0 [0]	17 [100]
2	17 [89.5]	2 [10.5]	19 [100]
3	5 [100]	0 [0]	5 [100]
4	1 [100]	0 [0]	1 [100]
5	2 [100]	0 [0]	2 [100]
Total	42 [95.5]	2 [4.5]	44 [100]

2.1. Microbiological analysis

The mediastinal lavage specimens taken before and after biopsy were sent to the Medical Microbiology Laboratory. Specimens were sterilized by using sodium hydroxide [4% NaOH]. After concentration by centrifugation at 3000 g for 15 minutes, the sediment was re-suspended in 1.5 mL of 0.5 M phosphate buffer [pH 6.8] and inoculated onto Lowenstein-Jensen [LJ] medium and MGIT-7H9 broth supplemented with oleic acid-albumin-dextrose-catalase [OADC] and PANTA [Becton Dickinson]. The test tubes containing the inoculum and growth media were then incubated in Lowenstein-Jensen [LJ] medium at 37°C in a MGIT 960 unit [Becton-Dickinson and Company, Sparks MD, USA]. *Mycobacterium tuberculosis* complex strains grown on MGIT medium were tested for first-line anti-tuberculosis drugs in MGIT 960.

The Erlich, Ziehl and Neelsen staining method was applied to specimens that were then examined under a light microscope at 1000× magnification.

An XpertMLNTB/RIF device was used for the molecular identification of the *Mycobacterium tuberculosis* is complex. The testing was performed on samples by using version four cartridges, according to the recommendations of manufacturer. The Xpert assay sample reagent, which contains NaOH, and isopropanol was added within the ratio of 1 to 3 to the tubes to kill any mycobacteria present and to liquify the sample. The suspension was vigorously shaken and allowed to sit for 15 min before being shaken again and allowed to sit for another five min. Finally, 2 mL of the suspension was pipetted into anXpert assay cartridge and inserted into the GeneXpert unit for PCR testing. The measurements and analyses were conducted automatically, and reports were generated with Gene XpertDx software [Version 4.0].

2.2. Statistical analyses

In this study, descriptive statistical methods [percentage, frequency, mean] and the Chi-square test were used to analyze the data in the SPSS software program (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) For statistical calculations, each lymph node station was identified as an area and the level for statistical significance was set at $P < 0.05$.

3. Results

The general characteristics of patients are shown in Table 2. Sixty-one patients were female and 27 were male. [Group 1: Necrotizing granulomatous inflammation [n:44] and Group 2: non-necrotizing granulomatous inflammation [n:44].

Table 2. General features all of patients

General features	Group 1[n:43]	Group 2[n:45]
Age	53,52 [81-23]	50,34[75-25]
Sex		
Female	27	34
Male	16	11
Symptoms		
Cough	35	32
Sputum	20	12
Hemoptysis	2	0
Dispnea	6	10
Night sweats	12	5
Weight loss	10	10
No symptoms	8	12
AFB, tuberculous and common cultures		
in sputum	32	35
Negative	0	0
Positive	11	9
Notperformed		
Bronchoscopy		
EBL +	0	0
EBL –	17	24
Notperformed	26	21
Tuberculosis culture in BAL		
Negative	17	24
Positive	0	0
Lymph nodes that were biopsied		
Station 2nd		
Right	17	15
Left	7	4
Station 4th		
Right	35	39
Left	6	7
Station 7th	7	7
ML before biopsy		
PCR tbcDNA		
Negative	43	44
Positive	0	0
AFB		
Negative	43	44
Positive	0	0
Tbc culture		
Negative	43	44
Positive	0	0
ML after biopsy		
PCR tbc DNA		
Negative	43	44
Positive	0	0
AFB		
Negative	42	44
Positive	1	0
Tbc culture		
Negative	42	44
Positive	1	0

AFB: Acid-resistant bacteria EBL: Endobronchial lavage, BAL: Bronchoalveolar lavage, ML: Mediastinal lavage, PCR- tbc DNA: Polymerase Chain Reaction- tuberculous deoxyribonucleic acid, Tbc: Tuberculous

The mean age was 51.93 years with a range of 23 -81 years and the most common symptom was coughing. Twenty patients had no symptoms. Mediastinoscopy was performed on them due to the presence of pathological lymph nodes which were detected coincidentally. All patients had multiple mediastinal LAPs but none of them had endobronchial lesions. Additional radiological findings are shown in Fig. 2. All the patients were discharged at the first day after operation. There were no complications, except for hoarseness experienced in two patients which was resolved quickly.

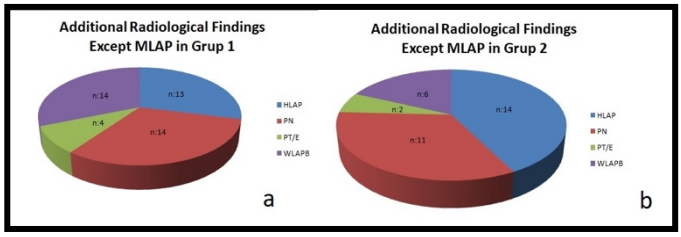

Fig. 2. a, b- Additionally radiological findings in Group 1(a) and in Grup 2 (b)

The most sampled lymph node station was the lower right paratracheal station [4R] and the least sampled station was the upper left paratrachealstation [2L]. A mean 1.9 [range 1-5] lymph node stations were sampled (Fig. 3). In 14 patients, pathological lymph nodes were detected in the subcarinal area, and all of them were sampled.

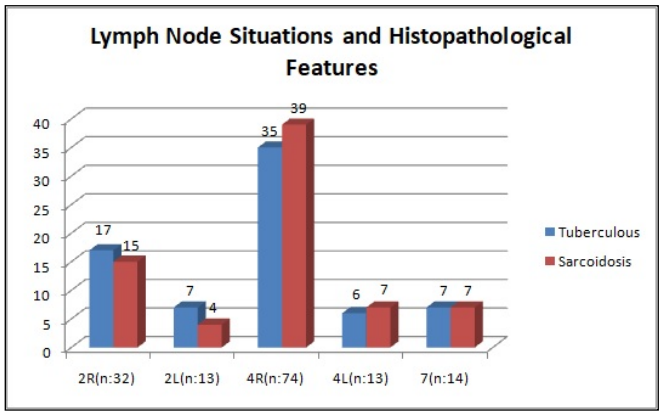

Fig. 3. Lymph node situations and histopathological features

Acid-fast *bacilli* (AFB) and *Mycobacterium tuberculosis* Polymerase Chain Reaction- tuberculous deoxyribonucleic acid (PCR DNA) testing and tuberculosis culturing were performed on all lavage fluids collected before and after biopsy. In all patients in Group 2, all microbiological tests were negative for all lavage fluids collected both before and after biopsy, and the pre-biopsy tests of the patients in Group 1 were all negative. However, the tuberculosis cultures of the post-biopsy lavage fluids of two patients in group 1 were positive (Fig. 4 a, b).

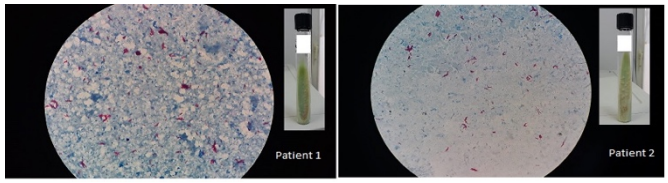

Fig. 4. a, b- Microbiological images of patients whose tuberculosis cultures of lavage fluids were positive: First patient (a), second patients (b)

Increasing the number of stations and / or the width of the dissection area did not have a significant statistical effect on the positive or negative expression of cultures. In addition, the rate of positive results for the tuberculosis culturing of mediastinal lavage fluids was 4.5%. The power of the decision was 99.8%, with a 5% margin of error, based on the power of the test and the sample size.

All of patients in group 1, antituberculosis treatment was

initiated. The patients were given on INH 300 mg [5 mg/kg], rifampicin 600 mg10mg/kg], ethambutol 1500 mg[20mg/kg], and pyrazinamide 2 g [25 mg/kg] for four months. Treatment was completed with INH and rifampicin for the next two months. All patients were followed up during the treatment period and for one year afterwards. There weren't seen any serius complications due to treatment. No recurrence was observed in any patient during the follow-up period.

4. Discussion

The most common form of tuberculosis after parenchymal tuberculosis is mediastinal tuberculosis. Mediastinal tuberculosis is mostly seen in children. MLNT without parenchymal lesion is a rare condition in adults. In Patients of our cohort, isolate mediastinal lymphadenopathy was detected in 46% of non-necrotizing granulomatous inflammation.; this rate was 25% in patients diagnosed with tuberculosis (7, 8). In our study, in both groups 1 and 2 the most common secondary pathologies were hilar LAP and parenchymal nodules (Figs. 2 and 3).

Mediastinal tuberculosis occurs more frequently in females than males, as same as the situation in our cohort of patients. Most patients are asymptomatic or present with non-specific symptoms. Coughing is the most common symptom in symptomatic patients. The most common symptoms in our patients were cough and sputum (Table 2). The probable cause of cough without parenchymal lesion is the irritation of the bronchi by mediastinal lymph nodes.

The most frequently affected lymph nodes in MLNT are the upper mediastinal and right hilar lymph nodes (9, 10). In our patients, the most frequently affected lymph nodes were the lower right paratracheal lymph nodes. The most affected lymph nodes after mediastinal lymph nodes were the hilar LAPs. Multiple biopsies were performed on all the pathological lymph nodes. The most frequently affected lymph nodes in both Groups 1 and 2 were the lower right paratracheal lymph nodes The least affected lymph nodes in both groups were the left upper paratracheal and subcarinal lymph nodes.

In some patients, bacilli from lymph nodes that are invading the bronchus can be detected in bronchoscopic lavage and / or sputum examinations. Our study was planned based on that information. In some patients with MLNT, bronchoalveolar lavage (BAL) can be found positive about tuberculosis due to mediastinal lymph node/nodes that invade bronchus in microbiological examination (11). This situation suggests that mediastinal lavages may be positive about tuberculosis after the mediastinoscopy of patients with MLNT.

The main purpose of this study was to determine the effects on prognosis of the seeding of the mediastinum with *M. tuberculosis bacilli* during biopsy procedures. In our study, tuberculosis cultures of mediastinal lavage fluids after biopsy were positive for only two patients. Those two patients did not show any differences from other patients in terms of response to treatment, complications, and recurrence during the follow-up period of two year.

Direct microscopy and culture are the 'gold standard' methods for the diagnosis of infections due to mycobacteria. The easiest and quickest method of diagnosis is ARB via the Ehrlich-Ziehl-Nielsen staining method. However, to show bacteria with direct microscopy, the material must contain at least 5000 to 10000 bacteria per mL [8]. In a study of newly diagnosed tuberculosis patients, it was reported that smear positivity could be shown in 50% to 80% of patients. Culturing is 500 times more sensitive than direct microscopy. However, the deficiency mentioned earlier in relation to the direct microscopic examination of tuberculosis bacilli and / or the amount of time consumed in culturing them prompts the use of molecular methods (12).

PCR is becoming used more widely because it has higher sensitivity and specificity rates and a wider identification spectrum than other molecular methods. It provides several advantages over culturing, including confirmation of the presence of *M. tuberculosis* within 1 to 3 days, compared to 2 to 6 weeks for culture techniques (13). The rapid diagnosis of tuberculosis with sensitivity like that of culturing has been reported for fresh specimens such as sputum and aspirated fluid by using PCR. Moreover, the sensitivity of PCR was 56.7%, the specificity was 100%, and the general efficiency of the test was 96.4% in a study conducted with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TTAB) and endoscopic ultrasound-guided fine needle aspiration (EBUS-FNA) patients (14).

In our study, we used the three methods for the examination of mediastinal lavage fluids. Direct microbiological examination and PCR were used for the rapid and reliable detection of bacteria. In addition, tuberculosis culture, which is the 'gold standard' diagnostic method, was applied to mediastinal lavage fluids of all patients to prevent any false negative tests (15). Also in our study, while tuberculosis was diagnosed by pathological examination, mediastinal lavage examinations were performed microbiologically. We did not expect that other, atypical mycobacterial bacteria could be among the etiological agents. Because there was no additional immunodeficiency in our patients, that meant to be a low incidental of isolated mediastinal atypical mycobacterial infections in our patient groups. In addition to, successful results were obtained for all patients with anti-tuberculosis therapy. All these results collectively indicate that M. tuberculosis was the only factor directly impacting on the health status of the studied cohort.

A lot of complications, such as severe bleeding, mediastinitis, and tumor cell seeding in the mediastinum and along the incision line etc., can be seen during

mediastinoscopy (16, 17). However, no information was found in the literature regarding the seeding of tuberculosis bacilli during mediastinoscopy and its effects on follow-up treatment. In our study, the post-biopsy mediastinal lavage tuberculous cultures of two patients were positive. Our results showed that the seeding of tuberculosis bacilli in the mediastinum can occur during mediastinoscopy in patients with mediastinal tuberculosis.

The most likely explanation is the direct seeding of tuberculous bacilli into the mediastinum during biopsy. In these patients, biopsies were taken from only two stations which did not include the subcarinal area. These results suggest that the increased dissection and number of biopsies during mediastinoscopy are not predisposing factors for the seeding of bacilli in the mediastinum. In other words, our results showed that mediastinoscopy is a safe method that minimizes bacillus seeding of the mediastinum in MLNT. Statistically, according to the power and sample size of the applied test, the power of the decision was 99.8%, with a 5% margin of error. In addition, no difference was observed between the two patients' positive cultures of M. tuberculosis and others in terms of treatment period, response to treatment and recurrence during the follow-up period.

Especially in recent years, the new, non-invasive methods such as EUS-FNA and EBUS-TBNA have become frequently used in the diagnosis of mediastinal diseases. However, the diagnostic value of these methods in malignant diseases is higher than non-cancerous, mediastinal lymphadenopathies such as tuberculosis. In addition, with these methods, difficulties of exploration of the lymph nodes which are smaller than pathological dimensions and / or around the great vessels can lead to false negative results. This can also lead to delays in the initiation of treatment. For this reason, the diagnostic value of mediastinoscopy increases further, especially in non-cancer, mediastinal pathologies (6, 18).

This study has some limitations. First, because this study was prospective clinical study, mediastinal lavage fluids samples were obtained all of patients who performed mediastinoscopy and had not malign diagnosis. Patients whose pathology results were not reported as tuberculosis were excluded from the study. Secondly, since the follow-up of patients diagnosed with tuberculosis was carried out by tuberculosis dispensaries, the surgical follow-up of the patients could only be made by phone calls. Patients who could not be reached by phone during the follow-up period were also excluded from the study.

The authors of the presents study suggest that during mediastinoscopical biopsy, tuberculous bacillus seeding into the mediastinum was a rare complication. Furthermore, this situation had no effect on both the prognosis and treatment response. Therefore, mediastinoscopy remains the 'gold standard' diagnostic method in that it can be used safely, with a high diagnostic success rate and low morbidity and mortality, in the diagnosis of mediastinal tuberculosis.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this study.

Acknowledgments

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Comparison of the gastric biopsy results of Afghan refugees and Turkish people

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Abstract

Helicobacter pylori- (H. pylori) infection is one of the effective factors in the development of gastric premalignant lesions, and it is known that socioeconomic conditions are closely related to *H. pylori* infection. Our aim was to show whether there were differences regarding *H. pylori* infection and gastric histopathological findings between humans who had to manage an exhausting escape out of their own country and residents of a coastal town in the black sea region of Turkey. Endoscopic findings of Turkish and Afghan patients who underwent gastroscopy for various reasons, gastric biopsies, and their histopathological results (*H. pylori,* intestinal metaplasia, and gastric atrophy) and some biochemical parameters were retrospectively screened from the hospital online data system. A total of 222 patients, 41 Afghan and 181 Turkish, were included in the study. There were no significant differences regarding age and gender of the patients between the groups. The percentage of the patients with intestinal metaplasia and *H. pylori* infection was higher in the group of the Afghan patients than in Turkish patients. Afghan refugees had similar rates of atrophic gastritis (23.1% versus 21.5%; p=0.834), when compared to resident controls. Risk factors of gastric cancer include the presence of *H. pylori* infection, atrophic gastritis, and intestinal metaplasia. This study supports the knowledge that socioeconomic factors such as low economic conditions and poor health infrastructure are one of the major causes of widespread global H. pylori infection status.

Keywords: gastric biyopsy, *H. pylori*, intestinal metaplasia, gastric atrophy

1. Introduction

Due to ongoing socioeconomic turmoil and civil war like circumstances almost four million Afghan refugees had to leave their country and to move to neighboring countries and to the middle east, as well. According to the Journal of UN (1) there are 300.000 Afghan refugees in Turkey with the world's largest refugee population of about four million refugees in total, being under official protection.

It is classically described that both refugees and immigrants have lower socioeconomic status and have diminished access to health care centers due to lack of proper supports in their residential areas. Overcrowded immigration centers, poverty and low education levels are also contributed to some communicable diseases among Afghan refugees (2).

H. pylori is a gram-negative, spiral rod-shaped bacterium mainly seen in Asia, affecting almost half of the world's population (3). It is one of the responsible reasons for gastric cancer and gastric mucosa-associated lymphoid tissue (MALT)-lymphoma which comprises 5% of all cancer types in humans (4). Environmental etiological factors for developing *H. pylori*-infection include consuming contaminated drinking water, living in overcrowded houses and dormitories, having either poverty or low education level (5).

Thus, immigrant populations are still the main targets of H. pylori studies to evaluate the spreading patterns of these infectious diseases.

Other hand, premalignant conditions and gastric cancer are one of the main health problems in some Asian countries including Japan, Afghanistan, Iran, and Turkey. Although the exact reason is not well established, those high rates of gastric cancer in such countries could be related to dietary habits and genetic predisposing factors (6). Intestinal Metaplasia (IM) means the emerging and presence of both colonic and intestinal mucosa in the gastric mucosa without well-established underlying factors. It is strongly associated and presented with intestinal type gastric adenocarcinoma and should be screened in all high populations (7). Risk factors of gastric IM have been reported as the presence of H. pylori infection, older age, smoking history, strong spicy food, occupation status and the presence of IL10-592 C/A (8).

Other hand, atrophic gastritis is defined as immunologically destructed parietal cells in either gastric fundus or corpus (9).

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Both of atrophic gastritis and gastric IM are implicated in gastric carcinogenesis and should be tracked by endoscopic screening programs (10).

Our aim in this study is to determine the frequency of *H. pylori* infection and associated gastric precancerous lesions in the Afghan patient group with poor access to health-sufficient socioeconomic conditions and to compare these findings with the resident Turkish patient group living in the same region.

2. Materials and Methods

This study is a retrospective, unicenter trial. All Afghan refugee and Turkish resident patients over 18 years of age who underwent gastroscopy with a diagnosis of dyspepsia between May 2018 and October 2019 were included in the study.

We had previously excluded patients with severe underlying disease, including gastric cancer and gastric resection. All Patients without gastric biopsies or with pathology results, which could not be obtained, were excluded.

The control group was selected from native Turkish subjects presenting with dyspepsia. Gastroscopy with antral biopsy was performed in all patients at enrollment of the study. Laboratory parameters were obtained from hospital data system.

2.1. Endoscopy and histologic examination

All endoscopic examinations were performed with propofol anesthesia using Fujinon videoscope (Tokyo, Japan). Biopsy samples were reviewed by a pathologist for GPL and *H. pylori* status. Gastric biopsy specimens were fixed in formalin and assessed for *H. pylori* (by Giemsa staining) and intestinal metaplasia (by staining with hematoxylin and eosin). Intestinal metaplasia was classified in two grades (absent or present). Atrophic gastritis was defined as absence or presence of parietal cells in gastric mucosa with similar pathologic methods.

2.2. Ethical approval

Ordu University Training and Research Hospital / Ordu, Decision of Invasive Clinical Research Ethics Committee, 2020.

2.3. Statistical analysis

All statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.). The demographic, clinical, pathological and laboratory data and characteristics of the patients were compared by Student's t-test and Fisher's Exact-test to assess the difference between the proportions. All p-values were two-sided; significance was indicated by a p-value of less than 0.05.

3. Results

During the same time with fifty-five Afghan patients being gastroscopies, the gastroscopic findings of coincidentally found two hundred-forty Turkish patients were screened via the computer data system of the hospital. Fourteen Afghan and fifty-nine Turkish patients were excluded because of at least one exclusion criteria. Finally, forty-one Afghan and one hundred eighty-one Turkish patients were included into the study. The characteristic sociodemographic features at baseline were well balanced between refugees and control subjects with respect to age (40.5±13.3 versus 44.8±13.7 years) and gender (all p >0.05). The total of the demographic and laboratory results of both groups are presented in Table 1.

Table 1. Demographic and laboratory results of the Afghan and Control group

	Afghan Group		Turkish group		
	Mean values (95 % CI)	SD	Mean values (95 % CI)	SD	P
Age	40.53 (36.52- 44.55)	13.7	44.8 (52.8- 56.9)	13.7	<0.001
Gender					
Female	20 (48.78)		68 (37.6)		0.054
Male	21 (51.21)		113 (62.4)		0.054
Hemoglobin	13.43 (12.93- 13.94)	1.67	13.1 (12.8- 13.43)	2.12	0.413
Hematocrit	40.79 (39.51- 42.08)	4.27	40.56 (39.7- 41.4)	5.62	0.954
MCV	85.97 (84.12- 87.81)	6.15	85.45 (84.5- 86.4)	6.36	0.765
WBC	6.60 (5.91- 7.28)	2.28	7.85 (7.48- 8.21)	2.47	0.002
Thrombocytes	235 (211.97- 258.03)	76.5	279.0 (250.1- 308)	197.4	0.109
Glucose	108 (93.76- 122.24)	43.3	106.6 (99.7- 113.5)	49.9	0.148
Urea	27.88 (26.09- 29.67)	5.67	31.2 (29.2- 33.2)	13.1	0.210
Creatinin	0.69 (0.65- 0.73)	0.13	0.80 (0.76- 0.84)	0.27	0.003
AST	23.05 (18.94- 27.16)	13.2	23.74 (21.03- 26.46)	17.9	0.585
ALT	19.6 (15.4- 23.8)	13.8	23.64 (20.47- 26.82)	21.4	0.273
Albumin	4.1 (3.7-4.5)	0.4	4.57 (4.41- 4.72)	0.53	0.039
Ferritin	4.57 (4.41- 4.72)	56.1	52.34 (38.21- 66.47)	42.9	0.004
TSH	2.04 (1.36- 2.71)	2.25	2.02 (1.69- 2.34)	1.92	0.435

MCV: mean corpuscular volume; WBC: white blood cells; AST: aspartat-aminotransferase; ALT: alanin-aminotransferase; TSH: thyroid-stimulating hormone; CI: confidence interval; sd: Standard deviation

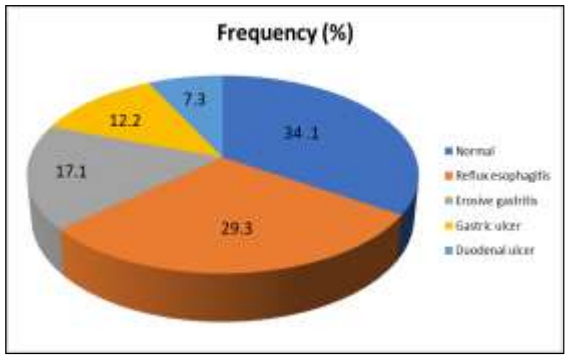

Fig. 1. Endoscopic findings of the Afghan patients

The histopathologic results of the gastric biopsies as *H. pylori,* intestinal metaplasia and gastric atrophy are demonstrated in Table 2. The gastric biopsy specimens unveiled a significantly higher rate of *H.pylori* infection and gastric intestinal metaplasia in Afghan patients in comparison to

Turkish patients (78% versus 60.8%; p= 0.037 and 19.5% versus 3.3%; p=0.001, retrospectively). Interestingly, Afghan refugees had similar rates of atrophic gastritis (23.1% versus 21.5%; p=0.834), when compared to resident controls.

The mean serum albumin levels among Afghan refugees were lower than those of the Turkish control group (4.1 vs. 4.57 g/dl). The ferritin values in the Afghan group were higher (89.58ng/mL) than in the Turkish group (52.34 ng/mL).

The means of serum creatinine and leucocyte levels were significantly higher in the Turkish group than in the Afghan refugee group (0.80±0.27 mg/dl versus 0.69±0.13 mg/dl; p=0.003 and 7.85±2.47mm³ versus 6.60±2.28/mm³; p= 0.002, respectively).

Table 2. Histopathologic results of *H. pylori*, intestinal metaplasia, and gastric atrophy

		Afghan group	Turkish group	P-value
H. Pylori; n (%)	No	9 (22)	71 (39.2)	<0.001
	Yes	32 (78)	110 (60.8)	
Intestinal Metaplasia; n (%)	No	33 (80.5)	175 (96.7)	0.000
	Yes	8 (19.5)	6 (3.3)	
Atrophy; n (%)	No	32 (78.04)	142 (78.5)	0.834

H. Pylori: Helicobacter Pylori

4. Discussion

H. pylori has infected millions of people worldwide and has caused millions of gastric cancer cases. Risk factors of gastric cancer include the presence of *H. pylori* infection, atrophic gastritis, and intestinal metaplasia. Possible gastric cancer related environmental factors include living in a weak health infrastructured area and being in low socioeconomic status. The turmoil in the middle east and central Asia, where health organizations still face major limitations, caused further dislocations of a huge number of immigrants into Turkey in recent years.

Supporting the setting of this study, we found that the rate of *H. pylori*-infection in the Afghan refugee group was statistically significantly higher than Turkish patients. An Afghan study pointed out, that the prevalence of *H. pylori* infection was found as 59.1% by using an enzyme linked immunosorbent assay test. In our study, the rate of *H. pylori* infection in the Afghan group was significantly higher with 78% compared to this study. The reason for this difference can be attributed to the fact that Afghan refugees had to leave their hometown for various reasons and live in lower socioeconomic and poor sanitation conditions. Its presence was reportedly correlated with as follows; hypertension, smoking cigarettes, higher body mass index, diabetes mellitus and higher total cholesterol levels (all p<0.05) (11). Unfortunately, we did not analyse underlying factors that prone to *H. pylori* infection due to the retrospective nature of the study.

The importance of intestinal metaplasia in the development of gastric cancer was first described as the Correa sequence in the 1970s. According to this hypothesis, *H. pylori* infection results in superficial gastritis, atrophic gastritis, and intestinal metaplasia (12). Later, the close relationship between *H. pylori*, glandular atrophy, and intestinal metaplasia was defined by Matsuhisa et al. (13). The lower socioeconomic status in Asia is one of the fundamental reasons for the higher seroprevalence of *H. pylori*. It is assumed to be responsible of emerging gastric cancers and MALT-lymphoma (6). It is supposed that the rate of intestinal metaplasia in the Japanese population leads to more frequent gastric cancer compared to other Asian countries (13). Another study was conducted in Afghan humans complaining dyspepsia. 364 native Afghan humans were screened by upper gastrointestinal endoscopy without sedation, unveiling rates of esophageal cancer and gastric cancer of 25.3% and 3.6%, respectively (14). In our study, we found higher rates of gastric intestinal metaplasia in Afghan refugees. We did not detect any gastric cancer cases in our study subjects. The reason for this situation can be considered as the low number of Afghan patients in the study and the general condition of the patients with gastric cancer not being able to take refuge.

The circumstance of lower albumin levels among Afghan refugees could be explained by malnutrition, as it was the case in our Afghan group (15), the higher levels of ferritin at normal hemoglobin in the Afghan group were interpreted as acute phase protein reaction rather than anemia.

The fact of higher creatinine-levels in the Turkish control group than in the Afghan group could be due to the lower weight and muscle mass because of malnourishment in the last months.

Our study was conducted retrospectively, so it could not be planned systematically like a prospective study. Another limiting factor of this study is that patients may be using a proton pump inhibitor before endoscopy, which may affect *H. pylori* evaluation. Finally, in this small city where the study was conducted, the number of Afghan refugees is quite low compared to metropolises. Further on, it is questionable, whether these patients represent most of the Afghan people in Turkey.

Our endoscopic findings may provide a novel opportunity to draw attention on the health problems, in particular the gastric cancer risk among Afghan refugees or asylum seekers all over the world. Of course, more studies are necessary on this topic to maintain a sufficient health care for the global challenge of refugees.

Conflict of interest

No conflict of interest was declared by authors.

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None to declare.

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Patients' approach to medicines in COVID-19

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Abstract

Several different guidelines and therapeutic recommendations have been reported for the treatment of COVID-19 since the announcement of the pandemic. In our study, the attitudes and approaches of patients with a medical indication for COVID-19 who were given drugs towards drug usage were evaluated. We aimed to present our data on the drug usage characteristics of patients to contribute to the literature. A total of 399 patients were included in the study. In the study, 51.1% of the patients were female, and 48.9% were male. The highest number of the patients were in the 18-30 age group (27.6%), the lowest number of the patients were 65 years old or older (9.8%). Twenty-five questions prepared by the researchers were asked to the patients to evaluate "their knowledge and attitudes on drug usage and disease prevention in COVID-19." Of the patients, 75.7% were not smokers. No history of chronic disease was present in 65.5% of the patients. It was determined that no drug was recommended for 9.8% of the patients, and hydroxychloroquine and favipiravir were recommended together in 49.9%. The rate of the use of chloroquine alone was 4.8%, and the rate of using only favipiravir was 32.8%. Eighty-two percent of the patients reported that they regularly used the drugs that were recommended. Among the patients, 11.5% either never used the recommended drugs or did not use them at the recommended dose and time. Of the 46 (11.5%) patients who did not use the prescribed drugs regularly, none died. In other words, improvement was observed in the patients who did not use the drugs that were recommended to them. Our aim in this study was to determine the rate and characteristics of the drugs prescribed by physicians in diagnosed patients. In this cross-sectional sample of Turkey, it was determined that the rate of recommended drug usage was sufficient with the data of the city where the study was carried out.

Keywords: COVID-19, drugs, patients, hydroxychloroquine, favipiravir

1. Introduction

Several different guidelines and therapeutic recommendations have been reported for the treatment of COVID-19 since the announcement of the pandemic. Accordingly, at the beginning of the current pandemic, in China, several agents were used first and successively. Furthermore, numerous clinical studies were initiated to investigate the potential efficacy of treatments for COVID-19, highlighting the need to obtain high-quality evidence as soon as possible (1-5).

Urgent responses and high-quality evidence were needed regarding the efficacy and safety of the therapeutic agents currently used at the beginning of the pandemic process. For this reason, several clinical studies with different approaches, different drug combinations and different durations were approved during the pandemic period. Therapeutic agents such as hydroxychloroquine, remdesivir, lopinavir/ritonavir, favipiravir, tocilizumab, immune plasma and immunoglobulins were recommended by Clinical Research Agencies. Most of these randomly designed trials with these drugs are still ongoing, and the effectiveness and efficacy of these drugs are not yet clear (3-8).

In Turkey, the Scientific Advisory Board was established by the Ministry of Health with the announcement of the pandemic. Epidemic management, monitoring and control were planned in line with the recommendations of this board. Moreover, each subject title was made available in the name of "Guidelines" on the Ministry of Health's webpage. Thus, the approach to the patient, treatment plan and follow-up were standardized throughout the country. The guidelines include how the COVID-19 pandemic started and spread, the characteristics of the SARS-CoV-2 virus that caused the pandemic, the form of the transmission of the disease, its epidemiology, diagnosis, treatment and follow-up, and individual and institutional measures to be taken to control the pandemic. These guidelines presented which cases would be treated and where and how they would be treated (outpatient, service or intensive care units), the doses of drugs used in treatment, side effects, at which stage of the disease these drugs should be initiated/discontinued, as well as supportive treatments. The guidelines handled in detail every issue related to the management of COVID-19 patients, from

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evaluation of the patient's response to the treatment, the isolation/quarantine periods/rules of the patient, to the burial procedures of the deceased patients, and they presented recommendations and algorithms for implementation (9-11). Since the pandemic's announcement, the guidelines have been and still are frequently updated considering new data and information. They have provided the opportunity to find the most accurate and up-to-date information that health professionals will need in the management of the disease. Drug indications and doses to be used have been clearly stated in the guidelines, and treatment protocols have been applied accordingly.

In our study, we evaluated the attitudes and approaches of patients with a medical indication for COVID-19 who were given drugs to drug usage. We aimed to present our data on the drug usage characteristics of patients to contribute to the literature.

2. Materials and Methods

The ethics committee approval of the study was obtained from the Ahi Evran University Clinical Research Ethics Committee with the decision no.: 2021-02/15. Consent was obtained from each patient participating in the study.

2.1. Study Population

The study was conducted with patients diagnosed with COVID-19 registered by the Provincial Health Directorate of our city. There were 17436 cases registered in the city at the end of January 2021. To select the sample of the study, 600 adult patients were called randomly from these cases. 153 patients could not be reached on the phone number they had provided, and 47 patients did not agree to participate in the study. Patients in the pediatric age group were excluded.

The sample of the study was formed of 400 randomly selected patients who were interviewed by phone and volunteered to participate. The required sample size of the study was calculated by power analysis. As a result of the power analysis performed by taking the effect size of w=0.25, power (1-β)=0.95, df=9, it was calculated that the total sample size should be at least 378. Power analysis was performed using the G*Power 3.1.9.6 software.

The data were collected from the 400 randomly selected patients comprising the initial sample by contacting the patients on the official phone line of the Provincial Health Directorate. Twenty-five questions prepared by the researchers were asked to the patients to evaluate "their knowledge and attitudes on drug usage and disease prevention in COVID-19" (Table I). The answers to the questions asked to the participants one by one through the official phone line were recorded. The questions were created under the guidance of the guidelines of the Ministry of Health to evaluate the demographic characteristics of the participants, as well as their data on COVID-19 diagnosis characteristics, drug usage and their compliance with the protection methods recommended in the Ministry of Health guidelines (9).

Information about the study was given to each patient who agreed to participate in the study, and consent and voice recording of the interview were obtained. Only 1 patient stated that they did not want to participate in the study by returning our call. The data of this patient were excluded from the study. A total of 399 patients were included in the study.

2.2. Statistical Analysis

The statistical analyses in the study were performed using the Statistical Package for the Social Sciences version 21.0 software for Windows (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp., USA). The descriptive statistics of the variables are presented as n (%). Chi-squared and Fisher-Freeman-Halton tests were used for the univariate analysis of the variables. In all statistical analyses, results with a p-value below 0.05 were interpreted as statistically significant.

3. Results

A total of 399 patients were included in the study, where 51.1% of the patients were female, and 48.9% were male. The highest number of the patients was found in the 18-30 age group (27.6%), and the lowest number of the patients were 65 years old or older (9.8%). It was observed that the education levels of the patients were mostly on the primary education (35.8%) and bachelor's degree (32.3%) levels. No history of chronic disease (such as Diabetes Mellitus (DM), Essential Hypertension (HT), Coronary Artery Disease (CAD), Congestive Heart Failure (CHF), Malignancy) was detected in 65.5% of the patients. The most common chronic disease history was determined to be DM (9.32%) and HT (9.32%). Of the patients, 75.7% were not smokers (Table 2).

Most of the patients stated that they used masks (96.7%) when they went out of the house when necessary (e.g., grocery shopping). While 57.4% of the patients did not work in any job, 41.1% of them were working. When this group of employees was evaluated, 13.3% of them stated that they were eating and drinking together with their colleagues in their work environment. The ratio of those who stated that they paid attention to the recommendations of the Scientific Advisory Board (social distancing, limitation of the number of people in an indoor environment and ventilation of the environment) during eating and drinking was 92.2%. While 6.8% of the patients stated that they accepted guests to their houses and/or went to visit others, a significant portion (90.5%) stated that they did not accept guests during this period, and they did not go to visit others either (Table 2).

A significant proportion (86.2%) of the patients were diagnosed with COVID-19 in the 3-month period prior to the starting date of the study. In other words, the 3-month period (November, December, January) before February 2021, when the study was conducted, was determined as the period with the highest number of the patients included in this study during the pandemic (Table 2).

Table 1. Sample follow-up form to evaluate patients' drug usage, prevention from the disease, knowledge and attitudes in COVID-19

	Date: …/…/2021 City/District where you live:
1	Age? □18-30 □31-40 □41-50 □51-64 □+65
2	Sex? □Female □ Male
3	Education status? □Illiterate □Primary school □High school □Bachelor's degree □Postgraduate/Doctorate
4	Do you have any chronic disease? □Asthma/COPD □Diabetes □Hypertension □Heart Diseases □Other
5	Do you smoke? □Yes □No
6	Do you wear a mask when going out of the house (when you go shopping, etc.)? □Yes □No
7	Are you currently in a job? □Yes □No (If your answer is No, move to the question 9)
8	Do you get together with your colleagues at work, drink tea, coffee, etc., and eat something? □Yes □No
9	When drinking tea, coffee or eating, do you pay attention to the Scientific Advisory Board's recommendations (distance and number of people in a closed environment)? □Yes □No
10	Do guests come to your house, or do you go on house visits? □Yes □No
11	When did you get the diagnosis of COVID-19? □0-3 months ago □4-6 months ago □7-9 months ago □ 10-12 months ago
12	Which drugs were recommended to you by the pandemic outpatient clinic/contact tracing team? (you can check more than one option) □Plaquenil □Favipiravir □Plaquenil + Favipiravir
13	Did you regularly use the drugs recommended by the pandemic outpatient clinic/contact tracing team? □Yes □I started using them when my condition got worse □No
14	If your answer was I started using them when my condition worsened, or no, why did you not use them? □I do not think coronavirus drugs are beneficial. □I think coronavirus drugs are harmful. □I did not use them because I was afraid of their side effects. □I did not use them because I was feeling good. □I do not like taking drugs. □Other
15	Did you use the drugs recommended by the pandemic outpatient clinic/contact tracing team in the amount recommended by them? □Yes □No
16	Did you adjust the dosage of the drugs recommended by the pandemic outpatient clinic/contact tracing team by yourself? □Yes □No
17	Did you use the drugs recommended by the pandemic outpatient clinic/contact tracing team more than the amount recommended by them? □Yes □No
18	Where did you get information about drugs used against COVID-19? □The website of the Ministry of Health □The physicians working in the pandemic outpatient clinic □Physicians I know □The contact tracing team staff □The pharmacy (pharmacist/pharmacy employee) □Healthcare personnel (nurse/technician) I know □The drug package insert □Internet/tv □Neighbors or relatives □Other
19	Did your neighbors or relatives give you non-drug recommendations for the coronavirus disease, and did you follow these recommendations? □Yes (cupping/leech/amulet/herb mixture) □No
20	Did you take any food supplements or drugs other than coronavirus drugs? □Yes (*Vitamin D/ *Vitamin B/ *Omega 3/* Propolis/* Mg /* Zn/ *Coraspin /*Other:……) □No
21	Are you thinking of getting vaccinated? □Yes □No (Move to the question 23)
22	Where did you get information about the vaccine? □TV/Social Media □The website of the Ministry of Health □Relatives □Other:
23	Why do you not want to be vaccinated? □I do not think it is safe. □I think it is harmful. □Other:
24	Were you vaccinated against flu and pneumonia? □Yes □No
25	Do you get the flu vaccine regularly every year? □Yes □No

It was determined that no drug was recommended for 9.8% of the patients, and hydroxychloroquine and favipiravir were recommended together in 49.9%. The use of chloroquine alone was 4.8%, and the rate of using only favipiravir was 32.8%. In the study, 82% of the patients reported that they regularly used the drugs recommended by the pandemic outpatient clinic and/or the physician of the contact tracing team. Among them, 11.5% either never used the recommended drugs or did not use them at the recommended dose and time. Of the 46 (11.5%) patients who did not use the prescribed drugs regularly, none died. In other words, improvement was observed in the patients who did not use the drugs.

In the evaluation questions, the patients' reasons for not using drugs were questioned by providing them with the options "I do not think drugs are beneficial, I think drugs are harmful, I did not use them because I was afraid of their side effects, I did not use them because I felt good, I do not like taking drugs". During the pandemic process, most of the patients (50.6%) received their information about the drugs

used in COVID-19 from the contact tracing team. Many patients (21.3%) also searched for information about drugs on the internet/TV. Accordingly, it was observed that the patients preferred the Ministry of Health's website (1.3%) and pharmacies (0.5%) much less to obtain relevant information (Table 2).

Table 2. Frequency and % values of the patients participating in the study

		N (%)
Sex		
	Female	204 (51.1)
	Male	195 (48.9)
Age		
	18-30	110 (27.6)
	31-40	97 (24.3)
	41-50	75 (18.8)
	51-64	76 (19.0)
	65+	39 (9.8)
Education status		
	Illiterate	12 (3.0)
	Primary school	143 (35.8)
	High school	95 (23.8)
	Bachelor's degree	129 (32.3)
	Postgraduate	5 (1.3)
Chronic Diseases		
	Asthma	18 (4.20)
	Diabetes (DM)	40 (9.32)
	Hypertension (HT)	40 (9.32)
	Heart Diseases (CAD/CHF)	15 (3.5)
	Cancer	7 (1.63)
	Liver Disease	2 (0.47)
	Other Liver Diseases	3 (0.70)
	Thyroid Diseases	8 (1.86)
	Kidney Diseases	1 (0.23)
	COPD	2 (0.47)
	None	281 (65.50)
	Other (Rheumatic, skin-related, etc. diseases)	12 (2.80)
Do you smoke?		
	Yes	86 (21.6)
	No	302 (75.7)
Do you wear a mask when going out of the house (when you go shopping, etc.)?		
	Yes	386 (96.7)
	No	1 (0.3)
Are you currently in a job?		
	Yes	164 (41.1)
	No	229 (57.4)
Do you get together with your colleagues at work, drink tea, coffee, etc., and eat something?		
	Yes	53 (13.3)
	No	325 (81.5)
When drinking tea, coffee or eating, do you pay attention to the Scientific Advisory Board's recommendations (social distancing and number of people in a closed environment)?		
	Yes	368 (92.2)
	No	5 (1.3)
Do guests come to your house, or do you go on visits?		
	Yes	27 (6.8)
	No	361 (90.5)
When did you get the diagnosis of COVID-19?		
	0- 3 months ago	344 (86.2)
	4- 6 months ago	21 (5.3)
	7- 9 months ago	28 (7.0)
	10-12 months ago	2 (0.5)
Which drugs were recommended to you by the pandemic outpatient clinic/contact tracing team? (you can check more than one option)		
	Plaquenil	19 (4.8)
	Favipiravir	131 (32.8)
	Plaquenil +Favipiravir	199 (49.9)
	None (Pregnant/lactation)	39 (9.8)
Did you regularly use the drugs recommended by the pandemic outpatient clinic/contact tracing team?		
	Yes	327 (82.0)
	I started using them when my condition got worse	4 (1.0)
	No	46 (11.5)
If your answer was I started using them when my condition worsened, or no, why did you not use them?		
	I do not think coronavirus drugs are beneficial.	0 (0.0)
	I think coronavirus drugs are harmful.	0 (0.0)
	I did not use them because I was afraid of their side effects.	3 (0.8)
	I did not use them because I was feeling good.	2 (0.5)
	I do not like taking drugs.	
	Other	39 (9.8)

Did you use the drugs recommended by the pandemic outpatient clinic/contact tracing team in the amount recommended by them?		
	Yes	324 (81.2)
	No	61 (15.3)
Did you adjust the dosage of the drugs recommended by the pandemic outpatient clinic/contact tracing team by **yourself**?		
	Yes	7 (1.8)
	No	349 (87.5)
Did you use the drugs recommended by the pandemic outpatient clinic/contact tracing team more than the amount recommended by them?		
	Yes	16 (4.0)
	No	368 (92.2)
Where did you get information about drugs used against COVID-19?		
	The physicians working in the pandemic outpatient clinic	20 (5.0)
	Physicians I know	15 (3.5)
	The Contact Tracing Team	202 (50.6)
	The pharmacy	2 (0.5)
	Healthcare personnel I know	22 (5.5)
	The drug package inserts	1 (0.3)
	Internet/TV	85 (21.3)
	The website of the Ministry of Health	5 (1.3)
	Family physician	21 (5.0)
Did you take any food supplements or drugs other than coronavirus drugs?		
	Yes	26 (6.5)
	No	356 (89.2)
Supplement		
	Vitamin C	20 (60.60)
	Vitamin D	6 (18.18)
	Multivitamin	6 (18.18)
	Ginger	1(3.0)
	Propolis	0 (0.0)
Are you thinking of getting vaccinated?		
	Yes	262 (65.7)
	No	119 (29.8)
Where did you get information about the vaccine?		
	TV/social media	307 (76.9)
	The website of the Ministry of Health	0 (0.0)
	Relatives	15 (3.8)
	Contact tracing team/Provincial Health Directorate	22 (5.5)
	Other	35 (8.8)
Why do you not want to be vaccinated?		
	I do not think it is safe.	78 (19.5)
	I think it is harmful.	3 (0.8)
	Other	181 (45.4)
Were you vaccinated against flu and pneumonia?		
	Yes	54 (13.5)
	No	327 (82.1)
Do you get the flu vaccine regularly every year?		
	Yes	16 (4.0)
	No	366 (91.7)
Patients getting the COVID-19 vaccine		
	No	374 (93.7)
	Yes	25 (6.3)

Note: The rates that led to incomplete sums were caused by the fact that some participants did not respond to some questions.

A clear reason was not determined among these options as the reason for 9.8% of the patients to not use the drugs regularly as these patients stated that they did not want to answer this question in general. Among the patients who responded to this question, there were those who stated that the drugs are not beneficial, they have side effects, they are malaria drugs, and they did not use it because of stomach disorders (Table 3).

While 81.2% (n=324) of the patients reported that they used the drugs recommended by the pandemic outpatient clinic or contact tracing team at the recommended dose, 15.3% (n=61) did not use the recommended dose. There were no patients who died among the patients who stated that they did not use the drug/s at the recommended dose. When the study was terminated, a retrospective evaluation was made to detect the deceased. Two patients who died reported that they had used the exact doses of the drugs recommended to them during our evaluation.

According to the results, 1.8% of the patients adjusted the dose of the drugs recommended by the pandemic outpatient clinic or the physician of the contact tracing team by themselves. Dosage adjustment by oneself was considered as taking less or more tablets than the recommended dose. The number of the patients who reported using more tablets than the recommended drug dose was 16 (4%). These patients made their explanations as that they forgot that they had taken the drug and took it again or that they thought that the higher dose would be more effective, and they would recover quickly. All patients in this group were hospitalized and followed up, without any organ failure or death (Table 3).

Table 3. The patients' characteristics of using of drugs

Did you regularly use the drugs recommended by the pandemic outpatient clinic/contact tracing team?					
		Yes	I started using them when my condition got worse	No	p
Which drugs were recommended to you by the pandemic outpatient clinic/contact tracing team? (you can check more than one option)	Plaquenil	19 (100.0)	0 (0.0)	0 (0.0)	0.000
	Favipiravir	116 (90.6)	3 (2.3)	9 (7.0)	
	Plaquenil + Favipiravir	184 (93.9)	1 (0.5)	11 (5.6)	

Note: The rates that led to incomplete sums were caused by the fact that some participants did not respond to some questions.

Of the patients, 6.5% stated that they used food supplements and/or additional drugs other than the drugs that were recommended for them for their COVID-19 infection status. It was determined that vitamin C (60.6%) was the most frequently used supplement (Table 2).

While 65.7% of the patients were thinking of vaccination, 29.8% of them stated that they did not think of vaccination. Most patients reported that they obtained information about the vaccine from TV/social media (76.9%). According to the results, 19.5% of the patients stated that they did not think of having the vaccine because they did not find the vaccine safe. While 13.5% of the patients had had influenza and pneumococcal vaccines, 82.1% had not. At the end of the study, when the 399 patients participating in the study were evaluated retrospectively, it was found out that 2 patients (0.5%) died, and the vaccination rate was 6.3% (Table 4).

Table 4. Analysis of the patients' opinions about the COVID-19 vaccine and other vaccine-related characteristics

Are you thinking of getting vaccinated?				
		Yes (n=262)	No (n=119)	p
Where did you get information about the vaccine?				
	TV/social media	201 (77.3)	106 (89.1)	0.036
	The website of the Ministry of Health	0 (0.0)	0 (0.0)	
	Relatives	12 (4.6)	3 (2.5)	
	Contact tracing team	27 (10.4)	8 (6.7)	
	Other	20 (7.7)	2 (1.7)	
Were you vaccinated against flu and pneumonia?				
	Yes	38 (14.6)	16 (13.4)	0.773
	No	223 (85.4)	103 (86.6)	
Do you get the flu vaccine regularly every year?				
	Yes	14 (5.4)	2 (1.7)	0.094
	No	244 (94.6)	117 (98.3)	

Note: The rates that led to incomplete sums were caused by the fact that some participants did not respond to some questions.

4. Discussion

In our study, interesting results contrary to what is commonly known were presented. These were the results which were contrary to the information that individuals over the age of 65, those with chronic diseases and/or those who are smokers are more easily infected and evaluated in a higher-risk group. According to our data, the lowest number of the patients in our sample was in the group of individuals who were 65 years and older (9.8%) specified in the high-risk group. No history of chronic disease was detected in 65.5% of the patients, and 75.7% of them were not smokers. In other words, contrary to what is known, the rate of COVID-19 diagnosis was found to be high in the individuals in our sample who did not smoke and/or did not have any chronic diseases. We think that the low rate of infection in the patients in our sample aged 65 and over may have occurred due to the frequent emphasis on the warning that they are at risk, as well as the strict social isolation practices imposed upon this age group (12-18). Studies that reflect different views on the relationship between smoking and the disease have been conducted. It has been reported that there is a higher rate of disease progression in smokers compared to non-smokers, and smoking is a risk factor for the progression of COVID-19 (5, 6). On the other hand, there are also studies stating that the effects of smoking on the severity of the disease, duration of hospital stay, non-invasive mechanical ventilation need (NIMV), admission to the intensive care unit (ICU) and mortality are not statistically significant (7). According to the results of our study, although we cannot clearly state that smoking is a risk factor, we also cannot say that smoking has negative effect on COVID-19 progression. In this study conducted in the 11th month of the pandemic process, it was observed that the majority of the patients received their diagnosis in the 3-month period before the study was carried out. In other words, the disease diagnosis rate between the 8th and 11th months of the pandemic (November, December, January) was found to be high in our sample. In this result, we think the increase in the number of daily tests and the flexibility of the implementation of restrictions, measures and prohibitions across the country may have been effective (12, 17, 18).

Although most of the patients stated that they paid attention to the rules of protection and precaution in their workplaces and private lives, they became infected. However, studies conducted so far have clearly revealed that the most effective way to prevent infection with the disease is wearing

masks and complying with rules and recommendations on social distancing and hygiene (2, 9, 10). This result showed that individual compliance with rules and recommendations cannot be evaluated objectively. In other words, the person may think that they comply with the rules and/or recommendations, but they might actually be not applying these practices properly or in the correct manner. For example, the person may have used a mask, but they might have not applied the mask properly to cover their nose and mouth completely. Nevertheless, when studies evaluate this patient, they evaluate their use of masks positively based on the patient's self-report. This evaluation may also be considered in other measures and applications. For this reason, the rules and measures that affect public health should not be left to an individual approach, but they should be managed with strict control, criminal action and sanctions.

In Turkey, the treatment protocol was determined by the Scientific Advisory Board of the Ministry of Health, which was created with the announcement of the pandemic, and the treatment protocols have been made available to all healthcare professionals with the guidelines of this board. Thus, the treatment protocols have been standardized throughout the country. The New Coronavirus National Diagnosis and Treatment Guideline prepared by the Ministry of Health Coronavirus Scientific Advisory Board was published online on 14 January 2020 on the Ministry's website (9). According to this guideline, it was recommended to add only hydroxychloroquine at the beginning of the pandemic and favipiravir at later stages of all cases in the early period (viral replication) both in mildly symptomatic and even asymptomatic cases that can be treated on an outpatient basis and in cases requiring hospitalization. The recommended 5-day treatment was extended to 10 days when deemed necessary by the physician (19-22). Even though their PCR test was negative, these treatments could also be given to people with clinical and thoracic computed tomography (CT) findings compatible with COVID-19-related pneumonia. The pharmacy sales of these drugs were restricted and withdrawn, and they could be prescribed directly by the Ministry and free of charge in hospitals on a case-by-case basis. The drugs to be used by the patient were given from the hospital or brought to the homes of some patients who were found to be positive by contact tracing and response teams. It was also observed that healthcare workers with a high risk of contact sometimes used these drugs in terms of preventive/early/pre-treatment (9). These practices have differed in different countries, especially in European countries. In these countries, even PCR-positive asymptomatic patients were followed up without drugs.

According to the data collected in our study, medication was not indicated in 9.8% of the patients, only hydroxychloroquine was started in 4.8%, only favipiravir was started for 32.8%, and hydroxychloroquine and favipiravir were started together for 49.9%. The Patients without drug indication have consisted of those in pregnancy or lactation periods, those with cardiac disease diagnosis and/or electrocardiography (ECG) findings evaluated before drug prescription, as specified in the guidelines of the Ministry of Health. Pregnant or lactating patients indicated for medication have been hospitalized and treated (9-11). According to our data, the rate of physicians prescribing drugs for the patients in our study was 97.3%. The prescribed drugs were given to the patients from the hospital's pharmacy at that time. The rate of the patients in our sample who were not prescribed drugs was caused by the fact that the physician wrote a prescription, but prescription records could not be made due to computer system errors at the time. In other words, no system registration was made, but the manuscript prescription and the drug were given to the patient.

In Turkey, pandemic outpatient clinics were opened with the announcement of the pandemic, and patients whose RT-PCR tests were positive in the examinations there were collected in the system records and the provincial and countrywide data pool. The contact tracing teams formed by the provincial directorates also undertook the follow-up of individuals who had contact and home treatment in the field. Physicians and assistive health personnel were assigned in the contact tracing teams. PCR-positive contacts were identified by the team and tested by visiting homes. Medical treatment for contacts and patients was provided by the contact tracing teams according to the principles specified in the guidelines (9-11). While 82% of the patients in our study stated that they regularly used the drugs recommended by the pandemic outpatient clinic or contact tracing team physician, 11.5% did not use them regularly. A group among the patients who did not use the recommended drugs regularly did not state a clear reason for not using drugs regularly (9.8%). As it may be seen here, although concern for the efficacy and side effects of drugs seems to be common in society, the rate of drug usage was found to be quite high in our sample. However, the rate of not using drugs is exaggerated on social media. Nevertheless, the other striking result was that there was no death among the 46 (11.5%) patients who did not use the prescribed drugs regularly. Some of these patients also recovered without medication. In these patients, many factors such as being affected by the disease, their immune system, viral load, and maybe, genetic factors might have been effective. On the other hand, this result may have been obtained because the patients stated that the drugs were ineffective and that they did not intend to use them but in fact used the drugs in practice. Still, the interesting thing was that, among the patients who stated that they did not use the drugs at their recommended dosage, there were no patients who died. In the evaluation we made, 2 patients who were found to die afterwards, had reported in our study that they had taken the exact dose of the drugs recommended to them. The low rate of death in the patients who did not use drugs may have been found because of the low number of the patients who did not comply with drug usage. This result brings to mind the

question of whether drugs have individual efficacy, which has not been emphasized much in previous studies. This subject may also be considered as the topic of a separate study. It may be seen that, in the last three-month period before the study started (November, December, January), the infection rate was high, and the mortality rate was quite low (0.5%). This result gives the hope that SARS-CoV-2's virulence and mortal mutations/variants are reduced, and there may be mild mutations (10).

According to our data, the patients mostly (50.6%) obtained information about the drugs used in COVID-19 from the contact tracing team. This was a promising result in terms of informing patients accurately about drugs. We attribute the high rate of drug usage in the patients to their acquisition of drug-related information from the contact tracing teams. In this regard, a large number of patients (21.3%) received information about drugs also via the internet/TV. We think, during the pandemic period, social media and communication tools were not managed well, and control over accurate information/news could not be fully achieved. Non-physicians from many unrelated fields made comments, and people in anxiety and panic accepted what was said to be true without questioning it. Unexpectedly, the patients in our study used the Ministry of Health's website (1.3%) and pharmacies (0.5%) much less frequently for information. However, an up-to-date and comprehensible data network was created for the public on the website of the Ministry of Health (9-11). Another interesting result of our study was related to the usage of supplements. Although the rate of using supplements preferred in traditional medicine practices seems to be very high in the general public, only 6.5% of the patients in our study stated that they took food supplements and/or drugs other than the specified drugs. In studies on COVID-19 and the use of supplements, the usage of various herbal products such as propolis, vitamins C, D and B12, probiotics, Sambucus, sumac and herbal teas was mentioned (13,14,15). In our study, it was observed that the patients who used supplements mostly used vitamin C (60.6%), followed by multivitamin supplements and ginger during this period. This result may have been a consequence specific to our local population. There are no clear data on the level of evidence on supplements, and studies are ongoing (13-15).

In Turkey, the vaccination program was initiated on healthcare professionals as of 14 January 2021. During the period covering the study, only healthcare workers were included in the vaccination program, and the vaccination program of other individuals in the community was not initiated (9). In our study, where we also evaluated the opinions of the patients about the vaccination program, 65.7% of the patients stated that they were thinking of vaccination, while 29.8% said they were not. Most patients reported that they obtained information about the vaccine from TV/social media (76.9%). Moreover, because 19.5% of the patients did not find the vaccine safe, they did not think of having the vaccine. Different opinions on this matter and the vaccination comments of non-physicians might have been effective on this result. Routine influenza and pneumococcal vaccines are recommended for individuals with chronic diseases and/or those over 65 years of age in Turkey (23). While 13.5% of the patients in the sample of this study had had influenza and pneumococcal vaccines, 82.1% had not. However, when these vaccines were started, individuals showed interest in these vaccines like the COVID-10 vaccine, and the vaccines ran short, and it was difficult to obtain the influenza and pneumococcal vaccines from the market for a while. The interesting result was that the rate of having influenza and pneumococcal vaccines in the indicated individuals decreased during the pandemic period. In a study evaluating the media's relationship with patients' views on influenza and pneumococcal vaccines, it was reported that patients with chronic respiratory disease were not affected by the media regarding vaccination, and the rate of those receiving these vaccines was 44% (24). This rate was determined as 13.5% in our study. We think that the incomplete data obtain in research on vaccines might have caused this rate to decrease (25-28). As of February, the 11th month of the pandemic, only 6.3% of the 399 patients who participated in this study were found to have received COVID-19 vaccine. In Turkey, the gradual implementation of the vaccination program according to age, occupation and risk groups and the groups that have not been vaccinated yet are effective in the low vaccination rate.

A limitation of our study was the inadequate evaluation of the clinical course, complications, contamination, and mortality in the patient group who did not use the recommended drugs. In our study, the number of such patients was limited. This issue may be evaluated in more detail with studies with larger samples.

Consequently, our aim in this study was to determine the rate of use and characteristics of drugs prescribed by physicians in diagnosed patients. As a cross-sectional sample of Turkey, it was determined that the rate of the use of the recommended drugs was sufficient with the data of the city where the study was carried out. Moreover, as the process progressed, it was observed that the mortality rate decreased, but the number of infected individuals increased. In cases involving public health, compliance with personal protection and precaution rules should be more strictly controlled, and sanctions should be increased. Social media has a great impact and a great responsibility to provide accurate information. Controls and sanctions for providing accurate information should be increased.

Conflict of interest
None to declare

Acknowledgments
We dedicate our work to healthcare workers around the world who died from COVID-19.

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Investigation of university students' attitudes toward web-based distance education in terms of theoretical and applied courses during the COVID-19 pandemic period

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Abstract

University students had to switch from face-to-face education to web-based distance education (WBDE) owing to new coronavirus disease (COVID-19) pandemic. While theoretical courses can be provided properly with WBDE, it has been thought that applied courses cannot be sustained effectively by the same way. University students' attitudes toward WBDE regarding theoretical and applied courses taught in physiotherapy and rehabilitation department has not been investigated yet, which was therefore aimed in current study. This cross-sectional study included university students (n=180, 20.14±1.57 years) who still maintain actively WBDE at Izmir Democracy University, Physiotherapy and Rehabilitation Department. "Scale for Evaluating Students' Attitudes/Opinions/Thoughts Regarding Applied and Theoretical Courses in Distance Education" was generated by the researchers and performed through online platform. Scale comprised 26 items. Each item is scored as from 5 (completely agree) to 1 (strongly disagree). Proper factor analyses were performed and repeated until the items were found to be significant. Factor loads of final 16-item ranged from 0.27 to 0.84. All fit indices ($\chi 2$/SD=1.42) were within acceptable limits. One-dimensional structure of scale was confirmed with 16 items. Cronbach Alpha internal consistency coefficient was found to be 0.916, and total correlations of the items varied between 0.422 and 0.772. This scale was found to be highly reliable. Internal consistency between items was high. Maximum score obtained from scale is 80. Total score of students (39.91±10.97) showed that attitudes/opinions/ideas regarding theoretical and applied courses through WBDE were negative. These negative attitudes of students were same according to gender ($p>0.05$). Attitudes of university students studying at physiotherapy and rehabilitation department through WBDE regarding theoretical and applied courses were negative regardless of gender. This valid and reliable scale should be used to identify need of university students studying at applied sciences about WBDE. Advanced technology products should be urgently synchronized to WBDE.

Keywords: COVID-19, education, distance, physical therapy, students, attitude

1. Introduction

The COVID-19 infection caused by the new type of Coronavirus (SARS-CoV-2), which broke out in China in December 2019, spread all over the world in a short time due to its high contagious nature (1). According to the May 14, 2021 data of the World Health Organization, 160,813,869 confirmed cases and 3,339,003 deaths were recorded worldwide due to COVID-19 and 5,083,996 of these cases and 44,059 of the deaths were seen in Turkey (2). After the emergence of the first case in Turkey on March 11, 2020, many restrictions and bans such as lockdowns were put into effect in our society simultaneously with the rest of the world (3). The measures taken to reduce the spread of this infectious disease also included the closure of educational institutions (3). According to the United Nations Educational, Scientific and Cultural Organization (UNESCO), face-to-face education, which involved 1.4 billion students worldwide, had to be suspended between February 16, 2020 and May 15, 2020 due to the virus (4). As in many countries, schools, universities, and other educational institutions in Turkey had to be closed temporarily. The Council of Higher Education in Turkey took action rapidly in this process and decided to continue the teaching process through distance education until the next decision (5). Following these developments, face-to-face education was suspended at all levels of education. It was decided to switch to distance education, postpone local and central exams, and introduce web-based tests in measuring and evaluating student achievement (5).

Studies conducted on web-based distance education (WBDE) during the COVID-19 pandemic process have shown different results. Although some of the university students have a negative perception of the COVID-19 pandemic, they have positive opinions about web-based distance education during this challenging pandemic period and are satisfied with the outcomes (6, 7). In fact, male students have found distance education lessons more effective and have been more satisfied with distance education (8). Although students and lecturers have adapted quickly to the pandemic process (9), university students want to continue their education through face-to-face education in terms of focusing on lessons and vocational applied courses as a result of their experiences during the COVID-19 process so far (7). On the other hand, some students want to continue their education with a mixed type of education that blends face-to-

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face and web-based distance education (10, 11). Some studies that included the physiotherapy and rehabilitation department have shown that students do not find web-based distance education, which is compulsory during the pandemic process, as effective as face-to-face education and that they do not prefer it because the efficiency of education has decreased (12, 13).

Universities in Turkey continue the education process through web-based distance education. However, while theoretical courses can be provided effectively through WBDE at universities, the case is not the same for applied courses. In addition, there are no studies in the literature evaluating university students' attitudes toward web-based distance education during the COVID-19 pandemic period in terms of applied and theoretical courses in the undergraduate program of the physiotherapy and rehabilitation department, where applied courses are as important as theoretical ones. For this reason, this study was conducted to investigate the attitudes of the students in the undergraduate program of the physiotherapy and rehabilitation department toward web-based distance education in terms of applied and theoretical courses.

2. Materials and Methods

Our study used a cross-sectional design. It was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Izmir Democracy University Non-Interventional Clinical Research Ethics Committee with decision number 2021/03-5.

According to the inclusion criteria, students who were 18 years or older, volunteered to participate in the study, were attending online distance learning as a registered undergraduate program student at the Department of Physiotherapy and Rehabilitation in the Faculty of Health Sciences at Izmir Democracy University, and could understand and answer the questionnaires were included in the study. Exclusion criteria included freezing the undergraduate registration or dropping out of school and attending other departments. After the students who met the inclusion criteria were informed about the study, their consents were obtained.

The responses to the scale and other questions designed by the researchers were collected through Microsoft Forms. Within the scope of the study, the demographic data of the students (age, gender, height, body weight, body mass index, daily time spent on social media, and the status of having had COVID-19) were recorded.

The “Scale for Evaluating Students' Attitudes/Opinions/Thoughts Regarding Applied and Theoretical Courses in Distance Education”, whose items were prepared by researchers, was developed to evaluate students' perspectives on distance education and their attitudes towards conducting vocational applied courses and theoretical courses through web-based distance education. The first draft of the scale consisted of 26 items in total. Each item was scored on a five-point Likert-type scale using the following options: strongly agree (5), agree (4), undecided (3), disagree (2), strongly disagree (1). The scale did not have a cutoff point.

While creating the items of the scale, the problem was defined in the first stage. In the second stage, an item pool was created by reviewing the literature, and closed-ended questions were written. Then, the draft form of the scale was submitted to expert opinion in terms of suitability, and a pre-application form was created. In the last stage, the scale was given its final form by making the necessary changes according to the expert opinion. To measure the intelligibility and answerability of the items, the scale was first piloted to a small sample (n=10) (14).

2.1. Statistical analysis

Analyses were conducted by an expert statistician using the SPSS version 20.0 software package. Exploratory Factor Analysis (EFA) was conducted to determine the factorial structure and validity of the scale. The appropriateness of the sample size was evaluated using the result of Kaiser-Meyer-Olkin statistics, and the suitability of the data for factor analysis was evaluated with the Bartlett sphericity test. The internal consistency and reliability of the scale were determined by using the reliability coefficient (Cronbach's alpha) that varied between 0 and +1. A reliability coefficient that is close to 1 means that the reliability of the items and the internal consistency between them are high and acceptable. As a result of the factor analysis, the items with factor loading values that were lower than 0.30 were removed, and the factor analysis was repeated until the factor loadings of the items on the scale were found appropriate. Confirmatory Factor Analysis (CFA) was conducted to confirm the factorial structure of the remaining items as a result of the Exploratory Factor Analysis. As the multivariate normality assumption between the items was not met, parameter estimation was conducted by using the asymptotic covariance matrix with the Robust Unweighted Least Squares (ULS) method. As a result of this analysis, the analysis was repeated until the t values were found to be significant by removing the items with non-significant t values. Finally, the model-data fit of the scale was examined with the remaining single-factor items, and necessary care was taken to ensure that the scale was within acceptable limits (15-17).

According to the results of the scale obtained after validity and reliability analyses, descriptive statistics were represented using frequency (n), percentage (%), mean (x), standard deviation (sd), minimum (min.) and maximum (max.) values. The differences in scale scores by gender were analyzed by using Student's t-test. The probability of error in statistical analysis was determined as $p<0.05$.

3. Results

Table 1 presents the characteristics of the students.

3.1. Validity and reliability analyses

The Scale for Evaluating Students' Attitudes/Opinions/Thoughts in terms of Applied and Theoretical Courses in Distance Education, which consisted of 26 items rated using a five-point Likert-type structure, was administered to 180 students. Students scored the items on the scale with options ranging between 1 (strongly disagree) and 5 (strongly agree). However, in the analysis, 1,2,3,11,13,14,15,16,17,19,21,22,23,25, and 26th items had to be reversed as 5 (strongly disagree) and 1 (strongly agree). Accordingly, high scores on the scale showed that students found distance education positive and that low scores showed students evaluated distance education negatively.

Table 1. Demographic characteristics of the students

	University students (n=180) x±sd
Age (year)	20.13±1.57
Male/Female (n; %)	43; 23.9% / 137; 76.1%
Body weight (kg)	61.44±12.29
Height (m)	1.69±0.08
Body mass index (kg/m²)	21.44±3.18
Daily time spent on social media (n; %)	
0-1 hour	14; 7.8%
1-2 hours	31; 17.2%
2-3 hours	57; 31.7%
>3 hours	78; 43.3%
Undergraduate period (n; %)	
2nd semester	77; 42.8%
4th semester	67; 37.2%
6th semester	36; 20%
Status of having had COVID-19 (n; %)	29; 16.1%

n: frequency, %: percentage, kg: kilogram, m: meter, COVID-19: new coronavirus disease

Table 2. The total variance values explained for the factor analysis of the scale

Factors	Eigenvalue	Explained variance %	Cumulative variance %
1	9.106	43.362	43.362
2	2.075	9.879	53.241
3	1.392	6.628	59.869
4	0.992	4.722	64.591
5	0.785	3.738	68.329
6	0.772	3.676	72.005
7	0.663	3.158	75.163
8	0.633	3.015	78.178
9	0.611	2.909	81.087
10	0.502	2.390	83.478
11	0.467	2.223	85.701
12	0.449	2.138	87.839
13	0.396	1.885	89.724
14	0.340	1.620	91.343
15	0.334	1.591	92.935
16	0.302	1.438	94.373
17	0.286	1.362	95.735
18	0.282	1.342	97.077
19	0.252	1.199	98.276
20	0.227	1.083	99.359
21	0.135	0.641	100.000
Kaiser-Meyer-Olkin sample adequacy: 0.918			
Chi-square Bartlett sphericity test= 2145,484 **SD=** 210, p<0.001			

%: percentage, SD: degrees of freedom

Since the factor loadings of the 10th, 14th, 17th, and 20th items in the EFA were found to be lower than 0.30, these items were removed from the scale, and EFA was performed for the second time. In the factor analysis, the factor loading of the 26th item was found to be low this time, and this item was also removed from the scale, and EFA was performed for the third time. All factor loadings were found to be appropriate in the factor analysis conducted on the remaining 21 items. The explained variance table regarding the factor analysis is shown in Table 2. A Kaiser-Meyer-Olkin (0.918) statistic value of greater than 0.50 indicates that the sample size is enough. The result of the Bartlett sphericity test also showed that the data were appropriate for factor analysis (Table 2, p<0.05). When Table 2 was examined, the 21-item scale was found to have three factors with an eigenvalue of greater than 1. However, when the eigenvalues and scree plot were examined, it was observed that the scale was dominated by a single factor (Fig. 1). As a result of EFA, which was limited to a single factor, it was observed that the scale measured 43% of the intended features (Fig. 1). The factor loadings, item-total correlations, and reliability coefficient of the 21 items on the scale are shown in Table 3. Factor loadings of all items were greater than 0.30 and ranged from 0.474 to 0.815. Item-total correlations were also greater than 0.40 and ranged from 0.433 to 0.784. The reliability coefficient of the 21-item scale showed high reliability and high internal consistency between the items, and it was found acceptable (Table 3).

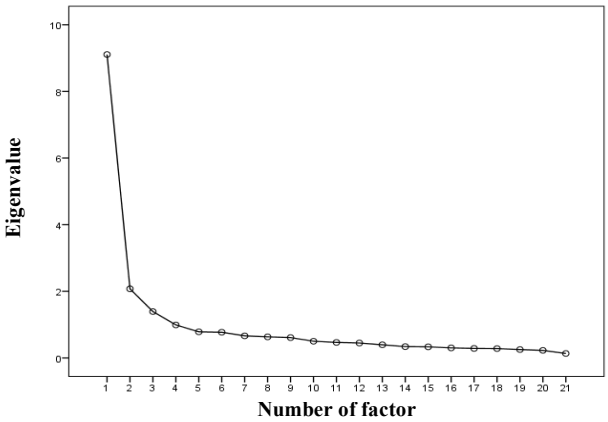

Fig. 1. Factor graph of eigenvalues

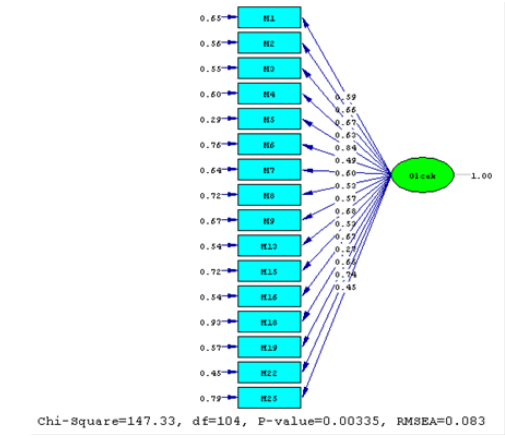

Fig. 2. Path graph for the remaining scale items

Table 3. Factor loadings of scale items and item-total correlations according to the results of exploratory factor analysis

Items	Factor loadings	Item-total correlations
1-I spend more effort understanding the applied lessons in distance education compared to the theoretical lessons.	0.614	0.545
2- It is more difficult to understand the applied lessons in distance education compared to other theoretical lessons.	0.679	0.614
3- I have difficulty in perceiving the extent of physical power to be applied in applied lessons in distance education.	0.720	0.657
4-I can easily understand the theoretical lessons in distance education by following them online.	0.645	0.626
5- I can easily understand the applied lessons in distance education by following them online	**0.815**	0.784
6- The increased number of videos or animations in applied lessons in distance education helps me grasp the subject.	0.482	0.455
7- I have been doing better in my lessons since the transition to distance education.	0.607	0.576
8-The resources and materials used in the theoretical courses in distance education are sufficient.	0.531	0.498
9-I can participate interactively in theoretical courses in distance education.	0.584	0.555
11-I feel I cannot do the same application myself after the applied lessons in distance education.	0.708	0.651
12-The possibility of accessing the theoretical lessons in distance education gets rid of my worries.	0.537	0.512
13-The delivery of the applied courses online in distance education prevents me from gaining experience.	0.707	0.646
15-Theoretical courses in distance education do not make us gain more knowledge than face-to-face education.	0.694	0.652
16-I believe that my success in applied courses will fall in distance education.	0.763	0.706
18- During the applied lessons in distance education, doing the lessons online by screen sharing makes me learn.	**0.474**	0.433
19- I get bored and have difficulty in understanding while listening to the theoretical lessons in distance education.	0.759	0.733
21- I feel that in the web-based distance education process, our opportunities to study in cooperation with instructors and classmates, to learn through discussion, and develop social relations are reduced.	0.672	0.619
22- I have concerns about evaluation and decision-making when a problem-based case study is given in distance education.	0.760	0.704
23-After returning to face-to-face education, I am not planning to participate in any online distance education.	0.515	0.484
24-I do not think that there is a change in my learning and understanding of both theoretical and applied courses in distance education.	0.683	0.636
25-I cannot practice by constantly thinking in applied lessons in distance education, and I cannot predict the results by following the patient or my peers.	0.730	0.674

Reliability coefficient: 0.932

As the multivariate normality assumption between the items was not met in the CFA, parameter estimation was conducted by using the asymptotic covariance matrix with the Robust Unweighted Least Squares (ULS) method. According to the results of the CFA, the t values of the 11th, 21st, and 24th items were not found to be significant, so they were removed from the scale. When CFA was performed for the second time with the remaining 18 items, the t values of items 12 and 23 were not found to be significant, so these items were removed, too, and the CFA analysis was performed for the third time. The t values on the remaining 16-item scale were found to be significant ($p<0.05$). Factor loadings, t values, and R^2 values of the scale items are shown in Table 4. Factor loadings ranged from 0.27 to 0.84. The path graph for the scale items is shown in Fig 2. The fit indices for the model-data fit of the single factor 16-item scale are shown in Table 5. All fit indices were within acceptable limits. Therefore, the one-dimensional structure of the scale was confirmed with 16 items. The reliability coefficient of the 16-item scale was found as 0.916, and item-total correlations were observed to vary between 0.422 and 0.772 (Table 6).

Considering all these results, the scale was found to be highly reliable, and the internal consistency between the items was high. The highest score that can be obtained from the scale is 80, and the lowest score is 16. As the score obtained from the scale increases, it means that attitudes toward distance education are positive, that is, the attitudes/opinions/thoughts of the students are positive in terms of applied and theoretical courses in distance education. As the score obtained from the scale decreases, attitudes toward distance education are considered negative. Items 4, 5, 6, 7, 8, 9, and 18 on the scale are scored as 1 (strongly disagree) and 5 (strongly agree). However, items 1, 2, 3, 13, 15, 16, 19, 22, and 25 are scored reversely as 5 (strongly disagree) and 1 (strongly agree).

Table 4. Confirmatory factor analysis results for scale items

Item number	Factor loadings value	R^2	t
1	0.59	0.35	4.90
2	0.66	0.44	5.38
3	0.67	0.45	5.97
4	0.63	0.40	4.94
5	**0.84**	0.71	9.73
6	0.49	0.24	3.69
7	0.60	0.36	5.47
8	0.53	0.28	4.07
9	0.57	0.33	5.01
13	0.68	0.46	6.13
15	0.53	0.28	4.10
16	0.67	0.46	6.71
18	**0.27**	0.07	2.04
19	0.65	0.43	6.09
22	0.74	0.55	7.06
25	0.45	0.21	3.78

3.2. Results of the scale in terms of the students

The students' total scores (x±sd: 39.91±10.97; min.: 16; max.:74) showed that their attitudes/opinions/thoughts toward theoretical and applied courses through web-based distance education were negative. These negative attitudes of the students were similar by gender (female: 39.33±10.74, male: 41.77±11.6) (p=0.204).

Table 5. Fit indices for model-data fit of a single factor 16-item scale

Goodness of fit index	Acceptable limit *	Value
X^2/SD	<5 Orta düzeyde <3 İyi uyum	147.33/104 =1.42
GFI	>0.90	0.96
CFI	>0.90	1.00
NFI	>0.90	0.92
RFI	>0.85	0.91
RMSEA	<0.08	0.083

SD: degrees of freedom., RMSEA: Mean Square Root Error Estimation

Table 6. Total correlations of the remaining 16 items

	Item-total correlations
1-I spend more effort understanding the applied lessons in distance education compared to the theoretical lessons.	0.534
2- It is more difficult to understand the applied lessons in distance education compared to other theoretical lessons.	0.614
3- I have difficulty in perceiving the extent of physical power to be applied in applied lessons in distance education.	0.652
4-I can easily understand the theoretical lessons in distance education by following them online.	0.598
5- I can easily understand the applied lessons in distance education by following them online	**0.772**
6- The increased number of videos or animations in applied lessons in distance education helps me grasp the subject.	0.458
7- I have been doing better in my lessons since the transition to distance education.	0.566
8-The resources and materials used in the theoretical courses in distance education are sufficient.	0.485
9-I can participate interactively in theoretical courses in distance education.	0.556
13-The delivery of the applied courses online in distance education prevents me from gaining experience.	0.644
15-Theoretical courses in distance education do not make us gain more knowledge than face-to-face education.	0.652
16-I believe that my success in applied courses will fall in distance education.	0.714
18- During the applied lessons in distance education, doing the lessons online by screen sharing makes me learn.	**0.422**
19- I get bored and have difficulty in understanding while listening to the theoretical lessons in distance education.	0.703
22- I have concerns about evaluation and decision-making when a problem-based case study is given in distance education.	0.704
25-I cannot practice by constantly thinking in applied lessons in distance education, and I cannot predict the results by following the patient or my peers.	0.675
Confidence coefficient: 0.916	

4. Discussion

Both theoretical and practical courses have an important place in the education of students in the physiotherapy and rehabilitation department. In our study, it was determined that regardless of gender, the attitudes, opinions, and thoughts of the undergraduate students who were actively attending web-based distance education in the physiotherapy and rehabilitation department due to the COVID-19 pandemic about theoretical and applied courses were negative. Contrary to the results of our study, Orçanlı and Bekmezci reported that undergraduate students' perceptions about the COVID-19 pandemic were negative, but their perceptions about distance education carried out in this process were positive (6). Similarly, Terzi et al. found the general satisfaction level of students with an associate degree from distance education during the pandemic period was high (7). On the other hand, some university students stated that face-to-face education was more efficient in terms of focusing on the lesson and especially in terms of the adequacy of applied courses, and therefore they wanted to continue the lessons through face-to-face education method at the end of the COVID-19 process (7). Genç and Gümrükçüoğlu on the other hand, reported that postgraduate students in the field of theology generally had positive opinions about distance education during the pandemic process (9). According to the opinions of these students, despite the sudden transition to distance education, both students and instructors were able to adapt to the process in a short time (9). All these studies were carried out in the early periods when the uncertainty due to the pandemic process and the fear of death due to infection were higher. Our study, on the other hand, was carried out in the one-year aftermath of the onset of the COVID-19 pandemic. Therefore, the differences between students' opinions in our study and aforementioned studies, which addressed distance education during the pandemic process can be attributed to this increased experience with the pandemic, in which the psychological and physical negative effects of the pandemic became more evident. Both students and instructors have been able to fully adapt to the pandemic conditions during this prolonged process. However, the negative opinions of our students may have stemmed from the inability to do enough practice on individuals with real pathology and the lack of one-to-one control of the practices by instructors. Therefore, advanced technology products including robotic approaches should be adapted to web-based distance education. According to another study, male students found distance education courses more effective than female students, and male students were more satisfied with distance education (8). This result, which is contrary to the result of our study, may be related to the fact that the students in the reported study were undergraduate students in the field of tourism. The students of the physiotherapy and rehabilitation department come from schools focusing mainly on science education and this department is mostly based on applied education. For this reason, students in the physiotherapy and rehabilitation

department had a negative opinion about distance education.

In some studies published in the literature, the proportion of undergraduate students preferring face-to-face and distance education for various reasons was found to be equal. Afşar and Büyükdoğan (10) reported that 50.7% of the undergraduate students in their study preferred distance education during the COVID-19 process, primarily because it allowed them to plan their own time and they did not need to commute to campus. Other students in the study (49.3%) did not prefer distance education due to technical problems, deprivation of the social environment, inability to ask questions about subjects that they did not understand, and lack of constant access to the internet. In universities where distance education is continued, it is recommended that students participate in live lessons more actively and that the lessons should involve more group works (10). Serçemeli and Kurnaz (11) suggested that accounting education should be given to undergraduate students by blending traditional and distance education methods during the COVID-19 pandemic period. In this process, we have been going on experiencing the negative effects of the pandemic deeply in all areas of our lives. We recommend that during the normalization phase in the teaching and learning process, theoretical courses should be given through web-based distance education and applied courses should be conducted with a reduced number of students after ensuring the suitability of the physical conditions of the universities.

Like the results of our study, Keskin and Özer Kaya reported that 84.4% of the students did not find web-based distance education, which was carried out compulsorily during the COVID-19 pandemic, as effective as face-to-face education (12). It was also emphasized in this study that the advantages and disadvantages of web-based distance education needed evaluating according to the feedback of students and that this type of education needed structuring appropriately (12). Similarly, Altuntaş Yılmaz (13) reported that during the COVID-19 pandemic process, undergraduate students from the physiotherapy and rehabilitation department found the efficiency of distance education low in terms of applied courses (87.5%) and theoretical courses (78.5%). While 90.3% of these students preferred face-to-face education, 9.7% preferred distance education (13). The delivery of all the courses given via web-based distance education due to the pandemic in the physiotherapy and rehabilitation department, which is among the applied sciences, has resulted in students' dissatisfaction. Nevertheless, it is not clear when the pandemic will end. Therefore, in the ongoing process, it must be ensured that students get the highest level of efficiency from physiotherapy and rehabilitation courses, which will contribute to shaping the future of society more healthily. For this reason, advanced technology products, such as robotic simulations, patient models, application devices, should be adapted to web-based distance education urgently.

In our study which was conducted to measure the attitudes of undergraduate students, who were studying in physiotherapy and rehabilitation department provided education through theoretical and applied courses and switched from face-to-face education to web-based distance education due to the COVID-19 pandemic, the attitudes of the students toward theoretical and applied courses were found to be negative regardless of gender. The scale that we created to evaluate these attitudes was found to be valid and reliable. For this reason, it can be used to determine the needs of university students studying applied sciences regarding web-based distance education. The quality and efficiency of distance education should be increased considering the opinions of the students.

Conflict of interest

None to declare.

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Research Article

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Is there a relation between serum vitamin D and ovarian reserve markers in infertile women?: A retrospective cohort study

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Abstract

Vitamin D is an essential molecule for reproductive health. There are studies in the literature showing contradictory results regarding te relationship between serum 25(OH) vitamin D levels and ovarian reserve markers. The aim of this retrospective cohort study was to investigate the relationship between ovarian reserve markers; follicle stimulating hormone (FSH), antral follicle count (AFC), and anti-Müllerian hormone (AMH), and serum 25(OH) vitamin D levels. 195 infertil women aged between 18-45 years were included in the study. After the participants were divided into 2 groups according to their 25 (OH) D levels (those with < 20ng/ml (vitamin D deficiency) and those with ≥ 20ng/ml (vitamin D insufficiency)), the age, body mass index (BMI), AFC, AMH, FSH levels of the groups were compared. The mean age of the 25(OH) vitamin D deficient group was significantly younger (p=0.025) than the other group. There was no statistically significant difference in BMI (p=0.47) or season of blood sampling (p=0.62) between groups. The levels of the ovarian reserve markers AFC, AMH, and FSH were not significantly different between groups (p=0.95,0.18,0.86, respectively). Multiple linear regression and logistic regression analysis after adjusting potential confounders showed no significant relationship between vitamin D and AMH (p=0.628) and AFC(p=0.107). In conclusion, we found no correlation between 25(OH) vitamin D concentrations and markers of ovarian reserve. We cannot, however, ignore the critical role of vitamin D in the female reproductivity. To determine the optimal 25(OH)D3 levels during the reproductive period and the amount of vitamin D supplementation required to achieve those levels for the numerous actions of vitamin D throughout reproductivity process, high-quality, large-scale randomized clinical trials are required.

Keywords: Vitamin D, infertility, anti-Müllerian hormone, antral follicle count

1. Introduction

Vitamin D is required not only for calcium and phosphorus homeostasis regulation, but also for a variety of other functions, including female reproduction. Vitamin D receptor (VDR) and 1-hydroxylase are found in reproductive tissues such as the ovary, uterus, placenta, testis, and hypophysis (1, 2). As a result, a link between vitamin D and reproductive health appears to be almost inevitable. The importance of 25 hydroxyvitamin D (25(OH) vitamin D) in female reproduction was initially demonstrated in mice lacking in either 25(OH) vitamin D or VDR, which developed uterine hypoplasia and ovulatory dysfunction, resulting in infertility (3).

Different markers are used to assess ovarian reserve. Serum follicle stimulating hormone (FSH), which is measured during the early follicular phase, has been widely used as an ovarian reserve marker; however, it only indicates the reserve indirectly, with its blood level increasing only when ovarian follicles are severely depleted (4). In addition, ovarian reserve can also be assessed via ultrasound on the second or third day of menstruation using antral follicle count (AFC). It demonstrates the number of ovarian follicles ranging in diameter from 2 to 10 mm in both ovaries (5). On the other hand, the other ovarian reserve marker, anti-Mullerian hormone (AMH) maintains a constant level throughout the cycle (6). Nonetheless, AMH levels can fluctuate seasonally in correlation with 25(OH) vitamin D levels (7).

So far, studies on the effects of 25(OH) vitamin D on ovarian reserve markers have yielded contradictory results. While some studies show a positive relationship between serum 25(OH) vitamin D levels and ovarian reserve markers (7), others do not (8). Given the contradictory literature and the importance of 25(OH) vitamin D in reproductive health, in this study we aimed to investigate the relationship between ovarian reserve markers; FSH, AFC, and AMH, and serum 25(OH) vitamin D levels.

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2. Materials and Methods

This retrospective cohort was conducted between October 2020 and October 2021, in two specialized maternity hospital centers on North-East Coast of Turkey. Patients aged 18–45 years who were admitted due to infertility (no conception after 12 months of no contraceptive methods) were included in the study. Patients who refused to give informed consent, were taking vitamin supplements, had any surgical procedure on the pelvis, were receiving chemotherapy or radiation therapy to the pelvis, were taking menstrual cycle-affecting medications or gonadotoxic therapy, had a history of gynecological malignancy, premature menopause, or had Mullerian anomaly were excluded from the study.

Baseline clinical characteristics including age, BMI, time of blood samples taken were obtained. AFC was determined using transvaginal ultrasonography by a gynecologist during the early follicular phase (the first five days of the cycle). AFC were defined as folicles ranging in diameter from 2 to 10 mm.

Blood samples were collected to measure AMH and FSH levels; the serum AMH level was measured by 'ECLIA' method (electrochemiluminescence immunological test), using the Cobas device (Roche Diagnostics, Risch-Rotkreuz, Switzerland) and the serum FSH level was determined using the immunochemiluminometric (ICMA) method with the ARCHITECT System kit (Abbott Laboratory Diagnostics, USA).

To measure 25(OH) vitamin D levels, the blood samples taken from the patients with EDTA tube were rotated for 5 minutes at 2500 rotation per minute (rpm) and yielded plasma was analysed by Beckman Coulter Unicel Dx1600 (Beckman Coulter, Ca, USA) immune analyser with the same branded kits. Due to the fact that none of the participants had a normal level of 25(OH) vitamin D, the patients were divided into two groups: those with < 20ng/ml (vitamin D deficiency) and those with ≥ 20ng/ml (vitamin D insufficiency) (9).

After the participants were divided into 2 groups according to their 25 (OH) D levels, the age, body mass index (BMI), AFC, AMH, FSH levels of the groups were compared. Our primary outcome was correlation of ovarian reserve markers with vitamin D levels. The study was approved by Health Sciences University Kanuni Educational and Research Hospital Ethics committee (23.12.2020/2020/80). All ethical principles of the latest version of the Declaration of Helsinki on human studies were met throughout the study.

2.1. Statistical analysis

Data were analyzed using SPSS, version 25.0 (SPSS, Chicago, IL). Categorical variables were described as percentages and compared using Pearson's chi-squared test and Fisher's exact test when necessary. For continuous variables, mean and standard deviation (SD) were given as descriptive variables. Correlation between 25(OH) vitamin D and AMH, FSH levels, and AFC was evaluated by Pearson chi-square test. We used a logistic regression model adjusting for the potential confounders (age, BMI, season of blood sampling) to estimate the adjusted odds ratios (ORs) and measure the 95 % CI for the comparison of the two groups in relation to the primary outcomes. $p<0.05$ was considered statistically significant. Sixty-five subjects in each group were required to test the 10% reduction in AFC, AMH and FSH levels at 90 percent power.

3. Results

A total of 195 participants were enrolled in the study. The mean age of patients was 32.1±5.4 years and the mean BMI was 23.8±1.7 kg/m^2. Table 1 summarizes the baseline and biochemical characteristics of patients. Of all participants, 72.3% (n=141) were in vitamin D deficieny group (<20 ng/mL) and 27.7% (n=54) were in vitamin D insufficiency group (≥20 ng/mL). The mean age of the 25(OH) vitamin D deficient group was significantly younger (p=0.025) than the other group. There was no statistically significant difference in BMI (p=0.47) or season of blood sampling (p=0.62) between groups. The levels of the ovarian reserve markers AFC, AMH, and FSH were not significantly different between groups (p=0.95,0.18,0.86, respectively) (Table 2).

Table 1. Baseline characteristics of the study population

Variables	Group 1 (25(OH) vitamin D <20 ng/mL)	Group 2 (25(OH) vitamin D ≥20 ng/mL)	*p*
Number of patients, n (%)	141(72.3)	54 (27.7)	
Age (year), mean (SD)	31.5 ±5.4	33.5± 5.4	0.025[1]
BMI (kg/m^2), mean (SD)	23.9 ±1.6	23.7±1.7	0.47[1]
Season of blood sampling, n (%)			0.62[2]
Autumn	38 (19.5)	18 (9.2)	
Spring	26 (13.3)	7 (3.6)	
Summer	35 (17.9)	11 (5.6)	
Winter	42 (21.5)	18 (9.2)	

[1]Mann-Whitney U test , [2]Pearson ×² test, Plus-minus values are mean±standard deviation SD: standart deviation

Table 2. Relation of ovarian reserve markers and vitamin D level

	Group 1 (25(OH) vitamin D <20 ng/mL)	Group 2 (25(OH) vitamin D ≥20 ng/mL)	*p*
AFC, n (%)			0.95[1]
≥6	96 (49.2)	37 (19)	
<6	45 (23.1)	17 (8.7)	
AMH (ng/mL), mean (SD)	3.5 ±3.3	35 ± 4.4	0.18[2]
FSH, mean (SD)	8.6 ±5.2	9.01 ± 6.2	0.86[2]

Plus-minus values are mean±standard deviation SD: standart deviation. SD: standart deviation.[1]Pearson ×² test, [2]Mann-Whitney U test

Multiple linear regression analysis was conducted in order to evaluate the relationship between serum 25(OH) vitamin D levels and AMH levels, after adjusting for potential confounders (age and BMI) According to the adjusted

analysis no correlation was found between 25(OH) vitamin D and AMH levels (standardized coefficient=0.486, p=0.628) (Table 3).

Logistic regression analysis was conducted in order to evaluate the relationship between serum 25(OH) vitamin D levels and AFC, after adjusting for potential confounders (age, BMI, AMH and season of blood sampling) According to the adjusted analysis no relation was found between 25(OH) vitamin D levels and AFC (p=0.107) (Table 4). We found no correlation between serum 25(OH) vitamin D and AMH (r=-0.78, p=0.280), AFC (r=0.005, p=0.949) and FSH levels (r=0.049, p=0.497) (Fig. 1 and Fig. 2).

Table 3. Linear regression coefficients between all covariates and serum anti-Müllerian hormone

	Unstandardized Coefficients		Standardized Coefficients	t	*p* value	95,0% Confidence Interval for Beta	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	9.965	3.450		2.889	0.004	3.161	16.770
Age (year)	-0.329	0.043	-0.496	-7.666	0.000	-0.414	-0.244
25(OH) vitamin D (ng/mL)	0.017	0.034	0.031	0.486	0.628	-0.051	0.084
BMI (kg/m^2)	0.162	0.135	0.076	1.199	0.232	-0.104	0.428

a. Dependent Variable: AMH, BMI: Body mass index

Table 4. Logistic Regression coefficients between covariates and AFC

Covariates	*p* value	OR	95% CI for OR	
			Lower	Upper
Age (year)	0.008	1.122	1.031	1.223
25(OH) vitamin D(ng/mL)	0.107	0.952	0.897	1.011
AMH (ng/mL)	0.000	0.493	0.358	0.679
Constant	0.137	0.097		

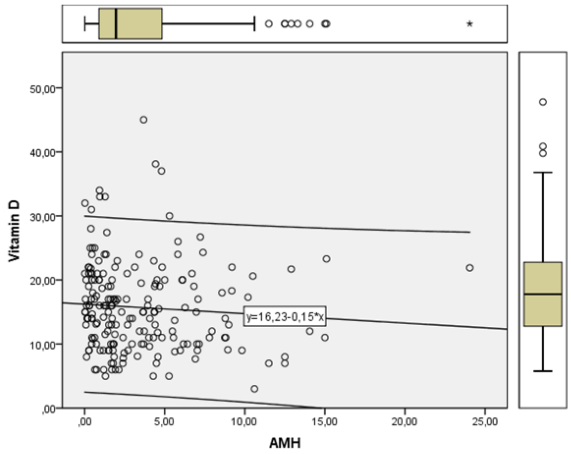

Fig. 1. Correlation plots of 25(OH) vitamin D and anti-Mullerian hormone (AMH)

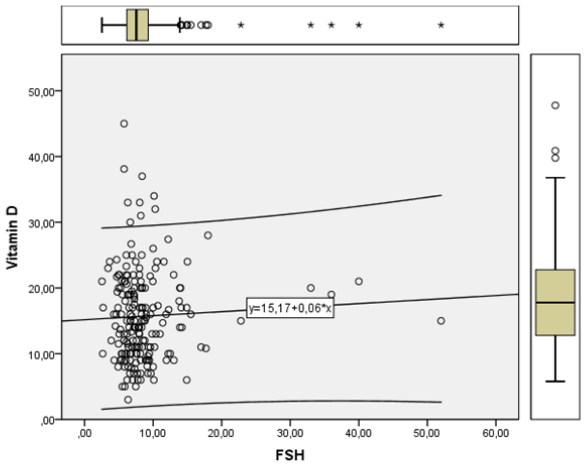

Fig. 2. Correlation plots of 25(OH) vitamin D and follicle stimulating hormone (FSH)

4. Discussion

In this present retrospective cohort study, we tried to investigate the correlation of ovarian reserve markers; AFC, AMH and FSH with vitamin D level, to study whether vitamin D has a role in increasing female reproductivity. Our results demonstrated no significant relationship between ovarian reserve markers, FSH, AFC and AMH, and serum 25(OH) vitamin D levels even after adjusting confounders such as age and season of blood sampling.

Previous studies on this subject yielded inconsistent results so far. Similarly to our findings, Drakopoulos et al. (10) reported that there was no significant association between serum 25(OH) vitamin D levels and AFC and AMH levels after adjusting for possible confounding variables. Furthermore, an Iranian cross-sectional study of 287 infertile women found no correlation between serum 25(OH) vitamin D concentrations and both AFC and AMH levels. Additionally, the majority of participants in this study had vitamin D levels in the deficiency zone (20ng/mL), possibly as a result of their clothing and religious practices (11). In another study, which was also conducted retrospectively and included a larger sample size of 340 women, the authors concluded that AMH levels did not exhibit seasonal variation, as 25(OH) vitamin D concentrations do, and that there is no significant correlation between AMH and vitamin D levels. Interestingly, a prospective study involving 22 women with polycystic ovary syndrome (PCOS) and 45 women without PCOS found that supplementing deficient participants with vitamin D reduced AMH levels in PCOS patients but had no effect on AMH levels in the control group (12).

However, there is some evidence in the literature that vitamin D 25(OH) is associated with ovarian reserve markers. Merhi et al. (13) reported that while AMH and 25(OH) vitamin D levels were positively correlated in women in their late reproductive years, no correlation could be founded in young women. Another study involving 33 women revealed a seasonal correlation between serum AMH levels and 25(OH) vitamin D, indicating that seasonal changes can be avoided by supplementing with vitamin D, particularly during the winter

(7). The study's findings, however, should be interpreted in light of the study's sample size. Naderi et al. (14) examined 30 infertile women with 25(OH) vitamin D concentrations less than 30 ng/mL and AMH concentrations less than 0.07ng/mL. They reported that after three months of weekly vitamin D replacement at a dose of 50.000 IU, participants' 25(OH) vitamin D and AMH levels increased concurrently. Furthermore, the authors concluded that vitamin D deficiency can impair AMH production, resulting in infertility, and that vitamin D supplementation increases fertility through AMH. Additionally, an Iranian study discovered a significant positive correlation between 25(OH) vitamin D levels and AFC in 189 infertile women with an average 25(OH) vitamin D concentration of 15.46 ng/mL (vitamin D deficient) (15). These contradictory findings can be explained by a variety of factors, not just methodological differences. Disparities in several reproductive health outcomes may be explained by genetic, ethnic, and racial differences, as well as religious and dressing habits and season. Another factor that could influence the results is the use of different AMH measurement methods and blood storage times (16). Additionally, because AFC is evaluated using ultrasound, which is influenced by individual experience, it is possible for different results to be obtained from the same patient.

One of our study's limitations is that it was conducted retrospectively, which meant that we could not access all of the participants' data. For instance, we could present AFC in two categories, as ≥6 and <6, without specifying the follicle count. Additionally, we did not evaluate the causes of infertility. Another limitation is that, in addition to BMI, age, and season of blood sampling, several factors can influence vitamin D levels. Beyond these limitations, one of this study's strengths is its relatively large sample size, which is sufficient to create objective results. Another factor is that the study population was drawn from two different tertiary care hospitals in the Black Sea region.

In conclusion, we found no correlation between 25(OH) vitamin D concentrations and markers of ovarian reserve. We cannot, however, ignore the critical role of vitamin D in the female reproductiviy. To determine the optimal 25(OH)D3 levels during the reproductive period and the amount of vitamin D supplementation required to achieve those levels for the numerous actions of vitamin D throughout reproductivity process, high-quality, large-scale randomized clinical trials are required.

Conflict of interest

None to declare.

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None to declare.

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Research Article

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The effects of vitamin deficiencies in the first trimester on pregnancy outcomes

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Abstract

Adequate maternal nutrition is crucial for pregnancy and fetal growth, and thereby influences pregnancy outcome. In this study, we investigate the relationship between certain vitamin levels of first trimester pregnancy and its maternal-fetal outcomes. This retrospective study was conducted between January 2020 and July 2020 by evaluating data drawn from the hospital database. Serum vitamin B12, 25OH-vitamin D, folic acid and ferritin levels were evaluated in 499 women during the first trimester of pregnancy and confounding factors were analyzed. The mean age was 27 years. The mean birth weight of newborn was 3300g. The vaginal delivery rate was 73.1% whereas caesarean delivery rate was 26.9%. Neonatal intensive care unit (NICU) was needed in 8% of newborns. Meconium was seen in 12.6% of newborns. There was a significant statistical difference between caesarean section and vaginal delivery group with respect to 25OH-vitamin D, vitamin B12, and folic acid levels($p<0.001$). All three vitamins were low in first trimester in caesarean delivery group. In contrast, ferritin levels were similar between two groups. 25OH-vitamin D, folic acid and vitamin B12 levels were significantly low in the presence of meconium($p<0.001$) whereas the level of ferritin was significantly high in the presence of meconium($p=.0.001$). 25 OH-vitamin D ($p=0.001$), vitamin B12 ($p<0.001$) and ferritin($p<0.001$) levels were significantly low in mothers of newborns hospitalized in NICU. In contrast, folic acid level was similar between two groups($p=0.066$). Adequate levels of certain vitamins in the first trimester of pregnancy are crucial for a healthy pregnancy and newborn.

Keywords: ferritin, folic acid, 25-OH vitamin D, pregnancy outcome, vitamin B12

1. Introduction

Vitamins are essential for growth and functions of the body. Therefore, it is crucial to supply vitamin deficiencies in pregnancy to decrease unwanted perinatal outcomes. There is a physiological hemodilution in pregnancy leading to decrease in plasma levels of some vitamins whereas others are not affected due to increased carrier proteins (1). Folate has an important role in the prevention on neural tube defects (NTDs). Also, epigenetic patterns and the phenotype of the offspring are affected from the maternal folate status (2). Vitamin B_{12} is also a co-factor of enzymes catalyzing reactions essential for growth and development (3). Ferritin is a kind of intracellular protein showing the iron stores of the body (4). A low level of serum ferritin is used as a parameter of iron deficiency anemia which is very common in pregnancy. Vitamin D including cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) is a precursor of hormones which are important in the regulation of calcium and phosphate metabolism (5). Higher requirement for vitamins during pregnancy makes women prone to vitamin deficiency therefore inadequate supply exhausts the body stores of pregnant women. Optimal vitamin supply is important during early pregnancy as it influences the future health and wellbeing of the fetus. Because of this, vitamin deficiency in pregnancy is a public health problem. In this study, we investigate the relationship between vitamin B_{12}, folic acid, ferritin, and vitamin D25(OH) levels of first trimester pregnancy and its maternal-fetal outcomes.

2. Materials and Methods

This retrospective study was conducted between January 2020 and July 2020 by evaluating data drawn from the hospital database of patients who underwent routine antenatal visit at Samsun Research and Training Hospital. This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of GOKA/2021/10/2. Informed consent was obtained from all individual participants included in the study. The eligibility criteria for study enrollment were: 1) pregnancy ≥ 37wk 2) age 18–45 years;3) without previous history of chronic illnesses (diabetes mellitus, thyroid problems, hypertension, autoimmune diseases); 4) without

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previous caesarean section history; 5) no alcohol or drug abuse; 6) singleton viable pregnancy. Serum vitamin B_{12}, 25OH-vitamin D, folic acid and ferritin levels were evaluated in 499 women during the first trimester of pregnancy and confounding factors were analyzed. Age, gravida, parity, birth weight, delivery by vaginal or caesarian section, neonatal intensive care unit (NICU) demand, apgar scores (0. and 5. min) and presence of meconium were recorded. Electrochemiluminescence immunoassay (ECLIA) was used for measurements of Vitamin B_{12}, folate and ferritin levels. High performance liquid chromatography (HPLC) was used for measurements of 25OH-vitamin D levels. Gestational age was calculated according to the last menstrual period and also confirmed by ultrasonography in all women. Descriptive statistics results will be given as mean ± standard deviation or median (min-max) for numerical variables and number and/or percentage of patients for categorical variables. All continuous data are expressed as mean ± standard deviation. The comparative analysis is made with the Mann-Whitney U test for continuous data and $\chi 2$ test for categorical data. The ratio of categorical variables will be compared between groups using the chi-square test. P <0.05 will be considered statistically significant. Patients with missing information or data on file were excluded from the study. SPSS statistical software for Windows (Statistical Package for Social Sciences, version 16.0, SPSS Inc. Chicago, Illinois, USA) was used to evaluate the study results.

3. Results

We enrolled a total of 499 pregnant women in this study. Demographic characteristics and pregnancy results are described in Table 1. The mean age was 27 years. The mean gravida and parity were 2 and 1 respectively. The mean birth weight of newborn was 3300g. The mean Apgar scores were 9 and 10 at 0 and 5 minutes respectively. The vaginal delivery rate was 73.1% whereas cesarean delivery rate was 26.9%. Neonatal intensive care unit (NICU) was needed in 8% of newborns. Meconium was seen in 12.6% of newborns.

Table 1. Demographic characteristics and pregnancy results

	Patients (n=499)
Age (y)	27 (18-46) [a]
Gravida (n)	2 (1-3) [a]
Parity (n)	1 (0-2) [a]
Birthweight of newborn (g)	3300 (1780-4900) [a]
Apgar scores	
0. min	9 (5-9) [a]
5. min	10 (6-10) [a]
Delivery	
Vaginal (%)	365 (% 73.1) [b]
Caesarean section (%)	134 (% 26.9) [b]
NICU demand	
No (%)	459 (% 92) [b]
Yes (%)	40 (% 8) [b]
Meconium presence	
No (%)	436 (% 87.4) [b]
Yes (%)	63 (% 12.6) [b]

a: median (min-max), b: n (%), y:year, g:gram

The vitamin levels of women were presented in Table 2. Mean 25OH-vitamin D level was 9 ng/ml, vitamin B_{12} was 177pg/ml, ferritin 11ng/ml and folic acid was 5.64 ng/ml respectively.

Table 2. The vitamin levels in first trimester

	Patient (n=499)
25OH-vitamin D (ng/ml)	9 (2-44)
Vitamin B_{12}(pg/ml)	177 (44-890)
Ferritin (ng/ml)	11 (1.53-344)
Folic Acid(ng/ml)	5.64 (1.11-28)

We compared the way of delivery and serum vitamin levels in Table 3. There was a significant statistical difference between caeserian section and vaginal delivery patients with respect to 25OH-vitamin D, vitamin B_{12}, and folic acid levels (p<0.001). All three vitamins were higher in first trimester in cesarean delivery group. In contrast, ferritin levels were similar between two groups.

Table 3. Comparision of delivery way with respect to vitamin levels

	Caeserian section (n=134)	Vaginal delivery (n=365)	p
25OH-vitamin D (ng/dl)	12 (2-41.62)	8.33 (2-44)	**<0.001**
Vitamin B_{12} (pg/ml)	202 (78-890)	168 (44-583)	**<0.001**
Ferritin (ng/ml)	10.25 (2.7-234)	11.34 (1.53-344)	0.715
Folic Acid (ng/ml)	6.73 (1.4-28)	5.12 (1.11-22)	**<0.001**

The relationship between vitamin levels and meconium presence was represented in Table 4. 25OH-vitamin D and vitamin B_{12} levels were significantly low in the presence of meconium (p<0.001) whereas the level of ferritin was significantly high in the presence of meconium (p=.0.001). In addition, folic acid level was also significantly low in the presence of meconium (p=0.031)

Table 4. The relationship between vitamin levels and meconium presence

	Meconium (+) (n=63)	Mekonyum (-) (n=436)	*p*
25OH-vitamin D (ng/dl)	4 (2-44)	9.55 (3-41.62)	**<0.001**
Vitamin B_{12} (pg/ml)	123 (55-567)	189 (44-890)	**<0.001**
Ferritin (ng/ml)	20 (3-344)	10 (1.53-94.6)	**0.001**
Folic Acid (ng/ml)	5 (1.9-15.6)	5.87 (1.11-28)	**0.031**

In Table 5 we presented the relationship between vitamin levels and NICU need. 25 OH-vitamin D (p=0.001), vitamin B_{12} (p<0.001) and ferritin (p<0.001) levels were significantly low in mothers of newborns hospitalized in NICU. In contrast, folic acid level was similar between two groups (p=0.066).

We performed correlation analysis to show if there was a relationship between vitamin levels and pregnancy results in Table 6. There was a positive correlation between 25OH-vitamin D level and birthweight (p<0.001 r=0.615), 0. minute

apgar score (p<0.001 r=0.292) and 5. minute apgar scores (p<0.001 r=0.315). Also, there was a positive correlation between vitamin B_{12} and birthweight (p<0.001 r=0.314), 0. minute apgar score (p<0.001 r=0.243) and 5. minute apgar scores (p<0.001 r=0.232). Moreover, there was a positive correlation between folic acid levels and birthweight (p<0.001 r=0.339), 0. minute apgar score (p=0.033 r=0.095) and 5. minute apgar scores (p=0.025 r=0.100). In contrast to other vitamin levels there was a negative correlation between ferritin and 0. minute apgar score (p=0.004 r=0.128) and 5. minute apgar scores (p=0.005 r=0.125).

Table 5. The relationship between vitamin levels and NICU need

	NICU (+) (n=40)	NICU (-) (n=459)	p
25OH-vitamin D (ng/dl)	4.5 (2-44)	9 (2-41.62)	**0.001**
Vitamin B_{12} (pg/ml)	127.5 (55-567)	180 (44-890)	**<0.001**
Ferritin (ng/ml)	37.35 (3-344)	9.92 (1.53-94.6)	**<0.001**
Folic Acid (ng/ml)	4.47 (1.9-15.6)	5.8 (1.11-28)	0.066

NICU: neonatal intensive care unit

Table 6. The correlation between vitamins and variables

	25OH-vitamin D	Vitamin B_{12}	Ferritin	Folic acid
Age	**p=0.001 r=0.147**	**p=0.006 r=0.123**	p=0.998 r<0.001	p=0.092 r=0.075
Gravida	**p=0.011 r=0.113**	P=0.051 r=0.088	P=0.946 r=-0.003	p=0.128 r=0.068
Parity	**p=0.011 r=0.113**	P=0.051 r=0.088	P=0.946 r=-0.003	p=0.128 r=0.068
Birth weight	**p<0.00 r=0.615**	**p<0.001 r=0.314**	p=0.415 r=0.037	p<0.001 r=0.339
0. min. Apgar score	**p<0.001 r=0.292**	**p<0.001 r=0.243**	**p=0.004 r=-0.128**	**p=0.033 r=0.095**
0. min. Apgar score	**p<0.001 r=0.315**	**p<0.001 r=0.232**	**p=0.005 r=-0.125**	**p=0.025 r=0.100**

r= correlation coefficient, p=statistical significance

Data analysis was performed in the SPSS 25 (Statistical Package for Social Sciences) package program. Results for P <0.05 were considered statistically significant. Descriptive statistics were shown as median (minimum-maximum) for numerical variables and as number of observations and (%) for nominal variables.

The normality of the distribution of numerical variables was investigated by Kolmogorov Smirnov test. Whether there was a statistically significant difference between the two groups in terms of numerical variables was evaluated using the Mann-Whitney U test. The correlation between vitamin levels and variables was evaluated by determining Spearman's "rho" coefficient and significance level (p).

4. Discussion

Folic acid and vitamin B_{12} play an important role in generating S-adenosyl methionine, a major methyl donor for all methylation reactions. Deficiency of these vitamins leads to increased homocysteine levels, which may cause increased oxidative stress and adverse pregnancy outcomes (6, 7). The physiological functions of folic acid include DNA replication, cell proliferation and antioxidant protection. It is important also in angiogenesis, placental development, invasion of trophoblasts, and matrix metalloproteinase secretion (8). Vitamin B_{12} is transported by transcobalamin II, which is produced by the human placenta. Moreover, the human placenta has receptors for binding transcobalamin (9). Similarly, to the study of Finkelstein et al, in our study, the levels of folic acid and vitamin B_{12} were lower in meconium positive group and NICU (+) group showing increased fetal distress (10). In some studies, it was shown that altered maternal folate, vitamin B_{12} and resultant increased homocysteine levels exist in women giving preterm birth (11,12). But in our study only pregnant women≥37 weeks were included and because of this we did not evaluate the effects of low folic acid and vitamin B_{12} levels on preterm delivery. 25OH-vitamin D is essential for calcium and phosphate metabolism. It was shown that the placenta and decidua express the nuclear vitamin D receptor (VDR) and it is also important for fetoplacental development (13). However, the studies about the impact of hypovitaminosis D in the development of pregnancy complications has conflicting results (14,15). In a study it was shown that the Apgar scores were not affected from 25OH-Vitamin D levels (16). In contrast, at our study there was a positive correlation between high 25OH-Vitamin D levels and higher Apgar scores. With regards to caesarean section (CS), an association was found in our study between high 25OH-Vitamin D and increased risk of caesarean section rates which was contrast to Zhou et al results (17). Also, in a study done by Merewood et al. there was an increased risk of caesarean section rates in women with low 25OH-Vitamin D levels (18). Increase in the CS rate in patients with high vitamin D level may be due to cephalo-pelvic disproportion. The most common hematological problem encountered in pregnancy is anemia. Because of increased demand for oxygenation and fetal requirements, iron supplementation is needed (19). In our study, ferritin level was significantly high in the presence of meconium (p=.0.001). It may be due to increased incidence of isolated oligohydramnios which was shown by Korkmaz et al. (19). Iron overload is thought to favor oxidative stress which may trigger fetal stress increasing NICU need as in our study.

Adequate vitamin levels in the first trimester of pregnancy are crucial for a healthy pregnancy and newborn. A healthy balanced diet during pregnancy, is the best source of adequate supply. Inadequate or high levels of certain vitamins can cause unwanted pregnancy outcomes.

Conflict of interest

None to declare.

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None to declare.

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The effects of first trimester cholesterol levels on pregnancy outcomes

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Abstract

The purpose of this study was to determine whether changes in lipid profile in pregnant women might have any effect on the perinatal outcomes. This retrospective study was conducted between January 2020 and December 2020 by evaluating data drawn from the hospital database. The total serum cholesterol(C), HDL-C, LDL-C, VLDL-C and triglycerides levels were measured in 587 women during the first trimester of pregnancy and confounding factors were analyzed. The mean age was 27 years. The mean gravida and parity were 2 and 1 respectively. The mean birth weight of newborn was 3280 g. The mean Apgar score was 9 at 0 and 5 minutes respectively. The vaginal delivery rate was 68.3% whereas caeserian delivery rate was 31.7%. Neonatal intensive care unit (NICU) was needed in 0.5% of newborns. There was no significant statistical difference between the rates of caeserian section and vaginal delivery in patients with respect to lipid profile levels. The total serum cholesterol(C), triglycerides, LDL-C and VLDL-C levels were significantly higher in mothers of babies hospitalized in NICU.HDL-C level was similar between two groups. Adequate lipid levels in the first trimester of pregnancy are crucial for the health of pregnant women and newborn. High levels of lipids can increase NICU need but not effect way of delivery.

Keywords: pregnancy, total cholesterol, HDL-C, LDL-C, VLDL-C, triglycerides

1. Introduction

In a normal pregnancy, lipid parameters including total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and phospholipids gradually increase starting in the 12th week of gestation and continue through the second and third trimesters (1, 2). Increased metabolic demands of the maternal organism and fetal growth can be reflected as changes in lipid profile of pregnant women. The two principal changes in lipid metabolism during pregnancy are hyperlipidemia and the accumulation of maternal fat depots (3). Many studies have shown that maternal dyslipidemia can predict the occurrence of adverse perinatal outcomes and some pregnancy complications. Herrera et al. reported that impaired maternal fatty acid metabolism was correlated with excessive fetal growth (3). Also, the Amsterdam born children and their development cohort study showed that maternal triglyceride concentrations in early pregnancy were linearly related with the prevalence of pregnancy-induced hypertension, induced preterm birth and large for gestational age (LGA) (4). The purpose of this study was to determine whether changes in lipid profile in pregnant women might have any effect on the way of delivery and neonatal intensive care unit (NICU)need.

2. Materials and Methods

The study group consisted of 587 pregnant women between 18-46 years age in the first trimester of pregnancy, followed in Samsun Eğitim Araştırma Hospital from January 2020 to December 2020.The data was drawn from the hospital database of patients who underwent routine antenatal visit in our hospital. This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Samsun Research and Training Hospital (2021/10/1-26.05.2021). Informed consent was obtained from all individual participants included in the study. The total serum cholesterol (C), HDL-C, LDL-C, VLDL-C and triglycerides levels were measured in 587 women during the first trimester of pregnancy and confounding factors were analyzed. Age, gravida, parity, birth weight, delivery by vaginal or caeserian section, neonatal intensive care unit (NICU) demand, and apgar scores were recorded. Gestational age was calculated according to the last menstrual period and also confirmed by ultrasonography in all women. Venous blood samples for lipid assessment were

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taken after overnight fasting from all the participants at the first trimester of pregnancy. The eligibility criteria for study enrollment were: 1) pregnancy ≥ 37wk 2) age 18–46 years; 3) without previous history of chronic illnesses (diabetes mellitus, thyroid problems, hypertension, autoimmune diseases); 4) without previous cesarian section history; 5) no alcohol or drug abuse; 6) singleton viable pregnancy. The total cholesterol (TC), HDL-C, VLDL-C and triglycerides levels were measured with the appropriate reagents. Total cholesterol and triglycerides were assayed with the cholesterol oxidase-phenol aminophenazone method, and glycerol-3-phosphatase oxidase-phenol aminophenazone method, respectively. HDL-C and LDL-C were measured by homogeneous enzymatic colorimetric assays. All the lipid measurements were performed on an automatic biochemical analyser (Abbott Architect C16000, Abbott Laboratories, USA) respectively with TC, TG, HDL-C and LDL-C detection kits (Abbott Diagnostic Kit, Abbott Laboratories, USA).

3. Results

We enrolled a total of 587 pregnant women in this study. Demographic characteristics and pregnancy results were described in Table 1. The mean age was 27 years. The mean gravida and parity were 2 and 1 respectively. The mean birth weight of newborn was 3280 g. The mean Apgar score was 9 at 0 and 5 minutes respectively. The vaginal delivery rate was 68.3% whereas caesarian delivery rate was 31.7%. Neonatal intensive care unit (NICU) was needed in 0.5% of newborns.

The lipid profile of women was presented in Table 2. The mean TC level was 178 mg/dl, triglyceride 134 mg/dl, HDL-C 60 mg/dl, LDL-C 106.7 mg/ml and VLDL-C 70 mg/dl respectively. In Table 3 we compared delivery way and lipid profile levels. There was no significant statistical difference between the rates of caesarian section and vaginal delivery in patients with respect to lipid profile levels ($p<0.05$). In Table 4 we presented the relationship between lipid profile and NICU need. The TC, triglycerides, LDL-C and VLDL-C levels were significantly higher in mothers of babies hospitalized in NICU ($p=0.003$, $p=0.02$, $p=0.0025$, and $p=0.01$ respectively). HDL-C level was similar between two groups ($p=0.279$).

We performed correlation analysis to show if there was a relationship between lipid profile and pregnancy results. There was a positive correlation between total cholesterol levels and age ($p=0.006$ $r=0.113$), gravidity ($p<0.001$ $r=0.216$) and parity ($p<0.001$ $r=0.216$). On the other hand, there was a negative correlation between total cholesterol levels and apgar scores ($p=0.006$ $r=-0.112$). There was also positive correlation between triglyceride levels and gravidity ($p<0.001$ $r=0.168$) parity ($p<0.001$ $r=0.168$). LDL-C levels also positively correlated with gravidity ($p=0.002$ $r=0.130$) and parity ($p=0.002$ $r=0.129$) LDL-C levels negatively correlated with apgar scores ($p=0.023$ $r=-0.094$). VLDL-C levels also positively correlated with gravidity ($p=0.002$ $r=0.126$) and parity ($p=0.002$ $r=0.126$). VLDL-C levels also negatively correlated with apgar scores ($p=0.01$ $r=0.107$). There was no correlation between HDL-C and other parameters.

Table 1. Demographic characteristics of patients

	Patient (n=587)
Age(y)	27 (18-46) [a]
Gravida(n)	2 (1-7) [a]
Parity(n)	1 (0-6) [a]
Birth weight(g)	3280 (1000-5200) [a]
Apgar score	9 (7-9) [a]
Delivery Caeserian Section(n)	186 (31.7%) [b]
Vaginal(n)	401 (68.3%) [b]
Neonatal Intensive Care Unit Need	
No	584 (99.5%) [b]
Yes	3 (0.5%) [b]

a: median (min-max), b: n (%)

Data analysis was performed in the SPSS 25 (Statistical Package for Social Sciences) package program. Results for $P<0.05$ were considered statistically significant. Descriptive statistics were shown as median (minimum-maximum) for numerical variables and as number of observations and (%) for nominal variables. The normality of the distribution of numerical variables was investigated by Kolmogorov Smirnov test. Whether there was a statistically significant difference between the two groups in terms of numerical variables was evaluated using the Mann-Whitney U test. The correlation between vitamin levels and variables was evaluated by determining Spearman's "rho" coefficient and significance level (p).

Table 2. The lipid profile of the patients

	Patient (n:587)
Total cholesterol (mg/dl)	178 (55-389)
Triglicerides (mg/dl)	134 (33-577)
HDL-C (mg/dl)	60 (33.7-119)
LDL-C (mg/dl)	106.7 (30-400)
VLDL-C (mg/dl)	70 (16-244)

Table 3. Comparison of delivery way with respect to lipid profile

	C/S (n=186)	Vaginal (n=401)	p
Total cholesterol (mg/dl)	177.15 (67-331.2)	178 (55-389)	0.438
Triglicerides (mg/dl)	127 (34-439)	136 (33-577)	0.230
HDL-C (mg/dl)	60 (34-96.1)	60 (33.7-119)	0.417
LDL-C (mg/dl)	103.65 (34-400)	110 (30-400)	0.113
VLDL-C (mg/dl)	70 (20-145.77)	70 (16-244)	0.257

C/S:caeserian delivery

Table 4. The relationship between lipid profile and NICU need

	NICU (+) (n=3)	NICU (-) (n=584)	p
Total cholesterol (mg/dl)	345 (344-348)	178 (55-389)	0.003
Triglicerides (mg/dl)	248 (218-378)	134 (33-577)	0.02
HDL-C(mg/dl)	69 (55-88.9)	60 (33.7-119)	0.279
LDL-C (mg/dl)	144 (138-145)	106 (30-400)	0.025
VLDL-C (mg/dl)	118 (117-125)	69.95 (16-244)	0.01

4. Discussion

During pregnancy, intestinal absorption capability of fat increased and is controlled by hormonal changes. As the pregnancy progresses, serum levels of triglycerides, TC, LDL-C were increased to store more fat required for maintaining pregnancy, fetal growth, and lactation. Placental trophoblast and endothelial cells can effectively transfer maternal cholesterol to the fetus throughout pregnancy, thus helping fetal growth and birth weight of infant. Chen et al. shown that elevated maternal HDL-C and LDL-C levels measured during third trimester are risk factor for small for gestational age (SGA), and high TC level during third trimester is inversely associated with SGA (5). In our study the mean birth weight of babies was in normal limits in contrast to Chen et al study. Like our study, many studies in the literature regarding lipid metabolism also are in accordance with the finding that lipid levels increase significantly during pregnancy (6-10). In contrast to Emet et al study the caeserian rate was higher in our study group. It may be due to increased request of patients (11). The mean birth weight of newborn in our study was like Zheng et al study results which was performed in 5089 pregnant women (12). As in our study, triglyceride levels did not predict fetal size in early pregnancy in Mossayebi et al study (13). Compared to the previous studies, we have a homogenous sample without diabetes mellitus, hypertension, and preterm labor. This homogenous population in our study excludes discrepancies due to different diseases such as diabetes and hypertension, and different strategies for treatment of such diseases and makes our sample as homogenous as possible. Retrospective nature of the study and possible selection bias could be accepted as limitations of the study.

Adequate lipid levels in the first trimester of pregnancy are crucial for the health of pregnant women and newborn. High levels of lipids can increase NICU need but not effect way of delivery. A healthy balanced diet is the best source of adequate supply for pregnant women.

Conflict of interest

None to declare.

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None to declare.

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Research Article

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Consequences of the COVID-19 pandemic on fracture distribution: Epidemiological data from a tertiary trauma center in Turkey

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Abstract

Redefinition of our social life for COVID-19, with social distance, prohibition of entering and exiting cities, closure of social areas and curfews effects every aspect of our lives, from psychological to physical. The aim of this study was to evaluate the injury mechanisms, fracture frequencies and priority treatment preferences in a tertiary trauma center from Turkey during the COVID-19 pandemic, both in adult and pediatric populations, and to compare them with pre-COVID-19 period. In this single-centered study, 960 patients (with 1039 fractures) who were admitted to a tertiary trauma center in Turkey, between April 2020 and December 2020 were examined. A control group of 964 patients (with 1070 fractures) who were admitted in the same date range of 2019 was formed. Patient demographics, injury mechanisms, fracture type and preferred treatment methods were recorded. There was a significant difference regarding injury mechanism between groups in both adult and pediatric populations ($p=0.002$ and $p<0.001$, respectively). In adults, according to the residual values, there was significant difference between groups in terms of proximal humerus, elbow, forearm, hand, femoral shaft and knee fractures ($p<0.001$). Among pediatric patients, a significant difference was found between groups in terms of proximal humerus, hand and knee fractures ($p<0.001$). In the pediatric population, there has been a significant increase in the preference of conservative treatment in the pandemic group ($p=0.002$). With increased indoors time, restriction of outdoors physical activities and lesser time in traffic, fracture distribution and priority treatment preferences have inevitably changed. In Turkey, the frequency of almost all upper extremity fractures except proximal humerus and humerus shaft fractures have increased significantly in the adult population, while the frequency of lower extremity fractures associated with high-energy injuries have decreased. In the pediatric population, treatment preferences are shifting towards conservative methods rather than surgery during the COVID-19 pandemic.

Keywords: pandemics, vehicle accidents, fracture epidemiology, trauma

1. Introduction

Although new vaccines developed nowadays are a ray of hope, the threat of COVID-19 is still as valid as on the first day, given the new mutations seen, lack of therapeutic drugs and doubts about the long-term efficacy of vaccines. As a result, public health measures are seen as the only way to prevent the progress of the pandemic since the early days (1, 2). A new concept of normal has been formed that redefines our social life with many features such as compulsory social distance, prohibition of entering and exiting cities, closure of cafes, restaurants, cinemas and other social areas, and curfews.

This "New Normal" has unavoidable effects on every aspect of our lives. While anxiety, increased stress and depression constitute the psychological aspect (3, 4), the changing injury mechanisms and fracture prevalence due to the decrease in the duration of outdoors physical activity and time in traffic and the increase in the time spent indoors constitute the physical aspect (5).

The aim of this study was to evaluate the injury mechanisms, fracture frequencies and priority treatment preferences in a tertiary trauma center from Turkey during the COVID-19 pandemic, both in adult and pediatric populations, and to compare them with pre-COVID-19 period.

2. Materials and Methods

This study was approved by the Ministry of Health and the local ethics committee. After ethical board approval, between April 2020 and December 2020, patients who were admitted to the emergency department of our hospital, which is one of the biggest tertiary trauma centers in Turkey, and consulted to the department of Orthopedics and Traumatology, were examined retrospectively. Inclusion criteria were determined as patients who admitted to the emergency department due to isolated orthopedic trauma, regardless of the injury mechanism and age, between the specified dates. In this context, patients with any internal organ injuries were not included in the study and a total of 1408 patients were examined. The exclusion criteria were determined as isolated soft tissue injuries without any fractures, fractures of axial skeleton (vertebra, scapula/clavicle, and ribs), pathological or old fractures, isolated joint dislocations without any fractures, ischemic wounds or diabetic feet, septic arthritis, abscess formations and prosthetic infections. A total of 448 patients were excluded from the study and 960 patients (with 1039 fractures) were evaluated.

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A control group was formed from the patients who were admitted to the emergency department for any reason and consulted to the department of Orthopedics and Traumatology in the same date range of the previous year (April - December 2019). Considering the same inclusion and exclusion criteria, 458 patients were excluded from the 1422 patients that were examined and a control group of 964 patients (with 1070 fractures) was formed.

To evaluate adult and pediatric patients separately, pandemic (2020 admissions) and control (2019 admissions) groups were divided into subgroups. 18 years of age was accepted as the border and patients aged 18 and over were considered adults, while patients under 18 years old were considered children. Patient demographics (age and gender), injury mechanisms, fracture type and preferred treatment methods (conservative or surgery) were recorded. Injury mechanisms were defined as low-energy falls, high-energy falls (such as falling off balcony, ladder or tree), direct blows (commonly seen as domestic injuries), high-energy direct traumas (usually associated with assaults or working place accidents such as concrete falling on workers), traffic accidents (as passengers, drivers or pedestrians), sports injuries and gunshot wounds.

Fracture types were examined under 13 main headings, consisted with anatomical locations: Proximal humerus fractures, humeral shaft fractures, fractures of the elbow area (distal humerus, proximal ulna or proximal radius), forearm fractures, wrist fractures (distal radius or ulna), hand fractures (carpal, metacarpal or phalangeal), pelvis/acetabulum fractures, hip fractures (femoral neck, pertrochanteric or subtrochanteric), femoral shaft fractures, fractures of the knee area (distal femur or proximal tibia), tibia/fibula shaft fractures, ankle fractures (distal tibia metaphyseal or malleolar) and foot fractures (tarsal, metatarsal or phalangeal).

Statistical analyzes were performed using SPSS 18 software. The compliance of the variables to normal distribution were examined by visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. For variables that are not normally distributed, descriptive analyzes were defined using median and interquartile range whereas frequency tables were used for nominal variables. Whether there was a difference between the groups in terms of "Age" variable was compared using the Mann Whitney U Test. Comparison of categorical data, such as "Gender", "Injury mechanism" and "Fracture frequency", has been analyzed with the Chi-Square Test, and for data that does not meet the Chi-Square conditions, Monte Carlo was applied. Detailed comments were made using residual values. The situations where the P value was below 0.05 were considered statistically significant.

3. Results

The frequency of traffic accidents in the pandemic group for adult and pediatric populations were 11.7% (79 cases) and 4.2% (12 cases) respectively, with a significant difference between control group (p= 0.002 and p< 0.001, respectively). Patient demographics of adult and pediatric populations can be seen in Tables 1 and 2.

Table 1. Demographic data of the adult population

Adult Population (N= 1418)		**Pandemic Group** (N= 674)	**Control Group** (N= 744)	**P**
Age		46.9 (Range: 18-99)	49 (Range: 18-95)	0.139
Gender	Male	348 (51.6%)	394 (53%)	0.321
	Female	326 (48.4%)	350 (47%)	
Injury Mechanism	Low-Energy Fall	355 (52.7%)	380 (51.1%)	**0.002**
	High-Energy Fall	61 (9.1%)	52 (7%)	
	Direct Blow	111 (16.5%)	107 (14.4%)	
	High-Energy Direct Trauma	55 (8.2%)	41 (5.5%)	
	Traffic Accident	79 (11.7%)	143 (19.2%)	
	Sports Injury	4 (0.6%)	8 (1.1%)	
	Gunshot Wound	9 (1.3%)	13 (1.7%)	

N: number of patients. P: statistical significance value. P< 0.05 was accepted as statistically significant

Table 2. Demographic data of the pediatric population

Pediatric Population (N= 506)		**Pandemic Group** (N= 286)	**Control Group** (N= 220)	**P**
Age		8 (Range: 0-17)	9.4 (Range: 0-17)	**0.001**
Gender	Male	200 (69.9%)	156 (70.9%)	0.811
	Female	86 (30.1%)	64 (29.1%)	
Injury Mechanism	Low-Energy Fall	220 (76.9%)	167 (75.9%)	**<0.001**
	High-Energy Fall	8 (2.8%)	13 (5.9%)	
	Direct Blow	40 (14%)	10 (4.6%)	
	High-Energy Direct Trauma	0	8 (3.6%)	
	Traffic Accident	12 (4.2%)	22 (10%)	
	Sports Injury	6 (2.1%)	0	

N: number of patients. P: statistical significance value. P< 0.05 was accepted as statistically significant

In adults, most common fractures seen in the pandemic group were hand (17.8%) and foot (15.8%) fractures. According to the residual values, there was significant difference between pandemic and control groups in terms of proximal humerus, elbow, forearm, hand, femoral shaft and knee fractures (p< 0.001) (Table 3).

Most common fractures seen in the pandemic group in pediatric population were elbow (25.1%) and wrist (19.1%) fractures. According to the residual values, there was significant difference between pandemic and control groups in terms of proximal humerus, hand and knee fractures (p< 0.001) (Table 4).

Table 3. Fracture frequency of adult fractures in pandemic and control groups

Fracture (N= 1571)	Pandemic Group (N= 736)	Control Group (N= 835)	P
Proximal Humerus	34 (4.6%)	66 (7.9%)	< 0.001*
Humerus Shaft	13 (1.8%)	22 (2.6%)	
Elbow	43 (5.8%)	20 (2.4%)	
Forearm	26 (3.5%)	8 (1%)	
Wrist	94 (12.8%)	90 (10.8%)	
Hand	131 (17.8%)	114 (13.7%)	
Pelvis/ Acetabulum	71 (9.6%)	82 (9.8%)	
Hip	93 (12.6%)	99 (11.9%)	
Femur Shaft	13 (1.8%)	34 (4.1%)	
Knee	32 (4.3%)	70 (8.4%)	
Tibia/Fibula	16 (2.1%)	15 (1.8%)	
Ankle	54 (7.3%)	73 (8.7%)	
Foot	116 (15.8%)	142 (17%)	

N: number of fractures.

In adults, surgical treatment was preferred in 316 fractures (42.9%) in the pandemic group and 325 fractures (38.9%) in the control group, with no significant difference between groups (p= 0.186). On the other hand, in pediatric population, there was a significant difference between groups regarding preferred treatment methods (p= 0.002) (Table 5).

Table 4. Fracture frequency of pediatric fractures in pandemic and control groups

Fracture (N= 538)	Pandemic Group (N= 303)	Control Group (N= 235)	P
Proximal Humerus	2 (0.7%)	8 (3.4%)	< 0.001*
Humerus Shaft	7 (2.3%)	4 (1.7%)	
Elbow	76 (25.1%)	62 (26.4%)	
Forearm	31 (10.2%)	18 (7.7%)	
Wrist	58 (19.1%)	33 (14%)	
Hand	44 (14.5%)	13 (5.5%)	
Pelvis/ Acetabulum	12 (4%)	10 (4.3%)	
Hip	0	1 (0.4%)	
Femur Shaft	11 (3.6%)	17 (7.2%)	
Knee	5 (1.7%)	18 (7.7%)	
Tibia/Fibula	16 (5.3%)	10 (4.3%)	
Ankle	11 (3.6%)	12 (5.1%)	
Foot	30 (9.9%)	29 (12.3%)	

Table 5. Preferred treatment methods of adult and pediatric populations

Preferred Treatment Method	Adult Fractures (N= 1571)		Pediatric Fractures (N= 538)	
	Pandemic Group (N= 736)	Control Group (N= 835)	Pandemic Group (N= 303)	Control Group (N= 235)
Conservative Treatment	420 (57.1%)	510 (61.1%)	234 (77.2%)	153 (65.1%)
Surgical Treatment	316 (42.9%)	325 (38.9%)	69 (22.8%)	82 (34.9%)
P		0.186		**0.002**

4. Discussion

Although there are many studies in the literature analyzing the effects of the COVID-19 pandemic on social life, studies focusing the effect of changes in our social habits on fracture frequency and priority treatment preferences are usually limited to the countries in which they have been conducted (5-11)**.** To our knowledge, this is the first study in the literature that examines this subject to such a wide extent in Turkey. This is the main strength of our study. One of the most important findings in our study was that there was a significant difference between pandemic and control groups in terms of proximal humerus, elbow, forearm, hand, femoral shaft and knee fracture frequencies in adult population. Additionally, in the pediatric population, there was significant difference between pandemic and control groups in terms of proximal humerus, hand and knee fracture frequencies. Furthermore, there was a significant difference between groups regarding treatment methods in the pediatric population.

The "pandemic of our age", which deeply affects the whole world, changes, and shapes everything from our work patterns to our kinship relationships, from our social habits to our health routines. For this reason, it is inevitable that the injury mechanisms will change during this period. It is essential to master this change and to be shaped accordingly, in order to provide maximum benefit to our patients. One of the most important lifestyle-changes we encountered in this period was the increased indoors time. It is a logical assumption that, with increased indoors time, common reasons for fractures such as traffic accidents will decline while minor fractures due to domestic accidents will increase. Our study supports this hypothesis. Even though the frequency of low-energy falls is similar in both groups, the frequency of traffic accidents declined while the frequency of direct blows has increased in the pandemic group, both in adult and pediatric populations (p= 0.002 and p< 0.001, respectively). Another notable increase was observed in the frequencies of high-energy direct trauma and high-energy falls in adult population. Curfews, prohibitions on city entrance and exits, flexible working patterns, increased indoors time and increased stress are the main reasons for the change in injury mechanisms. In particular, with the curfews and the prohibitions of city entrance and exits, traffic rates decrease significantly, which reduces the frequency of traffic accidents. With flexible working patterns and lesser workforce engaging in manual labor, it is inevitable to have an increase in occupational accidents, despite all workplace safety measures taken. The decrease in children's playing time in parks and playgrounds and a considerable increase in indoors activity time results in a decrease in high-energy injury mechanisms seen in the pediatric population and an increase in household accidents (12). Finally, increased stress and anxiety during the COVID-19 pandemic, with combination of fear of infection,

can damage the mechanisms of people to cope with stress, resulting in an increase in boxer's fracture cases, especially in adolescents (13).

In the pandemic group, average age of patients in pediatric population was 8 years (Range: 0-17 years) whereas in the control group average age was 9.4 years (Range: 0-17 years) (p= 0.001). Our findings are consistent with the literature. Turgut et al., in their study of 670 fractures, has stated that pediatric patients with a fracture was younger, compared to pre-pandemic period (5). The reason for this may be the restriction of the time spent outside and the decrease in sports activities, which are one of the main causes of adolescent fractures (5, 12).

Considering that phalanx fractures of hand and foot are among the most common fractures (14, 15), it was an expected result that the most common fractures of adults in our study were hand (17.8% vs. 13.7%) and foot (15.8% vs. 17%) fractures both in pandemic and control groups. According to the residual values, there was a significant increase in the frequency of hand fractures (carpal, metacarpal and phalangeal fractures) in both adult and pediatric patients (p< 0.001 and p< 0.001, respectively). Furthermore, a significant increase in elbow and forearm fractures were observed in adults during the COVID-19 pandemic. However, proximal humerus fracture frequency was decreased significantly, both in adult and pediatric populations. There are reports with similar results in the literature (5,9,16,17). As mentioned before, with increased stress during the COVID-19 pandemic, an increase of boxer's fracture cases, especially in adolescents, is expected (13). In addition, the increased indoors time leads to an increase in domestic accidents, which explains the increased frequency of phalanx fractures. The increase of elbow and forearm fractures of adults can be explained with the increase of occupational accidents, especially in heavy-duty workers and manual laborers, which is an inevitable result of flexible work-pattern. Absence of sports and school injuries of pediatric population may explain the decrease of proximal humerus fracture frequency (16). On the other hand, it is an unexpected result that proximal humerus fractures in adult population decreases, considering the increase in other upper extremity fractures and the fact that proximal humerus fractures of elderly usually occurs with domestic injuries, independently from the pandemic (17).

According to the residual values, knee fractures (distal femur and tibial plateau fractures) were significantly lower in both adult and pediatric populations in the pandemic group (p<0.001 and p<0.001, respectively). Additionally, a significant decrease was found in femoral shaft fractures in the adult population. Femoral shaft, distal femur and tibial plateau fractures are often associated with high-energy injuries in younger adults, such as traffic accidents. The reduced time spent in traffic during the COVID-19 pandemic may be the main reason for the decrease in the frequency of these fractures. On the other hand, in the pediatric population, femoral shaft fractures can be seen with domestic injuries, like falling from bunk beds. Therefore, it was not surprising that although femoral shaft fracture frequency was decreased in pediatric population, there was no significant difference, according to the residual values.

In adults, 316 fractures (42.9%) in the pandemic group and 325 fractures (38.9%) in the control group were treated surgically (p= 0.186). Most operated fractures were hip fractures in both groups (88 fractures, 12% and 76 fractures, 9.1% respectively), similarly with the literature (6,7), followed by ankle fractures (41 fractures, 5.6% and 66 fractures, 7.9%, respectively). Because hip fractures usually occur in the elderly population with osteoporotic background and with low-energy injuries such as domestic accidents, it was an inevitable fact that the frequency of hip fractures remained stable during the COVID-19 pandemic, as stated in the literature (5, 8, 18). Ankle fractures usually occur because of low-energy injuries such as basic falls or ankle sprains, and surgery is necessary if the fracture is instable (19). Therefore, it was an expected result that the frequency and necessity of surgery of ankle fractures did not change during the COVID-19 pandemic, just like hip fractures. Among pediatric patients, while 234 patients (77.2%) were treated conservatively and 69 patients (22.8%) surgically in the pandemic group, 153 patients (65.1%) were treated conservatively, and 82 patients (34.9%) were treated surgically in the control group (p= 0.002). Most operated fractures were elbow fractures in both groups (41 fractures, 13.5% and 31 fractures, 13.2%, respectively), with majority of cases being supracondylar fractures of humerus. Turgut et al. has stated that the rate of surgically treated fractures has increased during the early times of the COVID-19 pandemic (5). On the other hand, Iyengar et al. has suggested that conservative methods provide an alternative in non-obligatory fractures during the pandemic (20). Our study has shown that, while no significant difference was found among adults, treatment priority has shifted to conservative methods in children. Bram et al. have found a similar adaptation in their study of 1745 pediatric fractures (12). Parents' fear of increased virus exposure with hospitalization may be the main reason for this adaptation. Furthermore, the assignment of all available medical personnel to COVID-19-related wards and intensive care units, the conversion of most operating rooms into intensive care units, the provision of all available patient beds to COVID-19 patients and the reluctance of the surgeon to operate in an atmosphere of increased risk of viral exposure, in order to protect himself and his surgical team, also play an important role in this adaptation. Although all these factors are valid for adult fractures, the conservative treatment indications for adult fractures are

much more limited and the pediatric population responds much better to conservative treatment, which explains the limitation of this adaptation only to the pediatric population. Therefore, conservative methods have been the primary choice for all possible fractures in pediatric population during the COVID-19 pandemic.

There are some limitations in our study. First of all, there are many probable confound factors associated with fracture frequencies and injury mechanisms, such as weather conditions, which we were not able to take into account. Secondly, open phalanx fractures such as subtotal amputations were not included in the study. The reason for this is, in accordance with the internal regulations of our hospital, such fractures are consulted to the plastic surgery department and the treatment is planned by them. Thirdly, our fracture frequency analyses are based on anatomical classifications. However, more accurate results can be obtained with advanced statistics that evaluate specialized or common fractures such as pediatric supracondylar humerus fractures or physeal fractures as separate groups. Finally, although our findings as a single-centered study suggest a country-wide fracture epidemiology, the fact that our study was based on a single hospital is an important limitation.

The distribution and frequencies of fractures have inevitably changed during the COVID-19 pandemic, with increased indoors time, restriction of outdoors physical activities such as contact sports, lesser time in traffic and increased stress. In Turkey, the frequency of almost all upper extremity fractures except proximal humerus and humerus shaft fractures have increased significantly in the adult population, while the frequency of lower extremity fractures associated with high-energy injuries have decreased. In the pediatric population, treatment preferences are shifting towards conservative methods rather than surgery during the pandemic of our age.

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article

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Depth-labeled lumbar disc forceps for safe lumbar disc surgery: Our experience with 405 patients

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Abstract

Injury of intraabdominal structures by rupturing the anterior longitudinal ligament is a known complication of discectomy. Despite its very low incidence, it has a high mortality. Although various minimally invasive methods are defined for discectomy, no significant reduction in this complication has been achieved. Positioning of the patient, aggressive discectomy, and deep-seated use of disc forceps are important risk factors. The aim of this study is to share our experience with modified instruments to minimize the risk of vascular and visceral injury during discectomy in surgically treated 405 patients with lumbar disc herniation. We routinely perform preoperative depth measurements at the level of lumbar disc herniations for the patients undergoing lumbar disc surgery and check the neighborhood with the prevertebral structures. During the operation, we perform discectomy with custom disc forceps that were labeled with centimeter measurements in accordance with these lengths. We performed discectomy on 405 patients using these forceps between January 2015 and May 2021. In this retrospective study, disc depth measurements differed according to disc levels and gender. Disc depth was longer in males at all lumbar disc levels. It is very important to avoid vascular and visceral injuries for spinal surgeons. For this reason, we believe that knowing the safe preoperative discectomy depth and area and using centimeter-labeled disc forceps is the best method to prevent such complications.

Keywords: vascular injury, bowel injury, ureter injury, safe discectomy, depth labeled disk forceps

1. Introduction

Posterior lumbar discectomy is the most common, best described and most experienced operation in spinal surgery (1, 2). Mortality and morbidity are low in lumbar discectomy, in which the most common complications are wound infection and CSF fistula (3). Although it is such a well-known surgical procedure, in the absence of intraoperative attention and care, retroperitoneal and intraabdominal organ injuries may occur, and it may become a nightmare for the surgeon. These are vascular injuries and hollow organ perforations such as bowel and ureter (4). Vascular complication rate during lumbar discectomy is 0.01% -0.06%. However, its mortality ranges between 40% -100% (5-9). The clinical presentation of vascular injuries may vary. For example, symptoms related to large artery injuries develop acutely due to excessive intraoperative blood loss, whereas arteriovenous fistulas and pseudoaneurysms may manifest themselves months and years later (10-13). Ureter and bowel injuries are less common and usually are not noticed intraoperatively. Postoperative abdomen and flank pain, hematuria and fever are observed in ureter injuries. Fever, abdominal pain, sepsis signs, air-fluid levels in the abdomen x-ray, wound infections, discitis and peritonitis symptoms suggest intestinal perforation (1, 2, 4, 14-17).

Defects in the anterior longitudinal ligament, adherence of organs to the anterior longitudinal ligament, surgery for recurrences, aggressive and deep discectomy, obesity, previous intraabdominal surgery, and prone surgical position which causes an increase in intraabdominal pressure are the factors that are blamed for these complications with high mortality during lumbar discectomy (4, 18, 19). Anterior longitudinal ligament defect may have occurred preoperatively or by instruments used during discectomy. To prevent intraoperative visceral organ injury from this defect and to perform a safer discectomy, the disc forceps were marked with centimeter measurements by the author. The aim of this retrospective study is to present the labeled disc forceps and to share our experience with the patients we operated with these forceps.

2. Materials and Methods

405 patients who underwent lumbar discectomy with depth-labeled disc forceps in our clinic between January 2015 and May 2021 were included in the study. The patients' gender, age, discectomy levels, posterior-anterior (1st length) and posterior-oblique (2nd length) disc depths were evaluated retrospectively from digital patient files and PACS system. (Fig. 1, Fig. 2). This study was approved by Amasya University Non-Interventional Clinical Research Ethics Committee (date/decision no: 03.06.2021/81).

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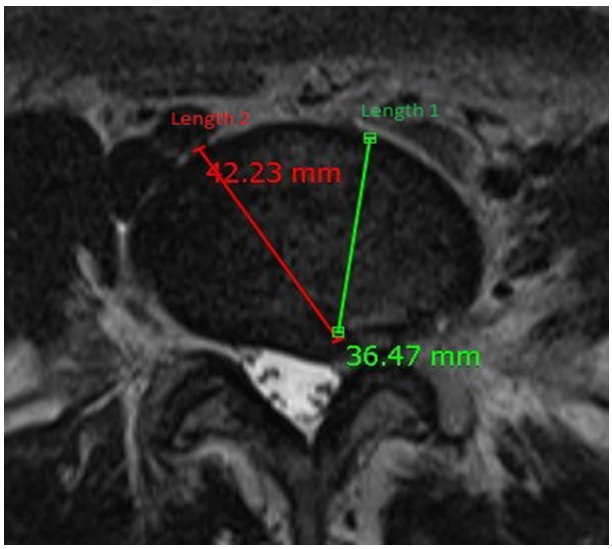

Fig. 1. Depth measurements on the left at L4-5 disc level

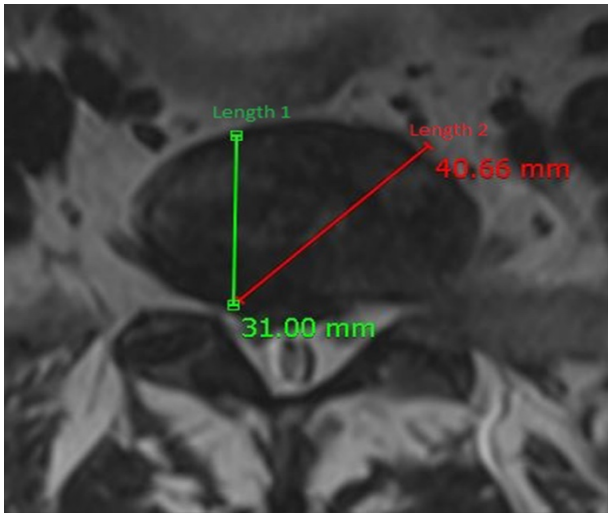

Fig. 2. Depth measurements on the right at L5-S1 disc level

2.1. Our preoperative evaluations

MRI examination was performed on all patients with lumbar disc herniation for which we decided to operate. T2 axial sections passing through the level with disc herniation were examined. Depth from the posterior longitudinal ligament where it will be opened for discectomy to anterior disc margins were measured vertically and obliquely. The relationships between anterior disc boundaries and visceral structures were evaluated (Fig. 1, Fig. 2).

2.2. How we do discectomy

When the patient is placed in the prone position on the operating table, silicone pads are placed slightly laterally to avoid an increase in intra-abdominal pressure. The lumbar disc forceps are marked with numbers and lines up to 5cm with laser engraving. Each line on the instruments corresponds to a centimeter, and the numbers correspond to half centimeters. In other words, the place where we see the number 4 points to 3.5 cm, and the line above the number 4 points to 4 cm. (Fig. 3). In addition, this marking encircles the instrument in 360 degrees; It can be easily seen from the right, left, bottom and top. In our operations, we used these disc forceps. We performed discectomy in accordance with the measurements we made in preopoperative axial MRI sections. (Fig. 4). We usually used disc forceps in 3-4mm less depth than these measurements. (Fig. 5). We did not expand our discectomy window in the posterior longutinal ligament towards the midline as much as possible. In this way, we created a safe discectomy area in the depth of the disc level and in the oblique direction towards the contralateral side.

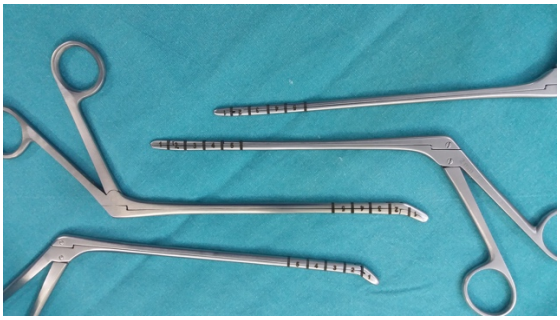

Fig. 3. Depth-labeled disc forceps (measurements in centimeter)

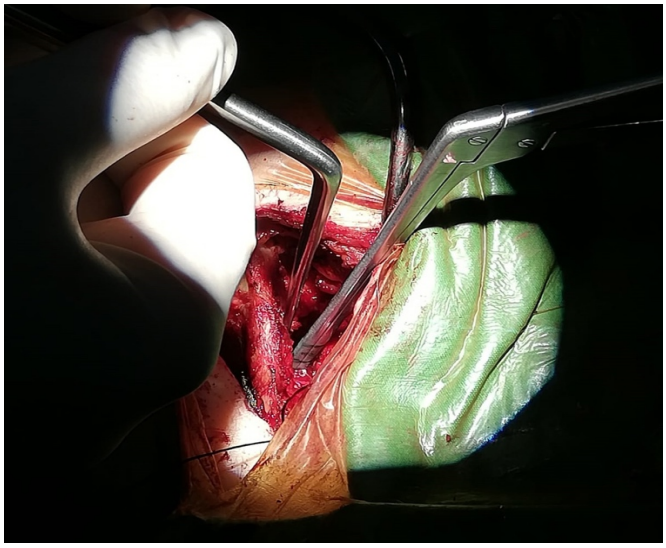

Fig. 4. Discectomy at 3.5 cm depth

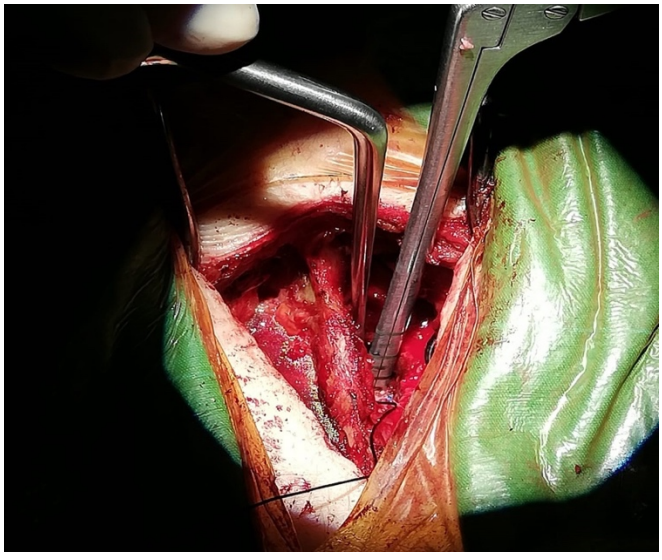

Fig. 5. Discectomy at 2.5 cm depth

3. Results

215 (53%) of the patients were female and 190 (47%) were male. The mean age was 50.6 (23-82) years, 49.67 years for women and 51.7 years for men. 4 patients were operated at

L2-3, 68 patients at L3-4, 163 patients at L4-5 and 170 patients at L5-S1 level. The patients were followed up for an average of 33.3 (65-0.3) months postoperatively. (Table 1). The detailed results of the 1st and 2nd lengths of the disc levels in male and female patients who underwent discectomy, are presented in Table 2. Disc depths were longer in males at all levels. Although the average lengths of each disc level were measured, there were significant differences between the longest and shortest measurements. For example, the 1st and 2nd longest measurements for women were 46.75 mm and 52.48 mm at L5-S1 level, respectively, and 51.37 mm and 56.51 mm at L4-5 level for men. The shortest measurements were 23.91 mm and 30.13 mm at the L5-S1 level for women, and 28.95 mm and 33.45 mm at the L5-S1 level for men. In the postoperative follow-up of the patients, no clinical complaints of vascular, ureter and intestinal injuries were detected.

Table 1. General characteristics of the patients

Discectomy level	Female (215/ 53%)	Male (190/47%)	Total (405)
L2-3	3	1	4
L3-4	38	30	68
L4-5	84	79	163
L5-S1	90	80	170
	215	190	405
	Average age (years)		Postoperative follow-up (month)
Female	Male	Overall	
49.6 (23-82)	51.7 (25-76)	50.6 (23-82)	33.3 (65-0.3)

Table 2. Measurements at herniated disc levels by gender

	Female		Male	
Herniated disc level	Length 1 (mm)	Length 2 (mm)	Length 1 (mm)	Length 2 (mm)
L2-3	31.73 (36.85-27.13)	39.52 (45.02-36.1)	36.04	40.19
L3-4	33.93 (42.70-26.50	39.34 (49.88-32.39)	38.33 (45.96-33.71)	42.88 (49.32-37.23)
L4-5	34.23 (43.13-26.86)	39.46 (49.1-30.15)	37.80 (51.37-31.11)	43.59 (56.51-33.48)
L5-S1	34.10 (46.75-23.91)	39.96 (52.48-30.13)	35.60 (44.47-28.95)	41.65 (55.11-33.45)

4. Discussion

Regardless of the technique performed, posterior lumbar discectomy is generally considered a reliable surgical procedure. Although prevertebral injuries during discectomy are very rare, they are well-defined complications (11). Suspicion, early diagnosis and timely interventions for these intraoperative and/or postoperative complications are lifesaving. Otherwise, mortality is high (18, 20, 21).

Prevertebral vascular injury as a complication of posterior lumbar discectomy was first reported in 1954 by Linton and White (22). Later, bowel and ureter injuries were presented in the literature, but they were less common (1, 2, 4, 17, 23, 24, 25, 26, 27, 28). It is interesting that although microscopic discectomy techniques are widely used today, there is no evidence that such complications have been reduced (29). Visceral organ and vascular injuries are mostly available as case reports in the literature.

Vascular injuries are most common at L4-5 and L5-S1 levels. The most commonly injures structure is the contralateral common iliac artery. This is followed by injuries in the external iliac artery, inferior vena cava and aorta, respectively (5, 18, 30, 31). Intestinal injuries are most associated with L5-S1 discectomies (4, 15, 23). The prone knee-chest position, which increases the anatomical convergence between the intestines and the vertebral column due to increased intraabdominal pressure, and previous abdominal surgery increases the risk of complications (4, 20, 21). Ureter injuries are most common in the contralaterally located ureter at the L4-5 level (25, 32). We act in accordance with the recommendations in the literature by minimizing the increase in intra-abdominal pressure positionally in our operations.

In prevertebral injuries during discectomy, crossing the anterior longitudinal ligament at the anterior or contralateral side following deep placement of the disc forceps is the most blamed cause (21, 33). In routine practice, the depth of intraoperative disc forceps is adjusted based on the surgeon's experience. However, for a surgeon who has performed more than 15,000 discectomies, 3 cases of vascular injury complication cannot be ignored (34). Surgical microscope and magnification loops, which are widely used today, may cause overestimation of the intervertebral disc depth (35). When the desire for aggressive discectomy is added, crossing the anterior longitudinal ligament and prevertebral injuries are inevitable (36). Thus, Nilsonne and Hakelius (37) radiologically demonstrated that the disc forceps were inserted too deep during discectomy to minimize the risk of recurrent disc herniation, resulting in vascular and visceral organ injury. Anda et al. (38) found that the sagittal diameter of the L3-4, L4-5 and L5-S1 intervertebral discs was between 33mm and 56mm and suggested that advancing the disc forceps less than 30mm (3cm) would prevent vascular and visceral organ injury. Schwartz and Brodkey (39), reported that the safe discectomy depth was 2.85 cm. Antar et al. (40) found different depths at each disc level for each person and proved that the disc depth was greater in men than in women. In our study, we found that disc depths were very different both between disc levels and between genders. Therefore, we did not insist on a fixed depth. In addition, disc depths were longer in males than females, consistent with the literature.

In very few anatomical and clinical studies in the

literature, authors recommended marking the disc forceps to prevent vascular and visceral organ injuries in the prevertebral region and adjusting the depth using patient-based measurements during discectomy (24, 38, 40, 41). However, this is only a suggestion, and there is no report about the routine use of depth-labeled disc forceps. In addition, there are no length-measuring disc forceps in the catalogs of companies that produce surgical instruments in our country. In this sense, the disc forceps in the laminectomy sets in our clinic were marked with cm measurements by the author, and their routine use in discectomy operations was ensured by preoperative disc depth measurements of all patients. No evidence of vascular, ureter and intestinal injury was found in 405 patients who underwent discectomy in this way and followed up for an average of 33.3 months postoperatively.

Vascular, bowel and ureter injuries during discectomy are complications that cause nightmare for spinal surgeons. To avoid this disastrous complication, we recommend routinely measuring the intervertebral disc depth preoperatively, marking the existing disc forceps with depth measurements, having the new ones to be manufactured in the same way, thus performing discectomy within the safe area.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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The effect of laparoscopy in chronic pelvic pain on quality of life

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Abstract

Chronic pelvic pain (CPP) is a problem facing gynecologists. Laparoscopy is a minimally invasive surgical technique used for both diagnosis and treatment of CPP. This study aimed to investigate the determination of women with pelvic pain who will benefit from diagnostic laparoscopic surgery and its effect to on quality of life. A prospective designed study conducted between October 2013 - August 2015 including 90 patients at University of Health Sciences, Zekai Tahir Burak Women Health Care, Training and Research Hospital, Turkey. While 45 patients in reproductive age with complaints of non-cyclic pelvic pain for more 6 months constituted the study group, 45 patients with no active complaints who admitted for laparoscopic tubal ligation constituted the control group. Short Form-36 (SF-36) and Visual Analog Scala (VAS) Questionnaire was applied to patients in preoperative and postoperative periods. While VAS score in study group patients before surgery was 6,91±0,92, it was 4,33±1,64 after surgery ($p<0.001$). In addition, there were statistically significant difference between SF-36 Physical Health and SF-36 Mental Health scores before and after surgery. There was a significant improvement in quality of life in the study group. Laparoscopic approach should be preferred for direct visualization and immediate treatment in patients with CPP. Laparoscopy keeps its importance for patients with CPP, improving quality of life.

Keywords: chronic pelvic pain, laparoscopy, quality of life, surgery

1. Introduction

Pain has been described as an unpleasant emotional sensation that originates from a specific part of the body, is related to tissue damage or not, and is also related to the past experiences of the person (1). New theories in the perception of pain emphasize the importance of emotional, environmental, and cognitive factors as well as physical factors. These “Biopsychosocial models” recognize that chronic pain is the result of complex relationships, each of which can affect the other, such as sensory stimulation, psychological factors, and socio-environmental factors (2). Although there is no generally accepted definition of chronic pelvic pain (CPP), it is one of the most complex problems facing gynecologists (3). It has been defined as pain felt in anatomical pelvis, anterior abdominal wall that fits under the umbilicus, lumbosacral region and hips for at least 6 months which disrupts the quality of life and is severe enough to need medical assistance (2, 4-6). On the other hand, this definition is not very useful in clinical practice and is rarely used.

There may be many different disorders of visceral or somatic origin in the etiology of CPP. The wide scope of etiology causes confusion in the diagnosis and treatment of patients who apply to gynecology clinic. Depression, anxiety, low quality of life, low productivity, decreased energy, sexual dysfunction and relationship problems were thought to be associated with CPP (7,8). Despite focused anamnesis and examinations, most of the reasons remain unclear and patients leave the polyclinics unsatisfied (5). Therefore the diagnostic treatment should be planned in a multidisciplinary manner.

Nowadays laparoscopy, which is a minimally invasive surgical technique used for both diagnosis and treatment, is thought to be the most important diagnostic tool in determining the CPP (6,9,10). In line with the developing technology and possibilities, it has gained an important place. While the rate of laparoscopy performed for CPP was 17% in 1987, this rate has reached 40% these days. It also accounts for 20% of hysterectomies performed for benign reasons (3,5,11). When the literature is examined, it is seen that there are few studies on the effect of laparoscopy on quality of life, especially in women of reproductive age, despite the high cost. Although some studies have shown that, laparoscopy has a positive psychological effect on CPP (12), the other studies incidated that laparoscopy do not affect either pain symptoms or quality of life in the long term and over half of women with CPP still take analgesics and have reduced quality of life (3,13).

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In this study, it was aimed to determine the effect of laparoscopy in CPP on quality of life. In addition it was planned to evaluate the organic pathologies in patients who underwent diagnostic laparoscopy in the reproductive age with a pre-diagnosis of CPP, and to select patients who would benefit from surgery.

2. Materials and Methods

After receiving approval from the institutional review board, the medical records of consecutive patients who were admitted to Ankara Dr. Zekai Tahir Burak Women's Health Training Research Hospital gynecology outpatient clinic between October 2013 and August 2015 were reviewed. The study was performed in accordance with the 1964 Helsinki declaration and ethical permission has been obtained. While patients who applied with the complaint of chronic pelvic pain and underwent laparoscopy were defined as the study group, patients who had laparoscopic tube ligation for contraception without any complaints were defined as the control group.

The diagnosis of CPP was accepted as pain felt in anatomical pelvis, anterior abdominal wall that fits under the umbilicus, lumbosacral region, and hips for at least 6 months (7). Patients' age, obstetric and gynecological history, initial clinical symptoms, laboratory, and transvaginal imaging findings were recorded as study parameters. Patients who had gastroenterological, musculoskeletal, urological, or psychiatric diseases, those with cardiovascular system and pulmonary disease that would constitute absolute contraindications to laparoscopy, and those with morbid obesity were excluded from the study. The Short-Form 36 (SF-36) quality of life scale and the Visual Analog Scale (VAS) were administered to the patients before the laparoscopy operation and 6 months after the operation (14). The patients in the study group were evaluated within the scope of the pelvic pain assessment form created by the International Pelvic Pain Association (15).

During conventional laparoscopy under general anesthesia, the uterus, bilateral ovaries, tubas, douglas, sacrouterine ligaments and pelvic side walls were evaluated and pathological areas were sampled. The patients were invited for examination in the 6th postoperative month. The primary outcome was relief of pain after treatment and detection of the most common pathologies in the reproductive age, and the secondary outcome was the changes in quality of life.

Data were analyzed via SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Pearson's Chi-Square Test and Fisher's Exact Test were used to evaluate categorical variables. Normal distribution of the variables was evaluated using visual (histogram and probability graphs) and analytical methods (Shapiro-Wilk Test). Student's T Test for statistical significance between two independent groups and Paired Sample T Test for significance between two dependent groups were used for variables with normal distribution. For the variables found to be non- normal distribution; Mann-Whitney U Test was used as statistical method for significance between two independent groups, and Wilcoxon Signed-Ranks Test between two dependent groups. According to the results of laparoscopy, the sensitivity, specificity, positive and negative predictive values and accuracy of the pelvic examination and USG results were calculated. A p value of less than 0.05 was taken to be significant.

3. Results

For this study, 45 patients admitted to the hospital with the diagnosis of CPP and 45 patients who had laparoscopic tube ligation for contraception without any complaints were determined. While the mean age of the study group patients was 37.84±5.49 years, it was 37.27±4.05 years in the control group (p=0.226). There were no significant differences between the groups in terms of body mass index (BMI), status of education, profession, chronic disease status. Furthermore, diseases present in patients with chronic diseases, history of operation and type of surgery in patients with a history of surgery were similar between the groups (Table 1).

Table 1. Demographic and descriptive data of patients

Age	Study Group (n=45)	Control Group (n=45)	p
Age	37.84±5.49	37.27±4.05	0.226[a]
Body Weight (kg)	70.38±10.82	73.78±8.98	0.108[b]
Height (cm)	162.31±5.30	163.80±5.88	0.210[b]
BMI (kg/m^2)	26.71±3.96	27.52±3.25	0.293[b]
Status of Education			
Primary School	22 (48.9)	15 (33.3)	0.512
Middle School	7 (15.6)	10 (22.2)	
High School	11 (24.4)	14 (31.1)	
College/ University	5 (11.1)	6 (13.3)	
Profession			
Housewife	27 (60.0)	25 (55.6)	0.699
Teacher	3 (6.7)	6 (13.3)	
Slogger	8 (17.8)	6 (13.3)	
Officer	7 (15.6)	8 (17.8)	
Chronic Disease Status			
None	26 (57.8)	32 (71.1)	0.186
Yes	19 (42.2)	13 (28.9)	
Diseases Present in Patients with Chronic Diseases (n=32)			
Depression	9 (47.4)	5 (38.5)	0.871
Asthma	2 (10.5)	2 (15.4)	
Migraine	4 (21.1)	2 (15.4)	
Hypertension	4 (21.1)	4 (30.8)	
History of Operation			
None	33 (73.3)	25 (55.6)	0.078
Yes	12 (26.7)	20 (44.4)	
Type of Surgery in Patients with a History of Surgery (n=32)			
Laparotomy	8 (66.7)	14 (70.0)	0.998[c]
Laparoscopy	4 (33.3)	6 (30.0)	

[a]Mann-Whitney U Test; [b]Student's T Test; [c]Fisher's Exact Test
Values were presented as mean±standard deviation and number (%)
BMI: Body Mass Index
p<0.05 was considered statistically significant

Table 2. Distrubution of some pregnancy related features, duration of pain, history of pelvic inflammatory disease and treatment method of the groups

	Study Group (n=45)	Control Group (n=45)	p
Gravidity	2.87±1.41	3.84±1.41	**0.002**[a]
Parity	2.33±1.15	3.00±1.04	**0.007**[a]
Abortus	0.53±0.62	0.84±0.90	0.135[a]
Duration of Pain (months)	12 (6-120)	0 (0-4)	**<0.001**[a]
Type of Delivery			
Nulliparity	3 (6.7)	0	0.843*
Vaginal Delivery	30 (66.7)	33 (73.3)	
Cesarean Section	12 (26.7)	12 (26.7)	
Difficult Labor and Delivery History (n=87)			
None	30 (71.4)	30 (66.7)	0.631*
Yes	12 (28.6)	15 (33.3)	
Pregnancy Contraception Status			
None	10 (22.2)	11 (24.4)	0.803
Yes	35 (77.8)	34 (75.6)	
Type of Contraception Used (n=69)			
Traditional	14 (40.0)	11 (32.4)	0.150
Condom	11 (31.4)	8 (23.5)	
Intrauterine device	9 (25.7)	7 (20.6)	
Oral Contraceptive	1 (2.9)	5 (14.7)	
Other	0	3 (8.8)	
History of Pelvic Inflammatory Disease			
None	29 (64.4)	36 (80.0)	0.099
Yes	16 (35.6)	9 (20.0)	
Type of Treatment in Patients with a History of Pelvic Inflammatory Disease (n=25)			
Outpatient	12 (75.0)	7 (77.8)	0.998[c]
Inpatient	4 (25.0)	2 (22.2)	

[a]Mann-Whitney U Test; [b]Student's T Test
*Nulliparous patients were excluded from the statistical analysis.
Values were presented as mean±standard deviation, median (min-max) and number (%)
p<0.05 was considered statistically significant

The gravidity and parity were higher in the study group than in the control group. Furthermore, duration of pain was significantly more in the study group (12 (6-120) months vs 0 (0-4) months) (p<0.001). However, there were no significant differences between the groups in terms of history of pelvic inflammatory disease and treatment method of the groups (Table 2). The percentage of patients with ovarian cysts in the study group was significantly higher than the control group. On the other hand, there was no statistically significant difference in terms of adhesions, paratubal cysts and myomas because of laparoscopy (p> 0.05) (Table 3).

Table 3. Laparoscopy results of the groups

Laparoscopy Results	Study Group (n=45)	Control Group (n=45)	p
Ovarian Cyst	17 (37,8)	7 (15,6)	**0,017**
Adhesion	12 (26,7)	5 (11,1)	0,059
Paratubal Cyst	3 (6,7)	2 (4,4)	0,998[a]
Myoma	1 (2,2)	1 (2,2)	1,000[a]

Values were presented as number (%)
[a]Fisher's Exact Test

In table 4, VAS of the groups before surgery is shown. The visual analogue scale score was significantly more in the study group than in the control group (6.91±0.92 vs 2.09±1.58) (p<0.001).

Table 4. Visual Analogue Scale (VAS) of the Groups Before Surgery

	Study Group (n=45)	Control Group (n=45)	P*
	$\bar{X}$±SD	$\bar{X}$±SD	
VAS Score Before Surgery	6.91±0.92	2.09±1.58	**<0.001**

$\bar{X}$: Mean; SD: Standard Deviation
*Mann-Whitney U Test
VAS: Visual Analogue Scale
Values were presented as mean±standard deviation
p<0.05 was considered statistically significant

While VAS score in study group patients before surgery was 6,91±0,92, it was 4,33±1,64 after surgery (p<0.001). In addition, there were statistically significant difference between SF-36 Physical Health and SF-36 Mental Health scores before and after surgery (Table 5).

Table 5. Visual Analogue Scale (VAS) and Short Form Survey-36 scores of the study group before and after the surgery

(n=45)	Before Surgery	After Surgery	P
	$\bar{X}$±SD	$\bar{X}$±SD	
VAS Score	6.91±0.92	4.33±1.64	**<0.001**[a]
SF-36 Physical Health	33.77±10.05	39.83±10.33	**<0.001**[b]
SF-36 Mental Health	36.90±9.90	41.14±9.25	**<0.001**[b]

$\bar{X}$: Mean; SD: Standard Deviation
VAS: Visual Analogue Scale
SF-36: Short Form Survey
[a]Wilcoxon Test; [b]Paired T Test
Values were presented as mean±standard deviation
p<0.05 was considered statistically significant

4. Discussion

Chronic pelvic pain is one of the most common complaints in gynecology. CPP, which may be of pathological, physiological, or psychological origin, is not always easy to evaluate and the results can be troublesome for both the doctor and the patient. The absence of a pathological finding on physical examination and the tendency to establish a relationship between pelvic pain and psychogenic origin generally lead to inappropriate orientation of patients and temporary symptomatic treatment methods. Although one can have an idea about the female genital organs with bimanual pelvic examination, it is an indisputable fact that it cannot be as accurate as a diagnosis made with laparoscopy under direct observation. The appropriate treatment of CPP can shorten

the duration of pain and increase quality of life, resulting in less morbidity and cost. In addition, it reduces the workload of the clinician.

Laparoscopy offers a key advantage over the medical treatment allowing definitive histologic diagnosis and surgical treatment in one procedure. Therefore, it is very useful. However, despite these there is no consensus on this subject in the literature. Also, there is little research on this subject. In this study, the preoperative VAS scores of those in the study group were found to be significantly higher than the control group. Also, the postoperative VAS scores of the patients in the study group were found to be decreased significantly while SF-36 physical health and SF-36 mental health scores increased significantly.

The results of the studies investigating the effect of laparoscopy in CPP are controversial. Furthermore, there is little research focusing on long-term outcome after laparoscopy that uses standardized measures to evaluate quality of life. While some studies have reported a reduced quality of life up to 2 years after laparoscopy (13) and found a lack of evidence of benefit with high rate of negative laparoscopy findings (16) the others indicated that laparoscopy improves quality of life in patients with CPP (17).

Similar our study, in a study by Swanton et al. pain scores of 39 patients with CPP before and after laparoscopy were evaluated. VAS was used to evaluate the pain scores. And significant decreases were observed in the pain scores of the patients before and after the operation (18).

Moreover, in a prospective randomized controlled trial, laparoscopy has been shown to be superior to medical therapy in the treatment of mild to moderate endometriosis over a 6-month period. Also in this study, although where endometriosis cannot be completely removed, it has been shown that 50% of the patients had less pain. It may be thought there is also a significant placebo response to surgical treatment (19). That the decrease in the pain scores of patients with normal genital findings can be explained by the placebo effect of laparoscopy in our study too. This placebo effect, which may be due to peritoneal cavity insufflation, anesthesia, or painkillers, has been reported to provide symptomatic improvement for up to six months (20). In addition, in the current study, in the group of patients for whom we could not detect organic pathology and whose complaints continued, a multidisciplinary approach was preferred after necessary interviews.

Whereas the routine use of laparoscopic adhesiolysis is not recommended for the management of CPP, in some studies laparoscopy has been found to be effective in the treatment of adhesive diseases. In a study of 187 cases, reduction or complete improvement in pain was observed in approximately one third of the patients after adhesiolysis (21). In some studies, up to %85 of patients has been shown to have postoperative improvement in pain (19,22,23).

Despite the increased interest in noninvasive methods, laparoscopy under general anesthesia still maintains its importance in the investigation of CPP. However, perhaps one of the more important issues is who will do the laparoscopy and the information must be carefully recorded. Surgeons who perform laparoscopy for chronic pelvic pain should be able to complete laparoscopy in sufficient time and in good standards in diseases such as endometriosis, adhesions, ovarian cysts, and hydrosalpinx. In addition, the surgeon should follow up the patient after the operation by keeping a multi-disciplinary approach. One of the strengths of this study is that the surgery was performed by expert surgeons who went through the same training process. This research focused on long-term outcome after laparoscopy using standardized measures to evaluate quality of life. In addition, careful patient selection was done excluding patients with high-risk anesthetic profile, strong preoperative suspicion for severe intra-abdominal adhesions, or history of psychiatric disorders.

Although there are several limitations to this study, we believe it may be valuable for the literature. Once, a relatively small number of subjects may limit the reliability of data. Moreover, the current study is limited to provide results that depict the general reproductive age female population. Visual analogue scale of the groups before surgery was shown. However, VAS and SF-36 physical and mental health scores of the control group after surgery were not determined.

In conclusion, in this current study, a significant increase in quality of life has been observed in patients with CPP after the surgery. We think, each patient should be evaluated individually and if an underlying gynecological pathology is considered, laparoscopic approach should be preferred in terms of direct diagnosis and simultaneous treatment. Although the diagnoses made by laparoscopy vary according to the selected patient population and the accepted definition of CPP, diagnostic laparoscopy still maintains its importance in the diagnosis of CPP. However, further studies in larger populations are needed.

Conflict of interest

The authors declare that they have no conflict of interest.

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Relationship between anxiety, depression, symptom level, and quality of life in individuals with COPD

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Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive obstructive pulmonary disease. COPD is a major cause of workforce loss and may affect 7-12% of the adult population. The current study aimed to investigate the relationship between anxiety, depression, symptom level, and quality of life in patients with COPD who were in a stable period. The present study included 125 patients with COPD (66.1±9.011 years) in a stable period. Data were obtained using the St. George Respiratory Questionnaire (SGRQ), Hospital Anxiety and Depression Scale (HAD), and COPD Assessment Test (CAT). There was a significant positive correlation between HAD-anxiety, HAD-depression, HAD-total, CAT, SGRQ-symptom level, and SGRQ-total scores in each pairwise relationship ($p<0.05$). The present study showed a positive relationship between anxiety, depression, symptom level, and quality of life in patients with COPD who were in a stable period. COPD patients with lower quality of life had higher levels of anxiety, depression, and symptoms. Furthermore, COPD patients with higher symptom levels had higher levels of anxiety and depression. Therefore, multidisciplinary approaches such as breathing exercises and relaxation techniques are remarkable to reduce symptoms and increase the quality of life in patients with COPD.

Keywords: COPD, anxiety, depression, quality of life

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive obstructive pulmonary disease characterized by persistent airflow limitation and associated with an increased chronic inflammatory response of the airways and lungs to noxious gases and particles. Although COPD is the fourth most common cause of death in the world, it is an important preventable and treatable health problem. Globally, the burden of COPD is expected to increase with greater exposure to COPD risk factors and the increasing elderly population (1).

Because dyspnea occurs due to airway obstruction in COPD, daily activity levels are restricted, and functional status gradually worsens (2). COPD is a major cause of workforce loss and may affect 7-12% of the adult population (3). In the study of Penña et al. (4), it has been reported that the prevalence of COPD was 9.1% in the adult population aged 40-69 years in Spain. When evaluated in terms of the community health care system, it is stated that COPD has an important place in both primary health care services and hospital admissions. Considering the aging of the population and the ever-increasing prevalence of the disease, the socioeconomic impact of COPD is gradually increasing (5).

In addition to being a chronic disease, COPD is a condition that can lead to a series of psychological, emotional, social, and psychosexual problems and conflicts for the patient (6). COPD severely affects emotional, social, and behavioral functions, self-care, mobility, enjoying hobbies, sleep, and rest functions. When dyspnea is acute and severe, it causes emotional stress. In some cases, it reaches the level of fear of death (7).

In the study of Gore et al. (8), it has been shown that patients with severe COPD had worse activities of daily living and physical, social, and emotional functions than patients with inoperable non-small-cell lung carcinoma. Furthermore, while depression and anxiety were detected in 90% of COPD cases, the rate was found to be 52% in the group with malignancy. It has been reported that patients with COPD have less knowledge about their diseases, receive less social support, and have a shorter life than patients with cancer (8).

COPD may lead to psychological disorders by affecting brain functions and occur psychological symptoms depending on the perception of the disease and its impact on the patient's life areas (9, 10). It has been reported that psychological disorders, especially depression and anxiety, are common in COPD patients compared to the general population (10, 11). It is stated that anxiety seen in COPD patients is 55%. Anxiety negatively affects the quality of life and functional independence of COPD patients (9, 12). It also causes an increase in physical findings such as breathlessness, dryness in the mouth, and palpitations seen in COPD patients (10). In the study of Van Ede et al. (11), it has been shown that hypoxemia in COPD accompanies depression by causing changes in

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neurophysiological functions. In the treatment, it is recommended to apply psychotherapeutic approaches in addition to giving medication for symptoms. The prevalence of depression in patients with COPD has been the issue of many studies. The rates obtained in these studies are in the range of 6-42% (10). Depression can rarely be realized or treated since depressive symptoms are often regarded as the manifestation of the disease in patients diagnosed with COPD.

Because COPD is a chronic disease and causes problems such as dyspnea, it is very important to evaluate parameters that affect the daily activities of the patient, such as anxiety, depression, symptom level, and quality of life, as well as respiratory functions and performances in patients with COPD. The current study aimed to investigate the relationship between anxiety, depression, symptom level, and quality of life in patients with COPD.

2. Materials and methods

2.1. Study population

125 patients with a diagnosis of COPD who applied to the chest diseases policlinic were included in the present study. Inclusion criteria were being diagnosed with COPD according to the GOLD (Global Initiative for Obstructive Lung Disease) 2017 criteria, being in a stable period, and not having a mental problem that prevented them from completing the questionnaires used in the current study. Exclusion criteria were being uneducated, being in the attack period, and having cognitive problems.

2.2. Study design

The present study was planned as cross-sectional. An information form was created to query the demographic information and other data of the patients. Name, surname, gender, job, age, height, weight, marital status, education status, duration of disease, pain, history of disease and surgery, devices used, medications, accompanying diseases, social assurance, habits, allergies, curriculum vitae, family history, vital signs, years of smoking, and how many packs of cigarettes a day were questioned in this form. After the patients were evaluated with this form, the evaluation questionnaires described below were applied to each patient separately.

Necessary permissions were obtained from Non-Interventional Research Ethics Committee (2016/79) to carry out the study. The current study followed the principles of the Declaration of Helsinki. Detailed information about the study was given to volunteers participating in the study, and informed consent forms were signed by all patients.

2.3. Measurements

2.3.1. St. George respiratory questionnaire

Developed by Jones et al. (13), the St. George Respiratory Questionnaire (SGRQ) consists of 50-item. It is a questionnaire used to evaluate the quality of life in patients with airway obstruction. SGRQ is a specific test used for respiratory diseases. The number of answer options per question ranges from two to five. Scores are calculated separately in three areas as symptoms (8 items), activity (16 items), and psychosocial impact (26 items), and the total score is obtained by summing these scores. The symptoms section involves shortness of breath, cough, sputum, wheezing, and attacks. In the activity section, physical activities that are affected or restricted due to shortness of breath are asked. The psychosocial impact section includes the panic state of the patient due to respiratory disease and the psychosocial impact of the disease on the patient. A score between 0 and 100 is taken. While a high score indicates poor health, a low score represents good health. It has a high repeatability and sensitivity level. The validity and reliability of SGRQ was conducted by Polatli et al. (14). It is especially used in asthma and COPD (15).

2.3.2. Hospital anxiety and depression scale

The Hospital Anxiety and Depression Scale (HAD) was developed to determine the risk of anxiety and depression in individuals applying to primary health care services and to measure the level of anxiety and change in severity. HAD, which is a self-assessment scale, consists of 14 questions. While seven of the questions investigate anxiety levels, the other seven evaluate depression levels. Turkish validity and reliability study was performed by Aydemir (16).

2.3.3. COPD assessment test

The COPD Assessment Test (CAT) is recommended in the GOLD guideline for scoring COPD symptoms and grading the severity of COPD (17). CAT provides to measure the symptom level of patient with COPD and to obtain information about the patient's quality of life (18). In CAT, which consists of 8 items, each item is scored between 0 and 5, so a maximum of 40 points can be obtained from this test. A high score indicates worsening of symptoms and increased severity of COPD. Turkish validity and reliability study of the CAT was conducted by Yorgancioglu et al. (17).

2.4. Statistical analyses

Shapiro-Wilk's test was used to determine whether variables were normally distributed. Descriptive analyzes of the obtained data were stated as mean (x), standard deviation (SD), frequency (n), and percentage (%). Since variables were normally distributed, relationships between measurements were investigated using Pearson correlation analysis. Statistical significance level was taken as $p \leq 0.05$ and analyzes were made using PASW (SPSS 18.0) statistical analysis program.

3. Results

Demographic characteristics of 125 patients with COPD participated in the current study were given in Table 1. The mean age of all patients was 66.1±9.011 years, the mean height was 1.69±0.065 m, the mean weight was 77.29±16,087 kg, and the mean body mass index was 27.135.49 kg/m^2.

3.1. Correlation between variables

Pairwise relationship between HAD-anxiety, HAD-depression, HAD-total, CAT, SGRQ-symptom level, and SGRQ-total scores were analyzed using Pearson correlation

analysis. The correlation coefficients and the statistical significance level of these coefficients were shown in Table 2. According to these findings, there was a positive and significant correlation between HAD-anxiety, HAD-depression, HAD-total, CAT, SGRQ-symptom level, and SGRQ-total scores. In addition, all scores positively correlated with each other at the p=0.001 significance level.

Table 1. Demographic characteristics of patients with COPD

	Patients with COPD (n=125)
Characteristics	**X±SD / n; %**
Age (year)	66.10±9.011
Male/female	115; 92% / 10; 8%
Weight (kg)	77.29±16.087
Height (m)	1.69±0.065
Body mass index (kg/m²)	27.13±5.49
Marital status	
Married	111; 88.8%
Single	14; 11.2%
Job	
Public officer	4; 3.2%
Artisan or self-employment	9; 7.2%
Worker or servant	7; 5.6%
Retired	93; 74.4%
Others	12; 9.6%
Social assurance	
Yes	121; 96.8%
No	4; 3.2%
Working status	
Working	16; 12.8%
Retired	109; 87.2%
Individuals living together	
Alone	6; 4.8%
Spouse/child	116; 92.8%
Mother/father	2; 1.6%
Others	1; 0.8%

kg: kilogram, m: meter, x±SD: mean±standard deviation, n: frequency, %: percentage

4. Discussion

In the present study, a significant positive correlation was found between anxiety, depression, symptom level, and quality of life in patients with COPD who were in a stable period. In other words, it was concluded that COPD patients with decreased quality of life had higher levels of anxiety, depression, and symptoms. In addition, our study showed that COPD patients with higher symptom levels had higher levels of anxiety and depression.

Anxiety and depression negatively affect individuals' self-care and lifestyles. At the same time, it directly affects the health status of patients, the frequency of hospitalization, and symptom control. Therefore, detection of anxiety and depression is vital (19,20). It has been reported that depression is associated with exacerbations of COPD, hospitalizations, and mortality (21). Studies in the literature have shown that the depression rate in patients with COPD varies between 11% and 40%. However, it has been stated that depression is difficult to diagnose because its symptoms can be confused with the symptoms of COPD. For this reason, the patient's history and physical examination were expressed to be important (22,23). In the literature, it has been reported that depression and anxiety disorders are more common in patients with COPD compared to the general population and patients with other chronic diseases (10,11). Quality of life and functional independence are negatively affected in COPD patients with higher levels of anxiety (9,12). In the current study, COPD patients with decreased quality of life were showed to have higher levels of anxiety and depression. In parallel with our results, in the study of Balcells et al. (24) conducted on patients with mild and moderate COPD, it has been reported that COPD patients with decreased quality of life had higher levels of anxiety and depression.

Table 2. The relationship between variables in patients with COPD

		HAD-anxiety	HAD-depression	HAD-total	CAT	SGRQ- symptom level	SGRQ-total
HAD-anxiety	**r**	-	**0.841**	**0.959**	**0.521**	**0.615**	**0.613**
	p		**p<0.001***	**p<0.001***	**p<0.001***	**p<0.001***	**p<0.001***
HAD-depression	**r**	-	-	**0.960**	**0.493**	**0.661**	**0.639**
	p			**p<0.001***	**p<0.001***	**p<0.001***	**p<0.001***
HAD-total	**r**	-	-	-	**0.529**	**0.666**	**0.653**
	p				**p<0.001***	**p<0.001***	**p<0.001***
CAT	**r**	-	-	-	-	**0.764**	**0.827**
	p					**p<0.001***	**p<0.001***
SGRQ-symptom level	r	-	-	-	-	-	**0.963**
	p						**p<0.001***
SGRQ-total	r	-	-	-	-	-	-
	p						

r: Pearson correlation coefficient, COPD: Chronic obstructive pulmonary disease, HAD: Hospital Anxiety and Depression Scale, CAT: COPD Assessment Test, SGRQ: St George's Respiratory Questionnaire. *p<0,05. Pearson correlation coefficient was used because all values were normally distributed.

In the present study, 92% of patients with COPD were men and the mean age was 66.10 years. In the study of Balcells et al. (24), which had a similar population to patients in our study, 93% of the patients with COPD were men and the mean age was 68 years. We think that since variables such as age range and gender in the study of Balcells et al. (24) are similar to our variables, the results of this study may be parallel to ours. Consistent with our study, the study of Burgel et al. (25) conducted on COPD patients with a mean age of 65 (male patient rate = 77%) stated that quality of life decreased in COPD patients with higher levels of anxiety or depression.

In line with our study, the study of Ekici et al. (26) carried out on patients with COPD in a stable period reported that there was a significant correlation between the lower quality of life and higher levels of anxiety and depression. Furthermore, as a result of the study, a significant relationship was found between quality of life and anxiety, while there was no relationship between quality of life and depression (26). In the study of Ekici et al. (26), men comprised 98.4% of patients with COPD, and 70.9% of participants had bronchiectasis. However, it has been stated that the presence of bronchiectasis did not affect the quality of life and psychological disorders.

Anxiety and depression complaints are common in patients with COPD. Depression is observed to be two to four times more often than in healthy individuals (19,20). The study of Cully et al. (27) showed that higher levels of anxiety and depression were associated with lower quality of life in COPD patients. In the study of Giardino et al. (28), the relationship between anxiety and quality of life in clinically stable patients with moderate to severe emphysema was investigated. Although the mean age (66.7 years) of the participants in the study was similar to our study, the rate of male participants (62%) was lower than ours. Consistent with our finding, this study showed that a higher anxiety level was associated with decreased quality of life (28). When we searched for studies investigating the relationship of quality of life with anxiety and depression in COPD patients with similar age groups and different gender ratios in the literature, we saw that almost all of them support each other. The results of our study are also compatible with the literature.

As far as we know, there is one study showing a relationship between anxiety, depression, symptom level, and quality of life in patients with COPD. In our study, in addition to the quality of life, a positive correlation was found between higher symptom levels and higher levels of anxiety and depression. In the study of Cleland et al. (29), the relationship between gender, age, anxiety, depression, symptom level, and quality of life in patients with COPD was analyzed. As a result of the study, in which 51.8% of the participants were men, it was reported that higher age and higher symptom levels were associated with higher levels of anxiety and depression (29). In our study, symptom level was also found to be positively associated with levels of anxiety and depression. The rate of men in our study was much higher than in this study. The relationship of gender with levels of anxiety and depression was not analyzed in our study. However, in the study of Cleland et al. (29), it was shown that there was no relationship between gender and levels of anxiety and depression. As the symptom level increases in COPD patients, the levels of anxiety and depression worsen (29). Based on this information, it was concluded that anxiety and depression levels are more in COPD patients with higher symptom levels.

As a result of our research, a significant relationship was revealed between anxiety, depression, symptom level and quality of life in COPD patients who were in the stable period. It was showed that the levels of symptom, anxiety and depression were more in COPD patients with poor quality of life. In addition, it was found that the levels of anxiety and depression were also higher in COPD patients with higher symptom levels. COPD is a disease with severe symptoms. Furthermore, anxiety and depression are more common in COPD. As with other chronic diseases, psychological health is also very important in COPD. For this reason, psychosocial approaches, as well as the appropriate medical treatments, gain importance. We would like to emphasize that multidisciplinary approaches are remarkable in reducing symptoms such as anxiety and depression and increasing the quality of life by using breathing exercises and relaxation techniques in patients with COPD.

Conflict of interest

None to declare.

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None to declare.

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Effect of COVID-19 quarantine on patients admitted to neurosurgery outpatient

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Abstract

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Throughout the pandemic period, numerous countries around the world have implemented nationwide isolation measures to control the spread and transmission of COVID-19. During this period, the prevalence of some physical and mental diseases have increased due to prolonged home isolation measures. In the present study, we aimed to examine the effect of the COVID-19 isolation measures imposed in Turkey on patients admitted to our neurosurgery outpatient clinic.

Keywords: isolation, COVID-19, pandemic, low back pain, headache

1. Introduction

Coronavirus disease 2019 (COVID-19) emerged in Wuhan, China, in December 2019 and then spread to the entire world and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the primary cause of COVID-19 (1). Throughout the pandemic period, numerous countries around the world have implemented nationwide isolation measures to control the spread and transmission of COVID-19 (2).

In Turkey, as of March 2020, the government has imposed nationwide restrictions to prevent the risk of COVID-19 infection, such as closing schools, bars, nightclubs, theaters, gyms, mosques, and all public gathering places. Additionally, a permanent isolation was declared for the elderly and individuals with chronic diseases. In later periods, weekend curfews were imposed and the people were ordered to stay at home, work remotely, and engage in distance learning (3). Of these measures, the stay-at-home order has been shown to be an effective way to prevent COVID-19 infection and reduce the mortality rates (4).

Nevertheless, although the voluntary and compulsory stay-at-home measures are highly effective for preventing exposure to COVID-19, they have been shown to have several disadvantages such as causing reduced physical activity, weight gain, behavioral addiction, and social problems (5). In turn, reduced physical activity may lead to an increased prevalence of musculoskeletal disorders and pain (6). Additionally, long-term inactivity during the COVID-19 pandemic has been associated with a number of health problems (7).

Despite technological advancements and new treatment methods, low back pain and related conditions remain an important health concern around the world, even in developed countries (8). The global incidence of low back pain is estimated to be between 1.4% and 20% (9). Low back is one of the most common sites of work-related pain and low back pain poses significant problems in both private and professional lives of individuals (10). These problems include sleep disturbances, physical and mental disability, work absenteeism, decreased work efficiency (11). Additionally, the economic impact of low back pain also represents a major concern worldwide. Of note, the cost of low back pain is estimated to represent 1-2% of the gross national product in Western countries (12). Low back pain is primarily associated with occupational exposures in awkward postures, such as heavy lifting and repetitive lifting, as well as trunk flexion, rotation and hyperextension, pushing, pulling, carrying, and whole-body vibrations (13). In addition, some factors such as age, gender, hypertension, smoking, ergonomics, job satisfaction, excessive body weight or obesity, lack of physical activity, and depression may intensify low back pain (14). However, the prevalence of low back pain may change depending on the alterations in individual habits and lifestyles. Accordingly, a number of measures have been taken in many countries to prevent the risk of COVID-19 transmission (15).

Following the outbreak of COVID-19, a number of innovations were introduced into working conditions. To

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illustrate, many corporations introduced remote working models based on the use of technological devices in order to minimize the risk of contamination (16). Expectedly, the home environment has numerous differences when compared to the working environment. Of note, the absence of ergonomic office furniture at home may prevent a healthy posture and thus may lead to the onset of musculoskeletal disorders (17). Prolonged sedentary behavior increases the risk of spinal disorders such as neck and back pain (18). On the contrary, home working has several positive effects as well, such as reducing psychological stress, improving the family life, and increasing the work efficiency (19).

The pandemic has also changed the amount of time spent at home and the daily routine of most people. Due to the reduced face-to-face interaction opportunities during the COVID-19 pandemic, people have resorted to technological devices with internet-based services (20). Moreover, people have started to spend more time on the internet and social media via smartphones in order to overcome boredom, seek information, utilize educational services, and do research (21). Internet usage has also increased significantly during the pandemic period (22). There are many psychiatric and musculoskeletal disorders associated with excessive smartphone use (23), which mainly typically include discomfort and pain in various parts of the body, including the neck, shoulder, elbow, wrist, hand, and thumb (24).

In a study conducted with a home working population in Italy, it was found that the prevalence of existing neck pain increased in 50% of the workers and decreased in 8% of them (25).

Headache is one of the most common diseases worldwide. Moreover, tension-type headache and migraine are reported as the second and third most common diseases in the world, respectively (26). According to the international classification of headache disorders, 50.1-78.4% of headaches are associated with primary headaches, while 2.5-23% of the cases cannot be classified (27). Correct classification of headache disorders is a prerequisite for targeted therapy both for headache specialists and clinicians (28).

Belvis et al. evaluated more than 41,000 COVID-19 patients and detected headache in 8-12% of them (29). After an incubation period of 2 to 24 days, a clinical picture including fever, dry cough, and difficulty breathing may be seen. Additionally, various combinations of weakness, muscle aches, headache, nasal congestion, nausea, vomiting, diarrhea, hemoptysis, sore throat, myalgia, arthralgia, anosmia, and ageusia may occur. On the other hand, the initial clinical manifestations may be complicated by pneumonia, acute respiratory distress syndrome, and sepsis in some patients [30]. Additionally, headache has been shown to be the 5th most common symptom of COVID-19 after fever, cough, myalgia, fatigue, and shortness of breath (31).

During the pandemic period, the loneliness caused by the isolation measures has led to an increased prevalence of many pain conditions and to a significant increase in the prevalence of headaches (32).

There are numerous mental health problems associated with the isolation measures imposed during the COVID-19 pandemic (33). A previous study compared clinical data of patients before and after the pandemic and showed an increase in the prevalence of average psychological disorders (34). Since the cure of the pandemic has not yet been found and the uncertainty continues, it has led to an increases prevalence of psychiatric disorders including panic, anxiety, and depression (35). Additionally, some other studies showed that the individuals forced to quarantine at home are at increased risk for depression and post-traumatic stress disorder symptoms (36).

To date, numerous studies have investigated the increased prevalence of psychological and physical disorders resulting from the sedentary lifestyle during the COVID-19 pandemic. However, to our knowledge, there has been no retrospective study evaluating the changes in patients admitted to neurosurgery outpatient clinics. In the present study, we aimed to examine the effect of the COVID-19 isolation measures imposed in Turkey on patients admitted to our neurosurgery outpatient clinic.

2. Materials and Methods

2.1. Study design and participants

The retrospective study reviewed pre- and post-pandemic clinical records of 4,950 patients aged 18-100 years who applied to our outpatient neurosurgery clinic over the 10-month period between April 1, 2020 and January 15, 2021. Patients with conditions associated with trauma, those with a history of surgery, and patients who regularly visited the clinic for postoperative follow-up were excluded from the study.

Age, gender, occupation, presence of chronic disease, duration and progression of pain, ongoing medication, history of psychiatric diseases, clinical examinations and treatments, duration of home stay, and complications associated with delayed hospital admission were recorded for each patient. Patients were divided into two groups according to the duration of home stay due to COVID-19: (i) group 1 (0-4 months; n=1,913) and (ii) group 2 (≥5 months; n=2,036).

The study was conducted in accordance with the principles of Helsinki Declaration and the study protocol was approved by Van Yuzuncu Yil University Ethics Committee.

2.2. Statistical analysis

Data were analyzed using SPSS for Windows version 27.0 (Armonk, NY: IBM Corp.). Variables were expressed as mean, standard deviation (SD), median, minimum-maximum, frequencies (n), and percentages (%). Normal distribution of continuous variables was assessed using Kolmogorov-

Smirnov test. Continuous variables were compared using Mann-Whitney U test and categorical variables were compared using Chi-square test. A p value of <0.05 was considered significant.

Table 1. Demographic and clinical characteristics

		Min-Max	Median	Mean±SD/n-%	
Age (years)		17.0 - 92.0	43.0	44.0 ± 14.4	
Duration of home stay (months)		0.5 - 9.5	6.0	5.8 ± 2.5	
Duration of home stay	0-2 months			546	11.0%
	3-4 months			1367	27.6%
	5-7 months			1318	26.6%
	≥ 8 months			1718	34.7%
Gender	Male			2202	44.5%
	Female			2747	55.5%
Presenting complaints					
Low back pain				2989	60.4%
Headache				1523	30.8%
Neck pain				526	10.6%
Leg pain				364	7.4%
Arm pain				46	0.9%
Back pain				38	0.8%
Vertigo				12	0.2%
Carpal tunnel				7	0.1%
Cranial mass				4	0.1%
Hydrocephalus				2	0%
Comorbidity	(-)			4416	89.2%
	(+)			533	10.8%
LDH				169	31.7%
Cranial mass				136	25.5%
HT				59	11.1%
SDH				49	9.2%
DM				44	8.3%
Hydrocephalus				26	4.9%
Chiari malformation				21	3.9%
Spinal mass				7	1.3%
Epilepsy				6	1.1%
Other				34	6.4%
Chronic diseases	(-)			4827	97.5%
	(+)			122	2.5%
Psychiatric disorders	(-)			4913	99.3%
	(+)			36	0.7%
Complications associated with delayed hospital admission	(-)			4925	99.5%
	(+)			24	0.5%

LDH: Lactate dehydrogenase deficiency, HT: Hypertension, SDH: Subdural hematoma, DM: Diabetes mellitus

3. Results

No significant difference was found between the group with a duration of home stay of 0-4 months and the group with a duration of ≥5 months with regard to age and gender (p>0.05 for both). Similarly, no significant difference was found between the two groups with regard to the prevalence of low back pain, headache, neck pain, arm pain, back pain, carpal tunnel, cranial mass, and hydrocephalus (p>0.05), whereas the prevalence of leg pain was significantly lower and the prevalence of vertigo was significantly higher in patients with a duration of ≥5 months (p<0.05 for both) (Table 2).

No significant difference was found between the two groups with regard to the prevalence of all comorbidities (p>0.05 for all) except for Chiari malformation, which was significantly higher in patients with a duration of ≥5 months (p<0.05). Similarly, no significant difference was found between the two groups with regard to the prevalence of chronic diseases and the complications associated with delayed hospital admission (p>0.05 for both). However, the prevalence of psychiatric diseases was significantly higher in patients with a duration of ≥5 months (p<0.05) (Table 2).

Table 2. Statistical comparison of demographic and clinical characteristics between the groups

			Duration of home stay (0-4 months)			Duration of home stay ≥5 months			
			Mean±SD/n-%		Median	Mean±SD/n-%		Median	*p*
Age (years)			44.4 ± 14.8		43.0	43.8±14.1		42.0	0.272 m
Duration of home stay (months)			3.1 ± 1.1		3.0	7.4±1.4		7.5	
Gender	Male		883	46.2%		1319	43.4%		0.062 x^2
	Female		1030	53.8%		1717	56.6%		
Presenting complaints									
Low back pain			1163	60.8%		1826	60.1%		0.649 x^2
Headache			584	30.5%		939	30.9%		0.766 x^2
Neck pain			197	10.3%		329	10.8%		0.549 x^2
Leg pain			166	8.7%		198	6.5%		***0.005*** x^2
Arm pain			15	0.8%		31	1.0%		0.398 x^2
Back pain			16	0.8%		22	0.7%		0.661 x^2
Vertigo			1	0.1%		11	0.4%		***0.031*** x^2
Carpal tunnel			2	0.1%		5	0.2%		0.584 x^2
Cranial mass			1	0.1%		3	0.1%		1.000 x^2
Hydrocephalus			1	0.1%		1	0.0%		1.000 x^2
Comorbidity		(-)	1708	89.3%		2708	89.2%		
		(+)	205	10.7%		328	10.8%		0.923 x^2
LDH				35.1%		97	29.6%		0.180 x^2
Cranial mass				22.4%		90	27.4%		0.198 x^2
HT				12.7%		33	10.1%		0.348 x^2
SDH				7.3%		34	10.4%		0.236 x^2
DM				10.7%		22	6.7%		0.100 x^2
Hydrocephalus				5.9%		14	4.3%		0.408 x^2
Chiari malformation				1.0%		19	5.8%		***0.005*** x^2
Spinal mass				0.5%		6	1.8%		0.186 x^2
Epilepsy				1.0%		4	1.2%		0.795 x^2
Other				5.9%		22	6.7%		0.695 x^2
Chronic diseases		(-)	1858	97.1%		2969	97.8%		0.140 x^2
		(+)	55	2.9%		67	2.2%		
Psychiatric disorders		(-)	1905	99.6%		3008	99.1%		***0.042*** x^2
		(+)	8	0.4%		28	0.9%		
Complications associated with delayed hospital admission		(-)	1908	99.7%		3017	99.4%		0.072 x^2
		(+)	5	0.3%		19	0.6%		

[m]Mann-Whitney U test / [X²] Chi-square test, LDH: Lactate dehydrogenase deficiency, HT: Hypertension, SDH: Subdural hematoma, DM: Diabetes mellitus

4. Discussion

The world is looking to an uncertain future for the first time in long years and it seems extremely difficult to win the war against this virus. More importantly, it is expected that the globalization of the world, the emergence of repeated infections due to COVID-19 mutations, and the outlook for new types of pandemics will lead to the prolongation and continuity of isolation measures (37). Although the isolation measures are loosened from time to time, the consequences of the pandemic can be aggravated and thus require repeated isolation measures. Moreover, although isolation measures help prevent virus transmission, the order and nature of the epidemic remain uncertain, thereby causing social and economic deterioration by affecting the functioning of the health system (38).

Despite the ongoing efforts to develop an effective vaccine, many people are concerned about vaccine safety. Bogart et al. showed remarkably high rates of potential vaccine hesitancy in the general population (39). In the present study, we evaluated the effects of COVID-19 isolation measures on neurosurgical patients based on the assumption that these measures would be further prolonged.

In the present study, we evaluated a total of 4,950 patients who applied to our neurosurgery outpatient clinic over a period of approximately 10 months from the beginning of the COVID-19 isolation period. We excluded patients who were previously operated on in our clinic or had complications due to previous surgeries and those affected by the COVID-19 virus. In doing so, we aimed only to determine the effects of isolation measures on our patients. We divided the patients into two groups according to the duration of home stay due to COVID-19: (i) group 1 (0-4 months) and (ii) group 2 (≥5 months), and we analyzed the results statistically. The results indicated no significant relationship between the isolation measures and age and gender.

In our study, no significant correlation was found between the duration of isolation measures and the prevalence of regional pains such as low back pain, headache, neck pain, arm pain, and back pain. This finding contradicts with the findings reported in the literature and may be due to the

relaxation of temporary isolation measures. In contrast, the prevalence of leg pain decreased significantly as the duration of isolation measures increased. This finding could be attributed to the relaxing effect of home isolation on spinal disc herniation. On the other hand, the prevalence of vertigo increased significantly as the duration of isolation measures increased. Although the occurrence of vertigo in patients with COVID-19 infection has been reported in the literature, to our knowledge, there is no meaningful research on the effect of isolation on vertigo (40). Literature indicates that organic vertigo syndromes are closely associated with psychiatric disorders (41). Accordingly, we considered that the increased prevalence of vertigo in our patients could be associated with the increased prevalence of psychiatric disorders.

In our patients, the prevalence of Chiari malformation increased significantly as the duration of isolation measures increased. In the literature, social isolation has been reported to be positively associated with interleukin (IL)-6 and it has also been shown that the methylation of RNA leads to increased proinflammatory responses, thereby leading to epigenetic effects that are known to have adverse effects on health (42). Reducing loneliness is associated with decreased pro-inflammatory gene expression, which further reinforces the relationship between loneliness and inflammatory responses (43). Studies have shown that the increased symptoms of Chiari malformation has significant effects on loneliness and stress factors (44).

In our study, no significant relationship was found between the duration of isolation measures and the prevalence of chronic diseases. Based on this finding, we assume that the elderly population with chronic diseases are not significantly affected by the isolation measures. Additionally, it was also observed that the prevalence of psychiatric disorders increased in line with the duration of isolation measures, which could be associated with the increased prevalence of loneliness caused by isolation measures and with the increase in stress factors (45)

.In line with the globalization of the world, infectious viral diseases pose the risk of turning into a pandemic. Despite technological advancements and scientific studies, pandemics cause negative effects on humans' lifestyles. During the COVID-19 pandemic, the restrictions imposed by governments around the world encourage people to perform voluntary and involuntary home isolation. Additionally, these restrictions further increase the sedentary behavior of people, which is a prevalent problem brought by the modern age, and thereby increase the prevalence of some physical and mental diseases, ultimately leading to serious individual and social problems.

Conflict of interest

None to declare.

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None to declare.

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Effects of favipiravir on hematologic parameters and bone marrow in the rats

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Abstract

Favipiravir, a selective RNA polymerase inhibitor agent, is an antiviral drug currently used effectively in treating pandemic diseases such as Covid-19. The present study aims to determine the effects of favipiravir use on bone marrow and blood cells. Twelve male Wistar rats were divided into two groups, namely control and favipiravir groups. Physiological saline at a dose of 1 ml/kg was administered to the rats in the control group by oral gavage for 10 days. Rats in the favipiravir group were administered favipiravir by oral gavage at a dose of 200 mg/kg for 10 days. At the end of the study, the blood tissue was collected from the heart, and bone marrow samples were collected from the femur bone of the rats sacrificed under anesthesia. The hematologic parameters in the blood samples obtained were measured using an auto-analyzer device with the help of rat compatible kits. Bone marrow cell counts were performed by examining structural changes and myeloid and erythroid cell series in the smear samples. The results obtained in the study revealed that favipiravir use caused a decrease in the counts of some hematologic parameters containing erythrocytes, lymphocytes, and monocytes. In addition, it was determined that the ratio of myeloid and erythroid cells in bone marrow smears changed significantly with the use of favipiravir. It was concluded that treatment with favipiravir caused suppression of erythrocyte and some leukocyte series. The suppressor effects were also determined in bone marrow cell series in the rats.

Keywords: bone marrow, favipiravir, rats, RBC, WBC

1. Introduction

Favipiravir, also known as T-705 (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), is an antiviral agent used against RNA viruses developed by the Japanese Toyama Chemical Co. Ltd. Nowadays; drugs with the active ingredient of favipiravir are particularly used in the treatment of Covid-19 disease caused by the SARS-Cov-2 virus. In addition, favipiravir, an RNA-dependent RNA polymerase enzyme selective inhibitor used against influenza and some viruses, has been determined to be effective against arenavirus, bunyavirus and flaviviruses in rodent and in vitro studies, while it has also been reported to have a potential activity against alphavirus, paramyxovirus and noroviruses (3).

RNA polymerase (RNAP) is a family of enzymes that copy genetic information in the DNA or RNA molecule as an RNA molecule. The process of copying the information contained in a gene into a RNA molecule is called transcription. RNAP in cells allows genes to be read as RNA strands. RNAP enzymes are found in many living organisms as well as in viruses. RNAPs are a nucleotidyl transferase enzyme and allow the polymerization of ribonucleotides at the 3' end of an RNA 20 molecule. Molecular studies have revealed that viral proteases play a critical role in the life cycle of many viruses by affecting the cleavage of high molecular weight viral polyprotein precursors to obtain functional products or by catalyzing the process of structural proteins required for the aggregation and morphogenesis of virus particles. Currently, many studies are in progress on protease inhibitors in the treatment of a large number of RNA and DNA viruses, such as HIV, HCV, picornaviruses, RSV, herpes viruses, rotaviruses, and SARS (4, 8, 11).

Traditionally, cytological examinations of peripheral blood and/or bone marrow smears have been based on the screening of these cell types and their morphology, one after the other and one by one. The classification of bone marrow cell populations, on the other hand, has been carried out as manual determination of myeloid / erythroid (M / E) ratio. These analyses are important in the determination of morphological structures and series of cells (14). It has been determined that drug use may cause certain disorders in the hematological systems, as well as affect the leukocyte and platelet series and the entire coagulation system through various mechanisms (10). Some studies conducted on humans and animals have indicated that hematological values of individuals changed with favipiravir use (15, 16). However, there are no studies in the literature showing the effects of favipiravir use on bone marrow cell lines.

Favipiravir is a broad spectrum antiviral agent used in the treatment of many diseases, including covid-19 pandemic

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disease. The aim of the present study is to examine the numerical and morphological changes of blood cells, and bone marrow cell structures due to favipiravir use.

2. Materials and methods

2.1. Animals

Twelve male outbred Wistar albino rats to be used in the study were randomly divided into two groups as control (n = 6) and favipiravir (n = 6) groups. The study is in agreement with the principles of scientific research and publication ethics according to ethical norms approved by the Local Animal Care Committee of Bingöl University Veterinary Faculty (15668). Oral favipiravir (Favicor, Atabay, Turkey) was administered at a dose of 200 mg/kg for 10 days to the rats in the favipiravir group. For this purpose, the tablets containing 200 mg favipiravir were ground in a mortar and suspended in saline solution and then administered to the rats by oral gavage for 10 days. The animals were sacrificed after blood samples were taken from their hearts under xylazine and ketamine anesthesia 24 hours after the last favipiravir administration.

2.2. Hematologic analysis

The complete blood count of samples was conducted using a BeneSphera 3 Part Differential Hematology Analyzer (Avantor Performance Materials India Limited, India) with the help of rat compatible kits. The femur bones were collected from the sacrificed rats, and the bone marrow cells were collected.

2.3. Bone marrow smear analysis

The femur was cut from the caput femoris region and bone medulla was washed 1 ml DPBS solution containing 1mm-EDTA. In the cytological examination of bone marrow, the preparations were made by spreading the cells onto the slides, drying in the air, and then staining with May-Grunwald-Giemsa (MGG] (2).

Table 1. The hemogram analysis results for control and favipiravir administrated groups

Groups		WBC (K/uL)	NEU (K/uL)	LYM (K/uL)	MON (K/uL)	EOS (K/uL)	BAS (K/uL)	RBC (K/uL)	HCT (%)	PLT (K/uL)
Control	Mean	**13.79**	**2.77**	**9.46**	**0.74**	**0.61**	**0.01**	**8.56**	**46.89**	**332.83**
	Stand. Dev.	0.82	0.48	0.36	0.13	0.17	0.01	0.30	1.34	65.90
Favipiravir	Mean	**12.00**	**2.22**	**8.24**	**0.82**	**0.27**	**0.02**	**7.69**	**51.87**	**631.83**
	Stand. Dev.	0.77	0.49	0.73	0.24	0.19	0.02	0.49	2.33	115.60
*** P Value**		**0.04***	**0.065**	**0.04***	**0.39**	**0.09**	**0.51**	**0.004***	**0.002***	**0.045** *

* Statistical analysis was conducted with the Mann-Whitney U test. The $p < 0.05$ was accepted as statistically significant. The value is the mean of groups. The Asterix indicate the statistical differences between control and favipiravir administrated groups.

2.4. Assessment of bone marrow cells

Two hundred cells were selected from the random regions of each preparation, and myeloid and erythroid cells were identified and counted to determine the ratio of these cells (M:E ratio] in the assessment of bone marrow cells. Myeloid and erythroid cell ratios in these counted cells were determined separately for each animal and averaged. A trinocular light microscope (Leica, DM2500 / DFC295, Germany) was used in the examinations and cell count determination of bone marrow (Bolliger, 2004).

2.5. Statistical analyses

The data obtained in the study were statistically analyzed using the SPSS 20.00 (IBM Co. Armonk, NY, USA) software package. Since the Kolmogorov-Smirnov analysis revealed that the data were normally distributed (asymp. Sig.) and the p-value was less than 0.05, the statistical analysis of the data was conducted by applying the Mann-Whitney U test that is used for the comparison of two independent groups. The p-values less than 0.05 were considered statistically significant.

3. Results

3.1. Hematologic results

The results of hematological analysis indicated that leukocyte (WBC), lymphocyte (LYM), monocytes (MON), erythrocyte (RBC), hematocrit (HCT) and thrombocyte (PLT) counts significantly reduced in the blood samples of rats treated with favipiravir than those in the control group ($p < 0.05$). On the other hand, there was no statistically significant difference in terms of neutrophil (NEU), eosinophil (EOS), and basophil (BAS) counts between the control group and the favipiravir administrated group ($p > 0.05$). Hematological parameters and their comparisons are presented in the Table 1.

3.2. Assessment of bone marrow cells

It was determined from the manual counting of the cells obtained from the bone marrow under the light microscope that the percentage ratio of myeloid cells was 42.7% in the control group and 41.6% in the favipiravir group, while there was no statistical difference between the two groups ($p > 0.082$). The percentage ratio of erythrocyte cells in the bone marrow was detected to be 31.4% in the control group and 28.6% in the favipiravir group, and the difference was statistically significant ($p < 0.043$). The M:E ratio was 1.36 in the control group and 1.45 in the favipiravir group and the statistical comparison revealed that the difference was significant ($p < 0.037$). The myeloid and erythroid cell counts and M:E ratios are presented in the Table 2, and bone marrow swab images are shown in the Fig. 1.

Table 2. Femoral bone marrow myeloid and erythroid cell percentages and M:E ratios in the control and favipiravir administrated groups

	Control (n = 6)	Favipiravir (n = 6)	p-value
Myeloid (M) cell (%)	42.7±4.5	41.6±5.1	0.082
Erythroid (E) cell (%)	31.4±2.5	28.6±3.2	0.043
M:E ratio	1.36±0.3	1.45±0.5	0.037

* Statistical analysis was conducted with the Mann-Whitney U test. The $p < 0.05$ was accepted as statistically significant. The value is the mean of groups

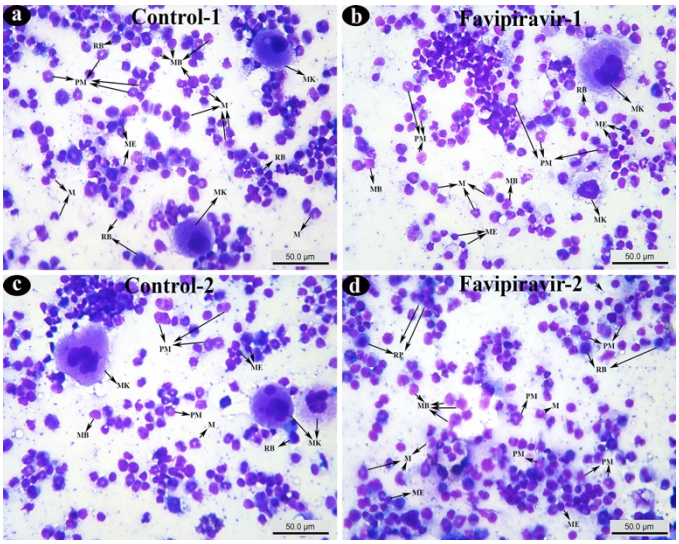

Fig. 1. Cytological illustration of femoral bone marrow cells for control and favipiravir administrated groups, MK: megakaryocyte, PM: Premyoblast, MB: Myeloblast, M: Myelocyte, ME: Metarubricides, RB: Rubriblast, May-Grunwald-Giemsa (MGG) staining

4. Discussion

Favipiravir, a selective RNA polymerase inhibitor and a broad-spectrum anti-viral agent, has become very widely used with the emergence of Covid-19 pandemic disease. Although favipiravir was originally developed for the treatment of influenza viruses, it is also used in the treatment of other viral diseases as it is effective against RNA viruses with its broad spectrum antiviral activity. In the present study, the effects of favipiravir administration on systemic hematological cell lines were investigated.

It has been reported in the literature that the hematopoietic system was affected with the use of certain antiviral agents (10). McHutchison et al. (2007) found that the antiviral agent ribavirin used for the treatment of hepatitis-C caused anemia. In another study, it was stated that lamivudine used for the treatment of human immunodeficiency virus (HIV) and ribavirin for hepatitis C treatment induced pure red cell aplasia (6). Similarly, a case study indicated that thrombocytopenia developed due to the use of antiviral agents such as daclatasvir and asunaprevir (13, 1). In an animal study, it was reported that the administration of favipiravir in Marburg virus-infected animals caused changes in hemogram parameters, as well as reduced lymphocyte counts, and increased neutrophil counts (16). It was stated in another study that favipiravir use prevented leukopenia and thrombocytopenia in Junin virus-infected guinea pigs (5). However, the results of our study show that favipiravir administration resulted in the development of anemia, in addition to leukopenia and thrombocytopenia in the healthy rats.

In the study, hematopoietic cell lines were evaluated by examining bone marrow cells obtained from all rats. Myeloid (premyeloblast, myeloblast, myelocyte) and erythroid (metarubricytes, rubriblast) serial cells of the bone marrow were counted and their ratios were calculated. It was found that, the ratio of myeloid cells (42.7%) and erythroid cells (31.4%) in the control group was 1.36, while the ratio of myeloid cells (41.6%) and erythroid cells (28.6%) in the favipiravir group was 1.45. A significant difference was determined between the groups in the statistical comparison of the M:E ratio ($p < 0.037$). Schomaker et al. (2002) found that 14-day treatment of Cyclohexanone Oxime (CHO) caused a significant decrease in the M:E ratio (Control: 1.96, CHO: 0.41) based on erythroblastic hyperplasia. It was stated in the same study that there was a decrease in erythrocyte counts as well as hemoglobin and hematocrit levels, and an increase in the counts of reticulocytes and nucleated erythrocytes (12). Several other studies indicated that the use of daunorubicin reduced erythroid and myeloid cell lines (79% reduction in myeloid cell count and 90% reduction in erythroid cell count) and affected erythropoietin responsive cells and erythroid repopulating cells in the rat bone marrow (9, 12). Yaylaci et al. (2020) investigated the effect of favipiravir use on the blood parameters in Covid-19 patients and reported that erythrocyte count significantly decreased.

One of the limitations of the study is that animal models are poor predictors of drug safety in humans. Also, flow cytometric examination of bone marrow cells can enrich our study. Similar studies conducted in the future may focus on these issues.

In conclusion, it was determined in the present study that favipiravir use did not affect the myeloid cell line, suppressed the erythrocyte, thrombocyte, monocytes, and lymphocyte series, and caused a significant decrease in these cells. It is considered that the study would contribute to the relevant literature about the effects of favipiravir use on the hematopoietic and hematological system, on which there are limited studies in the literature.

Conflict of interest

The authors declare that they have no conflict of interest to the publication of this article.

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None to declare.

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Research Article

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Changes in pelvic floor mobility in uncomplicated pregnant women over 28 gestational week and its relation with subjective urinary incontinence complaints

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Abstract

To describe the mobility of the anterior pelvic compartment and hiatal enlargement measures in pregnancy with urinary stress incontinence complaints and their relation to the perceived subjective urinary incontinence severity. Forty-six pregnant women were included in this observational prospective cohort study, the ultrasonographic parameters of the pelvic anterior compartment including hiatal anteroposterior (AP) diameter, retrovesical angle (RVA), bladder neck descent (BND), urethral rotation angle (URA) and cystocele level were compared with the subjective urinary complaints in healthy third trimester pregnant women. Hiatal AP diameter, RVA and BND on Valsalva did not significantly correlate with gestational week (p=0.292, r=0.096; p=0.079, r=0.159; p=0.901, r=0.011, respectively). Urethral rotation angle was significantly increased in women after 39th gestational week (p=0.037, t=-2.17). Hiatal AP diameter, BND and RVA on maximal Valsalva did not differ with estimated fetal weight above and below 3000 gr. Total severity and bother scores of the M-ISI scale was found as similar among women with open (>1400) RVA and intact (<1400) RVA (p=0.556 and p=0.779, respectively). Only nocturia frequency (β=.379, t=4.035, p=.000) positively predicted the incontinence severity score. The pelvic floor ultrasound parameters of the anterior compartment may not predict the subjective urinary incontinence severity in third trimester of pregnancy. Nocturia was found to contribute for subjective impaired urinary function. The idea of being pregnant may suppress the general complaints related with changes in pelvic floor mobility.

Keywords: pelvic floor ultrasound, urinary incontinence, cystocele, pregnancy

1. Introduction

Urinary incontinence during pregnancy is very common, affecting more than half of pregnant women (1). The prevalence of any urinary incontinence increases substantially during pregnancy with a doubling when compared to pre-pregnancy (2). Vaginal childbirth and pregnancy itself were known to have detrimental effect on levator hiatus, ligamentous structures of pelvic floor and pelvic floor function (3,4). Urinary incontinence during pregnancy has 3.5 times increased risk for persistent incontinence at 6 months of postpartum period compared with those who were continent antenatally regardless of the mode of delivery (5, 6).

Pelvic floor ultrasound (PFU) is promising and efficient method to dynamically assess functional anatomy with ease. PFU was shown to successfully describe the significant changes due to the affected pelvic organ mobility/prolapse following vaginal childbirth resulted in highly significant changes to all parameters used to describe pelvic organ mobility (7).

Changes in mobility of anterior compartment regarding pregnancy and its subjective effects is scarce in the literature. The burden of urinary incontinence in pregnancy and its impact on the quality of life is controversial (8-11). This study aimed to describe the mobility of the anterior pelvic compartment and hiatal enlargement measures in pregnancy and their relation to the perceived subjective urinary incontinence severity.

2. Patients and Methods

Pregnant women with singleton and cephalic fetus over 28 gestational week who has complaint of any urinary incontinence was included to this observational prospective cohort study. Pregnant women in their first trimester, who were in active labour phase or with progressive cervical dilatation and with clinically visible pelvic organ prolapse were excluded. Vaginal digital examination was not performed to any women. This study was approved by the local Institutional Scientific Researches Ethical Board (No.21/73). The results of preliminary analysis have been presented in the 6th International Urogynaecology Congress, Istanbul, 2018.

Transperineal ultrasound was performed to all women with

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a 3D probe of Mindray Diagnostic Ultrasound System DC-8 PRQ model (Shenzhen Mindray Bio-medical Electronics Co. Ltd., China) in a standardized fashion according to the method described by Shek and Dietz (12). All examinations were performed by two obstetricians who were experienced in pelvic floor ultrasonography. Third senior obstetrician was involved in cases of controversy. The inferior margin of the pubic symphysis was taken as the line of reference (13). Uretral rotation angle (URA), retrovesical angle (RVA), bladder neck descent (BND) and hiatal anteroposterior (AP) diameter were measured on maximal Valsalva lasted for at least 6 seconds to avoid levator co-activation. URA was defined by the angle between the proximal urethra at rest and on Valsalva. Cystocele of at least 10 mm below the pubic symphysis at maximum Valsalva were regarded as significant (12, 13). RVA was defined by the angle of the proximal urethra and trigonal surface of bladder on Valsalva maneuver (14). Patients with a RVA of more than or below 140° were classified as Green Type II and III, respectively. RVA was discriminated by 140 degree as open RVA (over 1400) and intact RVA (below 1400). Position of the bladder neck determined relative to the posterior inferior margin of the symphysis pubis (SP) was measured, the difference between the measurements on maximal Valsalva and at rest was defined as BND with a numerical value. The hiatal AP (AP) diameter which indicates hiatal ballooning was measured on maximal Valsalva as the shortest distance from the posteroinferior margin of the pubic symphysis to the anterior margin of the most central aspect of the puborectalis muscle in the midsagittal view.

A validated into Turkish language version of Michigan Incontinence Severity Index (M-ISI) was used to assess the quality of life related to the incontinence (15). M-ISI has ten items, consisting of a total M-ISI domain (the sum of items 1-8) and a distinct Bother domain (the sum of items 9 and 10). The total M-ISI score consists of three subdomains (items 1-3 for stress urinary incontinence [SUI], items 4-6 for UUI, and items 7 and 8 for PU).

The responses for each item range from 0 to 4 on a Likert-type scale, with higher values representing greater symptoms and greater bother. The minimally important difference has been determined for the following domains/subdomains: total M-ISI (4 points), SUI (2 points), UUI (2 points), and PU (1 point) (16).

Nocturia was defined as the episodes of involuntarily micturition reflex during sleep. The severity of nocturia was assessed by the clinician using a non-validated Likert type scale (0 – 3) (17). Nocturia was scored as follows: 0 no, 1=one episode, 2=two to three episodes, 3=four or more episodes.

The primary clinical hypothesis was that the subjective incontinence severity can be predicted by several possible factors consisting of maternal, obstetric and ultrasonographic variables including age, parity, gestational week, fetal biometry, nocturia frequency, EFW, RVA, Cystocele degree, URA, Hiatal AP diameter and BND. Multiple linear regression analysis was used to test this hypothesis. SPSS-22 software was used for data analysis. The Kolmogorov-Smirnov test was used to assess normality. Paired T test was performed to compare normally distributed variables. Parameters were given as mean ± standard deviation (SD), minimum, maximum and median. A p-value of less than 0.05 was considered significant.

3. Results

Forty-six pregnant women were included in this study. One pregnant woman was excluded from the study due to painless cervical dilatation. Seven women were excluded from the statistical analysis, 4 out of those was due to low image quality and three women was excluded due to observed levator co-activation. A total of 38 women was included to the final statistical analysis.

Mean age was 26.37 ± 5.8 and gestational week was 37.2 ± 3.5 (Min = 28, Max = 41). Median parity was found to be 1 with an interquartile range of 2 (Range = 0-5). Mean BMI (kg/m2) was 29.32 ± 5. Descriptive statistics were given in Table 1.

Table 1. Demographic and obstetric outcomes, pelvic floor ultrasound results and subjective scale measures

	Min	Max	Mean	SE	SD
Age (year)	17	39	26.37	.94	5.79
Parity (n)	0	5	1.11	.20	1.23
Gestational week	28	41	37.26	.58	3.55
BMI (kg / m^2)	18.37	41.55	29.32	.81	5
BPD (mm)	73.0	96.3	88.45	.92	5.67
HC (mm)	260.3	347.2	317.95	3.23	19.92
EFW (gr)	1356.0	3962.0	2972.16	104.20	642.36
Nocturia (n)	0	3	1.90	.12	.76
Hiatal AP-Rest (mm)	36.6	77.9	54.10	1.39	8.57
Hiatal AP-Valsalva (mm)	37.4	83.0	58.30	1.57	9.71
Cystocele (mm)	-25.1	2.1	-11.97	1.17	7.17
Urethral rotation (degree)	2.0	67.0	26.79	2.72	16.80
Retrovesical angle (degree)	66.0	174.0	129.18	4.88	30.90
Bladder neck descent (mm)	.30	22.40	6.75	.85	5.22
SUI	0	12.00	2.68	.58	3.61
UUI	0	12.00	3.31	.62	3.83
PAD	0	8.00	1.52	.36	2.20
BOTHER	0	6.00	.87	.22	1.36
Total M-ISI SCORE	0	29.00	7.53	1.33	8.20

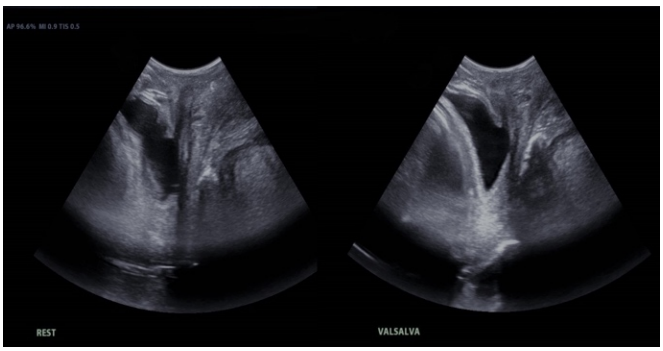

Fig. 1. Changes in pelvic floor mobility of a pregnant women at rest and on Valsalva

Hiatal AP diameter, RVA and BND on Valsalva did not significantly correlate with gestational week ($p = 0.292$, $r = 0.096$; $p = 0.079$, $r = 0.159$; $p = 0.901$, $r = 0.011$, respectively). Hiatal AP diameter, RVA and BND on Valsalva did not differ regarding gestational week in women over and below 39 weeks ($p = 0.378$, $p = 0.176$ and $p = 0.874$, respectively). UR angle, Hiatal AP diameter, BND and RVA on maximal Valsalva did not differ with estimated fetal weight above and below 3000 gr ($p = 0.258$, $p = 0.824$, $p = 0.499$ and $p = 0.822$, respectively).

URA was significantly increased in women after 39th gestational week ($p = 0.037$, $t = -2.17$). BND was positively correlated with URA and also the extent of the cystocele ($p = 0.031$, $r = 0.351$; $p = 0.014$, $r = 0.222$, respectively). Both URA and BND did not show a significant correlation with subjective scores (SUI domain: p=0.571 and p=0.615, r=0.052 and r=0.046, respectively; Bother domain: p=0.390 and p=0.912, r=0.078 and r=0.010).

Total severity and bother scores of the M-ISI scale was found as similar among women with open (>1400) RVA and intact (<1400) RVA ($p = 0.556$ and $p = 0.779$, respectively). Total severity score of M-ISI was not statistically significant regarding urethral and bladder neck mobility measures, gestational week, biparietal diameter (BPD) of the fetus, estimated fetal weight, extent of cystocele over symphysis pubis ($p > 0.05$). Nocturia episodes was significantly related with M-ISI severity score ($p = 0.008$, $t = -2.833$). Multiple regression analysis showed a significant effect on the subjective incontinence severity ($F(13,108) = 1.967$), $p < .001$), with $R2=0.191$ suggesting that 19.1% of the variation was predicted by the possible factors. Standard residual and Cooks' distance were between -1.85 to 2.89 and 0 to 0.169, respectively. Looking at the unique individual contributions of the predictors, the results showed that only nocturia frequency ($\beta=.379$, $t=4.035$, $p=.000$) positively predicted the incontinence severity score (Part correlation: 0.349).

4. Discussion

The findings of this study showed that the pelvic floor ultrasound parameters of the anterior compartment did not predict the subjective urinary incontinence severity of women in their third trimester of pregnancy. The measured parameters did not show significant correlation as gestational week changes. Subjective incontinence severity scores did not change with anterior prolapse, gestational week, fetal weight and fetal BPD. Nocturia was found to contribute for subjective impaired urinary function.

Female urinary incontinence is a common but neglected issue during pregnancy. However, the quality of life of pregnant women barely gets affected by urinary incontinence (11). A cross-sectional study showed that the urinary incontinence is not uncommon in women even during their first pregnancy (8). While stress urinary incontinence was the most common type among others with 65%, more than half of the women included in the study in their third trimester reported that their daily activities were not affected from urinary incontinence (8). Another cross-sectional study comparing the prevalence and severity of urinary incontinence in between first and third trimester showed that the incidence of urinary incontinence is doubled in third trimester comparing with the first trimester of pregnancy (19% vs. 39.8%, $p = 0.008$) (18). Half of the women reported to have stress incontinence without significant effect on their daily life activities, however their quality of life was found to be changed in particular domains including physical, mental and social. Interestingly, urinary frequency affected the four of every ten women and caused distress in seven of every ten women (18). Similarly, nocturia frequency was significantly related with incontinence severity scores in the current study, moreover it positively predicted the incontinence severity score. We believe that the idea of being pregnant may suppress the general complaints related with changes in pelvic floor mobility.

Dietz et al showed that higher degrees in URA and BND level was correlated with the anterior vaginal wall relaxation (19). This relation was also significant in the current study with a moderate correlation between the degree of cystocele and BND level. Another study of Dietz et al showed that the bladder and urethral mobility increase as pregnancy progresses when compared the non-pregnant women with women in their third trimester of pregnancy, but not with the first trimester.3 Similar to Dietz, Chan et al showed significant descent in bladder neck, apex and anorectal junction as the pregnancy progresses (20). In contrary, the current study did not support the Dietz's hypothesis with no significant relation in between the gestational week and anterior compartment mobility. These different findings may be caused by relatively a small number of cohort. However, a prospective longitudinal study conducted in Norway showed that the majority of the vaginal POP-Q measures made a cranial shift from mid to late pregnancy (21). They interpreted that the larger uterus fills the bony pelvis, pends anteriorly over the rim of the bony pelvis, and therefore pulls the cervix and vagina in a cranial direction, in accordance with the literature (22). Our findings that shows a non-significant relation of anterior compartment mobility with the gestational week can be interpreted as in accordance with Reimers et al.

The strengths of this study are its prospective nature and the use of pelvic floor ultrasound in transperineally approach. It is known that pregnant women find the transperineal ultrasound more comfortable than digital examination (23). This approach may become more common in the research settings, and therefore should be studied more extensively. The logistic regression model that showed the nocturia as the only factor in predicting the subjective urinary incontinence severity can be considered as the other strength of the study.

A limitation of this study is the lack of an a priori power analysis. Furthermore, the size of the study is relatively small, potentially giving rise to bias in showing the change of anterior compartment mobility parameters as the pregnancy progress. Another limitation is the lack of detailed POP-Q data.

The pelvic floor ultrasound parameters of the anterior compartment may not predict the subjective urinary incontinence severity in third trimester of pregnancy. Nocturia episodes was the only determinant of impaired subjective urinary dysfunction. Urethral and bladder mobility and levator hiatus measures did not significantly differ with regard to neither gestational week nor estimated fetal weight and BPD.

Conflict of interest

None to declare.

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None to declare.

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Effects of COVID-19 pandemic on management of acute cholecystitis: A single tertiary center's experience

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Abstract

Following the spread of novel coronavirus (COVID-19) pandemic, surgical associations have issued their different recommendations for managing the acute cholecystitis (AC) clinic during the pandemic. We aimed to examine the effects of the COVID-19 pandemic period on our clinical approach in patients who presented to the emergency department with abdominal pain and were diagnosed with AC. Medical records of patients diagnosed with AC in the emergency room between 11 March 2020 and 10 March 2021 and in the same period of one year before the pandemic were retrospectively reviewed. Patients were divided into 2 groups as COVID-19 period (Group 1) and non-COVID period (Group 2). Demographics and clinical characteristics, treatment modalities, and outcomes of these two groups were compared. The number of patients diagnosed with AC in the emergency department decreased during the ongoing COVID-19 pandemic. When the time between the onset of the complaints and the admission to the emergency service was evaluated, no statistically significant difference was found between the groups ($p>0.05$). The distribution of cholecystitis type and TG18 severity grading for AC were similar in both groups ($p>0.05$). While percutaneous cholecystostomy (PC) is more preferred in the treatment of AC during the pandemic period and the number of delayed interval laparoscopic cholecystectomy decreased, AC management was similar in both periods with no significant statistical difference ($P>0.05$). In conclusion, our clinical approach and management in the treatment of AC did not differ when compared to the pre-pandemic period.

Keywords: acute cholecystitis, COVID-19, treatment modality, clinical approach

1. Introduction

Acute cholecystitis (AC) is one of the most common gastrointestinal diseases and is considered a surgical emergency. The most common cause of AC is gallstone-related but may also be associated with diabetes, immunosuppression, chronic kidney disease, viral illness, hemoglobinopathies, or vasculitis (1,2). The severity of AC was classified into three grades by Tokyo guidelines 2018 (TG 2018), as mild (grade I), moderate (grade II), and severe (grade III) (3,4). Early cholecystectomy (EC) during first admission is the preferred treatment method in patients suitable for surgery. Laparoscopic cholecystectomy (LC) is considered the "gold standard" for the surgical treatment of AC (5). Surgical management of critically ill patients remains a controversy due to high risk of postoperative morbidity and mortality (6,7). Therefore, percutaneous cholecystostomy (PC) can be valuable treatment as an alternative to EC in high-risk patients and in those with moderate or severe cholecystitis (8).

The novel coronavirus (COVID-19) pandemic was first reported in December 2019 in Wuhan, Hubei Province of China, and spread rapidly all over the World. On March 11, 2020, The World Health Organization (WHO) declared COVID-19 a global pandemic and recommended that all possible intervention procedures and surgeries be postponed except in very urgent situations (9). The American College of Surgeons COVID-19 Elective Case Triage Guide (2020) advised that LC should be performed healthy patients with AC to minimize hospital stay, and if the patient is too high risk for surgery or operating room conditions are not available, IV antibiotics should be administered. In this guideline, PC was recommended in addition to antibiotic administration for patients who did not improve clinically with antibiotics and had signs of sepsis.The present study aims to examine the effects of the pandemic period on our clinical approach in patients admitted to the emergency department with the complaint of abdominal pain and diagnosed with AC.

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2. Materials and Methods

This study was carried out in the General Surgery Clinic of Ondokuz Mayis University Medical Faculty Hospital. Ethical approval was obtained from the local ethics committee for the study (IRB approval number OMU: 2021/168). The first COVID-19 case in Turkey was announced on March 11. The medical records of patients who presented to the emergency department with the complaint of abdominal pain between 11 March 2020 and 10 March 2021 and in the same period of one year before the pandemic and were diagnosed with AC according to the Tokyo 2018 guideline were retrospectively reviewed. Patients with acute cholangitis or acute pancreatitis accompanying AC and outpatients whose data were not accessible were excluded this study. Patients were divided into 2 groups as COVID-19 period (Group 1) and non-COVID period (Group 2). Age, gender, time between the onset of complaints and admission to the emergency room, C-reactive protein (CRP), white blood count (WBC), alanine transaminase (ALT), aspartate transaminase (AST), total and direct bilirubin, TG18 severity grading for AC, type of cholecystitis, COVID 19 status, patient management, length of hospital stay, bile duct injury and mortality rates were determined as parameters to be investigated. During the pandemic, chest computed tomography (CT) was performed and COVID-19 test was applied to all patients who were asked for surgical consultation in the emergency department. Patients with suspicious lesions showing COVID-19 pneumonia on chest CT were approached as positive for COVID-19, and optimum isolation conditions were attempted to be provided in these patients. PCR test results of the patients were followed. Patients with positive PCR tests were admitted to COVID-19 isolation wards. In the presence of symptoms such as shortness of breath, cough, fever, or worsening of vital signs, COVID-19 tests and chest CT were repeated, even if this was due to any other medical reason.

2.1. Statistical analysis

For statistical data analysis SPSS 21 (Statistical Package for the Social Sciences) program was used. As a first step in SPSS, descriptive statistics and normalization test was performed to analyze if the data were normally distributed. As a result of the normalization test according to Kolmogorov Smirnov the data was not normal distributed. Considering that the distribution was not normal, Mann Whitney U test which is a nonparametric test was used to find significance. Also Chi-Squared test was performed for the data.

3. Results

In the present study, one year covering the COVID-19 period and the other one year non-COVID period, 91 patients in the emergency department before the pandemic and 67 patients during the pandemic period was diagnosed with AC. The number of patients diagnosed with AC in the emergency department decreased during the ongoing COVID-19 pandemic. The age and gender distribution were similar between the groups ($p>0.05$). When the time between the onset of the complaints and the admission to the emergency service was evaluated, no statistically significant difference was found between the groups ($p>0.05$). Laboratory values were presented in Table 1 ($p<0.05$). The distribution of cholecystitis type and TG18 severity grading for AC were similar in both groups ($p>0.05$). When the treatment approaches of AC were evaluated, although there was no statistically significant difference between the groups, it was observed that more PC was preferred in addition to antibiotic treatment during the pandemic period, and the number of delayed interval laparoscopic cholecystectomy decreased. There was no statistical difference between the groups in terms of length of hospital stay (LOS) (Seven days for group 1 and 6 days for group 2, $p>0.05$).

Strasberg Type A bile duct injury occurred in 1 patient in Group 1 and in 2 patients in Group 2 ($p>0.05$). Bile leakage managed with endoscopic retrograde cholangiopancreatography and biliary stenting in all patients. While the COVID-19 test was positive in 2 patients at the time of diagnosis of AC during the pandemic period, COVID-19 was detected in 4 patients who were hospitalized for AC and whose tests were repeated with suspicious symptoms. Mortality rates were similar in both groups, four (6%) patients in Group 1 and 6 (6.6%) patients in Group 2 died ($p>0.05$). One of the two patients who underwent open cholecystectomy (OC) due to gallbladder perforation during the pandemic period contracted COVID-19 in the postoperative follow-up and died secondary to COVID-19 pneumonia. The other patient who was operated on died due to acute coronary syndrome. One patient who underwent PC died due to pulmonary embolism and the other patient with a history of lung cancer died due to sepsis. In the non-COVID period, three patients, one of whom was a postoperative patient, died due to sepsis, two patients died due to acute coronary syndrome and 1 patient died due to pulmonary embolism.

4. Discussion

All current guidelines recommend LC as the gold standard treatment for AC, as it provides better outcomes in terms of mortality, morbidity, and postoperative hospital stay. World Society for Emergency Surgery (WSES) guidelines emphasize that early laparoscopic cholecystectomy (ELC) should be performed as soon as possible (11) Murray et al. (2018) investigated the timing of surgery for AC and reported the rate of EC as 52.7% in the USA and 15.7% in the UK. They noted that the rate of LC in these patients was 82.8% and 37.9% for the USA and UK, respectively. We mostly do not prefer EC in the treatment of AC due to the high intensity of the operating room caused by working in a tertiary center. While our rate of ELC was 11% in the pre-pandemic period, this rate was 10.4% in the pandemic period, and the rates are similar. The similarity of the results indicates that early surgery is performed in emergency conditions in patients who absolutely need surgery in both periods.

Table 1. Demographics and clinical features, laboratory values, management of acute cholecystitis and treatment outcomes of patients admitted to the emergency department due to AC during the COVID-19 pandemic and pre-pandemic period

	Group I (COVID-19)	Group II (Non-COVID)	P value
Total number fo patients	67 (42.4%)	91 (57.6%)	
Age	63.6 ± 17.04	62.99 ± 17.63	0.827
Gender			
Male	32 (47.8%)	44 (48.4%)	0.941
Female	35 (52.2%)	47 (51.6%)	
Time between the onset of complaints and admission to the emergency room			
< 24 hours	18 (26.9%)	25 (27.5%)	0.985
≥ 24 hours and < 48 hours	14 (20.9%)	18 (19.8%)	
≥ 48 hours	35 (52.2%)	48 (52.7%)	
C-reactive protein (CRP) (mg/L)	145.7 ± 120	113.3 ± 82.9	0.924
White blood count (WBC) ($\times 10^9$/L)	14194 ± 8201	13092 ± 7079	0.273
Alanine transaminase (ALT) (IU/L)	150.2 ± 205.7	114.1 ± 214.8	0.108
Aspartate transaminase (AST) (IU/L)	169.7 ± 251.4	132.7 ± 337.9	0.065
Bilirubin total (mg/dL)	2.09 ± 2.38	2.15 ± 2.49	0.707
Bilirubin direct (mg/dL)	1.43 ± 2.23	1.45 ± 2.06	0.820
Tokyo Guidelines 2018 severity grading for acute cholecystitis			
Grade I (mild) acute cholecystitis	33 (49.3%)	56 (61.5%)	0.123
Grade II (moderate) acute cholecystitis	21 (31.3%)	16 (17.6%)	
Grade III (severe) acute cholecystitis	13 (19.4%)	19 (20.9%)	
Type of cholecystitis			
Calculous	63 (94%)	84 (92.3%)	0.674
Acalculous	4 (6%)	7 (7.7%)	
COVID 19 Status			
Positive at the time of diagnosis	2 (3%)	-	
Positive on follow-up time	4 (6%)	-	
Index admission early laparoscopic cholecystectomy			
No	67 (100)	88 (96.7%)	0.133
Yes	0	3 (3.3%)	
Index admission open cholecystectomy			
No	60 (89.6%)	84 (92.3%)	0.371
Yes	7 (10.4%)	7 (%7.7%)	
Non-operative management			
Conservative management with antibiotics	42 (62.7%)	69 (75.8%)	0.092
Conservative management with antibiotics and percutaneous cholecystostomy	18 (26.9%)	12 (13.2%)	
Delayed interval laparoscopic cholecystectomy			
No	55 (82.1%)	64 (70.3%)	0.065
Yes	12 (17.9%)	27 (29.7%)	
Length of hospital stay (day)	10.43 ± 13.29	7.32 ± 6.31	0.172
Bile duct injury			
No	65 (97%)	90 (98.9%)	0.386
Yes	2 (3%)	1 (1.1%)	
Mortality			
No	63 (94%)	85 (93.4%)	0.573
Yes	4 (6%)	6 (6.6%)	

Following the spread of the COVID-19 infection, surgical associations have issued their recommendations for managing the effects of the pandemic on clinical practice. The UK's Intercollegiate General Surgery Guidelines on COVID-19 (2020) recommended non-surgical management whenever possible during the outbreak. The American Society of Gastrointestinal and Endoscopic Surgeons (2020) and the European Association of Endoscopic Surgery (2020), have recommended a patient- and hospital-centered approach. On the other hand, the American College of Surgeons (2020) emphasized that planned ELC through real-time reverse transcriptase polymerase chain reaction testing may be an option to consider. In an article published from Turkey, it was noted that LC in AC is a high-risk procedure for surgical teams during the COVID-19 pandemic. It was stated that PC is a potential alternative treatment method (17).

After WHO declared the COVID-19 pandemic, a study by the National Syndromic Surveillance Program found a 42% reduction in emergency room visits compared to historical trends, as well as a significant decrease in AC admissions to hospital (18). Due to the pandemic conditions, TG 18 grade I admissions decreased significantly, while severe cases (TG 18 grade II and III) remained stable. Cholecystectomy rates worldwide have fallen (19). In a recent study, surgeons opted for a non-surgical approach because of the COVID-19

pandemic in 97.2% of patients with mild-to-moderate cholecystitis defined according to the TG 18. The reason why non-surgical follow-up was preferred in this study was associated with the simultaneous service of the hospital operating room (20). However, it was determined that the LOS of the patients increased significantly due to the non-surgical treatments preferred during the pandemic period (Martínez et al. 2021). In our series, the number of patients diagnosed with AC in the emergency department during the pandemic period decreased. Although the number of TG 18 grade I patients decreased, the TG 18 grades were similar when both periods were compared and no statistically significant difference was found. While PC is more preferred in the treatment of AC during the pandemic period and the number of delayed interval laparoscopic cholecystectomy decreased, AC management was similar in both periods with no significant statistical difference (P>0.05).

Acalculous acute cholecystitis (AAC) is an acute necroinflammatory disease of the gallbladder with high morbidity and mortality rates. Most of these patients have trauma, major surgery, burns, cardiopulmonary resuscitation, mechanical ventilation, long-term total parenteral nutrition, and multiple risk factors that suppress the immune system (22, 23). COVID-19 infection increases the expression of proinflammatory cytokines such as IL-6 and tumor necrosis factor alpha. These cytokines activate the coagulation cascade and explain the thrombosis of vascular structures in the gallbladder and the formation of AAC with ischemic gangrene (24, 25). In the light of this information, it was investigated whether there was an increase in the frequency of AAC in our clinic during the pandemic period, but no significant difference was found compared to the pre-pandemic period.

The COVIDSurg Collaborative group stated that 26.1% of 1128 patients who underwent surgery during the COVID-19 pandemic developed COVID-19 infection, and about half of these patients progressed with pulmonary complications, and 23.8% of the patients died from these causes (26). Our mortality rates were similar between the groups in the patients we followed up for AC in our series. Discussions intensified over the question of whether we should change our surgical indications for emergencies in this global situation. Despite all these controversies, LC remains the first-line treatment for AC even during the COVID-19 pandemic (27). It is known that the COVID-19 virus is found in blood, gastrointestinal tissues, peritoneal fluid, feces, nasopharyngeal swab, sputum or tracheal aspirate (Brat et al. 2020). However, although SARS-Cov-2 RNA has recently been detected in the peritoneal cavity, there is no evidence to suggest the presence of the virus in surgical smoke. It is unclear whether aerosolized viral particles were exposed during laparoscopy. No evidence emerged that the risk of COVID-19 infection due to LC could be higher than OC for either patient or healthcare workers. Many studies recommend the use of ultralow particulate air filters to remove most viral particles and filter the pneumoperitoneum during laparoscopy (29, 30). Since we could not provide this filter in our hospital, we did not have the opportunity to use it during the ongoing pandemic.

The retrospective design of the study, the exclusion of patients whose data could not be reached, and the small number of patients are the main factors limiting the study. In our study, although the number of patients with AC who applied to the emergency department during the pandemic period decreased, the clinical approach and management in the treatment of AC did not differ when compared to the pre-pandemic period. Due to the large population we provide health services and the high density of operating rooms secondary to working in a tertiary center, we generally do not prefer early surgery in the treatment of AC unless it is necessary. We attribute the similarity of our results to this situation. Although the results in the two periods were similar, four of patients who were hospitalized for treatment with the diagnosis of AC during the ongoing pandemic period, were infected with COVID-19 and one of these patients who underwent emergency OC due to gallbladder perforation, died secondary to COVID pneumonia in the postoperative period. In the light of the literature, we should never forget the risk of morbidity and mortality caused by being infected with COVID-19 in patients who underwent surgery during the pandemic period.

Our clinical approach and management in the treatment of AC did not differ when compared to the pre-pandemic period. While emphasizing that the protection of healthcare providers is the top priority to ensure the sustainability of the healthcare system, we recommend a patient- and hospital-centered approach in the treatment of AC during the pandemic period.

Conflict of interest

None to declare.

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None to declare.

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The effects of quarantine on postpartum depression, sleep quality and breastfeeding: Comparison of two different intensity period

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Abstract

The aim of this study is to investigate the effects of quarantine/social isolation on maternal depression, breastfeeding and sleep quality in mothers who have just given birth during the pandemic period that has affected the whole world. This cross-sectional study included women who gave birth during either in the first peak of the first wave (April, 2020) or the end of the first peak (July, 2020) of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic in a tertiary pandemic regional referral centre. A total of 210 patients were enrolled to the study. The research data were collected using specific questionnaires including the Pittsburgh Sleep Quality Index (PSQI), the Edinburgh Postpartum Depression Scale (EPDS) and the Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF). As a result, maternal postpartum depression and sleep quality scores did not differ significantly among postpartum women with different timelines according to the intensity of the SARS-CoV-2 pandemic (p=0.205 and p=0.352, respectively). The Breastfeeding Self-Efficacy Scale was significantly better (p=0.000) in the post-quarantine period than in the early stages of the pandemic when there were strict quarantine regulations. In conclusion, Sleep quality and postpartum depression remained unchanged with regard to the severity of the quarantine among women who gave birth during the SARS-CoV-2 pandemics. The breastfeeding self-efficacy of mothers was found as improved in the post-quarantine period.

Keywords: breastfeeding, postpartum depression, quarantine effects, sleep quality

1. Introduction

Coronavirus Diseases-19 (COVID-19) pandemic had devastating effect on public health, mental health and caused financial crisis at global level (15). Vulnerable populations including children, elder, disabled people and pregnant women were the most affected. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic condition creates an additional risk factor likely to increase the stress on pregnant women who are already prone to depression and anxiety (4, 12, 28). Besides that being pregnancy is already known as an important risk factor for having more severe disease during the pandemic, pregnancy may be a delicate state for possible social and mental consequences (28).

The mostly studied mental health issues including anxiety and depression were found to be impaired in pregnancy during the outbreak (4, 28). Quarantine has physiological and psychological impacts on individuals and social groups (9). Emotional and mental wellbeing of new mothers can seriously be affected from the possible long-term consequences of quarantine.

Postpartum depression may negatively affect a woman's self-esteem, self-efficacy, children's care and development, and responsibilities and roles related to her family and spouse (22). Therefore, early diagnosis and treatment of postpartum depression is important. Unfortunately, despite its negative impact on maternal health, postpartum, postpartum depression is often under-diagnosed and under-treated (5). The period of postnatal mothers with poor mental or emotional health are less likely to breastfeed (26). In addition, breastfeeding has a positive psychological impact on the postpartum mother period, improving her well-being, increasing her self-efficacy and her interaction with the infant (19, 21). The relationship between breastfeeding and postpartum depression may be bidirectional in nature, suggesting that while postpartum depression may reduce rates of breastfeeding, not engaging in breastfeeding may increase the risk of postpartum depression (14). Sleep disturbances may affect mood or even precede or

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develop as a result of mood disorder as the first symptom of new or recurrent depressive episodes (3). Breastfeeding of the baby in the postpartum period may protect against depression or help the symptoms improve faster (14). Impaired maternal sleep may disrupt the mother's mood and thus impair breastfeeding self-efficacy (22, 18).

Depression, breastfeeding and sleep are three important factors that can affect the emotional/mental wellbeing of mothers following birth. The detrimental mental impacts of quarantine and social isolation can be massive and long lasting (7). The aim of this study was to investigate the extent of quarantine/social isolation effect on maternal depression, breastfeeding and sleep quality in mothers recently gave birth during the pandemic.

2. Methods and Methods

This cross-sectional study included women who gave birth during either in the first peak of the first wave (April, 2020) or the end of the first peak (July, 2020) of the SARS-CoV-2 pandemic in a tertiary pandemic regional referral center. April and July of 2020 were the most and least intense of the first peak of the first wave of the pandemics in Turkey, respectively. Strict restrictions were in effect in April, 2020 while easening the restrictions and re-opening for tourism were in action in July, 2020 in Turkey (T.R. Ministry of Health Covid-19 Information Platform [web page]., 2020).

Table 1. Patient characteristics and demographics

	Overall				April & June
	Mean	**SD**	**Median**	**IQR**	**P***
Age	28.15	5.753	27.00	8	0.226[a]
Parity	2.28	1.131	2.00	2	0.919[b]
	April	June	April	June	
	15 (20%)	15 (20%)	15 (20%)	15 (20%)	0.319[c]
Education level	2.18	.998	2.00	2	0.068[c]
Profession	.07	.357	.00	0	0.211[c]
Education of partner	2.53	.999	3.00	1	0.579[c]
Profession of partner	.96	.218	1.00	0	0.412[c]
Health insurance	.95	.247	1.00	0	0.485[c]
Support of mother	.22	.416	.00	0	0.065[c]
Covid-19	.08	.270	.00	0	0.299[c]
Delivery method	1.37	.485	1.00	1	0.562[c]
Newborn incubator	.11	.317	.00	0	0.120[c]
Planned pregnancy	.83	.378	1.00	0	0.094[c]

*Sub-groups comparison between patients evaluated in April (n= 98) and in June (n=106). [a]Independent Samples T test, [b]Mann Whitney U test, [c]Chi-Square tests

Mothers aged between 18 and 44 years, who gave birth to healthy babies following a low-risk pregnancy. Women with active SARS-CoV-2 infection, an ongoing or a history of neuropsychiatric or psychological disease, any chronic health problems that may affect breastfeeding and sleep quality, newborns with anomalies, those with a birth weight below 2500 g, those who gave birth before <37 weeks and those who had perinatal problems were excluded. Syrian refugees who were not able to make phone calls were also excluded.

Primary outcome was to capture the emotional/mental wellbeing related to the motherhood of women during the SARS-CoV-2 pandemic including the postpartum depression status, sleep quality, breastfeeding confidence/self-efficacy and infant feeding practices. Our null hypothesis was that emotional wellbeing of new mothers did not change by the intensity of the SARS-CoV-2 pandemic. To test the null hypothesis, Edinburgh Postpartum Depression Scale (EDPS), Pittsburgh Sleep Quality Index (PSQI) and the Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF) were performed by phone interview. Women were asked to complete the questionnaires at 6-8 weeks after birth in order to avoid misleading results due to the motherhood sadness. The infant feeding practices were categorized as exclusive breast milk, breast milk and formula, or exclusive formula, according to the WHO criteria (29). Social, demographic and obstetric data were noted. All patients gave written informed consent and approved for publication before data collection. All procedures were in accordance with the 1964 Helsinki Declaration and its later amendments. This study followed the principles of the Declaration of Helsinki and was approved by the Ethics Committee University of Health Sciences Turkey, Sehit Prof. Dr. Ilhan Varank Sancaktepe Training and Research Hospital (registry no: 20/22), Scientific Board of the Health Ministry and the local institutional administration board approved the study.

2.1. Measures

2.1.1. Edinburgh Postnatal Depression Scale (EPDS)

This scale, which aims to determine the risk of depression in women in the postpartum period, was prepared for screening purposes and is not intended to diagnose depression. EPDS is a self-report scale in 4-point Likert format, consisting of 10 items. Answers consisting of four options are scored between 0 and 3, the lowest score that can be obtained from the scale is 0 and the highest score is 30. In the evaluation, items 1, 2, and 4 were scored as 0,1,2,3, while items 3, 5, 6, 7, 8, 9, and 10 were scored as 3,2,1,0. The cut-off point of EPDS was previously calculated as 13, and women with a scale score of 13 or more were considered as in the risk group (16).

2.1.2. Breastfeeding Self-Efficacy Scale-Short Form (BSES-SF)

The BSES-SF is a 14-item self-administered instrument derived from the original 33-item BSES that measures breastfeeding confidence (11). All items are in positive direction and are preceded by the phrase ‘‘I can always’’ and rated on a 5-point Likert scale, ranging from 1 (not at all confident) to 5 (always confident). Total scores range from 14 to 70, with higher scores reflecting more significant levels of breastfeeding self-efficacy.

2.1.3. Infant Feeding Practices

The questionnaire asked for current infant feeding (exclusive breast milk, breast milk and formula, or exclusive formula).

Feeding practices were then categorized as exclusive breastfeeding (EBF) (exclusive feeding on mother´s own milk) or mixed breastfeeding (MBF) (infant who had received predominantly formula along with breast milk or other milk, without complementary foods) according to World Health Organization criteria (29).

2.1.4. Pittsburgh Sleep Quality Index (PSQI)

Sleep was assessed using the 19-item PSQI, which is a self-report questionnaire that assesses sleep quality and disturbances during the previous month (8). The seven component subscales include subjective sleep quality (i.e., subjective self-rating of sleep quality), sleep latency (i.e., how long it takes to fall asleep at night), sleep duration (i.e., amount of nighttime sleep), habitual sleep efficiency (i.e., percentage of time asleep when in bed), sleep disturbances (i.e., number of awakenings during the night), use of sleep medication, and daytime dysfunction (i.e., difficulty staying awake during the day). This scale has good internal consistency, test-retest reliability, and validity. Poorer sleep quality is indicated by higher PSQI global and subscale scores, with a global score of > 5 indicating poor sleep in the general population. The diagnostic sensitivity and specificity were 89.6% and 86.5% respectively in one study among adults with and ithout sleep disorders (2). Several studies have used the PSQI with postpartum women (17).

2.2. Statistics

The collected data were analyzed with SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The normality of the demographic data was assessed with the Shapiro-Wilk test. Demographic data were summarised as the median and interquartile range for non-normally distributed data and as the mean and standard deviation for normally distributed data. Specific statistical tests were stated in each tables. A p-value of less than 0.05 was considered significant.

3. Results

A total of 210 patients were enrolled to the study. Five of those were excluded due to psychiatric disorders (n=2), low data quality (n=3) and not giving consent (n=1). A total of 204 women were included to the final analysis.

Ninety-eight women (48%) gave birth during the strict quarantine regulations in April and 106 (52%) gave birth while controlled social life regulations were in effect following the end of the first wave of the pandemic. Out of all women, 7.8% (n=16) previously had SARS-CoV-2 infection. Social and demographic features of women were found as similar in both different timelines (Table 1).

Maternal PSQI and EPDS did not significantly differ between postpartum women in different timeline according to the intensity of the SARS-CoV-2 pandemic (Table 2). BFES-SF were found decreased in women who gave birth during the strict quarantine when compared to women in post-quarantine period with a mean difference of 4.5 points (95% CI: 6.28-2.66, p<0.001, Table 2). Out of all women, 70.59% (n=144) reported that they solely breastfed, 27.94% (n=57) required additional formula and 1.47% (n=3) used formula exclusively. The use of additional formula did not affect the PSQI and EPDS test scores with a mean difference of 0.105 and 0.614, respectively. (Independent Samples T test; p=0.804 and p=0.411, respectively).

In the postpartum period, depressive symptoms are observed in approximately 80% of mothers in the first two weeks and these symptoms regress spontaneously after two weeks. The depressive mood seen in this period is defined as “motherhood sadness-baby blues” and is considered as an entity separate from postpartum depression (24). Considering this situation, mothers with 2 weeks-18 months old babies were included in the study, considering that the application of EPDS to mothers who did not complete two weeks after birth would cause misleading results.

Table 2. Comparison of maternal depression, breastfeeding and sleep quality between postpartum women in different timeline according to the intensity of the SARS-CoV-2 pandemic

	Overall		**April**[a]	**July**[b]			*P*
	Mean±SD	**Min-Max**	**Mean**±SD	Mean± SD	95% CI	Mean Difference	
EPDS (n=204)	3.93±4.85	0-19	4.38±5.21	3.51±4.48	-0.48 to 2.21	0.87	0.205
BSES-SF (n=201)[*]	64.54±6.72	29-70	63.2±7.83	66.68±4.61	-6.28 to -2.66	-4.47	0.000
PSQI (n=204)	7.04±2.79	1-20	6.85±3.26	7.22±2.27	-1.15 to 0.41	-0.37	0.352

Independent Samples T Test. [a] Denotes the strict quarantine regulations, [b] controlled social life without restrictions. [*] Three patients were excluded due to inability to breastfeeding BSES-SF: Breastfeeding Self-Efficacy Scale-Short Form, EPDS: Edinburgh Postnatal Depression Scale, PSQI: Pittsburgh Sleep Quality Index.

4. Discussion

This study showed that women who gave birth during the COVID-19 pandemic had poor sleep quality and relatively low risk for postpartum depression. A vast majority of women (98.5%) breastfed with or without formula support. The postpartum depression risk and the sleep quality of mothers were found similar when compared within two distinct period of the pandemic including the peak of first wave with strict quarantine regulations and after the end of the first wave where pro-active regulatory measures were softened. The breastfeeding self-efficacy was found as improved in post-quarantine period.

Postpartum women tend to experience more psychological disturbances due to additional concerns about their babies when facing a major public health event (12). Postpartum depression and poor sleep quality are important health problems that seriously affects the quality of life of postpartum women and, care and nutrition of their babies (10, 23). Women after giving birth may be more susceptible to depression and deterioration in sleep quality during the quarantine measures when compared to the general

population due to safety concerns for their babies, fair of getting SARS-CoV-2 infection, increased need for social support and postpartum care and their physiological and psychosocial adaptive conditions (9).

In the current study, the postpartum depression risk scores of postpartum women were found lower than the generally accepted cut-off scores. Moreover, this low-risk trend did not change in between the quarantine and post-quarantine periods. We speculate that this finding can be explained by the feeling of mothers that quarantine is helping to keep themselves and newborns safe (7). Therefore, comply with isolation and protection rules may have been unchanged during the transition from strict quarantine regulations to post-quarantine period. Adequate public information with the visual and printed media during the study setting may have increased the level of knowledge on COVID-19 in the society including pregnant and postpartum women, and therefore, may have helped to prevent from postpartum depression and its related effects (28) It is known that inadequate information about the SARS-CoV-2 infection plays an important role in increasing the levels of fear, anxiety, depression, and other symptoms (7). The quarantine precautions may disturb the sleep patterns and quality (9). Physical inactivity during the quarantine period, and the breastfeeding of mothers may cause the sleep quality to deteriorate (1). During the early phases of the COVID-19 pandemic, many people reported not being able to fall asleep early or maintain an adequate amount of sleep (13). Postpartum women are already more likely to experience sleep deprivation and chronic sleep disturbances compared to non-pregnant women (23). In this study the sleep quality scores of women in their postpartum period were found to be poor in two different periods of the quarantine. However, it was not possible to distinguish whether this effect was either due to the naturally poor sleep quality of women in the postpartum period or the quarantine effect. Despite all these findings, the decrease in the physical activity of postpartum women, particularly during the quarantine period, breastfeeding at night and the time spent by mothers for the care of their babies, and the anxiety caused by the fear of catching the disease may have a negative effect on sleep quality.

BSES-SF is a strong predictor of breastfeeding duration and level. Maternal BSES-SF is a modifiable factor that reflecs the confidence of postpartum women in breastfeeding (6). Therefore, it is important to have a better BSES-SF score for the breastfeeding continuity as well as high breastfeeding rates. In this study, the rate of pure breastfeeding and breastfeeding plus formula were found to be quite high in both quarantine periods. Early in the pandemic, there was no consensus on guidelines recommending women with COVID-19 infection to breastfeed. Those uncertainties and limited data have raised concerns about breastfeeding in women infected with SARS-CoV-2 (20). As time progress, the Royal College of Obstetrics and Gynaecology has begun to recommend the promotion and support of breastfeeding for mothers with suspected or low COVID-19 infection (https://www.rcog.org.uk/globalassets/documents/guidelines/2021-02-19-coronavirus-covid-19-infection-in-pregnancy-v13.pdf, Accessed on 25.05.2021). Supporting this information may lead to an increase in breastfeeding self-efficacy, especially in the post-quarantine period, as in our study.

However, the stress caused by strict quarantine measures in April, 2020 had deleterious psychological effects on society and breastfeeding postpartum women may have caused their self-efficacy scores to decline (27). In our study, we found impaired BSE scores during the strict quarantine period, while we observed an increase in breastfeeding self-efficacy scores in the post-quarantine period.

In conclusion, sleep quality and postpartum depression were found to be remained unchanged with regard to the severity of the quarantine among women who gave birth during the SARS-CoV-2 pandemics. The breastfeeding self-efficacy of mothers was found as improved in post-quarantine period.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Comparison of quality of life, depression and fatigue in patients with psoriasis and psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA) is a chronic inflammatory multisystemic disease. Limitations due to skin and joint involvement of the patients; can lead to negativie suffix in emotional state, social and physical activities. The aim of this study is to investigate the effects of parameters such as skin joint involvement and disease severity on factors such as fatigue, quality of life, depression, etc. in psoriasis and PsA patients. Thirty-four psoriasis and 48 PsA patients matched with each other in terms of age, sex, and other factors were included in the study. Disease severity was measured by Psoriasis Area Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Disease Activity in Psoriatic Arthritis (DAPSA) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores. In order to determine the depression status, quality of life and fatigue levels of the patients, respectively; Beck Depression Inventory (BDI), Health Assessment Questionnaire (HAQ) and Functional Assessment of Chronic Illness Therapy - fatigue scale (FACIT) scores were used. SPSS 17 for statistical evaluation (SPSS Inc. Released 2007. SPSS for Windows, Version 17.0. Chicago, SPSS Inc.) software package was used for analyses. Written informed consent was obtained from all patients who were enrolled to the study. PsA patients were found to have worse quality of life scores than psoriasis patients who were similar in terms of age, gender and other demographic characteristics. (0.22±0.36-0-0.48±0.52 $p=0.017$ respectively). There was a strong correlation between DAPSA scores and HAQ scores of the cases in the PsA group (r:0 ,615 $p<0.05$). Likewise, disease activity measured by DAPSA was found to have moderate correlation with FACIT score, and weak but statistically significant correlation with BDI score. (r: -0.578 $p<0.05$ and r:0.346 $p<0.001$, respectively). No correlation was found between NAPSI-PASI scores and HAQ, BDI - FACIT scores in both the psoriasis and PsA groups. Both psoriasis and PsA affect the quality of life, and our findings suggest that this effect is more pronounced in PsA patients. Our study supports that; the disease severity in PsA patients is related to depression, bad quality of life and fatigue level.

Keywords: psoriasis, arthritis, disease activity, inflammation

1. Introduction

Psoriasis is a common, chronic, inflammatory skin disease with remission and relapses, where genetic, immunological, and environmental factors are suggested to play a role in its etiology (1). During the course of the disease, psoriatic arthritis (PsA), a chronic inflammatory rheumatic disease that can be seen in both sexes, may develop. PsA was defined as an inflammatory arthritis associated with psoriasis, in which rheumatoid factor (RF) was generally negative (2, 3). Some attributes of PsA include distal interphalangeal (DIP) joint involvement, asymmetric distribution, dactylitis (diffuse inflammation of the finger), enthesitis, spinal involvement, and association with HLA-B27 (4, 5). Based on the above characteristic features, PsA was classified within the family of HLA-B27 associated spondyloarthropathy (3, 5). The prevalence of arthritis varies between 7-42% in patients with psoriasis, while its prevalence is 2-3% in the general population (4, 5). The prevalence of psoriasis varies between 0.1 and 2.8% in the general population, while it is between 2.6% and 7.2% in patients with arthritis (2, 6). The onset of psoriatic skin disease is usually observed in the 2nd and 3rd decades, whereas PsA appears after an average of 1 or 2 decades. Prevalence increases from the 3rd to the 6th decade. Average onset is seen between 30-55 years of age. Unlike rheumatoid arthritis (RA), men and women are equally affected (2-6). This rate is different in subgroups of the disease: In the group with spine and DIP involvement, male dominance is observed, and in the group with symmetrical polyarthritis involvement, female predominance is observed. Although the prevalence of skin disease is not correlated with the severity of joint damage, synchronized exacerbations of joint and skin complaints are seen in PsA at a rate of 30-40% (6-9).

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The severity of psoriatic nail involvement is closely related to the severity of both skin and joint disease, and DIF joint involvement is more common in such patients (5, 10, 11).

A patient survey published in 1998 by the United States National Psoriasis Foundation showed that patients with psoriasis believed this disease had profound emotional, social, and physical effects on their quality of life (12). In the said survey, most patients felt that the ineffectiveness of their treatment affected their quality of life. PsA was found to be strongly associated with reduced quality of life consistent with previous studies. Patients with PsA frequently reported emotional problems and body pain in their assessments of quality of life. Although it was shown that both psoriasis and PsA had major effects on individual's perception of quality of life, a very limited number of studies compared only cases with skin involvement with PsA patients (12).

Although Rosen et al. reported lower quality of life levels in PSA cases based on such criteria as the Health Assessment Questionnaire (HAQ) and Short Form 36 in their study in the Canadian population, statistically worse results in psoriasis cases were reported in the Dermatological Life Quality Index (DLQI), which is a dermatological and cosmetic evaluation (13). The results of the aforementioned limited number of studies comparing the two diseases are still controversial. In this study, it was aimed to compare quality of life, fatigue, depression and other parameters in psoriasis and PsA patient groups with similar characteristics in terms of age, gender, socio-demographic characteristics, and disease activity.

2. Materials and Methods

This cross-sectional study was conducted at Ondokuz Mayıs University Faculty of Medicine, Rheumatology Clinic. Prior to the study, relevant approval was obtained from the 19 Mayıs University Faculty of Medicine Ethics Committee (Approval no:2011/480) and the principles of the Declaration of Helsinki were followed. Written informed consent was obtained from all patients enrolled in the study.

Thirty-four consecutive patients, who were diagnosed with psoriasis and met the study criteria and 48 cases with PsA, matched with the psoriasis group in terms of age and gender, were included in the study. Study inclusion criterias were; being diagnosed with psoriasis as a result of dermatologist examination or diagnosed with PsA according to CASPAR Criteria and regularly using the recommended medical treatment for these diseases, being older than 18 years of age and younger than 60 years of age, and volunteering to participate in the study. Exclusion criterias for the study were; having an additional disease (such as uncontrolled hypertension, diabetes, lung and heart diseases) that may affect quality of life, having another rheumatological disease requiring different medical treatment, presence of pregnancy, presence of neurological or orthopedic insufficiency that may cause disability, and being employed in heavy work. Joint involvement was excluded by detailed rheumatological examination in patients in the psoriasis group.

2.1. Study parameters

In order to determine disease activity, PsA activity index Disease Activity in Psoriatic Arthritis (DAPSA) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores were used in PsA cases, whereas Psoriasis Area Severity Index (PASI) and Nail Psoriasis Severity Index (NAPSI) were used in psoriasis cases. Pain level during the last week was determined by Visual Analog Scale (VAS) for both groups.

The DAPSA score is a scoring system developed from the Disease Activity in Reactive Arthritis (DAREA) score previously defined for reactive arthritis patients, and it was shown to be effective in indicating the severity of PsA disease (14). Swelling in 66 joints and tenderness in 68 joints is checked in this scoring system. The patient's pain score and the patient's global self-assessment of the disease are calculated in the Visual Analog Scale (VAS) 10-point system. Finally, the patients' C-reactive protein (CRP) value at the time of calculation is recorded as mg/dl. The DAPSA score is obtained by adding the number of tender joints, the number of swollen joints, the patient pain score, the patient global assessment, and the CRP value. High scores represent active and severe disease (14).

The PASI score is a scoring system in which the severity and extent of psoriasis disease are evaluated together, by which the size of the lesions in the head, upper extremities, lower extremities and trunk regions, and the severity of erythema induration and dandruff are evaluated (15). The sum of the scores in all 4 regions is expressed as a maximum of 72 points, with the increased scores representing the severe psoriasis case (15).

NAPSI is a scoring method developed to determine the severity of nail involvement in psoriasis patients (16). For all nails, the nail matrix and nail bed are divided into four quadrants and each quadrant is checked for involvement. A nail gets a minimum of 0 and a maximum of 8 points (16).

Patients are asked to mark the severity of pain by explaining that no pain is 0 on a 0-10 cm chart and 10 is the most severe pain that can be felt in life, when calculating the severity of pain with the Visual Analog Scale (VAS). Afterwards, the pain intensity is evaluated by measuring the point marked on the chart with a millimetric ruler (17).

The quality of life of the patients in both groups was evaluated by means of the Health Assessment Questionnaire (HAQ). HAQ is a questionnaire that consists of 20 questions to evaluate the quality of life of patients. Daily tasks such as dressing, eating, walking ability and maintaining personal hygiene are questioned (18). In the questionnaire, where each

answer is evaluated between 0-3 points, the total score is divided by 20 and the result is obtained The HAQ score, which is a good indicator of functional status, is widely used in PsA publications and its validity and reliability was shown for Turkish Language (18, 19).

Depression levels of the patients in both groups were evaluated by means of the Beck Depression Inventory (BDI). Having been a questionnaire consisting of 21 items in total, each item is composed of 4 sentences and patients are asked to choose the sentence that best fits their situation in that scale (20). These sentences are scored between 0-3, with the most severe case being rated as 3 points. Relevant validity and reliability studies were conducted for patients in Turkey (20). The fatigue levels of the patients in both groups were evaluated by means of the FACIT Fatigue Scale. FACIT is questionnaire that has been used in many studies to evaluate fatigue and consists of 13 items each question is given points between 0 and 4, and questions 7 and 8 are scored inversely and a total value of 0-52 is obtained. Lower scores indicate that the patient's fatigue is more severe (21).

2.2. Statistics analysis

SPSS 17 for statistical evaluation (SPSS Inc. Released 2007. SPSS for Windows, Version 17.0. Chicago, SPSS Inc.) software package was used. Kolmogorov-Smirnov test was used to test the conformity of the obtained data to the normal distribution. The Mann-Whitney U test was used to compare the mean of the two groups, when the data did not fit the normal distribution. Chi-square test was used to compare the data obtained by counting method. As regards the correlations within the groups, the Pearson correlation test was applied for the data conforming to the normal distribution and the Spearman correlation test was used for the data not conforming to the normal distribution.

3. Results

The descriptive features of the cases in both groups are provided in Table 1. There was no significant difference in demographic data of psoriasis and PsA patients, such as age, gender, education status, and duration of disease. When comparing psoriasis and PsA groups with similar characteristics, a statistically significant difference was observed in the HAQ scale (0.22±0.36-0 - 0.48±0.52 p=0.017 respectively). While PsA patients showed more disability than psoriasis patients, there was no difference between the two diseases in terms of the depression and fatigue parameters measured by BDI and FACIT scales between the groups (BDI score 10.58 ± 8 -10.91± 9.04 FACIT score 36.91 ± 12.26 – 36.89±11.23 for both p>0.05, respectively) (Table 2).

Table 1. Comparision of Psoriasis and PsA group

	Psoriasis (n:34)	PsA (n:48)	*p*
Gender Female (%)	24 (70%)	29 (60%)	0.325
Age (years) (Mean±SD)	38,35 ± 12,01	46,50 ± 10,93	0.122
Disease duration (years) (Mean±SD)	13,54 ± 9,93	13,66 ± 10,70	0.475
Marital status: Married (%)	30 (90%)	44 (92)	0.319
Educational status n (%)			0.141
Elementary school	18 (53%)	32(67%)	
High schools	8 (23%)	3(7%)	
University	6 (17%)	10 (20%)	
DAPSA (Mean±SD)	-----	13,90± 2,84	--
BASDAI (Mean±SD)	-----	2,06± 1,11	--
PASI	10,71 ± 10,56	5,92 ± 8,22	0.110
NAPSI	10,67 ± 25,10	6,54 ± 11,56	0.135
VAS	4,12± 3,01	5,36± 3,19	0.097
Subtypes of Psoriasis		-----	--
Plaque	85,3%	91.7%	--
Pustuler	2,9%	2.1%	--
Erythrodermic	2,9%	-	--
Palmoplantar	8,8%	6.3%	--
Pure Axial Disease %	-----	4.2%	--
Oligoarthritis		45.8%	--
Polyarthritis		39.6%	--
Dif+Polyarthritis		6.3%	--
Axial+ Polyarthritis		2,1%	--
Axial+ Oligoarthritis		2,1%	--
Treatment Regimen n (%)			0.245
DMARD	10	23	0.011
Biologic Therapy	2	18	0.009

DAPSA: Disease Activity in Psoriatic Arthritis, BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index, PASI: The Psoriasis Area Severity Index, NAPSI: The Nail Psoriasis Severity Index, VAS: The Visual Analog Scale, DMARD: 'Disease Modifying Anti-Rheumatic Drugs

Table 2. Comparision of HAQ, BDI and FACIT scores

	Psoriasis	PsA	*p*
HAQ	0,22 ± 0,36	0,48 ± 0,52	0,017
BDI	10,58 ± 8	10,91 ± 9,04	0,966
FACIT	36,91 ± 12,26	36,89 ± 11,23	0,817

HAQ: Health Assessment Questionnaire, BDI: Beck Depression Inventory, FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue Scale, PsA: Psoriasis Arthritis

There was a strong correlation between DAPSA scores and HAQ scores in the PsA group (r:0 ,615 p<0.05). Likewise, disease activity measured by DAPSA was found to have moderate correlations with FACIT score, and weak but statistically significant correlations with BDI score. (r: -0.578 p<0.05 and r:0.346 p<0.001, respectively). In the subgroup of patients with spondylitis, there was a correlation between BASDAI scores with HAQ and FACIT scores (r:0.498 and r:-0.513 p<0.05). There was no significant correlation between BDI scores (Table 3).

Table 3. Assesment of the Relation Between Disease Severity with HAQ, BDI and FACIT scores

	DAPSA correlation "r"	*p*	BASDAI correlation "r"	P
HAQ	.615	<0.05	.498	<0.05
BDI	.346	<0.05	.147	>0.05
FACIT	-.578	<0.01	-.513	<0.05

HAQ: Health Assessment Questionnaire, BDI: Beck Depression Inventory, FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue Scale, DAPSA: Disease Activity in Psoriatic Arthritis, BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index

More severe deterioration in depression symptoms, disability and disease activity parameters were found in the group with severe fatigue, when the FACIT score cut-off value was taken as 30 in the PsA group. Similarly; more fatigue, more severe disease severity and worse disability scores were found in the severely depressed group, when patients with mild depression and severe depression were compared (Table 4).

Table 4. Effects of Severe Depression and Fatique on PsA study group

Psoriasis Arthritis	FACIT≤30	FACIT>30	P
HAQ	0,91±0,47	0,30±0,43	<0.001
BDI	19,85±9,50	7,23±5,74	<0.001
DAPSA	23,25±14,87	10,94±8,26	<0.001
Psoriasis Arthritis	BDI>17	BDI≤17	p
HAQ	0,82±0,44	0,37±0,50	<0.002
FACIT	24,50±9,39	41,02±8,46	<0.001
DAPSA	20,18±11,19	12,65±11,63	<0.02

HAQ: Health Assessment Questionnaire, BDI: Beck Depression Inventory, FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue Scale, DAPSA: Disease Activity in Psoriatic Arthritis

As regards the psoriasis group, it was observed that HAQ, FACIT and BDI scores did not show a significant correlation with clinical disease activity that evaluated by PASI and NAPSI scores, and this was also true for PsA patients (Table 5).

Table 5. The relation between PASI/NAPSI with HAQ, BDI and FACIT scores

Psoriasis	PASI correlation "r"	p	NAPSI correlation "r"	p
HAQ	,078	>0.05	-,054	>0.05
BDI	-,209	>0.05	,028	>0.05
FACIT	-,040	>0.05	-,108	>0.05
Psoriasis Arthritis	PASI correlation "r"	p	NAPSI "correlation r"	p
HAQ	-,061	>0.05	,041	>0.05
BDI	-,008	>0.05	,002	>0.05
FACIT	-,020	>0.05	-,013	>0.05

HAQ: Health Assessment Questionnaire, BDI: Beck Depression Inventory, FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue Scale, PASI: The Psoriasis Area Severity Index, NAPSI: The Nail Psoriasis Severity Index

4. Discussion

Studies in psoriasis and PsA cases revealed that both diseases reduced the quality of life. Again, studies in which these two diseases were evaluated separately showed that the two negatively affected depression and fatigue levels (22, 23). However, there is only a limited number of studies comparing these two disease groups, taking into account similar age, gender, and disease duration criteria(13). In this study, both disease groups in Turkish society were evaluated on quality of life, fatigue, and depression parameters. According to the results of the study, only HAQ scores were significantly lower in the PsA patient group in terms of quality of life compared to the psoriasis patient group.

Skin diseases such as psoriasis are considered among the important causes of disability because they cause negative feelings such as anxiety and worry due to the presence of a skin disease rather than the itching-like discomfort they actually cause (22, 23). Similarly, some studies showed that the level of disability in skin diseases such as psoriasis did not always correlate with the severity of the disease (22, 24). Krueger et al. suggested in their study conducted in the USA on a national basis that the patients with psoriasis reported that the disease affected their quality of life at a moderate or advanced level at a rate of 75% (12). It was shown in a study conducted with generic quality of life indices based on physical, social, and psychological health assessment, that psoriasis patients and patient groups with atopic dermatitis had similar negative outcomes (25). Decreased quality of life and social comfort in patients with psoriasis were reported in studies conducted with criteria such as Dermatology Specific Quality of Life (DSYK) and Psoriasis Functional Loss Index (PDI), which allow a more sensitive assessment in terms of skin involvement (24-26). Generic scales offer the opportunity to compare two different disease groups, although these original scales were prepared by taking the concerns of psoriasis patients to the forefront. In our study, quality of life and disease activity were determined by means of the Health Assessment Questionnaire (HAQ). Lower scores were obtained especially in the physical health and psychological well-being domains compared to the healthy controls in the psoriasis cases as evaluated by WHOQOL-B in a study by Skevington et al., while it was reported similar results with the control group in the social relations and environment domains. In the same study, statistically significantly lower scores on physical health, psychological well-being, and environment domains were reported in patients with joint involvement compared to patients without joint involvement. In particular, it was emphasized that the items about body image and negative feelings negatively affected psychological well-being domain scores, and items about physical safety and bodily mobility negatively affected environmental domain scores (27). Similar results were reported in the social environment domain in groups with and without joint involvement. In the present study, quality of life was also evaluated by means of HAQ, and while significantly lower results were obtained in the PsA patient group compared to the psoriasis patient group, similar scores were found in the other domains of the quality of life. In a similar study conducted by Tezel et al. within the Turkish society, Psoriatic Arthritis Quality of Life (PSAQoL) scale and HAQ, which were prepared specifically for these patient groups, were used

to compare the quality of life in psoriasis and PsA cases (23). The authors reported that there was no significant difference between the groups in terms of PSAQoL scores, but the increase in HAQ scores in the PsA group was statistically significant. In addition, the authors suggested, the fact that especially psychological mood and social relations values were predominantly included in the calculation of this scale, affected the result in obtaining similar results with regard to PSAQoL scores between the groups (23). Rosen et al. compared the same two disease groups in their study, in which quality of life was evaluated both with the Short Form 36 (SF-36) scale, a generic scale, and with the DSYK, a scale specific to skin diseases (13). According to the results of this study, worse scores were obtained for SF-36 and HAQ results in the PsA patient group, while worse results were found in the psoriasis patient group for DSYK scores (13). Although the presence of arthritis was found to be a negative risk factor for quality of life and functional capacity in that study, the fact that there was an age difference between the groups included in the study (mean age was 46.8 in the psoriasis group, while the mean age was 51.7 in the PsA group) required a statistical correction by logistic regression during the computation of the results (13). In our study, however, the groups were chosen methodologically similar to each other in terms of age and gender in order not to encounter a similar problem; our results showed that high DAPSA scores significantly affected HAQ, FACIT, and BECK scores in PsA patients. These findings are consistent with the studies of Rosen et al. and support the fact that the severity of arthritis affects quality of life and function.

Studies showed that the mental health and activities of daily living of patients with high anxiety levels due to skin lesions were adversely affected. Rüschenschmidt et al. emphasized that although there was no difference in terms of psychological effects, functional disability might be more pronounced in cases with joint involvement (28). In our study, although HAQ scores were higher in the PsA patient group, there was no significant difference between the two groups in terms of BDI scores. Lee et al. suggested in their study that a significant improvement in quality of life, anxiety and depression scores could be recorded in patients with psoriasis, whose disease control could be achieved with treatment, although it was considered that the relationship between psoriasis and psychological well-being was negatively affected by low quality of life, fatigue, sleep disorders, presence of inflammatory cytokines, low vitamin D levels, anxiety, and similar reasons (29). According to a study by Lewinson et al., which offered another point of view, the presence of depression in patients with psoriasis was defined as a risk factor for the manifestation of joint involvement (30). However, although BDI scores were higher in the PsA patient group in our study, it did not lead to a statistically significant difference between these groups. Relevant studies considered fatigue a common symptom in both PsA and psoriasis patient groups (4-11). In their study, McDonough et al. compared the cases with PsA and psoriasis in terms of anxiety, depression, fatigue, quality of life, and functional capacity(31). In that study, more negative results were obtained in the PsA group in measures of anxiety, depression, fatigue, and functional capacity(31). However, there was no difference between the groups in the mental component of quality of life as assessed by SF-36(31). However, the fact that 60% of the cases in the PsA group were men and most of these men were unemployed due to functional disability disrupted the similarity of the study groups (31). Again, inconsistent with this study, female sex was shown as a risk factor for both depression and fatigue for both disease groups in the literature(32, 34). In our study, however, there was no difference between the groups in fatigue and depression scores.

The strengths of our study are ; the diagnosis of psoriasis and PsA was confirmed by both a rheumatologist and a dermatologist, that the PsA group was matched with the psoriasis group in terms of age and gender variables, when forming the groups, and the use of generic scales for comparison between groups. However, the fact that the sample size was not calculated before the study, because it was a cross-sectional study, and that variables such as changes in attack periods and response to treatment did not yield results are included in the important limitations of our study.

As a result, both psoriasis and PsA are diseases that negatively affect such parameters as quality of life, functional capacity, density and depression, as in many chronic diseases. Nevertheless, the results of studies investigating these two diseases or the clinical effect of joint involvement in psoriatic cases are inconsistent. In addition, factors such as different age group, sex, disease activity, disease duration, and treatment regimens make it difficult to compare these two disease groups methodologically. In future prospective comparative studies that start with the diagnosis period, more meaningful results can be obtained by revealing the process, in which both diseases become chronic, and the response to treatment.

Conflict of interest

None to declare.

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None to declare.

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The effect of maternal food consumption habits to the neonatal outcomes, blood biochemical parameters and nutrient elements: A cross-sectional study

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Abstract

Optimal nutrition during prenatal, antenatal and postnatal period is one of the most desired conditions for the healthy birth of new generations and proper care of mother. The aim is to evaluate the effect of each maternal food consumption habit and supplementary intakes to the neonatal outcomes, blood biochemical parameters, macronutrient and micronutrient composition of body and address sufficient healthcare during antenatal care in a middle-income region. A group of 77 women at 3rd months postpartum were asked to complete the 43 items dietary questionnaire. Among all the women, 44 of them completed the questionnaire properly. The results of the questionnaire were evaluated by a nutrient database program (BeBiS software program) designed to evaluate nutrient elements of the human body. The blood biochemical parameters of all the patients were analyzed. The socio-demographic features, neonatal outcomes and maternal-neonatal anthropometric measurements were noted. The mean infant's 3rd month height was statistically significantly higher in walnut consumed group 3-4 days a week (mean =66.57 ± 2.07 cm; CI: 95%) than in the non-consumed group (63.25 ± 2.08 cm; CI: 95%) (p =0.021). The mean weight gain was 10.94 ± 5.16 kg (CI 95%) in walnut non-consumed group and 18.43 ± 6.50 kg (CI 95%) in consumed group 3-4 days a week which is statistically significantly different (p =0.012). Iodine level was significantly statistically higher in the egg consumed group 5-7 days a week than the non-consumed group as secondary outcome (2.80 ± 0.24; 2.15 ± 0.64 respectively, p=0.022). The walnut consumption was related to the greater weight gain during pregnancy and the increase in infant's height. Although, optimal weight gain is essential to maintain physiological well-being during pregnancy, we should consider the positive effect of walnuts on infant's development.

Keywords: BeBIS, dietary questionnaire, pregnancy, maternal nutrition, neonatal development

1. Introduction

Pregnancy is an important period in which both a healthy fetal development is required, and many maternal physiological changes are observed. Optimal nutrition during prenatal, antenatal, and postnatal period is one of the most desired conditions for the healthy birth of new generations and proper care of mother (1). As well as intrauterine environment, placental factors, and genetic conditions; the nutrition of pregnant women also has effects on fetal development such as birth weight, head circumference and birth height (2). On the contrary, maternal malnutrition is known to increase both maternal and fetal morbidity and mortality rates such as chronic diseases, iron or vitamin deficiencies, neurological developmental disorders throughout infant's life and maternal metabolic diseases such as diabetes and obesity (3). Thus, women need to regulate her nutrition habits starting from preconception and there are antenatal programs to improve the nutrition quality during pregnancy.

There are some studies conducted with certain food groups such as vegetables and fruits which have been associated with birth weight and birth height (4). In addition, there are many supplements regularly recommended for use in pregnancy such as folic acid, omega 3 and vitamin D. Folate is necessary for cell division and tissue growth and acting role in nucleotide biosynthesis, amino acid metabolism and several methylation reactions (5) (6). Folic acid supplementation during pre-conception and first trimester pregnancy period is recommended to prevent neural tube defects and improve child cognitive developments (6). Omega 3 intake is also associated with the reduced risk of preterm birth, low birth weight and need of neonatal intensive care (7). Vitamin D intake and daily sunlight exposure during pregnancy improves the pregnancy outcomes by preventing preterm birth, preeclampsia, gestational diabetes, and asthma (8).

There is lack of research which evaluates the benefit of each food consumption habit and each supplement intake on neonatal outcomes; maternal micronutrient and macronutrient status; maternal hematological and biochemical blood parameters. Therefore, the aim of this study is to evaluate the potential effect of each maternal food consumption habit and supplementary intakes to the neonatal outcomes and to address sufficient antenatal care in terms of nutrition in a middle-income region.

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2. Materials and Methods

A cross sectional single center study was performed with women in puerperium who were undergoing regular antenatal visits during their pregnancy in Giresun University Women and Children Research and Education Hospital between January, 2020 and March, 2021. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards; all patients agreed written informed consent. The study approved by local ethical committee (Decision number: 18/04.03.21).

Table 1. Demographic and anthropometric characteristics

Characteristic	Mean ± SD (n=44)	Std error	95% Confidence Interval for Mean		Minimum	Maximum
			Lower	Upper		
Age (n)	29.07 ± 6.87				19	36
BMI (kg/m²)	24.48 ± 4.01	0.60	23.26	25.70	19.53	36.73
Weight gained during pregnancy (kg)	13.66 ± 5.52	0.83	11.98	15.34	1.00	28.00
Birth weight (kg)	3.32 ± 0.58	0.87	3.15	3.50	2.05	4.38
Birth height (cm)	50.31 ± 2.09	0.31	49.68	50.95	45.00	53.00
Current birth height (cm)	64.32 ± 2.61	0.39	63.52	65.11	59.00	70.00
Head circumference (cm)	41.76 ± 1.27	0.19	41.38	42.15	39.00	44.50
Daily energy intake (kcal)	1935.96 ± 597.22	90.03	1754.38	2117.53	712.42	3334.05

A total of 77 women were included to the study and 44 of them completed the required questionnaires properly. Patients have got involved to the study in their 3rd month after birth. Inclusion criteria included single healthy term births that were over >38 weeks of gestation, had not need to stay in the intensive care unit and exclusively breastfed neonates. Exclusion criteria included multiple gestations, adolescent pregnancies (age<18), advanced age pregnancies (age>36), maternal eating disorders (Anorexia Nervosa, Bulimia etc.), maternal chronic diseases (Celiac Disease, Diabetes Mellitus, Chronic Hypertension etc.), smoking and alcohol consumption.

The survey was totally two parts, including firstly 9-items questionnaire as sociodemographic and pregnancy related features, secondly 34 items questionnaire as nutrition habits and pregnancy related features.

Sociodemographic and pregnancy related features as body mass index (BMI), maternal age, gestational week at birth, weight gain during pregnancy, birth weight, infant's head circumference, birth height and infant's current height were asked by using 9-item questionnaire. Anthropometric measurements were taken by researchers as individual height measurement with 1 mm interval wall-mounted height meter and body weight with 100gr weight sensitive Sinbo Sbs 4429 during their routine antenatal and postnatal visits. BMI was calculated according to the Center for Disease Control and Prevention's criteria (9).

Secondly, all participants were asked to fill the detailed 34-item nutrient habits and pregnancy-related features questionnaire that evaluates attitudes about food consumption frequency for red meat, chicken meat, fish, egg, legume, milk and milk products, nuts, fruits, vegetables, walnut, hazelnut and supplements intake as Folic acid, Omega 3, Vitamin D and sunlight exposure. The nutrient habits questionnaire was evaluated by the nutrient database program (BeBiS software program; Turkish version of Bebispro for Windows, Stuttgart, Germany) designed to evaluate daily intake estimates of various nutrients by the food consumption frequencies which reflects the antenatal period of intake (10). BeBiS is a software program that contains the data more than 20,000 foods and reports nutritional elements such as calories, protein, carbohydrate, fat, vitamins, minerals, amino acids, fatty acids, and antioxidants.

All women's hemoglobin (hgb), hematocrit (hct), platelet (plt), lactate dehydrogenize, sodium, potassium, chloride, calcium, C reactive protein, triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), vitamin D, uric acid, total protein, albumin, globulin, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, aspartate aminotransferase levels were also analyzed with autoanalyzer Cobas 6000 (Roche Diagnostics).

2.1. Statistical analysis

Calculations were performed using SPSS statistical software package 17.0 (IBM). The required sample size calculated as 39 with a 5% margin error. Cronbach's alpha and inter item correlation matrix were calculated for reliability statistics. ANOVA, Friedman's test and Chi-square test were used to analyze the differences between individuals and items. Tukey's test for nonadditivity was done as a post hoc test. $P < 0.05$ was used to determine statistical significance.

Table 2. Comparison of clinical characteristics of daily nuts consumption

Consumption type	Frequency	N	Weight gain during pregnancy (kg)			Current height (cm)			
Nuts	None	3	22.63 ± 2.87	9.00 ± 7.94	2.61 ± 0.50	41.33 ± 0.58	48.00 ± 2.00	62.33 ± 1.53	1623.19 ± 476.41
	1-2	17	25.25 ± 3.85	13.82 ± 4.22	3.45± 0.59	42.16± 0.96	50.47 ± 2.35	64.47 ± 2.53	1845.47 ± 583.34
	3-4	10	23.22 ± 3.03	18.00 ± 5.54	3.46 ± 0.49	41.58 ± 1.31	50.90 ± 1.79	66.50 ± 2.22	2034.81 ± 609.02
	5-7	14	24.84 ± 4.93	11.36 ± 4.78	3.23 ± 0.56	41.50± 1.62	50.21 ± 1.81	63.00 ± 2.11	2042. 23 ± 645.21
	Total	44	24.48 ± 4.01	13.65 ± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935.96 ± 597.22
	p		0.616	0.071	0.853	0.618	0.051	0.352	0.566
Walnut	None	16	24.30 ± 4.93	10.94 ± 5.16	3.23 ± 0.58	41.80 ± 0.89	49.94 ± 2.26	63.25 ± 2.08	1798.57 ± 596.00
	1-2	14	25.60 ± 3.77	14.14 ± 5.08	3.30 ± 0.61	41.48 ± 1.70	50.21 ± 2.01	64.79 ± 2.61	2125.13 ± 586.51
	3-4	7	24.10 ± 3.84	18.43 ± 6.50	3.61 ± 0.56	42.00 ± 0.50	51.00 ± 2.31	66.57 ± 2.07	2211.54 ± 635.25
	5-7	7	22.99 ± 1.73	14.14 ± 2.61	3.28 ± 0.57	42.00 ± 1.66	50.71 ± 1.80	63.57 ± 2.99	1596.04 ± 402.52
	Total	44	24.48 ± 4.01	13.66± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935.96 ± 597.22
	p		0.558	**0.020**	0.556	0.765	0.682	**0.025**	0.107
Hazelnut	None	5	23.98 ± 4.21	12.80 ± 5.22	3.06 ± 0.66	41.80 ± 0.84	49.20 ± 2.28	63.20 ± 2.17	1750.56 ± 432.50
	1-2	19	24.80 ± 3.91	13.37 ± 4.19	3.33 ± 0.55	41.98 ± 1.13	50.11 ± 2.10	64.05 ± 2.30	1866.35 ± 616.10
	3-4	10	25.06 ± 4.56	13.50 ± 7.95	3.41 ± 0.62	41.50± 1.41	50.70 ± 2.26	65.20 ± 3.49	2254.12 ± 743.59
	5-7	10	23.54 ± 3.97	14.80± 5.77	3.36 ± 0.61	41.58± 1.63	50.90± 1.79	64.50 ± 2.46	1842.74 ± 396.79
	Total	44	24.48 ± 4.01	13.66 ± 5.52	3.32 ± 0.58	41.76± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935.95 ± 597.22
	p		0.863	0.881	0.623	0.861	0.334	0.393	0.293

Bold values indicate statistically significant difference ($p < 0.05$)

3. Results

Seventy-seven postpartum women 3rd month after birth participated in the study. Thirty-three of them failed to complete the questionnaire properly and were excluded. A total of 44 participants were evaluated. Demographic and anthropometric features were given in Table 1.

Daily nuts consumption and daily food consumption of participants were shown in Table 2 and Table 3, respectively. There was no statistically significant relationship between red meat, chicken meat, fish, egg, legume, milk and milk products, nuts, fruits, vegetables, hazelnut consumption and pregnancy related features such as BMI, weight gain during pregnancy, infant's birth weight, birth height, birth head circumference, current head circumference, current height, and daily energy intake ($p > 0.05$). Also, the significant relationship was not stated between these consumption groups and nutrition elements or blood biochemical parameters.

The statistically significant relationship between walnut consumption and weight gain during pregnancy ($p=0.012$), infant's current height has been shown as primary outcome ($p=0.021$) (Table 2). Sixteen out of 44 women did not consume walnut at all, 14 of them consumed 1-2 days a week, seven of them consumed 3-4 days a week and seven of them consumed 5-7 days a week (Table 4). The mean level of weight gain during pregnancy was statistically significantly lower in non-consumer group (mean = 10.94 ± 5.16 kg; CI 95%) than in the consumed group 3-4 days a week (Mean = 18.43 ± 6.50 kg; CI 95%) ($p =0.012$) (Table 4). The mean level of infant's current height was 63.25 ± 2.08 cm (CI: 95%) in non-consumer group and 66.57 ± 2.07 cm (CI: 95%) in the consumed group 3-4 days a week which is statistically significantly different ($p=0.021$) (Table 4). Mineral, pantothenic acid, folic acid, free folic acid, and sodium levels were significantly higher in the walnut consumed group 1-2 days per week than the non-consumed group ($p = 0.010$; $p= 0.028$; $p= 0.017$; $p= 0.008$; $p=0.018$ respectively) (Table 4). In biochemical parameters, serum C-reactive protein was found to be higher in those who consumed a handful of walnuts, compared to those who consumed half or 1 whole walnut per day according to the daily amount of walnut consumption (CRP =9.45 ± 0.35 vs. 8.75 ± 0.30 mg/dl; $p=0.011$). There was no significant difference in other biochemical parameters ($p>0.05$).

Iodine mean level found 2.15 ± 0.65 µg in non-consumed group and 2.80 ± 0.24 in 5-7 days a week consumed group (CI: 95%). Iodine level was significantly statistically higher

in the egg consumed group 5-7 days a week than the non-consumed group as secondary outcome (2.80 ± 0.24; 2.15 ± 0.64 respectively, p=0.022) (Table 5).

There was no statistically significant relationship between the intake of folic acid, vitamin D or omega 3 supplements with pregnancy outcomes, micronutrient, or biochemical parameters (p >0.05).

4. Discussion

In this cross-sectional study, we assessed the relation of food consumption during pregnancy using the validated BEBIS program and found that red meat, chicken meat, fish, egg, legume, milk and milk products, nuts, fruits, vegetables, hazelnut consumption was not related to the BMI, weight gain during pregnancy, neonatal outcomes, and blood biochemical parameters. Specifically, we found that only the walnut consumption during pregnancy was associated with greater weight gain and higher chance of increase in infant's height. Surprisingly, serum C-reactive protein was higher in those who consumed higher amounts of walnut per day according to the daily amount of walnut consumption, although there was no such a relation with other biochemical parameters. Additionally, iodine level is the most important factor for neurological development of infants and this data have confirmed the significant effect of egg consumption on iodine level (11).

Table 3. Comparison of clinical characteristics of daily food consumption

Consumption type	Frequency	N	Weight gain during pregnancy (kg)			Current height (cm)			
Meat	None	13	24.29± 4.54	13.92± 6.96	3.29 ± 0.48	41.67± 1.52	50.08 ± 2.10	64.00± 1.73	1922.39± 517.29
	1-2	21	24.75 ± 4.22	13.14 ± 5.76	3.29 ± 0.63	41.78± 1.10	50.33 ± 2.29	64.38 ± 3.02	1945.25± 714.53
	3-4	9	24.48± 3.07	14.22 ± 2.54	3.33 ± 0.57	41.72± 1.39	50.44 ± 1.81	64.33 ± 2.87	1924.53 ± 487.67
	5-7	1	21.31	16.00	4.31	43.00	52	67.00	2019.98
	Total	44	24.48± 4.01	13.66 ± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.31 ± 2.09	64.32 ± 2.61	1935.96 ± 597.22
	p		0.871	0.927	0.402	0.806	0.846	0.752	0.998
Chicken	None	14	24.09± 2.93	13.07 ± 4.99	3.29 ± 0.38	41.76 ± 1.29	50.29 ± 1.73	63.71 ± 1.38	1772.78 ± 424.06
	1-2	21	23.83 ± 3.75	13.52 ± 5.90	3.29 ± 0.69	42.06 ± 1.25	50.24 ± 2.45	64.95 ± 3.14	1963,32 ± 674.61
	3-4	7	27.79± 5.81	13.43 ± 5.06	3.38 ± 0.65	40.64± 0.85	50.86 ± 1.86	63.71 ± 2.98	2055.07 ± 598.32
	5-7	2	22.45± 0.19	20.00 ± 7.07	3.58 ± 0.63	42.50± 0.71	49.50 ± 2.12	64.00 ± 1.41	2373.95 ± 993.47
	Total	44	24.48± 4.01	13.66 ± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935.96 ± 597.22
	p		0.129	0.195	0.873	0.074	0.736	0.871	0.379
Fish	None	25	24.87± 4.74	12.80 ± 4.93	3.31 ± 0.45	41.94± 1.28	50.20 ± 1.91	64.08 ± 2.40	2061.61 ± 621.87
	1-2	13	23.43± 2.04	14.69 ± 6.30	3.48 ± 0.73	41.73 ± 1.42	50.85 ± 2.30	64.92 ± 2.87	1781.23 ± 625.43
	3-4	5	24.36 ± 3.95	13.60 ±6.11	2.90 ± 0.70	40.90 ± 0.55	49.40 ± 2.61	64.00 ± 3.54	1719.95 ± 324.05
	5-7	1	29.02	22.00	3.76	42.20	51.00	64.00	18816.13
	Total	44	24.48± 4.01	13.66 ± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935.96 ± 597.22
	p		0.506	0.351	0.255	0.423	0.591	0.814	0.464
Egg	None	3	26.04± 4.22	12.00 ± 3.46	3.60 ± 0.50	41.67± 1.53	50.00 ± 2.0	62.67 ± 3.21	1863.96 ± 336.74
	1-2	2	26.17 ± 3.87	11.00 ± 1.41	3.47 ± 0.29	41.75 ± 0.35	51.00 ±1.41	64.50 ± 0.71	1641.23 ± 182.67
	3-4	5	23.65± 1.58	16.20 ± 2.39	3.40 ± 0.61	41.90 ± 1.43	50.40 ± 1.67	64.80 ± 3.70	2022.67 ± 588.38
	5-7	34	24.36± 4.31	13.59 ± 6.05	3.28 ± 0.6	41.75± 1.31	50.29 ± 2.24	64.38 ± 2.51	1946. 89 ± 638.68
	Total	44	24.48 ± 4.01	13.66 ± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935.96 ± 597.22
	p		0.834	0.585	0.883	0.995	0.920	0.693	0.829
Milk and milk products	None	1	25.54	10.00	3.07	42.0	48.0	59.0	1619.49
	1-2	1	23.44	12.00	3.67	42.0	52.0	64.0	1512.06
	3-4	4	28.99± 5.33	15.25± 12.09	3.72 ± 0.49	42.18 ± 0.62	51.50 ± 1.29	64.75 ± 2.50	1770.98 ± 199.09
	5-7	38	24.00± 3.72	13.63± 4.78	3.28 ± 0.59	41.71 ± 1.35	50.21 ± 2.13	64.42 ± 2.57	1972.80 ± 631.98

	Total	44	24.48 ± 4.01	13.66 ± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935. 95 ± 597.22
	p		0.121	0.845	0.462	0.910	0.363	0.231	0.758
Fruits	1-2	2	24.49± 1.48	11.00 ± 4.14	3.37± 0.42	42.00± 0.00	50.00 ± 2.83	61.50 ± 3.54	1565.78± 75.96
	3-4	5	23.55± 1.27	15.40 ± 8.50	3.17 ± 0.69	41.50 ± 1.94	49.80 ± 2.86	65.60 ± 3.65	2468.21 ± 884.01
	5-7	37	24.61± 4.34	13.57 ± 5.25	3.34 ± 0.58	41.78 ± 1.22	50.41 ± 2.01	64.29 ± 2.38	1884.04 ± 537.88
	Total	44	24.48± 4.01	13.66 ± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935.96 ± 597.22
	p		0.927	0.501	0.879	0.845	0.912	0.067	0.074
Vegetables	3-4	2	21.78± 0.74	21.00 ± 5.66	3.63 ± 0.70	42.00± 0.00	50.50 ± 3.54	66.00 ± 1.41	3026.00 ± 71.33
	5-7	42	24.61 ± 4.06	13.31 ± 5.34	3.31 ± 0.58	41.75± 1.30	50.31 ± 2.07	64.24 ± 2.64	1884.04 ± 559.67
	Total	44	24.48 ± 4.01	13.66 ± 5.52	3.32 ± 0.58	41.76 ± 1.27	50.32 ± 2.09	64.32 ± 2.61	1935.96 ± 597.22
	p		0.336	0.053	0.457	0.789	0.901	0.358	0.007

Bold values indicate statistically significant difference ($p < 0.05$)

Table 4. Weekly walnut consumption's multiple comparison analysis

	Frequency A	Frequency B	Mean difference (A-B) ± Std error	Sig.	95% Confidence Interval *Lower Bound*	*Upper Bound*
BMI	None	1-2*	-1.29 ± 1.48	0.82	-5.27	2.68
		3-4*	0.21 ±1.84	0.99	-4.72	5.13
		5-7*	1.31 ±1.84	0.89	-3.61	6.23
	1-2	3-4	1.50 ±1.88	0.86	-3.53	6.52
		5-7	2.60 ± 1.88	0.51	-2.42	7.63
	3-4	5-7	1.10 ± 2.17	0.96	-4.70	6.91
Weight gain during pregnancy (kg)	None	1-2	-3.21 ± 1.86	0.32	-8.18	1.77
		3-4	-7.49 ± 2.30	**0.01**	-13.65	-1.33
		5-7	-3.21 ± 2.30	0.51	-9.37	2.96
	1-2	3-4	-4.29 ± 2.35	0.28	-10.58	2.01
		5-7	0.00 ± 2.35	1.00	-6.29	6.29
	3-4	5-7	4.29 ± 2.71	0.40	-2.98	11.55
Birth weight (kg)	None	1-2	-0.07 ± 0.21	0.98	-0.64	0.50
		3-4	-0.38 ± 0.27	0.50	-1.09	0.34
		5-7	-0.04 ± 0.27	0.99	-0.76	0.67
	1-2	3-4	-0.31 ± 0.27	0.67	-1.03	0.42
		5-7	0.03 ± 0.27	1.00	-0.70	0.75
	3-4	5-7	0.33 ± 0.31	0.72	-0.51	1.17
2nd head circumference (cm)	None	1-2	0.32 ± 0.48	0.91	-0.95	1.60
		3-4	-0.20 ± 0.59	0.99	-1.78	1.38
		5-7	-0.20 ± 0.59	0.99	-1.78	1.38
	1-2	3-4	-0.52 ± 0.06	0.82	-2.13	1.09
		5-7	-0.52 ± 0.60	0.82	-2.13	1.09
	3-4	5-7	0.00 ±0.69	1.00	-1.86	1.86
Birth height (cm)	None	1-2	-0.28 ± 0.78	0.98	-2.36	1.81
		3-4	-1. 06 ± 0.96	0.69	-3.64	1.52
		5-7	-0.77 ± 0.96	0.85	-3.36	1.81
	1-2	3-4	-0.79 ± 0.98	0.85	-3.42	1.85
		5-7	-0.50 ± 0.98	0.96	-3.14	2.14
	3-4	5-7	0.29 ± 1.14	0.99	-2.76	3.33
Current height (cm)	None	1-2	-1.54 ± 0.88	0.32	-3.90	0.83
		3-4	-3.32 ± 1.09	**0.02**	-6.25	-0.39
		5-7	-0.32 ± 1.09	0.99	-3.25	2.61
	1-2	3-4	-1.79 ± 1.12	0.39	-4.78	1.21
		5-7	1.21 ± 1.12	0.70	-1.78	4.21
	3-4	5-7	3.00 ± 1.29	0.11	-0.46	6.46
Daily energy intake (kcal)	None	1-2	-326.56 ± 210.18	0.42	-889.93	236.81
		3-4	-412.97 ± 260.26	0.40	-1110.58	284.64
		5-7	202.53 ± 260.26	0.86	-495.08	900.14
	1-2	3-4	-86.41 ± 265.86	0.99	-799.02	626.20
		5-7	529.09 ± 265.86	0.21	-183.53	1241.70
	3-4	5-7	615.50 ± 306.99	0.20	-237.35	1438.35

Mineral (g)	None	1-2	-5.11 ± 1.69	**0.02**	-9.64	-0.59
		3-4	-5.87 ± 2.09	**0.04**	-11.47	-0.27
		5-7	-1.64 ± 2.09	0.86	-7.25	3.96
	1-2	3-4	-0.75 ± 2.13	0.98	-6.47	4.97
		5-7	3.47 ± 2.13	0.38	-2.25	9.19
	3-4	5-7	4.22 ± 2.46	0.33	-2.38	10.83
Pantotenic acid (mg)	None	1-2	-2.05 ± 0.69	0.03	-3.91	-0.20
		3-4	-1.70 ± 0.86	0.21	-4.00	0.59
		5-7	-0.61 ± 0.86	0.90	-2.92	1.69
	1-2	3-4	0.35 ± 0.88	0.98	-1.99	2.70
		5-7	1.44 ± 0.88	0.37	-0.90	3.79
	3-4	5-7	1.09 ± 1.01	0.70	-1.62	3.80
Folic acid (µg)	None	1-2	-46.65 ± 15.27	**0.02**	-87.59	-5.71
		3-4	-45.18 ± 18.91	0.10	-95.88	5.52
		5-7	-15.39 ± 18.91	0.85	-66.08	35.31
	1-2	3-4	1.47 ± 19.32	1.00	-50.32	53.26
		5-7	31.26 ± 19.32	0.38	-20.52	83.05
	3-4	5-7	29.79 ± 22.31	0.55	-30.00	89.59
Free folic acid (µg)	None	1-2	-39.13 ± 11.56	**0.008**	-70.11	-8.15
		3-4	-37.29 ± 14.31	0.059	-75.66	1.07
		5-7	-15.63 ± 14.31	0.696	-53.99	22.73
	1-2	3-4	1.84 ± 14.62	1.00	-37.35	41.02
		5-7	23.50 ± 14.62	0.39	-15.68	62.69
	3-4	5-7	21.67 ± 16.88	0.58	-23.58	66.92
Sodium (mg)	None	1-2	-1205.40 ± 462.36	0.60	-2444.71	33.91
		3-4	-1577.98 ± 572.53	**0.04**	-3112.59	-43.38
		5-7	-283.33 ± 572.53	0.96	-1817.94	1251.28
	1-2	3-4	-372.59 ± 584.84	0.92	-1940.20	1195.03
		5-7	922.07 ± 584.84	0.40	-645.54	2489.68
	3-4	5-7	1294.66 ± 675.31	0.24	-515.47	3104.78

*times a week. Bold values indicate statistically significant difference (p <0.05)

Table 5. Comparison of micronutrients characteristics of daily egg consumption

	Frequency A	Frequency B	Mean difference (A-B) ± Std error	*P* value	95% Confidence Interval *Lower Bound*	*Upper Bound*
Vitamin D (µg)	None	1-2*	-0.11 ± 0.95	1.0	-2.66	2.44
		3-4*	-1.18 ± 0.76	0.42	-3.22	0.87
		5-7*	-1.28 ± 0.63	0.19	-2.97	0.40
	1-2	3-4	-1.07 ± 0.87	0.62	-3.41	1.27
		5-7	-1.17 ± 0.76	0.42	-3.21	0.86
	3-4	5-7	-0.11 ± 0.50	0.99	-1.44	1.23
Vitamin K (µg)	None	1-2	-43.57 ± 185.3	0.96	-540.25	453.11
		3-4	-100.37 ± 148.24	0.91	-497.71	296.97
		5-7	-145.25 ± 122.25	0.64	-472.94	182.45
	1-2	3-4	-56.80 ± 169.83	0.99	-512.01	398ç41
		5-7	-101.67 ± 147.69	0.90	-497.55	294.20
	3-4	5-7	-44.87 ± 97.22	0.97	-305.47	215.73
Total folic acid (µg)	None	1-2	-19.97 ± 92.32	0.99	-267.43	227.50
		3-4	-63.45 ± 73.86	0.83	-261.42	134.53
		5-7	-83.27 ± 60.91	0.53	-246.54	80.00
	1-2	3-4	-43.48 ± 84.62	0.96	-270.29	183.33
		5-7	-63.30 ± 73.59	0.83	-260.55	133.94
	3-4	5-7	-19.82 ± 48.44	0.98	-149.66	110.02
Free folic acid (µg)	None	1-2	-4.83 ± 32.91	0.99	-93.05	83.39
		3-4	-4.87 ± 26.33	0.99	-75.45	65.70
		5-7	-17.67 ± 21.71	0.85	-75.87	40.54
	1-2	3-4	-0.04 ± 30.16	1.00	-80.89	80.82
		5-7	-12.83 ± 26.23	0.96	-83.15	57.48
	3-4	5-7	-12.79 ± 17.27	0.88	-59.08	33.49
Vit B12 (µg)	None	1-2	2.07 ± 1.90	0.70	-3.02	7.16
		3-4	0.19 ± 1.52	0.99	-3.88	4.26
		5-7	1.81 ± 1.25	0.48	-1.54	5.17
	1-2	3-4	-1.89 ± 1.74	0.70	-6.54	2.79
		5-7	-0.25 ± 1.51	0.99	-4.31	3.81
	3-4	5-7	1.63 ± 0.99	0.37	-1.04	4.30
Iodine (µg)	None	1-2	-0.50 ± 0.28	0.31	-1.28	0.28

		3-4	-0.12 ± 0.26	0.11	-1.33	0.09
		5-7	-0.65 ± 0.21	**0.02**	-1.22	0.08
	1-2	3-4	-0.12 ± 0.26	0.97	-0.83	0.59
		5-7	-0.15 ± 0.21	0.89	-0.72	0.42
	3-4	5-7	-0.03 ± 0.17	0.99	-0.51	0.45
Mono unsaturated fatty acid (g)	None	1-2	1.28 ± 17.18	1.00	-44.78	47.34
		3-4	-9.11 ± 13.75	0.91	-45.96	27.73
		5-7	-6.77 ± 11.34	0.93	-37.16	23.62
	1-2	3-4	-10.39 ± 15.75	0.91	-52.61	31.82
		5-7	-8.05 ± 13.70	0.94	-44.76	28.66
	3-4	5-7	2.34 ± 9.02	0.99	-21.82	26.51
Poly unsaturated fatty acid (g)	None	1-2	7.83 ± 7.34	0.71	-11.84	27.50
		3-4	10.52 ± 5.87	0.29	-5.21	26.25
		5-7	7.97 ± 4.84	0.37	-5.00	20.95
	1-2	3-4	2.69 ± 6.72	0.98	-15.33	20.72
		5-7	0.14 ± 5.85	1.00	-15.53	15.82
	3-4	5-7	-2.55 ± 3.85	0.91	-12.87	7.77
Omega 3 (g)	None	1-2	2.80 ± 2.12	0.55	-2.87	8.48
		3-4	2.26 ± 1.69	0.55	-2.28	6.80
		5-7	1.70 ± 1.40	0.62	-2.04	5.45
	1-2	3-4	-0.54 ± 1.94	0.99	-5.75	4.66
		5-7	-1.10 ± 1.69	0.91	-5.63	3.42
	3-4	5-7	-0.56 ± 1.11	0.96	-3.54	2.42
Omega 6 (g)	None	1-2	3.47 ± 6.35	0.95	-13.54	20.48
		3-4	7.25 ± 5.08	0.49	-6.36	20.86
		5-7	5.03 ± 4.19	0.63	-6.19	16.25
	1-2	3-4	3.79 ± 5.82	0.92	-11.80	19.38
		5-7	1.56 ± 5.06	0.99	-11.99	15.12
	3-4	5-7	-2.22 ± 3.33	0.91	-11.15	6.70
Biotin	None	1-2	2.32 ± 18.62	1.00	-47.58	52.23
		3-4	-3.51 ± 14.89	0.99	-43.44	36.41
		5-7	-10.34 ± 12.28	0.83	-43.27	22.59
	1-2	3-4	-5.84 ± 17.06	0.98	-51.57	39.90
		5-7	-12.66 ± 14.84	0.83	-52.44	27.12
	3-4	5-7	-6.83 ± 9.77	0.90	-33.01	19.36

*times a week. Bold values indicate statistically significant difference ($p < 0.05$)

The relation between maternal nutrition and fetal development has been well defined previously (12). Malnutrition during pregnancy is the important risk factor for adverse perinatal outcomes such as fetal growth restriction, low birth weight and increased morbidity (13, 14). Hajianfar et al. compared three identified major dietary patterns, a western dietary pattern, a traditional dietary pattern, and a healthy dietary pattern (2). Although the healthy and traditional dietary patterns did not show remarkable association, the western dietary pattern was associated with significant improvement in low-birth-weight infant's rates which may be attribute to a higher intake of desserts and sweets, sugar, saturated fat, potato and pizza in this dietary pattern (OR 0.80, 95%(CI) (0.34-1.93), P < 0.01) (2). Unlike our study, they did not analyze the foods individually, they evaluated the whole diet. Additionally, their data did not support any relation between maternal dietary patterns and neonatal height (OR 0.80, 95% (CI) (0.34-1.85), P< 0.93) (2).

Guzel et al. investigated the relation between maternal amino acid levels and pregnancy outcomes with the same nutrition database program (BeBiS software program, Bebispro for Windows, Stuttgart, Germany) in two different groups as reproductive aged women (n:130) and adolescents (n:39) (10). They found that the lower amino acid levels were related with low birth weight and preterm delivery in adolescents ($p<0.05$) (10). In our study, nutritional survey was carried out in the postpartum 3rd month and only healthy term deliveries with maternal age over 18 were included to standardize the population. We could not confirm the correlation of amino acid levels with pregnancy outcomes in any type of food consumption group.

Our study differs from findings of previous studies showing that high adherence to walnut consumption during pregnancy may improve the neonatal outcomes. As far as we know, there is not any study about maternal walnut consumption in the literature. In our study, walnut consumption significantly increases the infant's height and weight gain during pregnancy. The National Academy of Medicine recommends 11.5 to 16 kg weight gain for BMI 18.5 to 24.9 kg/m2 individuals (15). In this study, 3-4 times a week walnut consumed group has significantly unfavorable weight gain as 18.43 ± 6.50 kg ($p=0.02$). In a randomized controlled trial, Rock et al. compared the weight reduction diets and found that walnut enriched reduced energy diet can provide weight loss like a standard diet, but this type of diet also has benefits to lower cardiovascular disease risk factors (16). Assaf-Balut et al. investigated the consumption of virgin olive oil and nuts (especially pistachios) in normal

pregnancies and observed similar gestational weight gain between consumed and non-consumed groups (p=0.713) (17). Jang et al. followed infant's growth up to 6 month and documented that maternal vitamin C intake was related positively with the abdominal circumference of the fetus and infant birth length (18). Ramon et al. determined the correlation of increased maternal vegetable consumption with birth height whereas Loy et al. investigated that both vegetable and fruits consumption have significant effects on birth length (4, 19).

Iodine is an important micronutrient that plays role during thyroid hormone synthesis (11). Adequate iodine intake during pregnancy is essential for maternal health, fetal neurodevelopment and sufficient cognitive levels which are common issues affecting public health and population intellectual capacity (20, 21). Dietary iodine necessities are increasing 50% during pregnancy because human chorionic gonadotropin (hCG) acts like thyroid stimulating hormone (TSH) and binds to the TSH receptors. High estrogen concentrations during pregnancy lead the increasing levels of thyroid binding globulin, thus more triiodothyronine (T3) and thyroxine (T4) production is required to maintain free T3 and free T4 levels. Fetus supplies the thyroid hormone maternally, especially as T4 through the placenta and converts into T3 for fetal growth and brain development. The U.S Institute of Medicine suggests overall dietary and supplement iodine intake as 150 µg/day during preconceptional period, 220 µg/day during gestation and 290 µg/day during lactation (22). Recently, American Thyroid Association emphasizes the importance of dietary iodine intake instead of its supplements (23). Previous studies recommended fish, iodized salt consumption, some type of breads and milk products since they have proved that these products can avoid the iodine deficiency (24). There are also studies which have longer follow-up periods for years to investigate the effect of iodine intake to the neurological development of offspring's (25). In this study, the sufficient iodine intake was only shown in egg consumption group, but no immediate effects of iodine on pregnancy outcomes and infant's anthropometry were observed.

Strengthen of this study was the using of BEBIS software program which provides a comprehensive assessment of the nutritional intake. The program captures all types of usual food items consumed by participants and estimates micronutrient and macronutrient values. So, it overcomes the difficulty of determinative effect of specific nutrient as part of the whole diet. This program was offered to be a consistent measure of diet quality in Turkey (10).

Limitation of the study was the small cohort of postpartum women who accepted to fill out the dietary questionnaire. Furthermore, the food consumption and supplementary intake habits may change according to the geographical region, country welfare and personal income. Several physiological changes occur even during normal pregnancies and lactation, so it is difficult to provide standardization in nutrition studies conducted with women in puerperium

Sufficient macronutrient and micronutrient status are necessary to develop healthy offspring and to maintain maternal well-being. In this study, the walnut consumption was related to the greater weight gain during pregnancy and the increase in infant's height. Although, optimal weight gain is essential to maintain physiological well-being during pregnancy, we should consider the positive effect of walnuts on infant's development. Further studies with larger cohort are needed to demonstrate our findings.

Conflict of interest

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Neck metastasis in transglottic laryngeal carcinomas

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Abstract

In laryngeal cancers, the first metastasis occurs in the cervical lymph nodes This study aimed to determine the levels of cervical metastatic lymph nodes in patients with transglottic laryngeal carcinoma, the effect of tumor prognostic factors on cervical lymph node metastasis. The research retrospectively examined 32 patients who underwent total laryngectomy and neck dissection, with the diagnosis of transglottic squamous cell carcinoma (SCC). Age, gender, complaint, smoking status, and other prognostic factors were evaluated. All patients underwent total laryngectomy with 63 neck dissections. Seven patients had metastatic cervical lymph nodes. Among the prognostic factors, thyroid cartilage invasion, combined perineural–perivascular invasion, subglottic extension, extra laryngeal extension, and preoperative tracheotomy procedure had statistically significant effects on neck metastasis. In conclusion, dissection at level IIB should be reassessed to decrease morbidity due to the low prevalence of level IIB metastasis, both clinically and pathologically. In locally advanced laryngeal cancers, considering the prognostic factors, it is ideal to plan specific treatments for each patient.

Keywords: transglottic laryngeal carcinoma, level IIB, cervical metastasis, prognostic factors.

1. Introduction

Laryngeal squamous cell carcinoma (SCC) is the second most common malignancy in the head and neck region. It constitutes 20–25% of head and neck tumors and 2–5% of all body tumors (1). More than 90% of malignant laryngeal tumors are SCCs, and over 40% of cases are advanced (2). Tumors that originate from one part of the larynx, cross the ventricle, and cause vocal cord fixation are called transglottic cancers. Transglottic cancers make up less than 5% of all cases, and they cause paraglottic region involvement and neck metastasis at an early stage (3).

In laryngeal cancers, the first metastasis occurs in the cervical lymph nodes (CLN). Cervical lymph node metastasis (CLNM) is seen in 1–7% of early-stage glottic (T1–T2) cancers and 20–30% of advanced glottic (T3–T4) cancers (25-55%) (4). Occult or obvious metastases to the cervical region are the most important factor causing recurrence and a 50% reduction in survival time. In addition, if there is extracapsular extension (ECE) in the metastatic lymph node, survival is further reduced by 50% (5).

Radical neck dissection (RND), which Crile first implemented in 1906, has since evolved to be applied in the form of modified radical neck dissection (MRND) and selective neck dissection (SND) (6). It has been reported that SND does not negatively affect survival rates in patients without clinical lymphadenopathy (N0), and it is as effective as other comprehensive neck dissections and causes less morbidity (7). In patients undergoing SND, shoulder syndrome symptom scores were found to be better than those in patients who underwent RND (8). Surviving laryngeal carcinomas is associated with tumor, nodes, metastases (TNM) stage, subglottic extension, perineural–perivascular–thyroid cartilage invasion, extralaryngeal extension, and preoperative tracheotomy procedure (9,10).

This study examined the effects of age, gender, preoperative tracheotomy procedure, anterior commissure involvement, perineural invasion, perivascular invasion, thyroid cartilage invasion, subglottic and extralaryngeal extension, and pathology on CLNM to determine which lymph node levels exhibited cervical spreading and whether level IIB dissection was necessary in this context.

2. Materials and Methods

This research retrospectively compiled the files of 32 patients (three female, 29 male), who underwent total laryngectomy and neck dissection, with the diagnosis of transglottic laryngeal SCC, in University of Health Sciences-Samsun Education and Research Hospital, between January 2017 and December 2019. The study began by receiving numbered ethical approval (GOKA/2020/5/12) from the ethics

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committee of the University of Health Sciences-Samsun Education and Research Hospital Non-Interventional Clinical Researches Ethics Board. Patients who had undergone partial laryngeal surgery, as well as those with a history of radiotherapy, chemotherapy, or non-SCC laryngeal pathologies, were excluded.

Patients who were admitted with hoarseness and dyspnea and were diagnosed with laryngeal carcinoma after endoscopic examination were hospitalized. Neck and thorax contrast tomography was conducted. Then, direct laryngoscopy was performed; biopsies were taken; and the laryngeal lesions were mapped. Tracheotomies were opened in the same session for patients with breathing difficulties. Total laryngectomy and radical and/or functional neck dissections were performed in patients with advanced (T3–T4) transglottic tumors whose pathology results reported SCC. As a result of clinical, radiological, and preoperative evaluation, RND was performed on the side with suspected lymphadenopathy, and functional neck dissection (FND) was performed on the opposite side. Bilateral FND was applied to N0 patients. Neck dissection specimens were also reviewed with the relevant pathologist and ordered separately as levels I, IIA, IIB, III, IV, and V. According to the pathology specimen report, patients with more than one metastatic lymph node, with ECE, subglottic extension (1cm anteriorly and 0.5cm posteriorly), and perineural cartilage invasion were treated based on the decision of the tumor council. Local–regional recurrences and overall survival were recorded by following the patients for between six and 29 months (average: 12.8 months).

Information concerning age, gender, complaint, smoking status, tumor placement, tumor histopathology in the pathology specimen report, anterior commissure involvement, subglottic extension, extralaryngeal spread, perineural–perivascular–thyroid cartilage invasion, metastatic–reactive lymph nodes, and ECE (especially level IIB) was compiled. Pathological TNM staging was also determined according to the American Joint Committee on Cancer (AJCC) (2017). The data obtained from the study were analyzed via the Statistical Package for the Social Sciences (SPSS) program (version 22.0, SPSS Inc.). During this evaluation, qualitative data were expressed as numbers (n) and percentages (%); the measurement data were expressed as means and standard deviations. In the statistical analyses, the consistency of continuous variables with the normal distribution was evaluated via the Kolmogorov–Smirnov Test. Pearson's Chi-squared test was used to compare categorical data. P = 0.05 was accepted as the statistical significance limit.

3. Results

The study included 32 patients with transglottic laryngeal cell carcinoma, who were aged 44 to 75 years (mean: 58.4 years). Three patients were female (average age: 46), and 29 were male (average age: 58.8). There was no statistically significant difference in CLNM between male and female patients (p = 0.536) or between smokers and non-smokers (p = 0.591). When the relationship between smoking and lymph node metastasis by gender was examined, again no statistically significant difference was found (p = 0.541). Although the complaints of patients with transglottic tumors varied, hoarseness was observed in 19 patients and respiratory distress in 13. Tracheotomy was performed in seven patients (21.8%) due to breathing difficulties (Table 1).

Table 1. Demographic features, habits and laryngeal location of the tumor

		Patient number	CLNM	p*
Age	58.8 (44-75) years			
Gender	Female	3	1	p=0,536
	Male	29	6	
Smoking	Female	2	1	p=0,541
	Male	29	6	
Complaint	Hoarseness	19		
	Respiratory distress	13		-

*p Pearson Chi-square test.

Patients underwent bilateral neck dissection along with total laryngectomy. Of the 63 neck dissections, five were RND and 58 were FND. In the clinical examination, 18 patients (56.25%) had palpable lymphadenopathy in the neck (56.25%). Six of these (18.75%) presented metastatic cervical lymph nodes, confirmed by pathology; these were bilateral in four patients (12.5%) and unilateral in two (6.25%). In 12 (37.5%) patients with clinical lymphadenopathy (N+), there were no metastatic lymph nodes in the neck. In one N+ patient (right, level IV), a metastatic lymph node was reportedly caused by prostate adenocarcinoma. As a result, of pathological evaluation in one N0 patient (3.1%), metastasis was detected at level IIA. 13 patients (40.6%) without clinical adenopathy presented metastatic adenopathy in the neck. One of these had two lymphadenopathies at level IV, which is reported as thyroid papillary carcinoma metastasis, and a total thyroidectomy was performed.

In seven patients, 19 metastatic lymph nodes were identified as pathological: 42.1% at level IIA, 26.3% at level III, 21% at level IV, 5.2% at level V, 5.2% at level IIB, and 0.0% at level I. Level IIB metastasis was seen in only one patient. This patient had bilateral level IIA, level III, and level IV metastasis. In the same patient, ECE was seen at level IIA and on the opposite side at level IV. While the level IIB metastasis rate was 3.12% among all patients, the rate among patients with metastatic lymphadenopathy was 14.2%. Six of the 32 patients included in the study were T4aN+M0; one was T3N+M0; 14 were T4aN-M0; and 11 were T3N-M0 (Table 2).

Table 2. Tumor location, histopathology, clinical and histopathological cervical lymphadenopathy and TNM classification

Patient no	Tumor location	Histopathology	CLN	Clinical		Histopathological		Level IIB	TNM
				Right	Left	Right	Left		
1	Transglottic	SCC	cN+/pN+ (n=6) %18.75	IIA,III,IV	IIA,III,IV	IIA,III,IV (ece*)	IIA (ece), III,IV	+	pT4N3bM0
2	Transglottic	SCC		III,IV	V	III(ece), IV	V(ece)	-	pT4N3bM0
3	Transglottic	SCC		IIA,III,IV	IIA, III	IIA, III(ece)	-	-	pT4N2aM0
4	Transglottic	SCC		IIA,III,IV,V	IIA	III,V	IIA	-	pT4N2cM0
5	Transglottic	SCC		IIA,III	-	IIA	-	-	pT4N1M0
6	Transglottic	SCC		IIA,III,IV	IIA	IIA, IV	IIA	-	pT4N2cM0
7	Transglottic	SCC	cN+/pN0 (n=12) %37.5	IIA,III	-	-	-	-	pT4N0M0
8	Transglottic	SCC		III	-	-	-	-	pT4N0M0
9	Transglottic	SCC		IIA	-	-	-	-	pT4N0M0
10	Transglottic	SCC		IIA,III,IV	IIA	-	-	-	pT4N0M0
11	Transglottic	SCC		IIA	-	-	-	-	pT4N0M0
12	Transglottic	SCC		IV	-	Prostate met (IV)	-	-	pT4N0M0
13	Transglottic	SCC		IIA, III	-	-	-	-	pT4N0M0
14	Transglottic	SCC		IIA	IIA	-	-	-	pT4N0M0
15	Transglottic	SCC		III	-	-	-	-	pT4N0M0
16	Transglottic	SCC		III	-	-	-	-	pT4N0M0
17	Transglottic	SCC		IIA,II,IV	III	-	-	-	pT4N0M0
18	Transglottic	SCC		IIA	-	-	-	-	pT4N0M0
19	Transglottic	SCC	cN0/pN+ (n=1)%3.1	-	-	IIA	-	-	pT3N1M0
20	Transglottic	SCC	cN0/pN0 (n=13) %40.6	-	-	Papillary ca met (IV)	-	-	pT4N0M0
21	Transglottic	SCC		-	-	-	-	-	pT4N1M0
22	Transglottic	SCC		-	-	-	-	-	pT3N0M0
23	Transglottic	SCC		-	-	-	-	-	pT3N0M0
24	Transglottic	SCC		-	-	-	-	-	pT3N0M0
25	Transglottic	SCC		-	-	-	-	-	pT3N0M0
26	Transglottic	SCC		-	-	-	-	-	pT3N0M0
27	Transglottic	SCC		-	-	-	-	-	pT3N0M0
28	Transglottic	SCC		-	-	-	-	-	pT3N0M0
29	Transglottic	SCC		-	-	-	-	-	pT3N0M0
30	Transglottic	SCC		-	-	-	-	-	pT3N0M0
31	Transglottic	SCC		-	-	-	-	-	pT3N0M0
32	Transglottic	SCC		-	-	-	-	-	pT3N0M0

*ece=extracapsular extension

In this study, thyroid cartilage invasion, combined perineural–perivascular invasion, subglottic extension, and extralaryngeal spread were found to be statistically significant in the occurrence of CLNM (p = 0.020, p = 0.006, p = 0.000, p = 0.000, respectively). The difference between CLNM incidence was also significant in patients with and without preoperative tracheotomy (p = 0.006) (Table 3).

Table 3. Effect of prognostic factors on CLNM

Prognostic factors	n=32	CLNM	p
Ant. commissure involvement	24	7	0.084
Thyroid cartilage invasion	20	7	0.020
Perineural invasion	3	1	0.614
Perivascular invasion	2	1	0.320
Perineural-perivascular invasion	2	2	0.006
Subglottic extension	9	6	0.000
Extralaryngeal spread	9	7	0.000
Preop tracheotomy	7	2	0.006

Adjuvant radiotherapy was applied to 20 patients, who presented thyroid cartilage invasion, extralaryngeal spread, subglottic extension, and multiple and/or ECE metastatic lymphadenopathy. The patients were followed from six to 29 months (average: 12.8 months). Three patients with ECE lymphadenopathy and one patient with peristomal recurrence died within six months. One patient who underwent total laryngectomy and right RND refused opposite-neck surgery and radiotherapy. This patient was admitted with a mass in the opposite neck 1.5 months later. Only 12 patients who underwent surgery and 16 patients who underwent adjuvant radiotherapy (total: 28 patients) were examined at regular intervals.

4. Discussion

There is no ideal treatment protocol for advanced laryngeal carcinomas. Treatment plans are devised according to the extent of each tumor and the presence of cervical lymphadenopathy. CLNM is the most important prognostic factor affecting survival (11). It is difficult to detect the primary site in the examination because patients with transglottic tumors of the larynx usually go to the doctor late. Clinically or radiologically, lymphadenopathy has been reported to cause poor prognosis in patients with laryngeal carcinomas. In neck surgical treatment, which began with RND, shoulder atrophy and loss of function may be caused by cutting the spinal accessory nerve, and morbidities—such as increased intracranial pressure and, thus, increased mortality—have made MRND, and, later, SND, more commonly applied treatments (12). Muzaffer applied RND to 61 patients, MRND to 54 patients, and SND to 61 patients, and reported no difference between the three groups in terms

of regional relapse and overall survival over a two-year follow-up period (13). Chepeha et al. compared MRND and SND patients in terms of shoulder function and found shoulder function to be more limited in patients who underwent MRND (12). In the present study, 63 neck dissections were performed in 32 patients with transglottic laryngeal carcinoma. RND was applied to five necks and FND to the remaining 58 necks, according to the clinical, radiological, and preoperative findings. Metastatic lymphadenopathies with ECE were reported in three of the RND necks and in one of the FND necks. Three patients who underwent RND died within six months due to regional recurrence and one due to peristomal recurrence. One patient with RND rejected opposite-neck surgery and radiotherapy. This patient was admitted with a mass in the opposite neck 1.5 months later.

According to the predictable cervical metastasis model for head and neck SCCs, dissection of the most affected areas and elective dissection of other regions, if there is no metastasis in these nodes, is controversial (2). Among 164 patients with laryngeal carcinoma, Mnejja et al. found 7% of the metastases at level IIA, 4.3% at level III, 2.7% at level IV, and 2.4% at level IIB (14). Gross et al. reported the results of elective and therapeutic neck dissections performed on patients with laryngeal and hypopharyngeal carcinoma and found level IIB metastasis to be 4% and 17%, respectively (15). In these patients, Gross et al. did not find a significant relationship between primary tumor stage, metastasis at levels IIA and III, clinical nodal stage, or ECE and level IIB metastasis. Sezen et al. dissected 673 lymph nodes from level IIA and 340 lymph nodes from level IIB because of 98 neck dissections performed in 67 patients with supraglottic, glottic, and subglottic laryngeal carcinomas. They reported that 11 (3.23%) of 340 lymph nodes dissected from level IIB were metastatic. They did not detect level IIB metastasis in any N0 patients. The distribution of cervical lymph node metastases in the patients who underwent neck dissection was as follows: eight (42.1%) at level IIA, five (26.3%) at level III, four (21%) at level IV, one at level V (5.2%), and one at level IIB (5.2%) (16). In the present study, level IIB metastasis was observed in only one patient, who had clinical and pathological bilateral metastases at levels IIA, III, and IV. In the same patient, ECE was detected at level IIA on one side, and metastases were detected on the opposite side at level IV. While the level IIB metastasis rate was 3.12% among all patients, the rate among patients with metastatic lymphadenopathy was 14.2%. In this study, the total number of reactive lymph nodes detected at levels I, IIA, III, IV, and V in the cervical region was 17.5 on the side where the tumor in the larynx was predominant, 14.3 on the opposite side of the neck, 4.3 at level IIB on the same side as the tumor, and 3.2 on the opposite side of the neck at level IIB.

It has been reported that the most important prognostic factor affecting survival in laryngeal carcinoma is N stage. The other prognostic factors determine survival rate as they increase cervical metastasis. Yilmaz et al. reported that perivascular and perineural spread affect survival and recurrence by causing an increase in CLNM (17). Aydin et al. found a significant relationship between thyroid cartilage invasion and CLNM, and Bai et al. determined that extralaryngeal involvement was associated with CLNM (18,19). Lucioni et al. reported a correlation between paratracheal lymph node and laterocervical node involvement in patients with posterior subglottic extension (20). Özağaç et al. found no significant correlation between preoperative tracheotomy and neck metastasis in patients with laryngeal carcinoma (21). In the present study, combined perineural–perivascular invasion, thyroid cartilage invasion, extralaryngeal spread, and subglottic extension were found to significantly affect CLNM ($p=0.020$, $p=0.006$, $p= 0.000$, $p=0.000$, respectively). However, anterior commissure involvement and solely perineural or perivascular invasion did not significantly affect CLNM ($p=0.084$, $p=0.614$, $p=0.320$, respectively). The authors also found a significant difference between the incidence of CLNM in patients with and without preoperative tracheotomy ($p = 0.006$).

Approximately 60% of locally advanced laryngeal SCC patients require adjuvant radiotherapy. Skora et al. reported that adjuvant radiotherapy was given to 138 patients in the T3-4N0M0 stage, who underwent total laryngectomy and neck dissection; 34 patients experienced recurrence, and the five-year survival rate was 76% (22). Kennedy et al. found a five-year local and regional control rate of 92% after adjuvant radiotherapy in their study consisting of 36 patients in the T3-T4aN0 stage (23). In the present research, adjuvant radiotherapy was applied to 20 patients with postoperative thyroid cartilage invasion, subglottic extension, and multiple or ECE metastatic lymphadenopathy. The patients were followed between six and 29 months (average: 12.8 months). Local and regional recurrence occurred in five of the patients receiving adjuvant radiotherapy, and four of them died. Disease-free follow-up of 27 (84.3%) patients continues. Limitations of the present study included its retrospective design, the low number of patients, the short follow-up period, and the examination of only transglottic tumors.

In conclusion, transglottic laryngeal carcinomas, latent or overt neck metastases can be seen due to the locally advanced stage of the tumor. Dissection at level IIB should be reassessed to decrease morbidity, especially in N0 necks, due to the low incidence of level IIB metastasis, both clinically and pathologically. In treating advanced laryngeal cancers, considering the prognostic factors, the ideal approach would be to create an appropriate treatment plan for each patient.

Conflict of interest

The authors declare no conflict of interest.

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Iron deficiency in women with thyroid-specific autoantibodies: A case control study

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Abstract

Autoimmune thyroid diseases are multifaceted conditions in which the thyroid gland is infiltrated by lymphocytes, resulting in the production of thyroid-specific auto-antibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TGAb). Iron deficiency is a common nutritional deficiency and has multiple adverse effects on thyroid metabolism. The association between iron status and thyroid autoimmunity has not been well-evaluated. This retrospective study aimed to determine whether the frequency of iron deficiency was higher in patients with thyroid autoimmunity than in healthy individuals with negative thyroid autoantibodies. One-hundred-and-eighty female patients with positive thyroid auto-antibodies and 81 healthy controls were involved in the study. Hemoglobin, hematocrit, mean corpuscular volume (MCV), iron, thyrotropin (TSH), TPOAb, TGAb, free-T4, vitamin B12, ferritin and transferrin saturation (TS) were recorded. TSH, TPOAb and TGAb levels were significantly higher, while hemoglobin, hematocrit, MCV, ferritin, iron and TS were significantly lower in the patient group (all, $p<0.05$). Patients with thyroid autoimmunity had significantly higher frequency of lower levels of hemoglobin, iron, ferritin, MCV and TS than healthy controls (all, $p<0.005$). Correlations were found inversely between TPOAb and serum ferritin, iron, and TS levels, and also positively between TGAb and creatinine levels in the patient group. In conclusion, we found increased prevalence of iron deficiency in female patients with thyroid autoimmunity. Patients with autoimmune thyroid diseases were found to be at higher risk of iron deficiency development.

Keywords: anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, ferritin, hemoglobin, iron

1. Introduction

The thyroid gland plays an important role in the regulation of multiple functions, such as metabolic rate, energy expenditure, general homeostasis and the use of other hormones and vitamins in the body. It is also the organ most affected by autoimmune conditions (1). In autoimmune thyroid diseases, the thyroid gland is infiltrated by auto-reactive lymphocytes which cause the production of circulating thyroid-specific autoantibodies. Hashimoto thyroiditis is the most common form of autoimmune disease worldwide and is the most common cause of primary hypothyroidism in iodine-sufficient regions (2). It is more prevalent among women and the 40-60 years age group. The etiopathogenesis of Hashimoto's disease remains uncertain, but it is suggested to be caused by various complex interactions between genetic susceptibility, environmental and nutritional factors, and immune disorders (3). It is frequently accompanied by other autoimmune disorders, such as Celiac disease, chronic autoimmune gastritis, and type I diabetes mellitus (4). Hashimoto thyroiditis is characterized by clinical hypothyroidism and the presence of auto-antibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TGAb) (2). TPO is the key enzyme that oxidizes iodide to iodine that will be incorporated into thyroglobulin for the synthesis of thyroxine (T4) or triiodothyronine (T3) (5). TPOAb, the predominant antibody in autoimmune hypothyroidism, has been reported to be present in over 90% of patients and serves as a useful biomarker to identify disease without a need for thyroid biopsy or surgery (1).

Nutritional factors, including iodine, selenium, zinc, vitamin B12, vitamin D and iron may be associated with thyroid dysfunction (6). Iron deficiency is the most common nutritional disorder. In addition to being a very common cause of anemia, iron deficiency results in multiple adverse effects on thyroid metabolism by reducing activity of heme dependent TPO and interfering with the synthesis of thyroid hormones (7). However, the association between iron status and thyroid autoimmunity has not been well assessed. The present study aimed to evaluate whether the frequency of iron deficiency anemia was more common in patients with thyroid autoimmunity than in the individuals without thyroid disease.

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2. Materials and Methods

This was a retrospective single center study that was carried out from January 2013 to May 2015 in the Endocrinology and Metabolic diseases Departments of Göztepe Training and Research Hospital, Medeniyet University, Istanbul, Turkey. A total of 554 patients with positive TPOAb and/or TGAb who were admitted to outpatient clinics were selected to be included in the study. The study group consisted of euthyroid or subclinical hypothyroid Hashimoto patients irrespective of their treatment status with levothyroxine. Patients younger than 18 and those older than 70 years old, patients with infections, chronic diseases (including diabetes mellitus and hypertension), malignancy, liver, kidney or cerebrovascular diseases, gastrointestinal disorders (including oesophagitis, erosive gastritis, peptic ulcer disease, inflammatory bowel disease and hemorrhoids), endocrine disorders (Cushing syndrome, acromegaly, adrenal insufficiency), autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis) were excluded from the study. In addition, pregnant women, patients with alcohol or substance abuse, those receiving medications other than levothyroxine, patients diagnosed with hypochromic microcytic anemia (other than iron deficiency: thalassemia, sideroblastic anemia) were excluded from the study. A total of 63 patients were excluded from the study with regard to exclusion criteria. Twenty-four patients were not involved to the study, due to taking iron supplementation at screening. Thirteen patients were excluded from study because they had autoimmune diseases including celiac disease and autoimmune chronic gastritis, which are co-morbidities with Hashimoto's disease and could affect the iron status (4). Twenty-six patients were excluded from the study in terms of menstrual disorders. Previous studies have shown that gender differences could affect iron status, so we included only female patients to attain a homogenous patient cohort (8). A final group of 180 female patients with positive thyroid auto-antibodies were included in the study. The control group consisted of 81 healthy women admitted to the hospital for routine examination who were euthyroid or had subclinical hypothyroidism but had no thyroid auto-antibodies. The study protocol was approved by the Research Ethics Committee of Göztepe Training and Research Hospital, Medeniyet University (2015/0023).

According to the World Health Organization criteria, anemia is defined as a hemoglobin value of <12 g/dL in non-pregnant women (9). Patients with serum ferritin level <12 ng/mL, serum iron level <50 µg/dL, MCV <80 fL and transferrin saturation <16% were considered as having abnormal results (10).

Demographic characteristics, co-morbidities and laboratory findings were retrospectively retrieved from patient charts. Hemogram parameters, including hemoglobin (Hb), hematocrit (Hct) and mean corpuscular volume (MCV) were measured with CELL-DYN 3700 System (Abbott Laboratories, IL, USA). Blood biochemistry parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, blood urea nitrogen (BUN), iron, and unsaturated iron binding capacity (UIBC) were determined with spectrophotometric methods using Abbott Architect c8000 autoanalyzer (Abbott Laboratories, IL, USA). Serum thyrotropin (TSH), TPOAb, TGAb, free T4, vitamin B12 and ferritin levels were measured with the chemiluminescent microparticle immunoassay method by Abbott i2000 immunochemistry analyzer (Abbott Laboratories, IL, USA). Results above the manufacturer's reference limit for TPO-Ab and Tg-Ab were considered positive (TPOAb 5.61 IU / ml; TGAb 4.11 IU / ml). All blood samples were obtained from each patient in the morning and examined within less than one hour after the sampling. Each of the biochemical analyses were performed with the same analyzers and the same test kits in the central laboratory of our hospital.

2.1. Statistical Analysis

Data were presented as mean ± standard deviation or median (minimum-maximum) for continuous variables according to normality of distribution for quantitative variables, and frequency (percentage) for categorical variables. In comparison of quantitative data, Student's t-test was used for comparing two groups of normally distributed variables, and Mann-Whitney U test was used for comparing non-normally distributed variables. The Pearson chi-squared test, Fisher's exact test and Yates' continuity correction (Yates corrected Chi-square) were used to compare categorical variables. The Pearson correlation analysis was performed to evaluate the relationship between the variables. All analyses were performed using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). A p value <0.05 was accepted as statistically significant.

3. Results

One-hundred-and-eighty female patients with positive TPOAb and TGAb and 81 healthy women were included in the study. The median age was 43.2±13.1 years in the study group and 46.1±15.3 years in the control group (p=0.143). TSH levels were significantly higher in the patient group (p=0.001). Hemoglobin, hematocrit, MCV, ferritin, iron and transferrin saturation values were significantly lower in patients with positive TPOAb and TGAb (p<0.05 for all). No differences were found between the two groups regarding AST, ALT, vitamin B12, and creatinine levels (p<0.05 for all). Demographic characteristics and laboratory values of the patient and control groups are shown in Table 1.

Table 1. Mean age and laboratory values of the patient and the control groups

	Patients (*n*=180)	Controls (*n*=81)	*p*-value
Age (years)	43.2±13.1	46.1±15.3	0.143
TSH (µIU/mL)	2.7±3.0	1.8±1.1	**0.001**
Free T4 (ng/dL)	1.07±0.30	1.04±0.23	0.267
TPOAb (IU/mL)	107 (0.5-1095)	0.5 (0.5-3.2)	**0.001**
TGAb (IU/mL)	26.58 (0.79-1000)	1.1(0.27-4)	**0.001**
Hemoglobin (g/dL)	12.2±1.3	12.7±1.2	**0.003**
Hematocrit (%)	36.4±3.4	37.7±3.3	**0.004**
MCV (fL)	83.2±7.0	84.8±5.3	**0.037**
Iron (µg/dL)	59.5±33.4	71..6±32.7	**0.007**
UIBC (µg/dL)	285.9±70.6	269.7±71.6	0.092
Ferritin (ng/mL)	24.9±30.9	37.8±33.1	**0.004**
Vitamin B12 (pg/mL)	351±188	377±287	0.457
AST (U/L)	17.8±8.2	18.8±10.4	0.433
ALT (U/L)	17.9±11.0	20.6±13.8	0.126
Creatinine (mg/dL)	0.8±0.5	0.7±0.1	0.059
BUN (mg/dL)	22.5±7.7	26.1±10.0	**0.005**
Transferrin saturation (%)	23.2±16.8	29.3±16.9	**0.008**

TSH: Thyrotropin, T4: Thyroxine, TPOAb: Thyroid peroxidase antibodies, TGAb: Thyroglobulin antibodies, MCV: Mean corpuscular volume, UIBC: Unsaturated iron binding capacity, AST: Aspartate amino-transferase, ALT: Alanine amino-transferase, BUN: Blood urea-nitrogen.

According to the World Health Organization criterias, 83 (46%), 78 (43%), and 79 (44%) TPOAb and TGAb positive patients were found to have abnormal levels of iron, hemoglobin, and ferritin, respectively. TPOAb- and TGAb-positive patients had a significantly higher frequency of having abnormal values in hemoglobin, iron, ferritin, MCV and transferrin saturation compared with the control subjects ($p<0.005$ for all) There is also a significant relationship between TPOAb level and serum iron, ferritin, and transferrin saturation values. (Table-2). When we divided the study group according to serum ferritin levels (for determination of iron deficiency; serum ferritin levels <12 ng/mL), we did not observe any differences between the groups ($p=0.120$ and $p=178$, respectively) (Table 3).

Table 2. Number and percentage of individuals with abnormal levels of MCV, ferritin, transferrrin saturation in patient and control group

	Patients (*n*=180)	Controls (*n*=81)	*p*-value
Low MCV (<80 fL)	53 (29%)	14 (%17)	**0.001**
Low Ferritin (<12 ng/mL)	79 (44%)	19 (%23)	**0.001**
Low Transferrin saturation (<16%)	80 (44%)	19 (%23)	**0.001**
Low Serum Iron (<50 µg/dL)	83 (46%)	22 (%27)	**0.001**
Decreased Hemoglobin (<12 g/dL)	78 (43%)	21 (%26)	**0.001**

In correlation analyses, we found negative correlations between TPOAb and serum ferritin, iron, and transferrin saturation levels in the patient group (Table-4). Also, there was a positive correlation between TGAb and serum creatinine level in patients.

4. Discussion

This study aimed to determine the frequency of iron deficiency anemia in patients with positive thyroid-specific antibodies and to compare results with healthy individuals. We found decreased levels of hemoglobin, hematocrit, MCV, iron, ferritin, and transferrin saturation in TPOAb and TGAb positive patients compared to control subjects. Our results demonstrated higher frequencies of abnormal levels of hemoglobin, iron, and ferritin in patients with thyroid auto-antibodies than the control subjects. We also observed a significant correlation between TPOAb level and serum iron, ferritin, and transferrin saturation values.

Iron is an essential micronutrient and is contained in hemoglobin, myoglobin, and numerous iron-containing enzymes; therefore, it is involved in various metabolic processes including oxygen transport and storage, oxidation-reduction reactions, electron transfer, ATP production, DNA synthesis (11). Iron deficiency is a highly prevalent nutritional deficiency worldwide, with the most common results being anemia, decreased oxygen transport and impaired activity of iron-containing enzymes. Iron metabolism is related with the synthesis and metabolism of thyroid hormone. Several animal and human studies have demonstrated that iron deficiency may lower circulating levels of T3 and T4 and may also decrease peripheral conversion of T4 to T3 (12). TPO is the unique heme-dependent enzyme required for thyroid hormone synthesis through iodide oxidation into iodine and incorporation of iodine to the tyrosyl residue of thyroglobulin for formation of mono-iodotyrosine and di-iodotyrosine (13). TPO becomes active at the apical surfaces of thyrocytes only after binding a prosthetic heme group (14). Iron deficiency may decrease TPO activity, causing lower T4 production –and higher serum

TSH levels due to negative feedback. Iron deficiency triggers ineffective erythropoiesis and reduced oxygen transport to different tissues, which may lead to hypoxia and impaired enzymatic activity in a variety of enzymes, including the enzymes contributing to thyroid metabolism (15). Iron deficiency can also increase in-vitro hepatic reverse triiodothyronine deiodination, suggesting that thyroid hormones tend to be metabolized in inactivating pathways under iron-deficient conditions (16). Therefore, iron sufficiency is important for thyroid hormone synthesis.

Table 3. Comparison of thyroid functions in study and control groups with different ferritin levels

	Patients with iron deficiency* in study group (n=79)	Patients with iron deficiency in control (n=19)	*p* value	Patients with non-iron deficiency in study group (n=102)	Patients with non-iron deficiency in control group (n=62)	*p* value	*p* value**
TSH	2.87±3.03	1.73±1.12	**0.010**	2.56±3.00	1.72±1.11	**0.012**	0.449
T4	1.05±0.25	1.03±0.10	0.507	1.09±0.33	1.04±0.26	0.248	0.306
TPOAb	297.54±337.79	0.55±0.12	**0.001**	222.75±292.97	0.69±0.62	**0.001**	0.120
TGAb	125.18±234.87	1.53±1.09	**0.001**	82.19±177.76	1.45±0.94	**0.001**	0.178

TSH: Thyrophin. T4: Thyroxine. TPOAb: Antibodies against thyroid peroxidase. TGAb: Antibodies against thyroglobulin. Iron deficiency defined as serum ferritin level <12 ng/mL. **p value for comparison of iron deficiency and non-iron deficiency patients in the study group

Thyroid autoimmunity is the leading cause of thyroid dysfunction in iodine-sufficient countries (17). It has multi-factorial etiology and is considered to result from a combination of genetic and environmental factors, as well as nutritional determinants. Erdal et al. showed lower iron and selenium levels in 43 auto-immune thyroiditis patients than healthy controls (18). However, limited studies have investigated the relationship between iron status and thyroid auto-immunity through TPOAb and TGAb. Huet al. found that TPO activity, total T3 and T4 levels, and thyroid follicular volume were lower in iron deficiency rats than in those without iron deficiency (19). However, they did not evaluate TPOAb levels. Veltri et al. showed a cross-sectional study in 1900 pregnant women that iron deficiency was related with a higher prevalence of TPOAb and higher serum levels of TSH and lower free T4, independent of confounding factors including age and body mass index (20). Zhang et al. found in 1592 pregnant women that iron deficiency is a risk factor for increased TGAb, but not for TPOAb or subclinical hypothyroidism (21). Wang et al. demonstrated in 190 patients with TGAb or anti-thyroid microsomal antibody (TMAb) positivity that higher frequencies of hemoglobin and iron was observed in TGAb and TMAb positive patients than healthy subjects (22). They found anemia in 16.3% and iron deficiency in 14.2% of patients with positive anti-thyroid antibody titers. In accordance with these studies, we demonstrated decreased levels of hemoglobin, hematocrit, MCV, iron, ferritin, and transferrin saturation in patients with TPOAb and TGAb positivity compared to healthy individuals. We found higher prevalence of iron, ferritin, MCV, hemoglobin and transferrin saturation deficiency in patients with thyroid-specific antibodies. We also observed correlations between TPOAb and serum iron, ferritin, and transferrin saturation levels. Our results suggest that patients with thyroid-specific autoantibodies were at higher risk of development of iron deficiency and anemia. This may be due to the relationship between TPO activity and iron levels. It may indicate that low TPO activity resulting from low iron status causes an increase in thyroid autoimmunity with aim to maintain function. Low iron status may increase thyroid autoimmunity, as it could alter the binding of T3 to hepatic nuclear receptors and oxygen transport. Iron deficiency may also reduce the activity of other iron-containing enzymes, including myeloperoxidase and cytochrome oxidase, and therefore antibodies against these molecules could cause cross-reaction with TPOAb, leading to higher prevalence of thyroid autoimmunity (23). The relationship between thyroid autoimmunity and iron status may also result from the complex immunological etiopathogenesis of thyroid dysfunctions, in which common genetic and environmental factors play an important role. Besides, iron-deficiency anemia may be the first symptom leading to the diagnosis of subclinical hypothyroidism and thyroid autoimmune diseases. Patients with treatment-resistant anemia should be assessed for thyroid disorders. Autoimmune thyroid diseases should be considered in the differential diagnosis of anemia with unknown origin.

Several strengths of the present study are worthy of mention. Since inadequate intake of iodine could affect thyroid autoimmunity, we carried out the study in an iodine-sufficient area. There are many conditions in the etiology of iron deficiency anemia (24). We excluded conditions that might interfere with iron status, such as chronic inflammation, infections, drugs, pregnancy, smoking and obesity (25). In patients with autoimmune thyroid disease, the risk of iron deficiency may increase with concomitant autoimmune diseases including celiac disease, pernicious anemia, atrophic gastritis, SLE and rheumatoid disorders (4). We also excluded patients with these conditions from the study. Several limitations of the current work should also be mentioned. First, the study had a relatively small sample size. Second, to homogenize the study group, we conducted this study in only females. Thirdly, the study was limited to iodine-sufficient areas; thus, the results may not be generalized for women in iodine-deficient or iodine-excess

areas.

In conclusion, we found increased prevalence of iron deficiency in female patients with thyroid autoimmunity. Patients with autoimmune thyroid diseases were at higher risk of development of iron deficiency and anemia. We think that thyroid-specific antibodies should be investigated in patients with treatment-resistant iron deficiency anemia.

Conflict of interest

None to declare.

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The study protocol was approved by the Research Ethics Committee of Göztepe Training and Research Hospital, Medeniyet University (2015/0023).

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Evaluation of poisoning cases admitted to the pediatric emergency clinic retrospectively

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Abstract

We aimed to analyze the demographic and epidemiologic features of the acute poisoning cases admitted to the pediatric emergency department. We evaluated 439 cases aged 18 and under applied to Ondokuz Mayıs University Medical Faculty Pediatric Emergency Department between 01/01/2019 and 01/01/2020 retrospectively. The mean age of patients was 7.5±6.39 years.242(55.1%) patients were female. Intoxications were most common in winter season (36.4%) and most seen with caustic corrosive substances. Of the poisoning agents, 35.5% (n:156) were nonpharmacologic and 57.4% (n:252) were pharmacologic agents. In poisonings with pharmacological agents, central nervous system drugs were the most common, while caustic-corrosive substances were most common in nonpharmacological poisonings. While caustic corrosive substances are in the first place in poisonings between the ages of 0-5 (47.4%), in the 5-11 age group; carbon monoxide (25%) and in the 11-18 age group; multiple drug poisonings (15%) were most common observed. Naphthalene intoxication was seen in 4.8% and alcohol was in 4.5%, higher than the literature. In our study, it was observed that alcohol use was high among young people in our region. Also, it is observed that naphthalene poisoning was in high rate. We believe that this study will guide the measures to be taken.

Keywords: adolescents, childhood, pediatric emergency, poisoning

1. Introduction

Poisoning is when a substance is taken into the body through the skin, eyes, mouth, respiratory or vascular access, causing toxic symptoms and sometimes even life-threatening (1). Poisoning is among the preventable causes of mortality and morbidity in children. Among the causes of death between the ages of 1-14, poisoning ranks first in developed countries, and comes after respiratory tract infections and gastroenteritis in developing countries such as our country (2, 3). Mortality from poisoning is four times higher in low- and middle-income countries than in high-income countries (4). The global death rate from poisonings for children younger than 20 years is 1.8 per 100 000 population (5).

While the annual frequency of intoxication caused by accident and suicide is between 0.02-0.93% in developed countries, it is known that this rate is 0.46-1.57% in Turkey (6). We decided to investigate pediatric poisonings in our area retrospectively because we thought that alcohol and naphthalene poisoning was high among the pediatric emergency admissions in our hospital and there were not enough studies about them.

Approximately two-thirds of all poisonings occur in childhood. Children under 6 years of age constitute 55% of all pediatric and adult cases and 80% of pediatric cases (7). Poisoning varies geographically according to different socio-cultural and environmental risk factors. Drugs given by parents in the first 1 year of age, drugs kept in closets at the age of 3-5, and suicidal poisoning in school age and adolescence are common (5).

In this study, we aimed to retrospectively evaluate intoxication cases brought to our hospital's pediatric emergency service.

2. Materials and Methods

Ethics committee approval for the study was received from Ondokuz Mayıs University Ethics Committee (2020/411) on 13/07/2020. This study was conducted in accordance with the International Ethics and Declaration of Helsinki.

439 patients who applied to the Pediatric Emergency Service of the Ondokuz Mayıs University Faculty of Medicine in Turkey between 01/01/2019 and 01/01/2020 and whose hospital records could be accessed were evaluated retrospectively. The cases were evaluated in terms of age, gender, month of application, cause of poisoning, application complaint, treatment applied and prognosis. Drugs causing intoxication were grouped to determine their properties.

All patients under 18 years of age and considered intoxication were included in the study. Food poisoning, snake poisoning, allergic reactions and by-drug reactions that can be considered within the scope of toxicology were not included in the study. After a thorough evaluation by the principal investigator, children with suspected intoxication without a clear etiology were also excluded from the study.

All poisoning cases were consulted with the Poison

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Information Center, and if necessary, gastric lavage was performed and / or activated charcoal was given. It was administered if the agent causing the poisoning had an antidote. The routes of exposure of the patients were oral or inhalational. According to the examination and vital signs after admission, the child was admitted to the emergency or intensive care units.

Our patients were categorized in 4 classes according to age groups as 0-2 years, 2-5 years, 5-11 years, 11-18 years.

2.1. Statistical Analysis

SPSS (Statistical Package for Social Sciences for Windows v.21.0 SPSS (Chicago, IL, USA)) program was used for statistical evaluation. Data are given as numbers and percentages.

3. Results

A total of 439 cases whose ages were between 0 and 18 years (mean 7.5±6.39 years) and whose records were available were evaluated. The ratio of poisoning cases to all emergency admissions was 1.2%. 55.1% of the patients were female patients and the male: female ratio was 0.81. According to age groups, the proportion of boys between the ages of 2-5 (41.7%) was higher, while girls were more between the ages of 11-18 (43.8%). The most common age group for poisoning was 11-18 years (Table 1).

Table1. Distribution of the cases by age group and gender

	0-2 age n (%)	2-5 age n (%)	5-11 age n (%)	11-18 age n (%)	Total n (%)
Male	43 (21.8)	82 (41.7)	12 (6.1)	60 (30.4)	197 (44.9)
Female	49 (20.2)	75 (31)	12 (5)	106 (43.8)	242 (55.1)
Total	92 (21)	157 (36)	24 (5.4)	166 (37.6)	439 (100)

35.5% (n:156) of the cases were poisoned with non-pharmacological agents and 57.4% (n: 252) of them were with pharmacological agents (Table 2, 3). Central nervous system drugs were the most common (13.2%), antidepressants were the most common among pharmacological agents (7.2%), while multiple drug intoxications were in the second order (7%). Paracetamol poisoning was in third place (3.8%) grouped among analgesics (Table 2). Caustic-corrosive substances were the most common in non-pharmacological intoxications (13.2%), followed by naphthalene (4.8%) and alcohol intoxication (4.5%) (Table 3). In 31 patients (7.1%), the cause of poisoning could not be evaluated due to missing data records.

Considering the time of application according to the season (January-February-March are called winter, April-May-June are spring, July-August-September are summer, October-November-December are autumn), intoxications were seen most frequently in winter (36.4%) and with caustic corrosive substances. The autumn was in second place and poisoning with nonsteroidal anti-inflammatory drugs was the most common in this season (Table 4).

In current study, while poisoning with caustic corrosive substances was in the first place (34.7%) between the ages of 0-2, naphthalene poisoning was the second (6.52%). Caustic corrosive substances were again most common (12.7%) between the ages of 2-5, naphthalene intoxication was the second (8.2%), and paracetamol poisoning was also common in this age group (6.3%). In the 5-11 age group, poisoning with carbon monoxide (25%) and caustic corrosive (20.8%) substances was common. Multiple drugs (15%) and antidepressant (12.6%) poisonings were observed between the ages of 11-18. Alcohol intoxication was seen in 12% of this age group (Table 5).

Table 2. Pharmacological factors caused poisoning

Agent	n	(%)
Central nervous system drugs	58	(13.2)
Antidepressants	32	(7.2)
Antipsychotics	18	(4.1)
Antiparkinsonian drugs	4	(0.9)
Amitriptyline	1	(0.2)
Psychostimulants	3	(0.6)
Antiepileptics	12	(2.7)
Antihypertensives	7	(1.6)
Antibiotics	6	(1.3)
Antigribals	14	(3.1)
Analgesic-antipyretics	29	(6.6)
Ibuprofen	4	(0.9)
Paracetamol	17	(3.8)
Salicylate	8	(1.8)
Nonsteroidal anti-inflammatories	23	(5.2)
Antihistamines	5	(1.1)
Antidiabetics	3	(0.6)
Hormone-containing drugs	12	(2.7)
Cardiovascular system drugs	12	(2.7)
Vitamin-minerals	7	(1.6)
Respiratory system drugs	6	(1.3)
Gastrointestinal system drugs	10	(2.2)
Iron-containing drugs	11	(2.5)
Musculoskeletal system drugs	6	(1.3)
Myelorexanes	1	(0.2)
Colchicine	5	(1.1)
Multiple drug intake	31	(7)
Total	**252**	**(57.4)**

24.1% of the poisoning cases were caused by suicide, and 75.9% were caused by accident. Suicidal poisoning was more common in girls (79.2%) and multiple drugs were the most taken drugs, followed by antidepressant and antiepileptic drugs. Child psychiatry consultation was requested for all patients who took drugs for suicidal purposes.

A poison counseling center was called for all poisoning cases and when necessary, gastric lavage was performed and activated charcoal was given. In the follow-up of the patients,

it was determined that 97.5% were hospitalized in the emergency department and 2.5% in intensive care. There were no cases that resulted in death.

Table 3. Non-pharmacological factors caused poisoning

Agent	n	(%)
Mushrooms	11	(2.5)
Pesticide-insecticides	9	(2)
Carbon monoxide	13	(3)
Caustic-corrosive substances	58	(13.2)
Mercury	4	(0.9)
Alcohol	20	(4.5)
Opiate	5	(1.1)
Detergents	1	(0.2)
Antiseptics	1	(0.2)
Hydrocarbons	32	(7.3)
Naphthalene	21	(4.8)
Thinner	8	(1.8)
Other	3	(0.6)
Plants	2	(0.4)
Total	**156**	**(35.5)**

Table 4. Distribution of poisoning cases according to the seasons and the most common factors

Season	Most common factor	Total number of patients / most common factor n (%)
Winter	Caustic corrosive substance	160/21 (36.4%)
Spring	Caustic corrosive substance	96/13 (21.8%)
Summer	Caustic corrosive substance	84/16 (19.1%)
Autumn	Nonsteroidal anti-inflammatories	99/11 (22.5%)

Table 5. The most common causes of poisoning by age

Age	The most common factor	Number of Cases / Total number of patients (n) (%)
0-2 years	Caustic corrosive substance	32/92 (34.7%)
2-5 years	Caustic corrosive substance	20/157 (12.7%)
5-11 years	Carbon monoxide	6/24 (25%)
11-18 years	Multiple drug intake	25/166 (15%)

4. Discussion

The purpose of the study was to evaluate poisoning cases in our rural area and calling attention to common poisoning agents.

In acute poisonings, which constitute a significant part of emergency admissions, early diagnosis and treatment are of great importance because of the high mortality and morbidity rates when intervened late (8).

Poisoning in the first year of life is usually caused by parental mistakes. Intoxications between the ages of 1-5 are caused by unconscious and careless parents leaving the drugs or other toxic substances in the reach of children and not following their children closely enough or keeping them in containers that do not belong to them. The children aged 12-19 are mostly caused using drugs or substances for suicide purposes (1).

In our study, the average age of the patients was 7.5 years. Poisoning in children under six years of age constitutes approximately 80% of childhood poisonings (7). The reason for this those children at this age are very active, inquisitive, curious about learning and try to recognize every item they find by putting them in their mouths (9). In the multicenter study conducted by Dayasiri et al. (10) on 1621 children, 80% of the children were under five years old. In the study of Berta et al., (11) 72.9% of the children were under four years old. In another multicenter study conducted on 2154 children, 67% of children were younger than four years (12). In current study, it was found that 57% of the cases were under 5 years old. In our study, the smallest case was a 22-day-old baby and the mother accidentally prepared and drunk formula with water containing descaler and intoxication occurred. Another youngest patient was a one-month-old baby, and he was poisoned by his older brother because he took a motility-reducing drug containing diphenoxylate and atropine sulfate.

Gender factor is important in intoxication cases. Most studies have shown that the cause of poisoning is mostly accidents and that poisoning cases in children are most common in boys between the ages of 1-5, and in adolescents when drugs taken for suicide are more common in girls (12). In our study, the male/female ratio was found to be 0.8. When grouped by age, the ratio of boys/girls for 0-5 years old was one, after the age of 11 this ratio was found to be 0.6. In the study of Berta et al. (11) 55% were male and Dayasiri et al. (10) the ratio of males was 60%.

When all our cases were evaluated, it was seen that the poisoning occurred because of an accident in 75.9% of the cases and suicide in 24.1% of the cases. In literature it is reported that 85% of poisonings were accidental, 10.6% therapeutic error, 2.3% suicide attempt and 1.5% recreational (11). In current study suicidal poisoning in adolescent girls was found to be frequent, consistent with the literature (n=84) (male/female ratio 0.27) (13). It made up 79.2% of the total suicide cases (n=106) and it was mostly by their own antidepressant drugs or by multiple drug poisoning. The high rate of suicide in girls may be related to their early maturity, emotional behavior, pressure, and intense psychological conflicts during adolescence.

The most common factors that increase the possibility of poisoning in our country are small children are often left at home alone, with a sibling or friend, and medicines and cleaning agents are kept within easy reach of children. In addition, the low level of education and unconsciousness of the families is another reason for this. It is thought that

increasing the level of education, packaging the medicines and cleaning materials in protected packages, and keeping the cleaning materials in their own packaging will significantly reduce poisoning.

We observed that poisonings were most common in winter and then autumn months compared to other seasons. Like our study, Biçer et al. (14) showed that, poisoning was most common in winter and autumn months, while Kösecik et al. (15) found most frequently seen in spring and summer. In another study, no seasonal differences were found in poisoning cases (16).

In our study, while poisoning with caustic corrosive substances was the most common (34.7%) between the ages of 0-2, naphthalene poisoning was the second (6.52%). Caustic corrosive substances were again most common (12.7%) between the ages of 2-5, naphthalene poisoning was the second place (8.2%), and paracetamol poisoning was also common in this age group (6.3%). Among the children in the 5-11 age group, the most common poisonings were carbon monoxide (25%) and then caustic corrosive (20.8%) substances. In the age group of 11-18 years, the most common intoxications with multiple drugs (15%) and intoxications with antidepressants (12.6%) were observed. Alcohol intoxications occurred in 12% of this age group and 4.5% of all intoxications, and this rate was higher than the literature. In a study conducted by Biçer et al. (14) from Istanbul, the rate of alcohol intoxication was found to be 1.14%, and in a study conducted in Konya, it was found to be 1.4% (17). In our study, drug poisoning rate was 3% of 11-18 age group children and 1.1% among all children. In a study conducted by Yazar et al. (18) from Konya, this rate was 2.8%.

In current study, the high rate of poisoning with naphthalene was remarkable and was higher than the literature (4.8%). In the study of Biçer et al. (14) naphthalene intoxication rate was found to be 1.5%.

57.4% (n:252) of the cases were poisoned with non-pharmacological agents and 35.5% (n:156) were poisoned with pharmacological agents. Biçer et al. (14) and Çam et al. (19) found drugs in the first place among the intoxication agents (44.9%). In the study of Berta et al. (11) non-pharmacological agents (59%) were the most common, and household cleaning products were the most common among them, while pharmacological agents constituted 41% of poisonings. Among the pharmacological agents, analgesics (20.8%) were the most common, followed by psychotropics (18.2%) and cardiovascular drugs (12.6%). Dayasiri et al. (10) reported that, the most common poison was kerosene oil, followed by paracetamol. In the study of Mintegi et al. (12) conducted from Spain, 54.7% of the cases (the most used drug paracetamol) included local products in 28.9%, alcohol in 5.9%, carbon monoxide in 4.5% and illegal drugs in 1.5%.

Among the non-pharmacological intoxication agents, caustic-corrosive substances (13.2%) took the first place, followed by naphthalene (4.8%) and alcohol intoxication (4.5%), respectively. The rate of mushroom poisoning was 2.5%. In a similar study conducted in our region, the rate of naphthalene poisoning was 6.09% and the rate of mushroom poisoning was close to our study (3.65%) (20). Naphthalene poisoning is rare in children due to its pungent odour, taste, insolubility in water, and poor absorption from the gastrointestinal tract. The small size and coloration of naphthalenes may attract the attention of children and cause accidental ingestion. It results from intravascular hemolysis. Supportive therapy includes transfusion of packed red blood cells, if needed, monitoring of fluid and electrolyte balance, and administration of alkalis (21).

Central nervous system drugs were the most common cause of intoxication with drugs and among these, antidepressants (7.2%) followed by multiple drug intake (7%) and analgesic-antipyretic (6.6%). Çam et al. (19) and Ağın et al. (22) reported that central nervous system (44.6%, 45% respectively) and analgesic-antipyretic drugs (15.7%, 26.3% respectively) were the leading agents. In the study of Biçer et al., (14) analgesics took the first place (22.3%) and the second was antidepressants (16.9%). In the study of Boran et al. (23) central nervous system drugs took first place among drugs (41.2%), while analgesics (20.2%) were the second.

The first treatment in poisoning is the emergency patient approach protocol (ABCD). In addition, giving specific antidotes for the poisoning agent, changing its metabolism, or increasing its excretion from the body, preventing its absorption, and treating the symptoms are other treatment methods (18). It is of great importance to apply to a health institution as soon as possible when poisoning is exposed or when this situation is noticed. Early initiation of the treatment process is directly proportional to the reduction in mortality and morbidity. Applications such as gastric lavage and drinking activated charcoal are highly effective in the first hour. In our study, most of the patients were referred and gastric lavage and activated charcoal application were performed before they arrived. The mortality rate of intoxication cases ranges from 0.1% to 3.9% (24). While there were some patients presenting with colchicine intoxication, which is known to have high mortality, none of our patients died, 11 patients were followed up in intensive care. The average follow-up period of all cases was 1 day.

One of the limitations of our study is the use of secondary data based on patient treatment forms, which prevents us from controlling the quality of information recorded in medical records. So, we could not determine the time between the time of poisoning and the emergency application.

In conclusion, significant progress has been made in the treatment of poisoning, but the most valid method is preventive measures. For this, these are recommended; family education, keeping drugs or toxic substances out of the reach of children and not putting them in bottles that do not belong to them, producing boxes and lids that cannot be opened by children, placing warning labels on drugs, increasing the number of poisoning centers and increasing the number of health personnel trained on poisonings.

In current study, it was observed that alcohol use was at a high level among the youth in our region. In addition, it is seen that naphthalene poisoning is higher than the literature. Alcohol use among adolescents is alarming. We believe that this study will guide the measures to be taken.

Conflict of interest

None.

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Ethics committee approval for the study was received from Ondokuz Mayıs University Ethics Committee (2020/411) on 13/07/2020.

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Evaluation of the protective effects of folic acid on the lung exposed to 900-MHZ electromagnetic field: A stereological and histopathological study

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Abstract

There is strong scientific evidence that radio frequency (RF) radiation is harmful to life. Exposure to radiation may cause lung toxicity and respiratory disorders. Folic acid (FA) is one of the powerful antioxidants that minimize oxidative stress in the biological system. In this study, we evaluated the effectiveness of the FA against the EMF-induced potential negative effects on the lung. Twenty-four male *Wistar albino* rats were divided into the four groups; control group (Cont), electromagnetic field group (EMF), FA treated group (FA), and electromagnetic field exposure + FA treated group (EFA). After the routine histological procedures, volumes of the alveoli, bronchioles and blood vessels have been estimated by the Cavalieri principle. It was found that a significant decrease in the mean volume of alveoli, bronchioles and blood vessels in EMF group in comparison of the Cont group ($p<0.01$). Besides this, histopathological analysis demonstrated that there was impaired lung structure, shrunken alveoli, and increased thickness of the alveolar wall in the EMF group sections. In the EFA group, significant protective effects were observed in the structures volumes and histopathology ($p<0.01$). These findings corresponded with the antioxidant effect of FA treatment. Our results suggest that FA protected alveoli, bronchioles, and blood vessels against EMF-induced lung injury. Thus FA has the potential to be a therapeutic agent.

Keywords: electromagnetic fields, folic acid, lung injury, Cavalieri Principle, stereology, antioxidant

1. Introduction

The exposure to electromagnetic fields (EMF) is increasing as a parallel of the developing technology. Many of electrical equipment especially mobile phones, emits the EMF, which ultimately negatively affects the human health. Several studies have reported that EMF caused cognitive impairment (1), depressive disorder (2), anxiety-like behaviour (3) and obsessive-compulsive disorder-like behaviour in brain (4). Moreover, exposure to EMF has been associated with reproductive function failure such as decreasing of sperm motility, inhibin B, prolactin, activin B, FSH and LH hormone levels in male Sprague dawley rats (5). Saygın et al. (6) have found a decrease the serum testosterone levels in the rats exposed to 2.45 GHz EMF.

EMF causes an increasing the free radicals by the Fenton reaction in the tissues; this may change the cellular balance and leads to the cell damage (7,8). The oxidation products are harmful for the cellular components such as lipids, proteins, and DNA. Furthermore, the oxidative stress is associated with the apoptotic and necrotic cell death (9). It is known that, H_2O_2 plays an important role in carcinogenesis due to its diffusion capability throughout the mitochondria and across the cell membranes (10). Apart from this, EMF may have cytotoxic, genotoxic and carcinogenic effects on different organ (11-13). It was shown that the increased levels of reactive oxygen cause breast cancer as well as cell loss and dysfunction (14). Soffritti et al. (15) detected that increased genotoxicity in several tissues such as; heart, liver, pancreas, brain, skin, kidneys. In the tissue, generation of large amounts of free radicals can also disrupt the intracellular antioxidant defence mechanism. In this regard, it is very important that an antioxidant treatment can be applied to minimize possible cell damage. FA is a water-

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soluble vitamin with a high antioxidant capacity. It is involved in the synthesis, repair and methylation of DNA or RNA thus functions in the prevention of the cancer formation (16). It has been reported that FA inhibits EMF-induced oxidative brain damage (17). In a stereological study, it was found that folic acid has protective effects on the kidney against the side effects of exposure to electromagnetic radiation (18). Therefore, in this study we aimed to investigate the potential protective role of FA against the 900-MHZ EMF exposure in the lung.

2. Material and methods

2.1. Animals

Twenty-four male *Wistar albino* rats (12 weeks old, weighing 250 ± 50 g) were obtained from Experimental Animal Center of the Ondokuz Mayis University (Samsun, Turkey). All the experimental procedure was approved by the Ethical Committee at the Ondokuz Mayis University (HADYEK/2013-23, 27.08.2014). Animals were randomly divided into four experimental groups with six rats each groups (n=6). The animals were maintained *ad libitum* feeding schedule, housed individually in a 12-h light: 12-h dark cycle (lights on at 08.00 am–08:00 pm) at a temperature of 22 ± 2°C and 45–55% humidity. All experiments were performed in accordance with the guidelines of the European Community Council for experimental animal care.

2.2. Groups

Control (Cont): The rats were not received any treatment and EMF exposure. Electromagnetic field exposure (EMF): The rats were placed in a special apparatus and exposed to 900 MHz EMF for one hour per day (13: 30-14: 30) during the 21 days. No treatment was given to this group (17). Folic acid (FA): FA was given by gavage during the 21 days (50 mg/kg/day of FA, dissolving in 2 ml distilled water). This group was not received EMF exposure (17). EMF+FA: During the 21 days, FA was given by gavage (50 mg/kg/day of FA, dissolving in 2 ml distilled water) and subsequently animals were placed EMF apparatus and they were exposed to 900 MHz EMF one hour (13: 30-14: 30) per day (17).

2.3. Electromagnetic field exposure system

The system we use for EMF exposure; it is a signal generator (Microwave Test Transmitter, Set Electronic Ltd, Turkey) with 1-2 watt output (PW=Pulse Wave) that can operate at 900-1800 MHz frequency. This system works by connecting a 16-section round cage made of polycarbonate with a monopole antenna that can emit electromagnetic waves. In the setup, the antenna is placed in the center, equidistant and perpendicular to all the partitions in the cage, in order to provide an equal distribution of EMF from the monopole antenna to the compartments. In addition, the power density in the area close to the monopole antenna was precisely measured with the electric field probe (EXTECH RF EMF strength meter) during the experiment. For exposure, rats are positioned equidistant from each other with their heads facing the monopole antenna. The rats belonging to the EMF groups were exposed to 900 MHz EMF for 1 hour a day at the same point for 21 days (17).

2.4. Histological and stereological procedure

End of the experimental processes, the tissues of animals were fixed by cardiac perfusion (10% formalin). The lung tissues, after the processed of using routine histological techniques, were embedded in paraffin and were cut the section (10 μm) by using the microtome (Leica RM 2135, Leica Instruments, Nussloch, Germany) then stained with hematoxylin-eosin (H&E).

2.5. Stereology

The calculation of the reference volume by the Cavalieri method is based on multiplying the surface area of the object by the average section thickness. Surface areas of the sections can be estimated using the point-counting grid that is consists of systematic points (+), which is separated at an equal distance from each other. Each of the points in this grid represents a unit grid area between four points. After superimposing of the grid randomly on the sections, total point numbers that are hit to related area or region would give an estimation of surface area. When the area of a point multiplies with the total number of points intersecting with the structures in the section, the total area is calculated (19, 20).

$$V_{ref} = \Sigma P_i \cdot \hat{t}$$

$$P_i = P(a)$$

V_{ref} is the reference volume, ΣPi is the total number of point superimposed to related area in the sections, $\hat{t}$ is the average section thickness and P(a) represents the area represented by a point (20).

For this method, sampling interval determined by the pilot study and cross-sectional images were taken in tissue sections with a 4X objective (Olympus BX43, Center Valley, PA). By using the Image J program (Image Processing and Analysis in Java, NIH, USA), the point counting grid was placed on the images and calculated interested structures' (alveoli, bronchioles and vessel) area.

2.6. Statistical analysis

After the normality test, data were analyzed with the One-way ANOVA (Tukey-Post Hoc Test). Results were expressed as the means ± SEM. Statistical analyses were performed on SPSS 20.0 for Mac IBM Corporation (SPSS Inc., Chicago, IL, USA). All statistical values under 0.05 were considered significant.

3. Results

3.1. The mean volume of alveoli

The mean volume of alveoli in EMF group was significantly decreased compared to the Cont group ($p<0.01$). It was observed that significant increase in the alveoli volume of EFA group compared to the EMF ($p<0.01$). Moreover, there were no significant differences between the Cont and EFA group's alveoli volume ($p>0.05$), Table 1, Fig.1.

3.2. The mean volume of bronchioles

The mean volume of bronchioles in the EMF group was significantly decreased compared to the Cont group ($p<0.01$).

Furthermore, the volume of bronchiole in the EFA group showed significant increase compared to the EMF groups ($p<0.01$). There were significant differences between the Cont with the EFA groups ($p<0.01$), Table 1, Fig. 2.

Table 1. The mean coefficient of error (CE) and coefficient of variation (CV) values of stereological analysis of total volume of alveoli, bronchioles and blood vessels were given for the all groups

Groups		Alveoli	Bronchioles	Blood vessels
Cont	CE	0.05	0.05	0.05
	CV	0.06	0.07	0.08
EMF	CE	0.01	0.02	0.05
	CV	0.04	0.02	0.06
FA	CE	0.05	0.05	0.04
	CV	0.07	0.03	0.07
EFA	CE	0.06	0.03	0.03
	CV	0.04	0.04	0.07

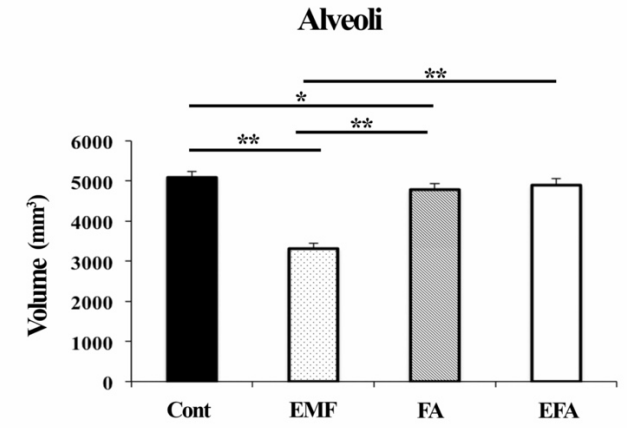

Fig. 1. The graph shows the mean alveolar volume between the groups in the lung tissue (mean± SEM). (*) and (**) show statistical differences under $p<0.05$ and $p<0.01$ level, respectively

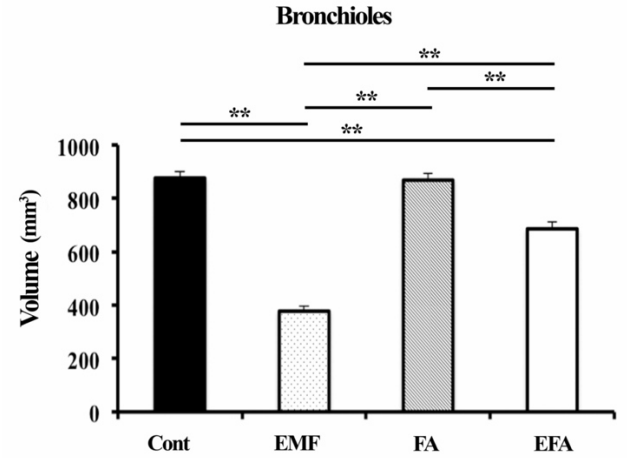

Fig. 2. The graph shows the mean volume of bronchioles between the groups in the lung tissue (mean± SEM). (**) Show statistical differences under $p<0.01$ level.

3.3. The mean volume of blood vessels

The mean volume of blood vessels in the lung was decreased in the EMF groups compared to the Cont group ($p<0.01$). In contrary to this, a significant increase was found in the EFA groups compare to the EMF group ($p<0.01$). There were differences between the Cont and EFA ($p<0.05$).

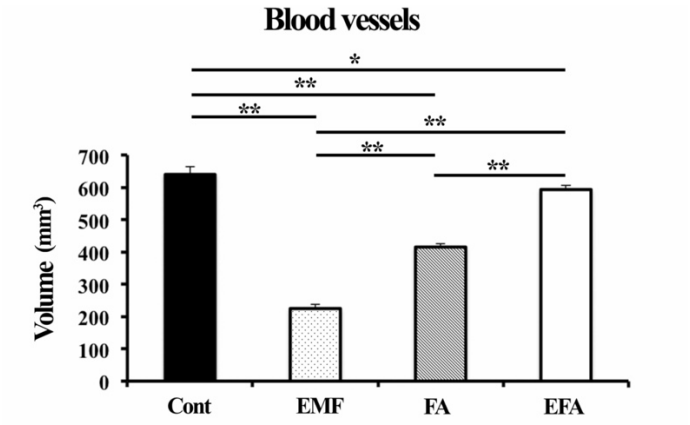

Fig. 3. The graph shows the mean volume of blood vessels between the groups in the lung tissue (mean± SEM). (*) and (**) show statistical differences under $p<0.05$ and $p<0.01$ level, respectively

3.4. Histopathological results

Histopathological observations were done in the HE stained sections. In the Cont group, general structure of lung were look in normal, the alveoli components were clearly observed; its walls thickness was normal. The bronchioles and vessels have well-structured layers and their lumens were seen open. The alveolar wall in the EMF group was thicker than Cont and EFA groups. Most of the area was seen with edematous. Also, alveolar haemorrhage was seen in the alveolar walls in the EMF exposed group. In the EMF group alveoli there is pronounced blood cells infiltration, which are neutrophil, lymphocytes and monocyte were seen. Also, it was observed that the wall of the bronchioles was split and the epithelial cells were damaged in the EMF exposed group. On the other hand, in the EFA group, the protective effect of folic acid was seen in the alveoli, bronchioles and vessels structures since they look very healthy and all structures could be seen clearly. It is observed that there is a clear delineation of the alveoli walls as well as the bronchial walls well organized in the EFA group. Similarly, In the EFA group, the vessels were well preserved and their walls were visible (Figs. 4-6).

4. Discussion

Today, individuals are exposed to electromagnetic waves throughout their lives, starting from the womb. The effects of electromagnetic waves, which are also defined as environmental pollution factors, on the human body are undoubtedly an issue that needs to be investigated. For this aim, in the present study, we evaluated that the protective effects of FA on EMF exposed lung tissues. Studies have reported that the radiation emitted by mobile phones can cause oxidative stress by increasing free oxygen radicals (ROS) in various tissues (21, 22). It has been shown that EMF exposure causes abnormal changes in intracellular antioxidant defence systems such as MDA and GSH due to excessive production of ROS in the body (17, 21). Odacı et al. (23) found that prenatal exposure to 900-MHz EMF causes a significant decrease in the total number of granule neurons in the dentate gyrus.

Similarly, it was found that pyramidal cell number significantly reduced in the EMF exposed group (24). The dentate gyrus and hippocampus cell loss may be mediated by the induction of oxidative stress in the nerve tissues by the EMF.

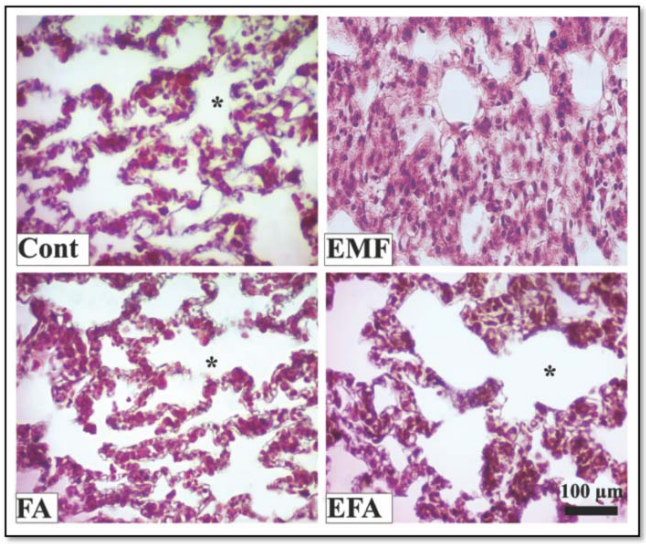

Fig. 4. Light microscopic images were taken from the sections of the alveolar region of the lung. There was no clear delineation of the alveolar structures in the EMF group. Moderate pulmonary oedema was detected in the EMF exposed group. Based on histological structure a significant protective effect of the FA treatment was observed in the EFA group. It was observed that the general morphology of the cells in these group alveoli was seen healthy. Not only all structures were preserved but also the alveolar cell borders were clear in the EFA group. The FA ameliorates the side effect of EMF on the lung tissue. *; Healthy alveoli, Hematoxylin and eosin staining

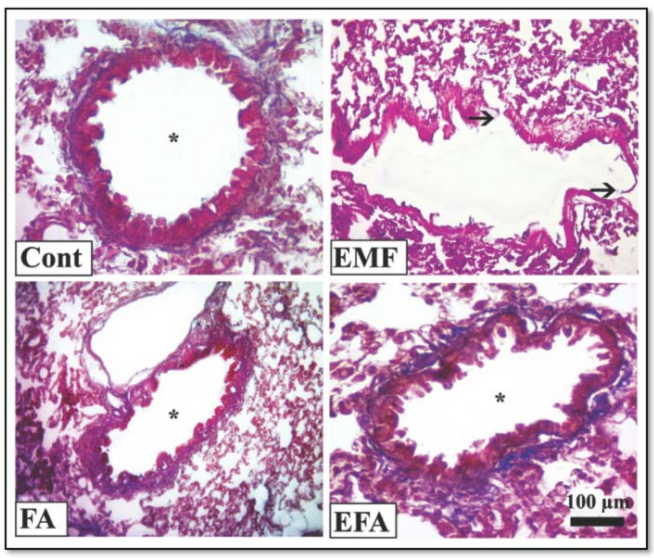

Fig. 5. Light microscopic images shows bronchioles in the lung. The normal structured bronchioles (star) were seen in the Cont, FA and EFA groups. It is noticed that there was heavily impaired wall (arrow) of bronchioles in the EMF group. Hematoxylin and eosin staining

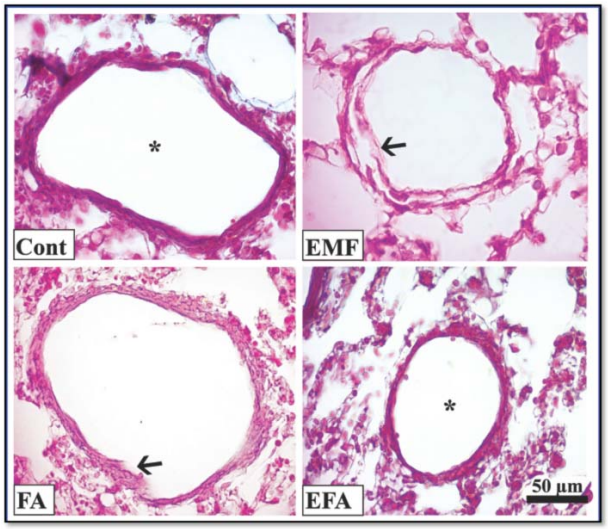

Fig. 6. Light microscopic images shows that blood vessels. The stars indicate the normal structured vessels in the Cont and EFA groups. In the EMF group sections, it was observed that the vascular wall was thinned and the endothelial integrity was impaired (arrow). It is seen that FA administration has protective effects on the vessels in the EFA group. Hematoxylin and eosin staining

Yahyazadeh et al. (25) investigated that effect of 900-MHZ EMF on the lung. They showed that mean volumes of alveoli, bronchioles and blood vessels were significantly decreased in EMF group compared to the Cont group. They also detect histopathological alterations such as irregularity of the epithelial border and dispersion of connective tissue in bronchiole in the EMF group sections. Baltacı et al. (26) found that 50-Hz EMF leads to increases of MDA level in the lung tissue. Although GSH levels were also increased in response to increased MDA levels in this study, they were insufficient to restore MDA levels to control values. In the light of these findings, the researchers concluded that despite the increased antioxidant system activity, the increased tissue damage in the lung tissue as a result of exposure to EMF could not be prevented. Another study reported that exposure to a 50-Hz EMF increased the levels of SOD and TBARS in lung tissue (10). Similarly, Seyhan and Canseven (27), reported that exposure to 50-Hz EMF negatively affects the antioxidant defence systems in many organs such as the spleen, skin, lung, kidney and brain. According to all these studies results, it is clear that EMF causes to tissue damage by negatively affecting the antioxidant defence system. In several in vivo studies with the mice and rats, the EMF is thought to be cause cell death (apoptosis) (8, 28, 29). It has been reported that folic acid has free radical scavenging properties and antioxidant activity (30). The antioxidant activity of folic acid is mediated by many mechanisms that can increase total antioxidant capacity (TAC) and reduce ROS formation (30). In one study, it was reported that folate intake supports lung functions and is beneficial (31). In a meta-analysis study, it was reported that folic acid supplementation could significantly improve markers in the antioxidant defence system by increasing serum GSH and TAC

concentrations and decreasing serum MDA concentrations (32). Kivrak et al. (17) reported that folic acid showed neuroprotective effects in the brain cells due to the its antioxidant activity. In another study, folic acid administration in diabetic rats has been shown to reduce oxidative damage (33).

In conclusion, we observed that EMF causes a reduced volume of blood vessels, bronchioles volume, and alveolar volume in the lung. This might cause serious side effects on the oxygen-carrying capacity of the organ. According to these results, it would be suggested that EMF might lead to impairment in the lung structure, so it causes loss of function. FA, that antioxidant properties are known, ameliorated these effects.

Based on the stereological results, although FA reduced the negative effects of EMF, it could not normalize bronchiole and blood vessel volumes. The inability of FA to show sufficient antioxidant effect may be due to insufficient dose or duration of use. There is a need for new studies on the duration and dose of FA.

On the other hand, although we attribute the protective effects of FA to its antioxidant properties, the lack of biochemical methods limits our study. We believe that this subject needs to be investigated using different techniques such as biochemical analysis of lung tissues, electron microscopic observation, and immunohistochemical staining processes for a better understanding of the side effect of EMF exposure on the lung.

Conflict of interest statement

The authors have declared that there is no conflict of interest.

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Multidrug resistant microorganisms in the intensive care unit without COVID-19 during pandemic

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Abstract

There are very few reports on the prevalence of multidrug-resistant microorganisms during the COVID-19 pandemic. In addition, these publications usually cover covid-19 patients.Our study aimed to compare the prevalence of multidrug-resistant microorganisms in patients without COVID-19 undergoing treatment in an intensive care unit (ICU) during the COVID-19 pandemic with those in the pre-pandemic period. The study was planned retrospectively. In our country, the prevalence of multi-drug-resistant microorganisms was evaluated in the intensive care unit where internal and surgical patients were hospitalized in a single center in 6-month periods before and after the occurrence of covid-19 cases. The prevalence of multidrug-resistant microorganisms increased in patients being followed up in our ICU during the pandemic period ($p<0.05$). Statistically significant relationships were found between the incidence rate of microorganisms with multi-drug resistance and sex ($p=0.028$), presence of malignancy ($p=0.011$), and nurse's duration of work in the ICU ($p=0.04$). The increased prevalence of multidrug-resistant microorganisms and the infections caused by these microorganisms are other challenges that must be tackled during the pandemic period.

Keywords: coronavirus pandemic, multidrug-resistant microorganisms, intensive care, COVID-19

1. Introduction

At present, there is a global endeavor to manage the third and most severe corona virus-related disease in the last two decades (1). By June 03, 2021, there have been 170. 812. 850 confirmed cases and 3.557.586 deaths worldwide due to coronavirus disease (COVID-19) (2). Although various antiviral, antibiotic, and antimalarial drugs have been used in treatment, no treatment with proven efficacy specific to COVID-19 infection has been found in randomized controlled studies (3). Therefore, preventive strategies and breaking the transmission chain of the disease have been major targets. Hand hygiene and the use of personal protective equipment are recommended by health authorities since the early days of the pandemic (4).

Along with primary infection with severe acute respiratory syndrome-coronavirus-2, infection with other microorganisms (as coinfection or superinfection), complicates diagnosis and treatment and adversely affects the prognosis (5). In order to prevent this, World Health Organization (WHO) initially recommended the use of empirical antibiotic treatment during COVID-19 pandemi (6). It was reported that, despite coinfection being found in 3.5% and secondary infection being found in 14.3% of patients hospitalized due to COVID-19, 70% of the patients used broad-spectrum antibiotics (7). With increasing knowledge on and experience with COVID-19, the use of empirical or prophylactic antibiotic treatment is no longer recommended in patient management in both WHO guidelines andthe local guideline that we take as basis (8, 9). In addition, COVID-19 outbreak has had an impact on healthcare services. A significant number of healthcare workers have contracted COVID-19, and in many cases, the disease was fatal. The resulting healthcare personnel shortage has been mitigated by employing less experienced healthcare professionals. Moreover, healthcare workers have had to face many issues such as psychological stress, extreme workload, extra working hours, and insufficient personal protective equipments (10).

Uncontrolled use of unproven treatment regimens (therapy with steroids, immunosuppressives, cytokine binders), reserve hospital staff being channeled to COVID-19 clinics, and in particular, inexperienced and exhausted healthcare workers, as well as intensive use of empirical antibiotics in intensive care units (ICUs), added a serious problem for medical professionals; multidrug-resistant (MDR) microorganisms. In our study, we aimed to analyze whether the incidence rate of MDR (resistance against at least three categories of antibiotics) microorganism-related infections increased during the COVID-19 pandemic compared to the pre-pandemic period in

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patients in ICU.

2. Materials and Methods

The study was planned retrospectively after obtaining ethics committee approval (OMUKAEK: 2020/618). Patients in the 20-bed ICU in which patients who have undergone internal surgery during 10.01.2019–10.01.2020 (two 6-month periods before and after COVID-19 notification in our country) are monitored were included in the study. The included patients wereover the age of 18 years, and their cultures were positive for MDR microorganisms. The factors analyzed included the following: patients' demographic data (age, sex, chronic diseases); Acute Physiology and Chronic Health Evaluation II (APACHE II) score (a mortality prediction score based on acute health problems and chronic health conditions of patients in ICUs); indications for intensive care admission;the location from where the patients were admitted to the intensive care unit (hospital, emergency service, home, operating room); culture results before intensive care admission and date of sample collection before intensive care admission, culture results during intensive care (on which day of intensive care admission reproduction happened and the microorganism that reproduced); need for mechanical ventilation; whether tracheotomy was performed; invasive procedures performed (central catheter, urinary catheter, nasogastric catheter); presence of open wound; presence and degree of decubitus ulcer;and need for renal replacement therapy.

Simultaneously, the number of intensive care physicians, nurses, auxiliary healthcare personnel, number of new healthcare personnel starting work in the COVID-19 pandemic period, amount of hand disinfectant used in the ICU in the 6-month time periods before and after the beginning of COVID-19 pandemic, and number of personal protective equipment were evaluated to determinethe incidence rate of microorganismsin patient samples in our ICU before and after the pandemic.

The data were analyzed using IBM SPSS Statistics 21.0 software. Friedman and Wilcoxon tests were used for intragroup comparisons. Mann–Whitney U test was used for numerical variables, and chi-square test was used for categorical variables for intergroup comparisons. Logistic regression models were used to determine the risk factors in the culture results with MDR (+) microorganisms, and $p < 0.05$ was considered significant.

3. Results

Over a period of 1 year, 1731 patients were admitted to our ICU. Monitoring and treatment of 857 patients were conducted in the 6-month period before March 2020 when COVID-19 cases started to occur in our country and that of 874 patients were conducted in the 6-month period after this date. MDR microorganism growth was detected in the cultures of 118 out of 857 patients admitted in the first six months before March 2020 and in those of 157 out of 874 patients admitted in the first six months after March 2020 (Fig. 1). When MDR microorganism cultures grown in both periods were compared, it was found that the rate increased significantly during the COVID-19 pandemic period ($p < 0.05$).

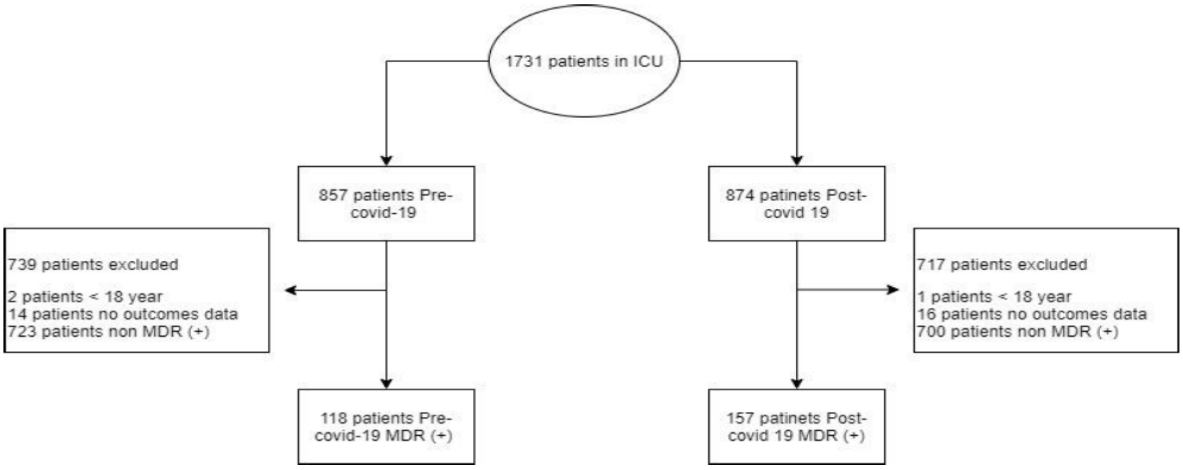

Fig 1. Flow chart of the patients included in the study; ICU: Intensive Care Unit, MDR: Multidrug Resistance

Demographic data, additional systemic diseases, and clinical characteristics of patients with MDR microorganisms grown in their cultures in the ICU during the two different time periods are summarized in Table 1. It was observed that the average intensive care stay of the patients was 24 days (range 1–233 days) in the 6-month period before the COVID-19 pandemic and 18 days (range 1–149 days) in the 6-month period after the pandemic, whereas intensive care stay durations of the patients in both periods was found to be statistically similar ($p = 0.108$). The average day on which microorganism growth was observed was found to be the 10^{th} day (range 1^{st} – 213^{th} days) after admission among the patients who were monitored in the 6-month period before the pandemic, whereas this was the 9^{th} day (range 1^{st} – 326^{th} days) in the patients admitted in the 6-month period after the pandemic ($p = 0.86$). MDR microorganisms and the site of their growth in the body in both periods evaluated in the study are shown in Table 2 and 3. *Acinetobacter baumannii* was found as the dominant MDR ICU pathogen in the first samples collected after the patients were admitted to the ICU, according

to the surveillance data during ICU stay.

Table 1. Relationship between patients with multi-drug resistant microorganisms in their cultures before and after the Covid-19 pandemic and demographic, additional systemic diseases and their clinical characteristics

	Pre Covid-19 MDR (+) n=118	Post Covid-19 MDR (+) n=157	P value
Age, year mean ± SD	61.9 ± 18.2	60.2 ± 18.9	0.337
Gender (F / M) %	47.4 / 52.6	60.4 / 39.6	0.028
Systemic Disease			
Diabetes Mellitus %	18.1	21.4	0.231
Hypertension %	32.4	29.9	0.342
Malignancy %	17.2	28.9	0.011
COPD %	8.6	4.4	0.144
APACHE II Score mean ± SD	21.2 ± 8.5	22.5 ± 10	0.342
Intensive Care Admission			
Postoperative %	76.7	60.4	0.037
Sepsis %	10.3	18.9	0.054
Trauma %	9.5	12.6	0.611
Post Resüscitation %	3.4	8.2	0.413
Blood-Blood Product Transplantation			
Erythrocyte Suspension %	18.1	21.4	0.691
Fresh Frozen Plasma %	5.2	6.9	0.614
Platelet Suspension %	3.4	6.3	0.446
Mechanical Ventilation %	87.1	81.1	0.184
Tracheotomy%	24.1	22.6	0.993
Central Catheter%	57.8	54.1	0.583

MDR: Multi Drug Resistance, COPD: Chronic Obstructive Pulmonary Disease, APACHE II = Acute Physiology and Chronic Health Evaluation

The intensive care work experience of our intensive care nurses was an average of 124 months before the pandemic. Instead of our 12 nurses who had positive Covid-19 swab culture, intensive care service was tried to be provided with our nurses with no or less intensive care experience. After the pandemic, our nurses' intensive care experience decreased to an average of 108 months, due to our newly recruited inexperienced nurses. The rate of MDR that increased during the pandemic period was found to be statistically significant with decreased nurse experience (p = 0.04)

Table 2. Resistant microorganisms that grow in 6-month time periods before and after the Covid-19 pandemic

	Pre Covid-19 MDR (+) n=118	Post Covid-19 MDR (+) n=157	P
Acinetobacter Baumannii %	14.7	20.1	0.814
Staphylococcus Epidermidis %	19.0	15.1	1,000
Staphylococus Hominis %	10.3	12.6	0.406
Klebsiella Pneumoniae %	9.5	11.9	0.810
Escherichia Coli %	9.5	10.1	0.976
Enterococcus Faecalis %	7.8	8.2	0.414
Staphylococcus Haemolyticus %	2.6	5	0.536
Staphylococcus Aureus %	2.6	4.4	0.273
Pseudomonas Aeruginosa %	9.5	2.5	0.346
Candida Albicans %	1.7	1.4	0.721
Corynebacterium Striatum %	1.7	1,3	0.661
Enterobacter Cloacae %	0.9	1,3	0.423
Enterococcus Avium %	1.7	1.3	0.589
Staphylococcus Capitis %	2.6	1.9	0.638
Haemophilus İnfluenzae %	2.6	0.6	0.999
Providencia Rettgeri %	0.9	1.2	0.488
Streptococcus Pneumoniae %	1.7	0.6	0.885
Staphylococcus Caprae %	0.9	-	-

Table 3. Resistant microorganism breeding sites for 6 months before and after Covid-19 pandemic

	Pre Covid-19 MDR (+) n=118	Post Covid-19 MDR (+) n=157	P value
Peripheral Blood Culture %	36.2	30.2	0.428
Tracheal Aspirate Sample %	23.3	26.5	0.896
CSF %	11.2	14.5	0.899
Catheter Blood Culture %	12.1	13.8	1,000
Urine Sample %	11.2	8.2	0.310
Surgical Material %	3.4	3.1	0.620

Wound Culture %	2.6	3.1	0.955

CSF: Cerebrospinal Fluid

The mortality rates of patients with MDR microorganisms detected in culture follow-ups in the ICU of our hospital was 36.4% in the first 6 months period (before the COVID-19 pandemic) and 51.6% in the second 6-month period (COVID-19 pandemic period) and this increase was statistically significant (Fig. 2) ($p < 0.05$).

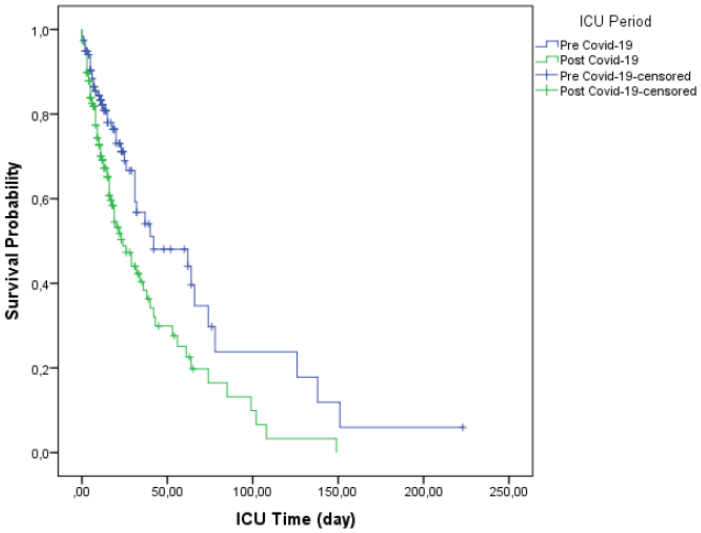

Fig 2. Mortality rates with Kaplan Meier curve in patients with resistant microorganism culture (+) in Intensive Care Unit during Pre Covid-19 (6 months before Covid-19) and Post Covid-19 (6 months after Covid-19) periods, ICU: Intensive Care Unit ($p < 0.05$)

4. Discussion

MDR microorganism culture-positive rates increased statistically significantly during the pandemic period compared to the prepandemic period in the patients included in the present study. MDR microorganism species and growth sites during the pandemic period were found to be similar to those of prepandemic period. During the COVID-19 pandemic period, it was observed that among important MDR microorganisms; incidence of *Acinetobacter baumannii* (14.7% / 20.1%) and *Klebsiella pneumoniae* (9.5% / 11.9%) increased, whereas that of *Pseudomonas aeruginosa* (9.5% / 2.5%) decreased.

MDR infections are a growing public health problem.(11) Risk factors for the development of resistant infections observed in ICUs are mainly stated as sex, surgical history, central venous catheterization, mechanical ventilation, previous antibiotic therapy, and duration of stay in the ICU (12-14).

Sex is a controversial risk factor for MDR microorganism growth (15). In a meta-analysis evaluating 17 studies, male sex was specified as a risk factor for MDR growth, and it was explained withpossible related physiopathology, physiological differences, and lifestyle (12). In our study, MDR microorganisms were observed in 151 male and 124 female patients in the total study period, and a significant relationship was found between the presence of MDR microorganism culture, which increased during the pandemic period compared to the prepandemic period, and female sex. In previousstudies, urinary tract infections in particular are stated as a risk factor for MDR microorganism growth in patients of the female sex (16). In our data, no relationship could be demonstrated between female/malesexand MDR microorganism growth sites.

Surgical procedures, stress response, medical treatments during the process, and surgery-related immunosuppression increase the possibility of the occurrence of MDR microorganisms (17). In our center, based on the guidelines of our country's Ministry of Health, elective surgeries were postponed within the framework of the fight against the pandemic, while emergency and malignancy surgeries continued to be performed. Therefore, the number of postoperative patients admitted to our ICU decreased during the pandemic period (76.7% / 60.4%). Despite decreased number of surgical procedures being performed in our center during the pandemic period, the incidence rate of MDR microorganisms observed in the ICU increased compared to that of the pre-pandemic period.

Immunodeficiency occurring in patients with malignancy increases the likelihood of MDR microbial growth (18). When our data are examined, it is observed that admission of patients with malignancy to the ICU increased significantly between the periods before and after the pandemic. The presence of malignancy and the likelihood of detection of MDR microorganisms were directly correlated in our study. Most of the patients with malignancy admitted to the ICU during the pandemic period were admitted for postoperative follow-up rather than due to terminal malignancy and possible complications. It was observed that the ratio of patients with malignancy and those with MDR samples detected to non-operative patients admitted to postoperative intensive care before pandemic was 86.4%, whereas the corresponding ratio during the pandemic was 71.3%. Since most palliative care units in our country were transformed into “COVID-19 ICUs” during the pandemic period, treatment of the patient population for whom the follow-up and treatment processes should be carried out mainly in palliative care centers was arranged in “Non-COVID-19 Internal Surgery ICUs” As a result, the rate of patients with malignancy accepted for medical treatment, which was 13.6% before the pandemic in our ICU where internal surgery patients were admitted, increased to 28.7% during the pandemic period. Despite the generally reduced number of surgical procedures, the increased rate of patients with malignancy being admitted to the ICU during the postoperative period might have contributed to the increased incidence of MDR microorganisms.

It is known that invasive procedures in ICUs increase the

rate of MDR microbial reproduction (19, 20). Pathogenic microorganisms colonize and multiply in the invasive material (such as a central venous catheter, endotracheal tube, and urinary catheter) inserted for prolonged periods and consequently increase the possibility of infection. MDR infections can be reduced with proper nursing care and catheter management (21, 22). During the pandemic period, 18 healthcare professionals (3 doctors, 3 assistant healthcare personnel, 12 nurses) in our ICU were infected with SARS-CoV-2. The staff shortage that occurred during the treatment and quarantine process of infected healthcare professionals was filled with healthcare professionals who did not have sufficient intensive care experience. As a result, the average level of intensive care experience of the nurses in our center, who were the most affected group, decreased during the pandemic period. In our study, it was found that decreased intensive care experience level correlated with the prevalence of MDR microorganisms.

When the mortality rates before and during the pandemic period were compared, it was observed that the mortality rate was significantly higher during the pandemic period. Admission of the increased number of patients with malignancy to our ICU during the pandemic period could have led to an increased mortality rate. However, an increase in mortality during the pandemic period was also observed in patients without malignancy according to the results of the subgroup analyses performed on these patients.

At present, the world is facing a test of large magnitude in the form of COVID-19. However, it is likely that we will also encounter problems triggered by the pandemic in addition to the pandemic itself. Although a solution for antibiotic resistance does not exist at the moment, it is important to identify the factors that cause its increased prevalence. We believe that our study, by revealing the increased prevalence of MDR microorganism growth in the ICU of our center during the pandemic period, will enable healthcare personnel worldwide to take adequate measures to avoid this public health issue.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Silymarin ameliorates cisplatin-induced nephrotoxicity by downregulating TNF-α and NF-kB and by upregulating IL-10

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Abstract

Cisplatin (CP) is one of the antineoplastic agents used to treat many types of cancers. Besides these effects of CP, it causes various side effects such as nephrotoxicity. Inflammation is considered to be one of the main pathogeneses of CP-induced nephrotoxicity. Silymarin (SIL) is a flavonoid with beneficial pharmacological properties such as antioxidant and anti-inflammatory. The current study aimed to investigate the beneficial effects of Silymarin against CP-induced nephrotoxicity. Albino Wistar male rats were randomly divided into four groups (n=7): Control group was administered saline (0.5 ml) for 10 days intraperitoneally (IP), CP group was received CP (a single dose of 8 mg/kg, IP), CP+ SIL group was administered saline (0.5 ml) for 10 days and was received CP (a single dose of 8 mg/kg). To measure the inflammatory response, TNF-α, NF-kB and IL-10 expressions were performed. As a result, TNF-α and NF-kB expressions significantly increased while IL-10 expression decreased in the kidney of the CP group compared to the control group. However, SIL treatment significantly decreased TNF-α and NF-kB expressions and increased IL-10 expression in kidney CP-treated rats. These findings reveal that SIL may ameliorates the CP-induced nephrotoxicity in rats by inducing downregulation of TNF-α and NF-kB expressions and upregulation of IL-10 expression

Keywords: Cisplatin, IL-10, Nephrotoxicity, NF-kB, Silymarin, TNF-α

1. Introduction

Cisplatin (CP) is a platinum-derived anticancer agent used to treat many types of human cancers such as lung, bladder, ovary, testicular, leukemia, brain, kidney, head and neck tumors. It also plays a key role in the treatment of germ cell cancer (1). Despite its very strong effects in cancer treatment, it has side effects such as neurotoxicity and ototoxicity, especially neurotoxicity. More than 30% of patients receiving CP treatment suffered from renal dysfunction (2). Even though the toxic effects of CP have been proven, it is still a widely prescribed drug. Because it is a standard drug for some cancer treatments such as head and neck (3). Although the pathophysiology of acute kidney injury (AKI) caused by CP is complex, it mainly includes oxidative stress, apoptosis and inflammation (4). Inflammation is critical for understanding the pathogenesis of CP-induced nephrotoxicity (5). TNF-α is a major inflammatory factor that plays a crucial role in CP-induced nephrotoxicity. Production of TNF-α is mostly dependent on ROS and NF-kB activation (6). IL-10 is an anti-inflammatory cytokine that inhibits the production of proinflammatory cytokines mainly produced by T cells, macrophages and Dendritic cells (7). Since CP is both nephrotoxic and an indispensable drug in the treatment of many tumors, reducing or preventing kidney damage caused by it becomes an important problem to be solved.

Studies have reported that the administration of natural compounds may be a protective strategy against CP-induced nephrotoxicity (8, 9). Silymarin is a natural polyphenol compound extracted from the thistle (Silybum marianum) plant (10). It has been reported to have anti-inflammatory, antioxidant, antiviral, immunomodulatory, anti-proliferative properties (11, 12). Silymarin has been proven to have a hepatoprotective effect against liver toxicity induced by various hepatotoxic agents (13, 14, 15, 16). Recently, some studies have reported the protective effects of Silymarin to prevent CP-induced nephrotoxicity (17, 18). However, the effect mechanism of Silymarin in CP-caused nephrotoxicity has not been fully elucidated. Therefore, in our study, the beneficial effects of Silymarin were investigated by evaluating the expressions of TNF-α, NF-kB and IL-10 in the treatment of CP.

2. Material and Method

2.1. Experimental animals and drug treatment

Twenty-eight healthy *Albino Wistar* male rats weighing 180-200 g were randomly divided into four groups (n=7): Control (C) group was administered 0.5 ml saline for 10 days, CP group was received a single dose of 8 mg/kg cisplatin intraperitoneally (IP) on the 5th day of the study (19), Cisplatin + Silymarin group was received 50 mg/kg silymarin (Sigma

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Aldrich Biotechnology, CAS Number: 65666-07-1) orally for 10 days, and a single dose 8 mg/kg cisplatin IP was administered on the 5th day of the study, Silymarin group was received 50 mg/kg silymarin orally for 10 days (20). Animals were obtained from Van Yüzüncü Yıl University Experimental Medicine Application and Research Center. Animals were maintained normal light and dark cycles (12h:12h light/dark), at temperature (21 ± 2 ºC) and humidity (50 % ± 10), their feed and water were given in accordance with the standards (*ad libitum*). All protocols of the experiment have been approved by the Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (approval number: 2021/05-01). At the end of the experiment, the rats were anesthetized with intraperitoneal ketamine (75mg/kg). The kidney was removed and was fixed in 10% neutral buffered formalin for immunohistochemical evaluation.

2.2. Immunohistochemical preparation

Kidney tissue was embedded in paraffin after undergoing routine histological processing stages. The sections of 4 µm thickness were taken from paraffin blocks. The taken sections were deparaffinized and dehydrated. After incubation with 3% Hydrogen peroxide (H_2O_2), the sections were incubated in citrate buffer (ph 6.1) by heating in a microwave oven. They were incubated in Ultra V Block. Antibodies of TNF-α (Santa Cruz Biotechnology, dilution:1/50), NF-κB (Santa Cruz Biotechnology, dilution:1/50) and IL-10 (Santa Cruz Biotechnology, dilution:1/50) were used as primary antibody. The sections were incubated with primary antibodies +4C overnight, then they were incubated in Biotinylated Goat Anti-Polyvalent, and Streptavidin–peroxidase conjugate respectively. Diaminobenzidine (DAB) was used as a chromogen, and then stained with Mayer's hematoxylin. TNF-α, NF-κB and IL-10 immunopositive cells were counted using cellSens Software imaging systems (Olympus, Japan) in a light microscope (Olympus BX53, Japan) and assessed by H-score.

3. Results

3.1. Immunohistochemical findings

According to the results of the immunohistochemical assay performed to measure the inflammatory response showed that CP significantly increased TNF-α and NF-kB expressions, while decreased IL-10 expression compared to the control group ($p<0.05$). However, treatment with silymarin reduced TNF-α and NF-kB expressions and increased IL-10 expression in CP-induced rat kidneys ($p<0.05$). Only a few TNF-α, NF-kB and IL-10 immunopositive cells were observed in the Control and Silymarin groups (Fig. 1 and 2).

4. Discussion

This study aimed to investigate the beneficial effects of Silymarin in CP-induced nephrotoxicity. The findings of our study showed that Silymarin has a nephroprotective effect by reducing kidney inflammation caused by CP treatment. The effect mechanism of silymarin is schematized in Fig. 3.

One of the most prominent complications of CP used to treat many solid tumors is acute kidney injury (AKI) (4). It has been reported that inflammation is one of the most main pathogeneses of CP-induced AKI. Inflammation is a complex biological response that occurs after tissue damage (21). Previous studies have proven the role of inflammatory mechanisms in AKI caused by toxic substances (22). After kidney injury, the balance between pro-and anti-inflammatory mediators in the kidney significantly influences the extent of tissue damage and repair (23). Since AKI is closely related to inflammation, it is important to clarify inflammation in determining the necessary treatment modalities to prevent or treat AKI (21). The cellular damage and its associated molecular products are thought to be key triggers for inflammation after acute tissue injury (24). Pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-6, IL-1β, IL-23, IL-17 and anti-inflammatory cytokines such as IL-4, TGF-β, IL-10 are crucial factors in determining tissue damage and treatment strategies (25).

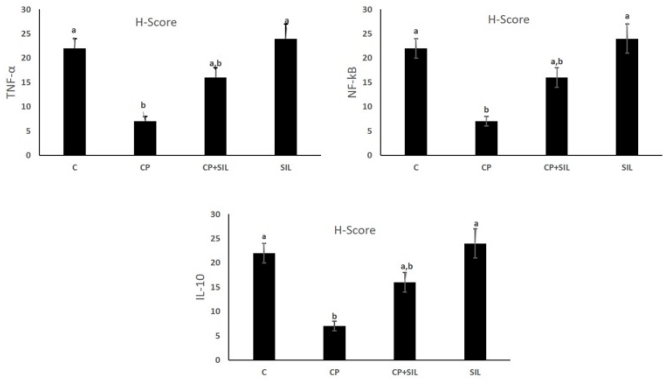

Fig. 1. The effect of silymarin on TNF-α, NF-kB and IL-10 expressions in kidney tissue of CP induced rats. H-Score

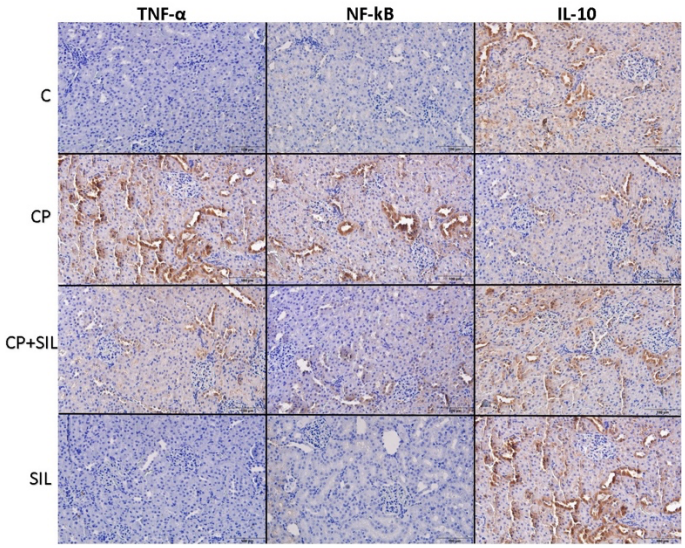

Fig. 2. Immunohistochemical figures of kidney tissues of rats. CP increased TNF-α and NF-kB expressions, while decreased IL-10 expression. However, treatment with silymarin reduced TNF-α and NF-kB expressions and increased IL-10 expression

NF-κB is an important factor that plays an active role in the activation of transcription of genes encoding proinflammatory

cytokines especially TNF-α, and thus mediates inflammation (26). TNF-α is a potent cytokine that mediates inflammatory tissue damage in the kidney, and specifically activates IL1-β, MCP-1, and IL-6 pro-inflammatory cytokines (28). Previous studies have reported that CP causes an inflammatory response by stimulating the production of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, MCP-1 and NF-kB in the kidney (5). It has been demonstrated that CP administration activates NF-kB which stimulates the expression of other pro-inflammatory cytokines such as TNF-α in the kidney. It also inhibits the production of IL-10 which suppresses the expression of TNF-α. IL-10 has protective effects on tissue damage as well as inhibiting the production of inflammatory cytokines (28). In parallel to studying of Kim et al. (2010), the current study revealed that CP treatment-induced inflammation by increasing the expression of NF-kB and TNF-α in the kidney. On the other hand, it inhibited the anti-inflammatory mechanism by suppressing IL-10 expression.

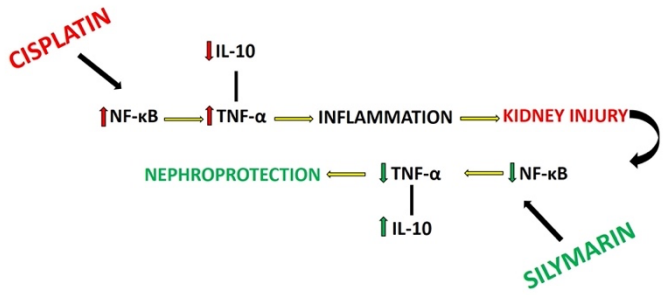

Fig. 3. Mechanism of action of silymarin in CP-induced nephrotoxicity. CP treatment upregulates TNF-α and NF-kB expression in the kidney, while it downregulates IL-10 expression. However, silymarin treatment exerts a renoprotective effect by suppressing TNF-α and NF-kB expressions and stimulating IL- expression in CP-induced kidney

Recently, it has been reported that antioxidants have a nephroprotective effect by suppressing oxidative stress and inflammation in CP-induced nephrotoxicity (29). Soetikno et al. (2018) reported that increased NF-κB and TNF-α expressions in CP-induced kidneys were significantly inhibited by curcumin treatment, and it also showed a nephroprotective effect by increasing IL-10 expression (30). Similarly, Sánchez-González et al. (2017) reported that CP-induced inflammatory markers such as TNF-α, iNOS and neutrophil infiltration, and Quercetin treatment improved these inflammatory markers (31). Similar to previous studies, in the current study, the increase in the expression of NF-kB and TNF-α caused by CP was significantly restored with Silymarin treatment. On the other hand, IL-10 expression suppressed by CP was significantly increased with Silymarin treatment (30, 31). These findings of our study reveal that Silymarin has an anti-inflammatory effect against inflammation caused by CP in the kidney of rats.

One of the most important ways of preventing CP-induced kidney damage is to inhibit increased TNF-α. It has been reported that TNF-α can directly damages the glomerular and tubular cells and activates internal and external apoptotic pathways (32). Gawad and Mohamed (2010) revealed that it was observed histopathological changes such as diffuse renal tubular necrosis, degeneration and mononuclear cellular infiltration in the kidney tissues of rats treated with CP (33). They also reported that Silymarin can be used as a nephroprotective agent by improving these structural changes induced by CP. Similarly, Abdelmeguid et al. (2010) reported that CP application caused deteriorations in the kidney such as glomerular atrophy, dilated filtration gap, loss of brush border of proximal collecting tubules, hypertrophied podocyte pedicels and tubular cell vacuolization, but Silymarin treatment ameliorated these changes (34). It is estimated that the inflammation caused by CP may be related to the histopathological findings of previous studies (13, 33). This study shows that increased TNF-α, which is an important marker of inflammation, can have a direct toxic effect on kidney cells (32). In addition, the current study reveals that silymarin suppresses the expression of TNF-α and increases the expression of IL-10, which is both an anti-inflammatory and tissue-protective cytokine, and it may be a protective agent for cells in kidney tissue. In this respect, our study is thought to support previous studies (13, 33).

The results of our study showed that silymarin may have a renoprotective effect by reducing the increased inflammation in the kidney induced. It is considered that the renoprotective effects of silymarin are mainly related to the downregulation of the expression of TNF-α and NF-kB and the upregulation of the expression of IL-10. Therefore, it is estimated that silymarin may be used as a protective agent against CP-induced nephrotoxicity.

Conflict of Interest

The authors declare that there are no conflicts of interest

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The role of platelet mass index in the prediction of preeclampsia full

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Abstract

To assess the possible roles of platelet indices including platelet mass index (PMI), platelet count (PC), mean platelet volume (MPV) and PC/MPV in prediction of preeclampsia. 190 pregnant women diagnosed with preeclampsia and 100 healthy uncomplicated control patients were included in this retrospective study. Age, gestational week, fetal weight, alanine transaminase (ALT), aspartate transaminase (AST), creatinine, blood urea nitrogen (BUN), complete blood count parameters and platelet indices were compared. ROC curve was applied to analyze the cut-off values of the significantly differing parameters for prediction of preeclampsia. Preeclamptic patients gave birth significantly earlier than the controls. In preeclamptic patients, the mean values of PC, PC / MPV and PMI were significantly lower than the control group. Although mean MPV values were lower in preeclampsia patients, the difference was not significant. The cut-off values of PC, PC/MPV and PMI were found to be 207,500, 18448.16 and 2411.75 with a-sensitivity/specificity of 45.3%/ 44.3%, 42.2%/ 42.6% and 44.1%/ 44.3%, respectively. Indices such as PC, PC / MPV and PMI changed significantly in preeclampsia. Although they have low sensitivity and specificity, these indices can be combined with other parameters and used in the prediction of preeclampsia.

Keywords: mean platelet volume, platelet indices, platelet mass index, preeclampsia

1. Introduction

Preeclampsia is defined as the presence of systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria 300 mg or more per 24-hour urine collection (or this amount extrapolated from a timed collection) or protein/creatinine ratio of 0.3 mg/dL or more or dipstick reading of 2+ (used only if other quantitative methods not available) (1). In the absence of proteinuria, new-onset hypertension with the new onset of any of the following; Thrombocytopenia: Platelet count less than 100,000 10^9/L; Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal diseases; Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration; Pulmonary edema; New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms (2). Approximately 3% to 8% of pregnancies are complicated by preeclampsia and preeclampsia causes a significant increase in maternal and fetal complications in these pregnancies (between 14-53 % and 22-92 %, respectively) (3). Approximately 7% of patients who have preeclampsia in their current pregnancy also have preeclampsia in their later pregnancy (4). Although the exact pathophysiology of preeclampsia is not known, inadequate invasion of trophoblasts into the maternal placental vascular bed and as a result the decreased placental blood flow have been accused (5). Inadequate placental invasion causes perfusion deficiency and increased maternal endothelial dysfunction and maternal endothelial dysfunction also causes intravascular coagulation resulting in platelet consumption. In these patients, the production of new platelets begins in the bone marrow to compensate for platelet consumption (6). As the severity of preeclampsia increases, it further increases platelet consumption (7). For this reason, some indices used to measure platelet numbers and functions are used in the estimation of preeclampsia severity. Platelet count (PC), mean platelet volume (MPV), platelet count/mean platelet volume (PC/MPV), and platelet count x mean platelet count/10^3 (platelet mass index [PMI]) can be used for preeclampsia prediction (8). From these indices, PC and MPV have been investigated before for association with preeclampsia (9,10). In some studies, high MPV value was detected due to new platelets are produced in the bone marrow in bleeding-related platelet consumption and, instead of this, low MPV value was detected in diseases that progress with thrombocytopenia related increased destruction (11). The MPV value of young platelets arising from the bone marrow is high and these platelets form better hemostatic plugs (12). This study aimed to assess these platelet indices in preeclampsia including PMI which has not been assessed in this disease before and to

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investigate the possible roles in the prediction of preeclampsia.

2. Materials and Methods

The study was conducted retrospectively by reviewing the files of 190 pregnant women with preeclampsia and 100 control patients hospitalized between 2012 and 2020 in the Mersin University Faculty of Medicine Obstetrics and Gynecology Department. This retrospective case-control study was approved by the hospital ethics committee on 08/07/2020 with an approval number of 2020/491. Patients with proteinuria (>1 positive in spot urine or > 300 mg protein in 24-hour-urine) and systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg measured every 6 hours after 20 weeks of pregnancy were accepted as "preeclamptic" and included in the study. Control patients were included from pregnant patients who were admitted to the service during the same period with similar age, body mass ındex (BMI), and gestational weeks without preeclampsia. Patients who have chronic hypertension, hyper/hypothyroidism, diabetes mellitus, chronic liver/renal/hematological disease, multiple pregnancies, or who suffered from PE during their previous pregnancies were excluded. Age, gestational week, fetal weight, alanine transaminase (ALT), aspartate transaminase (AST), creatinine, blood urea nitrogen (BUN), and complete blood count parameters and platelet indices of the patients were compared.

IBM SPSS version 22.0 statistics program was used to analyze the data. Before statistical analysis, all variables were checked for normality. Mean values were compared using Independent Samples T-Test and Mann-Whitney-U-Tests.ROC curve was applied to platelet indices that differed significantly. In the ROC curve, threshold values and specificity and sensitivity of these values were detected for preeclampsia prediction. P-values less than 0.05 ($P < 0.05$) were accepted as significant.

3. Results

290 pregnant women were enrolled in the study; 190 preeclamptic patients and 100 age-gravida and BMI matched healthy pregnant control patients. Preeclamptic patients gave birth significantly earlier than the control patients (35 weeks vs 38 weeks, p=0.002). WBC count, absolute neutrophil count, ALT, AST, BUN, and creatinine levels of preeclamptic patients were significantly higher than the control group. In preeclamptic patients, the mean values of PC, PC / MPV, and PMI were significantly lower than the control group. Although mean MPV values were lower in preeclampsia patients, the difference was not significant (10.99±2.34 vs 11.12±1.17, respectively, p=0.19) (Table 1). ROC curve was applied to analyze the PC, PMI and PC / MPV levels that are significantly different in preeclampsia patients compared to the control group (Fig. 1).

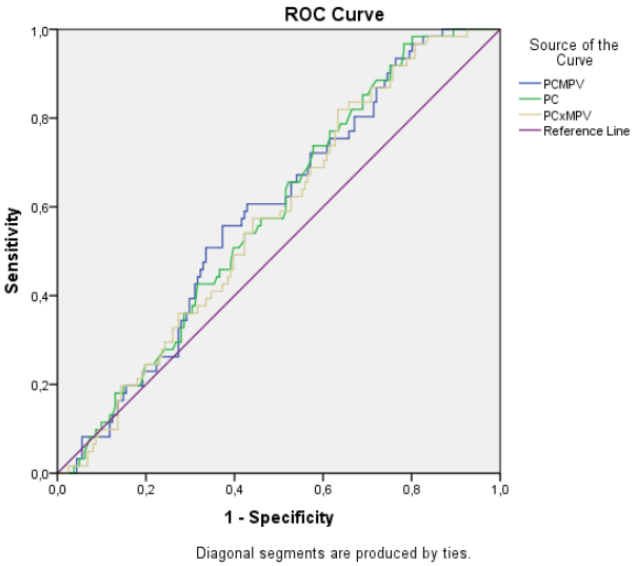

Fig 1. ROC curve of platelet indices in patients with preeclampsia

Table 1. Clinical and biochemical analyses of preeclampsia and control patients

	Preeclampsia patients (N=190)	Control Patients (N=100)	p
Age (year)	31.1±6.1	29.9±5.8	0.20
Gravida	3 (1-8)	2 (1-5)	0.119
Body Mass Index (BMI)	26.57± 2.91	27.86± 3.23	0.105
Birth week	35±3	38±1	***0.002****
WBC (10^3/µL)	11.741±3.655	9.971±2.318	***0.001****
Absolute neutrophil count (10^3/µL)	9.163±6.106	7.210±1.689	***0.001****
Absolute monocyte count (10^3/µL)	705±345	703±163	0.39
Absolute lymphocyte count (10^3/µL)	2.044±1.074	2.071±538	0.17
Haematocrit (%)	34.9±4.2	34.7±3	0.81
Hemoglobin (g/dL)	11.8±1.5	11.8±1.2	0.83
ALT (U/L)	45±80	13±5.5	***0.001****
AST (U/L)	70±124	17.8±5.3	***0.001****
Blood urea nitrogen(BUN) (mg/dL)	25.3±12	14.5±3.8	***0.001****
Creatinine (mg/dL)	0.68±0.23	0.46±0.08	***0.001****
MPV (fL)	10.99±2.34	11.12±1.17	0.19
PC (10^3/µL)	206.500±96.485	222.639±60.992	***0.03****
PMI	2248.4±1.105.7	2449.6±603.2	***0.04****
PC/MPV	18894±9.735	20.434±6.740	***0.04****

Independent Samples T Test and Mann-Whitney-U-Tests. * p<0.05. N-Number of Patients. m±SD: mean ± standard deviation. WBC: White Blood Cells. ALT: Alanine transaminase. AST: Aspartate transaminase. MVP: mean platelet volume. PC: Platelet count. PMI: Platelet Mass Index. PC/MPV: Platelet count / mean platelet volume

Table 2. Threshold values of platelet indices in the prediction of preeclampsia and sensitivity and specificity of these threshold values

	Threshold Value	Sensitivity	Specificity	AUC±SE	95% Confidence Interval Lower Bound	Upper Bound	P
PC (10^3/μL)	207,500	45.3%	44.3%	0.59±0.04	0.51	0.66	***0.038****
PMI	2411.75	44.1%	44.3%	0.59±0.04	0.51	0.66	***0.045****
PC/MPV	18448.16	42.2%	42.6%	0.59±0.04	0.51	0.67	***0.043****

ROC test was applied* p<0.05 AUC-Area Under the Curve. SE: Standard error. Platelet count-PC. platelet count x mean platelet volume-PMI. Platelet count/mean platelet volume-PC/MPV

The sensitivity and specificity of PC, PMI and PC / MPV to predict preeclampsia are shown in table 2 with ROC curve. Accordingly, it was determined that certain threshold values of these three parameters could predict preeclampsia with low sensitivity and specificity [(PC 45.3 % sensitivity, 44.3 % specificity (AUC: 0,59; 95%CI 0,51-0.66; p=0.038), PMI 44.1 % sensitivity, 44.3 % specificity (AUC: 0,59; 95 % CI 0,51-0.66; p=0.045), PC/MPV 42.2 % sensitivity, 42.6 % specificity (AUC: 0,59; 95 % CI 0,51-0.67; p=0.043)] (Table 2).

4. Discussion

In preeclampsia the trophoblastic invasion of the myometrial arterioles is inadequate and as a result, maternal endothelial dysfunction occurs. Damaged endothelial cells stimulate clotting factors, which causes platelets to migrate to these regions. Migrating platelets also stimulate clotting factors. A vicious circle develops as this stimulus continues from the damaged endothelial cells. Disseminated intravascular coagulation develops for this reason (13). Platelet destruction in the intravascular environment causes a stimulus for the production of new and young platelets in the bone marrow. Studies are indicating that these young platelets will be larger and MPV values will be higher (13-16). In some other studies, it was found that consumption was higher than production (low PC), but the MPV value of the new platelets formed was normal (9,10,14,17). In the present study, although the PC was significantly lower, MPV was not found to be significantly different than the control group.

There may be some possible causes for the different results found in the literature regarding MPV values in preeclamptic patients (14). First, there are differences in the methods for collecting the blood specimen. As an example adding EDTA to the hemogram tube increases MPV. Secondly using different hematological cell counters may result in different results (18). Thirdly MPV values change throughout the gestational weeks and ignoring gestational weeks may result in different results. Finally, comorbid diseases accompanying preeclampsia such as diabetes mellitus which itself increases MPV should be considered. Therefore these results indicate that MPV values are not always significantly higher in preeclamptic patients and it cannot be a reliable predictor of preeclampsia (18).

In patients with preeclampsia, an increase in platelet consumption due to endothelial damage and a decrease in PC / MPV index with newly produced platelets are expected. In a study by Freitas et al. PC was found to be lower in patients with preeclampsia than in the control group (19). In another study, Doğan et al found that not only PC but also PC / MPV values were lower in preeclampsia cases than in the control group (15). Yavuzcan et al did not find any difference between pregnant women with preeclampsia, pregnant women without preeclampsia, and non-pregnant women in their study. However, in another study by Yavuzcan et al., it was concluded that PC and PC / MVP may predict preeclampsia (18,20). Von Dadelszen et al suggested that the MVP / PC ratio reflects platelet consumption and can be used as a weak indicator of maternal progression in preeclamptic cases (21). In another study, Altınbaş et al did not find a significant relationship between preeclampsia and PC / MPV (9). In our study, PC and PC / MPV indices were found to be significantly lower in the patient group with preeclampsia than the control group.

Another index, PMI, is obtained by multiplying the platelet count by the mean platelet volume. As we mentioned before, in cases with preeclampsia, it is expected that PC would decrease due to consumption and MPV would increase with the production of new platelets. Therefore, PMI is expected to be different in preeclamptic patients compared to the controls. PMI has previously been studied in many different diseases, but there is no data regarding PMI in preeclampsia. Gerday et al. found that PMI is associated with prolonged PT time without increasing the risk of hemorrhage (12). Zisk et al found that the transfusion requirement would decrease by 11.5% if the PMI value was taken into consideration in platelet transfusion in a newborn study (22). However, despite the decrease in the need for transfusion in the group with high PMI, they did not indicate any difference in terms of bleeding episodes and mortality (23). In another study, it was found that in premature infants with low PMI which reflects decreased platelet activity, the incidence of intracranial hemorrhage increases, and this incidence decreases with increasing PMI (24). In addition, PMI was found to be more significant than the number of platelets used to evaluate the pathology in the second phase of premature retinopathy (25). In the review of the studies, it was concluded that PMI showed platelet activity better than PC (26). As far as we know, our study is the first study to evaluate PMI in preeclampsia. In the present study it was found that although MPV did not change in preeclamptic cases, it was found that PMI was significantly lower compared to control cases. Therefore, PMI appears as a parameter that can be used in the evaluation of platelet functions in preeclampsia patients.

In the literature, no threshold value has been defined for

platelet indices associated with preeclampsia. Dundar et al found the sensitivity for preeclampsia as 69% and the specificity as 71% when the PC threshold value was 221,000 (27). Howarth et al reported that the sensitivity of low PC high MPV was 90% and the specificity was 83% (28). In our study, since there was no significant relationship between preeclampsia and MPV, no threshold or sensitivity test was performed for MPV. The threshold values of the significant PC, PMI, and PC / MPV indices were determined in the ROC curve for the diagnosis of preeclampsia (207,500; 2411.75; 18488.16, respectively). According to these threshold values, the sensitivity and specificity of all three indices were found to be moderate. One reason why the previously studied PC sensitivities may differ from our study may be due to the calculated threshold value. The evaluation of different indices together in our study was an advantage of our study.

The positive aspect of the study is that a new parameter such as the PMI index is being evaluated in patients with preeclampsia. This study has several limitations. Limitations are that it is a single-center study and meaning our results may not be appropriate to the general population. In addition, low AUC value, sensitivity, and specificity values of PC, PC / MPV, and PMI parameters examined in the study are another weakness. Conducting a multi-center study can provide more precise results.

Evaluation of platelet functions is important because bleeding is a common complication in patients with preeclampsia. Many studies have been conducted on platelet indices in preeclampsia and the relationship between PC, MPV, and preeclampsia was mostly investigated in these studies. Although there is a consensus on the low PC in patients with preeclampsia, there is no complete consensus on MPV. In our study, we evaluated not only PC and MPV but also PC / MPV and PMI as platelet indices. The superiority of this study is the evaluation of all of these indices together (especially PMI was studied for the first time in preeclampsia). As a result, it was found that MPV value was not important in cases with preeclampsia, but indices such as PC, PC / MPV, and PMI changed significantly. Although they have low sensitivity and specificity, these indices can be combined with other parameters and used in the prediction of preeclampsia.

Conflict of interest

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article

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Do interventional pain procedures increase the risk of COVID-19?

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Abstract

This study's main aim was to evaluate the risk of COVID-19 in patients who were performed interventional pain procedures during the pandemic. The secondary aim was to evaluate if steroid injection in the procedures increases the risk of COVID-19. In this retrospective study, the records of patients who were performed interventional pain procedures (Group I) and were only examined (Group E) between the 1st of April and 30th of November 2020 were evaluated. The rate of COVID-19 infection in the first sixty days after the hospital visit was recorded. Results of patients who were injected steroids during the procedures were also evaluated. The records of 885 patients were investigated. While 485 of them were in Group I, 400 of them were in Group E. A total of 30 patients had COVID-19 in the assessment period. COVID-19 infection rates were similar between groups. Infection rates were not increased in patients who received steroids. The infection rate was significantly higher in the first 15 days after the hospital visit in both groups comparing the remaining 45 days. We conclude that neither interventional pain procedures nor single dose steroid injections increase the risk of COVID-19. However, 'coming to hospital' is a promoting factor itself. We assume that our results are also valid for all kinds of outpatient procedures. We suggest obeying the precaution recommendation guidelines of international communities during the pandemic.

Keywords: COVID-19, pain, steroid, pandemic, outbreak

1. Introduction

At the end of 2019, a new type of coronavirus has emerged in Wuhan, China, and caused an outbreak in a short while. The World Health Organization (WHO) announced the official name of the 2019 novel coronavirus as 'Corona Virus Disease-19' (COVID-19). On the 30th of January of 2020, COVID-19 was registered as the sixth Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO), which was officially declared as a pandemic on the 11th of March, 2020 (1,2).

According to the WHO records, COVID-19 has infected more than 155 million people and killed more than 3.2 million people worldwide. The numbers continue to increase, and the actual numbers are expected to be much higher.

Major symptoms of COVID-19 are fever, cough, fatigue, dyspnea. Minor symptoms include headache, dizziness, diarrhea, nausea, vomiting (2). The most common complication of COVID-19 is Acute Respiratory Distress Syndrome (ARDS), and other life-threatening complications are pneumonia, type-I respiratory failure, septic shock, metabolic acidosis, heart failure, renal failure, and hypoxic encephalopathy (3-6)

COVID-19 can spread by droplets, human-human contact, and indirect contact (contaminated objects and airborne contagion) (7). Due to the extremely high contagious potential of COVID-19, public places such as schools, restaurants, sports centers are closed worldwide. Particularly at the beginning period of the outbreak, almost most of the countries stopped surgical operations or treatment procedures unless they are urgent or critical for life.

COVID-19 made a huge and detrimental impact on pain treatment. Besides, pain clinics decreased their patients admitting daily capacities, and patients showed hesitation to apply to the pain clinics because of the fear of getting infected by the virus. Most pain clinics took a defensive attitude. Therefore, they canceled or postponed interventional pain procedures, considered medical treatments, and used telemedicine opportunities as much as possible.

Chronic or single-dose use of corticosteroids in the COVID-19 pandemic is another issue. Corticosteroids have immunosuppressant effects and may delay the immune response to the virus. In vitro studies have suggested that corticosteroids may impair antiviral innate immune responses (8-10).

Weak pain control is linked to the opioid crisis. It is shown that chronic pain is associated with increased mortality

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rates in cancer patients, structural and functional alterations in the brain, poverty, and decreased life expectancy when controlling for other factors (11-14). Therefore, total cessation of medical or interventional pain treatment during the pandemic would also have worse consequences.

The purpose of this retrospective study was to investigate if there is an increased risk for infection in patients who were performed interventional pain procedures in the COVID-19 outbreak. Secondary goals were to examine if there is an increased risk for patients who received corticosteroids as part of their interventions and evaluate the efficacy of the control measures applied in the clinic to prevent the virus's spread.

2. Materials and Methods

This retrospective study was conducted in the pain clinic of the anesthesiology and reanimation department of Ondokuz Mayis University Faculty of Medicine, Turkey. Approval of the institutional ethical committee was taken before the study. Data were obtained from the electronic application of the Turkish Ministry of Health and the software system of the hospital. In case of unavailability of data of a patient, information was taken by a phone conversation.

Patients older than 18 years old and admitted to the pain clinic between the 1st of April and 30th of November were included in the study. Patients were divided into two groups. Group I consisted of patients who were performed interventional pain procedures during the study period, and Group E consisted of patients admitted and examined in the pain clinic during the study period, but interventional pain procedures were not applied. Patients with cancer were not included in the study due to their possible immunosuppressive health condition to protect the study's homogeneity.

To evaluate the effects of corticosteroids on the frequency of COVID-19 infection, Group I was divided into 'Subgroup CS' and 'Subgroup NCS.' Subgroup CS consisted of patients who were injected corticosteroids in the pain procedures, while Subgroup NCS consisted of patients who were not injected corticosteroids in their procedures.

For the evaluation of infection frequencies regarding the types of the interventions, interventions classified into five groups: 1- Epidural steroid injections (ESI), 2- Radiofrequency techniques (RF), 3-Peripheric nerve blocks (PNB) and trigger point injections (TPI), 4- Intraarticular injections 5- Sympathetic blocks.

Demographic features, including the age and gender of the patients, were recorded. Positivity of COVID-19 infection following 1-15, 16-30, 31-45, and 46-60 days after the intervention or examination visit was recorded for each patient. Additionally, for patients who had got COVID-19 infection, the requirement of hospitalization, the intensive care unit (ICU) requirement, and loss of life were recorded.

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) version 15.0 program. Student t-test was used for the comparison of patients' age between groups. A Chi-square test was used for the statistical analysis of gender distribution between groups. A Chi-square test was used to analyze the frequency of COVID-19 infection between groups in specific periods. P values less than 0.05 were considered significant.

3. Results

A total of 885 patients' data were included in the study. While Group I consisted of 485 patients, Group E consisted of 400 patients. Demographic features of the patients regarding the groups were presented in Table 1. The number of females in the groups was higher than males but without statistical significance (p=0.17 in Group I and p=0.47 in Group E). The ratio of female/male was similar between Group I than Group E (p=0.47). The mean age of patients in Group I was higher than Group E (p<0.001).

Table 1. Demographic features of the individuals of the study

	Group I (n=485)	Group E (n=400)
Male	200 (41.2%)	149 (37.2%)
Female	285 (58.8%)	251 (62.8%)
Age (years)	61.0 ± 14.6	56,1 ± 16.4

There was no significant difference between Group I and Group E regarding the rate of Covid-19 infection. While 17 (3.5%) of patients in Group I had the infection, 13 (3.25 %) of Group E diagnosed the COVID-19 infection in the first 60 days after the hospital visit (p=0.86). There was also no significant difference in infection rates in the stated periods (Table 2).

Table 2. The frequency of COVID-19 infections and p values between Group Examination (Group E) and Group Intervention (Group I)

	0-15 days	16-30 days	31-45 days	46-60 days	Total
Group E (n=400)	5 (1.2%)	4 (1 %)	2 (0.5%)	1 (0.25 %)	13 (3.2%)
Group I (n=485)	9 (1.8 %)	4 (0.8%)	2(0.4 %)	2 (0.4%)	17 (3.5%)
P value	*0.47*	*0.78*	*0.50*	*0.67*	*0.74*
Total	14 (1.6 %)	8 (0.9 %)	4 (0.4 %)	3 (0.3 %)	30 (3.4%)

The number of patients in Subgroup CS was 307 (63.2%), and in Subgroup, NCS was 178 (26.8%). There was no significant difference in COVID-19 infection frequency between Subgroup CS and Subgroup NCS in any study's assessment periods (Table 3). There was no significant difference in terms of infection rates between the intervention types (Table 4).

Table 3. The frequency of COVID-19 infection regarding the use of steroids in the pain treatment procedures

	0-15 days	16-30 days	31-45 days	46-60 days	total
Corticosteroid + (n=307)	6 (1.9%)	3 (0.9%)	0 (0%)	2 (0.6%)	11 (3.5%)
Corticosteroid – (n=178)	3 (1.6%)	1 (0.6%)	2 (1.2%)	0 (0%)	6 (3.3%)
P value	*0.83*	*0.62*	*0.06*	*0.06*	*0.72*

When we evaluate the frequency of Covid-19 infection regarding the genders, we observed a significant elevation of infection rates in the male population in the first 30 days, particularly in 0-15 days. When we handle the whole study population of 885 pain patients, while 10 (2.8%) of males had Covid-19 infection in 0-15 days period, it was 4 (0.7%) for females (p=0.01). This significance was more evident for the males of Group I. 8 (4%) of males had the infection in 0-15 days, only one female in Group I was diagnosed with Covid-19 infection in those days (p = 0.009) (Table 5).

Table 4. The frequency of COVID-19 infection regarding the types of the interventional pain procedures

	1-15 days	16-30 days	31-45 days	46-60 days	Total (1-60 days)
Epidural Steroid injections (n= 147)	2 (1.3%)	0	1 (0.7%)	1 (0.7%)	4 (2.7%)
RF Procedures (n= 172)	3 (1.7%)	1 ((0.6%)	0	0	4 (2.3%)
PNBs or TPIs (n=92)	2 (2.1%)	2 (2.1 %)	1 (1.1%)	1 (1.1%)	6 (6.5%)
Intraarticular injections (n=49)	2 (4.0%)	0	0	0	2 (4.0%)
Sympathetic blocks (n=25)	0	1 (4.0%)	0	0	1 (4.0%)
p value	*0.72*	*0.15*	*0.15*	*0.69*	*0.45*

The mean age of thirty Covid-19 positive patients was 53.8 ±14.3 years, and the mean age of patients who did not have Covid-19 during the 60-day evaluation period was 58.7 ± 15.7 years (p=0.08).

When we discuss all the 885 patients who applied to our pain clinic in this study's evaluation period, we observed that the number of patients diagnosed with Covid-19 in a 0-15 days period was higher than all other intervals (Table 2). It was significantly higher than 31-45 days (p=0.04) and 46-60 days (0.008), but it was not significantly higher than 16-30 days (p=0.20). We observed that none of the thirty patients who had Covid-19 during the assessment period required hospitalization or advanced medical care.

4. Discussion

This study's primary aim was to search the possible inducing effect of interventional pain procedures on COVID-19 infection. The secondary aim was to search if steroid injections promote COVID-19 infection. Regarding our results, we have no evidence supporting these suspicions. However, our results were not very innocent because we detected a significant increase of the infection in the first 15 days after the hospital visit, but this finding was valid for the patients who were not performed interventional procedures. Therefore, we concluded that interventional pain procedures or single-dose steroid injections are not responsible for the infection but 'coming to hospital' is an increasing independent factor for COVID-19.

The symptoms of COVID-19 generally appear in a 7-10 days period. In their article, which was published on the 26th of March 2020, Li Q. et al. reported the incubation period to be 5.2 days; the 95th percentile of the distribution was 12.5 days (15). They also noted the mean duration from illness onset to first medical visit was 5.8 days. Nonetheless, due to the delayed incubation period or delayed medical visit, the infection diagnosis may put after 15 days in some patients. This may explain the statistically non-significant elevation in a 16-30 days period.

During the pandemic, particularly in the first months, there were no generally accepted precaution recommendations. We prepared a bundle of precautions in our clinic and strictly obeyed these items: 1- Obey on hand hygiene and general hygiene. 2- Use personal protective equipment (masks, gloves, glasses, etc.) as much as possible. 3- Reduce the number of patient admission to 50%. 4- Reduce the number of interventional procedures to 50%. 5- Consider medical treatment more than interventional treatment. 6- Avoid steroids as much as possible. 7- Use telemedicine opportunities as much as possible. 8- Change the clothing of the examination bed after each patient. 9- Limit non-essential patient escorts. 10- Do not allow more than eight patients and patient companions to exist in the clinic simultaneously. Some of our precautions were similar to the recommended guidelines of the American Medical Association (AMA), Centers for Medicare and Medicaid Services (CMS) , American Society of Regional Anesthesia and Pain Medicine (ASRA), European Society of Regional Anesthesia and Pain Therapy (ESRA), and the American Society of Pain and Neuroscience (ASPN) (16-19).

Despite the statistically significant increase of COVID-19 infection in the first 15 days after the hospital visit, we suggest that our bundle of precautions was not vain because there was no significant difference between Group E and Group I. To tell precautions were ineffective, Group I's frequency of infection in the 1-15 days period should be significantly higher due to the much longer time they pass in the pain clinic.

Table 5. The frequency of COVID-19 infection regarding the genders

Group I (n=485)					
	1-15 days	**16-30 days**	**31-45 days**	**46-60 days**	**Total**
Females (n=285)	1 (0.3%)	2 (0.7%)	2(0.7%)	2(0.7%)	7 (2.4%)
Males (n=200)	8 (4%)	2 (1%)	0	0	10 (5%)
P value	**0.009**	*0.72*	*0.68*	*0.68*	*0.13*
Group E (n=400)					
	1-15 days	**16-30 days**	**31-45 days**	**46-60 days**	**Total**
Females (n=251)	3 (1.2%)	3 (1.2%)	2 (0.8%)	1 (0.4%)	9 (3.6%)
Males (n=149)	2 (1.3%)	1 (0.7%)	1 (0.7)	0	4 (2.7%)
P value	*0.89*	*0.80*	*0.88*	*0.76*	*0.62*
Total (n=885)					
	1-15 days	**16-30 days**	**31-45 days**	**46-60 days**	**Total**
Females (n=536)	4 (0.7%)	5 (0.9%)	4 (0.7%)	3 (0.5%)	16 (3.0%)
Males (n=349)	10 (2.8%)	3 (0.9%)	1 (0.3%)	0	14 (4.0%)
P value	**0.01**	*0.91*	*0.37*	*0.45*	*0.32*

Regarding our results, the rate of COVID-19 infection of patients who received a steroid injection and patients who did not receive steroids were similar. Therefore, we could not report a correlation between steroid injection and COVID-19. Nevertheless, we do not recommend reckless use of corticosteroids in pain medicine because corticosteroids have immunosuppressant effects. Although some authors recommend treating severe COVID-19 infection, their role in promoting the infection is yet unclear (8,20,21). We declare, as an unwritten principle of our pain clinic, only equal or less than one ampule of Kenacort-A® (40 milligrams of triamcinolone acetate) or Celestone Chronodose® (6 milligrams of betamethasone) are used in our interventional procedures.

Additionally, independent from the outbreak, if a second steroid injection is necessary for the pain treatment, we wait at least four weeks between two injections. The risk of infection with steroid administration is dose-dependent, and increasing the steroid dose or shortening the interval between two steroid doses may have the potential of immunosuppression and, therefore, COVID-19 infection (22). In a multicenter study, Brenner et al. find that systemic corticosteroid use is associated with adverse COVID-19 outcomes in patients with irritable bowel syndrome (IBS) (23). Experts recommend that people taking cortisone or other steroids for chronic diseases should not stop them, except for their doctor's advice (21).

The Pain Management Community has made recommendations on using steroids for chronic pain during the COVID-19 pandemic. One Group recommends using epidural and other steroid injections at the lowest effective dose during the COVID-19 pandemic. However, the risks and benefits should still be weighed for each patient, and another group also suggests discussing treatment options with an infectious disease specialist (11,19).

According to our knowledge, this study is the first study that evaluates the frequency of COVID-19 infection following the pain treatment procedures. There are tens of different types of pain treatment interventions. We classified the procedures of our clinic into five categories to prevent mathematical chaos, and we did not observe a significant difference in COVID-19 infection rates in terms of the types of interventions.

A large-scale study demonstrated that older age and specific clinical conditions (diabetes, respiratory diseases, heart, kidney, and autoimmune conditions) are risk factors for death from COVID-19 (24). Luckily, all the thirty patients who had COVID-19 infection in the assessment period experienced the illness with mild symptoms. None of them required hospitalization or intensive care.

There are some limitations to this study. Due to the retrospective design, we could not prepare an information form including details (e. g. co-existing diseases, socio-economic status, COVID-19 history of acquaintances). Our control group did not consist of a normal population. This was due to the lack of availability to people who have no previous registration in our clinic. Another limitation was the lack of determination of asymptomatic cases. The actual ratio of asymptomatic COVID-19 cases is not known. Studies

report a 1.95% to 87.9% proportion of asymptomatic individuals among all confirmed cases. Result widely differ according to the study design and the population (25-27). Another foggy area is the people who had got the disease but never applied to a health institution; therefore stayed out of records. We considered the 'zero days' of Group E as the patients visited the clinic and been examined. The 'zero days' of Group I was regarded as the day that interventional procedures were applied. However, some of these patients were admitted and been examined in the clinic a few days before the intervention day. This could cause a bias, but results did not reveal a significant COVID-19 infection increase in Group I. Therefore, we had no evidence supporting bias.

In conclusion, regarding our results, neither interventional pain procedures nor steroid injections promote the COVID-19 infection alone. However, 'leaving home' and 'coming to hospital' are risk factors for getting infected by the COVID-19 virus. Despite the lack of original studies on this issue, we assume that this study's results are also valid for all kinds of outpatient procedures (endoscopy, biopsies, magnetic resonance imaging, etc.) This outbreak continues for more than one year, and it is unclear how long it will continue more. Therefore, stopping the pain treatment facilities is not the solution. We suggest precaution recommendations of international communities are particularly useful, and each clinic should follow and implement these precautions as much as possible.

Conflict of interest

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COVID-19 pandemic made detrimental effects on pain treatment as well as all fields of health care. This study is about the risk of getting COVID-19 infection due to the interventional pain treatments, particularly in the treatments containing corticosteroid injections. We suggest interventional pain treatments or single or lesser dose of corticosteroid injections do not increase the risk of COVID-19 but 'coming to hospital' is an independent risk factor.

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The effectiveness of coagulation parameters in classifying patients and predicting mortality in Covid-19

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Abstract

Covid-19 is a viral infection have a high pathogencitity and contagiousness that primarily targets the human respiratory system and leading to a global pandemic. Abnormal coagulation parameters are quite common in Covid-19 patients. In our study, we aimed to evaluate the relationship between coagulation function with disease severity and survival status in Covid-19 patients and the prognostic, predictive value of these parameters. Results of prothrombin time (PT), activated partial thromboplastin time (aPTT), Fibrinogen, and D-Dimer parameters at admission time of 76 Covid-19 negative healthy control with 188 confirmed Covid-19 patients, as well as death events were retrospectively analyzed. Compared with the healthy control group, higher levels of D-Dimer, PT, aPTT, fibrinogen, and CRP ($p < 0.001$ for each) were present during admission in Covid-19 patients. The non-survivor group had higher levels of PT, D-Dimer, and CRP ($p < 0.001$ for each) and aPTT ($p = 0.004$), fibrinogen ($p = 0.019$) compared to the survivor group. 28 (14.89%) of 188 Covid-19 patients lost their lives. Analysis of the ROC curve revealed that D-Dimer, Fibrinogen, PT, aPTT, and CRP had high diagnostic value in distinguishing Covid-19 patients from healthy control group, the critical group from the severe group, and non-survivors from survivors. This study shows that coagulation function is significantly impaired in patients with Covid-19 infection compared to normal patients, and as particularly marked high levels of D-Dimer, PT, aPTT, fibrinogen, and CRP are common. This condition is associated with disease severity and increased mortality. Coagulation parameters are an effective and useful marker for assessing prognosis and for the management of Covid-19 patients.

Keywords: coagulation parameters, prothrombin time, D-dimer, fibrinogen, Covid-19 severity

1. Introduction

Covid-19 is a viral infection have a high pathogencitity and contagiousness that primarily targets the human respiratory system and leading to a global pandemic (1). The World Health Organization declared the epidemic as an International Public Health Emergency of concern on January 30 th, 2020, and recognized it as a pandemic on March 11 th, 2020 (2). While the mild infection is observed 81% of symptomatic patients infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), occurs severe disease in 14% and critical disease 5% of patients (3).

The SARS-CoV-2 virus has been shown to cause a high expression of ACE2, which can cause alveolar damage by migrating from nasopharyngeal mucosa cells to the alveolar endothelium of the lungs. Virus taken from organs with ACE-2 receptor causes local infections in various organs, leading to multiple and fatal organ failure (4). In general, mortality occurs as a result of bilateral pneumonia that can progress to acute respiratory distress syndrome. Despite pulmonary pathophysiology is not yet fully known, severe COVID-19 is associated with a pronounced alveolar inflammatory cell infiltration, systemic cytokine storm response, and as a result of elevated inflammatory cytokines (5). The microvascular system is damaged by the occurrence of inflammatory reactions. As a result of abnormal activation of the coagulation system, generalized small vessel vasculitis and diffuse micro thrombosis develop, leading to venous and arterial thromboembolic diseases (6,7). It has been stated that the incidence of fatal pulmonary embolism (PE) in patients may be much higher than reported (8). Therefore, repeated evaluations and correct strategies are imperative to reduce the occurrence of venous thromboembolism (VTE), prevent fatal PE, ensure the safety of patients, and support early recovery. D-dimer results from the formation and degradation of cross-linked fibrin and reflects the activation of coagulation with fibrinolysis (9). Available data show that Covid-19 is associated with hemostatic abnormalities and that high D-dimer levels are associated with mortality, as well as being a common laboratory abnormality, and can be used as an independent biomarker for poor prognosis (10). In studies, patients with D-dimer levels above 3 µg/ml benefit from heparin treatment, and a decrease in mortality in Covid-19 with anticoagulant treatment also confirms these determinations (11).

One of the most important problems during the epidemic is the high volume of patients admitted to hospitals. Risk classification will be extremely helpful in managing the process, as available human support and mechanical capacities, especially intensive care support, are limited. For this, early and effective markers are needed, and coagulation parameters, which may have prognostic and predictive value, are very important in the course of the disease. Thus, the aim of this study is to investigate coagulation parameters in patients with

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Covid-19 and healthy control groups and to examine their role in predicting disease progression and survival.

2. Methods

2.1. Patients

This study was included 101 severe, 87 critical, a total of 188 adult patients and 76 healthy controls, whose diagnosis was confirmed, admitted to Başakşehir Çam and Sakura City Hospital in İstanbul between 15-30 November 2020. All patients were diagnosed according to the T.C. Ministry Department of Health's Covid-19 (SARS-CoV-2 infection) guidelines (12). Patients were defined and classified according to clinical, laboratory, and radiological parameters as those requiring hospitalization.

Nasal and/or pharyngeal swab samples of the patients were confirmed using the rRT-PCR test. Inpatients were divided into two groups: they were defined as admitted to the ward (Severe) and admitted to the Intensive Care Unit (ICU) (Critical). Inclusion criteria were those aged 18 years and older who had a positive Covid-19 rRT-PCR test were hospitalized for follow-up and treatment. Patients with hematological disease or who had a blood transfusion while hospitalized, data were incomplete, were excluded from the study. Again, 76 adult patients who were admitted to the hospital on the same dates whose clinical examination, CT and RT-PCR tests were found to be negative, were taken as the control group. Inclusion criteria for the control group were determined as rRT-PCR test negativity, and those with the comorbid disease were excluded. The routine parameters of all patients and the control group on the day of admission to the hospital were analyzed. This study was approved by the ethics committee of Başakşehir Çam and Sakura City Hospital (No.2021.04.65) and complies with the principles of the Declaration of Helsinki. Due to the retrospective and observational character of the study design, the requirement for informed consent has been waived.

2.2. Data collection

Epidemiological, demographic, clinical, radiological data of patients, laboratory results were obtained retrospectively from electronic medical records. Laboratory evaluations of the patients consisted of routine laboratory parameters such as coagulation, blood count, and biochemistry tests at the time of admission. The tests consisted of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, D-dimer, platelet (PLT), and CRP tests and were studied in the Laboratory of Başakşehir Çam and Sakura City Hospital. Blood samples of the patients were taken into a citrate tube for coagulation, a gel tube for biochemical parameters, and an EDTA tube for a complete blood count.

Coagulation analysis was performed on an automatic coagulation analyzer (Roche Cobas t 711 America), hematology analysis on (Sysmex XN-900, Japan) device, biochemistry analysis on SF-8200 (Roche Cobas 8000 America) brand device using original reagents. All measurements were made within 2 hours. Coagulation functions were compared between Covid-19 patients and the healthy control group, between the severe and critical patient group, as well as between survivor and non-survivor.

2.3. Statistical Analysis

A one-way ANOVA with Bonferroni multiple comparison tests was used for the quantitative data analysis. Pearson or Likelihood Ratio Chi-Square test was used to analyze the nominal scale data. Receiver operating characteristic (ROC) analysis was used to evaluate the diagnostic performance of study variables in Covid-19 disease. Youden's index was used as a criterion for choosing an optimal cut-off value. The level of statistically significance was set at $p < 0.050$. The statistical analyses were performed using SPSS v26 (IBM Inc., Chicago, IL, USA) statistical software.

3. Results

3.1. Basic characteristics, chronic diseases and coagulation parameters of control group with severe and critical Covid-19 patient groups

In this study, there were a total of 264 patients, 133 (50.40%) females and 131 (49.6%) males. The critical group was made up of 62.1% men, 37.9% women, and the severe group 47.5% men and 52.5% women ($p = 0.008$). The mean age of the critical group was 62.86±16.25, the mean age of the severe group was 60.22±14.29 and the mean age of the control group was 58.76±13.42. Differences between groups in terms of study variables were investigated with ANOVA (Table 1). Platelet count did not change significantly compared to groups ($p = 0.465$).

The change of patients' chronic diseases according to the groups was examined with the Chi-square test. It was determined that the frequency distributions of all chronic diseases showed significant changes according to the groups. It was found that Hypertension in 41.4% of the critical group, 27.7% of the severe group; Diabetes Mellitus (DM) in 40.2% of the critical group, 33.7% of the severe group; Chronic Obstructive Pulmonary Disease (COPD) in 12.6% of the critical group, 10.9% of the severe group; coronary artery disease (CAD) in 23% of the critical group, 11.9% of the severe group; chronic renal failure (CRF) in 9.2% of the critical group, 2% of the severe group; cancer in 3.4% of the critical group, 6.9% of the severe group.

3.2. Analysis of diagnostic effectiveness of routine coagulation parameters in determination of Covid-19 severity

The ROC curve was created to analyze the effectiveness of various coagulation parameters in the diagnosis of severe Covid-19 patients during admission (Fig. 1). ROC curve analysis revealed that CRP, fibrinogen, aPTT, PT and D-Dimer had high diagnostic value in distinguishing severe Covid-19 patients from healthy subjects ($p < 0.001$) (Table 2). ROC curve analysis revealed that D-Dimer, CRP, PT, aPTT and fibrinogen had high diagnostic value in distinguishing critical Covid-19 patients from severe Covid-19 patients ($p < 0.001$) (Fig. 2) (Table 3).

Table 1. Comparison of the study variables

Parameters	Control group (n=76)	Severe group (n=101)	Critical group (n=87)	F	p
Age (mean ± SD)	58.43 ± 13.42	60.22 ± 14.29	62.86 ± 16.25	1.880	0.155
Male n (%)	29 (38.2%)	48 (47.5%)	54 (62.1%)	9.565**	**0.008**
PT (sec)	8.93 ± 0.47[b]	9.53 ±1.01[b]	11.0 8± 3.61[a]	2.976	**0.000**
INR	0.99 ± 0.05[b]	1.05 ± 0.08[b]	1.21 ± 0.36[a]	23.097	**0.000**
APTT (sec)	28.92±3.19[c]	33.11±5.36[b]	37.36 ± 11[a]	26.627	**0.000**
D-Dimer (µgFEU/mL)	0.31 ± 0.14[b]	0.83 ± 1.02[b]	3.84 ± 3.85[a]	58.589	**0.000**
Fibrinogen (mg/dL)	353.75 ± 62.99[c]	528.77± 139.54[b]	587.02 ± 154.14[a]	70.886	**0.000**
Platelet (×10^9/L)	267.39 ±76.13	257.25 ± 98.82	249.8 ± 89.53	0.768	0.465
CRP (mg/L)	3.63 ± 2.63[c]	63.07 ± 42.45[b]	132.4 ± 97.1[a]	85.247	**0.000**
ALT (U/L	27.01 ± 12.86[b]	34.62 ± 23.38[b]	43.83 ± 45.98[a]	5.965	**0.003**
AST (U/L)	27.05 ± 11.9[c]	39.04 ± 22.88[b]	54.17 ± 55.29[a]	11.594	**0.000**
GGT (U/L)	23.85 ± 17.30 [b]	57.66 ± 42.20 [a]	60.85 ± 56.03 [a]	16.459	**0.000**
ALP (U/L)	73.67 ± 16.97[b]	75.39 ± 27.43[b]	91.46 ± 54.66[a]	5.311	**0.000**

F: One-way ANOVA, **Chi square test, PT = Prothrombin time; aPTT = Activated Prothrombin Time. Means that do not share a letter are significantly different (p <0.05). ap <0.05, b p <0.01, c p <0.001, (mean ± SD)

Table 2. Diagnostic value of some variables for the distinction between control and severe groups

Test Result Variable(s)	Cut off value	Sensitivity	1-spesifity	p	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PT (sec)	9.165	.797	.409	.000	.730	.653	.807
APTT (sec)	30.150	.725	.333	.000	.740	.665	.815
D-Dimer (mgFEU/mL)	0.4945	.884	.473	.000	.716	.638	.794
Fibrinogen (mg/dL)	446	.971	.247	.000	.889	.838	.940
CRP (mg/L)	8.85	.971	.043	.000	.990	.979	1.000

Table 3. Diagnostic value of some variables for the distinction between severe and critical groups

Test Result Variable(s)	Cut off value	Sensitivity	1-spesifity	p	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PT (sec)	9.78	.797	.607	.000	.763	.692	.834
APTT (sec)	37.05	.806	.733	.007	.619	.533	.704
D-Dimer (mgFEU/mL)	1.15	.884	.587	.000	.862	.808	.916
Fibrinogen (mg/dL)	843	.971	.947	.034	.593	.508	.678
CRP (mg/L)	101.15	.971	.660	.000	.740	.662	.818

Table 4. Comparison of the study variables

Parameters	Severe survivor group (n=101)	Critical group (n=87)		F	p
		Survivor group (n=59)	Non-survivor group (n=28)		
Age	60.22 ± 14.3	61 ± 17.01	66.79 ± 13.97	2.094	0.126
Male n (%)	48(47.5%)	35 (59.3%)	19 (67.9%)	8.596**	0.103
PT (sec)	9.53 ± 1.01 b	11.19 ± 4.2 ab	10.86 ± 1.96 a	8.520	0.000
INR	1.05 ± 0.08 b	1.22±0.41 ab	1.19±0.2 a	9.800	0.000
APTT (sec)	33.11 ± 5.36b	37.36 ±12.8a	37.38 ± 5.77 a	5..816	0.004
D-Dimer (µgFEU/mL)	0.83 ± 1.02 b	3.67 ± 3.76 a	4.2 ± 4.08 a	28.710	0.000
Fibrinogen (mg/dL)	528.77 ± 139.54 b	597.31 ± 159.67 b	564.08 ± 141.27 ab	4.058	0.019
Platelet (×109/L)	257.25 ± 98.82	263.19 ± 94.05	221.61 ± 72.92	2.006	0.137
CRP (mg/L)	63.07 ± 42.45 c	117.79 ± 93.73b	162.67 ± 98.61a	25.101	0.000
ALT (U/L	34.62 ± 23.38 b	35.38 ± 34.97 b	61.26 ± 60.42 a	6.583	0.002
AST (U/L)	39.04 ± 22.88 b	41.39 ± 32.66 b	81.15 ± 79.66 a	12.645	0.000
GGT (U/L)	57.66 ± 42.20	55.45 ± 52.74	72.14 ± 62.20	0.901	0.409
ALP (U/L)	75.39 ± 27.43 b	89.62 ± 50.79 ab	95.29 ± 62.95 a	3.036	0.051

Table 5. DIC in non-survivors with New Coronavirus Pneumonia (N = 28)

Platelet count (× 10^9/ L)	Number of patients (%)
< 50 (2 point); 50-100 (1 point)	0; 1 (3.57)
D-Dimer (µg/mL)	
1.0-3.0 (2 point); > 3.0 (3 point)	13 (46.43); 11 (39.29)
Fibrinojen (g/L)	
<1.0 (1 point)	24 (85.71)
Prolongation of PT (sec)	
3-6 (1 point); > 6 (2 point)	1 (7.14); 2 (3.57)
Meeting the ISTH criteria of DIC (Total points ≥5)	5 (17.86)

Table 6. Diagnostic value of some variables for the distinction between severe and non-survivor groups

Test Result Variable(s)	Cut off value	Sensitivity	1-spesifity	p	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PT (sec)	9.665	.710	.115	.000	.793	.695	.890
APTT (sec)	37.05	.806	.346	.001	.713	.599	.828
D-Dimer (mgFEU/mL)	1.11	.817	.154	.000	.879	.800	.958
Fibrinogen (mg/dL)	548.5	.624	.423	.252	.574	.448	.699
CRP (mg/L)	94.54	.828	.192	.000	.849	.757	.940

Table 7. Diagnostic value of some variables for the distinction between survivor and non-survivor groups

Test Result Variable(s)	Cut off value	Sensitivity	1-spesifity	p	AUC	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper Bound
PT (sec)	9.67	.345	.115	.554	.541	.410	.672
APTT (sec)	32.050	.455	.154	.082	.620	.496	.744
D-Dimer (mgFEU/mL)	1.55	.455	.308	.642	.532	.400	.664
Fibrinogen (mg/dL)	546.5	.491	.423	.624	.466	.334	.598
CRP (mg/L)	73.00	.345	.077	.049	.630	.512	.760

3.3. Basic characteristics, chronic diseases and coagulation parameters of survivor and non-survivor Covid-19 patient groups

111 (59.04%) patients were discharged, 28 (14.89%) patients died, and the remaining 49 (26.06%) patients remained in hospital in stable condition on December 9th, 2020. The non-survivor group was made up of 67.9% men, 32.1% women, and the survivor group 59.3% men and 40.7% women (p =0.103). The mean age of the non-survivor group was 66.79±13.97, the mean age of the survivor group was 61±17.01, and the mean age of the severe group was 60.22±14.3. Differences between groups in terms of study variables were investigated with ANOVA (Table 4). Platelet count did not change significantly compared to groups (p =0.137).

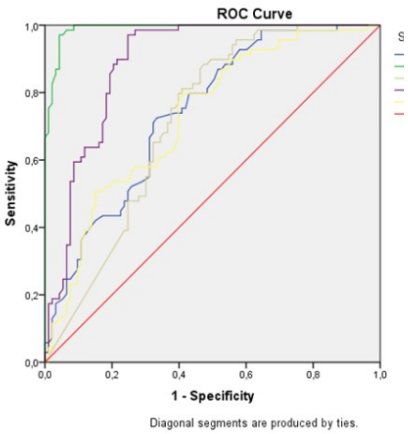

Fig. 1. ROC curve of CRP and coagulation parameters for comparing control and severe groups

It was found that Hypertension in 50% of the non-survivor group, 37.3% of the survivor group; DM in 50% of the non-survivor group, 35.6% of the survivor group; COPD in 7.1% of the non-survivor group, 15.3% of the survivor group; CAD in 14.3% of the non-survivor group, 27.1% of the survivor group; CRF in 3.6% of the non-survivor group, 11.9% of the survivor group; cancer in 5.1% of the survivor group.

In five of the patients who died from Covid-19 on admission, significant DIC was present according to the International Society for Thrombosis and Hemostasis (ISTH) criteria for disseminated intravascular coagulation (DIC) (Table 5) (10).

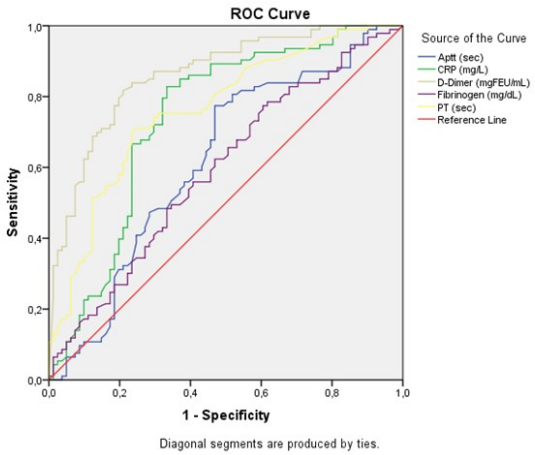

Fig. 2. ROC curve of CRP and coagulation parameters for comparing severe and critical groups

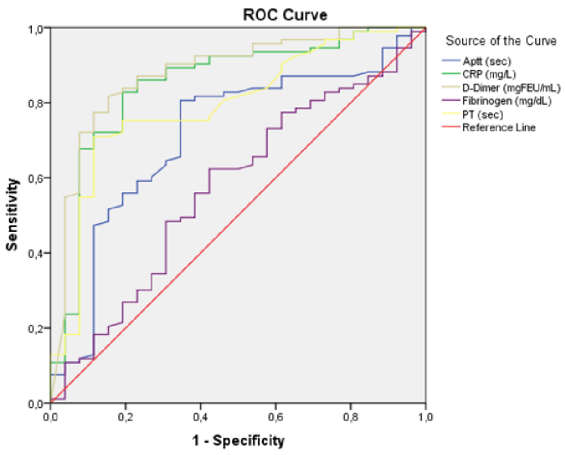

Fig. 3. ROC curve of CRP and coagulation parameters for comparing severe and non-survivor groups

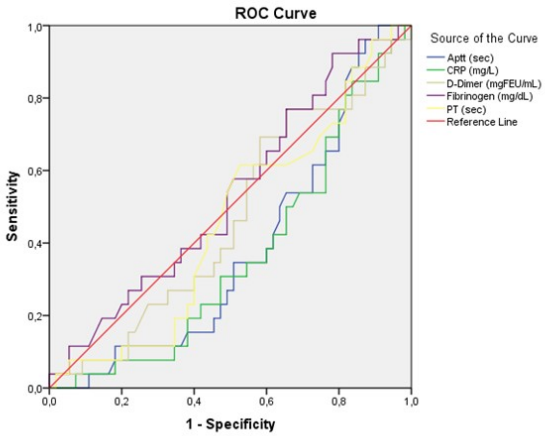

Fig. 4. ROC curve of CRP and coagulation parameters for comparing survivor and non-survivor groups

3.4. Analysis of diagnostic effectiveness of routine coagulation parameters in survival of Covid-19 patients

The ROC curve was created to analyze the effectiveness of coagulation parameters in comparing severe patients with non-survivor patients (Fig. 3). ROC curve analysis revealed that D-Dimer, CRP, PT, aPTT had high diagnostic value in distinguishing severe Covid-19 patients from non-survivor patients ($p < 0.001$) (Table 6). ROC curve analysis showed that parameters other than aPTT and CRP were not effective in determining the survival of critical Covid-19 patients ($p < 0.05$) (Fig. 4) (Table 7).

4. Discussion

Covid-19 is a viral infection with highly complex pathophysiology, leading to a pandemic starting from Wuhan, China in December 2019 (1). While mild infection is observed in the majority of symptomatic patients infected with SARS-CoV-2, severe and critical illness occurs in 19% of patients (3). Risk classification will be extremely helpful in managing the process due to the limitation of human support and mechanical capacities, support as well as tendency of SARS-CoV-2 to cause venous and arterial thrombosis, and the lack of an effective treatment. Early and effective markers are needed for diagnosis and follow-up, and coagulation parameters, which may have prognostic and predictive value in the course of the disease, are very important.

Consistent with previous studies in our study, hospitalized Covid-19 patients had abnormal coagulation parameters on admission compared to the healthy control group (10,13). Tang et al. reported that when coagulation parameters are abnormal, Covid-19 patients have a worse prognosis (10). The overactivation of immune cells and overproduction of proinflammatory cytokines during Covid-19 is called cytokine storms (14). It has been stated that the mechanism of inflammatory damage can develop as a result of T cell activation, increased granulocyte-macrophage colony-stimulating factor, and IL-6 production (15). As a result of the developing hyperinflammatory condition affecting the immune system, the microvascular system is damaged. The link between inflammation and hemostasis, defined as immunothrombosis, leads to abnormal activation of the coagulation system, thrombin formation, and inhibition of fibrinolytic reaction. These events that increase the likelihood of thrombosis are associated with increased production of proinflammatory cytokines (16).

Critical cases were older and had more underlying diseases compared to severe cases. similar to other studies (15,17). Covid-19 patients with major underlying conditions are at high risk of coagulation dysfunction. Our study showed that the incidence of abnormalities in parameters of coagulation function on admission was significantly higher in critical cases than in severe cases, that is, it was associated with disease severity (15,17). D-dimer elevation has been reported to be one of the most common laboratory findings recorded in Covid-19 patients requiring hospitalization (18). In our study, especially D-dimer levels were significantly higher in critical patients. D-dimer is a fibrin degradation product that is a reliable indicator of the activation of the hemostatic system and the activity of the fibrinolysis system. An analysis showed that D-dimer values were three times higher in severe Covid-19 patients than in those with milder forms (19). In a study of 138 patients, D-dimer levels were found to be significantly higher in patients who need ICU than in patients who do not (20). Huang et al. stated that patients with high D-dimer levels on admission need more ICU support (21). Since a marked increase in D-dimer is thought to be associated with the formation of multiple microthrombi, it has been stated that hospitalization of these patients should be considered even in the absence of other serious symptoms (22). In some studies, critical or non-survivor patients have been reported to have statistically significantly higher levels of D-dimer than non-critical or survivor patients (23).

Advanced age and chronic diseases in severe Covid-19 patients; hypercytokinemia, endothelial dysfunction, and inflammation are known risk factors for sepsis characterized by excessive, resulting in hipercoagulability (23,24). The cytopathic effect caused by the virus may lead to platelet activation and excessive thrombin formation as a result of widespread endotheliitis and inflammatory cell death (18). Hypoxia caused by respiratory failure in severe Covid-19 can not only increase blood viscosity, but also stimulate thrombosis through signaling (25). Refractory hypoxemia can lead to vasoconstriction, which reduces blood flow and increases vascular obstruction (23,24). Another risk factor is the aggressive proinflammatory response and insufficient control of the anti-inflammatory response. Stasis due to prolonged immobilization and invasive treatment, especially in severe Covid-19 patients, are risk factors for hypercoagulability or thrombosis (18). Some patients may develop sepsis-induced DIC (10,18). In the epidemiological analysis of 72,314 Covid-19 cases, most of the deaths were seen in people over 60 years of age with comorbidities (26,27). In our study, high levels of D-dimer and other coagulation parameters are associated with mortality in elderly and comorbidity patients. Individuals with

older, comorbidities and hypercytokinemia are known to be more likely to die from Covid-19 infection are known to be more likely to die from Covid-19 infection (7,26). The association between an increase in D-dimer levels and the deaths of patients infected with Covid-19 was also observed by Zhou and colleagues in a multicenter cohort study in China. It has also proven that high D-Dimer is an independent risk factor for mortality in Covid-19 patients (16,28).

Increased fibrin and conversion of and plasminogen to plasmine at the site of inflammation leads to a division of fibrin protofibrils and cumulative release of D-dimer, a known marker of Covid-19-associated thrombosis (16). In a logistic regression model, advanced age and D-dimer higher than 1 µg/mL during hospitalization was associated with an increased likelihood of death (19,29). When the increase in D-dimer levels reaches above 3 µg/mL, the mortality rate was determined to increases threefold (30). We found significantly higher D-dimer levels on admission in non-survivor. In a study Guan et al. analyzed with Covid-19 patients, they observed non-survivors had significantly higher D-dimer than survivors (31). In 183 patients at Wuhan Tongji Hospital, PT, fibrinogen, D-dimer, and fibrinogen degradation products (FDP) were shown to be significantly increased in Covid-19-related deaths. This condition suggested that coagulopathy is associated with prognosis and therefore these parameters may guide treatment (10). Since increased D-dimer levels in critical patients may be associated with a higher likelihood of developing DIC, these patients should be evaluated for DIC (15). Tang in the study found that 71.4% of non-survivors and 0.6% of survivors met criteria for DIC with high D-Dimer during their hospital stay and had a worse prognosis, increased risk of death (25). PT and APTT were significantly prolonged in non-survivors (10). Zhou et al found that 50% of non-survivors and only 7% of survivors met the DIC criteria (28). Hemostasis disorder may develop in patients with Covid-19, but excessive consumption of coagulation factors leads to the development of DIC. Development of DIC that adversely affects prognosis in Covid-19 is not uncommon (13). In five cases of death in our study, DIC was detected according to the ISTH SSC DIC score. DIC diagnostic scoring system parameters included PT, PLT, fibrinogen, and D-dimer. A score of >=5 is considered open DIC. DIC is a syndrome characterized by intravascular coagulation and causes the development of multiple organ failure (MOF) (26). Our data show that development of DIC in Covid-19 patients is not rare and caution should be exercised in critical patients due to its negative effect on the course of the due to disease. As a result of cytokine release syndrome affecting the immune system, the microvascular system is damaged and leads to abnormal activation of the coagulation system (15). This condition manifests itself as generalized small vessel vasculitis and diffuse microthrombosis (6). Cytokine storming interacts with coagulopathies and leading to vicious cycle associated with poor prognosis (32).

When the level of coagulation factors falls below 50%, coagulation tests are prolonged, and an abnormality may develop until the decompensation period of DIC due to the continuous activation and consumption of the exogenous coagulation pathway during DIC progression (23). Parameters PT and APTT that differences most in Covid-19 patients may increase due to coagulation activation or decrease due to consumptive coagulopathy (19). PT and APTT have been found to be longer in severe Covid-19 patients than in non-severe patients in some studies (10,21). We found that initial PT and APTT values were significant for risk classification and prognosis determination in Covid-19 patients. Prolonged PT on admission to the hospital has been shown to increase the risk of morbidity and mortality. The reason is that coagulopathy in Covid-19 is mostly due to sepsis in which the exogenous coagulation pathway is activated (23). One study found higher levels of fibrinogen in severe patients than non-severe patients (33). Fibrinogen, synthesized by the liver as an acutely reactive protein, is a coagulation protein. Fibrinogen promotes platelet aggregation and thrombosis, as well as hyperfibrinogenemia is commonly seen in the early phase of Covid-19 in both survivors and non-survivors. But in non-survivors, levels of fibrinogen may gradually decrease and hypofibrinogenemia may occur in the late stage of consumptive coagulopathy (10). In some studies, elevated fibrin levels have been detected in the lungs of patients with Covid-19 and it has been stated that fibrin accumulation in the alveoli causes acute bilateral pulmonary inflammation and chronic pulmonary fibrosis. The cytokine storm associated with Covid-19 also has a major effect on thrombin production and fibrin deposition in the lung. These data support the hypothesis that coagulopathy associated with Covid-19 contributes to the underlying pulmonary pathogenesis (34). In our study, fibrinogen and CRP levels were high in Covid-19 patients requiring hospitalization. The simultaneous increase in fibrinogen and CRP levels is probably due to an acute phase response (15). Free thrombin not controlled by natural anticoagulants can activate platelets (10). As in various viral infections, thrombocytosis due to platelet activation is common in the acute phase of Covid-19 and thrombocytopenia is common in its late stages (19). Development of thrombocytopenia may include direct or indirect factors such as inappropriate platelet activation and consumption due to DIC, immunological platelet destruction, and impaired megakaryopoiesis. In studies, platelet counts were found to be within the normal range in most COVID-19 patients at the time of admission (20,35), but thrombocytopenia was found in severe patients and non-survivors (10,31). Thrombocytopenia seen in critical patients is considered an indicator of bleeding and sepsis mortality as well as helping to detect the severity of coagulopathy (23).

In our study, in which we analyzed coagulation factors in Covid-19 patients, we found that age, comorbidity, elevated CRP, D-Dimer, fibrinogen, PT, aPTT levels have high diagnostic value. In addition, we determined that coagulation factors increased more in critical patients than in severe patients. In the non-survivor, we found abnormal coagulation parameters that reflect coagulopathy on admission.

There are several limitations of this study. It was a relatively small, retrospective study. Our findings should be confirmed by a larger, powerful clinical trial. But in our study, we analyzed changes in coagulation biomarkers in hospitalized Covid-19 patients and those who lost their lives. We correlated these parameters with disease severity and survival.

Coagulation disorder is common and negatively affects prognosis in Covid-19. Our findings showed that coagulopathy developed common and that coagulation markers were associated with disease severity and survival in Covid-19, largely determining patients ' clinical outcomes. We found that the presence of DIC significantly increased deaths in critical cases. Our data suggest that monitoring of early coagulation tests can be used as independent, effective, easily accessible markers to evaluate prognosis, prevent disease progression, and guide treatment in the disease process, as well as helping to identify early coagulation disorders.

Conflict of interest

None to declare.

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Adverse obstetric outcomes in early and late adolescent pregnancy

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Abstract

Adolescent pregnant women should be considered as a high risk patient group. The aim of our study is to compare pregnancies in adolescent with adult age group pregnancies and to evaluate maternal and fetal obstetric outcomes. Patients were admitted to Gynecology Department of Okmeydani Training and Research Hospital between January 1, 2015 and December 31, 2019. Pregnant women were divided into 3 groups as Group 1 (aged ≤16 years: n: 280), Group 2 (aged 17-19 years; n: 956) and Group 3 (aged 25-35 years; n: 656). Demographic characteristics of the patients and maternal and obstetric outcomes were recorded.In adolescent age groups,numbers of gravida, parity and abortus, and gestational age, fetal weight, and rates of cesarean delivery were found to be significantly lower relative to age group of 25-35 years Adolescents aged ≤16 years had a significantly lower risk than adults as for preeclampsia (AOR: 9,23 (6,36-11,82) p=0,001),had a significantly higher risk than adults as for low birth weight (AOR: 4,75 (2,26-9,21) p=0,001). and prematurity (AOR: 7,54 (5,12-9,43) p=0,001). Adolescents aged 17-19 years had a significantly higher risk than adults regarding small for gestational age (AOR: 4,48 (1,89-10,67) p=0,001), oligohidramnios (AOR: 2,29 (1,16-4,54) p=0,017), prematurity (AOR: 4,97 (3,1-7,97) p=0,0001) and LBW (AOR: 2,14 (2,71-9,74) p=0,0001).Our study was conducted with a large pregnant group, Since pregnant women in adolescent group are closely associated with preterm birth, delivery of small for gestational age and low birth weight infants, it is important to improve health services to reduce adverse pregnancy outcomes.

Keywords: adolescent pregnancy, adverse pregnancy outcomes, low birth weight, preterm delivery, teenage pregnancy

1. Introduction

Adolescence is the transition period of the individual from childhood to adulthood with psychological, social and biological changes. Adolescents constitute 20-25% of the population and 85% of those in this age group live in developing countries. The World Health Organization considers the age group 10-19 as adolescents (1). Worldwide, the rates of adolescent pregnancy increases in societies where poverty prevails and educational opportunities do not exist. While adolescent pregnancies occur due to marriages under pressure in developing countries, in developed countries it occurs because of insufficient contraception methods.

As babies born to adolescent mothers carry risks in terms of neonatal death and diseases, obstetric complications are more frequently encountered in adolescent mothers due to inadequate prenatal care. In adolescent pregnancies, adverse obstetric outcomes as low birth weight, preterm labor, perinatal death, maternal death, anemia, increased risk of fetal anomaly and preeclampsia may be encountered (2,3). Adolescent pregnant women have very low reserves since their own growth is not completed. Therefore, fetal growth and breastfeeding increase the nutritional needs of adolescents.

Early and unwanted pregnancies are associated with many unfavorable health, social, educational and economic consequences. In developing countries every year 12 million children between the ages of 15-19 and 777,000 children under the age of 15 give birth. Besides, 3.9 million unsafe abortions are seen every year in this age group (4,5). Teenage pregnancy has been found to be associated with low socioeconomic status, substance use during pregnancy, and mental health problems (6). The age at onset of substance use and smoking was found to be earlier in pregnant adolescents compared to non-pregnant adolescents (7).

Since Turkey is a receiving country, adolescent birth rate is increasing. The aim of our study is to compare pregnancies in this age group with adult age group pregnancies and to evaluate maternal and fetal obstetric outcomes.

2. Materials and Methods

Our study was carried out by retrospectively examining the records of patients who were admitted to Gynecology Department of Okmeydani Training and Research Hospital between January 1, 2015 and December 31, 2019 and gave birth between the ages of 10 and 19. As the control group, adult

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pregnant women in the age group of 25-35 who gave birth on the same dates as the adolescent group were selected. The study was initiated after the approval of the hospital Ethics Committee was obtained. Vaginal examination was performed in all patients in the study group at the time of admission to the hospital, and the presence of cervical effacement and dilatation was recorded. External monitoring was performed to determine uterine contractions, and obstetric ultrasonography to see fetal development. Gestational age was estimated based on the last menstrual period or findings of ultrasound performed before the 20th gestational week. Pregnant women below the 24th gestational week and those who delivered babies with chromosomal anomalies were not included in the study. A total of 1892 pregnant women were included in the study. Pregnant women were divided into 3 groups as Group 1 (aged ≤16 years: n: 280), Group 2 (aged 17-19 years; n: 956) and Group 3 (aged 25-35 years; n: 656).

Demographic characteristics of the patients were recorded. Groups were compared regarding the gestational week of delivery, delivery type, indications of cesarean section, gender, birth weight, gravida, parity, abortion, nationality, consanguineous marriage, use of Assisted Reproductive Technology (ART), multiple pregnancy, maternal anemia, need for blood transfusion. Besides, diseases as cholestasis, heart disease, thrombosis, asthma, and epilepsy were noted and evaluated.

Maternal and obstetric outcomes such as preeclampsia, abruptio placentae, gestational diabetes, intrauterine fetal demise, fetal anomalies other than chromosome anomalies, small for gestational age (SGA), preterm labor, preterm premature rupture of membrane (PPROM), premature rupture of membrane (PROM), oligohydramnios, polyhydramnios, low birth weight (LBW), macrosomia, chorioamnionitis, perineal laceration, need for intensive care and/ or maternal intensive care were compared among three age groups. Subsequently, logistic regression models were developed to investigate the correlations between age groups, maternal and neonatal outcomes, adjusted for parity.

The diagnosis of gestational diabetes mellitus (GDM) was made in 2 steps as recommended by the American College of Obstetricians and Gynecologists (AGOC) (8). Glucose tolerance test was performed between 24. and 28. gestational weeks using 100 g glucose for pregnants whose blood glucose level was 140 mg/dl one hour after a glucose tolerance test performed with 50 g glucose and the diagnosis of GDM was made when higher glycemic levels were found on 2 or more than 2 occasions. The diagnosis of preeclampsia and gestational hypertension was made according to the criteria determined by the International Society for the Study of Hypertension in Pregnancy (9). Diagnosis of gestational hypertension was made when systolic and diastolic blood pressures measured twice at 4 hour intervals were ≥ 140 mm Hg, and ≥ 90 mmHg, respectively in a normotensive pregnant woman who had not significant proteinuria after the 20th gestational week. Diagnosis of preeclampsia is made in consideration of above-mentioned findings and also high levels of protein (≥ 300 mg) in 24-hour urine samples or 2 (+) proteinuria at 2 different occasions were detected. Premature rupture of membrane (PROM) is defined as rupture of fetal membranes before the onset of labor. Preterm premature rupture of membranes (PPROM) was defined as spontaneous rupture of the amniotic membrane before the 37th gestational week and the release of amniotic fluid before the onset of labor. Small for gestational age (SGA) was defined as birth weight below the 10th percentile for gestational age. Preterm labor was defined as delivery with cervical dilatation and effacement accompanying uterine contractions before 37 gestational weeks. Deliveries after 42. gestational week were evaluated as postmature births. Macrosomia is defined as fetal weight over 4000 gr and low birth weight as a birth weight of less than 2500 g. Fetal loss (fetal demise) was defined as intrauterine fetal loss after 24 weeks of gestation. In polyhydroamnios, amount of amniotic fluid is 8 cm above the single quadrant or 20 cm above the sum of four quadrants in ultrasonographic measurements. In oligohydramnios amount of amniotic fluid is 2 cm below the single quadrant measurement or 5 cm below the total of four quadrants based on ultrasonographic measurements

In this study, statistical analyzes were performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA). One-way analysis of variance was used for intergroup comparisons, and Tukey multiple comparison test for subgroup comparisons of normally distributed variables. For intergroup comparisons of variables not normally distributed Kruskal- Wallis test, and for their subgroup comparisons Dunn's multiple comparison test were used. Chi-square test was used for comparisons of qualitative data. Logistic regression models were developed to investigate the associations between age groups, maternal and neonatal outcomes, adjusted for parity. Odds ratio (OR) and adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CIs) were generated. The results were evaluated at the significance level of $p < 0.05$. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences, Okmeydanı Training and Research Hospital (Date.04/05/2020./No. 48670771-514.10./117).

3. Results

The demographic characteristics and obstetric results of the patients were compared between age groups of ≤ 16, 17-19, and 25-35 years. (Table 1) In adolescent age groups, numbers of gravida, parity and abortus, and gestational age, fetal weight, and rates of cesarean delivery were found to be significantly lower relative to age group of 25-35 years. In the age group 25-35 years previous cesarean deliveries were performed more frequently, while rates of fetal distress and progress failure were found to be higher in adolescent Groups 1 and 2.

Table 1. Maternal characteristics and obstetric outcomes by maternal age groups

		All age group		Group 1 Age ≤16 years		Group 2 Age 17-19 years		Group 3 Age 25-35 years		p
Gravida	Mean (SD)	1.89±0.70		1.24±0.57		1.44±0.75		2.84±1.5		
	Median (IQR)	1 (1-2)		1 (1-1)		1 (1-2)		3 (2-4)		**0.0001ǂ**
Parity	Mean (SD)	0.70±0.99		0.2±0.54		0.33±0.55		1.46±1.17		
	Median (IQR)	0 (0-1)		0 (0-0)		0 (0-1)		1 (1-2)		**0.0001ǂ**
Parity Group	Nulliparity	1.047	55.34%	233	83.21%	680	71.13%	134	20.43%	
	Multiparity	845	44.66%	47	16.79%	276	28.87%	522	79.57%	**0.0001+**
Abortus	Mean (SD)	0.19±0.58		0.04±0.22		0.1±0.43		0.37±0.8		
	Median (IQR)	0 (0-0)		0 (0-0)		0 (0-0)		0 (0-0)		**0.0001ǂ**
Gender	Female	906	47.89%	146	52.14%	428	44.91%	332	50.61%	
	Male	986	52.11%	134	47.86%	525	55.09%	324	49.39%	**0.025+**
Gestational age	Mean (SD)	38.11±2.19		37.74±2.36		38.03±2.19		38.38±2.08		**0.0001***
Fetal Weight	Mean (SD)	3125.42±538.12		3061.14±547.15		3089.14±534.66		3205.74±530.61		**0.0001***
Assisted Reproductive Technology		1	0.05%	0	0.00%	0	0.00%	1	0.15%	0.390+
Delivery	Vaginal	1.297	68.55%	245	87.50%	696	72.80%	356	54.27%	
	Cesarean	595	31.45%	35	12.50%	260	27.20%	300	45.73%	**0.0001+**
Indications for Cesarean Sections	Previous Cesarean	254	42.69%	3	8.57%	77	29.50%	174	58.19%	
	Fetal Distress	135	22.69%	12	34.29%	75	28.74%	48	16.05%	
	Progress failure	66	11.09%	6	17.14%	37	14.18%	23	7.69%	
	Cephalopelvic disproportion	32	5.38%	3	8.57%	17	6.51%	12	4.01%	**0.0001+**
	Macrosomia	28	4.71%	2	5.71%	16	6.13%	10	3.34%	
	Malpresantation	63	10.59%	8	22.86%	34	13.03%	21	7.02%	
	Placenta previa	5	0.84%	0	0.00%	2	0.77%	3	1.00%	
	Multiple gestation	12	2.02%	1	2.86%	3	1.15%	8	2.68%	
Consanguineous marriage		416	21.99%	54	19.29%	238	24.90%	124	18.90%	**0.008+**
Nationality	Turkish	1.024	54.12%	73	26.07%	428	44.77%	523	79.73%	
	Foreign	868	45.88%	207	73.93%	528	55.23%	133	20.27%	**0.0001+**
Multiple gestation		14	0.74%	1	0.36%	5	0.52%	8	1.22%	0.199+
Hemoglobin	Mean (SD)	11.15±2.66		11.09±1.53		11.13±3.43		11.19±1.49		0.837*
Hematocrit	Mean (SD)	33.61±4.07		33.58±4.05		33.55±4.20		33.72±3.90		0.717*
Blood transfusion		111	5.87%	22	7.86%	63	6.59%	26	3.96%	**0.027+**
Fetal Anomaly		8	0.42%	3	1.07%	4	0.42%	1	0.15%	0.140+
Maternal Disorders	Astma	37	1.96%	3	1.07%	13	1.36%	21	3.20%	**0.016+**
	Tyroide	43	2.27%	1	0.36%	7	0.73%	35	5.34%	**0.0001+**
	Epilepsy	6	0.32%	0	0.00%	5	0.52%	1	0.15%	0.255+
	Cardiac disorders	8	0.42%	1	0.36%	1	0.10%	6	0.91%	**0.047+**
	Cholestasis	2	0.11%	0	0.00%	1	0.10%	1	0.15%	0.806+
	Trombosis	3	0.16%	0	0.00%	0	0.00%	3	0.46%	0.059+

*One-way Analysis of Variance, ǂKruskal Wallis Test, + Chi-Square test

A statistically significant difference was observed between the distribution of consanguineous marriages and nationalities among three groups (p = 0.008, p = 0.0001 respectively). Number of consanguineous marriages and foreign nationals were significantly higher in the adolescent group. Any significant intergroup difference was not detected as for hemoglobin, and hematocrit values, while rates of blood transfusions were statistically significantly higher in the adolescent group (p = 0.027). Incidence of maternal asthma, thyroid disease and heart disease were significantly higher in the age groups of 25-35 years (p: 0.016, 0.0001, 0.047 respectively) In Table 2, maternal and fetal obstetric adverse outcomes are evaluated. There was no significant difference as for rates of abruptio placentae, PROM, PPROM, SGA, fetal death, oligohydramnios, polyhydramnios LBW, postmaturity, maternal intensive care, and neonatal intensive care admissions, perineal laceration, chorioamnionitis among 3 groups.

Rates of preeclampsia, GDM, and macrosomia were found to be higher in the age group of 25-35 years than in the adolescent pregnant group (p = 0.002, p = 0.001, p = 0.032, respectively) A statistically significant difference was observed among all three age groups regarding premature births (p = 0.0001). Premature birth was significantly higher in age groups of ≤ 16 and 17-19 years. Logistic regression models were developed to investigate the associations between age groups maternal and neonatal outcomes, adjusted for parity. These findings were shown in Tables 3, and 4

Table 2. Comparision of adverse obstetric outcomes between age groups

	All age groups		Group 1 Age ≤16 years		Group 2 Age 17-19 years		Group 3 Age 25-35 years		p+
Preeclampsia	55	2.91%	1	0.36%	25	2.62%	29	4.42%	**0.002**
Abruptio Placantae	15	0.79%	1	0.36%	8	0.84%	6	0.91%	0.663
Gestational Diabetes Mellitus	28	1.48%	0	0.00%	9	0.94%	19	2.90%	**0.001**
PROM	50	2.64%	5	1.79%	27	2.82%	18	2.74%	0.623
PPROM	21	1.11%	2	0.71%	9	0.94%	10	1.52%	0.443
SGA	78	4.12%	7	2.50%	45	4.71%	26	3.96%	0.255
Fetal death	17	0.90%	2	0.71%	11	1.15%	4	0.61%	0.496
Oligohydramnios	76	4.02%	11	3.93%	39	4.08%	26	3.96%	0.990
Polyhydramnios	13	0.69%	1	0.36%	6	0.63%	6	0.91%	0.608
Low birth weight	179	9.46%	26	9.29%	104	10.88%	49	7.47%	0.071
Macrosomia	59	3.12%	3	1.07%	28	2.93%	28	4.27%	**0.032**
Preterm birth	372	19.66%	76	27.14%	201	21.03%	95	14.48%	**0.0001**
Postterm birth	15	0.79%	1	0.36%	8	0.84%	6	0.91%	0.663
Maternal intensive care	6	0.32%	1	0.36%	3	0.31%	2	0.30%	0.991
Neonatal intensive care	22	1.16%	5	1.79%	12	1.26%	5	0.76%	0.381
Perineal Laceration	3	0.16%	0	0.00%	3	0.31%	0	0.00%	0.230
Chorioamnionitis	3	0.16%	0	0.00%	2	0.21%	1	0.15%	0.740

+ Chi-Square test PROM: Premature rupture of membrane, PPROM: Preterm premature rupture of membrane, SGA: Small for gestational age

Table 3. Risk of adverse obstetric outcomes maternal aged ≤16 years versus aged 25-35 years

Age groups (years)	Age 25-35 years		Age ≤16 years		OR (%95 CI)	AOR (%95CI) [a]
Preeclampsia	29	4.42%	1	0.36%	7.91 (2.74-10.20) **p=0.012**	9.23 (6.36-11.82) **p=0.001**
Abruptio Placantae	6	0.91%	1	0.36%	0.38 (0.47-3.24) p=0.382	2.34 (0.15-7.66) p=0.547
Gestational Diabetes Mellitus	19	2.90%	0	0.00%	0.05 (0.0-0.96) p=0.989	0.01 (0.0-0.18) p=0.987
PROM	18	2.74%	5	1.79%	1.55 (0.57-4.22) p=0.390	1.69 (0.53-5.35) p=0.376
PPROM	10	1.52%	2	0.71%	2.15 (0.47-4.13) p=0.325	1.56 (0.26-9.42) p=0.624
SGA	26	3.96%	7	2.50%	1.61 (0.69-3.75) p=0.271	2.78 (0.92-8.34) p=0.069
Fetal death	4	0.61%	2	0.71%	0.85 (0.15-4.68) p=0.855	2.35 (0.15-7.68) p=0.547
Oligohydramnios	26	3.96%	11	3.93%	1.00 (0.49-2.07) p=0.980	1.17 (0.91-5.17) p=0.108
Polyhydramnios	6	0.91%	1	0.36%	1.00 (0.49-2.07) p=0.980	1.34 (0.15-7.64) p=0.547
LBW	49	7.47%	26	9.29%	0.79 (0.48-1.29) p=0.350	4.75 (2.26-9.21) **p=0.001**
Macrosomia	28	4.27%	3	1.07%	4.12 (1.24-9.65) **p=0.021**	1.17 (0.29-4.73) p=0.822
Preterm birth	95	14.48%	76	27.1%	0.46 (0.32-0.64) **p=0.001**	7.54 (5.12-9.43) **p=0.001**
Postterm birth	6	0.91%	1	0.36%	1.57 (0.31-6.49) p=0.382	1.34 (0.15-5.57) p=0.547
Maternal intensive care	2	0.30%	1	0.36%	0.85 (0.08-6.44) p=0.897	0.52 (0.04-0.75) p=0.764
Neonatal intensive care	5	0.76%	5	1.79%	0.42 (0.12-1.47) p=0.176	0.12 (0.02-0.57) p=0.243

PROM: Premature rupture of membrane, PPROM: Preterm premature rupture of membrane, SGA: Small for gestational age [a] Adjusted by parity

When adjusted for parity, adolescents aged ≤16 years had a significantly lower risk than adults as for preeclampsia (AOR: 9.23 (6.36-11.82) p=0.001).

When adjusted for parity, adolescents aged ≤16 years had a significantly higher risk than adults as for LBW (AOR: 4.75 (2.26-9.21) p=0.001), and prematurity (AOR: 7.54 (5.12-9.43) p=0.001).

The risk of having SGA newborns in the age group of ≤ 16 years was statistically insignificant in the age group of 25-35 years (OR: 1.61 (0.69-3.75) p = 0.271), but when adjusted for parity, although statistical insignificance persisted, the risk increased (AOR: 2.78 (0.92-8.34) p = 0.069).

The risk of macrosomia in the age group of ≤ 16 years was found to be statistically significantly lower when compared to the age group of 25-35 years (OR: 4.12 (1.24-9.65) p = 0.021), but when adjusted for parity the risk of developing macrosomia was found to be statistically insignificant. (AOR: 1.17 (0.29-4.73) p = 0.822).

When adjusted for parity, adolescents aged 17-19 years had a significantly higher risk than adults regarding SGA (AOR: 4.48 (1.89-10.67) p=0.001), oligohidramnios (AOR:2.29 (1.16-4.54) p=0.017), prematurity (AOR:4.97 (3.1-7.97) p= 0.0001) and LBW (AOR: 2.14 (2.71-9.74) p=0.0001).

Risks of preeclampsia and GDM were found to be statistically significantly lower in the age group of 17-19 than the age group of 25-35 years (OR: 1.72 (0.99-2.96) p = 0.049, OR: 3.14 (1.41-6) 98) p = 0.005, respectively), When adjusted for parity intergroup differences as for preeclampsia and GDM were found to be statistically insignificant (AOR: 1.17 (0.53-2.57) p = 0.697, AOR: 1.20 (0.35- 4.12) p = 0.770 respectively).

Table 4. Risk of adverse obstetric outcomes maternal aged 17-19 years versus aged 25-35 years

Age groups (years	Age 25-35 years		Age 17-19 years		OR (%95 CI)	AOR (%95CI) [a]
Preeclampsia	29	4.42%	25	2.62%	1.72 (0.99-2.96) **p=0.049**	1.17 (0.53-2.57) p=0.697
Abruptio Placantae	6	0.91%	8	0.84%	1.09 (0.38-3.17) p=0.869	2.14 (0.50-9.44) p=0.189
Gestational Diabetes Mellitus	19	2.90%	9	0.94%	3.14 (1.41-6.98) **p=0.005**	1.20 (0.35-4.12) p=0.770
PROM	18	2.74%	27	2.82%	0.97 (0.53-1.78) p=0.923	1.28 (0.97-3.35) p=0.057
PPROM	10	1.52%	9	0.94%	1.62 (0.65-4.03) p=0.291	1.84 (0.49-6.95) p=0.370
SGA	26	3.96%	45	4.71%	0.84 (0.51-1.37) p=0.475	4.48 (1.89-10.67) **p=0.001**
Fetal death	4	0.61%	11	1.15%	0.53 (0.17-1.66) p=0.274	5.53 (0.69-14.29) p=0.107
Oligohydramnios	26	3.96%	39	4.08%	0.97 (0.58-1.61) p=0.907	2.29 (1.16-4.54) **p=0.017**
Polyhydramnios	6	0.91%	6	0.63%	0.68 (0.22-2.13) p=0.513	1.75 (0.31-4.68) p=0.366
LBW	49	7.47%	104	10.88%	0.66 (0.46-0.94) **p=0.023**	2.14 (2.71-9.74) **p=0.0001**
Macrosomia	28	4.27%	28	2.93%	1.48 (0.87-2.52) p=0.151	2.31 (0.93-5.79) p=0.073
Preterm birth	95	14.48%	201	21.03%	0.64 (0.49-0.83) **p=0.001**	4.97 (3.1-7.97) **p=0.0001**
Postterm birth	6	0.91%	8	0.84%	1.09 (0.38-3.17) p=0.869	1.44 (0.40-3.54) p=0.259
Maternal intensive care	2	0.30%	3	0.31%	0.97 (0.16-5.83) p=0.975	0.03 (0.00-0.21) p=0.998
Neonatal intensive care	5	0.76%	12	1.26%	0.60 (0.21-1.72) p=0.346	0.01 (0.00-0.16) p=0.998

PROM: Premature rupture of membrane, PPROM: Preterm premature rupture of membrane, SGA: Small for gestational age[a] Adjusted by parity

4. Discussion

This large-scale retrospective study where we compared adolescent pregnancies with adult pregnancies has shown us that maternal, fetal, and obstetric complications are more common in adolescents. In our study, although gestational diabetes, preeclampsia, macrosomia and cesarean delivery were observed at a lower rate in teenage pregnancies; adverse obstetric outcomes such as preterm birth, low birth weight, small for gestational age, oligohydramnios have been observed more frequently. Adolescent pregnancy is an important problem in developed and developing countries. Complications during pregnancy and delivery are the leading causes of death in girls aged 15-19 years worldwide (10). They need nutritional support due to low socioeconomic level and nutritional deficiency (11). In our country, adolescent births have recently increased due to migration. In our study significantly higher rates of adolescent births were detected among foreign nationals (73,93% of the ≤ 16 age group, and 55.23% of the 17-19 age group) In a study comparing pregnant Turkish adolescents and pregnant immigrant adolescents, the researchers reported that adolescent pregnancies were very common among immigrants with an increase in low birth weight rates (12).

Since both the development of the fetus and adolescent pregnants occur simultaneously, iron stores of adolescents are depleted rapidly with higher risk of anemia (13,14,15). World Health Organization (WHO) has defined anemia in pregnancy as the hemoglobin (Hb) concentration of less than 11 g / dl (16). Higher incidence rates of anemia in adolescent pregnants were reported (17,18).(2,83, and 1,8 times higher when compared with adult pregnants, respectively). In a study performed in 12 clinical centers and 19 hospitals in the United States the researchers reported increased risk of maternal anemia in both younger and older adolescents, and higher rates of blood transfusion in the older adolescent group (19). In our study, any significant difference was not found in hemoglobin and hematocrit values between the younger and older adolescent pregnants when compared to adult pregnant women, and the mean values remained within the WHO recommended values. However, the need for blood transfusion was observed to be increased in all adolescents. The rates of transfusion at ≤16, and 17-19 years of age were 7.86%, and 6.59%, respectively with a statistically significantly higher rates in adolescent groups when compared with the adult group. (P: 0.027)

Many studies have examined the delivery methods in adolescent pregnancies. Some publications have reported similar cesarean and vaginal birth rates in adolescent and adult age groups (20). However, in most of the studies, cesarean delivery rates in adolescents were found to be lower than adults. In a study by Ganchimeg et al. 27.9% of the pregnant women under 15 years of age and 21,5% of those between the ages of 18-19 gave birth by cesarean section (21). Prophylactic uterotonics, and prophylactic antibiotics for caesarean section and antenatal corticosteroids for preterm delivery at 26-34 weeks of age were less frequently used in adolescent women. In our study, we found that statistically significantly lower rates of cesarean section were performed in pregnant women in all adolescent age groups. Normal birth rates for pregnants aged ≤ 16, and 17-19 were 87.50%, and 72.80%, respectively. It has been suggested that better myometrial function and elasticity in adolescents may contribute to a higher rate of vaginal deliveries. However, the rates of operative vaginal delivery, postpartum hemorrhage and episiotomy increased in adolescents (22). In the study of Torvie AJ et al. although cesarean and operative vaginal delivery rates were lower in young adolescents aged 11-14 years compared to young adults, higher risks of preterm delivery, delivery of low and very low birth weight newborns, and death were observed in this age

group (2).

Some studies have demonstrated that the rate of intervention in adolescents has increased due to the underdevelopment of the pelvic floor and the cooperation problem, and genital lacerations due to difficult labor increase the risk of bleeding (23). In our study, perineal laceration was observed in only 3 patients in the 17-19 age group. One study found that the second stage of labor in adolescents was shorter. However, the risk of postpartum hemorrhage and perineal laceration is higher in younger adolescents. Cesarean section due to progress failure and cephalopelvic disproportion was observed more frequently in younger adults than in older adolescents (19). In some studies, in adolescents higher rates of cesarean deliveries due to cephalopelvic disproportion and emergency conditions have been reported (24,25). In our study, cesarean deliveries due to fetal distress, progress failure, cephalopelvic disproportion and malpresentation were observed more frequently in the age group of ≤ 16 years compared to other age groups. There are publications showing that placenta previa is less frequently observed in adolescents (25,26). In our study, any incident of placenta previa was not observed in the age group of ≤ 16, while it was encountered in 2 patients in the 17-19 age group and 3 patients in the adult group, and all of these patients gave birth by cesarean section. Some studies have demonstrated that the rates of pregnancy-induced hypertension and eclampsia increase in adolescent pregnant women (18,21,26). In some studies, an increase in preeclampsia was observed in the younger adolescent group under the age of 16 years (19). In the study by Fleming N et al. gestational hypertension and placental abruption were observed less frequently in the adolescent group (25). In a study conducted with Indian adolescents, the risk of eclampsia was observed in adolescents. Although the risk of eclampsia increased in the adolescent group, the risk of mild pregnancy-induced hypertension, and preeclampsia was found to be higher over the age of 20 (14). In our study, when placental abruption was examined, no significant difference was found between the adolescent and adult groups. However, the risk of preeclampsia was observed to be significantly higher in adult pregnant women compared to the adolescent group. (p: 0.002) When compared with the adult pregnant group, the risk of preeclampsia was found to be statistically significantly lower in the ≤ 16 and 17-19 age groups. (p = 0.012, 0.049 respectively) Also, when adjusted for parity, with increased parity, the risk of preeclampsia was found to be statistically significantly lower in the ≤16 age group when compared with the 25-35 age group. (AOR: 9.23 (6.36-11.82) p = 0.001). There are publications stating that there is no difference in birth rates of small for gestational age (SGA) newborns, between adult and adolescent groups (25). In some studies, an increase in the rates of SGA was observed in adolescents (14,22,24). In our study, while no significant difference was found in the rates of SGA among all age groups, when adjusted for parity the risk of presence of SGA in the 17-19 age group was found to be statistically significantly higher than the 25-35 age group (AOR: 4.48 (1.89-10.67) p = 0.001). In most of the studies we examined, premature birth is more common in adolescent pregnancies compared to adult pregnancies (20,21,27). In primipara adolescents, preterm birth was found to be higher than in primipara adults (15). In our study, gestational age was significantly lower in the age group of ≤16 years. The prevalence of prematurity was significantly higher in the adolescent age group compared to the adult group. (0,0001). The risk of premature deliveries was found to be statistically significantly higher in the age group of ≤16 and 17-19 years than in the 25-35 age group. (AOR: 7,54 (5,12-9,43) p = 0.001, AOR: 4.97 (3,1-7.97) p = 0,0001 respectively). Post-mature births and macrosomic fetuses are less frequently observed in young gravidas (14,24). In our study, no significant difference was found between the groups as for postmature births. However, in accordance with the literature, greater number of macrosomic fetuses were observed in the adult group. (P = 0.032)

Low socioeconomic status and insufficient antenatal care may cause an increase in delivery of low birth weight (LBW) babies. In the study of Torvie AJ et al, LBW rate ratio increased significantly especially in the young adolescent group compared to the adult group (2). In our study, fetal weight was significantly lower in adolescent age groups compared to adult pregnancies. (P = 0,0001) Chen XK et al. found a relative risk of 1,4% in terms of low birth weight in their study with adolescent pregnancies aged 10-19 years (27). In addition to the studies showing that rates of LBW were higher among primipara adolescents (15), some other studies could not find any relationship between LBW and adolescents (25,28). In our study, the risk of LBW presence was found to be statistically significantly higher in the ≤ 16,and 17-19 age groups than in the adult age group. (AOR: 4,75 (2,26-9,21) p = 0,001; AOR: 2,14 (2,71-9,74) p =0,0001 respectively) Although there are publications (25) showing that the risk for PPROM is increased in adolescents, no risk increase was found in our study.

Considering the relationship between gestational diabetes mellitus (GDM) and adolescent pregnancy, GDM is less common in all age groups of adolescents compared to adults (20,22,25,26). The results in our study were also compatible with the literature. When all groups were compared, GDM was significantly higher in the adult group (p = 0.001) and the risk of GDM in the adult group was 3.14 times higher than in the 17-19 age group. However, as the parity increased, this significance decreased between both groups. (AOR: 1,20 (0,35-4,12) p = 0,770).Intrapartum fetal death may be seen in adolescents as a result of fetal asphyxia and shoulder dystocia depending on the immaturity of the bony pelvic structure. In some studies any difference cannot be found between adolescents and adults regarding intrapartum fetal mortality (24,25). In our study, no significant difference was found between adolescent and adult pregnant women in terms of fetal mortality. However, in some studies, the risk of stillbirth was

found to be 4 times higher in pregnants younger than 15 years of age. Also, early neonatal death may increase (22,29). In another study, the risk of infant death was increased in adolescents aged 11-14 years compared to adults (2). In our study, the need for maternal and neonatal intensive care did not increase in adolescents. In most of the studies, the need for treatment in the neonatal intensive care units increased in adolescents (18,21,25,30) and was found to be less common in older adolescents than younger ones (19). There are publications showing that puerperal endometritis increases in adolescents (21,22) The risk of chorioamnionitis was found to be higher in young adolescents compared to older adolescents (19). In a study comparing adolescent primigravidas and adult primigravida, puerperal infection and chorioamnionitis were observed to be increased in adolescents (26). In our study group, no difference was found among the groups in chorioamnionitis. Maternal mortality risk increases in pregnancies under 15 years of age (22). Hypertensive diseases and maternal heart diseases are the most important causes of death (26). Maternal death was not observed in any of our adolescent and adult cases.

Obstetric and perinatal outcomes were found to be similar in adolescents who gave birth to twins when compared with the adult age group. However, it has been reported in some publications that the risk of extreme preterm birth increases in adolescents (31). In our study twin birth rates were similar in both groups. There was no difference between adolescent and adult groups in the incidence of multiple pregnancies. When the risk of adolescent pregnancy and congenital anomaly is examined, there are publications stating that there is an increase in central nervous, gastrointestinal and musculoskeletal system anomalies in adolescent pregnants. Increases in the risk of circulatory / respiratory anomalies, urogenital anomalies, or Down's syndrome were not detected (32). In our study, higher rates of fetal anomaly were not detected in adolescents. In the study of dos Reis LV et al, congenital anomalies in adolescent births were also examined and they stated that they most frequently encountered neural tube defects. They concluded that this condition might be related to the inadequacy of folic acid supplementation in unplanned adolescent pregnancies (33).

We acknowledge that this study has some limitations. Data related to socioeconomic status, education status of the mother, maternal weight, nutritional status were not analyzed in this study.

Adolescent pregnant women should be considered as a high risk patient group and it is necessary to provide emotional and educational clinical support to pregnant women. Since pregnant women in this age group are closely associated with preterm birth, delivery of small for gestational age and low birth weight infants, it is important to improve pregnancy prevention strategies and health services to reduce adverse pregnancy outcomes. In addition, multidisciplinary prenatal management is required. Our study was conducted with a large pregnant group, but multicenter prospective studies are needed to better evaluate perinatal outcomes.

Conflict of interest

All authors declare that they have no conflict of interest.

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The effect of paranasal anatomic variations on chronic rhinosinusitis

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Abstract

Rhinosinusitis is the inflammation of the paranasal sinus mucosa and the most common pathophysiological event causing rhinosinusitis is the ostiomeatal complex disease. The aim of the study is to determine the prevalence of anatomical variations and mucosal pathologies in paranasal computed tomography images of patients with chronic rhinosinusitis and to reveal the relationship between anatomical variations and sinus pathologies. Anatomical variations and mucosal pathologies in coronal paranasal tomography images were evaluated in 100 patients diagnosed with chronic rhinosinusitis and 32 individuals in the control group without any sinus complaints. The rate of having at least one anatomical variation in the control group was 64.1%, while this rate was 87.5% in patients with chronic rhinosinusitis ($p<0.001$). The most common variation, Agger nasi cell, was found to be present in 34.3% of the individuals in the control group and in 53.5% in the rhinosinusitis group ($p<0.05$). In patients with rhinosinusitis, maxillary sinus was affected in 66.5%, anterior ethmoid sinus in 42.5%, frontal sinus in 32.5%, posterior ethmoid sinus in 20%, sphenoid sinus in 18.5% either in isolation or in combination. The relationship between anatomical variations and mucosal pathologies of the sinuses was evaluated. A significant correlation was found between anatomical variations such as Agger nasi cell, concha bullosa, septum deviation, ethmoid bulla and Haller cell with maxillary sinusitis, between Agger nasi cell and septum deviation with frontal sinusitis, and between Agger nasi cell, concha bullosa, septum deviation and ethmoid bulla with ethmoid sinusitis. In conclusion, it was concluded that anatomical variations are an important factor in the development of chronic sinusitis and that not only sinuses but also anatomical variations that impair drainage should be corrected during the surgical treatment of rhinosinusitis.

Keywords: paranasal sinus, tomography, variation, surgical treatment

1. Introduction

Rhinosinusitis is the inflammation of the paranasal sinus mucosa and is one of the common diseases in the population. Various causes from upper respiratory tract infections to systemic infections can be listed in its etiology, however, the most common pathophysiological event causing rhinosinusitis is the ostiomeatal complex disease. Small pathological changes in the mucosa of the ostiomeatal complex impair the drainage and ventilation of the sinuses by preventing mucociliary excretion of secretions in the paranasal sinuses (1, 2).

Direct radiography, computed tomography and magnetic resonance imaging are used to visualize the anatomical variations of the paranasal sinus. Direct radiography is insufficient for detailed imaging of lesions, differential diagnosis, and treatment planning. On the other hand, it is possible to evaluate the ostiomeatal complex pathologies that cause infection in the sinuses in detail using computed tomography. Moreover, using computed tomography, it is possible to evaluate the areas in contact with each other, the degree of mucosal inflammation, anatomical variations causing obstruction, mucocele, osteomyelitis, and complications related to sinusitis. As functional endoscopic sinus surgery has become the routine practice, computed tomography is now one of the most important diagnostic methods in revealing the mucosal pathologies and anatomical variations of the paranasal sinuses (3).

In addition to the fact that the anatomical structure of the nose differs from individual to individual, prominent anatomical variations have been detected in the population, especially in people with chronic sinusitis. It is known that such anatomical variations may cause chronic rhinosinusitis by narrowing the nasal passage and ostiomeatal complex. Agger nasi cell, concha bullosa, septum deviation, hyper-pneumatized ethmoid bulla, Haller cell, paradox middle concha and pneumatized uncinate process can be listed among the most frequently detected anatomical variations using computed tomography (4, 5).

The aim of the study is to determine the prevalence of anatomical variations and mucosal pathologies in patients with chronic rhinosinusitis using computed tomography imaging and to reveal the correlation between these anatomical variations and sinus pathologies.

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2. Materials and Methods

In the study, mucosal pathologies and anatomical variations in paranasal computed tomography scans were evaluated in 100 patients diagnosed with chronic rhinosinusitis referred to our clinic between February-October 2001, as well as 32 individuals as the control group.

Routine otolaryngological examinations were performed for the patients who had clinical complaints such as nasal discharge, postnasal drip, headache, facial pain, and pressure sensation. Patients with nasal or postnasal purulent discharge and/or erythematous changes in the nasal mucosa, and those with air-fluid level or opacity presence in direct radiography were diagnosed with acute sinusitis and administered antibiotic treatment for three weeks. In the follow-up, paranasal computed tomography was performed for patients who have on-going symptoms and findings after the medical treatment.

Patients with maxillofacial trauma, inverted papilloma, paranasal sinus malignancy, immunodeficiency, history of paranasal sinus surgery and patients under 18 years of age were excluded from the study. The control group consisted of 32 patients who did not have sinonasal complaints but had undergone paranasal tomography due to ophthalmologic or neurological complaints or whose tomography sections passed through the paranasal sinuses with no detected pathology in the sinuses.

Paranasal sinus tomography was performed using a General Electric CT Sytec Plus device with 3mm section thickness, 130 mA and 120 kV examination protocol. The images were evaluated by expert radiologists and otolaryngologists separately for each hemicranium and the findings were recorded in the study form. Anatomical variations including Agger nasi cell, concha bullosa, septum nasi deviation, hyper-pneumatized ethmoid bulla, Haller cell, paradox middle concha, and pneumatized uncinate process, as well as sinus pathologies were examined for the rhinosinusitis and control groups. Anatomical variations were evaluated as present or absent regardless of their shape or size. All changes in the sinuses ranging from minimal mucosal thickening to opacifications filling the entire sinus were considered pathological.

In the study, the distribution of mucosal pathologies to the sinuses, the frequency of the presence of at least one anatomical variation in the rhinosinusitis and control groups, the frequency of the presence of each anatomical variation in both groups, the correlation between the anatomical variations and rhinosinusitis in the experiment group, and the effect of the presence of multiple anatomical variations in the same hemicranium on the sinuses were evaluated.

The statistical analyses were performed using the Chi-square test and Fisher's exact test.

3. Results

Of the 100 individuals in the rhinosinusitis group, 65 (65%) were male and 35 (35%) were female. The ages of the patients in this group ranged between 18-81 years, with a mean of 37.4 years. Of the 32 individuals in the control group, 18 (56.2%) were male and 14 (43.8%) were female. The ages of the patients in this group ranged between 19-73, with a mean of 38.5 years.

In the rhinosinusitis group, 172 out of 200 hemicrania (86%) had mucosal pathology in at least one sinus, while no mucosal pathology was observed in any sinus in 28 (14%) hemicrania. It was observed that the most frequently affected sinus was the maxillary sinus in 133 (66.5%) hemicrania, and the least affected sinus was the sphenoid sinus in 37 (18.5%) hemicrania (Table 1).

Table 1. Mucosal pathology distribution over the sinuses

Sinuses (n=200)	Affected sinuses	
	Number	%
Maxillary sinus	133	66.5
Anterior ethmoid sinus	85	52.5
Frontal sinus	65	32.5
Posterior ethmoid sinus	40	20.0
Sphenoid sinus	37	18.5

In the rhinosinusitis group, the number of hemicrania with at least one variation was 175 (87.5%), while this number was 41 (64.1%) in the control group. The number of hemicrania with no anatomical variation present was 25 (12.5%) in the rhinosinusitis group and 23 (35.9%) in the control group. The probability of having at least one anatomical variation in the rhinosinusitis group was 3.9 times higher than in the control group ($p<0.001$).

One of the anatomical variations, agger nasi cell, was distributed differently between the two groups and the difference was statistically significant ($p<0.05$). The differences in the distribution of concha bullosa, septum nasi deviation, ethmoid bulla, Haller cell, paradox middle concha and pneumatized uncinate process between the two groups was not statistically significant ($p>0.05$) (Table 2).

In the evaluation of anatomical variations, it was found that Agger nasi cell presence correlated significantly with frontal, maxillary, and anterior ethmoid sinusitis ($p<0.01$), and the presence of concha bullosa correlated significantly with maxillary and anterior ethmoid sinusitis ($p<0.001$). Similarly, septum deviation was found to be significantly correlating with frontal, maxillary, and anterior ethmoid sinusitis ($p<0.001$), and hyper-pneumatized ethmoid bulla was found to be significantly correlating with anterior ethmoid and maxillary sinusitis ($p<0.001$). Moreover, it was statistically significant that Haller cell correlated with maxillary sinusitis ($p<0.001$), while no significant correlation was found between paradox middle concha or pneumatized uncinate process with sinusitis ($p>0.05$).

Table 2. Distribution of anatomical variations in rhinosinusitis and control groups

Variations	Rhinosinusitis group (n=200)		Control group (n=64)		p
	Number	%	Number	%	
Agger nasi cell	107	53.5	22	34.3	<0.05
Concha bullosa	89	44.5	28	43.7	>0.05
Septum deviation*	43	43.0	10	31.2	>0.05
Hyper-pneumatized ethmoid bulla	39	19.5	11	17.1	>0.05
Haller cell	20	10.0	2	3.1	>0.05
Paradox concha	11	5.5	5	7.8	>0.05
Pneumatized uncinate process	6	3.0	-	-	-

*n=100

It was determined that 32 sinuses were affected in 25 hemicrania without any anatomical variation, while 17 sinuses were found to be affected in 10 hemicrania with four anatomical variations each ($p<0.05$). These findings suggest that the risk of rhinosinusitis increases 1.67-fold in hemicrania with one anatomical variation compared to no anatomical variations, while hemicrania having three anatomical variations have an increased rhinosinusitis risk of 1.89-fold ($p<0.05$) (Table 3).

Table 3. Total number of variations and affected sinuses in the same hemicrania in the rhinosinusitis group

Total number of variations in the same hemicranium	Hemicranium number in the rhinosinusitis group	Total number of affected sinuses	Odds ratio	p-value
None	25	32	-	
1	87	159	1,67	<0.05
2	46	89	1,83	<0.05
3	32	63	1,89	<0.05
4	10	17	1,50	<0.05

4. Discussion

Rhinosinusitis is a commonly observed disorder in the population and has a significant socioeconomical impact. Sinusitis caused by impaired ventilation and mucociliary transport of the paranasal sinuses results in headache, nasal congestion, feeling of fullness on the face, and nasal or postnasal purulent discharge (6-8).

Today, endoscopy and computed tomography are used together and complement each other in the evaluation of paranasal sinus diseases and the detection of pathological conditions and anatomical variations in the ostiomeatal complex (5,9,10,11). Diagnosing the anatomical variations in the ostiomeatal complex, identifying their prevalence, determining whether they contribute to the development of chronic or recurrent sinusitis, and deciding whether to surgically correct these anatomical variations is important for treatment (3,12). Some anatomical variations in the region of the ostiomeatal complex predispose to infection in the middle meatus, leading to secondary infection of adjacent large sinuses (9,13,14,15).

In coronal paranasal tomography of patients with rhinosinusitis, agger nasi cell was detected in 33.7% of the patients in the study by Kaygusuz et al. (2000); in 52.2% by Ünlü et al. (1992); in 98.5% by Bolger et al. (1991); while Kennedy (1988) reported this variation to be present in all the cases studied (9,17,18,19). In our study, agger nasi cell was detected in 53.5% of the patients in the rhinosinusitis group and in 34.3% patients in the control group. The difference between the two groups was statistically significant ($p<0.05$). Stammberger and Wolf (1998) suggested that agger nasi cells pneumatized in varying degrees may cause frontal sinusitis because of frontal recess obstruction (5). In our study, agger nasi cell was found to be correlating with frontal, anterior ethmoid, and maxillary sinusitis ($p<0.001$).

Depending on the degree of pneumatization of the middle concha, if the concha is in contact with the lateral nasal wall, it may cause mucosal edema, polyp, retention cyst, mucocele, and pyocele (5). Yousem et al (2). (1991) reported that the size of the concha bullosa is more important than its presence only (20). When researchers evaluated all conchae with air density as bullous, they found that the prevalence increased up to 53%. Bolger et al. (1991) found the concha bullosa variation to be present in 50% in the control group and 53.6% in the rhinosinusitis group (3,9,13). In our study, all conchae with air density were considered bullous. Concha bullosa was detected in 44.5% of the patients in the rhinosinusitis group and in 43.7% in the control group. The difference between the two groups was not significant ($p>0.05$). Calhoun et al. (1991) reported that concha bullosa is associated with anterior ethmoid sinusitis, but not with ostiomeatal complex disease (13). In our study, a significant correlation was found between concha bullosa variation with maxillary and anterior ethmoid mucosal pathologies ($p<0.001$).

The most studied variation in association with chronic sinusitis is septum deviation. Severely deviated septum narrows the nasal cavity and middle meatus, preventing

proper ventilation and increasing susceptibility to sinus infection (1,3). Calhoun et al. (1991) detected septum deviation in 40% of patients with chronic rhinosinusitis and in 19.5% of patients without a sinus infection and reported that the deviation was associated with anterior ethmoid, posterior ethmoid, and ostiomeatal complex disease (13). In our study, septum nasi deviation was found in 43% of the patients in the rhinosinusitis group and in 31.2% of the control group. The difference between the groups was not significant ($p>0.05$). However, there was a significant correlation between maxillary, frontal, and anterior ethmoid mucosal pathologies on the deviated side of the septum in the rhinosinusitis group ($p<0.001$).

When the ethmoid bulla is excessively pneumatized to completely fill the middle concha cavity, it may cause contact headache without causing an infection. Cysts, polyps, and pus can be seen in the ethmoid bulla itself (16). In patients with rhinosinusitis, Kaygusuz et al. (2000) found hyper-pneumatized ethmoid bulla in 18.1%, while Ünlü et al. (1992) in 26.1% of the patients (17,18). In our study, we found hyper-pneumatized ethmoid bulla with a rate of 19.5% in the rhinosinusitis group and 17.1% in the control group. Although the difference between the groups was not significant ($p>0.05$), the correlation between hyper-pneumatized ethmoid bulla with maxillary and anterior ethmoid sinusitis was significant in the rhinosinusitis group ($p<0.001$).

Depending on their size, Haller cells are considered among the causes of recurrent maxillary sinusitis when infected (16). Milczuk et al. (1993) found ipsilateral rhinosinusitis in 66.7% of cases with Haller cells (21). In our study, maxillary sinusitis was present in 14 of 20 hemicrania with Haller cell in the rhinosinusitis group, and this relationship was statistically significant ($p<0.01$).

It is still debated which image is compatible with rhinosinusitis in the evaluation of paranasal sinuses using computed tomography. While Som (1985) considered all images in which the mucosa can be seen on tomography to be pathological, Havas et al. (1988) reported that the mucosa seen in tomography is not always pathological, but it would be appropriate to evaluate the image together with the clinical representation of the patient. Zinreich et al. (1987) evaluated 100 patients with chronic sinusitis and found that 72% of the ethmoid cells, 65% of the maxillary sinus, 34% of the frontal sinus, 40% of the posterior ethmoids and 29% of the sphenoid sinus were affected (3,16,22). In our study, it was determined that the most affected sinus in the rhinosinusitis group was the maxillary sinus (66.5%), and the least affected sinus was the sphenoid sinus.

Narrow recesses and ostia that provide ventilation and drainage of the sinuses become narrower in the presence of anatomical variations. Subsequent edema and mechanical obstruction affect the mucociliary system, impairing the ventilation and drainage of the sinuses. In our study, mucosal pathology was 1.6 times more common in hemicrania with one anatomical variation compared to no variation presence, while the rate is increased to 1.9-fold in hemicrania with three anatomical variations.

In conclusion, we suggest that the anatomical variations are an important factor in the development of chronic sinusitis and that not only sinuses but also anatomical variations impairing drainage should be corrected in the surgical treatment of rhinosinusitis.

Conflict of interest

None the declare.

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Digital dental models in orthodontics: A review

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Abstract

Digital 3 dimensional (3D) dental models are considered one of the most important advancements in modern dental history. Digital dental models are used in diagnosis, treatment planning, and appliance production phases in orthodontics. The present technology of digital dental models reached, and in some points, exceeded the plaster models' accuracy. The use of digital models with CBCT images and rapid prototyping techniques brought the possibility of new treatment techniques, some of which are considered as the future of modern orthodontics. This article aims to review the current use and success of digital 3D models in orthodontic practice.

Keywords: digital orthodontics, orthodontic model, orthodontic diagnosis, digital dentistry

1. Introduction

Orthodontic dental models of patient's dentitions provide important information during diagnosis, treatment planning, evaluation of treatment results and appliance production. Dental models successfully transfer the data about dental morphologies, occlusion and dental relationships, which are sometimes difficult to detect during intraoral examination (1). Impression materials and plasters were used to produce dental models for the last three centuries. Plaster models occupied a lot of storage space and providing optimal storage conditions were an important limitation for their long-term preservation (2). Today, using 3 dimensional (3D) digital technologies, dental models can be produced digitally and stored in a computer drive. Digital 3D models are considered as a revolutionary advancement in the orthodontic practice. Beside the simplicity of storing and transferring, 3D models also opened doors for new diagnosis and treatment options such as 3D planning of orthognathic surgery and clear aligner therapy, which are considered as the future of orthodontic mechanics. This article aims to review the current use and success of digital 3D models in orthodontic practice.

2. Dental 3D scanners and digital model acquisition

Although the designs for digitalization of dental models dated back to 1980's, widespread use of digital 3D models started lately. Digital models were commercially introduced in late 1990's (3). Digital scanners, printers and software technologies became more accessible with the competition in the market. Device and software development and variety allowed these systems to be more affordable as these devices became faster and more reliable. Study casts can be created with different technologies and devices. Intraoral and tabletop dental scanners are commonly used in orthodontic practice. Manual impression taking procedures either with or without stone model production procedures are still needed for the use of tabletop dental scanners. Intraoral scanners on the other hand; scans the patient's dentition directly intraorally without the need of any manual impression or plaster production.

While scanners provide superior 3D model qualities, their precision is still improving at the regions with sharp edges. Clinicians do not need micron-level sensitivity for diagnostic models in their orthodontic practices; therefore, intraoral scanners had an increasing popularity in orthodontics (4, 5). Researchers emphasized that intraoral scanning was also easily accepted by the patients and that the patients in their study preferred intraoral scanning over manual impression.

Digitally produced dental models also have the advantages of smaller size factor, ease in disinfection and cleaning, decreasing the chair time and eliminating additional laboratory work (6). The most important disadvantage of intraoral scanning when compared with model/impression scanning is that intraoral scanning must be done according to a scanning protocol and learning the protocol has a steeper learning curve; furthermore, scanners were considered costly when compared to the plaster models (7). As these technologies are getting more and more affordable, they are becoming more price efficient.

Digital dental scanners generate 3D view in their own file format but most of them can export the 3D file as an open source '*stereolithography*' (STL) format. STL format can be used universally for storage, diagnosis, treatment planning

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and appliance production. STL file format is the commonly used 3D model format in digital dentistry.

Digital models can be used virtually or can be printed with 3D printers using rapid prototyping, a group of techniques used to quickly fabricate a scale model of a physical part or assembly using three-dimensional computer aided design (CAD) data, techniques.

3. The use of 3D models in orthodontics

Digital dental models are used in diagnosis, treatment planning and appliance production in orthodontics.

4. Diagnosis

Dental study models provide valuable information for orthodontic diagnosis. Detailed inspection of the occlusal relationships and measurements of tooth and arch sizes are done on the study casts prior to orthodontic treatment.

4.1. Analysis of the occlusion

One of the drawbacks of using stone dental models as an archiving method is; if optimal storage conditions are not met, any damage or loss of dental stone models cause irreversible data loss of valuable patient information. Digital models on the other hand are reliable and can be reached easily at any point for re-evaluation. Storage of digital data is also as important; all the patient's digital data can be saved in a single usb drive. Setting systematic backup conditions is the key to prevent any data loss. With the many cloud solutions, data can be reached at any location, which improves productivity and saves both time and space. Although there were conflicting findings in the literature about the diagnostic value of digital dental models, current studies show that the digital dental models are equal to, if not exceeded, their plaster counterparts.

Santoro et al. (8) compared the overjet, overbite and tooth dimensions on plaster and digital models. They found that although there were statistical differences between plaster models, which was considered as the "golden standard", and digital models, the differences (0.16 to 0.49 millimeters) were minimal and were not clinically significant.

Mayers et al. (9) showed that Peer Assessment Rating (PAR) scores could be successfully derived from digital models.

Several other studies showed minor but statistically significant differences in occlusal contacts, overjet, bucco-lingual inclinations, alignment, and total American Board of Orthodontics (ABO) grade scores between the plaster and digital models (10, 11).

More recent studies concluded that there were no significant differences in diagnostic capabilities of plaster and digital dental models and that the digital models could be reliably used to observe the occlusal relationships (9, 12, 13). Different software algorithms and techniques might have been the cause of these differences. Advances in the technologies of modern intraoral scanners, are making them more reliable and precise every other day.

4.2. Arch length and tooth width

Calibrating rulers and references were used in 2D photographic and radiographic analysis. With the advances in digital models, 3D dental models are precalibrated and many measurements, such as arch length, tooth size discrepancies etc. can be done manually or automatically with a variety of software. With the help of dental software, different model analysis, like Bolton discrepancy, crowding analysis, intercanine width etc. can be completed much faster than manual methods. Clinicians spend less time on preparation for diagnosis, which leaves more time for the actual treatment planning.

Digital 3D models obtained with intraoral scanners were compared to digital models obtained with CBCT (Cone beam computer tomography) and plaster models in the previous literature. Most of these studies showed that intraoral scanners provided superior reliability than CBCT images and similar results with plaster models, especially for linear measurement made on two landmarks (14,15).

Differences in Bolton index calculation between plaster models and digital models obtained from CBCT image was studied by (16). The authors concluded that even CBCT images, which was shown inferior to intraoral scanning in current literature, was comparable with plaster models in Bolton index calculation.

Few relatively older studies report statistically significant but clinically irrelevant differences between digital models and plaster models in arch length and space measurements (17, 18). Erdinc et al. (19) found significant differences in mesio-distal widths of molar and premolar teeth and in total arch lengths between the measurements made on digital and plaster dental models, but they also emphasized that these findings were clinically acceptable. These are due to the lack of precise scanners and software, which were developed after these studies. Naidu and Freer (20) expressed that the mean differences in anterior and overall Bolton ratio between digital models and plaster models were below 1 millimeter, and that 95% of the errors were in a clinically insignificant range. Koretsi et al. (21) showed that digital workflow for orthodontic model analysis is more reliable than traditional manual plaster model analysis.

5. Treatment planning

Digital dental models brought various treatment applications into the field of orthodontics. Digital setups, visualization of treatment results, quality assessment of treatments, 3D analysis of the tooth movement, and Computer Aided Design and Manufacture (CAD-CAM) of the orthodontic appliances are among the examples of current digital applications. Digital models combined with 3D CBCT images and 3D facial scanning data already exceeded the conventional orthodontic and orthognathic planning techniques.

Digital 3D technology brought the possibility to communicate with the patient over their own models and made it possible for patients, to see and discuss proposed treatment plans using 3D setups and forecasted scenarios, before getting into the surgery room.

5.1. Model setup

Advanced 3D technology enabled the users to merge and calibrate multiple 3D images, which were acquired from different sources. The development of a 3D setup that displayed individual crowns, roots and craniofacial structures helped the clinicians in treatment planning to determine various treatment options, monitor changes over time, predict and display final treatment results and measure treatment outcomes accurately.

Macchi et al. (22) separated roots from craniofacial CBCT data and superimposed laser scanned 3D dental model data on extracted 3D root images to form a digital 3D dentoalveolar complex. The researchers then simulated premolar extraction therapy by eliminating first premolars to observe the possible final positions of the teeth and their relationship with the surrounding structures. Im et al. (23) asserted that plaster model setups and virtual setups of digital models lead to similar measurements. Barreto et al. (24) compared the reliability of digital model setups with plaster setups and post-treatment dental models of the patients and concluded that digital setups were as accurate and effective as the plaster setups and constituted a tool for treatment planning, which could be reliably reproduced in orthodontic treatments. Eliminating the additional laboratory work has been an important advantage of digital setups.

5.2. Digital orthognathic surgery planning

Cone beam computer tomography (CBCT) images, digital dental models and stereophotogrammetry images are superimposed to form a "virtual patient" for digital orthognathic surgery planning. This made it possible to eliminate most of the time-consuming conventional model surgery steps including the facebow transfer. Digital planning consists of two phases: osteotomy and wafer production. Digital models obtained with either model or intraoral scanning provide superior data of the teeth registered in occlusion, which are used in the planning phase (25).

Cousley et al. (26) confirmed that digital surgical planning and wafer production techniques achieved level of accuracy, that match the conventional facebow and model surgery. De Riu et al. (27) reported that digital planning was even more successful than conventional planning for the orthognathic correction of facial asymmetry. Chen et al. (28) reviewed the literature on comparison between virtual surgical planning and traditional surgical planning. They concluded that VSP technique has become a good alternative to TSP technique for orthognathic surgery.

5.3. Smile design

Mentality of orthodontic treatment planning shifted towards analyzing the smile aesthetics and soft tissue in the last two decades. Although smile analysis is not a new term for orthodontics, utilization of digital technology for forecasting the effects of the treatment plan on smile aesthetics is currently a popular trend. "Smile design" concept was acquired from aesthetic dentistry and its extensive use in orthodontics started a few years ago. Smile design technique is especially useful for the treatments when multidisciplinary approach is needed, like the orthodontic-restorative treatment of tooth shape anomalies. The technique depended on superimposing the photo of dentition after possible treatment over patients own smile photo, so that the possible effects of the treatment on the smile could be inspected. Frontal photographs were used for smile design and only one dimension could be seen during the planning (29, 30).

Digital models and stereophotogrammetry enabled superimposition of dental models inside 3D facial surface image, so that the effects of the treatment on smile could be analyzed three dimensionally.

The final 3D design (in STL format) can be exported to a 3D printer to generate the physical model of the new design. This model can be used to fabricate a matrix for a mock-up and provisional and guides for tooth preparation, crown lengthening, and implant placement can be produced. It can be integrated into treatments with digitally planned setups like clear aligner therapy. Digital smile design protocol made diagnosis more efficient, and treatment plans more consistent. It provides more logical and straightforward treatment sequences, reducing the risks and improving the results (30).

6. Appliance design and fabrication

High precision 3D printing technology is being used to produce variable orthodontic appliances like retainers, removable appliances, indirect bracket placement trays and occlusal splints (31, 32). Three-dimensional design and printing can be used to produce clear retainers for home bleaching (33). Today, one of the most important use of 3D printing technology is the production of clear aligners.

There are specific software programs on the market which allowed individual bracket and aligner designs. Even complicated appliances like Herbst and sleep apnea appliances can be digitally designed and fabricated to accurately fit the dentition (34).

Material technology plays an important factor in these advances in digital appliance design. Materials with more suitable characteristics and development of user-friendly design tools lead to the in-office production of orthodontic appliances, which is an important step towards individual appliance design and manufacture. Like its advantages in diagnosis and treatment planning, digital technology reduced the steps in orthodontic appliance workflow and eliminated the need of additional, and sometimes non-standard, laboratory procedures.

6.1. Clear aligners

In 1998 Align Technology Inc. released Invisalign, the first clear aligner method, which used digital models to build the appliances. Modern production of clear aligners depends on setup of digital 3D dental models and plans of incremental stages for specific tooth movements with different software. Various possible treatment options can be visualized on digital setups. The clinician can see and interfere with the treatment plan in sophisticated software programs (35). After the clinician's approval of the proposed plan, incremental movements can be used to 3D print dental models for each increment then, thermoform aligner materials can be used such as polyamide (36).

Although the indications of digitally produced clear aligners were limited at the beginning, with development of material, computer technology and clinical research, the indications of clear aligners have been greatly extended. There are plenty of studies that showed successful cases treated with clear aligners, that show how these aligners can treat various types of cases from mild to severe malocclusions (37) Digital 3D technologies played an important role not only in design and production; but addition of artificial intelligence (AI) into the equation showed very promising improvements in orthodontic treatments and AI is also used in the analysis of treatment effectiveness. Clear aligner therapy even has some advantages over fixed orthodontic treatment. Khosravi et al. (38) reported that clear aligner therapy especially managed vertical dimension relatively well and Ke et al. (37) asserted that clear aligner therapy had the advantages possibility of segmented tooth movements and shortened treatment durations.

6.2. Digital orthodontic laboratory work

Studies on automation of fabrication of orthodontic removable appliances date back to 1990's. The advancement was visible after the commercial use of digital 3D models. Digital models facilitated effortless transfer of data via digital mediums. With the widespread use of 3D printing, orthodontic laboratories started using digital models and appliance design software.

There are two different workflows for digital removable appliance fabrication. First method is that laboratories 3D prints the study models and build the appliances with conventional techniques. Fabricated appliances are then sent to the clinics. This method eliminates the time needed for impressions, plaster model preparations and transfer of the study models.

The second method of appliance fabrication is gaining popularity. In which, digital models are sent to the laboratory, appliances are designed virtually, and designs are sent back to the clinic in printable STL formats via digital mediums. The clinicians can either 3D print the appliance in-office or can send the STL file to a 3D printing center to be printed. Directly in-office printing the appliance, eliminates the need to build plaster or digital models and the time needed for the transfers (39).

Several researchers successfully fabricated all parts of a removable appliances, which were consisted of metal clasps and resin base plates with the help of 3D printers (40, 41).

Commercialization of metal 3D printers enabled the fabrication of complex metal devices. Graf et al. (42) applied a miniscrew supported expansion device, which was designed and produced with the aid of computer aided design and 3D printing technologies. It is now possible for the clinicians to have the appliances designed in another part of the world and receive the design by e-mail in a matter of days.

6.3. Customized orthodontic brackets

Lingual orthodontic brackets are one of the most aesthetic appliances currently in use, because they are placed on the lingual surfaces of the teeth. Because lingual morphology is quite variable standard bracket bases, like the ones in conventional labial brackets, are not preferable to be used in the lingual surface of teeth. Time consuming laboratory process was needed for model setup and preparation of individual composite bases, which also made the lingual brackets rather bulky.

Modern lingual bracket systems utilize digital dental models to virtually design customized base for every tooth. The brackets are manufactured using 3D printing processes (43). The customized bracket system was found so successful that it was adapted to labial bracket fabrication. When coupled with custom formed arch-wires, customized bracket systems were able to overcome the difficulties of different tooth morphologies and increase the efficiency of the treatment (44, 45).

6.4. Digital indirect bonding

Orthodontic brackets are commonly bonded on the teeth directly by the practitioner. Indirect bonding technique was developed to overcome the bracket positioning errors due to limited view of the teeth during direct bonding. Brackets were placed on their pre-planned positions on plaster casts and were transferred to patient's mouth with custom made transfer trays.

Digital version of indirect bonding eliminated the need for complex laboratory and clinical processes. There are currently three different ways for digital indirect bonding.

Like appliance production, the most basic way of incorporating digital technology to indirect bonding is; 3D printing the study models and applying conventional indirect bonding steps which were normally applied on plaster models.

Second method includes using of software individually designed for indirect bonding. Brackets are virtually placed on digital models in the software. Some of the programs can apply basic set-up on the dental models to show a forecast of

possible treatment options. Users can choose from the 3D data of the brackets which are stored in the software's own library. Digital study models with placed brackets can be 3D printed to fabricate the transfer trays from silicone or thermoform materials in the laboratory. Real brackets are then placed in the grooves on the transfer tray.

Thirdly, the users can finish all the above workflow digitally including the design of the transfer trays. The trays are 3D printed with a flexible resin and brackets are placed in their grooves (46).

Using digital setups during the digital planning of bracket positions, were shown to increase the precision in positioning (47).

Although digital indirect bonding technology is promising in decreasing chair time and laboratory steps, there are some concerns about high error rate of the system (48). Kim et al. (49) reported positioning errors were more frequent in posterior teeth and that the technique should be carefully used.

One of the main disadvantages of the system is that the user is limited by the types of bracket models that are stored in the software's library.

6.5. Miniscrew insertion guides

Miniscrew anchorage significantly reduced the need for patient compliance and allowed many advancements of orthodontic treatment mechanics. Manual insertion of miniscrews increased the risk of complications; therefore, surgical insertion guides can be used for precise positioning of the screws.

Digital insertion guides which use CBCT data and digital dental models were transferred from implant dentistry. The most important advantage of using CBCT images is being able to superimpose the 3D image of the roots, this enables the user to plan according to true 3D morphology (50).

Digital guides can be used for both buccal and palatal insertion fields and were found to greatly reduce the risk of root damage when compared with the direct manual placement method for insertion (50, 51).

7. Conclusion

Present technology of digital dental models reached, and in some points exceeded, the plaster models in accuracy. Use of digital models with CBCT and rapid prototyping techniques brought the possibility of new treatment techniques, some of which are the future of modern orthodontics. Studies reported minor differences between digital and plaster models which are not clinically relevant. Digital 3D models and technologies provide important advantages in orthodontics from diagnosis to treatment. These advances changed the orthodontic workflow significantly, soon today's innovations might be considered as the new "golden standard".

Conflict of interest

None to declare.

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Compendium of polycystic ovarian syndrome and its relevance in glycation and diabetes

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Abstract

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine and reproductive disorders observed in women. Its pathophysiology indicates its involvement in plenitude of diseases and/ or disorders. Although the absolute cause of PCOS has not been established, its prevalence in diabetic patients is noteworthy. Glycation and insulin resistance being key factors in diabetes, the present review tries to study their correlation with PCOS. Amongst the available drugs, four commonly prescribed drugs namely, metformin, inositol, thiazolidinediones, and spironolactone have been discussed. The current review also provides insights about usage of *M. oleifera* and *S. platensis* as a potential therapeutic agent for symptomatic relief of PCOS.

Keywords: altered steroidogenesis, glycation, insulin resistance, PCOS, *spirulina*, T2DM

1. Introduction

Polycystic Ovarian Syndrome (PCOS) most often characterized as an endocrine/hormonal disorder, which typically commences during the onset of puberty. It is one of the chief causes of oligomenorrhea (irregular periods), amenorrhea (no periods) or prolonged periods causing anovulatory infertility in women. This is believed to be due to the excess amount of androgen produced known as Hyperandrogenism (1). Hyperandrogenism in PCOS is due to a disturbed Hypothalamic-pituitary-ovarian axis (HPOA) affecting the ratio between luteinizing hormone (LH) and follicle stimulating hormone (FSH) (2). There are several factors that are responsible for the intricate pathophysiology so far identified in PCOS. Although the absolute cause of PCOS is not well comprehended, genetic, and environmental factors are believed to be responsible for the prevalence of the disorder (3). Therefore, it is also classified as an oligogenic disorder (disease inherited is not due to a simple single-gene mutation) implying interlinkage between various genetic and environmental factors causing the characteristic symptoms of the disease (4).

More often PCOS shows a constellation of symptoms and is simply responsible for the onset or cause of other metabolic disorders such as Type 2 Diabetes Mellitus (T2DM) (5). Most women diagnosed with PCOS, are more susceptible to develope Diabetes or prediabetes (borderline diabetes). Another life-threatening symptom which is commonly observed, includes cardiovascular disease (6). Prevalence of cardiovascular disease may be due to disturbed carbohydrate metabolism in PCOS (7). The chain of symptoms in PCOS is quite complex because of which the ultimate interlinkage between hormonal and metabolic disorder cannot be distinguished. However, in both the cases Insulin resistance (IR) plays a key role in giving rise to the disorders commonly observed in PCOS. Distress in Phosphatidylinositol-3-Kinase (PI-3K) enzyme is primarily held responsible for IR. Due to IR women with PCOS are diagnosed with hyperinsulinemia causing obesity in women. Both hyperinsulinemia and insulin resistance are observed in obese and non-obese women. IR is most possibly considered for the endothelial damage which can aggravate the cardiovascular disease or worsen the situation in some cases (8).

Various foregoing studies have associated defective insulin receptor-mediated signal transduction in PCOS (9, 10). With further investigation on the defective insulin receptor pathway, aberration in PI-3K insulin mediated glucose uptake has been observed in PCOS women (11). Function of PI-3K can be disturbed either by serine phosphorylation of insulin receptor substrate (IRS) or advanced glycation end products (AGEs). AGEs are protein products formed because of glycation (non-enzymatic glycosylation). PI-3K endocytotically uptake of AGE by their receptor (RAGE), regulating their degradation and elimination process (12). Although elimination of AGE can be mediated via the insulin receptor pathway (13).

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AGEs are also associated with Diabetes and their formation increases free radicals' activity (14). This facilitates biomolecular damage increasing the complication in the disorder increasing IR (15). AGEs are responsible for the onset of IR in PCOS and diabetes through insulin receptor-mediated pathways and free radicals, respectively, worsening the pathophysiology of the disorder. Reducing glycation and AGEs in the tissue by subsequently controlling the AGE-RAGE interaction might avert the complication raised due to IR in PCOS and diabetes (15).

2. Insulin Resistance (IR)

Understanding insulin resistance at the molecular level would be the first step in deciphering the abnormalities that occur. Insulin hormone plays a crucial role in glucose homeostasis. Any disturbance in insulin secretion directly initiates certain conditions, such as hypoglycemia, hyperglycemia and T2DM. Insulin transduction pathway consists of several enzymes, receptors and hormones which facilitates the proper functioning of insulin in the body. The signal transduction pathway of insulin generates a cascade of signals in the cell in response to its environment. Impairment in the insulin signal transduction pathway leading to cellular inflammatory pathway is a prime cause of IR (16). Albeit a decreased strength of IRS/PI-3K signaling pathway is the supreme culprit, the authenticity of which is still enigmatic. Two distinct but interdependent mechanisms confer a potential explanation for reduced strength in the IRS/PI-3K pathway, which includes increased expression of p85α and serine phosphorylation of insulin receptor substrate (IRS)-1 (16).

Apart from being a crucial component of the signally pathway, PI-3K also helps in maintaining insulin sensitivity in the liver. It is composed of two subunits, namely a regulator subunit (p85) which is tightly associated with a catalytic subunit (p110) forming a p85-p110 heterodimer or complex (16). The regulatory subunit (p85) is responsible for regulating the activity of PI-3K by binding to the active site of IRS-1. Over or under expression of p85α competes with the p85-p110 heterodimer on the binding site of IRS-1 leading to either increase or decrease in PI-3K activity, (17, 18) P85α an isomer of p85, competes with the p85-p110 heterodimer reducing PI-3K activity (19). However, other growth hormones, steroids, overfeeding, (20) and T2DM subsequently increases the activity of p85α (21).

In response to insulin binding to insulin receptors. IRS-1 is phosphorylated by tyrosine kinase activating PI-3K enzyme (22). PI-3k binds to a specific motif on IRS-1 which consist of phosphorylated tyrosine residue resulting to which PI-3K is activated initiating a cascade of events causing phosphorylation and activation of Akt (kinase B), mTOR (mechanistic target of rapamycin) and p70S6 kinase (ribosomal protein S6 kinase beta-1) (23). Akt activation is crucial for glucose transport across the cell, however, mTOR and p70S6 activation assist in protein synthesis. Although in case of IR hyperactivation of mTOR lead by a certain stretch of amino acids, Akt or hyperinsulinemia follows serine phosphorylation of IRS-1 by p70S6 kinase eventually giving rise to a decrease strength of IRS-1/PI 3-kinase signaling (16).

IR is also widely associated with lipids. Irregularities in insulin signaling and lower insulin-stimulated glucose transport are some of the major imputations resulting from Lipid-induced insulin resistance in skeletal muscle (24, 25). Activation of PKC (isoform PKCθ) is linked with muscle lipid accumulation hence altering the insulin intracellular signaling. Lipid induced IR, mediated by diacylglycerol (DAG) for the activation of PKCθ leading to impairment in insulin signaling (26). Although impaired Akt activation limits the translocation of GLUT4-containing storage vesicles to the plasma membrane, (permits the entry of glucose into the cell, and promotes glycogen synthesis via glycogen synthase (GS).), resulting in impaired glucose uptake therefore decreasing insulin-mediated Glycogen synthesis (27). Convincing evidence between DAG-mediated activation of PKC and muscle insulin resistance has been confirmed in human studies (23). Another study demonstrated hepatic insulin resistance relating to intrahepatic lipid content. Therefore, demonstrating that ectopic lipid accumulation of lipids within the liver leads to hepatic insulin resistance (28).

An alternate string signaling towards hepatic IR with non-alcoholic fatty liver disease (NAFLD) involves activation of unfolded protein residues (UPR). The initiation of UPR takes place in the endoplasmic reticulum (ER) lumen due to accumulation of unfolded protein, therefore known as ER stress. Unfolding of protein in the ER may occur due to environmental stress or genetic mutations. Accumulation of unfolded protein induces UPR in a eukaryotic cell (29). Studies noted a reduced activity of PKC in individuals provided with lipid infusion, shows reduction in insulin-related glucose transport, strongly suggesting a defect in the insulin signal mechanism (30). Although the relation between PKC and lipids is not yet clear.

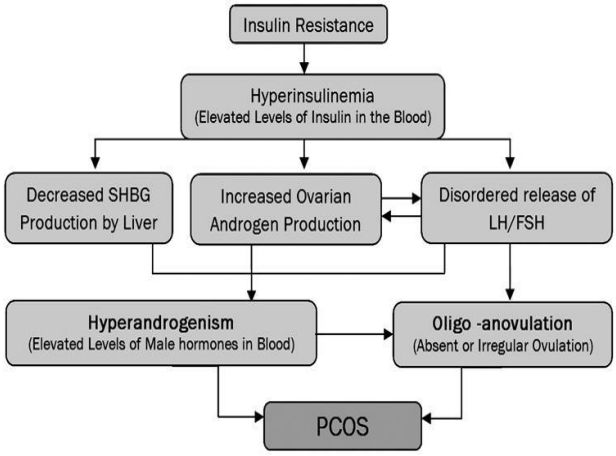

Fig. 1. Intricate linkage between Insulin resistance and PCOS

2.1. Glycation

Glycation is widely defined as a non-enzymatic reaction between reducing sugar, proteins, lipid and nucleic acid (15). The process of glycation leads to the formation of AGE's formed by a complicated molecular process also known as Maillard reaction (31). The electrophilic group of sugar molecules reacting with the free amino group of amino acids commences with the formation of the Schiff base (32). With further intramolecular rearrangement the Schiff base is reversibly converted into a more stable form known as Amadori product (ketoamine). Further engagement of Schiff base and Amadori products with protein or amino acid residue giving rise to protein adducts or protein crosslinks (33). After the formation of Amadori product, they undergo a slow oxidation process yielding dicarbonyl compound such as glyoxal, methylglyoxal (MG), 3-deoxyglucosone (3-DG), and deoxyglucosone in the span of 3 to 30 days (32). The final stage of the glycation reaction includes oxidation, dehydration, polymerization and oxidative breakdown advances in the formation of AGE's (34). Accumulation of AGEs leads to physiological and pathological changes, therefore AGEs are associated with T2DM, Alzheimer's disease, aging, etc. (35) AGE's characterized into three categories, namely pentosidine (fluorescent product; forms protein-protein crosslinks), carboxymethyl-lysine (CML), and glucosepane (a non-fluorescent protein adduct) (36).

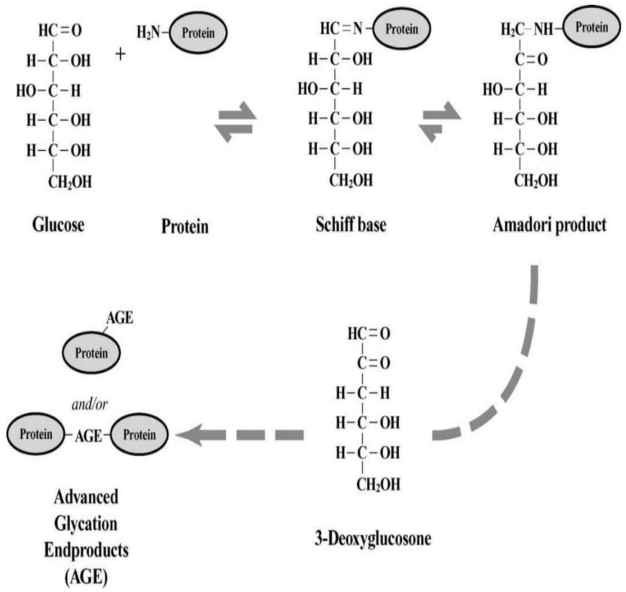

Fig. 2. Steps of protein glycation and formation of AGE (adapted from 15)

The formation of AGEs can take place through three distinct pathways. Apart from Maillard reaction, lipid peroxidation and glycolysis pathway are the alternative means through which AGEs are formed. In the case of lipid peroxidation, reactive oxygen species lead to the formation of reactive carbonyl compounds which then ultimately form AGEs or Advanced lipid end products (ALE) (37). Similarly, in the case of glycolysis pathways, oxidation of glucose to yield carbonyl compound, for example, methylglyoxal, undergoing a series of reactions with protein to yield AGEs (38). Although PCOS women are often diagnosed with an abnormal lipid profile, AGEs play a negative role in dyslipidemia (39). Studies show a positive correlation between serum MG level and triglyceride concentration in diabetic patients (40). Accumulation of AGEs intracellularly is mediated through specific AGE receptors (RAGEs) (41). Binding the ligand to RAGE activates signaling pathways such as mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinases (ERK-1/2), PI-3K etc. RAGE stimulation by AGE activates nuclear factor kappa-B (NFκB) (42). Activation of NFκB further increases the expression of RAGE, which in turn stimulates NFκB leading to a cycle of perpetuating proinflammatory signals (43). It also decreases cellular antioxidant defense, such as glutathione (GSH) by inducing oxidative stress. Decrease in GSH causes decreased activity of Glyoxalase-1 (Glo-1) which plays a key role in cellular defense against methylglyoxal (MG) leading to further formation of AGEs (44).

RAGE interaction with amyloid-β peptide (Aβ), β-sheet fibrils etc. involving RAGE in multiple cellular functions via distinct signal transduction pathway (43). Activation of MAPK activates the expression of proinflammatory cytokines which are believed to be associated with IR (45). Generation of ROS due to AGEs is a common link discussed in diabetes pathology. Physical and functional characteristics of stable protein products are altered when interacted with extracellular matrix membrane (ECM) leading to diabetes altering the basement membrane and microvascular system due to excessive AGE formed (46).

2.2. PCOS and IR

The main culprit in the prevalence of PCOS is contemplated as HPOA and hyperinsulinemia (47). Both factors are believed to be interconnected, as disrupted HPOA can cause loss in GnRH pulses resulting in an increasing amount of LH (48, 49). In the menstrual cycle, the role of increased spike of LH is to bring about ovulation and oocyte development and forming corpus luteum in a healthy woman with the help of another hormone progesterone, which suppresses the LH therefore maintaining the LH/FSH ratio (50). More than the required amount of LH secreted due to increased GnRH can inhibit the whole cycle and change the morphology of the ovary (48, 49). Also, increased LH leads to a substantial decrease of FSH in the ovary causing decreased conception and miscarriage in woman (47). LH is also responsible for provoking an increased ovarian androgen. Production of androgen occurs in ovarian cells (theca interna cells) and adrenal cortex (zona fasciculata cells) (51). Increased amounts of androgen or hyperandrogenism (HA) occur due to altered steroidogenesis.

Change in the ovarian morphology or presence of polycystic ovaries is the prime site of endocrine abnormality

causing hyperandrogenism. Affected P450c17a enzyme activity plays a principal role in excess ovarian androgen production (52). Serine phosphorylation also increases activity of P450c17 in both the ovary and adrenal gland, thus promoting androgen synthesis (53). The initial substrate, cholesterol, is used to produce androgens in both the organs. Both of which are strongly under endocrine control of LH and adrenocorticotropic (ACTH) in the ovary and adrenal cortex respectively (51). Androgen synthesis takes place through distinct steroid biosynthesis pathways, namely, D5-steroid pathway and D4-steroid pathway occurring parallelly and simultaneously (54). Although intraovarian androgen is crucial for the follicular development, excess of which can cause abnormalities in the follicular growth therefore poor follicular maturation. Both androgen and estrogen are the positive modulators of LH however Insulin-like growth factor-1 (IGF-1) is recognized as a positive modulator of LH. Increased LH stimulated androgen production also takes place via insulin or IGF-1 (52). Insulin and IGF-1 stimulate the production of estrogen mediating the action of FSH on granulosa cells for healthy follicle growth. Androgen production is moreover inhibited by corticotropin releasing hormone, transforming growth factor-β (TGF-β), epidermal growth factor (EGF), tumor necrosis factor (TNF) and cytokines. TNF and EGF inhibit the activity of aromatase, which determines androgen production. Action of activin on the granulosa cells increases estrogen secretion and therefore inhibits thecal androgen secretion (52).

PCOS also increases the prevalence of T2DM and IR. The role of insulin in androgen production is quite crucial and important. Due to affected endocrine signaling other metabolic pathways are also affected hence giving rise to T2DM. IR is considered as one of the pathogenic factors associated with an increased metabolic disturbance which also explains HA, irregular menstrual cycle (5, 55). A positive correlation between hyperinsulinemia and PCOS were recorded showing notable correlation between insulin, testosterone, and androstenedione (56). Elevated insulin level in PCOS concurrently elevating LH levels, suppression of follicle growth hence no ovulation (57). Hyperinsulinemia also affects the secretion of GnRH pulses which leads in the arrest of Sex Hormone Binding Globulin (SHBG) and escalating ovarian androgen production in PCOS (58-61).

Elevated levels of AGE along with their receptor RAGE was observed in the ovarian tissue. Potentially, accumulation of AGE's could alter steroidogenesis in PCOS, although the prime pathway or its potential role in steroidogenesis yet remains in scrutiny. Toxic AGE (TAGE), CML and pentosidine in follicular fluid and serum-TAGE (S-TAGE) show a negative correlation with estradiol (E2) in PCOS women. Earlier studies have reported an increased level of serum AGE's in PCOS women by examining the association of serum AGE's level and RAGE expression with testosterone (62). A different study showed a substantial association between AGE's and HA (62, 63). To understand the signaling mechanism of AGE-RAGE behind the altered steroidogenesis in PCOS Diamanti-Kandarakis and team (2013) pointed out that AGEs lead to inappropriate activation of ERK1/2 in KGN granulosa-like tumor cells alter steroidogenesis in granulosa cells (5). A vital role of glyoxalase in the ovary has been confirmed by dietary glycotoxins and hyperandrogenic decrease GLO1 (Glyoxalase 1) activity in the ovaries, contributing to enhanced accumulation of AGE in granulosa cells (5).

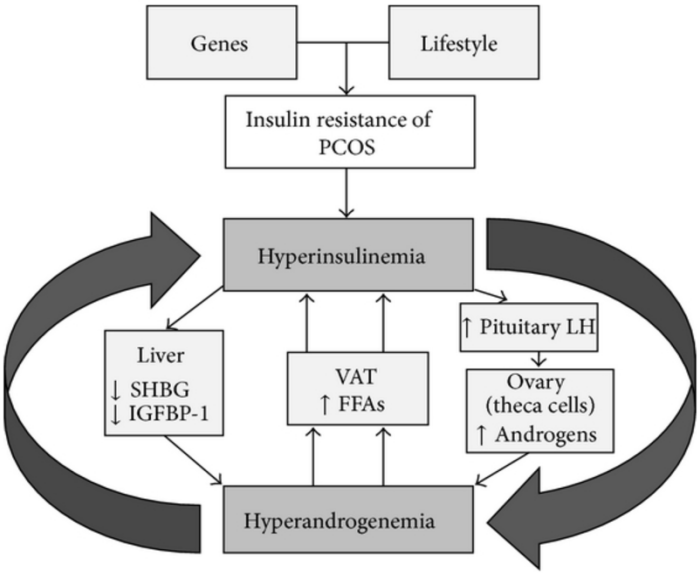

Fig. 3. Cycle between hyperinsulinemia and hyperandrogenemia (136)

2.3. PCOS and diabetes

Diabetes mellitus, a disorder which is often characterized due to elevated levels of blood sugar due to insufficient amounts of insulin produced by the body. Due to its characteristics, T2DM is often associated with hyperinsulinemia. As mentioned earlier, PCOS leads to a collection of syndromes which leads to reproductive disturbance and glucose metabolism disorder (64). HA and IR are identified features of PCOS which lead to hyperinsulinemia causing IR (5). IR arises due to an intrinsic defect in post-receptor insulin signaling in its ideal target tissue, such as muscle cells and adipocytes (47). Protein glycation (dicarbonyl stress) and MG combined, shows a chronic side effect in hyperglycemic diabetic patients which leads to the pathogenesis of various diseases associated with altered redox homeostasis (65).

Even though the molecular basis of AGE in the pathogenesis of T2DM is not well comprehended, certain study shows a strong relation between AGE-induced oxidative stress as well as inflammation (40). Some hypotheses also suggest direct impairment of insulin secretion in pancreatic cells due to AGE activating proinflammatory cytokines provoking inflammation in islet β cells. Inflammation in the pancreatic cells due to increased levels of IL-1 results in decreased cell proliferation, increased cell

death in β cells therefore giving rise to impaired secretion of insulin (40). Inhibition of cyt C oxidase and ATP production due to AGE, leads to the commencement of impaired glucose stimulated insulin secretion potentially through membrane depolarization (40, 65).

High amount of dietary AGE intake is strongly associated with T2DM. T2DM is also associated with weight gain or obesity, controlling dietary AGE is a common strategy used to control the Many studies conducted to understand the link between the PCOS and T2DM have associated overweight and obesity as the primary cause of IR (67). Other Meta-Analysis studies have confirmed a positive association of PCOS with a high prevalence of prediabetes and T2DM (68). However, the ultimate relationship between rapid weight gain, HA, prediabetes and T2DM shown by numerous studies is not convincing. Also, the prevalence of prediabetes, T2DM in PCOS is moreover independent of the BMI, (69-71) on contrary other studies have associated an elevated risk linked with obesity (72). Some studies have also associated women with normal body weight PCOS having a higher chance of progressing T2DM (73).

2.4. Drugs

Inter-relation between PCOS and diabetes reveals that insulin-sensitizing drugs and dietary or lifestyle modifications improve hyperandrogenism in patients suffering from PCOS (74, 5). It is observed that Insulin resistance increases hyperandrogenemia (75). Leptin, a hormone which is used as an insulin-sensitizing agent, is believed to decrease the androgen levels, and induces menstruation in lean women suffering from PCOS (75). This is considered as one of the remedial treatments for PCOS, which pointed out the consideration of insulin-sensitizing agents as part of the management of the disease. These insulin-sensitizing agents include metformin, MYO supplements, and thiazolidinedione. In previous studies, a few biomarkers have been used to detect insulin resistance in PCOS women. Insulin happens to inhibit the release of SHBG secreted from the liver and the production of insulin-like growth factor-binding protein 1 (IGFBP-1) (76). It is also believed to affect the homeostatic model assessment (HOMA-IR) and levels of insulin (77). Various markers have distinct sensitivities as well as specificities in testing for insulin resistance (78).

3. Treatment

The management of PCOS targets the symptoms present, such as anovulation, infertility, hirsutism, or acne.

3.1. Lifestyle changes

Therapy including exercise and calorie-restricted diet perform a crucial part in the management of obesity in women with PCOS. Lifestyle modifications are considered as a cost-effective first-line treatment and as a necessary adjunct to medication (79). Excessive weight is associated with adverse metabolic and reproductive health outcomes in women with PCOS. Female fertility significantly decreases with a BMI >30–32 kg/m^2 (81). Studies show that a decrease in the body weight of about 5% regulates the MC, reduces insulin and testosterone levels, improves fertility, reduces acne and hirsutism, and increases psychological well-being (82-85). However, no specific diet or exercise schedule is superior to another in the management of PCOS.

3.2. Medical treatment

If lifestyle changes are not enough to resolve symptoms, medical treatment is added for better management of the patient's complaints.

3.3. Oral contraceptive pills (OCP)

For an exceptionally extended period, OCP was commonly used as a first line of medicinal treatment for hyperandrogenism and MC irregularities as a treatment of PCOS, (79, 80). OCP suppresses the hypothalamic-pituitary-ovarian axis, it also decreases LH secretion and increases SHBG; decreases free testosterone level (86). This shows an improvement in hyperandrogenism-mediated symptoms like acne and hirsutism (86), also maintains the MC and provides positive contraception (87). Albeit the guidelines do not specify the use of one OCP over another, therefore, a low dose which contains anti-androgenic or neutral (88) of OCP is prescribed for symptomatic treatment.

The use of OCP in PCOS patients shows an extended risk of insulin resistance (74, 80). There are adverse impacts of OCP on cardiovascular risk in PCOS women (89). Clomiphene citrate is used for the primary treatment of infertility due to anovulatory (89). Administration with gonadotropins and ovarian diathermy is a secondary line of treatment (90) when other drugs fail to achieve fertility.

3.4. Metformin

Metformin, also known as Glucophage, is a biguanide anti-diabetic drug (Fig. 4), acts by preventing liver glucose production and increasing the peripheral insulin sensitivity (91, 92). Metformin was first studied in 1994 by Velazquez with his co-workers and showed a 35% decline in insulin and a 31% reduction in insulin to glucose ratio (89). Few studies also claim that metformin does not promote insulin resistance itself, it promotes glucose effectiveness, i.e., the ability of glucose to repress endogenous glucose synthesis and stimulate glucose uptake (93). Metformin therapy for obese PCOS adolescents and IGT proved beneficial in enhancing insulin sensitivity and glucose tolerance, in reducing insulinemia, and in elevated androgen levels (94). By contrast, a study done by Tang et al. showed no remarkable shift in insulin sensitivity in PCOS patients receiving metformin which could be explained due to the elevated level of obesity (BMI>30 Kg/m^2) and the limited weight loss of the patients (52). Ehrmann et al. (1997) also showed that metformin does not necessarily improve insulin resistance in PCOS women (95, 96). Açbay and Gündog˘du, (1996) stated that metformin has no visible effect on insulin resistance in PCOS patients.

Although studies show conflicting results of metformin effect, it is suggested as a primary line of treatment for pregnancy complications in PCOS women. Combination of Metformin with clomiphene citrate to improve fertility in clomiphene resistant patients (89).

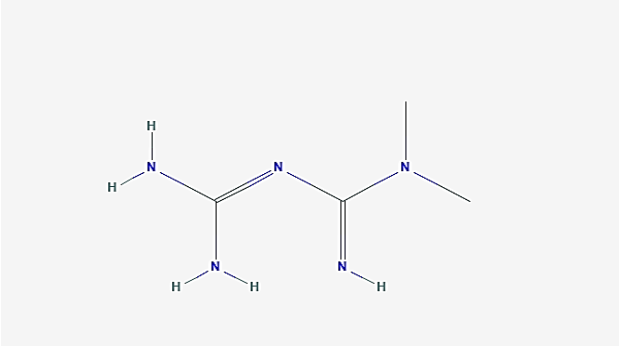

Fig. 4. Structure of Metformin (Source: https://pubchem.ncbi.nlm.nih.gov/compound/4091)

metformin alone is given as the primary line treatment of PCOS obese treatment by inhibiting liver glucose absorption, reducing peripheral insulin levels, increasing peripheral glucose uptake, and improving Glucose transporter type 4 (GLUT-4) (97, 98). Metformin affects the endothelium and adipose tissue independent of its action on insulin and glucose levels (99). Metformin does not help to body weight loss; it may help to distribute adipose tissue (100).

3.5. Thiazolidinediones

Thiazolidinediones (TZD), a class of drugs (insulin sensitizer) used in T2DM treatment. They activate the γ isoform of an adipocyte transcription factor, known as peroxisome proliferator-activated receptor (PPAR-γ) (101). The use of pioglitazone (glitazones) was studied in PCOS patients and data showed a decline in insulin resistance and fasting serum insulin levels (Hayek et al., 2016). However, pioglitazone showed an increased chances of bladder cancer (102, 103), therefore it has not been prescribed use or the use of other TZDs (namely rosiglitazone and troglitazone) in PCOS treatment due to its ill effects (89, 80).

3.6. Inositol

Different drugs are identified as a unique treatment for PCOS which are preferred due to their lack of side effects. D-chiro-inositol (C6H12O6) (DCI) as well as myoinositol (MYO), which is an insulin-sensitizing molecule (Fig. 5). Metabolic alteration of Inositol Phosphoglycan (IPG) secondary messengers and its mediators or due to a tissue defect, might induce insulin resistance (74). In PCOS women, use of MYO shows to increase insulin resistance (89). Increase in levels of fasting plasma insulin is observed to be positively correlating with a decline in insulin resistance, this supports the role of Inositol as a modulator of the insulin-mediator metabolic pathway (104).

Combining Inositol with monacolin K (Lovastatin) and lipoic acid shows dose-dependent changes in HA associated symptoms (105). Folic acid combined with MYO showed a decrease in ovarian hyperstimulation syndrome (OHSS) to a greater extent as compared to the use of folic acid alone in PCOS women (106). MYO along with α-lipoic acid also improved reproductive issues in women undergoing an IVF treatment (107, 108). Most importantly, MYO combined with DCI in a blood plasma shows a decreased risk of developing metabolic syndrome in obese PCOS women (107, 109). Another study shows notable improvement in PCOS symptoms, such as MC regularity, decreased insulin resistance, healthier lipid profile, and fewer acne, upon the use of MYO-DCI combination (89). Therefore, MYO and DCI in combination as a therapeutic approach can be used for the PCOS treatment (104).

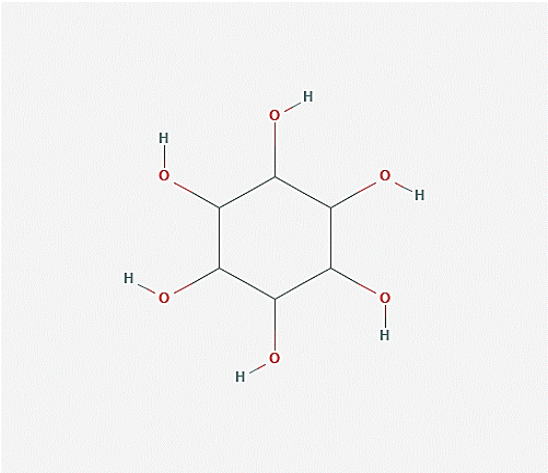

Fig. 5. Structure of Inositol (Source: https://pubchem.ncbi.nlm.nih.gov/compound/892)

3.7. Spironolactone

Spironolactone, a chemical steroid related to the aldosterone (Fig. 6) (mineralocorticoid), was observed to enhance insulin sensitivity; it was also suggested its use for HA associated symptoms such as hirsutism and acne (89, 110). Combination of Spironolactone with Metformin often shows an increase in menstrual frequency. However, Spironolactone is also known to induce menstrual irregularities when consumed at higher doses. Although, it is primarily in the management of hirsutism, acne, and androgenic alopecia (110).

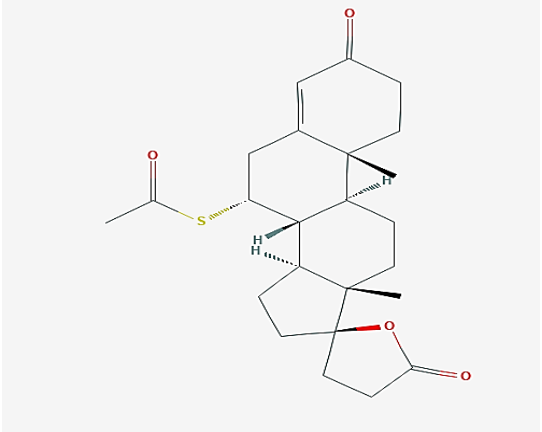

Fig. 6. Structure of Spironolactone (Source: https://pubchem.ncbi.nlm.nih.gov/compound/5833_

A clinical trial with two sub-groups including women with PCOS, lean and overweight, were subjected to spironolactone treatment. Women affected with oligomenorrhea, and amenorrhea were observed with a regular menstrual cycle. Other symptoms include acne development in lean (31%) and overweight women (33%). Spironolactone shows positive antiandrogenic properties. In some cases, use of spironolactone may cause Polyuria, Polydipsia during the initial days of treatment. Patients may also witness some minor to rare symptoms which includes headaches, increased appetite leading to weight gain, breast enlargement or tenderness & dizziness (111).

4. Treatment in adolescents

The aid of treatment for adolescents suffering from PCOS is OCPs, administered as an effective treatment for HA and contraception (112). OCPs bring menstruation in the regular cycle and reduce hirsutism and acne (113). Change in Lifestyle and weight loss are also considered as part of the primary line of treatment, especially in obese adolescents. Nevertheless, uncertainty prevails concerning the best OCPs and their duration of usage in adolescents (89, 114). Alternatively, metformin shows to improve irregular MC, insulin resistance, and HA in PCOS adolescents (89). Finally, adolescents PCOS treatment is recommended with OCPs which may reduce the chance of hyperandrogenism in adults (89) and early changes in lifestyle and metformin treatment show preventative results (89).

4.1. Natural products

Other synthetic drugs may show some side effects, which in turn would lead to some other disorder. Synthetically designed drugs may not work as efficiently/effectively in each patient. Use of synthetic drugs shows some mild symptoms and development of endometrial cancer in some adverse cases. Natural products, which are obtained from plants or organisms, minimize the risk of such side effects. The extract obtained from a natural product, such as moringa leaves, has shown significant results in lowering the blood insulin level. A decrease in insulin level leads to a subsequent decrease in androgen, promoting folliculogenesis. Due to its positive result and lowering the risk of side effects on PCOS women it is essential to switch more towards the utilization of natural products as compared to synthetic drugs.

5. Potential sources of natural drugs

5.1. Moringa

Moringa oleifera or Moringa (family- Moringaceas), extensively spotted in tropical climates. It emerged as a natural therapy as one of the alternatives in PCOS treatments, a food plant which originates from India, which grows in regions with temperatures around 25°C-35°C. Due to the side effect neutralizing the effect of food plants they are safe as compared to synthetic drugs (115). It is appreciated to be rich in various active medicinal chemicals. Recent studies on *Moringa oleifera* have potential as antioxidants, anticancer, antidiabetic, anti-inflammatory, and as antimicrobial agents (116). Flavanol quercetin was found with high concentrations in *Moringa oleifera* leaves (116). *Moringa oleifera* leaf is composed of Quercetin also known as 3,3',4',5,7-pentahydroxyflavone (117). Quercetin is a flavonoid which portrays a strong bioactive element with free radicals' effects, it also acts as a potential anti-inflammation, antihyperlipidemic, anticancer, and antiplatelet compound (118). Quercetin is also found to produce PI3K inhibin (119). The expression of CYP17A1 gene in the ovarian thecal cells is inhibited by the same quercetin P13K inhibin leading to which the activity of 17a-hydroxylase is decreased. 17a-hydroxylase is crucial to produce sex hormones and glucocorticoids therefore a decrease in its activity pay a crucial role in PCOS (120). The action of Quercetin in maintaining the levels of insulin, LH and testosterone and lipid profile have been profoundly noted. The influence of Quercetin is also associated with a decreased ovarian and uterine mass and enhancing the level of follicles and corpus luteum in PCOS (120).

Moringa leaf extract could increase folliculogenesis in the ovary with insulin resistance. Excess amounts of androgens directly inhibit the insulin action in the liver periphery, and indirectly influences the insulin sensitivity in the body through fat metabolism (121). Due to decreased effectiveness of Androgens and the impaired signaling of GLUT-4 insulin resistance is caused. The androgen produced affects the environment of the ovaries, leading to androgen aromatization system disorders into estrogen triggering defective follicular growth. Decrease in insulin resistance decreases LH pulsation and therefore increases the frequency of GnRH secretion hence increases folliculogenesis (early atresia does not occur). Conclusively, Moringa oleifera could potentially control the levels of insulin in the blood consequently decreasing androgen and hence folliculogenesis is increased (122).

5.2. Spirulina

Spirulina platensis, now changed to *Arthrospira platensis*, is a cyanobacteria (blue-green algae). It gained notable attention in the healthy food industry as a food supplement for humans, poultry, livestock, and aquaculture diets (123). Typically grown in alkaline water with efficient yield and can be processed easily. It is known to be enriched with macronutrient and micronutrient contents, such as proteins, amino acids, unsaturated fatty acids and a variety of minerals and vitamins (124). It has shown evident therapeutic benefits in a collection of disease conditions, including hypercholesterolemia, hyperglycemia, cardiovascular disorders, inflammatory diseases, cancer, and viral disease (125). The two major species of Arthrospira genus are *A. maxima* and *A. platensis*.

Studies including *Spirulina* sp. in a high-cholesterol and high-fat diet showed a notable decline in hepatic lipids and blood lipids (125-127). Blé-Castillo and his team in a 2002

study, reported reduction of total hepatic lipids by almost 40%, decreased TG by 50%, and decreased serum TG by 45%, and there was also a 45% rise in serum HDL cholesterol after feeding fatty liver mice with *Spirulina* sp. for about two weeks (128). *Spirulina* sp. induced by treatment of alloxan was also established in diabetic mice. Lowering fasting blood glucose, GSP, cholesterol, TG levels, averted MDA formation, raised the levels of hepatic glycogen, and maintained TAOC and hepatic glucokinase (GK) expression (126).

Hypolipidemic effects of *Spirulina* sp. were studied with 15 T2DM patients, (129) 2g/day of Spirulina consumed for two months shows a notable decrease in LDL, VLDL and serum total cholesterol levels in the blood Furthermore, a significant decrease in blood sugar and GSP levels were also observed. Subjects in a study group consuming Spirulina dosage of 2g/day for 4 weeks, (130) with a decrease in LDL, VLDL, and TG levels, there was a significant decrease in apolipoprotein B level and a parallelly increase in apolipoprotein A1 level. These discoveries noted in the early studies were proved in two recent human clinical trials with T2D patients, (131, 132). Another trial involved 60 male patients aged 40 to 60 years consuming 1 or 2 g of Spirulina every day for two months (132). A notable decrease in fasting and post-meal blood glucose, serum total cholesterol, triglycerides, LDL, and VLDL cholesterol was observed. Benefits of spirulina on hyperlipidemia were observed in patients with hyperlipidemia and nephrotic syndrome (126; 133). Spirulina supplementation at a dose of 1 g/day for four weeks proclaimed a decrease in total serum cholesterol, TG, and LDL fraction by 46 mg/dL,45 mg/dL, and 33 mg/dL, respectively. The ratios between total cholesterol/HDL and LDL/HDL also decreased significantly. Consumption of spirulina shows a significant decrease in the serum total cholesterol levels, LDL cholesterol, oxidized LDL, and apolipoprotein B levels. On the other hand, total plasma cholesterol and LDL fraction were significantly decreased in females. These data, therefore, largely support that spirulina supplements are helpful mostly in elderly people (134).

Another study has shown a positive action of Spirulina on alpha amylase inhibition consisting of antidiabetic properties. Apart from consisting of antidiabetic properties, Spirulina also possesses anti-glycation activity, with its action on the formation of ages and dicarbonyl stress (135). A significant increase in serum insulin level was observed due to its antioxidant enzyme activity and RNA expression. A decrease in the level of glycated hemoglobin (HbA1c) and malondialdehyde (MDA) with a proper recovery of the liver cells due its anti-inflammatory and antioxidant property was observed. Lowering levels of glucose eventually improved liver enzyme and increased insulin secretion was observed in the diabetic mice model when ingested with Spirulina extract (136).

6. Conclusion

Improper diet and altered steroidogenesis in women lead to the development of PCOS. PCOS is known for its collection of syndromes which affects the reproductive and psychological health of women. As the root cause of PCOS is not yet fully understood, various genetic factors and other environmental factors such as glycation which alter steroidogenesis in the ovary are assumed to be the cause for the pathology. Efforts to control the symptoms of PCOS are undertaken by using various drugs, diet management and lifestyle modification. Many synthetic drugs used for the treatment of PCOS have been recorded with significant side effects. Apart from synthetic drugs, natural products also have reported an improved condition in women with PCOS. Symptoms of PCOS include IR which leads to the development of T2DM. Women with PCOS are also observed with an increased risk of heart disease which may be due to hypercholesterolemia or hyperlipidemia. Spirulina has shown effective results in controlling high cholesterol and lipid levels when included in the diet. In recent studies Spirulina has also shown some antidiabetic and antiglycation activity. Since T2DM and PCOS are interrelated with the pathology mediated by insulin resistance, use of Spirulina in women with PCOS may control high cholesterol level and glycative stress caused in the ovaries due to the glycation of certain ovarian proteins and may function as a therapeutic aid. Thus, inclusion of Spirulina in the diet may be an effective alternative for the symptoms of PCOS which may regulate the steroidogenesis and maintain the menstrual cycle improving reproductive health and increase fertility. Further studies and analysis must be done for a conclusive result of the effects of dietary spirulina in PCOS.

Conflict of interest

No conflict of interest was declared by authors.

Acknowledgments

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Digital three-dimensional planning of orthodontic miniscrew anchorage: A literature review

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Abstract

Orthodontic miniscrews are used for skeletal orthodontic anchorage. An appropriate insertion technique is essential to avoid complications during miniscrew placement. The guides prepared using surface anatomy and 2D radiographs cannot correctly analyze bone volume. Advances in digital 3D medical technologies enabled orthodontists to use digital imaging, digital scanning, and 3D printing to accurately place miniscrews using a surgical guide developed with computer-aided design and manufacturing techniques. The objective of this article was to demonstrate the development of miniscrew placement techniques chronologically and provide brief information about the production, use, and efficiency of modern, digitally planned, and produced miniscrew insertion guides.

Keywords: orthodontic miniscrew, surgical guide, virtual planning, CAD-CAM, CBCT

1. Introduction

Orthodontic treatment depends on moving the teeth via a gentle force application. Orthodontic force is generated using orthodontic arch wires, springs and elastics. Although all of these elements have different features, they all need a supporting structure, an orthodontic anchorage, to generate a force vector. Undesired complications can be seen if anchorage unit was not planned properly thus, anchorage planning was considered as the most important part of the orthodontic treatment planning (1-4).

Intraoral and extraoral anatomical structures were used for orthodontic anchorage. Although extraoral devices are successful in providing the desired anchorage, they depend on patient compliance and are aesthetically difficult to accept therefore, intraoral anchorage can be a desired option generally (1). It is difficult to obtain a stationary anchorage with intraoral or extraoral anchorage devices even with excellent patient cooperation. Mini screw-implants were developed to use the skeletal structures as anchorage (1, 5). Orthodontic miniscrews provide the necessary support without the need for patient compliance. Retention of miniscrews during the orthodontic treatment is one of the factors to consider when using minisrew anchorage (6). The mechanical properties, placement technique, the region where they are inserted, the duration of use, the forces they are exposed to and the factors related to the patient affect the retention and clinical success of the miniscrews (5, 7-9).

Miniscrews have proven to be a useful addition to the orthodontist's armamentarium for the control of skeletal anchorage in less compliant or noncompliant patients, but the risks involved with miniscrew placement must be clearly understood by both the clinician and the patient (10-12). Complications like trauma to the periodontal ligament or the dental root, miniscrew slippage to the unwanted regions, nerve involvement, nasal and maxillary sinus perforation can arise during miniscrew placement and after orthodontic loading regarding stability and patient safety (6). A proper placement technique is imperative to avoid complications during mini screw placement.

A direct manual application is commonly used for the placement of miniscrews, and several methods for minimizing root damage have been suggested when using manual application. Root damage was reported to be reduced when insertion is 4 to 6 mm below the alveolar crest (13) A vertical insertion angle of 30° to 45° is advantageous, and distal tilting of 10° to 20° is reported to be safe (13, 14). However, according to Kuroda et al. (4), contact with or damage to anatomic structures around the roots occurred in 47.4% of maxillary and 48.3% of mandibular miniscrews placed with a direct manual method. Therefore, orthodontic miniscrews inserted using the direct manual method can cause unexpected damage to anatomic structures around teeth because this method depends on the operator's senses and visibility might be limited (15).

Several methods have been proposed for transferring the 2-dimensional (2D) information in the radiographs used for surgical planning to the 3-dimensional (3D) surgical site to

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minimize the risks of root damage. For example, inserting a radiopaque marker, such as brass or stainless-steel wire into the interproximal space of the selected implant site has been suggested as a practical method to help guide the drill between the dental roots (16).

The first guiding device was reported by Suzuki and Buranastidporn (2005). It was pre-manufactured and allowed 3D adjustments to be made; however, it was not found to be cost-effective. Two years later, same researchers published details of a simpler guide that had an auxiliary Gurin-lock attached to a vertical rod. The main advantages of this surgical guide were its horizontal articulation, having a metallic tube serving as inclination guide and low cost. The main disadvantage was the lack of vertical adjustment. In order to adjust the height of the device, rods of different lengths were required (17). Other designs of device include brass wire passed through the contact point between the teeth and with apical extension (18); devices with circular rings at their ends (which are easy to make, but are not necessarily accurate) (6); cross-welded devices made of rectangular stainless steel wires inserted into the bracket slots (19, 20) (which are individualized, but hard to make); plate-type devices with a pilot hole made in laboratory (21, 22) which, are accurate, but require laboratory fabrication, and articulated devices fixed to orthodontic appliance (17, 23) which, are adjustable, but expensive. There are also reports of plate-shaped devices (21, 24) that have the advantage of being individualized for each case. These guides are widely employed in those cases where a pilot drill is initially used, but also with self-drilling miniscrews. The main disadvantage of the plate-shaped devices is that they need to be made in a laboratory.

When the studies about conventional methods are reviewed, it is concluded that the guides prepared using surface anatomy and 2D radiographs cannot correctly analyze bone volume. At the same time, different surface anatomy due to maxillary sinus, dilated roots and alveolar bone loss cannot be detected with these methods.

The use of 3D technology brought the possibility of utilizing cone beam computer tomography (CBCT) images and 3D printers for digital implant guide production for a more accurate screw placement.

Cone-Beam Computed Tomography (CBCT) technology, which is used with the development of 3D imaging methods, provides more precise and detailed information in research and clinical studies for the placement of miniscrews. Additional advantages of CBCT include reduced cost and significant reduction of radiation exposure compared with typical medical CT devices. At the same time, with the development of computer-aided design and computer-aided production (CAD-CAM), minimally invasive and more accurate planning can be made by producing surgical plaques and palatal orthodontic appliances for planning.

With the use of intraoral scanners, the increase in the availability of CBCT devices, production of modelling software specially for dental field and in-office 3D printers, 3D screw guides became easy to produce in the clinic.

This review aims to enable the user obtain a thorough knowledge on the background and the production of the 3D guide for mini screw placement.

2. Digital aid in miniscrew application

Digital workflow has been widely applied in the area of implant dentistry (25, 26). In the “computer-guided” implant placement approach, virtual planning of implants’ positions and 3D printed customized surgical guides are used to help the clinician improve the accuracy of implants positioning in the jaw bones during the surgical phase (27, 28). In orthodontics, the placement of micro-implants with a 3D method method based on CBCT imaging has been described in recent years (29, 30).

3. Surgical guide production with replica model

In the first study on this subject, Kim et al. (2007) planned the size and location of the miniscrew to be used by making measurements on the CBCT (31). They produced the replica model of the patient's upper jaw using a prototype machine that was produced by stereolithography (SLA) method from the patient's CBCT images. Surgical guide plates were prepared to be used in the miniscrew application on the model. The miniscrew was applied according to the plan made in CBCT. They found that the occlusal surface of the replica model produced in the study was not clear and it was not able to clearly convey the amount of soft tissue located between the bone and the surgical plate. It is also stated that the replica model produced with SLA technique was not useful due to its high cost.

4. Surgical guide production with custom made impression material

Yu et al. (2012) developed a new navigation guide for addressing limitations of existing CBCT guide systems. Using this technique, a surgical stent was custom made from rubber polyvinylsiloxane impression material, and the rubber stent and jaw were scanned together using CBCT (32). They used a geometric algorithm to find the optimal orthodontic miniscrew placement site. By using the custom-designed surveyor and a Computer Numerical Control (CNC) machine, a guide hole was drilled in the surgical stent template according to the prescription angles measured on the cone-beam computed tomography data. Statistically significant differences were not observed between the predictive implant location and actual implant location. For this CBCT assisted orthodontics minicrews stent fabrication process, some potential sources of error include data from the CBCT scan (e.g., patient movement causing blurriness of images), transposing the guide hole planning data, manufacturing of the surgical stent, positioning of the surgical stent, and during installation of the orthodontics miniscrew.

5. Surgical guide production with cad-cam technology

One year after their first study, Kim et al. (2008) kept working on the same subject. The position of the miniscrews were planned to use CBCT (33). When planning the position of the miniscrews, an implant planning program called SimPlant (Materialize, Leuven, Belgium) was used. Because the reproducibility of a CT image relative to occlusal surface of the dentition was not as precise as a cast, they also shipped a cast of the patient's dentition to the processing center. A laser scan of the dental cast was superimposed on the CT scan, and the surgical guide was made on a computer-generated model of these images. The surgical guide contained metal guide cylinders placed according to the clinician's plan in the computer simulation. Surgical guide plates were prepared using the SurgiGuide (Materialize, Leuven, Belgium) program. The surgical guide was constructed with a Rapid Prototyping (RP) machine that uses stereolithography, a layer-additive rapid prototyping process based on photo-polymer liquid resins that solidify when exposed to UV light. The RP machine reads the diameter and angulation of the simulated implant, selectively polymerizes the resin around the implant, and forms a cylindrical guide on the replica corresponding to each implant. The technician then removes the supporting resin and uses the cylindrical guide to insert surgical grade stainless steel tubing to serve as the guide tube. C-implants (Cimplant, Seoul, South Korea) were used as the skeletal anchorage miniscrew. After insertion of the miniscrews with the surgical guides, another CBCT was taken to evaluate the outcome.

In the first years of studies on the subject, CBCT data and plaster dental models were sent to planning centers for processing because of the limited availability of the dedicated software. Even the early studies about the accuracy of miniscrew placement with digital aid showed promising results.

Qiu et al. (2012) intended to develop surgical stents for CBCT 3D image-based stent-guided orthodontic miniscrew implantation and to evaluate its accuracy (34). Impressions of the phantom dental models were taken with an alginate-based material and cast models of the phantom with special ‘‘blockouts’’ were acquired. The cast models were scanned using a 3D laser scanner (LPX-1200; Roland DG Corporation, Shizuoka, Japan) with a 0.1 mm slice pitch, and the reconstructed surface images (stereolithography (STL) files) were exported. The STL files were then imported into Simplant software (Materialise Dental Japan Inc, Tokyo, Japan) and superimposed on CBCT dentition images to acquire the fine 3D dentition images and to transfer the spatial data of blockouts. The data for the implantation plan, including the superimposed 3D laser-scanned image and a dental cast of the phantom, were sent to Materialise Dental Japan Inc for the fabrication of the surgical stents in a CAD-CAM process with photopolymerized resin using a stereolithographic appliance (SLA). They compared the surgical stent insertion against freehand insertion on maxillary and mandibular phantoms. Six parameters (mesiodistal and vertical deviations at the corona and apex and mesiodistal and vertical angular deviations) were measured to compare variations between the groups. They found no root damage in the stent group, whereas four of 10 miniscrews contacted with roots in the freehand group. Significant differences were found in all six parameters between the two groups. Their results showed that the apical mesiodistal deviation of miniscrews without root contact to be significantly lower than that of miniscrews with root contact in the freehand group. Among the six parameters, the apical mesiodistal deviation was the key indicator for root contact.

Bae et al. (2013) evaluated the accuracy of miniscrew placement by using surgical guides developed with computer-aided design and manufacturing techniques (15). Miniscrews were placed in cadaver maxillae using stereolithographic computer-aided design and manufacturing techniques with assistance from surgical guides or periapical x-rays. Insertion sites were selected using a 3D surgical planning program by fusing maxillary digital model images and CBCT images. In the control group direct manual method was used for the placement of miniscrew. They found that the deviations between actual and planned placements differed significantly between operators in the control group, but not in the surgical guide group. In the surgical guide group, there was no root damage from miniscrew placement, and 84% of the miniscrews were placed without contacting adjacent anatomic structures. In the control group, 50% of the miniscrews were placed between the roots. Surgical guide accuracy was improved when digital model imaging was used.

Accurate superimposition of CBCT image and intraoral scanning is important for accurate specification of the insertion area. In a trial by Cassetta et al. (2018) the patient wore a personalized radiological tray (Universal Stent, Bionova, Follo, La Spezia, Italy) with radiopaque landmarks during the CBCT exam; this radiological tray was properly positioned in the mouth with a transparent vinyl polysiloxane (Elite Transparent, Zhermack, Badia Polesine, Rovigo, Italy) and allowed a perfect overlap of the jaw and cast STL files. A software application (Guide Design) permitted the design of the surgical guide (Vector Guide, WHITEK, Lodi, Italy). The 3D STL model of the surgical guide was printed using a 3D printer. The surgical procedures were performed without complications in all cases. They found 1.38 mm coronal and 1.73 mm apical deviations with the surgical guide while the mean angular deviation was 4.60° (35).

Palatinal miniscrew placement requires special attention because of several reasons. Palatinal anchorage devices often use two symmetrically placed miniscrews and some of the devices need bicortical anchorage of the cortical bones of palatal vault and nasal floor. The cortical bone is thin in the nasal floor and orientation of the miniscrew should be

thoroughly planned so that it does not penetrate the nasal floor.

Maino et al. (2016) published an article to describe the construction and use of a miniscrew insertion guide designed especially for palatal applications, called the MAPA System. They asserted that the system ensured that miniscrews were placed at the correct depth in the maxillary bone and that multiple implants were parallel. CBCT scan or lateral cephalogram could be used for the identification of optimal site and direction of miniscrew insertion. The latter required a thermo-plastic polyethylene terephthalate glycol-modified bite registration to be made from the patient's plaster cast, with a series of radiopaque markers inserted along the median palatine raphe. Cylindrical guides were placed on the surgical splint to replicate the angle of insertion and were virtually joined to the template by transparent resin bridges, and the entire assembly was produced using a 3D printer. After guiding the miniscrew insertion, the bridges were removed with a dental bur (36).

Cantarella et al. (2020) published an article about miniscrew assisted rapid palatal expansion (MARPE) appliances (36). They placed Maxillary Skeletal Expander (MSE) with four miniscrews on the palate. Bicortical skeletal anchorage was required for the correct functioning of MSE, since it increased the stability of micro-implants (37). They concluded that the digital workflow enabled accurately place the MSE relative to the bizygomatic line, to enhance the biomechanics of the expansion, maximize the bone thickness at micro-implant insertion sites, define the minimum micro-implant length to penetrate the cortical bone of both palatal vault and nasal floor, obtain the parallelism between the four micro implants, the midsagittal plane, and the nasal septum. They too found that compared to the traditional approach, the methodology presented to position MSE with digital planning based on CBCT had the advantage of increasing the precision and safety of the procedure.

Giudice et al. (2020) followed the recent guidelines for digital workflow planning proposed by Cantarella et al. (2020) for the MSE appliance, however, they utilized the patient CBCT DICOM file that allows discriminating between cortical and cancellous bone (36). Also, they used the negative positional template of the MSE for virtual planning. This template allows lab technicians to construct the device in a reliable and accurate position, according to the virtual project planned by orthodontist. The investigators firstly used a printed template of expander connected to a handle which facilitates the test of adaptability of MSE avoiding discomfort to patient (38).

Modern workflow (Fig. 1.) for digital 3D miniscrew guide production starts with obtaining 3D CBCT data of the related area. Scanning of plaster models is replaced with intraoral scanning which provides detailed 3D data of the teeth and the surrounding tissues. Both the intraoral scanning and raw DICOM format of the CBCT image are exported as universal STL file. A dedicated software superimposes the teeth in the CBCT image with the intraoral scan so that CBCT gives the data about the bone and the roots while intraoral scanning gives high quality data about the teeth in the same 3D structure. User then can decide the placement of the miniscrews. DICOM slices can also be used during the placement zone planning. Surgical guide is digitally planned in the software and the guide is exported in a printable STL format to be printed in a 3D printer. Guide can be used after 3D printing.

Orthodontists often place miniscrews without a surgical guide and take only a panoramic radiograph or periapical images for presurgical treatment planning to estimate interradicular space. When implant installation is done manually without a surgical guide, the implant tends to follow the trajectory of least resistance. But the stability of miniscrew placement independent of the operator's skill level when the surgical guide was used. When miniscrews were placed by the 2 operators, who had different levels of experience, there can be little difference in the accuracy of placement between them when surgical guides were used. This implies that deviations between operators can be reduced using surgical guides.

When using the direct method, if the interradicular relationship appears clear and the interradicular distance seems sufficient in the 2D radiographic images, such as the panoramic or periapical view, miniscrews can be implanted successfully. Furthermore, if miniscrews are placed by an experienced orthodontist, the success rate will probably be higher. However, when 2D images of the desired implantation site do not portray an accurate interradicular relationship, when the interradicular distance is short, or when there are significant anatomic structures nearby such as the maxillary sinus or nerve canal, 3D imaging, such as CBCT, might be necessary for planning miniscrew implantation. Although CBCT imaging is not conventionally prescribed because of its cost and amount of radiation, it can be a valuable tool for fabricating surgical guides for successful placement of miniscrews when it is used selectively in patients with limitations to miniscrew placement (15).

Routine use of CBCT cannot be accepted in young patients, but its use can be justified on a patient case individual basis (39). The patient's exposure to radiation can be greatly reduced by the choice of a Field of View (FOV) as small as possible (5 x 11 cm) in the CBCT. This is particularly recommended in subjects under 18 years of age (40). Such FOV is large enough to select the skeletal landmarks required for the virtual positioning of MSE. This inconvenience is compensated by the added safety of the methodology, which allows to avoid the involvement of anatomical areas like the nasal septum, and to maximize bone thickness at miniscrew insertion sites, for a higher stability of

the skeletal anchorage during treatment (36). Surgical guides based on CBCT image are especially indicated for the patients with risky anatomic situations. (21)

When the studies about digital planning of miniscrew applications are reviewed, several different software programs were utilized by authors, which is time-consuming for the operator. For the use in the routine orthodontic clinical practice, it is advisable that the functions be unified in a single software to make the methodology more efficient.

6. Conclusion

The more intraoral scanning and virtual planning technologies advance, the easier the combination of TADs and other preformed parts will become for our orthodontic treatment. CAD-CAM procedure for manufacturing of 3D metal printed orthodontic appliances is an efficient and accurate method to fabricate miniscrew guides. The most important advantages of digital workflow in guide production are decreased risk of complications, decreased chair time and greater patient comfort. Advantages of this technique over conventional methods for miniscrew placement include elimination of impression trays and material.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Case Report

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An unusual upper GI bleeding: Angiodysplasia at the hepaticojejunostomy anostomosis

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Abstract

Upper gastrointestinal bleeding (UGIB) is a common condition causing a considerable number of admissions in clinics. The most frequent causes of UGIB are peptic ulcer disease, malignancies, variceal bleeding and Mallory Weiss tears. A 47-year-old male subject was admitted to the emergency service with recurrent episodes of melena. He had been hospitalized several times before, but he was discharged because the endoscopic procedures did not reveal any origin. There has been a history of Whipple surgery for pancreatic adenocarcinoma. When admitted he was tachycardic, melanic stool was noted on rectal examination and his hemoglobin level was decreased. Widespread angioectasia was detected at the borders of the biliary-enteric anastomosis, which was known to have bleeding on upper GI endoscopy. Despite their rare presentation, bleeding from the vascular ectasia near the anostomotic line should be kept in mind in the differential diagnosis of patients with gastrointestinal hemorrhage.

Keywords: angiodysplasia, gastrointestinal bleeding, vascular ectasia, whipple surgery, pancreaticoduodenectomy

1. Introduction

Upper gastrointestinal hemorrhage is a prevalent potentially lethal condition causing a great number of admissions in health services worldwide (1, 2). An upper gastrointestinal (GI) hemorrhage is described as blood loss from proximal GI tract (3). Patients with upper GI hemorrhage usually present with hematemesis (vomiting of blood and/or coffee-ground-like material) and/or melena (black, tarry stools), although hematochezia may be seen in a case of major bleeding and is typically associated with hemodynamic instability even hemorrhagic shock (4). The most frequent causes of upper gastrointestinal bleeding are peptic ulcer disease due to use of aspirin and/or other non-steroidal anti inflammatory drugs (NSAIDs), variceal bleeding, malignancies including gastric cancer and Mallory Weiss tears (5). Comparably uncommon causes are erosive gastritis/duodenitis, esophagitis, Dieulafoy's lesions and vascular ectasia (5). Here, we report a case of a gastrointestinal hemorrhage as a late complication of Whipple' s procedure.

2. Case Report

A 47-year-old male subject was admitted to the emergency service with recurrent episodes of melena. He had been hospitalized several times for further examination before, but he was discharged because the endoscopic procedures (3 times gastroscopy, 2 times colonoscopy) did not reveal any origin. There was a history of Whipple surgery (pancreaticoduodenectomy) for pancreatic ductal adenocarcinoma one and a half years ago. He had received adjuvant gemcitabine and capecitabine treatment, which was completed one year ago after the surgical procedure. Since then he has only been using NSAIDs on demand. When admitted he was tachycardic and his vital values; pulse rate 110 / min, blood pressure 110/80 mmHg, respiratory rate 14 / min, saturation O_2: 96% at room air, respectively. Melanic stool was noted on rectal examination. Hemoglobin level was 8.2 g / dl (normal: 13.5-8 g / dl). Laboratory values were otherwise not remarkable. Intravenous fluid replacement following two units of red cell suspension transfusion was planned in the emergency department. Later, the subject was taken to the gastroenterology service for further assesment and follow-up. An upper GI endoscopy was planned to examine the anastomotic region. Widespread angioectasia was detected at the borders of the biliary-enteric anastomosis, which was known to have bleeding and clots were seen in patches (Fig. 1). No active bleeding was observed. Argon plasma coagulation (APC) could not be performed due to technical issues. Additionally, there were several stones in the common bile duct. Endoscopic Retrograde Cholangiopancreatography was planned after recovery. In the following days, the hemoglobin level did not decrease and melena disappeared.

3. Discussion

Here, we have demonstrated the origin of bleeding by investigating the afferent jejunal loop anostomosis site in a

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patient with a history of Whipples procedure (pancreaticoduodenectomy) (6).

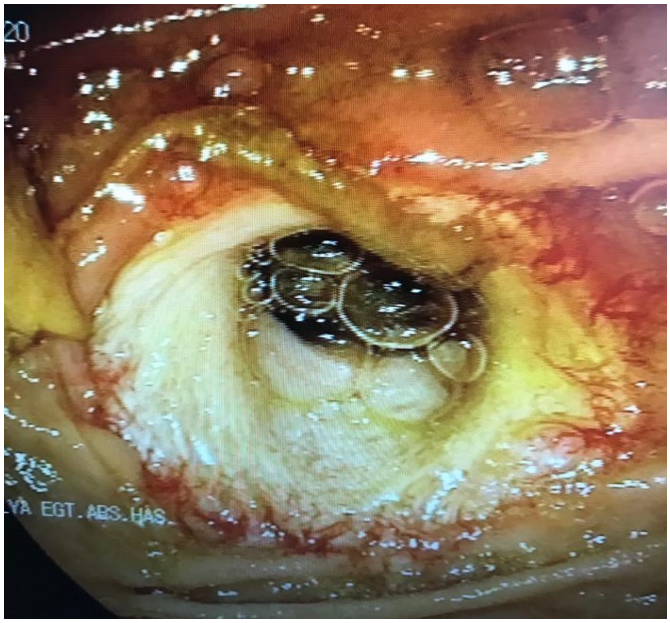

Fig. 1. Angioectasia detected endoscopically at the borders of the biliary-enteric anastomosis

Reviewing previously reported literature, in patients with pancreaticoduodenectomy, source of bleeding may include ectopic varices, pseudoaneurysms, erosions, ulcers, pancreatic fistula and intra-abdominal abcess (6). In our case, only angioectasia were present. In suspected cases of GI bleeding, diagnosis is usually made with endoscopy. In conditions when extended endoscopy is necessary and gastroscopes length is not enough, single-balloon endoscopy (SBE) and double-balloon endoscopy (DBE) and colonoscopy may be beneficial for investigating biliary anastomosis (7). In general, these lesions are treated endoscopically with APC successfully (8). In conclusion, despite their rare presentation, bleeding from the vascular ectasia near the anostomotic line should be kept in mind in the differential diagnosis of patients with gastrointestinal hemorrhage who have a history of Whipple's procedure.

Conflict of Interests

Authors declare that they have no conflict of interest.

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Case Report

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Acute motor axonal neuropathy associated with COVID-19

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Abstract

COVID-19, which is considered a global pandemic, is constantly being renewed. Acute motor axonal neuropathy (AMAN) is a rare, axonal variant of Guillain-Barré syndrome (GBS). This article presents a 69-year-old female patient diagnosed with AMAN due to a COVID-19 infection. Sixty-nine-year-old female patient who started myalgia, headache, cough 14 days ago, and was added diarrhea, fever, loss of smell and taste. Nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR) was found to be positive. Ten days later, numbness and weakness developed in the distal extremities. As a result of the patient's neurological examination, acute motor axonal neuropathy (AMAN) was diagnosed.

Keywords: acute motor axonal neuropathy, COVID-19, guillain-Barré syndrome, pandemic, SARS-CoV2

1. Introduction

This virus is called SARS-CoV-2 and is named by World Health Organization as Coronavirus Disease 2019; COVID-19 (1, 2).

Both SARS and COVID-19 bind to the angiotensin-converting enzyme-2 receptors (3). This receptor is situated in the cell membrane of several organs; including the lung, kidney, liver, skeletal muscle and nervous system (4).

The SARS-CoV-2 infection has been reported to have neurological complications such as febrile seizures, headache, dizziness, confusion, myalgia, loss of taste and smell, encephalitis, stroke, and acute peripheral nerve disorders (4-6).

Coronavirus starts as a nasal infection, and it enters the central nervous system through the olfactory bulb. It causes inflammation and demyelination, which may lead to temporary loss of smell and taste in patients without typical symptoms (6).

GBS is an inflammatory polyradiculoneuropathy characterized by acute, ascending motor weakness, or cranial nerve weakness, loss of deep tendon reflexes, mild sensory abnormalities, and dysautonomic symptoms, accompanied by muscle or radicular pain (7). AMAN is a very rare form of symmetric neuropathy. GBS, which affects the motor fibers, and is characterized by axonal degeneration. Two-thirds of GBS associated with a viral infection 1-3 weeks before. Diarrhea due to Campylobacter jejuni enteritis is usually observed in the prodromal period (8).

Here, we report the AMAN case related to COVID-19, which is a rare subtype of a GBS.

2. Case Report

A sixty-nine-year-old female patient, who started to have weakness and fatigue 14 days ago. With the addition of myalgia, headache, cough, diarrhea, high fever, inability to taste and smell, she underwent nasopharyngeal SARS-CoV-2 polymerase chain reaction (PCR), and it was found to be positive. Ten days after the PCR test, she came to the emergency department due to the numbness in the distal extremities and the subsequent ascending weakness.

The patient had a history of hypothyroidism, diabetes mellitus, hypertension.

The neurological examination of the patient's bilateral upper and lower extremities were 2/5 in the proximals, 3/5 in the distals. The deep tendon reflexes were globally abolic. The patient's clinic was consistent with progressive flaccid

The laboratory tests results were follows: serum glucose 147 mg/dL; blood urea nitrogen: 35 mg/dL; creatinine 0.5 mg/dL; alanine aminotransferase 18.8 U/L; aspartate aminotransferase 16.9 U/L; sodium 138 mEq/L; potassium 3.56 mEq/L; white blood cell count 15600/µL (neutrophils=81.8%; lymphocytes=11.3%); Erythrocyte sedimentation rate 42 mm/hour, C-reactive protein 24.9 mg/L, hemoglobin 12.7 g/dL. The patient's Campylobacter jejuni test was negative.

Lumbar puncture was performed on the patient. Cerebrospinal fluid (CSF) proteins=150 mg/dL (normal=0–40 mg/dL), white blood cells=0×106/L (normal=0–8×106/L). Microbiologic testing on CSF was negative (including HSV,

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VZV, EBV, CMV, HIV-1, Borrelia Burgdorferi IgM/IgG). CSF analysis demonstrated albuminocytological dissociation.

In the first electroneuromyography evaluation of the patient's (complaints on the 2nd day) is; median, peroneal, posterior tibial nerve compound muscle action potential (CMAP) could not be obtained, ulnar nerve CMAP amplitudes were reduced, ulnar nerve F response was prolonged, other F responses could not be obtained. All sensory nerve conduction studies were normal. No resting activity was observed in the needle examination.

Neurophysiologic findings at 2 days, and 7 days after neurological symptom onset were consistent with subtype of GBS; AMAN (Table 1).

Lung computed tomography showed diffused consolidations, ground-glass opacities in both lungs, and bilateral pleural effusion (Fig. 1).

The patient was hospitalized, intravenous immunoglobulin (0,4 g/kg per day during five days) was started. In addition; Favipiravir (in first day 2*1600mg, and next 4 days 2*600mg), low-molecular-weight heparin (LMWH) (enoxaparin sodium), intermittent O_2 (2L/min) were given. The patient's weakness improve on the 3rd day of treatmen

Table 1. Patient characteristics and results

Motor Nerve Conduction Study		First ENMG (2 days later)			Second ENMG (9 days later)		
Nerve (left)		Wrist	Elbow		Wrist	Elbow	
Median	Latency (ms)	PY			PY		
	NCV (m/s)						
	Amplitude (μV)						
	F Response Latency (ms)		PY			PY	
		Wrist	Bellow elbow	Above the elbow	Wrist	Below elbow	Above the elbow
Ulnar	Latency (ms)	3.5	7.04	8.42	3.42	7,02	8.36
	NVC (m/s)		53.7	50.7		50	41
	Amplitude (μV)	1790	1090	1150	2360	2250	2120
	F Response Latency (ms)		36.9			35.25	
		Ankle	Head of Fibula	Popliteal	Ankle	Head of Fibula	Popliteal
Peroneal	Latency (ms)	NP			NP		
	NCV (m/s)						
	Amplitude (μV)						
	F Response Latency (ms)		NP			NP	
		Ankle	Popliteal		Ankle	Poplitea l	
Posterior Tibial	Latency (ms) NP	NP			NP		
	NCV (m/s)						
	Amplitude (μV)						
	F Response Latency (ms)		NP			NP	

NP: No Potential *: All of sensory nerve studies and needle ENMG studies were normal

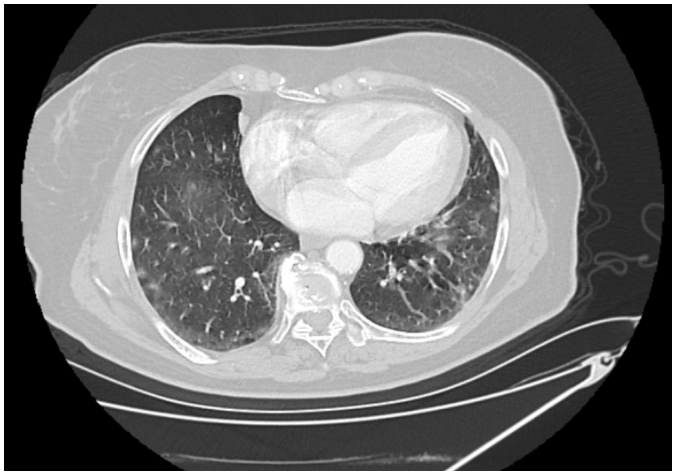

Fig. 1. Lung computed tomography showed diffused consolidations and ground-glass opacities in both lungs, and bilateral pleural effusion

3. Discussion

There are studies suggesting that the neuroinvasive potential of COVID-19 (4, 5). The neurological symptoms of COVID-19 infection are due to their effects on the central nervous system (headache, dizziness, changes in consciousness, acute brain disorder, seizure, and ataxia), and the peripheral nervous system (anosmia, ageusia, and visual impairment) (2, 4). There are also reports of a relationship between GBS and Coronavirus infections (2, 9).

COVID-19 has an incubation period of approximately 5.2 days. The interval between the onset of COVID-19 symptoms and the first symptoms of GBS ranged from 5 to 10 days. The average 10-day interval between the onset of viral disease and the first symptoms of GBS is similar to the interval seen in GBS occurring other infections. Furthermore, demyelinating polyneuropathy has been widely observed in most of these reports (2, 9). The period between the first day of onset of COVID-19 symptoms, and the onset of GBS was 12 days and an axonal polyneuropathy developed in our patient.

According to a report compiling previous case reports, most of the reported patients were over 50 years of age and male, reflecting the underlying demographic characteristics

COVID-19. The mean age of the patients was 57.2±15.82, the youngest patient was 5, and the oldest patient was 84 years old (1, 2).

The need for mechanical ventilation was reported to be more pronounced compared to patients with GBS without COVID-19 (11). Our patient was closely followed up with O_2 during her hospitalization, there was no need for mechanical ventilation. IVIg was preferred of our patient, and LMWH was administered simultaneously. We did not preferred plasma exchanges, because of the hemodynamic status of COVID-19 patients was unstable, and more healthcare professionals were exposed to the patient for longer-periods of time. Negative PCR analysis in CSF also means that there is no direct root infection or intrathecal viral replication, and supports a dysimmune response mechanism after infection (2, 10).

Although GBS has developed due to the follow-up of patients mostly in intensive care units, this may hinder them from being noticed. It should not be surprising that GBS does not come to mind immediately especially considering that these intensive care units are not neurological intensive care units.

It is difficult to diagnose, given that most of the GBS patients associated with COVID-19 do not have any symptoms of COVID-19 at the time of admission. In patients presenting with neurological diseases such as GBS, encephalomyelitis, myositis without systemic COVID-19 symptoms; the presence of anosmia/agusia/cranial neuropathy and lymphocytopenia/thrombocytopenia are red flags that increase the suspicion of early diagnosis for COVID-19 (6,10).

In patients with increased respiratory distress or in need of intensive care, this condition may not only be due to lung involvement but may also develop due to neurological diseases such as GBS. Early diagnosis and treatment of patients may provide treatment and follow-up without the need for intensive care units.

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Case Report

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Perihepatic and abdominal wall abscess mimicking hydatid cyst: A late complication of residual gallbladder stones

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Abstract

Intraoperational perforation of the gallbladder and the related residual intraabdominal gallbladder stone presence in cholelithiasis procedures are more commonly seen problems in laparoscopic cholecystectomy than those of open cholecystectomy procedures. Residual intraabdominal stones, though rare, can be encountered in early or late complications that can lead to diagnostic challenges and serious morbidity. A 44-year-old female patient presented with complaints of abdominal pain and swelling on her abdominal wall for the last 6 months. The patient had been in follow-up with hydatid cyst pre-diagnosis following abdominal ultrasonography performed at an external center. The patient's medical history revealed that she had undergone laparoscopic cholecystectomy surgery due to cholelithiasis 1.5 years before. Her abdominal computed tomography performed at our hospital showed abscess formations suggested to have been formed due to gallbladders stones. The patient, whose abscess was drained, and stones were extracted laparoscopically, was discharged on the second postoperative day. Residual intraabdominal gallbladder stones can lead to serious complications and misdiagnoses even years later. Utmost attention should be paid to prevent all these and not to perforate the gallbladder during surgery, while ultimate patience and effort should be put in to remove all the gallbladder stones if they are spilled.

Keywords: hydatid cyst, cholecystectomy, gallbladder, gallbladder stone

1. Introduction

Laparoscopic cholecystectomy surgery is considered the gold standard for the surgical treatment of symptomatic gall bladder stones. This procedure is quite safe with low morbidity and mortality rates. Yet complications like spillage of gallbladder stones into the abdominal cavity due to the perforation of the gallbladder during the surgery are more commonly seen in laparoscopy than in open cholecystectomy (1). It has been reported that gallbladder stones spilled into the abdominal cavity in 7% of laparoscopic cholecystectomy procedures while 16-50% of these stones could not be extracted (2). Nevertheless, complications brought about by such irremovable stones are rare and they are seen merely in 1.4% of the cases (3).

The aim of this study, therefore, was to present the case of a patient with abdominal wall and perihepatic abscess, which developed due to residual intraabdominal stones during laparoscopic cholecystectomy procedure, who was followed-up with hydatid cyst prediagnosis along with literature review.

2. Case Report

A 44-year-old female patient presented with complaints of pain on the upper right quadrant of the abdomen for the last six months. The patient's abdominal ultrasonography performed at an external center had shown a semisolid formation with calcified areas neighboring on the segment 6 of the liver. The patient had been evaluated to have uncomplicated calcified hydatid cyst and taken into a follow-up program. The patient, whose abdominal pain had deteriorated within the last month with palpable swelling in the right subcostal area, presented to our clinic. The patient's physical examination showed that she was obese. A sensitive, red swelling of about 3x4 cm in size with partially soft consistency was identified in the right subcostal area. Her laboratory results were within normal limits while the result of her indirect hemagglutination test for Echinococcus was negative.

The patient's medical history revealed that she had undergone laparoscopic cholecystectomy because of acute calculous cholecystitis. Her abdominal computed tomography showed an image likely of abscess that was 66x37 mm in size with multiple stones, the largest of which was 23 mm, in the right subhepatic area. Moreover, there was a calcified focus of 21 mm in size on the upper right quadrant associated with the abdominal wall likely to be consistent with gallbladder stone (Fig. 1a-1d). It was suggested that such images belonged to gallbladder stones that dropped into the abdominal cavity during the surgery. The patient was thus taken into surgery. Laparoscopic exploration revealed an

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abscess pouch neighboring hepatic segment 6 and on the abdominal wall. The abscesses were drained, and the stones were extracted laparoscopically (Fig. 2). The patient who had no postoperative problems was discharged on the second day.

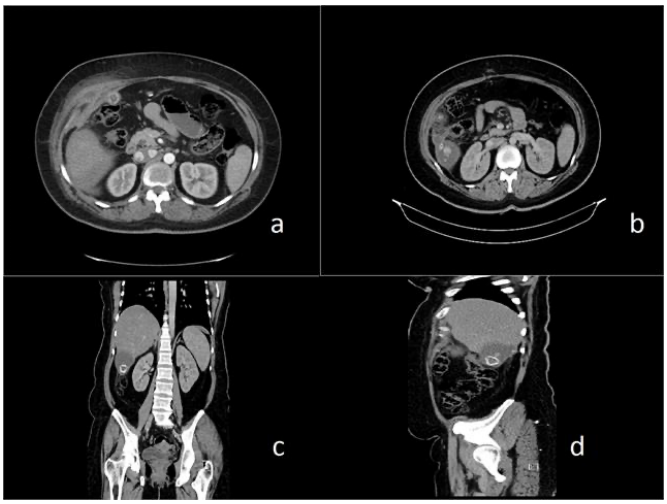

Fig. 1. Computed tomography images of abscess on the abdominal wall in transverse (1a), subhepatic abscess in transverse (1b), coronal (1c) and sagittal (1d) planes

3. Discussion

Intraoperational perforation of the gallbladder and the related residual intraabdominal gallbladder stone presence in cholelithiasis procedures are more commonly seen problems in laparoscopic cholecystectomy than those of open cholecystectomy procedures. Residual intraabdominal stones, though rare, can be encountered in early or late complications that can lead to diagnostic challenges and serious morbidity (1). Studies have reported that such factors as the inexperience of the surgeon, male sex, old age, acute inflammation of the gallbladder; tense, fragile, edematous, gangrenous gallbladder wall, presence of multiple stones within the gallbladder, large adipose tissue around the cystic duct, overweight patients, and thick abdominal wall increased the risk of perforation during laparoscopic cholecystectomy (4-6). Our case had risk factors like obesity and acute inflammation of the gallbladder as well. Gallbladder perforation often occurs during the traction of the gallbladder, dissection of the gallbladder from the hepatic bed or during the removal of the gallbladder from the trocar-site (6).

Researchers have recommended that surgeons be gentler and more careful during traction and dissection with gallbladder removed outside the abdomen in an endobag particularly in such patients with risk factors. It has also been stated that if gallbladder stones that spilled into the abdomen could not be retrieved despite necessary efforts by laparoscopy, this situation did not require conversion to open cholecystectomy, but these should be well documented, the patient should be informed and taken into a long-term follow-up program (5). In our case report the patient had neither been informed after her first surgery nor any documentation had been recorded.

The results of studies have revealed that gallbladder

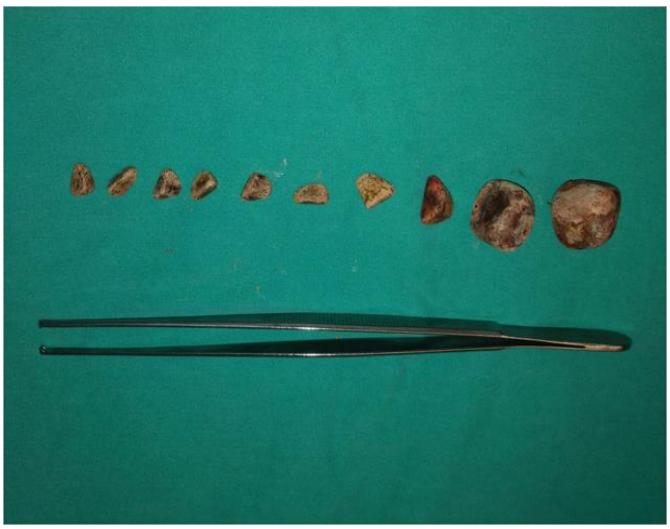

Fig. 2. Extracted residual gallbladder stone images

spillage occurred in 7% of laparoscopic cholecystectomy procedures, while 16-50% of these could not be retrieved and 1.4% of these residual stones led to complications (2, 3). Intraabdominal abscess, the most seen complication, is usually localized in the subhepatic or retroperitoneal sites (6). Other than abscess formations seen in these sites, rarer complications like fistulization, abscess formations including residual gallbladder stones in such places as the hernia sac, ovaries or fallopian tubes, hip joints and abdominal wall have been reported as well (6, 7). In our case report the patient also had gallbladder stone-related subhepatic and abdominal wall abscess.

The exact mechanism of the ways in which gallbladder stones caused abscess has yet to be explained. Studies have shown that pigmented stones were more likely to cause abscess than cholesterol stones. Microorganisms like E. coli, Klebsiella, Pseudomonas, and Enterococcus that cause acute cholecystitis are identified in abscess cultures (4). Although postoperative abscess formation is usually seen within two years, there are also patients in literature who were reported to have been diagnosed a long time after the fact like 20 years (4, 8). Abscess was seen in our patient 1.5 years after she had surgery.

Patients with complications due to retained gallbladder stones in the abdomen often present with complaints like abdominal pain, fever, loss of appetite, nausea, and weight loss although these may vary according to the localization of the abscess (4). Further, quite rare gallbladder stone cases have also been reported that presented with cholelitoptysis related to abscess migration up the bronchial tree through the erosion it formed in the diaphragm (9, 10). Our patient, too, presented with complaints of abdominal pain and swelling on the abdominal wall.

Identification of gallbladder stones within the abscess through abdominal computed tomography or magnetic resonance imaging is important for diagnosis (6). While pigmented stones are readily distinguishable due to their high-calcium content through computed tomography, pure cholesterol stones may not be so because of their low-calcium

content (6). Gallbladder stone-associated abscesses that appear particularly in later periods may radiologically mimic significant pathologies like retroperitoneal sarcoma, peritoneal metastasis, and gastric tumors (3, 6). A well-taken anamnesis proves to be quite important in the differential diagnosis of such cases. In our case, too, the patient had been in a follow-up program with hydatid cyst pre-diagnosis for a long time because her surgical data had not been well documented, she had not been informed, and her medical history had not been questioned sufficiently in subsequent presentations.

Percutaneous drainage and antibiotics treatment do not suffice in most gallbladder stone-related abscess cases. Abscess should be drained and the focus causing the abscess should be extracted either by open or by laparoscopic procedures in such cases (11). We, accordingly, planned laparoscopic abscess drainage and stone extraction for our patient as the preferred treatment modality.

Though rare, residual intraabdominal gallbladder stones may lead to serious complications that necessitate secondary surgical intervention years later after the surgery and misdiagnosis may set the treatment process back. Physicians should be careful during the dissection, traction, and extraction of the gallbladder to prevent such complications while ultimate patience and effort should be put in to remove all the gallbladder stones if they are spilled.

Conflict of interest

The authors declared no conflict of interest.

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Case Report

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Multiorgan failure due to strongyloides infection in liver transplant recipient: A case report and literature review

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Abstract

Strongyloidasis is caused by an intestinal nematode *Strongyloides stercoralis* which is widely distributed in tropical and subtropical countries. In immunocompetent individuals, *Strongloides stercoralis* infection usually does not produce any symptoms or causes gastrointestinal, cardiopulmonary, or skin symptoms. However, in some patients especially immunsupressive (e.g post-transplant, taking exogenous corticosteroids), its infection associated with severe and life-threatening disease like hyperinfection syndrome and disseminated tissue infestation. The limitation of diagnostic test make it challenging to diagnose strongyloidasis. Therefore, it is important to suspect infection of *Strongyloides stercoralis*. We describe a case of Strongiloides infection with a fatal outcome in liver transplant recipient.

Keywords: *Strongyloides stercoralis*, liver, liver transplatation, acute respiratory distress syndrome

1. Introduction

One of the most common problems caused by immunosuppressive treatments used after solid organ transplantation is infections (1). Strongyloidasis is a known complication of solid organ transplantation and it may cause severe parasitic infection which is lead to septisemia, multorgan failure and death (2). Strongyloidiasis is caused by infection with *Strongyloides stercoralis* which is an intestinal nematode and is widely found in tropical and subtropical countries (2, 3). Humans are the final hosts in the parasite cycle which has autoinfection which is rare and charecterstic feature in its life cycle (2, 4).

Human infection occurs by intact skin contact with filariform larvae and infection has also been induced by drinking water contaminated with the filariform larvae (2, 3). After contact with the skin, the larvae enter the venous system and can be found in the skin, gastrointestinal tract and lungs due their life cycle. However, in some patient, the larvae are found various tissue such as heart, brain, muscle, etc. The larval proliferation in tissue may leads to systemic sepsis, multi-organ failure and death (5).

Its infestation in human is usually asymptomatic or causes gastrointestinal, cardiopulmonary or skin symptoms in immunocompetent individuals. Immunosuppressed patients (e.g. taking exogenous corticosteroids or immunsuppressive drugs, solid organ tansplantation) are at risk for life-threating complication like hyperinfection syndrome and disseminated tissue infestation (2, 4). Mortality rate can be approaches upto 50% in hyperinfection syndrome and upto 70% in disseminated disease (6, 7).

In this article, we present a case of severe strongyloidiasis occurring in patient five years after liver tranplantation and that cause death due to Acute Respiratory Distress Syndrome (ARDS) and Multiple Organ Dysfunction Syndrome (MODS).

2. Case Report

A 45-year-old male patient having a history of liver transplantation due to chronic hepatitis B, was followed up tacrolimus monotherapy on the 4th year after transplantation without any problem. Acute hepatitis type transaminases (AST: 600 IU/L, ALT: 1300 IU/L, ALP:450 IU/L, GGT: 48 IU/L, bilirubin: 1.97 mg/dl) were found to be high in blood test performed during the control examinations of the patient; he was hospitalized considering the pre-diagnoses of recurrent hepatittis B, toxic hepatitis, de-novo autoimmune hepatitis. He did not use any new medication. HBV-DNA and HCV-RNA results were negative. On the laboratory tests after detection positive antinuclear antibody (ANA, 1/100) which is an autoimmune marker, liver biopsy was performed. The result of liver biopsy was reported as de-novo autoimmune hepatitis. Prednisolon 60 mg/day, mycophenolate mofetil 2x1000 mg, tacrolimus 2x1.5 mg treatments were started after the result of the liver biopsy.

Approximately 6 months after the new immunosuppresive

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therapy, he was hospitalized due to nausea, vomiting, diarrhea, loss of appetite, bloody sputum and detoriation in the general condition. On initial physical examination, he was conscious, co-operative and orientated. Mucous membranes were dry and pale. In respiratory examination, respiratory sounds were bilaterally coarse and there were rales in places. Blood pressure was 90/60 mmHg, heart rate was 110 bpm, respiratory rate was 22/minute. PA chest radiography showed an increase in the cardiothoracic index, centrally located infiltration in both lungs, increased opacity and occasional reticular densities (Fig. 1). In blood test hemoglobin was 7.9 gr/dl, leukocyte 650 /mm^3 and platelet 50.000 /mm^3. Owing to the findings on chest computer tomography examination including atelectasis area in the lower lobes of both lung, pleural irregularity and thickening, levofloxacin treatment was given.

The upper gastrointestinal endoscopy was performed due to anemia and vomiting, observing the fragile, spontaneous bledding areas and granular mucosal appearance in duodenum; biopsies were taken from these areas. Strongyloides were detected in duodenal biopsy (Fig. 2) and oral ivermectin treatment was initiated. Direct microscopic stool examination for diarrhea and their culture was unremarkable. No growth was detected in the tracheal aspirate culture taken due to ongoing bloody sputum. On the second day of ivermectin treatment, the patient's clinical condition gradually deteriorated, respiratory distress increased and ARDS developed. The patient, not responded despite all supportive treatment, died due to multiorgan's failure.

3. Discussion

Strongyloidiasis is usually an asymptomatic or mildly symptomatic disease in immunocompetent individuals (8). Chronic infection lasts for many years, and is usually asymptomatic. Sometimes causes gastrointestinal, cardiopulmonary or skin symptoms (9). Rapid replication and spread of filiform larvae are observed in some patients whose immune system is compromised due to exogenous steroid use and organ transplant. Strongyloides hyperinfection syndrome and disseminated disease may develop in these patients and cause acute severe illness and high mortality (10). *Strongyloides stercoralis* hyperinfection syndrome can develop many months or years after transplantation. However severe disseminated disease tends to occur within the first three month (11).

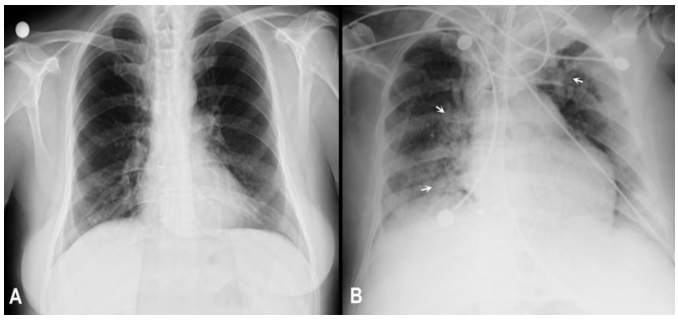

Fig. 1. PA chest radiography: (A) normal findings, (B) an increase in the cardiothoracic index, centrally located infiltration in both lungs, increased opacity and occasional reticular densities (arrows)

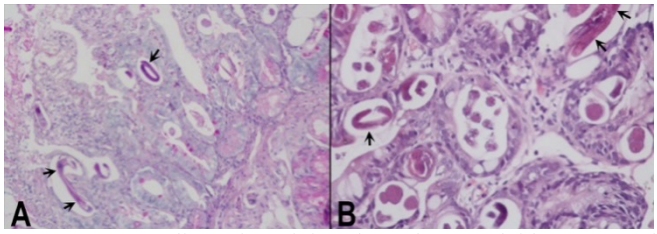

Fig. 2. Hematoxylin eosin staining showed strongyloides (arrows) in duodenal biopsy (A, B)

Table 1. Previously reported cases of strongyloidiosis in liver transplantation recipients

Age/ gender	Cause of transplantation	Time from transplantation (months)	Immunsuppresive treatment	Demograpic risk factor	Initial symptoms/ findings	Treatment for strongyloidiasis	Complications Of sepsis and/or Bacteremia	Outcome	Cause of death	Reference
59 / Female	Non-alcoholic steatohepatitis with cirrhosis	4	Induction:Alemtuzumab, methylprednisolone Maintenance: tacrolimus and prednisone	First donor from Puerto Rico Second donor's serologic test was negative	Nausea, poor appetite, weight loss, and constipation	Ivermectin and albendazole	Bacteremia / Coma	Alive	-	(1)
43 / Male	Hepatitis C infections and hepatocellular carcinoma	12	Tacrolimus and high dose corticosteroids	-	Elevation of liver enzymes	Thiabendazole and ivermectin	Septisemia	Death	ARDS	(2)
61 / Male	Alcoholic cirrhosis	7	Prednisone, Mycophenolate and tacrolimus	-	Progressive early satiety, bloating, weight loss, and fatigue	Ivermectin and albendazole	Bacteremia	Alive	-	(3)
67 / Male	Cholangiocarcinoma	2,5	Tacrolimus, micofenolic acid and prednisone	Donor from Ecuador	Fever, asthenia anorexia, diarrhea, dyspnea, cough, eosinophilia	Ivermectin and albendazole	Bacteremia	Alive	-	(15)
58 / Male	Hepatitis C / history of alcohol abuse	-	Induction: Basiliximab Maintenance: Mycophenolate,	Donor from Dominican Republic	Asymptomatic	Ivermectin and albendazole	None	Alive	-	(16)

			tacrolimus, and prednisone							
- / -	-	4	-	Donor from Suriname	Eosinophilia	Ivermectin	None	Alive	-	(17)
72 / Female	Hepatitis C infections and hepatocellular carcinoma	3	Tacrolimus, prednisone and mycophenolate mofetil	Donor from Guyana	Diffuse abdominal pain, nausea and nonbloody emesis	Ivermectin and albendazole	Bacteremia	Alive	-	(18)
60 / Male	Hepatitis B-related end-stage liver disease	2	Induction: methylprednisolone Maintenance: prednisone, mycophenolate and tacrolimus	Donor from Indian GCC-born recipients with a history of travel	Fever, anorexia, headache, and change in mental status	Ivermectin and albendazole	Bacteremia	Alive / GCS:6 connecting to MV	-	(19)
53 / Female	Liver cirrhosis due to Autoimmune liver disease	4	Mycophenolate Mofetil Tacrolimus, and Prednisolone	Donor from Bangladesh	Abdominal pain, nausea, vomiting, and diarrhea	Ivermectin and albendazole	None	Alive	-	(20)
58 / Male	Laennec's cirrhosis	104 days	Induction: antithymocyte globülin, rituximab and methylprednisolone Maintenance: tacrolimus	Donor and the recipient had positive *Strongyloides* serology	Abdominal rash, hyponatremia, ileus, and respirator failure	Ivermectin and albendazole	Bacteremia	Death	Multi-organ failure	(21)
66 / Female	End-stage hepatic cirrhosis by hepatitis C infection	9 days	Basiliximab, methylprednisolone, and mycophenolate mofetil.	Donor from Paraguay and has positive serology	Asymptomatic (On 9 day posttransplant, donor's serologic test was found positive)	Ivermectin	Abdominal septic shock, bacteremia and bilateral pneumonia	Death (Post-Tx 34th day)	Multi-organ failure	(22)
59 / Female	Non-alcoholic steatohepatitis with cirrhosis	4	Induction: Alemtuzumab, methylprednisolone Maintenance: tacrolimus and prednisone	First donor from Puerto Rico Second donor's serologic test was negative	Nausea, poor appetite, weight loss, and constipation	Ivermectin and albendazole	Bacteremia / Coma	Alive	-	(1)

Our PubMed literature review identified 11 cases of *Strongyloides stercoralis* infections in liver transplant recipients. Characteristics of 11 cases, such as: recipients's demographics including age and gender, cause of transplantation, time of onset *Strongyloides stercoralis* infection from the transplantation, epidemiology of donors (demographics risk factors), immunosuppressive therapy, initial clinical symptoms and complications including presence of bacteremia and sepsis, management and outcomes including death are shown in the Table 1.

The clinical symptoms of the disease are variable. Gastrointestinal symptoms are the most common and usually non-specific symptoms (such as abdominal pain, nausea, vomiting, diarrhea and bleeding) (12). Lung findings include cough, haemoptysis, wheezing and sometimes very severe lung collapse (13). In the present case, while the patient firstly admitted with gastrointestinal symptoms and bloody sputum, and then progressed to multi-organ failure and ARDS.

Filiform larvae can be detected in many secretions of the body in hyperinfection syndrome and disseminated disease. It may be found in stool, sputum, surgical drainage, and in bronchoalveolar lavage, pleural, and peritoneal fluid (14). In addition, as in our patient, larvae can be detected in biopsies taken from lesions detected in endoscopic findings (gastritis, duodenitis, aphthous ulcer, etc.). The limitation of diagnostic test makes it challenging to diagnose strongyloidasis and a delayed diagnosis may lead to severe illness especially in immumsupressed individuals. Therefore, it is important to suspect infection of *Strongyloides stercoralis.*

Epidemiological risk stratification should be determined for Strongyloides hyperinfection syndrome and disseminated infection in patients undergoing solid organ transplantation. If there is a history of living or visiting places where the parasite is endemic in immunosuppressive patients, it should be kept in mind that there is a risk of Strongyloidiasis infection. When a prompt diagnosis is not possible, Strongyloides hyperinfection syndrome and disseminated syndrome should be considered and due to its risk of fatal outcome, an urgent empirical preventive treatment planning should be done.

Opportunistic infections in transplant recipients have high mortality and it requires a multidisplinary approach. Here, we present a rare case of strongyloides infection with a fatal outcome. Therefore, it is important to suspect strongyloides infections due to severe disease and high mortality risk in immunosuppressed patients.

Informed consent: None.

Conflict of interest: The authors declare no conflict of interest.

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Case Report

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Atypically pulmonary arteriovenous malformations

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Abstract

Pulmonary arteriovenous malformations (PAVM) are abnormal connections between the pulmonary arterial system and the pulmonary veins. PAVMs, which are twice as common in women, are generally seen in 4-6 decades. It is thought that congenital origin, previous thoracic traumas and thoracic surgery, liver cirrhosis, mitral stenosis and infections are among the etiological reasons in PAVM.

Keywords: arteriovenous malformation, PAVM, thoracic surgery, lobectomy, anatomic lung resection

1. Introduction

Pulmonary arteriovenous malformations (PAVM) are very rare abnormal connections between pulmonary arterial system and pulmonary veins (1). The etiologic causes of PAVM are congenital origin, previous thoracic trauma and thoracic surgery, liver cirrhosis, mitral stenosis and infections. PAVMs, which are frequently located in the lower lobes and close to the pleural surface, can be single or multiple and usually 1-5 cm in diameter. Pulmonary angiography is gold standard for definitive diagnosis (2).

2. Case Report

A 21-year-old woman was admitted to our clinic with complaint of cough. Physical examination and vital signs were normal. Chest X-ray revealed a round and well-circumscribed mass in the right lower zone. Thorax tomography showed a 42x38 mm lesion adjacent to the hilus in the right lower lobe, feeding from the lower lobe segment branches and consistent with an aneurysm draining into the right inferior pulmonary vein (Fig. 1).

The patient was operated under general anesthesia with a right posterolateral thoracotomy. During exploration, pulsatile and trilled aneurysms originating from the bronchial artery extending into the inferior pulmonary vein were detected. The bronchial artery was ligated from the proximal of the aneurysmatic dilatation and loss of trill was occurred (Fig. 2). The right lower lobectomy was performed, because the arteriovenous malformation was deeply located in the parenchyma. The patient was discharged on the 4th postoperative day. She is still asymptomatic at the end of one year follow-up.

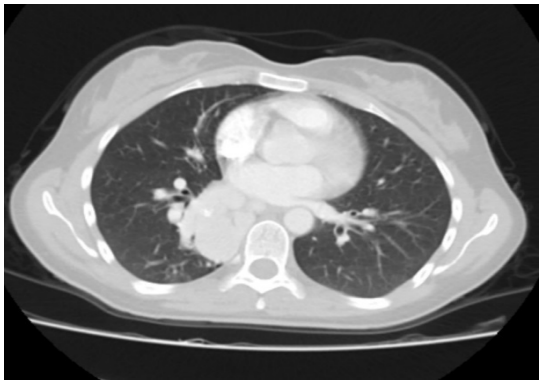

Fig. 1. Axial section of thorax tomography shows a lesion in the superior segment of the lower lobe of the right lung

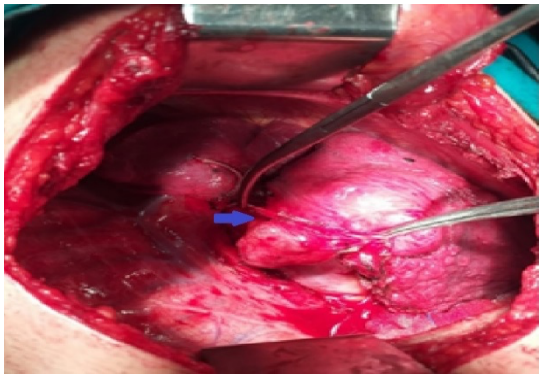

Fig. 2. The PAVM located in the posterior of bronchus intermedius (Blue arrow)

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3. Discussion

Follow-up of PAVMs without treatment is dangerous and has high morbidity/ mortality rates. Complications include size increase, hemoptysis, hemothorax and cerebral abscess. Embolization has high success rates in treatment (3). However, as in our case, when PAVM is large and located deep in the lung lobe, the cure will be provided by anatomic lung resection.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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A case of axillary traumatic neuroma mimicking local recurrence following cancer surgery and a review of the literature

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Abstract

Traumatic neuroma (TN) is a non-neoplastic proliferative response developing against neuronal injury. Its pathogenesis is unknown: While its overall incidence is low, the incidence of traumatic neuroma development following mastectomy is even lower. Thirty-eight post-mastectomy traumatic neuromas in 30 patients were reported in the literature. Only two of these were in the axillary region, whereas the others had originated from the mastectomy scar tissue. Even though the ultrasonographic examination reveals the features of a benign mass, performing a histopathological examination is a must for definitive diagnosis of the mass and exclusion of local recurrence, mainly when it has developed following cancer surgery. Here, we aimed to discuss in the light of the literature a patient who had undergone mastectomy and axillary dissection with the diagnosis of invasive ductal carcinoma eight years ago and underwent recurrent axillary dissection with the preliminary diagnosis of axillary metastasis.

Keywords: traumatic neuroma, local recurrence, mastectomy, breast cancer

1. Introduction

Traumatic neuroma (TN) is a rare non-neoplastic reactive proliferation (1). It is manifested as a palpable mass following neural injury or surgery. It is more common after lower extremity amputations and head & neck surgery. Traumatic neuroma within the mastectomy scar tissue is quite rare, and only two cases with post-axillary-dissection traumatic neuroma were reported in the literature (2, 3). Its differential diagnosis with a local recurrence should be made in patients who underwent cancer surgery. Here, we aimed to discuss in the light of the literature a patient who had undergone mastectomy and axillary dissection with the diagnosis of invasive ductal carcinoma eight years ago and underwent recurrent axillary dissection with the preliminary diagnosis of axillary metastasis.

2. Case Report

A 46-year-old female patient expressed in her routine follow-up examination that she had pain in her left axillary region for the last six months. She had undergone left mastectomy and axillary dissection with the diagnosis of invasive ductal carcinoma six years ago. A tender nodular lesion of approximately 6 mm in diameter was palpated on the left axillary bed on physical examination. The ultrasonographic examination revealed a round, subcutaneously located, hypoechoic 7.5x6 mm-sized solid lesion with a peripheral thin halo, showing partial internal blood supply with Doppler. Histopathological examination was recommended due to its interpretation as suspicious for metastatic lymph node or fat necrosis. Positron emission tomography-computed tomography (PET-CT) examination revealed an approximately eight mm-sized probably metastatic lymphadenopathy with fluorodeoxyglucose (FDG) involvement, which had not been present in her previous follow-up examinations, and thus, clinical follow-up was suggested. Axillary dissection was performed to safely exclude a probability of axillary metastasis, considering the patient's malignancy history.

On macroscopic examination, the cross-sectional surface of the fragmental fat tissue, approximately 6x4x3 cm in size, was generally fibrotic, and a nodular structure was present in a six mm-sized area. A structure compatible with a lymph node could not be dissected. All the described, white-colored areas were taken into consideration. The histopathological examination revealed a proliferation characterized by randomly arranged nerve fascicles within a significantly collagenized stroma and organized as well-circumscribed nodules (Fig.1a and 1b). The nerve fascicles were stained positive for S100 (Figure 1c). Giant cells with phagocyted suture material secondary to the previous operation were observed within the surrounding adipose tissue. The patient was diagnosed with a traumatic neuroma. Constent was obtained from the patient. The rate of post-mastectomy local recurrence is 5.5% to 8.95%. Because the rate of benign lesions developing in the scar region is less than malign lesions, the first thing that should be considered in a newly

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developing lesion is a local recurrence. Recurrent lesions are seen as hypoechoic lesions on USG (7). Even though most traumatic neuromas are well-circumscribed and avascular on USG, some of them may be vaguely circumscribed and vascular, mimicking local recurrence (7, 9).

Table 1. Clinical information and imaging features of traumatic breast neuromas published in the literature

Reference	Patients	ge-sex	Neuromas n	Neuroma Size m	Location	Time after surgery (yr)	Palpable	Pain/ Tenderness	USG	Mamografi	Pet	Treatment
Wenyi et al. (2019)	2	58F	3	6,4,10	Subcutaneus (2) Pectoralis muscle layer (1)	4,7	Yes (2) No (1)	No	Ovall, well circumscribed, homogeneously hypoechoic	N/A	N/A	Surgical excision(1),ultrasound guided core biopsy(1)
Nikolas S.Salemis (2018)	1	65F	1	N/A	Subcutaneus mastectomy scar area	2	No	Yes	Unremarkable	Clustered microcalcification	N/A	Surgical excision
Jason D.Mesinger et al (2017)	1	4F	2	6,16	Subcutaneus axilla	N/A	N/A	N/A	Oval, parallel, circumscbribed,hypoechoic	N/A	N/A	Ultrasound guided core biopsy
Kimberley Fitzparick et al. (2017)	1	73F	1	7	Lateral aspect	16	No	No	Oval, parallel,circumscribed, hypoechoic	Small, oval, circumscribed, equal density	N/A	Ultrasoun core nidle biopsy
Quanli et al. (2012)	1	45F	1	5	Subcutaneus next to mastectomy scar	2	Yes	N/A	Well circumcsribed,echo-heterogeneous	N/A	N/A	Surgical excision
Our case	1	46F	1	8mm	Aksilla	6	Yes	Yes	N/A	N/A	FDG uptake present	Surgical excision

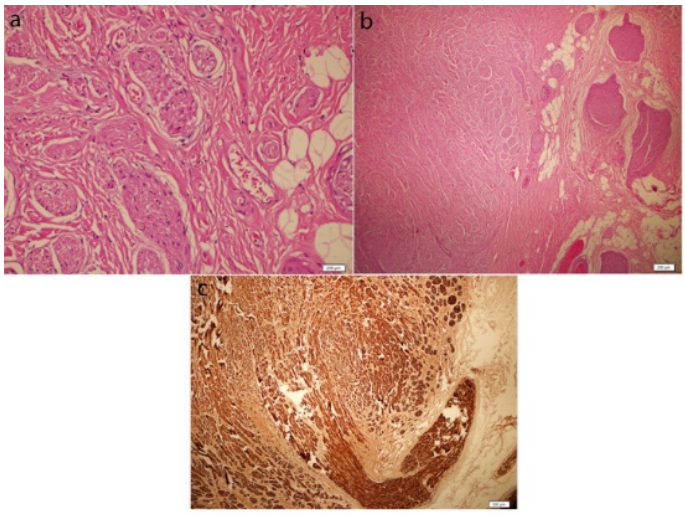

Fig. 1. Sections representing traumatic neuroma and immunohistochemistry study. Peripheral nerve sections of different diamaters are observed in connective tissue containing collagenized intermediate tissue and a small amount of adipose tissue, H&E x100 (a) Proliferataring nerve sections without a distinct organization are observed H&Ex200 (b) Peripheral nerves are stained dark brown with S100 immunohistochemical, staining x 200 (c)

3. Discussion

The traumatic neuroma is the reactive non-neoplastic proliferation of the nerve's severed proximal end due to failed repair in nerve injuries (1). It is frequently encountered in lower extremity amputations and head & neck surgery (1, 2,3,4) and may mimic local recurrence due to its clinical and radiological features (5,6). There are mostly post-amputation TN cases in the literature (7). Thirty-eight traumatic neuromas in 30 cases were reported in the literature. Some of these cases and the clinical and radiological features of our patient were presented in Table 1. The youngest patient was 31 years old, the oldest 78 years old, and all were female. TN developed post-surgery 1.9 years at the earliest and 22 years at the latest. The smallest was 0.4 cm, whereas the largest 1.6 cm (7). While some of the patients described pain-sensitivity (8), some others were asymptomatic (6, 7). If the patient has no complaint, surgical treatment is not necessary. Physical therapy, local injections, long-acting local anesthetics, steroids, or surgery can be used in patients with pain complaints. Most lesions are viewed as oval, well-circumscribed, avascular, and hypoechoic masses on ultrasonographic examination. In our case, partial vascularization was present. Mammography, MRI, and PET CT do not show any specific features (7). It may present findings such as clustered microcalcification (8,9) and well-circumscribed oval density (6). PET-CT did not reveal any FDG uptake in three cases (7). In our case, FDG uptake was present.

In conclusion, USG, mammography, and PET CT are commonly used for follow-up of patients in whom a mastectomy/lumpectomy procedure has been performed. A timely diagnosis of local recurrence has a positive contribution to the patient's outcome. Even though recurrence is considered the first possibility in nodular lesions detected within scar tissue of mastectomy and axillary dissection, traumatic neuroma should be kept in mind in patients describing neuropathic pain and sensitivity.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Abdominal wall endometriosis: Case-series study and a systematic review

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Abstract

Abdominal wall endometriosis (AWE) is the presence of endometrial gland and stroma in the abdominal wall that should be kept in mind in differential diagnosis of pelvic pain due to especially increased C-section rates. Between January 2000 and July 2018, MEDLINE and EMBASE databases were systematically reviewed using the search criteria "abdominal wall endometriosis," "abdominal wall endometriomas,". Only the studies having over 20 patients were included. Case-series, case-control studies, and articles in languages other than English were excluded. Number of the patients, patients 'age, study design, previous surgical history, most common symptom, time interval to symptoms, treatment, recurrence rate, and tumour size were investigated. In Total, 18 studies and 994 women were included in the study. Case studies, studies with less than 20 cases, non-English articles were excluded from the study. In the included studies, the numbers of minimum and maximum woman were 20 and 227, respectively. AWE significantly impairs the quality of life in reproductive age patients and is commonly seen in women with previous history of laparotomy, especially those who underwent cesarean section. Therefore, it must be kept in mind in the differential diagnosis of women who have a history of pain and a history of previous surgery.

Keywords: endometriosis, abdominal endometriosis, tumor, gynecology

1. Introduction

Endometriosis is a pathology defined as the presence of functional endometrial glands and stroma anywhere other than the uterine cavity (1). Although it is seen most commonly in pelvis, extrapelvic endometriosis is also observed with a frequency of 9-15% (2). Abdominal Wall endometriosis (AWE) is the most commonly seen extrapelvic endometriosis (3).

Abdominal wall endometriosis is defined as the presence endometrial gland and stroma in the abdominal wall (4). In other words, it is the presence of endometrial tissue anywhere on the peritoneum. It is seen in 0.03% to 1.08% of patients undergoing obstetric or gynecological procedures especially hysterotomy (5). Three different theories have been proposed in the development of abdominal wall endometriosis. According to the direct implantation theory, endometrial cells scattered around abdominal wall during surgery, under the effect of hormones proliferate or cause metaplasia of the surrounding fascia. The second theory is the dissemination of endometrial cells by lymphatic or hematogenous routes (6). The third theory is that the pluripotent mesenchymal cells differentiate and form abdominal wall endometriosis (7). In addition, the anti-apoptotic surviving gene is thought to be effective in the formation and invasion of endometrial implants (8). Although AWE is a rare condition, it significantly impairs the quality of life in women of reproductive age. In addition, AWE is now commonly seen due to the increased rates of cesarean section. Therefore, gynecologists, surgeons and radiologists should keep in mind this differential diagnosis in their daily practice.

In our study we aimed to present three cases of AWE who presented to our clinic. Most of previous studies on AWE were retrospective studies. Prospective studies are needed especially for diagnosis, treatment and follow-up. We have found that our results in this preliminary study are consistent with literature. We planned to do further prospective study regarding this topic.

2. Case Reports

2.1. Case 1

The patient was 33-year-old, G7P5L5 (gravida 7, parity 5, live birth 5). She had a history of four cesarean sections. The last cesarean section was five years ago. On superficial ultrasonography of the pelvic region at the right lower quadrant, lateral and to the right of the incision scar level, a poorly bounded heterogeneous hypoechoic, solid vascularized mass lesion seen with doppler, with a diameter of 24x11x15mm was observed on the posterior surface of the subcutaneous fat tissue. Surgical excision was performed. Histopathology was consistent with 4x2x2cm subcutaneous

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endometriosis. Within the first year no recurrence was observed in the patient.

2.2. Case 2

A 36 year-old patient G3P3L3 (gravida 3 parity 3 live birth 3) presented with pain and swelling in the left lower quadrant for the past one year. The patient had no history of operation other than bilateral tubal ligationwith laparatomy 3 years ago. Abdominal ultrasonography revealed amass with a size of 52x35x49mm,5-6cm inferior to the umbilicus, in the left, antero-medialto the rectus with an oval, well-circumscribed hypoechoic homogenous, smooth echogenic septum. The mass was non-vascularized on doppler and was growing towards the subcutaneous fat tissue. Surgical excision was performed. Pathology results were consistent with endometriosis. No recurrence was observed in one year follow-up.

2.3. Case 3

A 40-year-old patient G2P2L2 (gravida 2, parity 2, live birth 2) presented with swelling in pelvic region for three months. The patient had two cesarean sections. She had her last operation four years ago. Abdominal ultrasonography revealed an irregular lesion with heterogeneous margins with a size of 22x8x19mm in the rectus abdominis muscle. Endometrioma was excised from the rectus muscle with laparotomy. Pathology results were consistent with endometriosis. The surgical margins were negative. There was no complication. No recurrence was observed within six-months of follow-up.

2.4. Systematic review metodology and results

MEDLINE and EMBASE databases were systematically reviewed. Between January 2000 and July 2018, search criteria were used as follows; “abdominal wall endometriosis," "abdominal wall endometriomas”. The studies in which patients’ numbers lower than 20 were excluded. Case-series, case-control studies, and articles in not English were also excluded. Therefore, in total, 18 studies were included (Fig. 1). Number of the patients, patients’ age, study design, previous surgical history, most common symptom, time interval to symptoms, treatment, recurrence rate, and tumour size were investigated (Table 1).

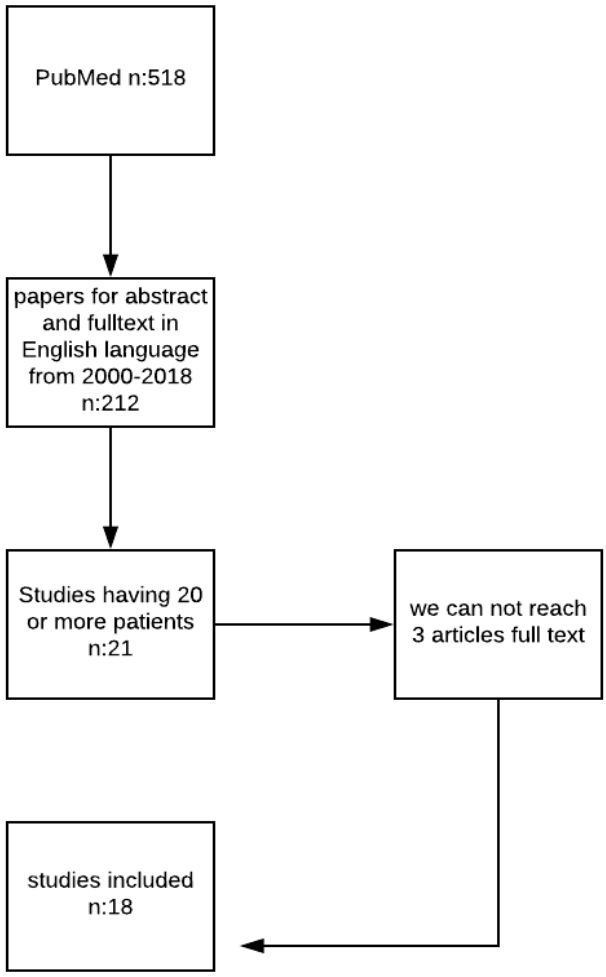

Fig. 1. Study flowchart

3. Discussion

AWE is usually a pathology that may develop after surgical procedures. It is most seen after cesarean and tubal surgery. In the literature it has also been reported in patients without previous surgical history (9-11). Furthermore, it may also occur after laparoscopy, amniocentesis, episiotomy, and appendectomy (12-14). AWE is usually seen in women of reproductive age most commonly between 25-35 years (15-19). In 5.3% of the patients, it may be associated with pelvic endometriosis (20). Some risk factors for AWE were presented in the literature. AWE is more frequent in obese patients. The reason for this was thought to be the technical difficulty during the closure of the uterus (21).

In addition, single part suturing of the uterus, not closing the parietal and visceral peritoneum during caesarean section are considered risk factors (22). The risk of AWE was found to be higher in patients with elective caesarean section than in patients who had undergone cesarean section following labor (23). High parity is thought to have a protective effect in AWE (24). Endometrioma is more common on the left side of cesarean section scar on the lower side of the midline incisions (20). The diagnosis of AWE can be easily made in the presence of the classic triad. History of caesarean section, increase in the intensity of pain during menstrual cycle, swelling around surgical scar (25). Although cyclic pain is characteristic for diagnose, noncyclic pain may be the presenting symptom and can cause misdiagnosis (26-30). Sometimes the presenting symptom may be only a palpable mass, dyspareunia, dysmenorrhea or cyclic hemorrhage from a superficial lesion (26). In order for the symptoms to occur AWE should reach a certain size. Onset of symptoms after first operation varies between 6 months to 20 years (14, 31-34).

Table 1. Results of studies

	Year	Patient number	Age	Study Design	Most Common Prior Surgical History N (%)	Most Common Symptoms N (%)	Time İnterval to Symptoms (months)	Treatment	Recurrence N (%)	Tumor Sıze cm (range)
Kang	2013	37	34	Retrospective	Cesarean section 37 (100)	Palpable mass 36 (97.2) Pain 21(56.8)	30 (Median) (6-96) range	WE 37	1 (2.7)	3.5 (median) (1.0-10.0)
Bektas	2010	40	32.3	Retrospective	Cesarean section 36 (90)	Palpable mass 40(100) Noncyclic pain 18(45) cyclic pain 16(40)	29.6 (Mean) (8-53) range	WE 40	3 (9.1)	4.6 (mean) Range (3-6)
Teng	2008	22	32.6	Retrospective	Cesarean section 22 (100)	Palpable mass and cyclic pain 20 (90) Noncyclic pain with mass 2(10)	N/A	WE 22	N/A	4.4 mean (3-7)
Francıca	2009	28	31	Retrospective	Cesarean section 28 (100)	Mass 27(96) Cyclic pain 22(78) Continous pain 6(21)	60 LSE 40 LSE	We28	0 (0%)	LSE 4.1 (3-6 cm) SSE 1.8 (0.7-2.6 cm)
Savelli	2011	21	36	Retrospective	Previous surgery for endometriosis 9 (25) Previous Cesarean section 8 (22)	Mass 18(86) Pain 19(91)	N/A	N/A	N/A	2 (0,5-5)
Zhao	2005	62	29,8	Retrospective	Previous Cesarean section 61 (98)	Cyclic pain 56(90) Constant pain 5(8) Asymptom atic mass 3(5)	28,6 (1-133)	WE 62	5 (8%)	3,1(1-15)
Ecker	2014	65	35	Retrospective	Cesarean section 53 (81.5)	Abdominal pain 48(74) Mass/lump 41(63)	48 (12-384)	WE 65 Laparoscopic 5 (7.7) Open 49 (75.4) Combined 11 (16.9)	N/A	N/A
Zhu	2017	51	30.1 HIFU 31.4 Surgical Excision	Retrospective	Cesarean section 51 (100)	N/A	24 (1–126) HIFU 17 (2–96) Excision	23 HIFU 28 Surgical	N/A	2,7 (1,3–6,8) HIFU 2,6 (0,7-5) Excision
Yela	2017	52	30.71	Retrospective	Cesarean section 34 (65.4)	Nodule pain 51(98) Mass 19(36)	N/A	N/A	14 (26,9)	3.98
Khamechian	2014	30	32,5	Retrospective	Cesarean section 30 (100)	Mass 30(100) Pain (noncyclic) 10(33) Pain (cyclic) 14 (47)	30.5 (2-53)	WE 30	1	2.59 (1-6)
Pas	2017	71	34	Prospective	Ceseraen section 71 (100)	N/A	12 (1-168)	WE 71	1	N/A
Maillot	2017	20	30,1	Retrospective	Cesarean 13 (65)	cyclic painful symptoms 19(95) Enlarged	N/A	We 13 Cryoablation 7	N/A	2.3 cm (0.5-7 cm)

						nodules 6(30)				
Ding	2013	227	31,7	Retrospective	Cesarean delivery 226 (99.6)	Abdominal mass 191(84) Cyclic pain 148 (65) Noncyclic pain 62 (27)	N/A	WE 227	3 (1.5%)	2,9 (1–9 cm)
Francıca	2012	30	30.6	Retrospective	Cesarean 30 (100)	Cyclic pain with mass 24(80) Contınous pain 6(20)	36 Median (12-120)	N/A	N/A	2,7 (0,7-6)
Luo	2017	32	39,4	Retrospective	Cesarean 31 (96)	N/A	11median (6-36)	32 HIFU	N/A	2,4 (1-5)
Khan	2017	34	35.2	Retrospective	Cesarean 30 (88.2%)	Abdominal pain 34(100).	N/A	WE 34	2 (5.9%)	3,3 cm
zhang	2016	151	31.27	Retrospective	Cesarean 151 (100)	cyclic abdominal pain 121(80) irregular abdominal pain 17(11)	31,4 (3-192)	151 WE	11 (7.3%)	2,1 (1-6)
Wang Y	2011	21	33.5	Retrospective	Cesarean 20 (95)	cyclic abdominal pain 21(100) palpabl mass 21(100)	10 (5-36)	21 HIFU	N/A	2,4 (range 1.0–5.3 cm)
Ayşe at al.	2018	3	36,3	Retrospective	Cesarean 2 (67)	Cyclic pain 2(67) Palpabl mass 3(100)	48 36-60	WE 3	0	3,8 (2,2-5,2)

The mean size of abdominal wall endometriosis varies between 2.3 and 3.2cm (35). Differential diagnosis includes tumor, hernia, lipoma, and hematoma. Ultrasonography is the first diagnostic tool. On abdominal ultrasonography, AWE shows deep pelvic endometriosis findings more than ovarian endometriosis findings (11). The ultrasound image is generally composed of a hyperechogenic ring showing edematous and inflammatory adipose tissue around a solid area (11).

CT and MR can be used in patients in whom a clear decision by ultrasonography cannot be made. Fine needle aspiration can sometimes be used for diagnosis. It is considered as a fast, reliable, and inexpensive diagnostic method (36). It can help in the diagnosis of malignant lesions. To make a diagnosis, at least two of the three criteria should be seen endometrial glandular cells, surrounding stromal cells and hemosiderin-laden macrophages (37). However, in this procedure there is a risk of spread of endometrial cells. For this reason, the needle tract should be removed during surgical excision. The histopathologic diagnosis of endometriosis is made in the presence of endometrial gland, stroma, and hemosiderin pigment (22).

Surgical excision used in the treatment is quite successful (16,20). During surgery, the nodule and the surrounding fascia should be removed so that there is a negative surgical margin. Otherwise, there may be recurrence (10). The surgical margin should be 1cm (22). Therefore, sometimes broad facial defects may occur, and mesh may be required. Medical treatment is not preferred because of the recurrence of symptoms and low chance of success when the drug is stopped (10). Progesterone and GnRH analogues decrease the size of the lesions and decrease symptoms by suppressing menstruation (38). Ultrasonography-guided high-intensity focused ultrasound ablation (HIFU) is another method for treatment. Wang et al. described this method, but its long-term efficacy is not clear (17).

The risk of recurrence was reported to be 1.5 to 7.5% (20). The probability of progression of AWE to malignancy is reported as 1% (35). The most common malignancy is clear cell carcinoma. Besides, endometrioid, serous papillary, carcinosarcoma and mixed types are seen (38).

There are many recommendations for the prevention of AWE in the literature. Sumathy and colleagues suggested taking out the uterus while closing (22). Washing of the abdominopelvic space, bringing parietal and visceral peritoneum together have been suggested. The incidence of AWE increases when the same needle that is used to suture uterus is also used when closing abdominal wall (22).

Most of previous studies on AWE were retrospective studies. Prospective studies are needed especially for

diagnosis, treatment, and follow-up. We have found that our results in this preliminary study are consistent with the literature. We planned to do further prospective study on this subject.

To conclude, AWE, a pathology which frequency increases with time due to an increase in cesarean section rate, should be kept in mind in for differential diagnosis by general surgeons, gynecologists, and radiologists because they will often come across this disease. It is a problem that affects reproductive age patients, and it decreases comfort and impairs their quality of life

Conflict of interest

None to declare.

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None to declare.

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Case Report

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Uterovesical fistula after uterine compression suture

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Abstract

Uterovesical fistula is a rare complication. In this case, a utero-fetal fistula developed in a patient with lower uterine segment compression suture in cesarean section due to placenta previa totalis is described.

Keywords: caesarean section, compression suture, uterovesical fistula, Youssef's syndrome

1. Introduction

Compression sutures are an alternative to hysterectomy in young patients with postpartum hemorrhage. Today, very different compression sutures are used. Although it does not require much surgical experience and is an effective method to control bleeding, its complications have not been clearly identified. Infection, pyometra, synechiae and infertility are some of them (1). In some cases, uterine rupture has been reported in the following pregnancy (2).

Uterovesical fistula is a rare complication that constitutes 1-4% of urogenital fistulas (3). There is a history of caesarean section in 88% of cases (4). Patients usually present with the classic Youssef Triad. Cyclic hematuria, urinary incontinence and amenorrhea constitute this triad (5).

In this case, we report a case of uterovesical fistula after compression sutures in lower uterine segment in a patient undergoing cesarean section due to placenta previa which was successfully repaired with early diagnosis.

2. Case Report

A 34-year-old patient with G4P3Y3 was taken to cesarean section with a diagnosis of placenta previa total is 38 weeks and 2 days. She had four cesarean sections. In her operation two U-shaped compression sutures were placed in the lower uterine segment by rejecting the bladder peritoneum due to intraoperative bleeding. The patient's foley catheter was withdrawn after 24 hours because there was no suspicion of intraoperative bladder injury. The patient was followed-up for 2 days and was discharged after no bleeding. Thirty days after surgery, the patient presented with hematuria, dysuria, and intermittent urine intake. No fistula tract was observed in the speculum examination of the patient and no urine was observed in the cervix. Her blood and urine tests were normal. MR imaging of the lower abdomen of the patient revealed a 11 * 31 mm vesicouterin fistula (Fig. 1). Cystoscopy was performed and the vesicouterin fistula was seen near the bladder dome and the orifices were observed naturally. Double J catheter was placed in bilateral ureters. The operation of the patient was planned, and the bladder and uterus were dissected from each other by laparotomy and the bladder was incised up to the fistula tract. The fistula tract was removed. Bladder and uterine incision repair were performed as double layer. The patient was followed-up for two days postoperatively. After 14 days with foley catheter, the patient had no problem.

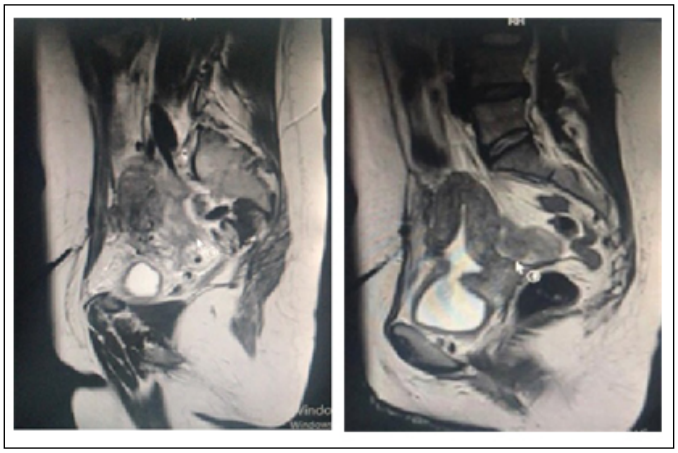

Fig. 1. Tract of uterovesical fistula is seen by Contrasted Magnetic Resonance Imaging

3. Discussion

Compression sutures are frequently used in postpartum hemorrhage control. In placenta previa cases, compression sutures have been described which are discharged into the lower uterine segment, which frees the patient from hysterectomy. Complications such as infection, pyometry, synechia and infertility have been reported in the literature regarding compression sutures. In our case, uterovesical fistula developed after the compression suture thrown into the

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lower uterine segment due to hemorrhage because of placenta previa. The diagnosis of uterovesical fistula can be made for the first time in 1957 by the triad defined by Youssef. Cyclic hematuria, urinary incontinence and amenorrhea form this triad. In the literature, patients with secondary infertility and abortus complaints and late diagnosis are also present (6). Definitive diagnosis of the fistula between the bladder and the uterus is established (6). Hysterosalpingography, methylene blue test, pelvic MRI, and cystoscopy can be used for diagnostic purposes (7). MRI is important in terms of being 100% diagnostic in diagnosis (8).

5% of vesicouterin fistulas may heal without surgery. Foley catheter is left for three weeks, the infection is avoided, and the defect is closed with the involution of the uterus (9). But the main method is surgical repair. Transvesical, retroperitoneal, and transperitoneal repair can be performed. Because vaginal repair is not easily accessible, it is not generally preferred (7). It is a rare diagnosis that should be kept in mind because of the increased cesarean rates. Although it is a complication that should be kept in mind because of hemorrhagic and risky surgeries, especially in our patient, it can be treated with early diagnosis without hysterectomy.

Conflict of interest

None to declare.

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Case Report

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Mesenter artery thrombosis despite effective oral anticoagulation treatment

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Abstract

An 87-year-old woman was admitted to our emergency department with palpitation and fatigue 5 days ago. The patient with electrocardiography (ECG) Atrial Fibrillation (AF) has been treated with low molecular weight heparin and 5 mg / day warfarin for 5 days. After the fifth day of treatment the patient was admitted to the emergency department again with diffuse abdominal pain. On her physical examination there was generalized tenderness in the abdomen with no rebound. Blood biochemistry revealed elevated white blood cells and INR parameter was normal as 2.96. ECG showed atrial fibrillation. Abdominal computed tomographic angiography revealed a thrombotic appearance in SMA. Surgical intervention was offered to the patient, but she had refused to get a surgery. Afterwards, endovascular intervention to the SMA was planned. She had had an acute cardiac arrest and the patient had died. Our patient treated with heparin and warfarin for five days after the diagnosis of AF and developed acute SMA thromboembolism leading to acute mesenteric ischemia, although the INR value was in the therapeutic range. It is rare for acute mesenteric ischemia to occur beneath optimal anticoagulation therapy. In conclusion, acute mesenteric ischemia should be kept in mind in patients with normal INR values in case of severe abdominal pain.

Keywords: acute mesenteric ischemia, atrial fibrillation, thromboembolism, warfarin

1. Introduction

Acute mesenteric ischemia has a high mortality rate due to delayed and prolonged diagnostic procedures (1). In this case, we presented an acute mesenteric ischemia due to superior mesenteric artery (SMA) thromboembolism despite optimal anticoagulation treatment in a patient with atrial fibrillation (AF).

2. Case Report

An 87-year-old woman was admitted to our emergency department with palpitation and fatigue five days ago. The patient with electrocardiography (ECG) Atrial Fibrillation (AF) has been treated with low molecular weight heparin and 5 mg / day warfarin for 5 days. After the fifth day of treatment the patient was admitted to the emergency department again with diffuse abdominal pain. On her physical examination there was generalized tenderness in the abdomen with no rebound. Her blood pressure was measured as 100-60 mmHg and she had tachycardia with 120 bpm. Blood biochemistry revealed elevated white blood cells and INR parameter was normal as 2.96. ECG showed atrial fibrillation (Fig. 1A). On echocardiographic evaluation she had normal left ventricular systolic function, mild mitral regurgitation, moderate tricuspid regurgitation, elevated estimated systolic pulmonary artery pressure as 45 mmHg, left ventricular concentric hypertrophy (Fig. 1B-C). Abdominal computed tomographic angiography revealed a thrombotic appearance in SMA as shown in Fig. 1D. Surgical intervention was offered to the patient, but she had refused to get a surgery. Afterwards, endovascular intervention to the SMA was planned. While the patient had been transferred to the catheterization laboratory, she had had an acute cardiac arrest. Despite the cardiopulmonary resuscitation, the patient had died.

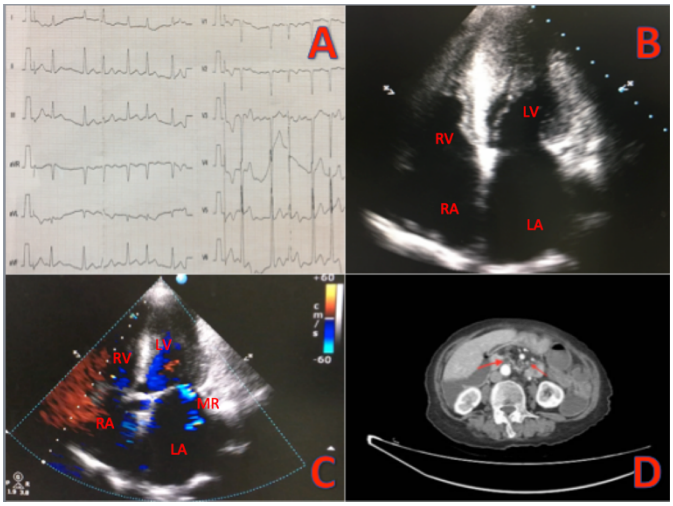

Fig. 1. A, ECG shows atrial fibrillation, B, apical four chamber view of echocardiography, C, Echocardiography shows mild mitral regurgitation, D, abdominal CTA shows SMA thrombus (shown with red arrow) (LA: left atrium, LV: left ventricle, RA: right atrium, RV: right ventricle, MR: mitral regurgitation)

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3. Discussion

Acute mesenteric ischemia is a potentially fatal disease. It requires emergency surgery especially for patients with signs of intestinal necrosis such as bloody diarrhea, abdominal rebound and tenderness. However, some studies have shown that percutaneous revascularization has a good clinical outcome (2-3). Our patient treated with heparin and warfarin for 5 days after the diagnosis of AF and developed acute SMA thromboembolism leading to acute mesenteric ischemia, although the INR value was in the therapeutic range. It is rare for acute mesenteric ischemia to occur beneath optimal anticoagulation therapy. It is well known that the development of acute mesenteric ischemia in patients with AF is often seen in patients not receiving anticoagulant therapy. As in our case, we think that it is a noteworthy issue to develop thromboembolism despite optimal anticoagulation. In conclusion, acute mesenteric ischemia should be kept in mind in patients with normal INR values in case of severe abdominal pain.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Case Report

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Unexpected diagnosis 'Foot Tuberculosis'

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Abstract

Tuberculosis is an infectious disease still causing significant health problems. Although it is basically a disease of the parenchyma of the pulmonary system, there can be extra-pulmonary involvement of the pleura, the central nervous system, the genito-urinary system, pericardium, eyes, skin, and the skeletal system. The primary source is pulmonary focused, and it is quite rare for infection to occur in the skeletal system by a hematogenous route. The increase in immune system compromised patients and medication resistant bacteria has caused a greater incidence of mycobacterial infection outside the lungs to have been observed. The main problem encountered in tuberculosis in the skeletal system is the diagnosis. Localized pain, high temperature and weight loss are not often seen clinically. A case is presented here for discussion of isolated foot tuberculosis, as a case which is rarely able to be diagnosed, and for which appropriate treatment was given early before the onset of function loss, giving good results.

Keywords: foot, trauma, tuberculosis, infection

1. Introduction

Tuberculosis is an infectious disease still causing significant health problems. According to World Health Organization data, an average of 9.2 million people per year contract the disease of which 1.7 million lives are lost (1). Although it is basically a disease of the parenchyma of the pulmonary system, there can be extra-pulmonary involvement of the pleura, the central nervous system, the Genito-urinary system, pericardium, eyes, skin, and the skeletal system. Supporting data from the Turkish Ministry of Health states an annual rate of 35,000- 40,000 new cases of tuberculosis, of which 18,500 are fully defined and only 6500 of them undergo effective treatment (2-4). There can be difficulties in the diagnosis of this disease; the primary source is pulmonary focused, and it is quite rare for infection to occur in the skeletal system by a hematogenous route. The increase in immune system compromised patients and medication resistant bacteria has caused a greater incidence of microbacterial infection outside the lungs to have been observed.

Mittel et al reported skeletal involvement in 10.3% of all cases (5). It has been accepted by researchers that the foot was affected in 10% of those cases (6). The main problem encountered in tuberculosis in the skeletal system is the diagnosis. Localized pain, high temperature and weight loss are not often seen clinically (7).

A case is presented here for discussion of isolated foot tuberculosis, as a case which is rarely able to be diagnosed, and for which appropriate treatment was given early before the onset of function loss, giving good results.

2. Case Report

A 42-year-old female patient presented with pain and swelling two days after having sprained her ankle. Physical examination showed widespread edema and swelling, localized sensitivity, raised temperature, no erythema, and painful foot and ankle movements. No special features were determined in the patient history. Having determined widespread soft tissue oedema and bone marrow edema from direct radiographs and MRI, a short leg plaster cast was applied, ice packs and diclofenac potassium 2x50mg was started (Figs. 1-3). On the 7th day follow-up examination, erythema and raised temperature were evident so cefuroxime axetil 2x500mg was started and the plaster cast was reapplied. At the end of the 3rd week, the plaster cast was removed and there was no erythema or raised temperature, but the oedema was still present. It was observed that the patient was unable to stand on the foot, so he was referred to the physiotherapy department. The patient did not attend for further follow-up but presented again with swelling and pain seven months after the trauma.

A diagnosis of osteomyelitis was made from the results of direct radiographs and MRI. Culture and biopsy were taken, and debridement surgery was performed (Fig. 4). As laboratory tests CRP and leukocytes were developed for the identification of active tuberculosis infection in the blood and Quantiferon (gamma interferon oscillation) tests were requested.

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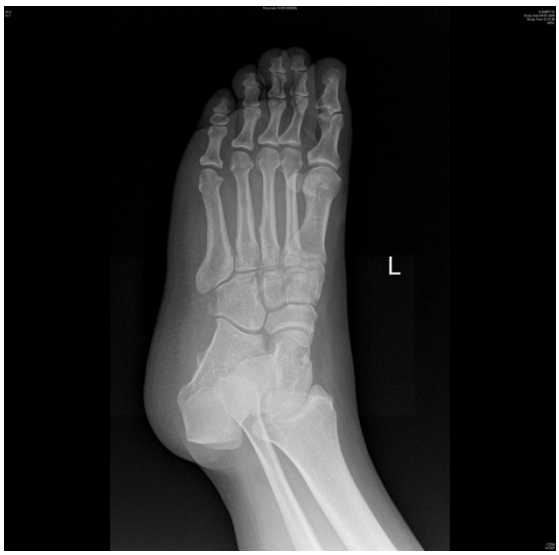

Fig. 1. Obliq x-ray image after the trauma

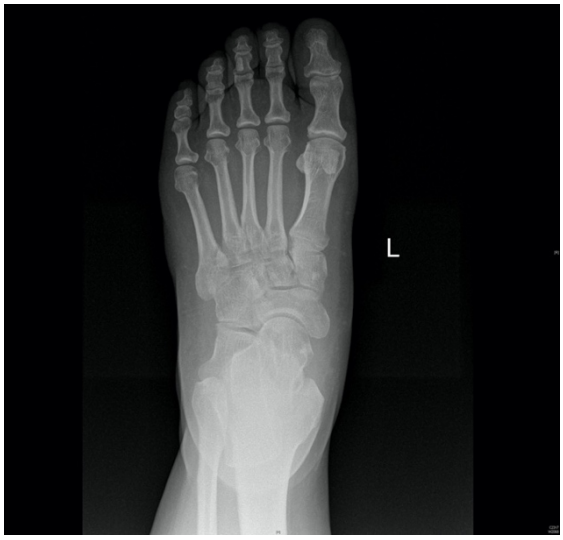

Fig. 2. Ap x-ray image after the trauma

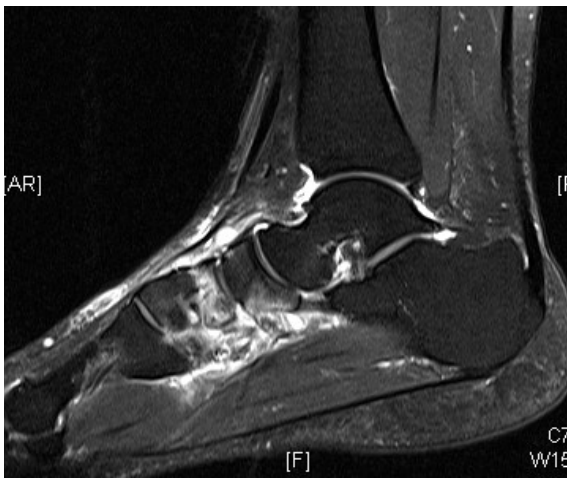

Fig. 3. Sagittal MR image after the trauma

The pathology results of leukocyte values of 10500 (3800 - 10000/ml indicator) and CRP 0.9 (0-0.5mg/dl) and Quantiferon test 3.38 IU/ml (normal <0.35 IU/ml), determined necrotizing granulomatous inflammation. *Mycobacterium tuberculosis* bacilli were produced in the culture. No pathology was determined from the lung radiograph, and there was no history of tuberculosis for the patient personally or in her environment. Quadruple antituberculosis treatment was started under the control of the infection department. After two months of quadruple treatment, seven months of double antituberculosis treatment were administered and at the 9th month postoperative, direct radiographs were taken (Fig. 5). Clinically there was a mild level of edema and no erythema or raised temperature. The patient was able to walk without pain with active, free ankle movement (Fig. 6).

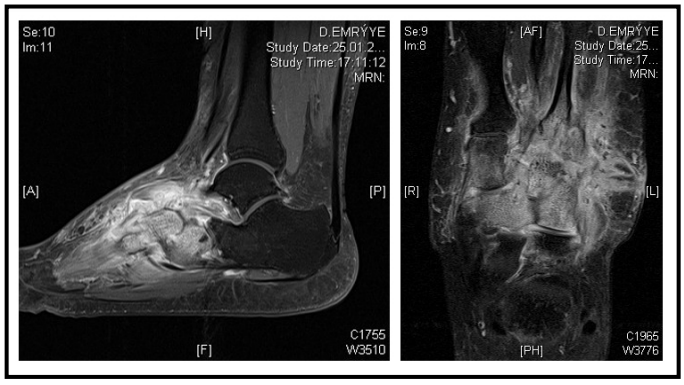

Fig. 4. MRI image that was diagnosed tuberculosis

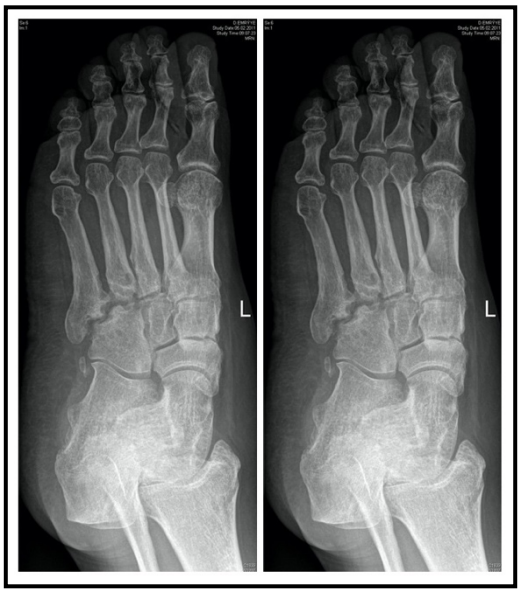

Fig. 5. Foot ap, oblique image that postoperative and using antituberculosis at the 9th month

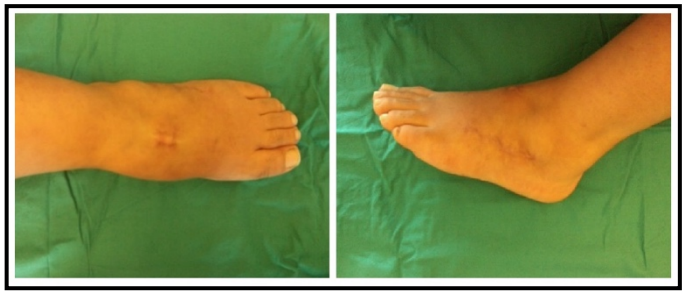

Fig. 6. Clinically ap and lateral foot image, postoperative 11 months

3. Discussion

Tuberculosis infection is rarely seen in the skeletal system. The most frequently involved areas in tuberculosis cases are the spine and the hips so diagnosis of infection in those areas is easier (8). In recent years the increase immune system compromised patients and multiple medication resistant bacilli have caused an increase throughout society in cases with involvement outside the lungs (14, 15).

In contrast, it is rarely seen in the foot and ankle and diagnosis may be made at advanced stages (9). Our case was only able to be diagnosed at her final presentation at the clinic with a differential diagnosis. The complaints with which she presented started following a trauma and as she withdrew from follow-up the diagnosis could only be made and confirmed at the 7th month.

Generally, tuberculosis in the foot has been seen to involve the midtarsal joint, and the same image reported by Martin et al was encountered in our case (9). While localized pain is typical clinically, high temperature and weight loss are rarely seen in foot and ankle cases (7). Our case had complaints of localized pain. We did not encounter early muscle atrophy as described by Messner. Several authors have reported the characteristics of raised ESR and CRP (8, 10, 11). No extreme increase was observed in our case. In addition, the Quantiferon test, which was first used in 2005, was applied and our case was determined as positive (12). Some risk factors have been defined for tuberculosis in the skeletal system. Besides malnutrition, poor hygiene and disease area, there is always a history of trauma. It is assumed that the tissue resistance to the trauma causes a localized weakness.

It has been reported that most patients have a common base of general characteristics, which are, a slow and long-lasting start, single joint or single bone involvement, concomitant tuberculosis in another organ, the presence of tuberculosis cases in close vicinity and a history of trauma in the related area. Our case developed in a single bone following trauma.

Tuberculosis of the skeletal system is a chronic disease generally involving a single joint or single bone, leading to progressive degeneration. As in our case, late diagnosis leads to arthrosis in a wider area because of involvement of more than one joint. Notwithstanding the importance of surgical treatment, it is important to start medical treatment early in cases without complications. In regions where tuberculosis is often seen, such as in our country, patients with long-lasting complaints which started following a trauma, should be considered for tuberculosis (13).

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Case Report

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Bilateral neck hematoma a complication of central venous catheterization: A case report

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Abstract

Mechanical complications of central venous catheterization include arterial puncture, vascular injuries, catheter malposition, pneumothorax, hemothorax, air embolism, subcutaneous hematoma, and arrhythmias. In this text; we report a case of bilateral neck hematoma due to catheter malposition after venous perforation which was not noticed during central venous catheterization. A 68-year-old female patient was admitted to the emergency department with diarrhea, vomiting and low oral intake for the last week. With complaints, the patient is diagnosed as acute renal failure in another center. Jugular catheter placement two attempts one is left, and one is right, did not yield a result. Then we placed to right femoral vein. The patient was intubated to secure the airway after bilateral cervical hematoma was observed in the cervical ultrasound. The bilateral hematoma was dissolved, and she was extubated on the fifth day of hospitalization and discharged without any sequelae. Complications that may affect the airway can be seen during central vein catheterization. Early intubation may be lifesaving if respiratory tract risk is seen.

Keywords: bilateral neck hematoma, central venous catheterization, complication, case reports

1. Introduction

Central venous catheterization is used for diagnosis and treatment especially in the operating theaters, intensive care units, dialysis units, emergency services and other services (1). Subclavian, internal jugular and femoral veins are frequently preferred for venous catheterization. Femoral vein is not usually preferred because of its short-term applicability and the risk of infection. Similarly, subclavian vein is not generally preferable due to its risk of stenosis; and the arteriovenous fistula that can be opened later is not preferred because it may create venous circulatory problems.

Complications due to central venous catheterization during the process, early complications may occur as hematoma, pneumothorax, peripheral nerve damage, air embolism, pericardial tamponade, and arrhythmias (2). In this report, we present a case of bilateral cervical hematoma due to central venous catheter placement.

2. Case Report

A 68-year-old female patient was admitted to the emergency department with diarrhea, vomiting and low oral intake for the last week. she has diarrhea for three days. In the anamnesis of the patient, it is seen that there is diabetes mellistus, hypertension. On her physical examination, the vital signs of the patient were recorded as follows: pulse: 87 beats/min, rhythmic, blood pressure: 100/61 mmHg, respiratory rate: 17 breaths/min, room air oxygen saturation: 98% and body temperature: 36.1°C. The physical examination revealed that the general status was moderate, and skin turgor was decreased.

The other system examinations were within normal limits. Electrocardiography was normal except for sinus tachycardia. When the laboratory values are examined; hemoglobin: 12.5 g/dL, hematocrit: 38%, platelet count: 112,500/mm3, blood glucose:87 mg/dL, urea: 124 mg/dL, creatinine: 6.4 mg/dL, aspartate aminotransferase (AST): 13 U/L, alanine aminotransferase (ALT):7 U/L, sodium: 139 mmol/L, potassium: 6.07 mmol/L. The patient's arterial blood gas had; Ph:7,20, pCO_2:58, pO_2:53. Urine output has never occurred in the last 24 hours. The patient was started on intravenous 0.9% saline infusion at 300 mL/h flow rate.

With these complaints, the patient is diagnosed as acute renal failure in another center. Double-lumened, 14 French catheters were decided to be placed in firstly left internal jugular vein and then right if it fails for hemodialysis. Bilateral jugular catheter placement attempts did not yield a result. Then it placed to right femoral vein. Patient lost consciousness and her Glasgow Coma Score was 14. She had tachypnea and stridor, half an hour after placement of femoral catheter. Two large hematomas on each side of the neck were noted (Fig. 1). The patient was intubated to secure the airway after bilateral neck hematoma was observed in the cervical ultrasound. After the intubation, neck computed tomography was performed (Fig. 2). It showed hyperdense areas in keeping with hematoma is noted in both sides of the neck. No free air observed. The patient was admitted to the intensive

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care unit. She had undergone dialysis three times during hospitalization. The bilateral hematoma was dissolved in five days. she was extubated on the fifth day of hospitalization and discharged without any sequelae on the seventh day of hospitalization.

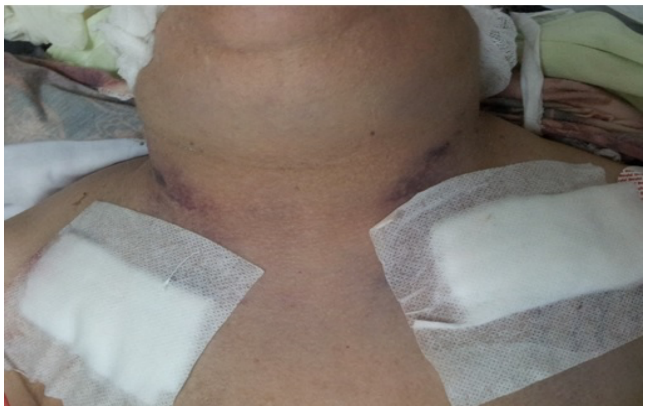

Fig. 1. The appearance of the patient's neck after the attemption of central venous catheterization. Significant edema and gauzes in the places where catheterization attempts are performed on both sides of the neck are observed

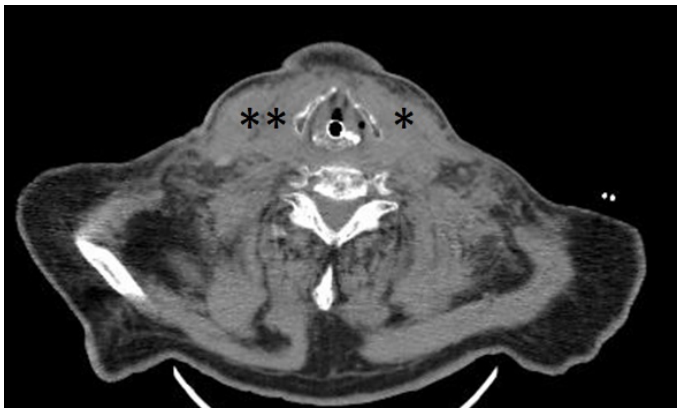

Fig. 2. The transverse section of the neck CT of the patient is demonstrated. Hyperdense areas in keeping with hematoma is noted in both sides of the neck (asterisks). Besides, heterogeneous dense in the subcutaneous and deep fat planes in the neck are noted due to edema

3. Discussion

Catheters such as nasogastric catheter, central venous catheter and bladder catheter are placed in the human body for the application of medical treatments. Placement of these catheters, although rare, causes life-threatening complications (3).

Central venous catheters are one of them placed for hemodynamic monitoring, administration of drugs likely to induce phlebitis, peripheral venous access when it lacks, and hemodialysis. They should be placed in the correct position for effective use and to avoid complications. In order to increase the success rate and decrease the incidence of complications, it is necessary to know the anatomical neighborhoods well (4). Central venous catheter application via internal jugular vein, which is one of the most suitable veins for access to large thoracic veins, has a low complication rate and a high success rate. Vascular and cardiac injuries are most mortal complications. Left-sided catheters have a higher incidence of vascular injury (5). Complications such as hemothorax, pneumothorax, cardiac arrhythmia, endocarditis, thromboembolism, vascular perforations, air embolism or nerve injuries may be seen due to malposition. Factors involved in complications are the inexperience of the person who performed the central venous catheter procedure, prior surgical operation and history of radiotherapy on the area where catheter will be placed, advanced age and obesity (6). It should be noticed that the use of ultrasound increases the rate of success significantly and when it is possible, the procedure must be applied with the aid of ultrasound (7).

In our case, traditional catheter application was preferred to the patient who needed hemodialysis. Bilateral neck hematoma was observed in the cervical ultrasound due to venous injury. It is thought that the patient developed unconsciousness because of the decrease in venous circulation and compression to the trachea. After placement of central venous catheter if soft tissues injury signs as swelling and ecchymosis or subcutaneous emphysema were seen further imaging should be performed to diagnose complications (8, 9). In our case we performed ultrasonography and computed tomography.

Complications that may affect the airway can be seen during central vein catheterization. Early intubation may be lifesaving if respiratory tract risk is seen. It is imperative that nurses and physician follow up patient for possible complications.

Conflict of interest

None to declare.

Acknowledgments

We asked the patient to help us to publish the case report in an international journal for discussion, including disease symptoms, diagnosis, and image related content. The patient agreed us to use his medical records and signed the consent form.

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Case Report

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A rare case of synchronous genital carcinoma involving endometrium and unilateral fallopian tube in a 24 years old patient

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Abstract
Multifocal synchronous development of malignancies of the female genital tract is a rare occurrence and less than 3% of primary malignancies of this region is synchronous. Although the simultaneous presentation of endometrial and ovarian carcinoma of the endometrioid type is well described little is known about a similar phenomenon involving the endometrium and fallopian tube. The relationship between the synchronous tumours is uncertain. More illuminating studies are being conducted on the relationship between synchronized endometrial and ovarian carcinomas in recent studies.This case is about synchronous genital carcinoma involving endometrium and unilateral fallopian tube in a 24 years old patient.

Keywords: synchronous tumors, endometrioid carcinoma, endometrial carcinoma, fallopian tube carcinoma

1. Introduction

Multifocal synchronous development of malignancies of the female genital tract is a rare occurrence and less than 3% of primary malignancies of this region is synchronous. Although the simultaneous presentation of endometrial and ovarian carcinoma of the endometrioid type is well described little is known about a similar phenomenon involving the endometrium and fallopian tube (1, 2).

2. Case Report

A 24 years old virgin patient was referred to us with abnormal uterine bleeding, anemia and a possible diagnosis of uterine fibroid. Her body-mass index was 21.1 kg/m2. Her personal history was unremarkable. Family history was negative for malignancies. Detailed systemic examination revealed no abnormalities. There was no palpable mass in abdominopelvic examination. In her initial transabdominal ultrasonography, 8 mm of endometrial thickness along with a 42x38 mm of heterogeneous solid mass image in the posterior uterine wall was observed. MRI scan revealed a 50x24 mm mass in endometrium without any other significant pathology in the abdomen. Tumor markers were also within the normal range. Initially a myomectomy was performed, and pathology result was reported as endometrial adenocarcinoma, endometrioid type Grade 2 (FIGO), afterwards total laparoscopic surgical staging was performed, and final pathology report revealed a synchronous grade 2 endometrioid adenocarcinoma of uterus and an intraepithelial carcinoma of the right fallopian tube without any implants in the abdomen or on the surface of tubes with no sign of disease in omentum and peritoneal lavage and samplings. All paraaortic and pelvic lymph nodes were negative with no lymphovascular invasion. Cervix was free of tumor, but myometrium was found to be more than ½ infiltrated with serosal surfaces intact. Case was discussed with pathology and decided as a synchronous genital malignancy of the endometrium and right fallopian tube (Fig. 1).

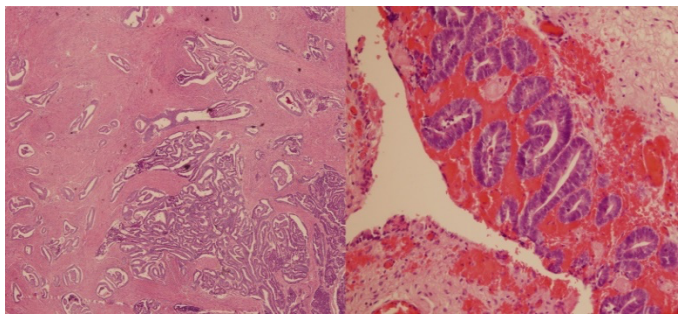

Fig. 1. Endometrioid adenocarcinoma (endometrium and fallopian tube)

3. Discussion

Surgical staging is the fundamental method for treatment of synchronous malignancies, but it must first be proved whether it is a primary or a metastatic tumour with pathological examination criteria described by Ulbright and Roth in the first place. Distinguishing an independent primary carcinoma from metastasis is mandatory since each situation means different prognosis and requires different management (1-3).

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Patients with synchronous malignancies have a better outcome than those with metastatic disease in the same organs (4, 5). Genetic transition must also be considered in synchronous malignancies especially mutations in BRCA-1 and BRCA-2 genes are regarded as improved risk factors for fallopian tubes and ovaries along with Lynch syndrome which should also be considered because of the risk for ovarian malignancy due to mutation in the mismatch-repair genes (6, 7).

Synchronous malignancies of the genital tract are extremely rare and concerning the age of the patient, her low BMI and negative family history our initial risk assessment for endometrial cancer was low leading us to a diagnosis of uterine fibroid due to abnormal vaginal bleeding and initial imaging. Concerning moral values in conservative societies, one should not hesitate in early surgical intervention primarily with endometrial sampling in persistent abnormal uterine bleeding, even if the patient is young and virgin.

Conflict of interest

None the declare.

Acknowledgments

None the declare.

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Letter to Editor

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Knotted nasogastric catheter

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1. Letter to Editor

A 64-year-old male patient called the emergency medical service with complaints of respiratory distress and high fever. He was brought to our clinic by the emergency medical service by ambulance. In the ambulance, ventilation was performed with a balloon mask for 10 minutes due to hypoxia. With balloon mask ventilation, his saturation was 70. endotracheal intubation was performed. The patient with a history of coronary artery disease was using 100 mg acetylsalicylic acid per day. It was learned from his anamnesis that the patient, who had cough and high fever for three days, had respiratory distress for one day. Vital parameters after intubation were arterial blood pressure 65/40 mmHg, pulse 96/minute, and temperature 38.3°C. On physical examination, Glasgow coma score was 5 (E1, M2, V2). There was widespread crackles in the right lung to the respiratory examination. There was distension in the abdominal examination. Among the laboratory parameters, leukocyte was measured as 18 000/µl, neutrophil as 10 500/µL, C-reactive protein as 81 mg/L. Other hematological and biochemical parameters were normal. Computed tomography of the thorax showed extensive consolidation and air bronchograms on the right lung. Empirical antibiotic therapy was initiated. During the nasogastric catheter application, it was noticed whether the tube encountered resistance and not progressed. When the tube was pulled out, it did not come. It was found that the end of the tube formed a very interesting knot when the oropharynx was controlled and pulled through the mouth with the help of a forceps (Fig. 1 and 2).

Nasogastric catheter is used for purposes such as cleaning out the contents of the stomach, preventing aspiration in unconscious patient and providing nutrition (1). Complications may be encountered in nasogastric tube applications (2). Knotting of the tube is a rare condition that may be encountered. It should be considered when resistance is encountered in advancing or withdrawing the nasogastric tube.

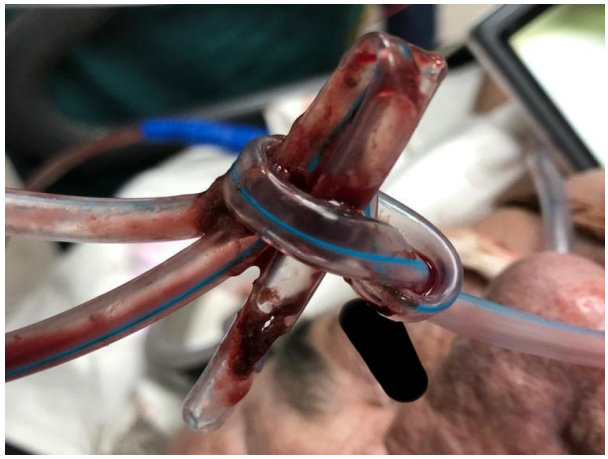

Fig.1. The knotted nasogastric tube.

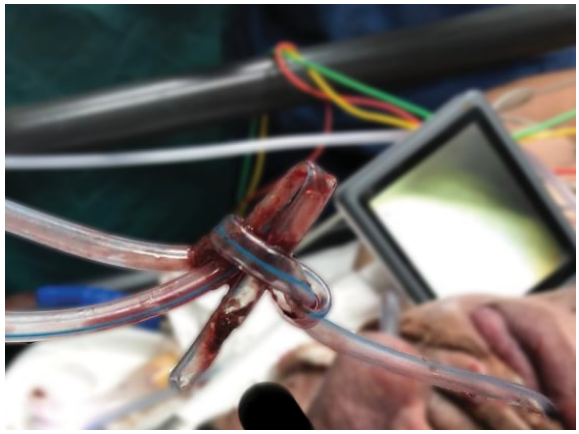

Fig.2. The knotted nasogastric tube.

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Letter to Editor

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Geographical information systems and health

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1. Letter to Editor

All over the world, to provide better services in the health sector with the aim of collecting the necessary data, and the use of information strategies for sharing studies are conducted. The purposes of the more widespread use of information technologies in many countries are to serve the system throughout the country, quick and easy access to information, to comply with high standards, to make use of new technologies and knowledge, and to help reveal the causes as well as the treatment of diseases.

Due to the increasing production of information and globalization throughout the world, the importance of correct information processing is increasing. Interdisciplinary cooperation is made to make information processing usable (1). Referencing health-related information based on geographical location is possible with Geographical Information Systems (GIS).

GIS is an information system that performs the functions of collecting, storing, analyzing, and presenting graphical and non-graphical data obtained through location-based processes in an integrity. It is a set of hardware, software, personnel, geographic data, and methods developed to assist users in location-based decision-making processes for solving complex social, economic, and environmental problems around the World. GIS is a system of computer-aided tools required to map and analyze landforms and events on the earth (2).

In recent years, a significant increase has been observed in GIS applications in the field of health. Because in health-related planning and administrative organizations, keeping all relevant information together, making the necessary analyzes easily and providing the results visually effectively can be performed with GIS technologies. The concept of Health GIS has emerged as a common working area of the professional disciplines that carry out health and cartography activities. As a result of developments in GIS technologies and statistical methods, it is possible to evaluate health and population data in a geographically defined region together and to investigate logical spatial variations in disease risks (2).

The uses of GIS in health are epidemiological studies, assessment of the spread of diseases and famine, evaluation of the spread of toxic spills and other extreme health events and monitoring these events on maps (3). Public health organizations such as disease control centers have been using GIS technologies in studies such as where and how diseases spread over the last decade or how various factors affect human health. For example, GIS was used to show the spread and intensity of the disease around the world during the COVID 19 pandemic (4).

As a result, with the use of GIS in the field of health, the need for health services can be determined, inequalities in the accessibility and execution of health services can be eliminated, the planning and evaluation of health services can be carried out effectively, and patients can be followed up quickly and reliably due to monitorization of the places and frequency of diseases (5). On the other hand, GIS can effectively present and share the information obtained by visualizing all these services and results using maps and graphics (5).

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Correction

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Correction to: Effects of ketogenic and western diets on proliferation, vasculogenesis and oxidative stress in the live

Songul DOGANAY*, Ozcan BUDAK, Nurten BAHTIYAR, Veysel TOPRAK

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Correction to Doğanay et al. (2021)

In the article "Effects of ketogenic and western diets on proliferation, vasculogenesis and oxidative stress in the live" by Songul DOGANAY, Ozcan BUDAK, Nurten BAHTIYAR, and Veysel TOPRAK (*Journal of Experimental and Clinical Medicine,* 2021, Vol 38, No. 3, pp 312-317. http://dx.doi.org/10.52142/omujecm.38.3.20), there was an error in the ethics committee date and number of the study in the material and method section. Approval date written in the material method section of the related article was 01/07/2020; no: 33. Ethics committee date and number of the study should read as follows: 02/09/2020; No. 52.

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