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RESEARCH ARTICLE

Evaluation of Systemic Immune-Inflammation Index in Patients With Idiopathic Sudden Sensorineural Hearing Loss

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Idiopathic sudden sensorineural hearing loss, systemic immune-inflammation index, prognosis, marker

Abstract

Introductıon: Systemic immune-inflammation index (SII) is an indicator of the inflammatory process. In this study we aimed to determine whether there is a relationship between the level of hearing loss and SII in patients diagnosed with idiopathic sudden sensorineural hearing loss (ISSHL), and to reveal whether SII has an indicator in the rate of improvement in hearing loss after treatment. **Methods:** Patients with ISSHL were included in the study. According to the audiometry performed before the initial treatment, the patients were divided into 3 groups (250, 500, 1000, 2000, 4000, 8000 Hz pure tone averages) below 40 dB defined as mild, between 40 and 80 dB defined as moderate and above 80 dB defined as severe. **Results:** In total 201 patients, 64 were in the mild hearing loss group, 115 in the moderate hearing loss group, and 22 in the severe hearing loss group. Multivariable logistic regression analysis revealed that higher SII [OR=1.002, 95% CI (1.001-1.003); p<0.001] associated with the severity of hearing loss. A statistically significant difference was found between the mean SII of the three groups (p<0.001). A negative correlation was found between improvement in hearing loss after treatment and SII levels. (R=-0.195, p<0.001). In addition, a negative correlation was found between the improvement in hearing loss and SII (R=-0.195, p<0.001). **Conclusıon:** SII is an easily available and relatively cheap marker, was associated with the severity of hearing loss. In addition, it was also associated with the recovery of hearing loss.

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Introduction

Idiopathic sudden sensorineural hearing loss (ISSHL) is a sensorineural hearing loss of 30 dB and above, which develops in three days or less and is seen in three consecutive frequencies in audiometry.[1] This disease, which is an otolaryngology emergency, is usually seen unilaterally. While viral infections are the most common etiology for sudden sensorineural hearing loss, vascular pathologies, autoimmune diseases, inflammatory conditions, acoustic neuroma may also be the underlying cause.[2] Sudden sensorineural hearing loss is not idiopathic; when a cause is found in the etiology. Although the etiology is not fully known, the association of ISSHL with chronic inflammation and the relationship between inflammatory markers and cochlear damage have been proven in previous studies.[3-4] Since the cochlea is fed by a single terminal branch, diseases such as thrombotic events, hypertension and diabetes mellitus that may cause impaired perfusion may predispose to the formation of ISSHL.[5]

Systemic immune-inflammation index (SII) is an inflammatory biomarker calculated by peripheral neutrophil, lymphocyte and platelet count (Neutrophil x Platelet count/Lymphocyte count).[6] It has been shown that high SII are associated with lower survival, recurrence of malignancies, and decreased response to treatment in malignancies.[7-8] Additionally, there are studies showing that higher SII, which is thought to be an indicator of increased inflammation, associated with adverse cardiovascular outcomes.[9-11]

Even if it is known that a higher inflammation is associated with the severe hearing loss,3 to date, there is only one study that shows SII is higher in patients with ISSHL compared with control group.[12] However the role of SII in the severity of ISSHL patients is unknown. Therefore, in the current study, we aimed to determine whether there is a relationship between the level of hearing loss and SII in patients diagnosed with ISSHL, and to reveal whether SII has an indicator in the rate of improvement in hearing loss after treatment and SII values.

Material and Methods

This study was carried out by retrospectively examining the electronic health records of patients who were diagnosed with sudden hearing loss in the otorhinolaryngology clinic between the dates of 20 Feb, 2019 and 1 Dec, 2021 in our hospital. Ethics approval was obtained from the institutional review board prior to initiation of the study (No.2 clinical research ethics committee).

Patients with a sensorineural hearing loss of 30 dB or more, which developed suddenly in the last three days, seen at 3 consecutive frequencies, were included in the study.

Patients with otological disease, malignancy, active infectious disease were excluded from the study. Complete blood count, liver function tests, kidney function tests, thyroid function tests, lipid profile, albumin, sedimentation and viral serology tests were studied from the patients included in the study before starting the treatment. SII was calculated for each patient using the Neutrophil x Platelet/Lymphocyte formula for complete blood count.[6]

According to the audiometry performed before the initial treatment, the patients were divided into 3 groups (250, 500, 1000, 2000, 4000, 8000 Hz pure tone averages) below 40 dB defined as mild, between 40 and 80 dB defined as moderate and above 80 dB defined as severe.13 As a standard treatment protocol, intravenous methylprednisolone treatment of 1 mg/kg per day was given to all patients for the first 3 days, and the dose was gradually reduced 10 mg every 2 days.

Age, gender, complete blood counts, SII values, pure tone averages in the first audiometry, pure tone averages in the audiometry performed 1 month after the treatment, and the difference between the first audiometry pure tone averages and the pure tone averages in the last audiometry of all patients were recorded.

Statistical analysis

Categorical variables were presented in frequency tables. Continuous variables were presented (mean, standard deviation (SD), or median, and interquartile ranges between 25% and 75%, as appropriate. Binary comparisons of numerical variables not conforming to a normal distribution were carried out using the Mann-Whitney U test. Correlation between age, gender and blood parameters according to mild, moderate and severe hearing loss groups in the first audiometry were presented. Univariable logistic regression analyses were performed to

investigate the predictors of ISSHL. Consequently, a multivariable logistic regression analysis (variables selected from univariable logistic regression analyses with a p-value less than 0.10) was performed to investigate significant independent predictors of ISSHL.

The correlation between the SII values and first audiometry values was plotted. The correlation between the SII values and the difference in the first audiometry and 1-month follow-up audiometry was also plotted. Correlations between the SII and hearing loss values were examined using the Pearson correlation analyses.

The receiver operating characteristic (ROC) curve was used to evaluate the performance of SII to predict hearing loss (first audiometry) and hearing loss recovery (the difference in the first audiometry and 1-month follow-up audiometry). All statistical analyses were performed in Stata version 17.0 (Stata Corporation, College Station, TX, USA). Statistical significance was defined as a p-value of less than 0.05.

Result

A total of 201 (99 male, 102 female) patients with sudden hearing loss were included in the final analyses. The mean and standard deviation (SD) age of patients 43.9 (14.4). When the patients are grouped as mild, moderate and severe hearing loss; there was no statistically significant difference between the three groups in terms of gender (p=0.875), hemoglobin levels (p=0.59), neutrophil counts (p=0.11), platelet counts (p=0.84), albumin (p=0.36), and lymphocyte counts (p=0.16). A statistically significant difference was found between the three groups in terms of age (p=0.046), white blood cell counts (p=0.026), monocyte counts (p=0.017), and SII values (p<0.001). All demographic information and laboratory results of the patients are presented in Table 1.

Multivariable logistic regression analysis revealed that higher age [odds ratio (OR)=1.039 confidence intervals (95% CI) 1.011-1.067; p=0.005], higher monocyte count [OR=26.368, 95% CI (1.304-533.095); p=0.033] and higher SII [OR=1.002, 95% CI (1.001-1.003); p<0.001] associated with the severity of hearing loss (Table 2). As shown in Figure 1, there was a significant positive correlation between the level of hearing loss and SII (R=0.461, p<0.001). The discrimination of the SII to predict hearing loss as assessed by ROC curve was 0.864 (Figure 2). As shown in Figure 3, the difference between the pure tone averages in the audiometry performed before the start of the treatment and the pure tone averages in the audiometry performed 1 month later was examined, a negative correlation was found between the improvement in hearing loss and SII (R=-0.195, p<0.001). The discrimination of the SII to predict hearing loss recovery as assessed by ROC curve was 0.663 (Figure 4).

Table 1: Demographic information and laboratory results of the patients

	Total N=201	Mild N=64	Moderate N=115	Severe N=22	p-value
Age	43.90 (14.44)	40.22 (11.49)	45.54 (15.53)	46.05 (14.82)	0.046*
Male	99 (%49.3)	31 (%48.43)	57 (%49.57)	11 (%50.0)	0.875
WBC (x109/L)	8.23 (2.75)	7.50 (2.06)	8.74 (3.09)	7.97 (2.42)	0.026*
Platelets (x109/L)	257.17 (60.60)	256.12 (60.61)	256.11 (60.00)	264.23 (65.35)	0.84
Neutrophils (x109/L)	5.31 (2.62)	4.74 (2.15)	5.67 (2.91)	5.25 (2.24)	0.11
Lymphocytes (x109/L)	2.13 (0.71)	2.06 (0.67)	2.22 (0.74)	1.94 (0.65)	0.16
Monocytes (x109/L)	0.44 (0.17)	0.39 (0.11)	0.47 (0.19)	0.47 (0.19)	0.017*
HGB (g/dL)	14.50 (1.54)	14.33 (1.54)	14.58 (1.56)	14.60 (1.51)	0.59
ALT (U/L)	26.25 (14.62)	24.16 (11.30)	27.29 (14.64)	27.10 (21.15)	0.44
AST (U/L)	21.25 (8.86)	21.85 (10.07)	21.01 (8.74)	20.71 (5.70)	0.82
TSH (mU/L)	2.12 (2.02)	2.20 (2.07)	2.16 (2.13)	1.81 (1.50)	0.81
SII	737.83 (477.59)	543.16 (315.32)	718.05 (417.77)	1315.21 (603.57)	<0.001*

The values are presented as mean (SD)

Abbreviations: WBC: White Blood Cell, HGB: Hemoglobin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, TSH: Thyroid Stimulating Hormone, SII: Systemic Immune-Inflammation Index

Discussion

The underlying cause of ISSHL is not clearly known. Although its etiopathogenesis is controversial, infectious, inflammatory, immunological causes and microvascular pathologies are frequently seen as etiological factors.[3] The fact that hearing loss does not always benefit from treatment or that it partially improves has been effective in investigating the factors affecting the prognosis of the disease. Prior studies, showed that severe hearing loss, the long period between the onset of hearing loss and the treatment given, hearing loss is accompanied by vertigo, hearing loss at high frequencies, the patient has hypertension, diabetes mellitus, hyperlipidemia, vascular diseases, and advanced age are negative prognostic factors.[14-17] Young age and accompanying tinnitus were found to be positive prognostic factors.[18]

In recent years, various inflammation markers related to the severity, prognosis and response to treatment of ISSHL, and calculations of blood values related to the inflammation process such as neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) have attracted the attention of researchers.[12-19-20] We also think that clues that can give an idea about the disease process and treatment response can guide the treatment management of the disease. For example, in patients who are predicted to have a poor prognosis, approaches such as adding hyperbaric oxygen therapy to steroid therapy can be decided in advance. In their study, Li et al. found that the decrease in NLR rates after hyperbaric oxygen therapy in ISSHL patients was associated with hearing gains.[21]

Table 2: Factors associated with the severity of hearing loss

Multi Variable Logistic regression

	Odds Ratio	95% Confidence intervals	p-value
Age	1.039	1.011-1.067	0.005
WBC (x109/L)	1.021	0.853-1.222	0.823
Monocytes (x109/L)	26.368	1.304-533.095	0.033
SII	1.002	1.001-1.003	0.002

Abbreviations: WBC: White Blood Cell, SII: Systemic Immune-Inflammation Index

SII was first used by Hu et al. to determine the prognosis in patients undergoing curative resection of hepatocellular cancer, and high SII values were found to be associated with poor prognosis.[6] It has been used in many studies on malignancy patients in the following years, and it has been found to be a more powerful tool than NLR and PLR in determining the prognosis in colorectal cancer and cervical cancer.[22-23] SII has been studied in malignancies in the otolaryngology field, and it has been found to be an important value in predicting prognosis in nasopharyngeal cancers,[24] it was found to be higher in patients with laryngeal cancer compared to the control group, and it was reported that it can give important clues for perineural invasion and lymphatic spread.[25]

There is only one study investigating SII values in ISSHL.[12] In that study, Ulu et al. showed that SII may be a diagnostic marker in ISSHL, it was determined that patients with high SII values may not have a treatment response, and it was reported that larger studies are needed to understand the importance of SII in ISSHL.[12] In he study of İkincioğulları et al., NLR and PLR values were found to be higher in ISSHL than in the control group, and it was found that patients with higher NLR values had a better response to treatment.[26] On the other hand, in the study of Aydoğdu et al., NLR values were found to be higher in the group with no improvement in hearing loss than in the group with improvement.[27] In our study, we investigated the relationship between the level of hearing loss and SII values and found that SII values were higher as hearing loss increased. When we looked at the treatment response, we found that the response to treatment was worse in patients with high SII values.

Since inflammatory events are the underlying cause of ISSHL etiology, inflammatory markers can provide important information about the severity, prognosis and response to treatment of the disease. For this reason, markers that give an idea about the inflammatory process have always attracted the attention of researchers. While researching new markers, the correlation with the severity and prognosis of the disease, being easily accessible, practical and inexpensive are important criteria. This study has several limitations that must be taken into account when evaluating the findings. First, the comorbidities of the patients,

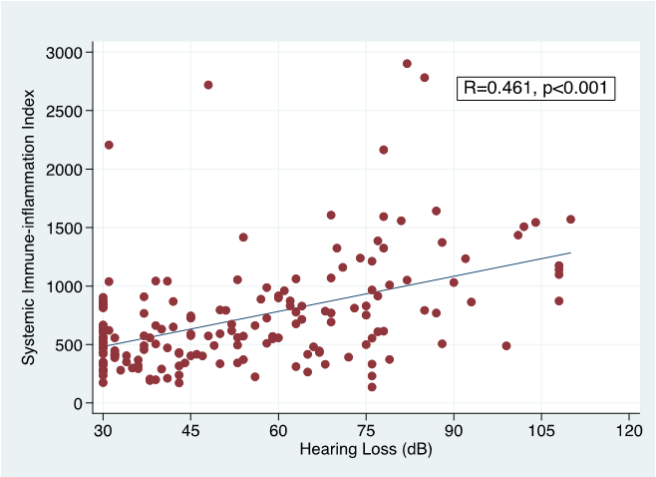

Figure 1: Correlation between the level of hearing loss and systemic immune-inflammation index

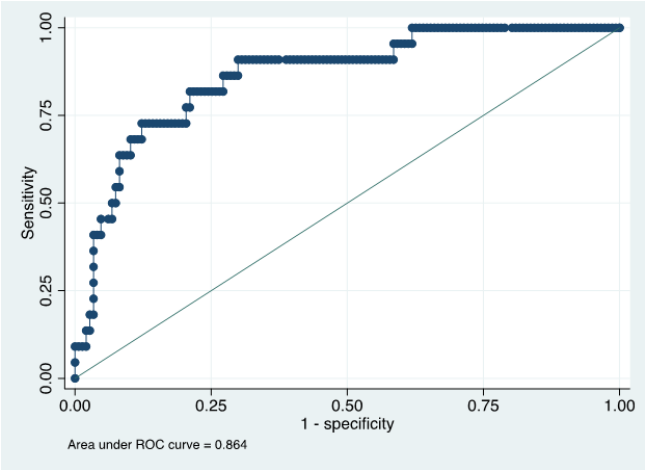

Figure 2: Receiver operating characteristic curves of hearing loss

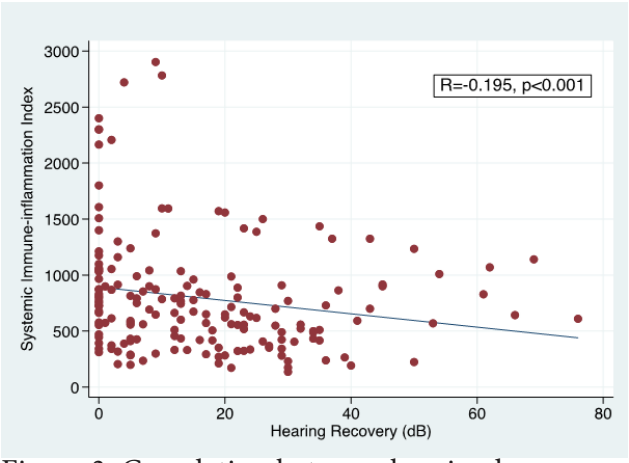

Figure 3: Correlation between hearing loss recovery and systemic immune-inflammation index

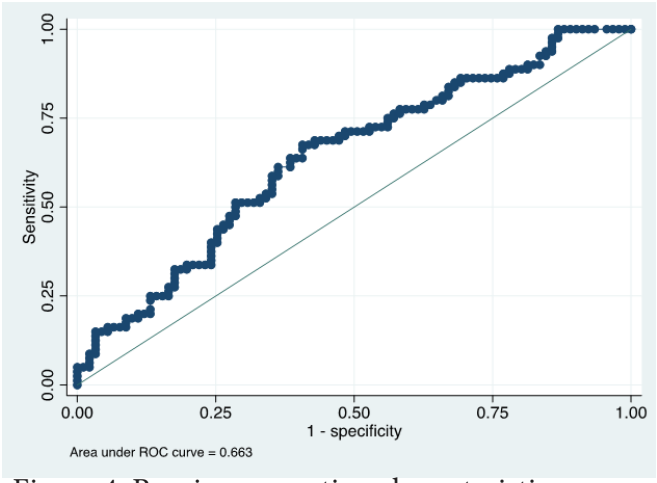

Figure 4: Receiver operating characteristic curves of hearing loss recovery

including diabetes mellitus and hypertension, cannot be determined due to the retrospective nature of study. Second, SII was not compared with other inflammatory markers, such as CRP, fibrinogen, or myeloperoxidase, because of the retrospective nature of our study. As a result of these limitations, our results may not apply to all ISSHL patients.

Conclusion

In conclusion; SII, an easily available and relatively cheap marker, was associated with the severity of hearing loss. In addition, this index was also associated with the recovery of hearing loss. To the best of our knowledge, this is the first and largest study showing that a high SII value, an indicator of an increased inflammation, was associated with severe hearing loss and also worse sign of recovery.

Disclosure Statement: The authors declare that there are no conflicts of interest.

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RESEARCH ARTICLE

Effect of Sglt-2 Inhibitors on Renal Tubular Damage

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Abstract

Introduction: In this study, it was aimed to evaluate the relationship between the use of two different sodium glucose transporter 2 (SGLT-2) inhibitors, dapagliflozin and empagliflozin, and renal tubular injury, with type 2 diabetes mellitus patients obtaining levels of neutrophil gelatinase-associated lipocalin (NGAL) in serum and arylesterase in urine. Methods: Sixty patients diagnosed type 2 diabetes mellitus were enrolled in the study; 30 of these patients used dapagliflozin and 30 patients used empagliflozin. The serum NGAL levels of the patients were measured by sandwich ELISA method while urine arylesterase levels were studied by centrifugation. Results: No significant relationship was found between the considered SGLT-2 inhibitors and the occurrence of acute tubular damage. There was no significant difference in serum NGAL levels or urinary arylesterase levels between the dapagliflozin and empagliflozin groups. The levels of microalbuminuria were significantly decreased in both groups. Conclusion: It can be said that there is no significant relationship between SGLT-2 inhibitors and renal tubular damage, with no significant difference found between dapagliflozin and empagliflozin.

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Introduction

Diabetes mellitus is a metabolic disease that occurs due to the inability to produce enough insulin in the pancreas and/or the ineffective use of the produced insulin.[1] Diabetes mellitus increases mortality by affecting all organ systems, and especially the cardiovascular, renal, and neural systems, with microvascular and macrovascular complications.[2]

Sodium glucose transporter 2 (SGLT-2) inhibitors are promising agents for the treatment of type 2 diabetes and various studies are being conducted on them in terms of side effect profiles. While research has shown that SGLT-2 inhibitors have renoprotective effects,[3] there are also suspicions that they may have toxic effects on renal tubules due to their glycosuric properties and there are currently not enough studies on this subject.

The neutrophil gelatinase-associated lipocalin (NGAL) protein and its lipocalin-2 variant are yielded by the LCN2 gene encoded in humans.Recent studies have shown that NGAL can be used as a new biological marker protein for the early diagnosis of Diabetic Kidney Disease (DKD) and is closely related to the development of DKD. Elevated levels of serum and urine NGAL can be detected in patients with early DKD. It has been shown that in acute kidney injury (AKI) serum NGAL levels increase with the occurrence of kidney damage. Therefore NGAL may play an important role in predicting early kidney disease. In the event of acute kidney injury (AKI) NGAL levels have been associated with the severity of prognosis and are used as a biomarker for AKI.[4]

Arylesterase is an enzyme that requires calcium ions for its activity. It belongs to the PON1 family and its levels decrease in the event of oxidative damage. Arylesterase levels have a potential role for the detoxification of lipid peroxides and suggests that individuals with a low levels may have a greater risk of developing a disease such as atherosclerosis, which may involve lipid peroxidation, than high-activity individuals. Studies of diabetic patients have shown a decrease in their arylesterase levels.[5]

There are a few studies in the literature investigating the relationship between SGLT-2 inhibitors and AKI, with researchers observing that some patients using SGLT-2 inhibitors may develop AKI and offering various hypotheses about the reasons for that occurrence.[6]

In the present study, the effects of SGLT-2 inhibitors on renal tubules were evaluated in groups of patients using dapagliflozin and empagliflozin, as these inhibitors affect proximal tubules of the kidneys.

Material and Methods

This study was conducted in Ankara City Hospital's Internal Medicine Clinic between June 2020 and December 2020 as an observational prospective study. The design and procedures of the study were approved by Ankara City Hospital's Ethics Committee and the Turkish Medicines and Medical Devices Agency in line with the principles of the Declaration of Helsinki and ethical standards for human experiments. Written informed consent was obtained from all participants.

A total of 60 patients comprising a mixture of men and women registered with the diagnosis code of type 2 diabetes mellitus in the general internal medicine outpatient clinic of Ankara City Hospital, aged 18-80 years and using oral antidiabetic drugs or insulin, were included in the study. Thirty of these patients were started on empagliflozin (10 mg) and the other 30 on dapagliflozin (10 mg).

Patients were excluded from the study for the following reasons: known hypertension; usage of ACE inhibitors, angiotensin receptor blockers, or diuretics; the presence of non-diabetic nephrotic syndrome, AKI, or chronic kidney injury with glomerular filtration rate (GFR) of <60; immunosuppressive therapy; diabetes mellitus due to secondary causes or diagnosis of type 1 diabetes mellitus; and the presence of malignancies or infectious diseases.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Labarotory parameters

Blood samples were taken from the antecubital vein after 10-12 hours of fasting and analyzed within 6 hours. Urine samples were taken after 10-12 hours of fasting and analyzed within 4 hours. The obtained blood samples were analyzed in the Ankara City Hospital Central Laboratory. Complete blood counts were performed with a Mindray BC-6800 device. Lipid parameters and HbA1c levels were examined with an ARCHITECT c16000 device. Spot urine tests were performed with an ARCHITECT c4000 model device. HbA1c was studied by immunoturbidimetric methods. In order to measure serum NGAL levels, venous blood samples of 10 mL were taken into vacu-

um biochemistry serum tubes and centrifuged at 1300 × g for 10 minutes. The separated sera were divided into Eppendorf tubes and stored at -80 °C until analysis. NGAL levels were measured using a quantitative sandwich enzyme immunoassay technique with an ELISA kit (BT Laboratory, Shanghai, China; Catalog Number: E1719Hu, Lot: 202003008). The detection range of the test was 5-600 ng/mL. Intra-study and inter-study precision were <8% and <10%, respectively. To measure urinary arylesterase levels, urine samples collected in disposable non-sterile urine containers were transferred to empty urine tubes of 10 mL. The samples were centrifuged at 1000 × g for 5 minutes and stored at -20 °C. Urine arylesterase levels were measured with an ADVIA 1800 device (Siemens Healthineers, Germany) and a commercially available kit (Rel Assay Diagnostics, Gaziantep, Turkey).

Statistical Analysis

Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The compliance of the variables with normal distribution was examined by histogram graphics and Kolmogorov-Smirnov tests. Mean, standard deviation, and median values were used to present the results of descriptive analyses. Among the numerical variables, those that showed normal distribution were given as mean ± standard deviation and those that did not show normal distribution were given as median (min-max). Categorical variables were compared with Pearson chi-square tests. The Mann-Whitney U test was used when evaluating non-normally distributed (nonparametric) variables between groups. The change in measured values was evaluated by the Wilcoxon test within groups and compared by repeated measures analysis between groups. Values of $p<0.05$ were considered statistically significant.

Results

The study population consisted of patients with type 2 diabetes mellitus, 30 of whom were using empagliflozin and 30 of whom were using dapagliflozin. A total of 60 people, 61.67% (n: 37) male and 38.33% (n: 23) female with a mean age of 52.60±8.78 years, were included in the study. Of these participants, 31 people smoked and 11 people consumed alcohol. There were 35 patients with hyperlipidemia, 10 with thyroid disease, 10 with coronary artery disease, 5 with anaemia, 1 with chronic obstructive pulmonary disease, and 9 with other diseases. There was no statistically significant difference between the groups in terms of demographic or clinical characteristics (Table 1).

Table 1: Clinical and demographic characteristics of the study population

Variables		Population n (60)
Age		52.60±8.78
BMI		28.35±2.39
Sex	Male	37 (61.67)
	Female	23 (3833)
Tobacco		31 (51.67)
Alcohol		11 (18.33)
CHF		0 (0.00)
Thyroid disease		10 (16.67)
Anemia		5 (8.33)
CAD		10 (16.67)
Other diseases		9 (15.00)
Hyperlipidemia		35 (58.33)
Asthma		0 (0.00)
COPD		1 (1.67)

BMI: Body mass index, CHF: Congestive Heart Failure, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease.

The patient groups using dapagliflozin and empagliflozin were compared in terms of other drugs being used. The rate of sulfonylurea use in the dapagliflozin group was significantly higher than that in the empagliflozin group (p=0.037). No significant difference was found in the comparisons made in terms of other drugs used (Table 2).

Table 2: Comparison of Patient Groups Using Dapagliflozin and Empagliflozin Regarding Other Drugs Used

Variables	Dapagliflozinn 30 (%)	Empagliflozin n 30 (%)	p
Metformin (%)	29 (96.67)	29 (96.67)	1.000
Sulfonylurea (%)	11 (36.67)	4 (13.33)	0.037
DPP4 (%)	10 (33.33)	11 (36.67)	0.787
Glitazone (%)	0 (.00)	3 (10.00)	0.076
Glinide (%)	1 (3.33)	1 (3.33)	1.000
Insulin (%)	4 (13.33)	4 (13.33)	1.000
NSAID (%)	4 (13.33)	2 (6.67)	0.389
PPI (%)	6 (20.00)	9 (30.00)	0.371
Statin (%)	17 (56.67)	13 (43.33)	0.302

Patient groups using dapagliflozin and empagliflozin were compared in terms of laboratory values before the use of those SGLT-2 inhibitors. While the median serum NGAL level was 23.5 ng/mL in the patient population using dapagliflozin, it was 22.7 ng/mL in the empagliflozin group, and while the urinary arylesterase level was 28.3 U/L in the dapagliflozin group, it was 26.3 U/L in the empagliflozin group. Total cholesterol (p=0.003), low-density lipoprotein cholesterol (LDL-C) (p<0.001), and Urine protein (p=0.017) values were significantly higher in the patient group using dapagliflozin compared to patients using empagliflozin. No significant difference was found in the comparison of other laboratory findings (Table 3).

In the dapagliflozin group, fasting blood sugar (p=0.008), triglyceride (p=0.015), total cholesterol (p=0.026), LDL-C (p=0.003), gamma-glutamyl transferase (p=0.033), HbA1c (p<0.001), and urinary microalbumin (UMA) (p<0.001) values decreased, while urea (p=0.002), total protein (p=0.042), albumin (p=0.027), phosphorus (p=0.015), haemoglobin (p=0.003), and red blood cell distribution width (RDW) (p=0.017) values increased significantly. No significant difference was found for other laboratory results (Table 4).

In the empagliflozin group, there was a significant decrease in FBS (p<0.001), triglyceride (p=0.027), HbA1c (p<0.001), platelet count (p=0.034), and UMA (p=0.022) values, while haemoglobin (p<0.001) and RDW (p=0.048) levels increased significantly. No significant difference was found for other laboratory results (Table 4).

There was a significant decrease in HbA1c levels in both groups. HbA1c levels before and after treatment are shown in Table 4. Serum NGAL levels and urinary arylesterase levels were compared before and after treatment and no significant difference was found between groups (Table 4).

Table 3: Comparison of Laboratory Findings of Dapagliflozin and Empagliflozin Groups Before SGLT-2 Inhibitors

Variables	Dapagliflozin	Empagliflozin	p
Fasting blood sugar (mg/dL)	180.0 (109.0-353.0)	161.0 (84.0-341.0)	0.391
Urea (mg/dL)	29.43±6.76	33.93±10.11	0.078
Creatinine (mg/dL)	0.80±0.12	0.80±0.13	0.923
GFR (mL/min/1.73 m2)	97.34±10.34	99.23±10.50	0.662
Sodium (mEq/L)	139.47±2.71	139.37±2.28	0.806
Potassium (mEq/L)	4.5 (3.1-5.4)	4.6 (3.0-5.1)	0.608
Total protein (g/L)	7.2 (5.7-8.1)	7.1 (6.3-7.7)	0.537
Albumin (g/L)	4.7 (4.1-4.9)	4.7 (4.3-5.2)	0.130
Triglyceride (mg/dL)	233.0 (46-968)	192.5 (46-638)	0.297
Total cholestero (mg/dL)	l219.57±42.05	188.83±35.22	0.003
HDL-C (mg/dL)	46.47±8.87	43.13±9.31	0.124
LDL-C (mg/dL)	135.68±30.83	100.47±23.92	<0.001
ALT (U/L)	41.07±29.17	32.60±23.22	0.198
AST (U/L)	34.33±57.28	24.03±14.96	0.836
GGT (U/L)	78.57±200.58	44.00±38.14	0.355
ALP (U/L)	98.10±80.26	80.86±27.78	0.282
Phosphorus (mg/dL)	3.54±0.56	3.75±0.59	0.188
Uric acid (mg/dL)	4.72±0.98	5.33±1.24	0.066
Magnesium (mg/dL)	1.89±0.26	1.95±0.25	0.633
Calcium (mg/dL)	9.63±0.32	9.70±0.48	0.600
HbA1c (%)	9.47±1.57	8.88±1.56	0.108
White blood cells (×109/L)	7.84±1.57	7.92±2.21	0.807
Neutrophils (×109/L)	4.28±1.29	4.44±1.52	0.988
Lymphocytes (×109/L)	2.75±0.58	2.68±0.84	0.391
Hemoglobin (g/dL)	14.61±1.45	14.61±1.26	0.900
Platelets (×109/L)	273.83±66.85	264.80±58.57	0.492
MPV (fL)	8.32±0.68	8.21±0.58	0.543
RDW (%)	13.3 (12.2-18.9)	13.5 (12.5-16.4)	0.695
UPR (mg/L)	147.0 (39.3-2098.5)	74.5 (26.5-376.3)	0.017
UKR (mg/dL)	88.3 (11.2-423.4)	85.4 (12.8-288.7)	0.797
UMA (mg/dL)	32.8 (0.59-865.5)	17.5 (1.7-556.2)	0.086
UPR/CR (mg/g CR)	107.5 (44-987)	99.0 (43.0-225.0)	0.793
Arylesterase level (U/L)	28.3 (17.8-54.2)	26.3 (8.5-66.0)	0.301
NGAL level (ng/mL)	23.5 (6.0-150.4)	22.7 (12.7-771.7)	1.000

GFR: Glomerular Filtration Rate; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; ALT: Alanine Transaminase; AST: Aspartate Transaminase; GGT: Gamma Glutamyl Transferase; ALP: Alkaline Phosphatase; MPV: Mean Platelet Volume; RDW: Red Blood Cell Distribution Width; UPR:Urine Protein Ratio ; UKR:Urine Creatinine Ratio ;UMA:Urine Microalbuminuria ; UPR/CR:Urine Protein Ratio/Creatinine Ratio.

Table 4.(Continued).

Variables	Dapagliflozin			Empagliflozin			
	Pre	Post	p	Pre	Post	p	Δp
Calcium (mg/dL)	9.63±0.32	9.74±0.47	0.165	9.70±0.48	9.80±0.50	0.508	0.996
HbA1c (%)	9.47±1.57	7.70±0.76	**<0.001**	8.88±1.56	7.51±0.91	**<0.001**	0.255
WBC (×109/L)	7.84±1.57	7.73±1.45	0.636	7.92±2.21	8.05±1.99	0.424	0.502
Neutrophils (×109/L)	4.28±1.29	4.05±1.23	0.369	4.44±1.52	4.77±1.47	0.210	0.074
Lymphocytes (×109/L)	2.75±0.58	2.95±0.98	0.607	2.68±0.84	2.50±0.82	0.116	0.089
Hemoglobin (g/dL)	14.61±1.45	15.13±1.55	**0.003**	14.61±1.26	15.11±1.23	**<0.001**	0.946
Platelet (×109/L)	273.83±66.85	278.23±70.00	0.697	264.80±58.57	256.33±58.41	**0.034**	0.129
MPV (fL)	8.32±0.68	8.16±0.69	0.420	8.21±0.58	8.36±0.61	0.161	0.090
RDW (%)	13.3 (12.2-18.9)	13.8 (12.2-19.7)	**0.017**	13.5 (12.5-16.4)	13.7 (12.7-16.3)	**0.048**	0.505
UPR (mg/L)	147.0 (39.3-2098.5)	119.1 (11.1-686.6)	0.194	74.5 (26.5-376.3)	92.6 (22.4-341.1)	0.524	0.572
UKR (mg/L)	88.3 (11.2-423.4)	100.3 (15.9-197.8)	0.964	85.4 (12.8-288.7)	85.6 (22.4-557.8)	0.719	0.570
UMA (mg/L)	32.8 (0.59-865.5)	4.7 (1.1-390.7)	**<0.001**	17.5 (1.7-556.2)	8.6 (2.0-472.0)	**0.022**	0.396
UPR/CR (mg/g creatine)	107.5 (44-987)	86.5 (37.0-490.0)	0.139	99.0 (43.0-225.0)	122.0 (40.0-156.0)	0.539	0.126
Arylesterase (U/L)	28.3 (17.8-54.2)	27.0 (19.5-39.0)	0.658	26.3 (8.5-66.0)	28.6 (14.5-87.4)	0.229	0.095
NGAL (ng/mL)	23.5 (6.0-150.4)	24.0 (7.3-466.8)	0.734	22.7 (12.7-771.7)	17.4 (0.2-673.4)	0.080	0.269

Please see Table 3 for abbreviations.

Discussion

This study is one of the rare studies to date examining the effects of SGLT-2 inhibitors on the renal tubule patients with type 2 diabetes mellitus. In this study, serum NGAL and urinary arylesterase levels were examined in terms of acute tubular injury in patients using dapagliflozin or empagliflozin at 10 mg.

Although there is no direct relationship between the usage of SGLT-2 inhibitors and AKI established in the literature, some research has stated that these patients may have AKI. Partial hypoxia in the tubules and a decrease in volume due to diuresis are among the main reasons for this. Peritubular hypervascularization due to increased synthesis of tubular apoptosis and vascular endothelial growth factor are also thought to be among the causes.[7]

In the study conducted by Dekkers et al., no significant correlation was found between using of SGLT-2 inhibitors and urinary NGAL levels in terms of acute tubular damage.[8] In the present study, no significant correlation was observed in serum NGAL levels of patients using SGLT-2 inhibitors. No significant difference was observed in either drug group and the obtained results were congruent with the findings of the literature to date.

Studies on urinary arylesterase levels in type 2 diabetes mellitus patients who use SGLT-2 inhibitors couldn't be found in the literature; the present study is thus a first in this regard. There are data in the literature showing that urinary arylesterase levels decrease in patients with type 2 diabetes mellitus, although no significant relationship was found with diabetic nephropathy.[5] In the present study, there are no significant change urinary arylesterase levels between the dapagliflozin and empagliflozin groups. Further research is needed on this subject.

In a study by Yale et al. involving canagliflozin, it was found that there was a 1.6-4 mL/min decrease in GFR levels in patients using SGLT-2 inhibitors.[9] However, no decrease was found in GFR levels in the present study. This may be related to the follow-up period and GFR levels of the patients in the respective studies. In the EMPA-REG OUTCOME study undertaken by Ferrannini et al., the mean follow-up period was 36 months and the GFR level was 74±21 mL/min. In the present study, the mean follow-up period was 12.3 weeks and the GFR level was 98.29±10.37 mL/min, which strengthens our suggestion that the follow-up period may be related to these outcomes.[10]

In this study, it was observed that there was a significant decrease in the level of microalbuminuria in both groups no significant difference was found between the dapagliflozin and empagliflozin groups. It is thought that the decrease in microalbuminuria was due to a decrease in blood sugar regulation and blood pressure in

the afferent arterioles within the proximal tubules of the kidney due to the effects of SGLT-2 inhibitors[11]- [12] Further studies are needed on this subject.

In the meta-analysis undertaken by Feng et al., a decrease of 6-9 mmol/mol (0.49-0.81 SD) in HbA1c level was observed with the use of dapagliflozin at 10 mg during the administration of monotherapy via SGLT-2 inhibitors.[13] In our study, the HbA1c level significantly decreased from 9.18 to 7.61. It was thought that a greater decrease in HbA1c level compared to the literature findings might be due to decreases in blood sugar levels.

A study by Kohan et al., observed that there was an increase in serum blood urea nitrogen (BUN), albumin, and phosphorus levels in patients during follow-up.[14] In the present study, a significant increase was observed in the levels of BUN, albumin, and phosphorus, and this was thought to be due to secondary hypovolemia caused by the diuretic effect of SGLT-2 inhibitors. Similarly, in the study undertaken by Merlin et al., an increase was observed in the levels of BUN, haemoglobin, and albumin.[15] In the present study, an increase in serum haemoglobin levels was also observed, which may have been due to the decrease in volume.[16]

Wu et al. showed that SGLT-2 inhibitors increase the rates of genital and urinary tract infections.[17] While dysuria was detected in 6 patients and urinary tract infection developed in 1 patient using dapagliflozin and 3 patients using empagliflozin, or a total of 4 patients. In this respect, the obtained findings are congruent with those of the literature to date. The reason why the patients in the present study did not have genital infections is likely owing to the low number of patients and the fact that the majority of the patients were male. In this study, there was no significant change in the biomarkers indicated for acute tubular injury via SGLT-2 inhibitors. When both the dapagliflozin and empagliflozin groups were examined comparatively, no difference was found between them in terms of acute tubular damage.Therefore, it is necessary to investigate better diagnostic biomarkers of DN, and in this study, we tested the diagnostic properties of NGAL, which is the most promising tubular biomarker in the diagnostic field of acute renal disease, considering that tubular dysfunction is an important component of diabetic renal disease. NGAL is mostly released in blood and urine from injured tubular cells after various conditions potentially detrimental to the kidney in experimental and human clinical models. NGAL release from renal tubule occurs precociously after damage, sooner than other ‘‘classic’’ parameter such as serum creatinine. Results of this study are thus in accordance with previous studies in literature. In addition, urinary microalbuminuria levels were decreased in both dapagliflozin and empagliflozin groups. This result supports the data that SGLT-2 inhibitors have a protective effect in terms of diabetic kidney disease. There was no significant difference in the reducing effect of microalbuminuria in both groups .[18] This study showed that empagliflozin and dapagliflozin do not increase acute tubular damage, on the contrary, they reduce microalbuminuria and have a protective effect on kidney functions.

There are some limitations of this study. As the research was conducted in the context of thesis research, conducted in a single centre, a placebo control could not be performed. The fact that the patients were not met in more frequent long-term follow-up visits was also among the limiting factors. In addition, the inability to control the optimal fluid intake of the patients in this period, the fact that the patients were not meeting optimal glycemic targets, and the inability to measure creatinine and arylesterase levels in the 24-hour urine of the patients also limited the study. Finally, psychosocial factors such as anxiety, stress, and worry experienced by patients during the time of the COVID-19 pandemic and the inability to monitor the blood pressure of the patients during this period may also affect the obtained results. Multicenter studies with more patients, longer mean follow-up periods with more frequent follow-ups, and placebo controls are needed. However, the effects of these differences on the results should be minimal, as the reduction rates in the results of the patients were calculated.

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RESEARCH ARTICLE

Abnormal Fetal Cardiac Function and Umbilical Cord Blood Brain Natriuretic Peptide Levels in Intrahepatic Cholestasis of Pregnancy

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Abstract

Introduction: We aim to evaluate fetal cardiac function and umbilical cord blood pro-BNP (pro-brain natriuretic peptide) levels in ICP (intrahepatic cholestasis of pregnancy).

Methods: The study included 41 ICP cases and 41 controls. All participants were evaluated after 34 weeks of gestation. The pro-BNP levels in umbilical cord blood were assayed, and perinatal outcomes were compared between the groups.

Results: In the ICP group SBA (serum bile acid) and pro-BNP levels were higher than the control group ($p<0.001$ and $p=0.001$). The left MPI (myocardial performance index) of ICP group was higher among the control group ($p=0.043$). A positive correlation was evaluated between the pro-BNP levels and MPI values ($p<0.001$).

Conclusion: Both the high MPI values obtained via ultrasonography and the high pro-BNP levels detected in umbilical cord blood may be attributable to the adverse fetal cardiac effects of ICP.

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Introduction

ICP (Intrahepatic cholestasis of pregnancy) is one of the specific liver diseases for pregnancy.[1] This liver disorder is accompanied by pruritus and high SBA (serum bile acid) concentrations, and its incidence ranges from 0.3–27.6%2,3. ICP typically develops during the late second and/or third trimester and is associated with an elevated risk of perinatal complications (e.g., premature birth, fetal distress, meconium-stained amniotic fluid, respiratory disorders, and stillbirth).[3-4] The mechanism of ICP-associated stillbirths is unknow[2-5]

However, the arrhythmic event is thought to cause intrauterine death and fetal cardiac dysfunction has been investigated in studies.[6] In addition, an increase in pro-BNP (pro-brain natriuretic peptide) levels has been observed and linked to heart failure and cardiac dysfunction.[7-8]

In the present study, we aim to evaluate fetal cardiac function and umbilical cord blood pro-BNP levels in pregnancies complicated by intrahepatic cholestasis.

Material and Methods

The prospective case-control study was conducted in Ankara City Hospital between March 1, 2021, and September 1, 2021. Approval for the study was obtained from Ankara City Hospital Ethics Committee with the decision number E2-21-166. Written consent was obtained from all participants. The study included 41 patients with ICP as the study group (ICP group) and 41 healthy pregnant women as the control group. ICP was diagnosed when SBA concentrations were >10 µmol/L in maternal blood serum. Patients with ICP were treated with UDCA (ursodeoxycholic acid) (750-1000 mg daily) upon diagnosis. All fetuses underwent cardiac scanning at 20-22 weeks. Exclusion criteria were maternal chronic medical or heart disease, twin pregnancy, maternal tobacco use, fetal chromosomal abnormality, and fetal anomaly. Gestational age was confirmed by first-trimester ultrasonography. Fetal 2D, PW (pulsed wave) Doppler, and M-mode ultrasonographic evaluations were performed using a Voluson S10 (GE Medical Systems, Solingen, NRW, Germany) Ultrasound machine C1-5-RS convex probe. The fetal cardiac function and morphology of all participants were evaluated after 34 weeks of gestation. The cardiothoracic ratio (obtained by dividing the heart circumference by the thoracic circumference), area of ventricles, ventricle wall thickness, interventricular septal thickness, and SI (sphericity indices) were measured in four-chamber view at end diastole.[9] The right and left ventricular areas were measured in the four-chamber view by tracing of the endocardium. The SI is derived by calculating the ratio between the base-apex diameter and transverse length.[10] Left MPI (myocardial performance index) shows both diastolic and systolic function as assessed by PW Doppler. The PR interval and the left MPI were measured in the junction between the mitral valve and the left ventricular outflow tract. The PR interval was measured from the beginning of the mitral wave to the end of the left ventricular isovolumetric contraction.[11] The MPI was obtained as follows: ((isovolumetric contraction time + isovolumetric relaxation time) /ejection time), i.e., ((IVCT + IVRT) ÷ ET).[12] Mitral and tricuspid annular plane systolic excursion (MAPSE/ TAPSE) were measured in a four-chamber view by placing the cursor at the atrioventricular lateral annulus. Measuring the left MPI, MAPSE, and TAPSE, and the peak velocities of the pulmonary and aortic arteries evaluated for fetal cardiac systolic function.[13] The mitral and tricuspid E/A ratio is the ratio between E (early) and A (late) ventricular filling velocity for evaluation of the diastolic function of fetal heart.[14] Maternal and fetal demographic data, delivery details, and the cardiac parameters of the participants were compared between the study groups. Umbilical cord blood serum was obtained and centrifuged for 10 minutes at 3,000 rpm after delivery. The Serum was frozen and stored at -80 C. The umbilical cord blood proBNP levels were observed with a human proBNP ELISA kit (Elabscience, Houston, Texas).

Statistical analysis was enforced using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were given as mean ± standard deviation for numerical data with normal distribution or median and minimum-maximum values for numerical data which do not follow a normal distribution. The normality of the variables was tested with both Shapiro–Wilk and Kolmogorov–Smirnov tests. Groups were compared with The Student's t-test and Mann-Whitney U test. The Spearman correlation test was used to investigate the strength of association between pro-BNP values and MPI. A type-1 error be-

low 0.05 was considered statistically significant.

Results

Forty-one cases of ICP and 41 control cases were recruited in the study. Table-1 shows demographic data of the study and there was no significant difference. At the date of ultrasound and laboratory assessment, the mean gestational age of the participants in the ICP group was 36,6±1,3 and that of the control group was 37,1±1,4 (p=0,110).

Table 1. Baseline data and characteristics of the groups.

	Control group (n=41)	ICP group (n=41)	P-Values
Maternal age, years	29,8 ± 6,1	29,6 ± 6,1	0,738
BMI	27,7 ±6 ,2	28,5 ± 4,1	0,846
Smoking	2 (4,9%)	0	0,152
Nulliparity	12 (29,3)	13 (31,7)	0,810
Gestational age at ultrasound and laboratuary assessment (week)	37,1 ± 1,4	36,6 ± 1,3	0,110
ALT (IU/L)	16,4 ± 8,6	92,4 ± 12,0	<0,001
AST (IU/L)	16,4 ± 8,6	92,4 ± 12,0	<0,001
SBA at diagnosis (µmol/L)	5,2 ± 0,4	22,3 ± 9,4	<0,001
Pro-BNP (pg/mL)	117,7 ± 23,5	182,7 ± 78,1	0,001

Data given as median (interquartile range), mean ± SD, number, percentile (n,%). ICP: İntrahepatic cholestasis of pregnancy, BMI: Body mass index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, SBA: serum bile acid, pro-BNP: pro-brain natriuretic peptide.

The alanine aminotransferase, aspartate aminotransferase, and SBA levels were increased among the ICP group than among the control group (p<0,001, p<0,001, and p<0,001, respectively). Furthermore, umbilical cord blood pro-BNP levels were higher in the ICP group than in the control group (p=0,001). Perinatal outcomes are shown in Table-2. The average gestational age (in weeks) at delivery was 36,6±1,2 in the ICP group and 38,0±1,8 in the control group (p=0,001). In the ICP group, preterm delivery, birth weight, cesarean section rate, and neonatal intensive care needs were high (p=0,031, p=0,035, p=0,008, and p=0,043, respectively). The indications for hospitalization of newborns in a NICU (neonatal intensive care unit) were prematurity, polycythemia, neonatal tachypnea, and sepsis. Stillbirth was not observed in either study or control groups.

Table 2. Perinatal outcomes of the groups.

	Control group (n=41)	ICP group (n=41)	P-Values
GA at delivery (weeks)	38,0 ± 1,8	36,6 ± 1,2	0,001
Meconium-stained amniotic fluid	1 (2,4%)	3 (7,3%)	0,305
Stillbirth	-	-	
Preterm delivery	9 (22%)	17 (44,7%)	0,031
Cesarean section rate	14 (34,1%)	26 (63,4%)	0,008
Indications of cesarean section	7 (17,1%)6	(14,6%)	
Previous cesarean1	(2,4%)	2 (4,9%)	
Breech presentation1	(2,4%)	4 (9,8%)	
Fetal distress			
Birthweight (g)	3044 ± 670	2944 ± 354	0,035
1-min Apgar score < 7	-	2 (4,9%)	0,152
5-min Apgar score < 7	- -		
Hospitalization in NICU	6 (14,6%)	13 (31,7%)	0,043
Composite adverse pregnancy outcomes	6 (14,6%)	14 (34,1%)	0,038

Data given as median (interquartile range), mean ± SD, number, percentile (n,%). ICP: İntrahepatic cholestasis of pregnancy, NICU: neonatal intensive care unit. Composite adverse pregnancy outcomes includes meconium-stained amniotic fluid, low APGAR score, fetal distress, and hospitalization in NICU.

Composite adverse pregnancy outcomes include meconium-stained amniotic fluid, low APGAR score, fetal distress, and hospitalization in NICU. Composite adverse pregnancy outcomes were increased in the study group than in the control group (p=0,038). Fetal cardiac morphological assessments are shown in Table-3 and there was no difference between groups (p>0,005).

Table 3. Fetal cardiac morphological assessment

	Control group (n=41)	ICP group (n=41)	P-Values
Fetal heart rate	138 ± 23	143 ± 12	0,513
CTR	0,53 ± 0,02	0,53 ± 0,02	0,127
Cardiac axis angle	42,9 ± 9,6	39,3 ± 8,6	0,119
Left sphericity index	1,63 ± 0,26	1,74 ± 0,35	0,105
Right sphericity index	1,53 ± 0,23	1,53 ± 0,32	0,809
Interventricular septum (mm)	3,3 ± 0,67	3,1 ± 0,54	0,623
Left wall thickness (mm)	3,4 ± 0,59	3,2 ± 0,67	0,296
Right wall thickness (mm)	3,4 ± 0,57	3,3 ± 0,52	0,605
Left ventricular area (mm2)	2,56 ± 0,53	2,53 ± 0,85	0,464
Right ventricular area (mm2)	2,44 ± 0,53	2,58 ± 0,96	0,616

Data given as mean ± SD. ICP: İntrahepatic cholestasis of pregnancy, CTR: cardiothoracic ratio.

Table 4 shows functional changes in the fetal heart. The left MPI values were significantly higher in the study group than in the control group (p=0,043). The correlation between cord blood pro-BNP and left MPI data is presented in Table-5 and figure-1. A positive correlation was observed between the pro-BNP levels and left MPI values (p<0,001).

Table 4. Fetal cardiac functional assesment.

	Control group (n=41)	ICP group (n=41)	P-Values
Aortic peak velocity (cm/s)	73,1 ± 18,7	72,6 ±16,6	0,792
Pulmonary peak velocity (cm/s)	67,5 ± 16,6	63,8 ±17,3	0,358
Left MPI	0,58 (0,42-0,91)	0,64 (0,40-1,02)	0,043
TAPSE (mm)	8,24 (4,48-12,30)	7,82 (4,70-12,00)	0,340
MAPSE (mm)	7,07 (3,70-12,30)	6,49 (4,00-10,70)	0,121
Tricuspit E/A	0,78 ±0,08	0,81 ± 0,09	0,169
Mitral E/A	0,77 ±0,08	0,73 ± 0,10	0,098
PR interval	123,5 ±15,6	127,1 ± 11,1	0,086

Data given as median (interquartile range), mean ± SD. ICP: İntrahepatic cholestasis of pregnancy, MPI: myocardial performance index, TAPSE: tricuspid annular plane systolic excursion, MAPSE: mitral annular plane systolic excursion.

Table 5. Correlation of cord blood pro-BNP values with MPI data.

	MPI	
	r value	p value
Pro-BNP	0,656	<0,001

Pro-BNP: pro-brain natriuretic peptide, MPI: myocardial performance index r, Correlation coefficient, Significant values (p<0,05).

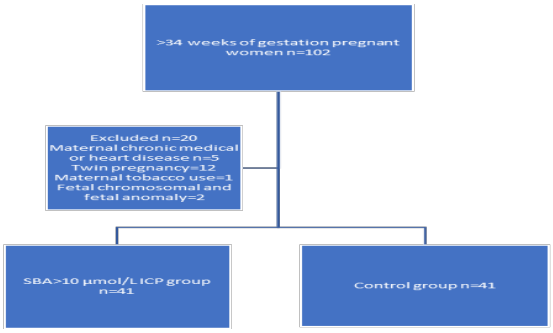
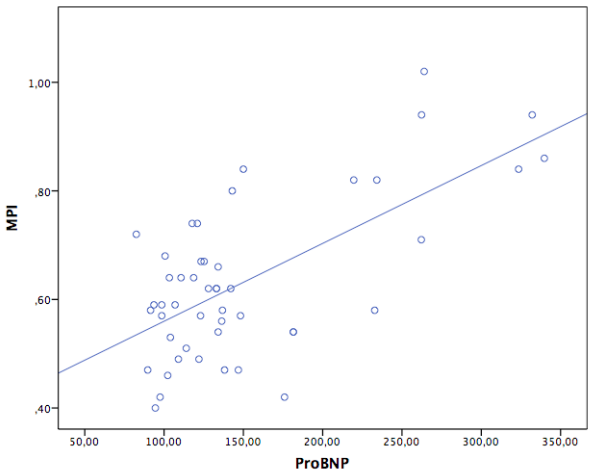


Figure 1. Flow diagram of study and control groups.



Discussion

In the current study, we investigated fetal cardiac function and morphology in women with ICP. We detected higher left MPI values and pro-BNP levels in the ICP group, indicating impaired cardiac function. Furthermore, we observed a positive correlation between the left MPI values and pro-BNP levels.

Patients with ICP are considered to have a high-risk pregnancy, and ICP is associated with obstetric complications even caused by IUFD (intrauterine fetal demise)2,4. The etiology of IUFD is speculative, as studies have failed to prove its association with chronic hypoxia, and it is considered a sudden event2,11. In addition, clinical evidence suggests that IUFD is associated with the alteration of cardiac events7,8,15. Kotake et al. reported that bile acids affect the sinoatrial node by suppressing the nodal action potentials15. A prolonged fetal mechanical PR interval has been demonstrated in the fetuses of mothers with ICP14. Furthermore, a positive correlation has been shown between fetal PR interval and disease severity16. In our study, the PR interval was higher among the ICP group than in the control group, but the difference observed was not significant. However, we found an impairment in cardiac function. ICP is not only associated with fetal cardiac arrhythmias but it also causes increased myocardial and contractile complications14,17,18. Ozel et al. evaluated 40 women with ICP and 40 healthy controls. They observed ventricular dysfunction with high left MPI values

in the ICP group and found higher left MPI values related to adverse perinatal outcomes18. Sansal et al. observed higher left ventricular modified MPI (mod-MPI) values and lower E/A ratio values among the ICP group than the control group17. In the present study, there are no significant differences in the mitral and tricuspid E/A ratios between the two groups. However, similar to other studies, we observed higher left MPI values among the ICP group. As fetal cardiac complications are considered the main pathology behind higher intrauterine fetal demise rate in ICP, higher MPI values showing both systolic and diastolic dysfunction may be important in the assessment of fetal well-being in these cases12. Fan et al. evaluated fetal cardiac function using different imaging techniques (e.g., velocity vector imaging), and the results are indicative of cardiac impairment8. The left ventricular longitudinal, systolic, and diastolic strain rates were significantly lower in the fetuses of patients with severe cholestasis compared to the controls. Furthermore, NT-proBNP (N-terminal pro-BNP) levels were significantly higher in the fetuses of the patients with ICP than the controls in the mentioned study8. Fetuses with congenital heart defects and intrauterine growth restriction have elevated circulating NT-proBNP levels, especially when abnormal Doppler indices are present. N-terminal proBNP has been used as an early indicator of intrauterine cardiovascular dysfunction and cardiac remodeling in some studies19,20. Markers such as pro-BNP, NT-proBNP, and cardiac troponin I in the umbilical cord blood were also used to evaluate heart failure and left ventricle systolic dysfunction8,9,21. In several studies, the umbilical cord blood concentrations of troponin I and NT pro-BNP were higher in the ICP fetuses8,21. Also, Zhang et al. observed a positive correlation between the concentrations of troponin I in the umbilical cord blood and fetal left ventricle MPI21. Among patients with obstructive jaundice, Padillo et al demonstrated that elevated BNP levels are associated with myocardial dysfunction. Internal biliary drainage not only reduces BNP levels but also improves cardiac function22. Similarly, we observed higher pro-BNP levels among the ICP group than in the control group, and we found a positive correlation between pro-BNP levels and left MPI values. The present study supported the possible fetal cardiac impairment in ICP cases with both ultrasonographic and biochemical markers. To the best of our knowledge, this is the first study in the literature evaluating the MPI values and cord blood pro-BNP levels in ICP. We acknowledge that this study has limitations. Firstly, cord NT-proBNP samples were not collected at the time of diagnosis, so the fetal cardiac function was compared with postnatal cord NT-proBNP in cases of ICP. There may be a difference between the cord NT-proBNP values at the time of diagnosis and the values measured after delivery. Secondly, our sample size was small because the study was planned at a single center. On the other hand, the strength of our article is the prospective design of the study. In addition, we evaluated the level of cord NT-proBNP and evaluated fetal cardiac function in all cases.

Conclusion

Functional assessment of the fetal heart reflects fetal well being. Our study with ultrasonographic findings and biochemical data seems to support this situation. Future studies with a larger population may guide physicians for the timing of delivery in pregnancies complicated with ICP. Moreover, earlier detection of fetal cardiac dysfunction may decrease adverse pregnancy outcomes in this specific patient group.

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Concept: RD, DŞ, AT, BS, NF, ET, KE, NY, EC
Design: ET, RD, AT, DŞ
Data collecting: BS, NF, ET, RD
Experiments and procedures; RD, DŞ, AT, ET
Writing of article: RD, ET, DŞ, AT

Disclosure statement

No potential conflict of interest was reported by the authors

Data availability statement

The data set that was created during the study is not publicly available. However, suggestion for data analysis can be made to corresponding author.

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RESEARCH ARTICLE

Association Between Serum HMGB-1 (High Mobility Group Box-1) Levels and Clinical Course in Patients With COVID-19

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Abstract

Introduction: We aimed to investigate the relationship between serum HMGB-1 levels and the clinical course of COVID-19 disease. **Methods:** A total of 86 patients, 43 patients in each group, were included in the study. According to the Ministry of Health's COVID-19 Diagnostic Guide, patients were divided into 2 groups as mild/moderate pneumonia and severe pneumonia. In addition to routine tests, blood samples were taken for serum HMGB-1 level analysis. At the time of blood draw, all patients were within the first 14 days of symptom onset. **Results:** HMGB-1 (High mobility group box protein 1) level of the patients in the mild Covid-19 pneumonia group was 4233.84 pg/ml, and the serum HMGB-1 level of the patients in the moderate-severe pneumonia group was 4804.35 pg/ml. There was no significant difference between the two groups (P=0.146). **Conclusion:** We did not find a significant difference between the two groups in blood samples taken in the first 14 days from the onset of symptoms in COVID-19 patients.

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Introduction

The new type of coronavirus, which emerged in Wuhan, China in December of 2019, spread rapidly around the world. COVID-19 can cause a wide clinical picture of disease ranging from self-limiting upper respiratory tract disease to severe pneumonia, multi-organ failure and death.[1] Current studies show that hyper inflammation, also known as cytokine storm, which is characterized by high levels of pro-inflammatory cytokines, is the main cause of high morbidity and mortality seen in COVID-19.[2]

High mobility group box protein 1 (HMGB-1) is a non-histone chromosomal protein.[3] HMGB-1 is involved in critical biological processes such as transcription, replication, repair and recombination by binding to DNA.[3] It is known that HMGB-1 is a strong activator of TLR 4 mediated pro-inflammatory cytokine release in COVID-19 infection.[2]

In this study, we aimed to investigate the relationship between serum HMGB-1 levels and the clinical course of COVID-19 disease.

Meterial and Method

Study Population

This study was designed as a prospective, cross-sectional single center study. Patients between the ages of 18-80 who were hospitalized with COVID-19 in Ankara City Hospital Internal Medicine Clinic and Internal Medicine Intensive Care Unit were enrolled in the study. Covid-19 infection of the patients was confirmed by RT-PCR. A total of 86 patients, 43 patients in each group, were included in the study. According to the Ministry of Health's COVID-19 Diagnostic Guide, patients were divided into 2 groups as mild/moderate pneumonia and severe pneumonia. In addition to routine tests, blood samples were taken for serum HMGB-1 level analysis. At the time of blood draw, all patients were within the first 14 days of symptom onset. Before starting treatment, blood samples were taken from patients who received pulse steroid therapy during their hospitalization.

Patients with chronic restrictive or obstructive pulmonary disease, patients with chronic renal failure with eGFR <60 ml/min, patients with type I and II diabetes mellitus, patients with known active or previous malignancy, and those with autoimmune disease were not included in the study.

Mild/moderate COVID-19 pneumonia was defined as respiratory rate <30/min, oxygen saturation in room air (SpO2) >90%, and mild/moderate pneumonia findings on chest X-ray or chest CT-scan. Severe COVID-19 pneumonia was defined as tachypnea (≥30/min), SpO2 level ≤90% in room air, and bilateral diffuse pneumonia findings on chest X-ray or chest CT-scan.

Demographic (age and gender), clinical characteristics and laboratory findings (symptoms and results) of the patients were recorded from the patient files. Radiological evaluation included radiography and computed tomography.

Ethical approval for the study was granted by the Ethics Committee of Ankara City Hospital (Date: 16/12/ 2020, Number: E2-20-54).

Biochemical Analysis

Blood samples were collected for each participant in the morning after at least 8 hours of night fasting. Blood samples were collected in tubes containing ethylenediamine tetraacetic acid for whole blood analysis. Biochemical parameters (glucose, urea, creatinine, sodium, potassium, alanine transaminase, aspartate transaminase, ferritin, fibrinogen, interleukin-6 (IL-6), c-reactive protein (CRP) and procalcitonin were measured using standard laboratory techniques.

Serum Hmgb-1 Level Measurement

For HMGB-1 level measurements, blood samples were allowed to clot in room air for 30 minutes and then centrifuged at 1700 g for 10 minutes to separate serum and plasma. Serum samples were stored at -80°C until the day of analysis. After sampling was completed, serum HMGB-1 level was measured by the same technician in the same laboratory.

HMGB-1 level measurements were performed in accordance with the manufacturer's instructions by Human HMGB-1 (High Mobility Group Protein B1) ELISA (Elabscience Biotechnology Inc, Houston, Texas, USA; Catalog No: E-EL-H1554 96T, LOT number: SVYW14WA6Q) 96 test kit. The sensitivity of the HMGB-1 kit was .6 pg/ml, the intra-assay coefficient of variation (CV) was <10%, and the inter-assay CV <10%. The measurable range was 31.25–2000 pg/ml.

RT-PCR Covid 19

Swab and sputum samples were obtained from upper respiratory tract (nose and throat). SARS-CoV-2 RNA detection was performed in Ankara City Hospital Clinical Microbiology Laboratory using Bio Speedy Bioeksen COVID19 RT-qPCR diagnostic kit (Istanbul, Türkiye) and Coronex COVID-19 RT-qPCR diagnostic kit.

Statistical Analysis

Statistical evaluation was performed using the Statistical Package for Social Sciences (SPSS) for Windows 22 (IBM SPSS Inc., Chicago, IL) program. The normality of data distribution was evaluated by Kolmogorov–Smirnov test. Normally distributed numerical variables were expressed as mean ± standard deviation, while numerical variables not showing normal distribution were expressed as median (quartiles 25–75). Categorical variables were expressed as numbers and percentages. Chi-Square and Fisher's exact test were used in comparison of categorical data. Student's t-test was used to compare normally distributed numerical variables according to the severity of pneumonia, and the Mann– Whitney U test was used to compare numerical variables that did not show a normal distribution. The distribution of the HMGB1 levels among 2 groups was evaluated with the Kruskal–Wallis H test. The relationship between HMGB1 levels and numerical variables was examined using Pearson Correlation Analysis. In statistical analysis, confidence interval (CI) was 95% and significance as 2 tailed $P < 0.05$.

Results

86 patients were enrolled in the study. 43 patients were in mild-moderate pneumonia group, 43 patients were in the severe pneumonia group. 59 (68.6%) patients were male and 27 (31.4%) were female (Mean ages were 54.7 ± 14.9 for male patients and 59.7 ± 17.4 for females). The mean age for all patients was 56.3 ± 15.8. The two groups were similar in terms of age and gender. The clinical parameters (Table-1) and laboratory findings (Table-2) of the patients are shown below.

While fatigue, fever, cough, and shortness of breath were common symptoms in patients, loss of taste and smell and chest pain were less common. While the mean hospital stay was 11 days in all patient groups, it was 9 days in mild pneumonia patients and 14 days in moderate-severe pneumonia group ($p<0.001$).

Favipiravir and enoxaparin were given as treatment to all patients in both groups during their hospitalization. Pulse steroid was given to 7 of the mild-moderate pneumonia patients for 3 days, while 22 of the severe pneumonia patients were given pulse steroids ($p<0.001$).

During the 28-day follow-up, the mortality rate was 2.5% (n = 8). No significant relationship was found between HMGB-1 levels and 28-day survival (P = .308).

Table1. Demographic Characteristics and Distribution of Clinical Findigs and Treatment According To the Severity of Pneumonia

Variables	Entire population (n:86)	Mild-Moderate Pneumonia(n=43)	Severe Pneumonia (n=43)	P value
Clinical Findings				
Age (Years)	56,3 ± 15,8	51,51 ± 15,04	61,16 ± 5,3	<0,001*
Female n(%)	59,7 ± 17,4	15 (17,4)	12(13,9)	0,043
Male n(%)	54,7 ± 14,9	28(32,5)	31(36,2)	
Comorbid diseases, n(%)				
Hypertension	43(50)	17(41,9)	26(59,1)	0,061
Coronary artery disease	7(8,1)	1(2,3)	6(14)	0,320
High flow-reservoir mask, n(%)				
Present	15(17,4)	-	15(34,8)	0,999
Absent	71(92,6)	43(50)	28(65,2)	0,040*
Oxygen therapy, n(%)				
Present	43(50)	-	43(100)	,999
Absent	43(50)	43(50)	-	,999
Symptoms, n(%)				
Weakness, loss of appetite	25(29,1)	12(27,9)	13(30,2)	<0,001*
Fever	43(50)	18(41,9)	25(58,1)	,0210
Cough	43(50)	14(32,6)	29(67,4)	0,043*
Shortness of breath	48(55,8)	14(32,6)	34(79,1)	0,610
Loss of taste/smell	19(22,1)	11(25,6)	8(18,6)	0,530
Chest pain	9(10,5)	2(4,7)	7(16,3)	0,999
Treatment n(%)				
Favipiravir	86 (100)	43 (100)	43 (100)	
Enoxaparin	86 (100)	43 (100)	43 (100)	
Prednol	46 (53,5)	14 (30,4)	32(74,4)	<0,001*
Pulse Steroid	29 (33,7)	7(16,3)	22 (51,2)	<0,001*
Antibiotic	68 (79,1)	26 (60,5)	42 (97,7)	<0,001*
28-day survival, n(%)				
Dead	8 (2,5)	2 (4,5)	6 (14)	<0,001*
Alive	78 (97,5)	41 (95,5)	37 (86)	

Numerical variables were expressed as mean ± standard deviation or median (min–max).
Categorical variables were expressed as number (%).
*p<.05 was considered statistically significant.

RT-PCR was positive for all patients. The serum HMGB-1 level of the patients in the mild Covid-19 pneumonia group was 4233.84 pg/ml, and the serum HMGB-1 level of the patients in the moderate-severe pneumonia group was 4804.35 pg/ml. There was no significant difference between the two groups (P=0.146).

IL-6 serum level was measured as 8.43 pg/ml in mild-moderate pneumonia patients, while it was measured as 30 pg/ml in severe pneumonia patients ($p<0.001$).

We did not detect any correlation between HMGB-1 and serum CRP, IL-6, ferritin and procalcitonin. We found a positive correlation between HMGB1 and leukocyte and lymphocyte counts.

Table 2. Laboratory Findigs According to the Severity Of Pneumonia

Variables	Entire population (n:86)	Mild-Moderate Pneumonia (n=43)	Severe Pneumonia (n=43)	P value
Laboratory Findigs				
Leukocytes (103/µL)	8,1 (1,56 -20,92)	6,2 (1,56 – 17,11)	9,31 (4,1 – 20,9)	P<0,001*
Neutrophils (103/µL)	6,6 (0,93 – 18,24)	3,58 (0,93 – 15,89)	8,58 (3,15 – 18,24)	P<0,001*
Lymphocytes (103/µL)	0,81 (0,2 – 3,3)	1,08 (0,29 – 3,3)	0,66 (0,2 – 2,36)	P<0,001*
Hemoglobin (g/dL)	13,35 ± 1,67	13,56 ± 1,38	13,14 ± 1,9	P=0,253
Thrombocytes (103/µL)	229 (108 -512)	212 (108 – 471)	274 (116 – 512	P<0,001*
Neutrophil/Lymphocyte Raito	7,7 (0,32 -72,4)	3,46 (0,32 - 25,22)	14,6 (1,4 – 72,4)	P<0,001*
Urea (mg/dl)	39 (13- 128)	32 (21 – 66	48 (13 – 128)	P<0,001*
Creatinine (mg/dl)	0,81 (0,32 – 1,37)	0,82 (0,47 – 1,14)	0,79 (0,32 – 1,37)	P=0,588
Albumin (g/dL)	38,1 ± 5,05	40,63 ± 4,2	35,7 ± 4,6	P<0,001*
CRP (g/L)	38,5 (1 – 195)	31 (1 – 185)	62 (1 – 195)	P<0,001*
INR	1 (0,8- 2,5)	1 (0,8 – 2,5)	1,1 (0,9 – 1,5)	P=0,253
D-Dimer (mg/L)	0,6 (0,19 – 4,53)	0,4 (0,19 – 2,2)	0,87 (0,19 – 4,53)	P<0,001*
Fibrinogen (g/L)	5,08 ± 1,57	4,42 ± 0,43	5,7 ± 1,59	P<0,001*
Ferritin (µg/L)	414 (9,68 – 1820)	238,5 (21 – 1412)	590 (9,6 – 1820)	P<0,001*
HMGB-1 (pg/ml)	4519,09 ± 1815,8	4233,84 ± 1589,5	4804,35 ± 1994,9	P=0,146
IL-6 (pg/ml)	12,15 (3,2 – 680)	8,43 (3,53 – 87)	30 (3,2 – 680)	P<0,001*
Hospitalization (day)	11 (3 -85)	9 (3 – 42)	14 (5 – 85)	P<0,001*
Symptom duration (day)	9 (1-14)	8 (1 -14)	10 (2- 14)	P<0,001*

Numerical variables were expressed as mean ± standard deviation or median (min–max). Categorical variables were expressed as number (%). *p<.05 was considered statistically significant. CRP: C-reactive protein, IL-6: Interleukin-6, INR: International normalized raito, HMGB-1: High mobility group box-1

Discussion

COVID-19 is a life-threatening viral infection in which the host has an abnormal response to SARS-CoV-2, which is closely associated with sepsis and septic shock.[4] Therefore, it is necessary to elucidate the pathogenesis and develop new treatments. HMGB-1 is a nuclear protein involved in the process of DNA repair and replication.[5] HMGB-1 stimulates cytokines by specific secretion from immune cells such as monocytes, macrophages and dendritic cells.[6] Excessive HMGB1 expression is associated with tissue damage as in ischemia and sepsis.[7] Various pathogens, such as bacterial and viral infections, can induce passive release of HMGB-1, leading to the release of proinflammatory cytokines and critical systemic inflammation.[8] In studies, high HMGB-1 serum levels have been reported in COVID-19 patients.[9] HMGB-1 activates signaling pathways such as JAK/STAT1 and MAPK by binding to its receptors on the cell surface, especially RAGE (receptor for advanced glycation endproducts) and TLRs (Toll like receptor). Activation of these signaling pathways has been associated with various inflammatory processes and cell apoptosis.[10] Din et al. reported that HMGB-1 is released from dead or damaged virus cells and it is necessary to work on treatments that will reduce HMGB-1 release in viral infections.[11] Musumeci et al. concluded that HMGB1 inhibitors, which would prevent the HMGB1-RAGE interaction, could be used in the treatment of viral infections.[12] In this study, we aimed to examine the relationship between COVID-19 disease and serum HMGB-1 levels. We included patients who did not need oxygen during their hospitalization in the mild COVID-19 pneumonia group. Patients who needed oxygen at or during hospitalization, were given oxygen by nasal cannula or mask depending on the course of the disease, or were connected to a high flow device were included in the moderate-severe COVID-19 pneumonia group. When we examined the serum samples taken in the first 14 days of the onset of COVID-19 symptoms, we concluded that serum HMGB-1 levels were high in COVID-19 patients. However, we did not find a significant difference between the patients in the mild-moderate pneumonia group and the patients in the severe pneumonia group (p=0.146). In previous studies, increased HMGB1 levels have been reported in COVID-19 patients.[13-15] In a ret-

rospective study conducted by Chen et al., it was reported that serum HMGB-1 level was high in intensive care unit patients and it was associated with high mortality.[14] It has been shown by Vogel et al. that HMGB-1 induces micro-thrombi with platelet activation and is a critical molecule in thrombosis formation.[16] It is thought that thrombi originating from HMGB-1 may affect the prognosis by causing severe COVID-19 pneumonia.[17] In our study, D-dimer levels differed significantly between the two groups (p=0.012). There was a positive correlation between serum HMGB-1 and D-dimer levels. Recent studies have determined that inflammatory molecules such as IL-6 have a role in acute respiratory failure and acute lung injury.[18] Chen et al. stated in their study that IL-6 causes cytokine release syndrome in Covid-19 patients.[19] Some studies have shown that elevated IL-6 levels and lymphopenia may be associated with impaired lymphocyte cytotoxicity.[20] In a study conducted in Germany, it was observed that the need for mechanical ventilation increased in patients with IL-6 > 80 pg/mL.[21] In our study, when mild-moderate pneumonia patients were compared with severe pneumonia patients, we found a significant difference between IL-6 serum levels. IL-6 levels were observed as 30 pg/dl in patients receiving oxygen support or connected to a high-flow device. The main limitations are the small number of patients, the fact that it is a cross-sectional study, and the course of the HMGB-1 level cannot be followed throughout the disease, the patients have not been screened for malignancy, whether there is a malignancy that has not yet been detected, and the fact that the baseline lung capacity is not known. The strengths of our study are that it is a prospective study, the duration of symptoms was similar in both groups, and the 28-day survival of the patients was included in the study. As a result, we did not find a significant difference between the two groups in blood samples taken in the first 14 days from the onset of symptoms in COVID-19 patients. Due to the limitations mentioned above, more comprehensive studies are needed.

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RESEARCH ARTICLE

Eosinophilia Due To Famotidine Use In COVID-19 Patients

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Abstract

Introduction: Famotidine has been suggested as a potential treatment for coronavirus disease 2019 (COVID-19). We compared the incidence of COVID-19 outcomes (i.e. death and need for oxygen therapy or intensive service use) among hospitalized patients who received famotidine therapy and those who did not. **Methods:** We conducted a retrospective cohort study using data from COVID-19 Ankara Bilkent City Hospital electronic health records. The study population was COVID-19 hospitalized patients aged 18 years or older. **Results:** A total of 99 patients, 52 male and 47 female, aged between 20 and 93, were included in the study. All patients received standard of care (SOC) medications (favipiravir, hydroxychloroquine, low molecular weight heparin, acetylsalicylic acid or dipyridamole). 63 patients received famotidine treatment.36 patients did not receive famotidine.47 patients had decreased saturation and needed oxygen therapy. 38 patients who received famotidine needed anti-inflammatory treatment.There were 53 patients with fever, 49 with headache, 52 with dyspnea, 65 with cough, and 31 with decreased taste. Compared to the patients who were not treated with famotidine, the oxygen requirement was found to be lower in the patients treated with famotidine (p1: 0.001), but the eosinophil value increased after the treatment (p1: 0.025). While there were 10 patients who needed ICU (Intensive Care Unit), mortality developed in 8 patients. The mean hospital stay was 10.89±6.6 days. **Conclusıon:** According to our study, treatment with famotidine achieved a better clinical outcome compared to the control group in severe COVID-19 illness, although no significant survival benefit was found. The eosinophil level was found to be increased after treatment with famotidine.There are studies in the literature showing that eosinophilia increases thromboembolism. We do not recommend the use of famotidine treatment in patients with COVID-19 who have high eosinophil levels, as this may further aggravate the clinical picture in COVID-19 patients.

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Introduction

Coronavirus disease 2019 (COVID-19) is predominantly a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) that first arose in December 2019 in Wuhan, China. Continued optimization of medical therapy remains essential in combating COVID-19 [1].

Famotidine is a competitive histamine H2-receptor antagonist. Its main pharmacodynamic effect is the inhibition of gastric acid secretion [2]. In February 2020, a study by Wu et al., used computational methods to predict structures of proteins encoded by the SARS-CoV-2 genome in order to identify available drugs that may be repurposed to treat COVID-19 [3]. Famotidine was found to be a potential candidate that may inhibit 3 chymotrypsin-like protease (3CLpro), a viral enzyme necessary for SARS-CoV-2 viral replication. Subsequently, several studies have reported on the use of famotidine in treating COVID-19 patients [4,5]. Specifically, Freedberg et al. and Mather et al. found that in patients hospitalized with COVID-19, famotidine use was associated with a reduced risk of clinical deterioration leading to intubation or death [6,7].

In light of a potential beneficial therapeutic effect, the purpose of the present study was to examine the impact of famotidine on clinical outcomes in a COVID-19 hospitalized patients. We hypothesized that famotidine would be associated with improved clinical outcomes among hospitalized patients with COVID-19. To explore this, we performed a retrospective cohort study at a single center located at the epicenter of the COVID-19 pandemic in Türkiye.

Material and Methods

Study population

The study group for this report was derived from an electronic database collected at Ankara Bilkent City Hospital encompassing consecutive patients screened for COVID-19 between January 20, 2020, and July 13, 2020. All patients who tested positive for severe acute respiratory syndrome (SARS-CoV-2) by nasopharyngeal polymerase chain reaction and who required inpatient admission were included in this study. Ethical approval for the study was granted by the Ethics Committee of Ankara City Hospital (Date: 15.03.2023, Number: E2-23-3598). red with an ADVIA 1800 device (Siemens Healthineers, Germany) and a commercially available kit (Rel Assay Diagnostics, Gaziantep, Turkey).

Famotidine use

All patients received standard of care (SOC) medications (favipiravir, hydroxychloroquine, low molecular weight heparin, acetylsalicylic acid or dipyridamole).Patients were classified as receiving famotidine if they were treated with oral drugs on hospital admission. Famotidine use was extracted directly from the electronic medical record.

Baseline data and covariates

COVID-19 was diagnosed by nasopharyngeal polymerase chain reaction. Severe COVID-19 infection was defined as SpO2 < 94% in room air, ratio of partial pressure of oxygen and inspired air fraction (PaO2/FiO2) < 300 mm Hg, more than 50% involvement of lungs, and respiratory rate > 30 breaths/min.

Statistical Analysis

Statistical analysis was made by Statistical Package for Social Sciences version 25. The conformity of the variables to the normal distribution was examined by histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation, median, min-max values were used while presenting descriptive analyzes. Categorical variables were compared with the Chi-Square Test. The Mann Whitney U Test was used when evaluating non-normally distributed (nonparametric) variables between two groups. Repeated Measures Analysis was used to evaluate the change in measured values between groups. Cases with a P-value below 0.05 were considered as statistically significant results.

Results

A total of 99 patients, 52 male and 47 female, aged between 20 and 93, were included in the study. Of these, 63 received famotidine. 47 patients needed O2.There are 53 patients with fever, 49 patients with headache, 52 patients with dyspnea, 65 patients with cough, 31 patients with decreased taste. While there were 10 patients who needed ICU, mortality developed in 8 patients. The mean hospital stay was 10.89±6.6 days. Evaluation of symptoms, mortality and need for intensive care unit admission according to famotidine treatment is shown in Table 1-2.

Table 1: Symptoms,mortality,clinical and demographic characteristics according to famotidine treatment

		n	%
Gender	Male	52	(52,53)
	Female	47	(47,47)
Famotidine		36	(36,36)
Oxygen supplementation		47	(47,47)
Fever		53	(53,54)
Headache		49	(49,49)
Dyspnea		52	(52,53)
Cough		65	(65,66)
Taste disorders		31	(31,31)
Mortality		8	(8,08)
Intensive care unit admission		10	(10,10)

n: Number of patients

Urea, NLR, Eosinophil, WBC values are given in Table 2.

Table 2:

	n	%
Age	59,8±18,24	61 (20-93)
Urea 1 (mg/dL)	46,94±29,2	38,73 (13-167)
Urea 2 (mg/dL)	54,99±43,67	41 (17-338,12)
NLR 1	7,19±7,74	4,42 (0,96-51,5)
NLR 2	6,86±7,41	4,3 (0,89-45)
Eosinophil 1 (x10^9/L)	0,05±0,07	0,02 (0-0,35)
Eosinophil 2 (x10^9/L)	0,09±0,13	0,04 (0-0,8)
WBC 1 (x10^9/L)	7,39±3,58	7,16 (0,03-19,34)
WBC 2 (x10^9/L)	9,03±4,34	8,42 (0,09-24,1)
Hospital admission	10,89±6,6	9 (1-33)

n is replaced by mean±s.d,% is replaced by median (min-max).

WBC:White Blood Cell Count (x10^9/L)
NLR:Neutrophil to Lymphocyte Ratio
Urea1:Urea Value Before Treatment (mg/dL)
Urea2:Urea Value After Treatment (mg/dL)
NLR1: NLR Before Treatment
NLR 2:NLR After Treatment
Eos1:Eosinophil Value Before Treatment (x10^9/L)
Eos2: Eosinophil Value After Treatment (x10^9/L)
WBC1:WBC Before Treatment (x10^9/L)
WBC2:WBC After Treatment (x10^9/L)

Table 3: Evaluation of symptoms, mortality and need for intensive care unit admission according to famotidine treatment

		Famotidine				
		No		Yes		p[1]
		n	%	n	%	
Age		67±15,58	69,5 (25-93)	55,68±18,48	54 (20-91)	**0,002**
Gender	Male	22	(61,11)	30	(47,62)	0,196
	Female	14	(38,89)	33	(52,38)	
Oxygen supplementation		25	(69,44)	22	(34,92)	**0,001**
Fever		16	(44,44)	37	(58,73)	0,170
Headache		15	(41,67)	34	(53,97)	0,239
Dyspnea		20	(55,56)	32	(50,79)	0,648
Cough		28	(77,78)	37	(58,73)	0,055
Taste disorders		9	(25,00)	22	(34,92)	0,306
Mortality		5	(13,89)	3	(4,76)	0,109
Hospital admission		12,11±7,34	10 (4-32)	10,19±6,09	9 (1-33)	0,238
Intensive care unit admission		5	(13,89)	5	(7,94)	0,344

n: Number of patients

Pre-treatment Urea, Post-treatment Urea, Pre-treatment NLR values are lower in those taking famotidine, while Eosinophil level is higher after treatment. There was no significant difference between those who took famotidine and those who did not in terms of changes in Urea, NLR, Eosinophil, WBC values. Those who took famotidine were younger than those who did not. O2 need was found to be less in those taking famotidine. Evaluation of laboratory values before and after famotidine treatment is shown in Table 4.

Compared to the patients who were not treated with famotidine, the oxygen requirement was found to be lower in the patients treated with famotidine (p^1:0.001), but the eosinophil value increased after the treatment (p^1:0.025).

Table 4: Evaluation of laboratory values before and after treatment

	Famotidine					
	No		Yes			
	n	%	n	%	p¹	p²
Urea 1 (mg/dL)	63,99±36,43	53 (23-167)	37,19±18,27	32,1 (13-98)	0,001	0,216
Urea 2 (mg/dL)	78,43±61,68	59,46 (24-338,12)	41,59±19,11	34,4 (17-96)	<0,001	
NLR 1	7,24±4,51	6,22 (1,5-18,19)	7,17±9,13	3,37 (0,96-51,5)	0,022	0,058
NLR 2	9,35±10,24	5,46 (1,1-45)	5,44±4,67	3,5 (0,89-20,45)	0,062	
Eosinophil 1 (x10^9/L)	0,05±0,06	0,03 (0-0,2)	0,05±0,07	0,02 (0-0,35)	0,915	0,055
Eosinophil 2 (x10^9/L)	0,06±0,09	0,02 (0-0,46)	0,11±0,14	0,07 (0-0,8)	0,025	
WBC 1 (x10^9/L)	7,19±3,5	7,29 (0,03-15)	7,49±3,64	7,07 (0,8-19,34)	0,907	0,436
WBC 2 (x10^9/L)	8,37±4,64	7,78 (0,09-22,28)	9,41±4,14	8,53 (1,5-24,1)	0,234	

n is replaced by mean±s.d, % is replaced by median (min-max).
p¹:Difference between pre- and post-treatment laboratory values with famodin
p²:The value showing the relationship between famodin and the parameters before and after treatment
Urea 1:Urea Value Before Treatment (mg/dL)
Urea 2:Urea Value After Treatment (mg/dL)
NLR1:Neutrophil to Lymphocyte Ratio Before Treatment
NLR 2:Neutrophil to Lymphocyte Ratio (After Treatment
Eos1:Eosinophil Value Before Treatment (x10^9/L)
Eos2: Eosinophil Value After Treatment (x10^9/L)
WBC1:White Blood Cell Count Before Treatment (x10^9/L)
WBC2:White Blood Cell Count After Treatment (x10^9/L)

Discussion

The treatment of famotidine has been shown to reduce the need for oxygen in some studies.[6] In our study, the oxygen requirement was also found to be lower in patients who received famotidine. However, the lower mean age of the patients receiving famotidine was the limitation of our study. Also, the low number of patients and the evaluation of patients who were suitable for service follow-up at the time of diagnosis were the limitations of our study.We recommend that similar studies be conducted in patients with intensive care hospitalization.

In the study of Mather et al[7] and Pahwani et al[8] famotidine was shown to shorten the length of stay, but in our study, no significant difference was found between the length of stay. Again, in the study of Mather et al,[7] famotidine was shown to reduce mortality, but in our study, no significant difference was found between the effect of famotidine on mortality in COVID-19 patients and the length of stay of the patients.According to our study, there was no significant survival benefit among patients who received famotidine therapy and those who did not. Also no significant difference was observed between those who used famotidine and those who did not, in terms of the need for intensive care admission, but in the meta-analysis of Chiu et al. it was observed that the need for intensive care hospitalization was less among famotidine users.[9]

Although the neutrophil-lymphocyte ratio was shown as a critical determinant for the assessment of disease severity in COVID-19 patients,[10] we did not find a significant difference between the neutrophil-lymphocyte ratio in both groups in our study.However we thought that generalization would be wrong and further studies were needed on this subject.

There are several studies showing that the use of histamine H2 blockers causes hypersensitivity. It has been reported that ranitidine may be associated with eosinophilic myocarditis,[10] famotidine causes erythema together with eosinophilia.[11] However, more studies are needed on famotidine and other histamine H2 blockers. In addition, the link between hypereosinophilic syndrome and ischemic stroke has been shown, and there are studies in the literature indicating that secondary eosinophilia also causes thromboembolism[12-13] In our study, there was no significant difference between the groups that received and did not receive famotidine for the number of eosinophils before treatment, but a significant increase was observed in the number of eosinophils after famotidine treatment. The relationship between eosinophilia and thromboembolism secondary to famotidine use has been reported in previous studies.[11-12] In the literature review published by Zerangian et al., it was stated that there were many embolism cases in patients hospitalized due to covid and similar viral infections, although the reason is not clear.[14] Eventually, hospitalized patients infected with the viral diseases could mainly suffer from an anomalous risk of coagulation activation with enhanced venous

thrombosis events and poor quality clinical course. Since this situation may aggravate the clinical picture in hospitalized patients with viral infections, we suggest that the risk of thromboembolism should be taken into account when using famotidine as a treatment option in COVID-19 patients with high pre-treatment eosinophil values and other thromboembolism-related viral diseases. Although no thromboembolic event was observed in our study, we thought that an increase in eosinophilia would predispose to hypercoagulability. From this, we suggest that the relationship between eosinophil levels and thromboembolism in patients hospitalized for COVID-19 patients and viral infections and who had a thromboembolic event should be retrospectively examined. In our study, we did not observe an increase in mortality secondary to a thromboembolic event related to COVID-19. However, the limitation of our study was that we did not observe an increase in mortality due to the small number of patients.

As a result, it was observed that the use of famotidine could increase the number of eosinophils. Therefore, we recommend paying attention to the use of famotidine to reduce the risk of thromboembolic events secondary to eosinophilia in patients with high eosinophil count before treatment.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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RESEARCH ARTICLE

Agreement Analysis of the Magnetic Resonance Defecography and Clinical Examination Findings in the Evaluation of Pelvic Floor Disorders

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Abstract

Introduction: Pelvic floor disorders (PFD) are more frequently seen in women and impairs quality of life. The aim of this study was to find agreement between the clinical examination and magnetic resonance defecography (MRD) findings of female patients with PFD related symptoms and to discuss the findings of MRD in PFD. **Methods:** Seventy-six female patients with complaints of PFD and undergone MRD were included in the study. The pubococcygeal line was used as the reference line for pelvic organ prolapse evaluation in MRD. MRD and clinical examination findings were compared. **Results:** Agreement between the MRD and clinical examination findings concerning the presence of cystoceles, rectoceles, entero/peritoneocele was 75%, 50%, and 60.52% respectively. However, the agreement was weaker in terms of pelvic organ prolapse grading (44% for cystoceles, 32% for rectoceles). Since there was no uterine prolapse detected on clinical examination an agreement test for uterine prolapse could not be performed. **Conclusion:** MRD is complementary to clinical examination in terms of its ability to comprehensively evaluate all compartments simultaneously. MRD provides additional information to the clinical examination in patients with symptoms related to PFD and should be utilized, in symptomatic cases, if the clinical examination findings are negative or if multicompartmental pathologies are suspected.

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Introduction

Pelvic floor disorders (PFD) include pelvic organ prolapse (POP), urinary incontinence (UI), obstructed defecation, and fecal incontinence.[1] PFD affect daily life causing a variety of symptoms such as pelvic pain, incontinence, constipation, sexual dysfunction, and perineal palpable mass.[2-4] PFD are 3-7 times more common in women than men.[5] Risk factors include advanced age, high body mass index, chronic increase in intra-abdominal pressure, genetics, race, connective tissue diseases, previous pelvic surgery, multiparity, and vaginal birth.[1,6] In the United States, the number of women presenting with at least one of the PFD was 28.1 million in 2010 and it is estimated to increase to 43.8 billion by 2050.[7] The high prevalence of PFD has led it to be labeled a "secret epidemic".[8] In the literature, the reoperation rates for UI and POP range from 17% in the general population to 43-56% in tertiary centers.[9-11] Although the reason for the failure of surgical treatment is not fully understood, it may be related to sole reliance on clinical examination for evaluation of prolapse. Magnetic resonance defecography (MRD) allows the complex, multiplanar, and multiparametric evaluation of the pelvic floor structures and pelvic organs in a single examination without using ionizing radiation, and provides both anatomical and functional information in a non-invasive way.[12] The aim of this study was to find agreement between the clinical examination and MRD findings of female patients with PFD-related symptoms and to discuss the findings of MRD in PFD.

Material and Methods

This study was designed as a prospective, cross-sectional observational study. The institutional review board approval was taken (Date:6.3.2013, File number:4113) before the study. The female patients, over 18 years of age who presented to gynecology outpatient clinics with PFD complaints (like incontinence, constipation, incomplete evacuation, sexual dysfunction, and perineal palpable mass, etc) and underwent dynamic MRD between March 2013 and May 2014 in our department were listed. Patients who had artifacts on MRD images that made evaluation impossible and those who could not complete the MRD were excluded from the study. Patients who did not have clinical examination results were also excluded. Seventy-six female patients who met the criterias were included in the study. The clinical staging of POP was performed by the gynecologist (FFD), using Baden–Walker halfway grading system that consists of four grades: grade 0 – no prolapse, grade 1 - halfway to hymen, grade 2 – to hymen, grade 3 – halfway past hymen, grade 4 –maximum descent.[13] Clinical examination results were recorded.

MRD procedure

The MRD procedure was explained to the patient and an informed consent form was obtained from the patients. Patient was directed to urinate 1 hour before the MRD appointment time. The patient was positioned in the right decubitus position on the MR table. Ultrasound gel was used to better examine the vaginal and rectal walls and to facilitate evacuation. The jelly was given by using a 50 cc syringe and 20/22 gauge catheter, approximately 30-50 ccs to the vagina and approximately 150-250 cc to the rectum until stimulation of evacuation. The patient was rolled into the supine position, and a supporting pillow was placed under the legs to bend the knees at an angle of approximately 45° to facilitate evacuation.

Imaging was performed with a 1.5T MRI machine (Signa HDi, GE Medical Systems, Milwaukee, Wisconsin, USA). An eight-channel phased-array coil was placed over the pelvic region. After resting axial, sagittal, coronal T2-weighted fast spin-echo (T2W FSE) and axial, and coronal Fast Imaging Employing Steady State Acquisition (FIESTA) sequences, dynamic scanning was initiated. Dynamic imaging was obtained by repeated acquisitions (3-second rate of each image acquisition) through a midline sagittal plane during rest, squeeze, and defecation. In case of a suspicion of prolapse and a patient who performs inadequate Valsalva maneuver or evacuation, dynamic post-defecation straining images in the sagittal, coronal and axial plane were obtained to take additional clues for diagnosis. Before the procedure was finalized, the images were evaluated by the radiologist (EÇ) and additional images were taken if necessary.

Image analysis

The image analysis was performed on a remote workstation (Advantage Windows, version 4.3;

GE Medical Systems) by two radiologists with consensus who were unaware of clinical examination. A dedicated read was performed for the research study.

The resting images were evaluated in terms of the morphology and configuration of the puborectal and iliococcygeus muscles, urethral ligaments, and the appearance of the vagina, posterior wall of the bladder. The integrity of the anal sphincter was also evaluated.

In the sagittal dynamic images, a pubococcygeal line (PCL) was drawn extending from the inferior border of the symphysis pubis to the last sacrococcygeal joint to be used as a reference line in the evaluation based on the 'three-compartment model'.[14] An enterocele, sigmoidocele, peritoneocele was defined as descensus or herniation of the small bowel or peritoneal cul- de sac or sigmoid colon below the PCL.[15-17] The reference points were the inferior border of the bladder base for the anterior compartment, the uterine cervix or the vaginal apex (for hysterectomized patients) for the middle compartment.[18] Presence of organ prolapsus, rectocele, entero-peritoneocele, sigmoidocele, and rectal intussusception/prolapse were evaluated and the presence, if any, cystocele, uterus prolapse and rectocele was graded. The grading was performed using the image obtained from the midsagittal region during maximum straining/defecation that showed the maximum organ descent. For cystocele and uterus prolapsus an organ descent of ≤3 cm was graded as mild (grade I), 3-6 cm as moderate (grade 2), and >6 cm as severe (grade 3).[19] A rectocele was defined as any rectal protrusion extended line of the anterior border of the anal canal.[20] Rectocele ≤ 2 cm was graded as small (grade I), [2-4] cm as moderate (grade 2), and > 4 cm as severe.[20]

Statistical analysis

The analysis of the data was performed using SPSS for Windows version 15. The descriptive statistics were expressed as mean ± standard deviation for normally distributed variables, as median (min-max) for variables with a non-normal distribution, and as the number of cases and percentage (%) for nominal variables. The nominal variables were assessed by Pearson's chi-square or Fisher's exact test. During the examination of the relationship between the continuous variables, Spearman's correlation test was used when the distribution was not normal, and the Pearson correlation test was utilized when it was normal. In order to compare the agreement between the clinical examination and MRD findings, the Cohens's kappa coefficient (κ) and significance were calculated. Values of κ as measurement of agreement were categorized as no agreement (κ<0.20), minimal (κ=0.21-0.39), weak (κ=0.40-0.59), moderate (κ =0.60-0.79), strong (κ=0.80-0.90), and almost perfect agreement (κ>0.90).21 The results were considered to be statistically significant if p was <0.05.

Results

Seventy-six patients participated in the study. All of the patients were female and the mean age was 46 +/- 11.8 years. Table 1 presents pathologic findings identified in the clinical examination of patients. Table 2 presents pathologic findings detected in the dynamic MRD of the patients. Sixty-two (82%) of the 76 patients had pathologic clinical examination findings, but 14 (18%) had complaints of PFD but no clinical examination findings. In 2 of 14 patients, no POP was detected on MRD while 12 patients had pathologic findings. MRD findings of patients with no clinical examination findings for POP were shown in Table 3.

Table 1: Pathologic findings detected in clinical examination of patients.

	Clinical Examination Findings	Number of Patients n (%)
Cystocele	Grade I	25 (32.89)
	Grade II	19 (25)
	Grade III	4 (5.26)
	Total	48 (63.15)
Entero/Peritoneocele		3 (3.94)
Rectocele	Grade I	16 (20.51)
	Grade II	15 (19.73)
	Total	31 (40.78)

The data were given as n (%)

Table 4 and Table 5 present the percentages of agreement between the MRD and clinical examination findings in terms of the presence of

Table 2: Pathological findings detected in the Dynamic MRD.

	MRD Finding	Number of Patients n (%)
Cystocele	Grade I	39 (51.31%)
	Grade II	25 (32.89%)
	Grade III	1 (1.31%)
Uterine prolapse	Grade I	24 (31.57%)
	Grade II	8 (10.52 %)
Entero/Peritoneocele		33 (43.42%)
Rectocele	Grade I	23 (30.26%)
	Grade II	44 (57.89%)
Rectal prolapse		23 (30.26%)
Rectal descent		
	Mild (< 3cm)	21 (27.63%)
	Moderate (3-6 cm)	31 (40.78%)
	Severe (> 6 cm)	24 (31.57%)

The data were given as n (%)

cystoceles, and rectoceles, and POP grading, respectively. Since uterine prolapse (UP) was not detected in clinical examination, an agreement test was not applicable to this condition. Although none of the patients had UP according to clinical examination, grade I in 24 patients (32.4%) and grade II in 7 patients (9.5%), UP was detected in the MRD. Furthermore, it was observed that as the severity of the cystocele or rectocele revealed by MRD increased, the grading of UP also increased (p=0.01 / 0.03 and r=0.662 / 0.249, respectively).

Table 3: MRD findings of patients with no clinical examination findings for pelvic organ prolapse.

		MRD Findings Uterine		
Patient	Age	Cystocele Grade	Uteri Prolapse Grade	Rectocele Grade
1	62	1		1
2	32	1		2
3	30			1
4	39	1		1
5	25	1		1
6	33			1
7	51	1		
8	55	2	2	2
9	59	1	1	2
10	43	1	1	2
11	46			2
12	56			2

Table 4: Results of agreement between the MRD and clinical examination findings concerning the presence of cystoceles, rectoceles, and entero/peritoneocele

		Dynamic MRD		Agreement	Disagreement	Kappa* (κ)	p**
		negative	positive	%	%		
Cystocele							
Clinical Examination	Negative	10	18	75%	25%	0.385	**< 0.001**
	Positive	1	47				
Entero/ peritoneocele							
Clinical Examination	Negative	43	30	60.52%	39.47%	0.102	**0.044**
	Positive	0	3				
Rectocele							
Clinical Examination	Negative	8	37	50%	50%	0.123	0.054
	Positive	1	30				

* Cohen's kappa (κ) coefficient; no agreement (κ<0.20), minimal (κ=0.21-0.39), weak (κ=0.40-0.59), moderate (κ =0.60-0.79), strong (κ=0.80-0.90), and almost perfect agreement (κ>0.90).21
** p<0.05 was considered statistically significant.

Seventy-two of the 76 patients (94.7%), we observed pathologies in MRD involving a compartment that had not been covered by clinical examination. Of the 23 patients that were referred to the clinic with a pre-diagnosis of a cystocele accompanied by a rectocele, 18 (78.2%) out of 23 patient had additional pathologies involving the middle compartment in MRD (UP in 3 cases, entero/peritoneocele in 2 cases and UP+entero/peritoneocele in the remaining 13 patients).

Table 5: Results of agreement between the MRD and clinical examination findings concerning cystocele and rectocele grading

		MRD grade				Agreement %	Kappa (κ)*	p**
		0	1	2	3			
Cystocele								
Clinical Examination	0	10(90.9%)	16(41.02%)	2(8%)	0(0%)	44.74	0.205	0.004
	1	1(9.09%)	13(33.33%)	11(44%)	0(0%)			
	2	0(0%)	9(23.07%)	10(40%)	0(0%)			
	3	0(0%)	1(2.56%)	2(8%)	1(100%)			
Rectocele								
Clinical Examination								
	0	8(88.88%)	18(78.26%)	19(43.18%)	-	32.89	0.108	0.058
	1	0(0%)	4(17.39%)	12(27.27%)	-			
	2	1(11.11%)	1(4.34%)	13(29.54%)	-			

* Cohen's kappa (κ) coefficient; no agreement (κ<0.20), minimal (κ=0.21-0.39), weak (κ=0.40-0.59), moderate (κ =0.60-0.79), strong (κ=0.80-0.90), and almost perfect agreement (κ>0.90).21
** p<0.05 was considered statistically significant.

Post-defecation straining images gave additional remarkable MRD findings. Figure 1 and Figure 2 demonstrate UP and peritoneocele detected only in post-defecation images taken during straining.

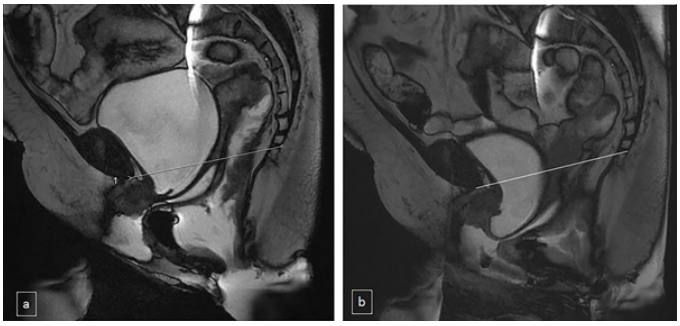

Figure 1: The MRD images of a 61-year-old patient presenting with the complaint of incontinence and a grade II cysto/rectocele in the clinical examination: a) defecation and b) post-defecation straining images. The white line in a and b is pubococcygeal line. The post-defecation image revealed further emptying of the patient's bladder and higher severity of the cystocele compared to the defecation image. In addition, the uterine prolapse and peritoneocele which did not appear in a were easily noticed in b.

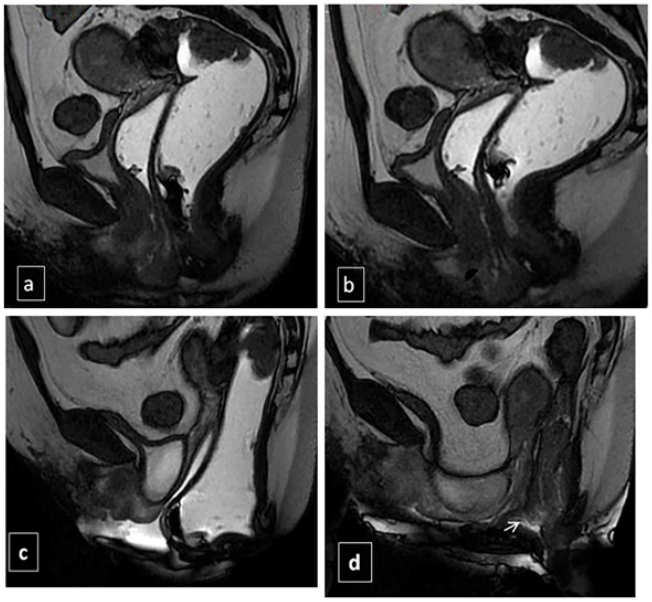

Figure 2: The MRD images of a 40-year-old patient presenting with the complaint of incontinence, and grade II cystocele and grade I rectocele in the clinical examination. The images taken during a) resting, b) squeezing, and c) straining revealed a grade II cystocele, a rectocele, grade I uterine prolapse, and a peritoneocele, and d) the post-defecation image showed rectal prolapse (white cursor).

Discussion

PFD are usually multicompartmental, rarely occur in isolation and that a thorough evaluation of the pelvis is necessary for any woman presenting with PFD symptoms.[20]-[22] Clinicians should bear in mind that patients may be reluctant to express some embarrassing symptoms related to PFD. Detailed assessment of extension of organ prolapse and the degree of pelvic floor relaxation is important for proper surgical planning and to reduce reoperation rates. Clinical examination is often insufficient to assess the whole pelvic organs and pelvic floor related pathologies. Differentiation of cystocele, enterocele, and high rectocele by clinical examination alone is often difficult.[22] MRD allows the complex, multiplanar, and multiparametric evaluation of the pelvic floor soft tissues and pelvic organs in a single examination without using ionizing radiation, and provides both anatomical and functional information, requiring no patient preparation.[10] Imaging has been shown to depict prolapse in asymptomatic compartments that may be occult on physical examination.[20] In many cases, the data obtained from imaging calls for changes to the operative approach, and the treatment method may need to be switched from surgical to medical or vice versa.[23] There are studies in the literature on the comparison of MRD and clinical examination findings in the evaluation of female POP.[24]-[28] In this current study, the highest agreement between MRD and clinical examination was seen in the detection of cystoceles. Other studies also showed a higher correlation between MRD and clinical grading for anterior compartment prolapse than middle and posterior compartment prolapse.[25]-[27] This suggests a better agreement in the anterior compartment. The lack of statistically significant correlation between MRD and clinical examination in the middle and posterior compartments suggests that MRD may provide additional anatomic information in these compartments.[27] In this current study, we found a weak agreement in the presence and grading of cystoceles (kappa = 0.385 and 0.205, respectively) and no agreement in the presence of entero/peritoneocele and rectocele (kappa = 0.102 and 0.123, respectively). Enteroceles are usually not detected in clinical examination. In the literature, the percentage of enterocele detection in MRD in patients without a previous clinical diagnosis of this condition has been reported as 15% by Elshazly et al., 20% by Rentsch et al. and

13.33% by Paetzel et al.[29-31] These researchers concluded that MRD is superior to clinical examination in the detection of cystoceles, enteroceles, and pelvic floor descent. In this current study, of the 73 patients that were not pre-diagnosed with an enterocele, 9 (12.3%) were found to have an enterocele and 27.3% had a peritoneocele, albeit mild, according to MRD. Lin et al. reported that clinical examination detected only 30% of total MRD detected enteroceles and misdiagnosed 10% of these patients with a rectocele.[25] However, there are also several studies reporting that MRD performed in the supine position may not be as adequate as x-ray defecography in the identification of invagination and entero/peritoneocele due to the inappropriate physical conditions and the supine position removing the effect of gravitation.[32-33] To overcome this deficiency, it was suggested that following the resting and straining sequences in MRD, post-evacuation scans should be obtained during strong straining.[34] Multiple defecatory attempts in MRD help to reveal cul-de-sac hernias.[26] Also, the images obtained at straining after defecation were particularly useful for detecting entero/peritoneocele and rectal prolapse. In this current study, no patient was found to have UP on clinical examination and 75% of UPs detected on MRD were of mild severity. Mild UP may not be detected on clinical examination due to patient and/or clinician-related factors. Clinician-related factors such as different examination methods, differences in measurement techniques, reader variability, or patient-related factors such as obesity, reluctance or embarrassment associated with symptoms, poor Valsalva performance of patients during clinical examination may have led to underdiagnosis of PFD. PFD are generally known to be multicompartmental, in accordance with this information, we identified a significant ($p< 0.05$) relationship between the detection of UP and the presence of cystoceles and rectoceles, and multi-compartment defects consistent with UP. We observed that as the severity of the cystocele or rectocele detected in MRD increased, the severity of UP also increased. This indicates that MRD provides additional findings to clinical examination, especially in cases where multi-compartment pathologies are suspected. In many cases, the data obtained from imaging calls for changes to the operative approach, and the treatment method may need to be switched from surgical to medical or vice versa.34 MRI is a useful extension of the clinical examination and is more accurate than clinical examination alone in diagnosing pelvic prolapse.[22] In this study, the overall findings showed that MRD detected more pathologies than clinical examination. The current study has limitations. First, the study sample size was relatively small. Secondly, since X-ray defecography was not performed in our department we could not compare our findings with a gold standard test. Thirdly, we could not compare the effect of MRD findings on treatment plans as we could not follow the treatment of patients. Fourthly, none of the patients in the study demonstrated UP or grade 4 prolapse in clinical examination so patient and/or clinician-related factors were another limitation of current study. Fifth, the coexistence of pathology involving more than one component may cause overlapping of symptoms and affect clinical examination findings.

Conclusion

MRD is complementary to clinical examination in terms of its ability to comprehensively evaluate all compartments simultaneously. MRD provides additional information to the clinical examination in patients with symptoms related to PFD and should be utilized, in symptomatic cases, if the clinical examination findings are negative or if multicompartmental pathologies are suspected.

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RESEARCH ARTICLE

Effect of Maternal Familial Mediterranean Fever on Fetal Pulmonary Artery Acceleration/Ejection Time

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Abstract

Introduction: Autoinflammation and increase in free oxygen radicals due to maternal familial mediterranean fever (FMF) may affect fetal lung maturation and cause changes in fetal pulmonary artery Doppler parameters. We aimed to investigate the fetal pulmonary artery acceleration time/ejection time (PATET) ratio in the pregnancies complicated with familial mediterranean fever (FMF).
Methods: This cross-sectional study included 32 pregnant women with FMF, and 64 gestational ages matched healthy pregnant women, between the 29-30 gestational weeks. Maternal characteristics and fetal ultrasonographic information were recorded. Fetal pulmonary artery acceleration time (AT) and ejection time (ET) were measured manually and PATET ratio were calculated in the study groups. The duration of the disease and the AT and PATET measurements were analyzed with the Pearson correlation test.
Results: The study groups were similar in terms of maternal characteristics, gravidity, parity and gestational week at the time of examination. AT and ET values were found to be significantly shorter and PATET (AT/ET) was found to be significantly lower in pregnant women complicated with FMF. A moderately significant negative correlation was found between the time elapsed since FMF diagnosis and fetal pulmonary artery acceleration time. (r=-.566, p=.001) and PATET (r=-.533, p=.002)
Conclusion: This is the first study to investigate the fetal pulmonary artery Doppler indices in the pregnancies with FMF. In the presented study, it was shown that FMF significantly shortened the fetal pulmonary acceleration and ejection time and significantly reduced the PATET ratio. In addition, as the time elapsed from the diagnosis of the disease increased, it was shown that the shortening in AT and the decrease in PATET were higher, with a significant moderate negative correlation between the duration of the disease and these values.

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Introduction

Familial Mediterranean Fever (FMF) is a chronic inflammatory disease manifested by recurrent attacks of fever, neutrophil induced painful serosal inflammations such as peritonitis, pericarditis, synovitis and amyloid deposition in the kidneys.[1] FMF with autosomal recessive inheritance is more common in certain populations such as Jewish, Armenian, Arab and Turkish. FMF occurs in recurrent and self-limiting episodes, with the first attack usually in childhood or early adolescence. The diagnosis of FMF is made under the age of five in approximately 60% of the patients and under the age of 20 in 90% of them.[2] It is caused by impaired pyrin protein function due to mutations in the MEFV gene on chromosome 16[3]. Disruption of this protein, which is mostly expressed in neutrophils, causes an increase in interleukin 1(IL 1) and reactive oxygen species secretions and excessive inflammatory response of body itself.[4] The main cause of organ and tissue damage in FMF is free oxygen radicals with increased secretion from neutrophils. Subclinical inflammation, which continues in silent periods between acute attacks, may cause Amyloid-A accumulation called amyloidosis in kidney, liver and cardiac tissues.[5] Colchicine is the treatment option that effectively prevents acute attacks and amyloidosis triggered by subclinical inflammation that continues between attacks in FMF.

Acute attacks in maternal FMF can complicate pregnancy and cause obstetric and perinatal problems. Peritonitis during acute attacks has been associated with an increased rate of preterm birth, premature rupture of membranes and cesarean section in FMF pregnancies.[6] In addition, complications such as fibrosis and amyloidosis, which develop due to autoinflammation in FMF, may lead to mechanical obstruction in the tuba uterine and difficulty in obtaining pregnancy. By disrupting sperm and oocyte proliferation and preventing implantation, the rate of recurrent pregnancy loss also increased in pregnancies with FMF.[7] Colchicine can also be used safely during pregnancy, significantly reducing recurrent pregnancy loss and obstetric complications caused by acute attacks during pregnancy.[8]

Fetal lung development may be interrupted and delayed by prematurity and many other maternal or obstetric complications. Free oxygen radicals, which also form the basis of the pathophysiology of FMF, may cause damage to the pulmonary epithelium and surfactant inactivation, thus disrupting fetal lung maturation.[9-11] Fetal lungs, which are the last to complete their development, begin to form in the embryonic period and continue to develop throughout pregnancy and even up to 8 years of age. As the fetal lungs mature, pulmonary blood flow increases while the resistance in the pulmonary vessels decreases in the later weeks of gestation[12,13] Therefore, fetal pulmonary artery Doppler examination gives information about fetal lung maturation.

There are many studies investigating whether fetal pulmonary artery Doppler may predict neonatal respiratory distress syndrome (RDS).[14-17] Many tests have been developed to detect lung maturity, but although they have been used in clinical practice for many years, most of these are time-consuming, expensive, and invasive tests. Pulmonary acceleration time/ejection time (PATET), an alternative method to invasive techniques, is a pulmonary artery Doppler parameter that can show fetal lung maturation non-invasively.[16,18-20]

We hypothesized that autoinflammation and increase in free oxygen radicals due to FMF may affect fetal lung maturation and cause changes in fetal pulmonary artery Doppler parameters. In the presented study, we aimed to compare fetal pulmonary artery acceleration/ejection time (PATET) in pregnancies with FMF and in healthy pregnancies.

Material and Methods

The study in Cross Sectional design was carried out between July 2022 and January 2023 in the maternal-fetal department. The study was started after ethics committee approval from Medical Research Ethical Department of Ankara City Hospital (E2-22-2141). All participants were informed and written consent was obtained.

Thirty-two pregnant women with FMF at 29-30 weeks of gestation and 64 randomly selected healthy pregnant women whose gestational week and maternal characteristics were matched with the study group were included in our study. Pregnant women with fetal anomaly, fetal growth restriction, preterm rupture of membranes, multiple pregnancy, and all maternal diseases except FMF were excluded from the study. Maternal characteristics, gestational week at which ultrasonography was performed, duration of FMF disease, drug use information, and the number of attacks during pregnancy were recorded according to the informa-

tion obtained from the patient and hospital records. Betamethasone treatment was administered after ultrasonographic examination in required patients.

The patients included in the study were evaluated at 29 and 30 weeks of gestation and all the ultrasonographic examinations were performed by a single perinatology fellow with experience in fetal ultrasound by using the 3-5 MHz convex ultrasound transducer of Voluson E8 (GE Healthcare, Milwaukee, WI). After routine fetal biometric measurements and fetal well-being were evaluated, the right ventricular outflow tract, pulmonary valves and pulmonary artery bifurcation were visualized in the short axis view of the heart, in which there was no fetal respiration and movement. By keeping the insonation angle below 15 degrees, and setting the sample interval to 3 mm, the Doppler precursor was placed between the pulmonary valves and the bifurcation of the main pulmonary artery, and minimum three optimal cardiac cycle waveforms were obtained. Acceleration time (AT), defined as the time from onset of ventricular systole to the peak flow rate and ejection time (ET), defined as the time from onset of the ventricular systole to the end, were measured manually and PATET (AT/ET) was calculated (Figure 1). Measurements were obtained in three separate waveforms and the average was recorded.

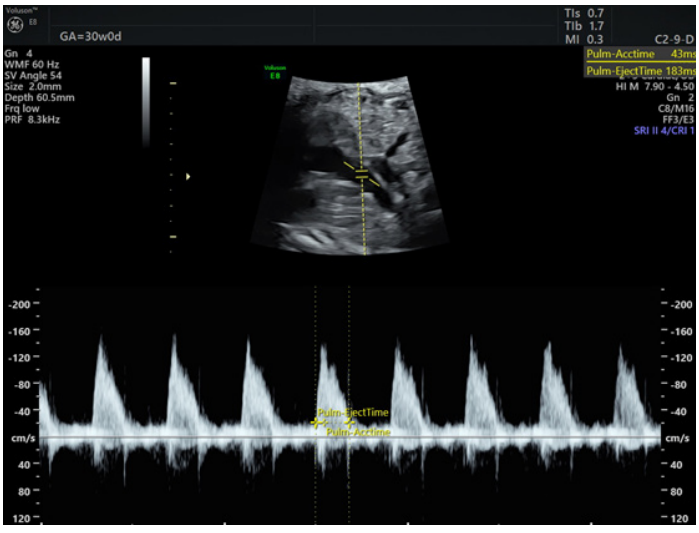

Figure 1: Measurement of the acceleration time and ejection time of the fetal pulmonary artery with spectral Doppler ultrasound

Statistical Analysis

The sample size was analyzed by using the G Power software ((version 3.1; Franz Foul, Universitat Kiel, Kiel, Germany) 21. A sample size of 32 patients in the case group and 64 control was calculated with an effect size of 0.80 and p-value of 0.05 (two-tailed) and a power of 95%. Statistical analyses were performed using Social Sciences (SPSS), software version 17.0 (SPSS Inc, Chicago, IL). Descriptive statistics were given as mean ± standard deviation for numerical data with normal distribution or median (IQRs (Interquartile Ranges)) values for numerical data that do not follow a normal distribution. For comparing the values of two independent groups, the " Independent t-test " for normal distribution variables and the "Mann-Whitney U test" for non-normal distribution variables were used. Distribution of the AT, ET and PATET measurement between the groups was shown with the error bar. Error bars indicate the mean and 95% confidence interval of AT, ET and PATET in study groups (Figure 2a, 2b and 2c). The duration of the disease and the AT and PATET measurements were analyzed with the Pearson correlation test and were shown with Scatter Plot (Figure 3a and 3b). In all analyses, an alfa level of 0.05 was considered significant.

Results

Thirty-two pregnant women with FMF were included in the study group and 64 healthy pregnant women were included in the control group. The study groups were similar in terms of maternal age, pre-pregnancy body mass index (BMI), gravidity, parity and gestational week at the time of examination. (Table 1).

AT and ET values were found to be significantly shorter and PATET (AT/ET) was found to be significantly lower in pregnant women complicated with FMF (Table 1). The distributions of AT, ET, and PATET measurements were also shown with error bars (Figure 2a, 2b, and 2c). Error bars indicate the mean and 95% confidence interval of AT, ET and PATET in the study groups. The mean duration of disease diagnosis was 9.8 years. The number of patients with FMF who had an attack during pregnancy was 4 (12.5%). There was no patient who had more than one attack during

pregnancy. Twenty-six pregnancies with FMF were using hydroxychloroquine. There was no one using corticosteroid therapy in patients who had an attack.

A moderately significant negative correlation was found between the time elapsed since FMF diagnosis and fetal pulmonary artery acceleration time. (r=-.566, p=.001) and PATET (r=-.533, p=.002) (Figure 3a and 3b).

Table 1: Comparison of fetal pulmonary artery Doppler indices of the all participants

	FMF (n=32)	Control group (n=64)	p value
Age (years)	31.1±5.6	30.5±4.2	.574*
Gravidity	2 (1-3)	1 (1-2)	.231†
Parity	0 (0-1)	0 (0-1)	.129†
Abort	1 (0-2)	0 (0-1)	.153†
Pre-pregnancy BMI (kg/m^2)	24.9±3.4	25.5±2.7	.307*
Gestational age at examination (Weeks)	30 (29-30)	30 (29-30)	.775†
Acceleration time (AT) (ms)	34.7±2.6	38.8±2.4	<.001*
Ejection time (ET) (ms)	189.8±11	195.2±10.1	.019*
AT/ET ratio	0.18±0.02	0.20±0.01	<.001*

Values are presented as mean± standard deviation
* Independent t-test
† Mann Whitney U test

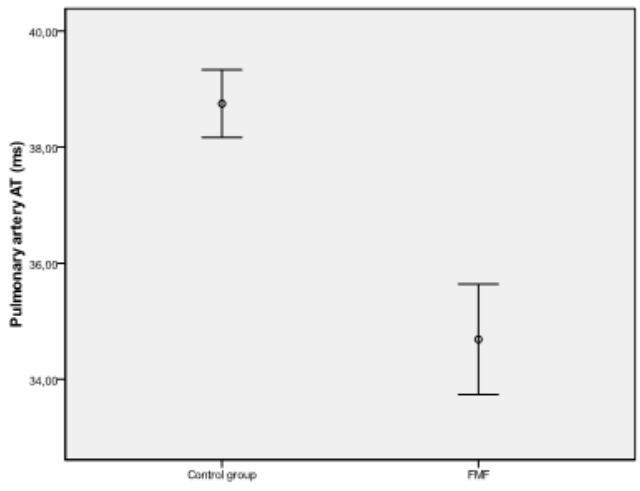

Figure 2a: Comparison of fetal pulmonary artery AT in pregnant women with FMF and control group with error bar

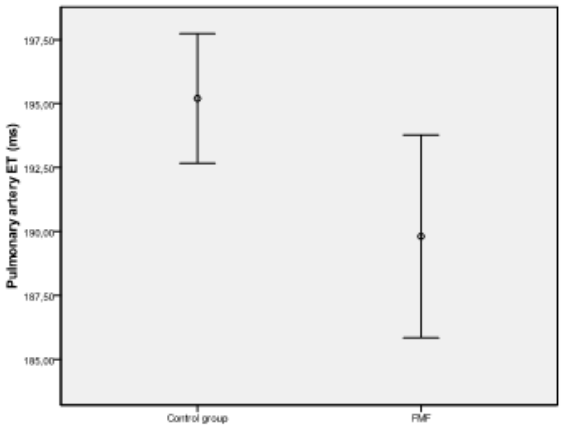

Figure 2b: Comparison of fetal pulmonary artery ET in pregnant women with FMF and control group with error bar

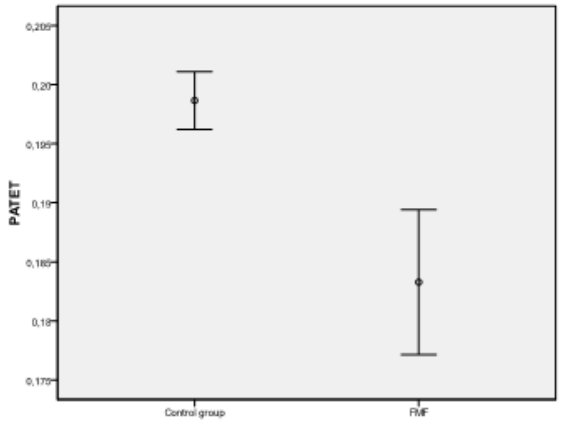

Figure 2c: Comparison of fetal pulmonary artery PATET in pregnant women with FMF and control group with error bar

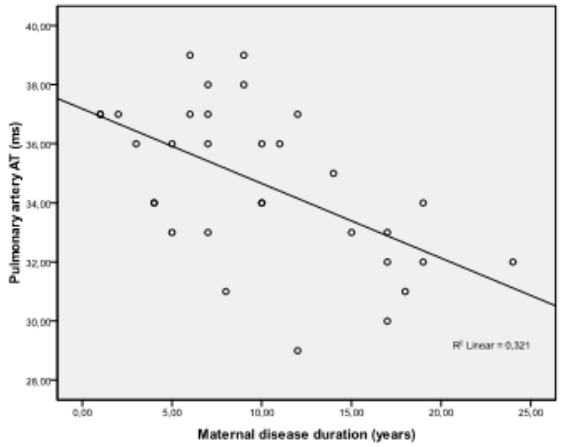

Figure 3a: Scatter plot demonstrating the correlation between maternal disease duration (years) and fetal pulmonary artery acceleration time (ms)

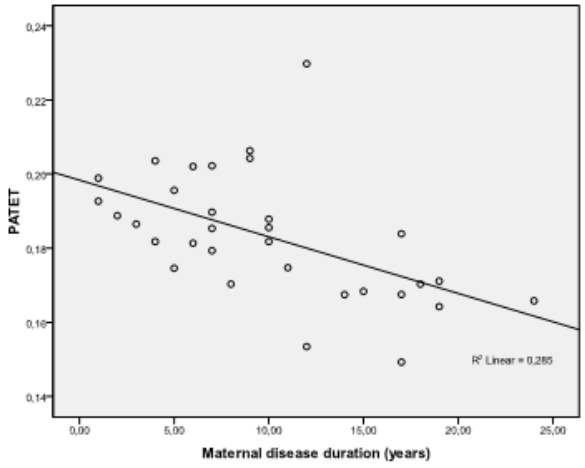

Figure 3b: Scatter plot demonstrating the correlation between maternal disease duration (years) and fetal pulmonary artery AT/ET ratio

Discussion

FMF is a regional and rare disease encountered in certain populations. The effect of FMF on pregnancy and perinatal outcomes has been investigated in many studies 6,7. However, this is the first study to investigate whether FMF affects fetal pulmonary circulation and hence lung maturation. In the presented study, it was shown that FMF significantly shortened the fetal pulmonary acceleration and ejection time and significantly reduced the PATET ratio. In addition, as the time elapsed from the diagnosis of the disease increased, it was shown that the shortening in AT and the decrease in PATET were higher, with a significant moderate negative correlation between the duration of the disease and these values.

Chaoui et al showed that blood flow and resistance in the fetal pulmonary circulation have been shown to change as pregnancy progresses and with fetal lung maturation in the previous studies 22. With the maturation of the fetal lungs, reduction in pulmonary arterial pressure and increase in blood flow have been demonstrated by the use of conventional Doppler and has become an alternative method to invasive tests used to determine lung maturation 12,13. It has been shown that the AT/ET ratio increases as the gestational week progresses, and it has been suggested that this was due to fetal lung maturation and a decrease in pulmonary artery resistance, thus prolonging the acceleration time. 22. The relationship between pulmonary artery Doppler indices and amniotic fluid markers showing fetal lung maturation was investigated, and an inverse correlation only between the PATET ratio and the lecithin/sphingomyelin ratio in amniotic fluid was found. No significant correlation was found with other indices of fetal pulmonary artery Doppler and fetal lecithin/sphingomyelin ratio 14.

It is known that maternal chronic autoimmune diseases that cause subclinical inflammation in the placenta are associated with an increased risk of fetal growth retardation and early and late intrauterine death 23. Mononuclear infiltration due to autoimmune diseases may cause placental villitis, chronic chorioamnionitis and/or chronic deciduitis. Intense inflammation and free oxygen radicals in the placenta may cause damage to fetal membranes and apoptosis in trophoblasts, which may be associated with poor perinatal outcomes such as unexplained bleeding during pregnancy, fetal growth restriction and fetal death 24.

Cytokines and free oxygen radicals due to maternal infection and inflammation may affect fetal pulmonary circulation. In a recent study investigating the effects of autoimmune diseases such as maternal systemic lupus erythematosus, Sjögren's syndrome and antiphospholipid antibody syndrome on the fetal pulmonary circulation, it was shown that inflammation significantly reduces the ratio of AT and AT/ET in the fetal pulmonary artery 25. Fetal pulmonary artery AT and PATET rates were significantly lower in COVID-19 recovered pregnancies 26. In the study examining the prediction of neonatal RDS of fetal pulmonary artery Doppler parameters in pregnancies infected with COVID-19, fetal pulmonary artery AT and PATET ratio were found to be significantly lower in newborns admitted to the neonatal intensive care unit (NICU) due to RDS 27. In the presented study, although the shortening in AT was more pronounced, we also observed a significant shortening in ET. The shorter AT in the FMF group was due to the high resistance in the fetal pulmonary vessels, high pulmonary artery pressure, and delaying fetal lung maturation by the inflammation. We thought that the shortening in ET was due to the fact that the inflammation in FMF may cause change in systolic function in the fetal heart. It was also previously showed that maternal FMF can cause diastolic and systolic function changes in the fetal heart 28. The efficacy of fetal pulmonary artery PATET ratio was investigated to predict neonatal respiratory

complications in preterm prelabor rupture of membranes pregnancies, and it was found that PATET, when the gestational age (confounding factor) was adjusted, could not predict respiratory complications 19. On the contrary, in the study investigating the prediction of fetal pulmonary artery PATET value for neonatal RDS, a negative correlation was shown with low PATET value indicating an increase in neonatal RDS 18. The PATET ratio was found to be inversely proportional to the pulmonary artery pressure in the fetal and adult periods and low PATET values were found to reflect pulmonary hypertension 29. In this study conducted in adults, shortening of both AT and ET was observed as a result of the change of pulmonary valve movements in the presence of pulmonary hypertension, and the PATET rate was also found to be significantly lower in patients with pulmonary hypertension. The most important limitation of our study is that it was in a cross-sectional design, only one measurement was made in the pregnant women included in our study, they did not have repeated examinations, and the obtained data were not associated with perinatal and neonatal outcomes. Longitudinal studies in which ultrasonographic data are associated with perinatal outcomes, with larger populations of patients in a prospective design will provide more information on this issue.

Conclusion

This is the first study to investigate the effect of maternal FMF on fetal pulmonary artery Doppler. FMF may affect the fetal pulmonary artery blood flow with the inflammatory environment it creates and the excess free oxygen radicals secreted. It should be kept in mind that maternal FMF, which causes shorter fetal pulmonary artery AT and ET, and lower PATET rate, may disrupt in the maturation of the fetal pulmonary vascular bed, and hence increase fetal pulmonary morbidity and mortality. Fetal pulmonary artery Doppler evaluation is a noninvasive and easily applicable method that shows the maturation of the pulmonary vascular bed and fetal lung. Clinical use of fetal pulmonary artery Doppler with other Doppler modalities and biophysical profile may provide additional benefit in predicting perinatal outcomes and taking precautions.

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Conflicts of Interest Interest

The authors have no conflicts of interest.

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None

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RESEARCH ARTICLE

Modified First Dorsal Metacarpal Artery Flap to Prevent Venosus Congestion: Retrospective Analysis of 37 Cases

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Modified first dorsal metacarpal artery flap, venosus congestion, thumb reconstruction

Abstract

Introduction: First dorsal metacarpal artery flap (FDMAF) is thin, pliable, sensate flap which is useful in the restoration of the contour and sensation of the thumb. Although FDMAF stands out with many positive aspects, venous congestion and related flap losses are frequently reported in the literature. In this study, we evaluated the clinical results of our modification, which prevents venous congestion and facilitates the inset of the flap to the defect area, with retrospective patient analyzes. We aimed to share surgical anatomy, surgical technique, tips and key points to get good results.

Methods: Between May 2016 and December 2019, 37 patients (32 males, 5 females) with thumb defects were included in the study. All patients were evaluated for flap size, defect size, sensory return, two-point discrimination (2PD), operation time, metacarpophalangeal (MCP) and interphalangeal (IP) range of motion.

Results: All 37 flaps survived complately. Venous congestion was not observed in the other flaps. Semmes-Weinstein sensory test score: 4,36 (range, 3,84-5,1) in the flap, 4,62 range, 3,9-4,92) in the donor site. Mean two-point discrimination (2PD): 8.8 mm (range, 7-22 mm) in the flap, 12 mm in the donor area (range 10-14 mm). MCP range of motion of the operated thumbs was 82o (range, 70o-86o) and IP range of motion was 84o (range, 15o-88o).

Conclusion: Modified kite flap is technically simple, and the learning curve is fast, even it may be performed with local anesthesia. Also it is a useful, reliable and sensory option for the thumb reconstruction. Our clinical results are encouraging.

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Introduction

Thumb defects frequently arise as a result of avulsion trauma. For superficial defects, skin grafts can often suffice as a treatment option. However, when bone and tendon exposures are involved, more intricate reconstruction methods become necessary. In thumb reconstruction, various techniques can be employed, such as Littler's neurovascular island flap, small free flaps, or sensory cross finger flaps. The restoration of the thumb pulp and sensory function is crucial for achieving optimal hand functionality. Therefore, the first dorsal metacarpal island flap (FDMAF) stands as a favorable choice for reconstructing thumb defects.[1-4]

The FDMAF is a thin, pliable, and sensate flap that proves valuable in restoring both the contour and sensation of the thumb pulp.[5] However, despite its numerous positive aspects, the literature frequently reports cases of venous congestion and associated flap losses.[4,6-9] Multiple studies have highlighted the occurrence of venous congestion in approximately 40% of flaps.[7] Preventing venous congestion becomes crucial in order to avoid partial flap losses, minimize hospitalization duration, and reduce the need for additional surgical interventions.

The primary objective of this study was to assess the clinical outcomes of our modification, designed to prevent venous congestion and enhance the successful insertion of the flap into the defect area. We conducted a retrospective analysis of patients to evaluate the effectiveness of our approach. Additionally, we aimed to share insights on surgical anatomy, surgical technique, as well as essential tips and key points that contribute to achieving favorable results in the procedure.

Materyal and Methods

This study received approval from the Ankara City Hospital Ethics Committee (number E2-23-4185) before its commencement. Between June 2016 and December 2019, a total of 37 patients (32 males and 5 females) with thumb defects were included in the study. The mean age of the patients was 34 years, with an age range spanning from 16 to 64 years. All cases involved either avulsion injuries (n = 26) or crush injuries (n = 11). The evaluation of each patient encompassed various factors, including defect size, flap size, sensory outcome, two-point discrimination (2PD), operation time, as well as the range of motion in both the metacarpophalangeal (MCP) and interphalangeal (IP) joints. It is worth noting that the operations and subsequent patient follow-ups were conducted by the same surgical team throughout the study.

Surgical Technique

The operations for FDMAF can be performed under local or general anesthesia with tourniquet control. No premedications used in all case before surgery. The patient is positioned supine on the hand table with the arm in abduction. Operation starts with debridment of the defect. The flap size is decided according to the size of the defect area. The dorsum of the second finger serves as a reference for flap design. Radial lateral of the flap must be on the midradial axis line because first dorsal metacarpal artery branch is located at the dorsoradial side of the second finger. Ulnar side of the flap can be determined by the required flap size. If a large flap required flap can be extended till the midulnar line serves as the ulnar lateral border. The entire dorsum of the second proximal phalanx can be harvested as a flap.

To prevent joint contractures, the authors does not recommend extending the distal portion of the proximal interphalangeal joint line. In the author's modification, the proximal part of the flap is planned in a V-shaped pattern as equilateral triangle. However, a vertical incision is made to relieve the tunnel neck at the proximal part of the defect. The lenght of the vertical incision should be equal to side lenght of equilateral triangle. The equilateral portion of the flap must precisely fits into vertical incision line (Figure 1). If it is not fits well, vertical incision line can ve lenghten. As a result, Due to the vertical incision, tunnel mouth widens by the side lenght of equilateral triangle which prevents vascular compression within the tunnel. This modification helps reduce venous congestion and its associated complications. Also this modification is the advanced version of authors venosus congestion preventing modification which presented in the First International Congress of Occupational Accidents, Hand Injuries and Amputations.[10]

Flap dissection begins from the distal ulnar lateral side, following the appropriate markings. The dorsal digital nerve and its radial branch are included in the flap with approximately 1 cm of remnant length. The radial branch of the nerve is subsequently coapted to the digital nerve stump in the defect area. The paratenone is not preserved in this region due to the

close proximity of the pedicle to the paratenon on the radial lateral side of the metacarpophalangeal joint. A lazy-S incision is made from the proximal end of the flap to the anatomical snuff box. During the elevation of the skin flaps, only the skin tissue is dissected, while the subcutaneous tissue and subcutaneous veins are included in the flap pedicle. This step is crucial in preventing the occurrence of venous congestion. The fascia of the first interosseous muscle is included proximally in the flap. The pedicle is dissected up to the radial artery (Figure 2). Subsequently, a subcutaneous tunnel is created between the thumb defect and the artery. It is important for the tunnel to be wide enough to prevent pedicle compression. To relieve the neck of the tunnel and prevent pedicle compression, a vertical incision is made on the distal portion of the tunnel. The planned proximal V-shaped part of the flap is then positioned in this area.

Lastly, the defect at the donor site on the dorsum of the second finger is reconstructed using a full-thickness skin graft harvested from the ulnar forearm.

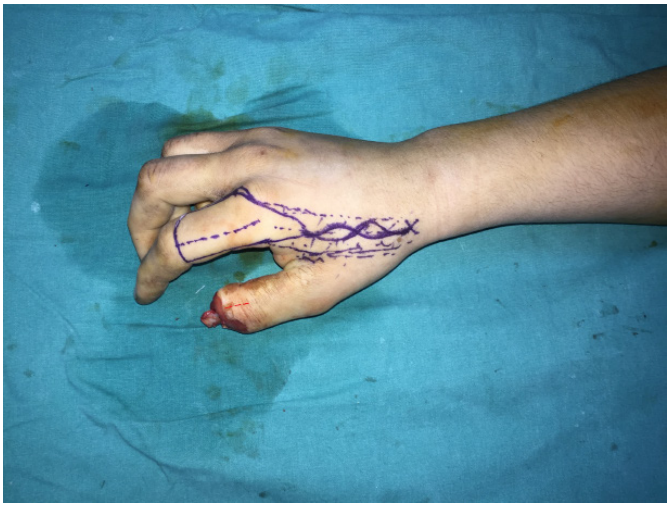

Figure 1:Skin markingd of modified FDMAF. Red dashed line: The tunnel neck at the proximal of the defect is relieved by this vertical incision. That maneuver is very important to prevent venous congestion.

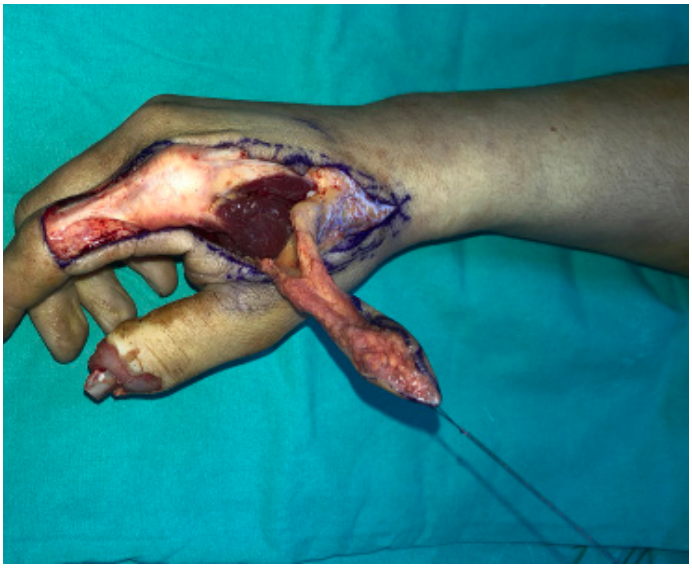

Figure 2:Flap dissection. Interosseos muscle fascia included to protect pedicle and support venous drainage.

Results

All 37 flaps in the study demonstrated complete survival, except for one flap that showed partial necrosis distally. In this particular case, satisfactory results were achieved through wound debridement and secondary wound healing. No instances of venous congestion were observed in the remaining flaps, and there were no reports of graft lysis at the donor site and there were no other wound healing problems such as infection and dehiscence.

The average operation time for flap dissection was 56 minutes, with a range of 50-80 minutes. It is noteworthy that all flap dissections were performed using loupe magnification, ensuring precision and accuracy during the procedure.

The mean follow-up period for the patients was 13,4 months, ranging from 5 to 20 months. At the last control of cases, all flaps exhibited good skin color and tissue compliance. Also donor site condition was acceptable as observed in Figure 3, 4, and 5.

There were no reports of pain in the donor site or recipient site scars. However, nine patients (24%) experienced cold intolerance in the flap, while three patients (8%) reported hypersensitivity to the flap. These are important

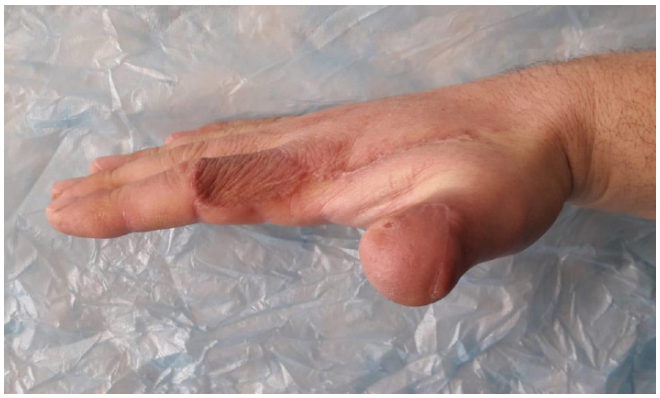

Figure 3: Postoperative 18 months. No deplession at the donor site. Flap is well healed, no contour deformity.

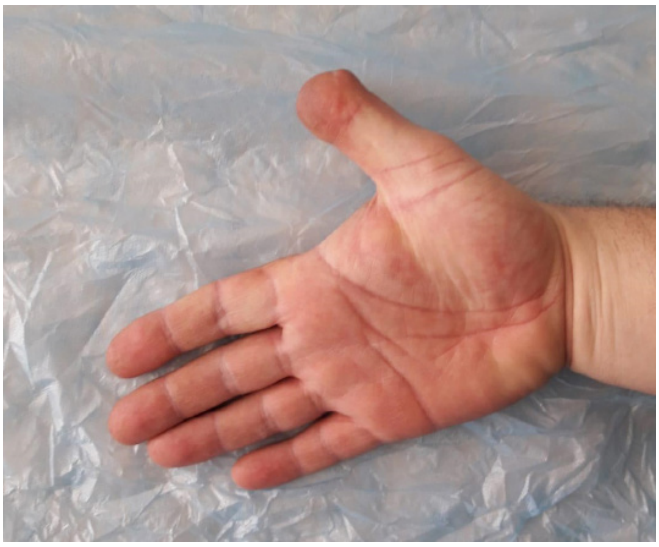

Figure 4:Postoperative 18 months. Full abduction and extension of MCP joint.

considerations in the assessment of patient outcomes and potential post-operative complications.

The Semmes-Weinstein sensory test scores for the flap were recorded as 4,36, with a range of 3.84 to 5.1, while the scores for the donor site ranged from 4,62 to 3,9-4,92. This indicates a relatively preserved sensory function in both the flap and donor site areas.

The mean two-point discrimination (2PD) was measured as 8,8 mm in the flap, with a range of 7-22 mm. In the donor area, the 2PD was 12 mm, ranging from 10 to 14 mm. These measurements reflect the ability to discern finer tactile stimuli and suggest a reasonably good sensory recovery. The mean defect size was 2,4 x 2,9 cm, ranging from 1,9 x 2,1 cm to 2,7 x 3,2 cm. The size of the flaps used for reconstruction had a mean measurement of 2,6 x 3,2 cm, with a range of 1,9 x 2,3 cm to 2,9 x 3,6 cm. These dimensions indicate the adequacy of the flaps in covering the thumb defects.

In terms of range of motion, the metacarpophalangeal (MCP) range of motion for the operated thumbs averaged 82 degrees, with a range of 70 to 86 degrees. The interphalangeal (IP) range of motion averaged 84 degrees, ranging from 15 to 88 degrees. These values indicate satisfactory mobility in the operated thumbs, contributing to functional hand movement.

Discussion

The reconstruction of tendon and bone exposed defects in the thumb presents challenges due to the limited availability of surrounding tissues. The primary objective of thumb reconstruction is to preserve thumb length and restore sensation. Various surgical options, including local, regional, and free flaps, are available for this purpose.

Littler's neurovascular island flap is a sensory flap commonly used for thumb reconstruction, typically harvested from the ulnar lateral of the third or fourth finger.1 However, this flap has certain limitations, such as its suitability for smaller defects and the sacrifice of one of the digital arteries. Additionally, it may pose challenges in terms of cortical learning.

The V-Y advancement flap is another option for reconstructing defects up to 1,5 cm in size. However, it is not a sensory flap, meaning it does not provide restoration of sensation. On the other hand, the Moberg flap can be used for larger defect reconstruc-

tions. It is important to note that during flap elevation, there is a risk of circulatory disorders and necrosis in the dorsal skin and nail bed due to damage to the dorsal nourishing veins. Furthermore, this flap may lead to flexion contracture of the interphalangeal joint, which should be considered in the surgical planning.[11]

Each of these flap options has its advantages and limitations, and the choice of technique depends on the specific characteristics of the defect and the patient's individual needs and goals.

In authors own practice, the innervated cross-finger flap is not a preferred due to the requirement of a two-stage operation and the potential for joint stiffness, particularly in elderly patients. Despite providing acceptable sensation in the thumb, these factors make it less favorable in our clinical practice.3

Similarly, the dorsoulnar thumb flap, as described by Brunelli, is not recommended by the authors due to its lack of sensory return and the absence of natural dimples in the webs. These factors make it a less ideal choice for thumb reconstruction.[12]

Regarding small free flaps, such as partial toe transfers, they are not considered as the first choice in our authors practice. Many patients are reluctant to sacrifice their big toe for the procedure, and the operation itself requires complex microvascular techniques. This complexity contrasts with the relative simplicity of the FDMAF procedure.

The FDMAF, with its wide rotation arc and innervation from superficial radial nerve branches, is the primary choice for thumb defect repair in our clinical practice. It offers technical simplicity and a fast learning curve, and can even be performed under local anesthesia. There are techniques with expanding FDMAF with a skin bridge to pivot point of the flap. [13] However skin bridge technique reduces venos congestion, donor site scar at the dorsum of the hand is expands with the skin bridge. Also a vertical scar at the junction of the first web space can lead to skin contracture at late onset. Aesthetically dorsum of the hand is important.[14] In our current study dorsal scar of the hand limited with the donor site and pedicle dissection area. As a limitation of our study, patients did not score aesthetic outcomes of operation. Comperative studies with large number of patients recommended.

In our study, the mean two-point discrimination (2PD) was 8,8 mm, within the range of 7-22 mm. This is consistent with the literature, where 2PD measurements typically average around 9-10 mm.[14] Günay et all found 15 mm of mean 2PD in their FDMA flap study with classical flap elevation. We think that our better 2PD results are associated with our modification which provides no pedicle compression. One case in our study demonstrated 22 mm of two-point discrimination, which can be attributed to the patient's hypersensitivity and noncompliance. Also patients need to improve cortical reorientation for proper sensation of the thumb in local sensate flaps such as heterodigital neurovascular island flap.[16] Cortical reorientation process can differ induvisually.

In our series, mean flap size was 2,6 x 3,2 cm which is same with literature. When harvesting local flaps from the hand, there is always size limitations cause of uniqe and fonctional anatomy of the hand. Similar to other local flaps in the hand, FDMAFs are constrained by size limitations. These flaps are capable of extending distally to the PIP joint and proximally to the metacarpophalangeal joint. In an effort to address this limitation, El-Khatib reported extended first dorsal metacarpal artery neurovascular island wrap-around flap, which demonstrated successful outcomes.[9] It should be kept in mind that our modification can be used in extended FDMAF too. Nonetheless, it should be noted that this particular procedure may be accompanied by an increased risk of donor-site morbidity.

Overall, the FDMAF technique has shown promising results in terms of sensory outcomes and patient satisfaction in our study, aligning with the existing literature in this field.

One limitation of the study is that we did not apply the cold intolerance questionnaire to patients who reported cold intolerance. This could have provided additional insight into the prevalence and severity of cold intolerance among the study participants.

Most patients in the study had satisfactory thumb metacarpophalangeal (MCP) and interphalangeal (IP) joint range of motion. It is thought that our V-shaped modification provided adequate tissue to recipient site. Also our equilateral triangle extention of flap acts as a 60 degrees of Z-plasty and that prevented any joint contracture.

In our study, only one flap (2,7%) experienced venous congestion and partial necrosis. It was determined in the postoperative period that this patient had trauma at the flap donor site, which was believed to be the cause of the congestion and necrosis. Si-

milar studies by Zhang et al.[6] Couceiro and Sanmartin[7], and Satish et al[8]. also reported cases of partial necrosis in their respective series. However, El-Khatip[9] reported no flap necrosis despite the presence of venous congestion in all of their cases. When comparing our study to the existing literature, our findings showed significantly less venous congestion compared to other case series. This may be attributed to the modifications made to the flap, such as the V-shaped proximal flap and the vertical incision that releases the tunnel through which the pedicle passes, allowing the flap tail to fit precisely in this line.

Overall, our study highlights the favorable outcomes and low incidence of venous congestion and necrosis associated with the FDMAF procedure, particularly when considering the modifications made to enhance flap survival.

Conclusion

Based on the results of the study, it can be concluded that the new kite flap modification is a technically simple and easily learnable procedure. It offers several advantages, including the ability to perform it under local anesthesia and its reliability in providing sensory reconstruction for the thumb.

The clinical outcomes of the patients who underwent this procedure in our study were encouraging, with high flap survival rates, satisfactory range of motion, acceptable sensation, and minimal complications such as venous congestion and necrosis. These findings suggest that the kite flap modification can be considered as a valuable option for thumb reconstruction, providing reliable results and sensory restoration. The simplicity of the technique and the fast learning curve make it an attractive choice for surgeons. However, it is important to consider individual patient factors and preferences when selecting the most appropriate reconstruction option. Further research and comparative studies may help to establish the long-term effectiveness and advantages of the Kite flap modification in thumb reconstruction.

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RESEARCH ARTICLE

Efficiency Of Medial Plantar Artery Flap in Patients With Plantar Defect: A Retrospective Study

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Defect, Medial plantar artery flap, Plantar area, Reconstruction

Abstract

Introductıon: Reconstruction of soft tissue defects of the lower extremities is a major challenge for plastic surgeons, and reconstruction options are limited. In this study, we aimed to evaluated the results of reconstructing plantar defects with the medial plantar artery flap, which is a safe and simple method for reconstruction. **Methods:** This study included patients who underwent reconstruction with a medial plantar artery flap in 15 patients with plantar defects between February 2019 and June 2021.Anatomical landmarks were marked. The flap was elevated and the dissection was extended proximally to prevent tension. **Results:** All defects were successfully reconstructed without complications except in one of 15 patients (12 males, 3 females).Due to the dehiscence of both flaps, the patient underwent a second operation for successful reconstruction. All harvest sites were reconstructed with a split thickness skin graft from the thigh. The necrotized flap area was reconstructed with a split-thickness skin graft from the thigh, which was vacuum-assisted closed after debridement. **Conclusıon:** All defects were successfully reconstructed without complications except in one of 15 patients (12 males, 3 females).Due to the dehiscence of both flaps, the patient underwent a second operation for successful reconstruction. All harvest sites were reconstructed with a split thickness skin graft from the thigh. The necrotized flap area was reconstructed with a split-thickness skin graft from the thigh, which was vacuum-assisted closed after debridement.

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Introduction

Although the reconstruction of defects in the plantar region is difficult, the treatment of tissue loss in this area is difficult both clinically and surgically. They cause significant morbidity and mortality, which can lead to osteomyelitis and subsequent amputations in patients.[1] It is very important to prevent ulceration that occurs when the defect remains open and to close the defects quickly.

The fact that the plantar region is hairless, has thick skin, supports all body weight, and has inadequate locoregional tissue complicates reconstruction of the region.[1,2] The plantar region serves as a stance surface and a counterbalance for the pressure exerted during locomotion, and the weight-bearing surface of the heel is separated by fibrous septa and consists of specialized fats.[1,2]

The vascular anatomy of the medial plantar artery (Mpa) was reviewed by Shanahan et al. in 1979.[3] It was defined as a free flap by Morrison in 1983.[4] The use of the medial plantar artery flap in the plantar region and at the heel was defined by Masquelet and Romana in 1990.[5] At the same time, the medial plantar artery is used as a vascular source for free flaps in foot defects.[5] Since then, it has been used as a local flap in foot and medial malleolar defects.[5] Its use in plantar and ankle defects is quite common reconstructed.[6]

In this study, we aimed to evaluate the use and results of the medial plantar artery flap in the reconstruction of plantar defects.

Materyal and Methods

Study Design

This single-center retrospective study was conducted between February 2019 and June 2021 in the xxxxxxxxxxxxxxxxxxxx. The study was planned in accordance with the Declaration of Helsinki and was granted approval by the Hospital Clinical Research Ethics Committee No. 1 (date 23/02/2022, decision number E1-21-2175)

Surgical technique

After preoperative preparation and planning, patients were taken to the operating room. After appropriate induction of anesthesia, the surgical area was prepared with antiseptic iodine solution and covered with sterile drapes. All surgeries and long-term and short-term follow-up of patients were performed by the same surgeon. Preoperative blood and imaging results were evaluated, and an anesthesia report was obtained. Initially, radical and complete debridement of all nonliving tissues was performed. After the boundaries of healthy living tissue were established, debridement was terminated. The use of tourniquets was avoided to separate necrotic tissue from healthy tissue. Reconstruction was performed in all patients after debridement. Flaps were planned from nonweight-bearing areas for reconstruction of the defects.

Preoperative patency of the arterial systems was confirmed by Doppler USG in all patients. In patients with diabetes, additional elective angiography was performed before surgery and found that the vessels were open.

Preoperative planning and marking

Preoperatively, the course of the posterior tibial artery and the medial plantar artery was determined topographically by Doppler. The boundaries of the flap were determined according to the size of the defect. Because the flap would contract, it was planned to be larger than the defect size. The long axis of the flap was planned parallel to the medial arch of the foot. The medial edge of the flap was not to exceed the navicular tuberosity. The lateral edge was planned as a medial longitudinal arch, which does not create pressure. The proximal margin was limited to the distal part of the calcaneal tuberosity, and the distal margin was limited to the proximal part of the first and second metatarsal heads to avoid pressureless parts of the plantar region. The areas of the flap incisions were marked (Figure 1).

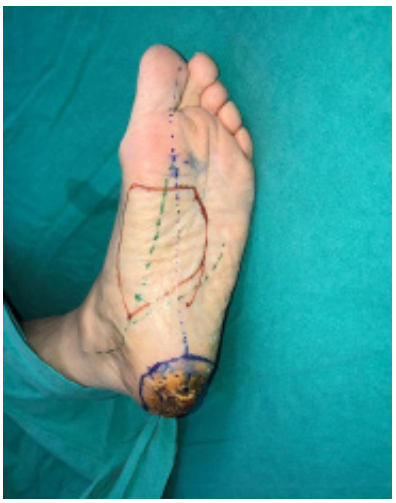

Figure 1: The planning and marking of the flap borders.

Dissection

The incision was made to include the skin, adipose tissue, and superficial fascia of the foot. Dissection of the flap began at the distal edge, and the free edge of the flap was elevated at the distal incision site. For the first few centimeters, the plantar fascia was cut with a sharp size 15 scalpel, followed by Metzenbaum scissors for safe dissection. The operation was performed with a combination of blunt and sharp dissection. The plantar fascia was separated from the flexor digitorum brevis muscle, taking care to spare the long flexor tendons and their crossing sensory nerves during this dissection. The anatomic location of the medial plantar artery was marked. (The medial plantar artery is located deep in the intermuscular septum between the abductor hallucis muscle and the flexor digitorum brevis muscle, lateral to the tendon of the flexor hallucis longus muscle). Later, the flap was elevated from the lateral, medial, and proximal sides. When the flap was elevated from the medial side, the paratenon of the abductor hallucis tendon and its peritendinous structures were preserved. During lateral dissection, the incision was deepened, the plantar fascia was included in the flap, and the flexor digitorum brevis muscle was lateralized to expose the pedicle. The distal, lateral, and medial edges of the flap were elevated, and the posterior tibial artery was visualized proximally under the retinaculum flexorum. The medial plantar artery was ligated distal to the flap. The proximal portion of the abductor hallucis longus tendon was transected to increase the length of the pedicle, and the medial and lateral plantar arteries were visible at this level. The dominant pedicle and accompanying concomitan veins were preserved and elevated. Pedicle length was increased by dissection in the direction of the posterior tibial artery.[7]

Dissection with a 2.5-fold magnification of the surgical loop reduces the risk of vascular injury. The use of the automatic retractor in the intermuscular septum between the muscles facilitates dissection. The vascular structure should be dissected proximally so that the flap is free of tension in the defect area.

Statistical analysis

For the statistical analysis, Statistical Package for the Social Sciences -SPSS 25.0 was used. Descriptive statistics for numerical variables are mean, standard deviation, median, min-max. expressed as values.

Results

Between February 2019 and June 2021, 15 patients with plantar defect were admitted to our clinic. 12 of these patients were male and 3 were female. The average age of the patients ranged from 44±19,2 years. The largest flap size was 6 x 6 cm, and the area ranged from 10 to 36 cm2. The number of patients with additional concomitant diseases was 5. All of these patients underwent surgery at least once. Data on the cases are shown in Table 1.

Table 1.Clinical and demographic findings of the study population

Case	Age	Sex	Etiology (year)	Defect Area	Defect Diameter (cm)	Duration of hospitalization (day)	Complication	Comorbidite
1	21	Male	Gunshot injury	Heel	6X4	14	None	None
2	42	Male	Diabetes mellitus	Heel	7X4	10	None	Hypertension, Diabetes mellitus
3	44	Male	Traffic accident	Plantar	7X5	12	None	None
4	18	Male	Traffic accident	Plantar	4X4	11	Dehissans, Necrosis	Hypertension, Diabetes mellitus
5	51	Female	Traffic accident	Heel	5X5	10	None	Hypertension,
6	50	Male	Diabetes mellitus	Heel	5X4	21	None	None
7	61	Male	Traffic accident	Plantar	7X3	15	None	None
8	46	Male	Diabetes mellitus	Plantar	6X5	10	Dehissans	Hypertension, Diabetes mellitus, Atherosklerosis
9	43	Female	Traffic accident	Plantar	6X2	12	None	None
10	63	Male	Traffic accident	Plantar	5X4	9	None	Hypertension, Atherosklerosis
11	54	Male	Gunshot injury	Heel	4X4	28	None	None
12	25	Female	Traffic accident	Heel	4X3	10	None	None
13	20	Male	Traffic accident	Heel	5X4	12	None	None
14	19	Male	Gunshot injury	Plantar	5X2	11	None	None
15	24	Male	Traffic accident	Heel	4x4	10	None	None

Cases

Case 2: The patient, injured by a traffic accident, with skin and subcutaneous necrosis on the heel, was taken by the orthopedic service because he had no bone pathology. The necrotic area was debrided and the bone was exposed. It was decided to make a medial plantar artery flap for the bony defect at the heel. A 7x4 cm medial plantar artery flap was planned. The flap was elevated and a hemovac drain was placed under the flap. The flap was sutured to the defect area with 3/0 monofilament suture in the subdermal plane. Then the skin was reconstructed by suturing with 3/0 polypropylene suture (Figure 2a). The defect of the flap in the donor site was reconstructed with a split thickness skin graft (STSG) taken from the anterolateral aspect of the lower extremity thigh. The donor site of the flap was reconstructed with stsg taken from the anterior aspect of the thigh. A tieover dressing was applied to the graft. Three days later, the tie-over dressing was opened. No complications occurred in the donor site.

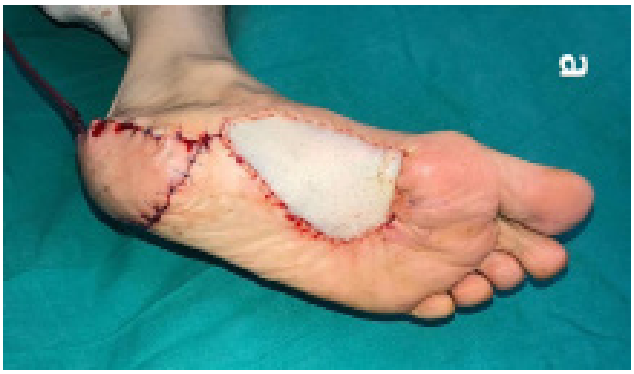

Figure 2a: Adaptation of the flap to the defect.

Case 4: The patient, who had a lesion on the plantar region and whose pathology at an external center revealed malignant melanoma, was admitted to our clinic and hospitalized after further examination. The patient had diabetes mellitus disease. The patient's lesion was marked and excised with wide excision. Frozen result was negative. The patient had additional comorbidities such as Hypertension and Diabetes mellitus. A medial plantar artery flap was planned for the patient with plantar defect. The flap was elevated and a hemovac drain was placed at the base of the flap (Figure 3a). The flap was sutured to the defect area with an absorbable 3/0 monofilament suture in the subdermal plane. The skin was then sutured with 3/0 polypropylene suture and successfully reconstructed. The donor area was reconstructed with STSG from the anterolateral thigh. A tie-over dressing was applied to the graft, which was opened 3 days later. The graft was seen to be adherent to the base. On the same day, the patient underwent secondary operation for dehiscence at the wound site and hematoma at the base of the flap. Hemostasis was performed at the bleeding sites, and capillary haemorrhage of the flap was observed. In the following days, flap necrosis occurred due to the development of arterial insufficiency after initial venous insufficiency in the flap. Debridement was performed, the proximal medial plantar artery was ligated, and the existing area was reconstructed with STSG from the anterolateral thigh after 2 Vacuum asisted closure sessions. No complications occurred in the donor area. Neither recurrence nor wound dehiscence was observed in the late postoperative period (Figure 3b).

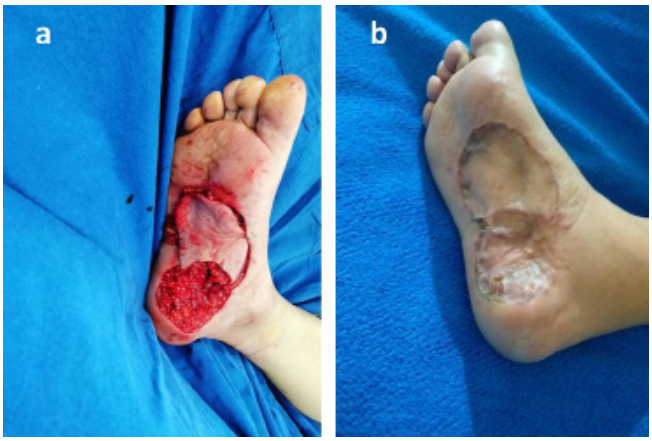

Figure 3a: Defect measured 4 cm × 4 cm after wide excision of the Melanoma in the left heel. Figure 3b: Late postoperative view (12th month) of the defect reconstructed with Split thickness skin graft from contralateral thigh after flap necrosis.

In all cases, the defects were examined for infectious diseases in terms of antibiotic therapy, and after negative culture results, they were operated. The defects were completely reconstructed in all patients. When the flaps were elevated, the plantar nerve was preserved, but although coaptation of the plantar nerve was performed in 2 diabetic patients (cases 2-8), no sensory return occurred at short and long follow-up.

After surgery, the flap was examined and closely observed 2-3 times per day for at least 10 days. All patients were discharged from the hospital after a recovery period of 2-4 weeks. Patients were followed up with controls every 4 weeks for at least 1 year, with an average of 14 months. After surgery, patients were allowed limited movement for 3 weeks. After the 3rd week, the operated foot was partially elevated from 5 minutes, and walking was allowed. Patients who did not experience complications were encouraged to return to their daily routine activities after week 5. Although a portion of the flap remained in the weight-bearing region in flaps placed at the heel, no wound dehiscence or necrosis occurred in late-stage flaps (postop 18th month) (Figure 2b).

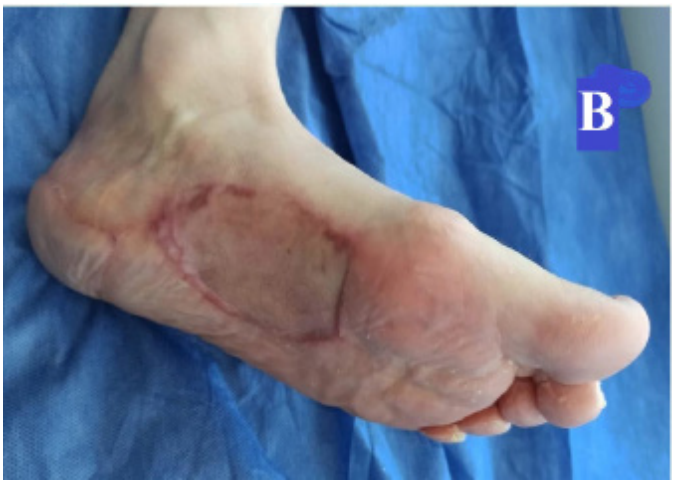

Figure 2b: The appearance of the flap in the 18th postoperative month.

Discussion

Defects of anatomical structures and weight-bearing parts of the foot, such as bones, tendons, joints, should be reconstructed with a flap. Reconstruction is difficult because of the limited number of flaps localized in the foot region.[8] Recently, foot defects have been reconstructed with skin-based island flaps. The general goal of reconstructing soft tissue defects in this region is to close the defect more quickly and easily by using skin with similar properties to the original skin.[9]

Cross leg flaps[10] and free flaps[11] can also be used in this area. However, in the cross-leg flap, postoperative care and immobilization are not acceptable nowadays when microsurgical methods are developed. Instead, microvascular free flaps are preferred. Most free flaps are done with flap thinning in secondary surgery. In addition, free flaps are technically difficult, require a long operative time and a surgeon trained in microsurgery.[12] These operations cannot be easily performed in small medical centers. Because of all these difficulties, pedicled flaps are preferred. There are a sufficient number of anatomic and clinical studies on the use of pedicled flaps in this region for defects in the foot.[13] The pedicled medial plantar artery flap, which we prefer, can be elevated in a short time. This flap does not need microsurgical expreience. It is a surgical technique with a rapid learning curve, as it can be performed in a single session without the need for surgery. Mpa flap is pliable, hairless, and its anatomy is reliable are important features.[14] In addition, this flap is one of the flaps that should meet all the requirements for defects in the plantar region because of its sensory feedback and thick glabrousness.[14] It has been reported that sensory recovery is more perfect in this reconstruction with tissue.[15] Although we performed nerve coaptation in two of our patients, there was no sensory recovery at late follow-up, and we think this is due to the insufficient number of patients and/or diabetes-related neuropathy because these patients are diabetic.

Another advantage of the flap is that it contains a sufficiently thick flap, donor site morbidity is minimal, the donor scar is not visible, there is no loss of function, it heals in a short time, and its vascularity is reliable.[6],[16] The medial plantar artery flap is very valuable for reconstruction of the plantar side of the foot with similar tissue. There were also no problems with the harvest site of the flap in our patients. We observed satisfactory functional gain in all patients. The gait pattern of the patients was normal, they could wear shoes and were satisfied with the cosmetic appearance of the flap.

The medial plantar artery-based flap is planned from the non-weight-bearing part of the plantar arch and is used in the reconstruction of the plantar region.[17] Since the medial plantar artery is not the dominant artery of the foot, it can be easily sacrificed.[17] It was easily used even in diabetic patients.[18] Although the number of patients in our study was limited, successful results were obtained in this flap used in diabetic patients, and additional studies are needed.

Although the medial plantar artery flap is safely used for foot defects, there are also some complications reported in previous publications.[19] Siddiqi et al.[17] reported one partial flap loss in their study of 18 patients. In a multicenter prospective study by Schwarz and Negrini, flap necrosis was reported in 1 of 51 patients, delayed healing in 4, and recurrent ulceration in 7.[18] Recurrent ulceration has been associated with diabetes-induced neuropathy.[18] In our study, the rate of dehiscence and necrosis was lower, and no ulceration was observed at all. Flap necrosis was observed in one patient. These results were similar to those of the study by Benito-Ruiz et al.[20] The reason could be the small number of patients or the antibiotic treatment we used in consultation with preoperative infectious diseases.

Khan et al reported necrosis in 1 of 16 patients. They attributed

the necrosis to impaired foot perfusion due to diabetes.[21] This is because the patency of the vessels participating in foot blood flow was confirmed by Doppler and angiography studies before surgery. However, there is a need to work with more patients on this issue. In the study by Schwarz et al, the overall complication rate (necrosis, dehiscence, infection, etc.) was 25%, and the number of patients with recovery was reported to be 11%.[18] In our study, the overall complication rate was 13,3%, and the wound dehiscence rate was 13,3%. This depends on the preoperative antibiotic treatment and glycemic control in diabetic patients.

Reconstructions with flaps of the medial plantar artery have some limitations. The disadvantage of this technique is that the foot includes the plantar apeneurosis, where the main blood flow is also located.22 Another disadvantage is that the distal vascular network cannot be relied upon to provide retrograde flow in the event of severe injury to the foot. Limitations of the flap and the risk of venous congestion are also among the limitations.23 In cases where larger flaps are required, muscle or fasciocutaneous other flaps (Anterolateral thigh flap, rectus abdominis flap...) should be preferred for defect reconstruction.

Conclusion:

The medial plantar artery flap is one of the flap options that can be used for plantar defects. It has provided satisfactory long-term results without compromising foot function and is a useful option for reconstruction of plantar zone defects. In our cases, the island flap allows the foot to move up to the instep area. The anatomical structure of this area is outside the weight bearing area of the foot and has the same characteristics as the plantar area. It has become a preferred technique in our clinic. In this study, it was found that the medial plantar artery flap is a practical and simple method that can be used for defects in the plantar region.

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RESEARCH ARTICLE

Evaluation of Sexual Function and Satisfaction Before and After Therapy in Couples Who Applied With The Diagnosis of Vaginismus

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GRISS, Sexual function, Sexual satisfaction, Therapy, Vaginismus

Abstract

Introductıon: The aim was to evaluate changes in sexual function and satisfaction after therapy in couples who applied with a provisional diagnosis of vaginismus.
Methods: : From December 2017 to December 2018, couples who applied with a provisional diagnosis of vaginismus at the Sexual Dysfunction Polyclinic of Hospital were assessed before and after therapy with the Female Sexual Function Scale (FSFI), the International Erectile Function Form (IIEF), and the Golombok-Rust Sexual Satisfaction Scale (GRISS), as well as the Beck Depression and Anxiety Form, and the results were recorded.
Results: Forty-one couples who presented to the sexual dysfunction outpatient clinic with a diagnosis of vaginismus participated in the study. After treatment, there was significant improvement in GRISS scores in men and women, FSFI scores in women, and IIEF scores in men.
Beck's depression scores decreased significantly in both men and women. In addition, Beck anxiety scores decreased significantly in women ($p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, $p < 0.01$, respectively).
Conclusıon: After sex therapy, there was a significant improvement in GRISS scores in both men and women, FSFI scores in women, and IIEF scores in men. Depression scores decreased significantly in both men and women. In addition, anxiety scores decreased significantly in females. The improvement in male sexual function in sex therapy during vaginismus treatment compared to pretreatment is new information in the literature

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Introduction

Vaginismus is the inability to have sexual intercourse as a result of irregular or continuous involuntary contraction of the vaginal muscles during sexual activity. In the new American Psychiatric Association (APA) guideline (DSM-5), vaginismus was identified as a genito-pelvic penetration disorder and included in the guideline.[1] Although the prevalence is reported in the literature to be approximately 0.5-6% [2,3] different prevalences have been found in many studies conducted in different countries. This suggests that vaginismus is a disorder influenced by cultural differences.

Vaginismus affecting couples was described many years ago. Trotula of Salerno, in her 1547 work The Diseases of Women, is said to have given the earliest description of vaginismus: 'a tightness of the vulva, so that even a seduced lady may look like a virgin." However, Sims was the first to describe vaginismus as it is known today .[4] This can affect the sexual compatibility of many couples and lead to stress, anxiety, and relationship problems in the partnership. Vaginismus has a complex etiology and can result from a combination of psychological, physiological, and relationship factors. Despite its complexity, vaginismus is a condition that is easily treated. A meta-analysis found that 80% of patients benefit from treatment.[5]

Vaginismus is attempted to be treated with methods such as cognitive behavioral sex therapy (CBT), pelvic floor training, and pharmacological therapy.[6] Behavioral therapy (IMB) is a relaxation-based pelvic floor sex therapy developed by Fisher.[7] The goal of this study is to compare the degree of sexual satisfaction in couples with vaginismus before and after treatment, as well as to look at the effects of the IMB-based therapy program on sexual satisfaction. This study will help us understand how sexual satisfaction changes in couples treated for vaginismus and evaluate the success of treatment strategies.

Material And Methods

This is a prospective study in which the sexual functions of couples who had registered at the Sexual Dysfunction Outpatient Clinic of Hospital between December 2017 and December 2018 with a provisional diagnosis of vaginismus were evaluated before and after therapy. Before therapy, all patients underwent gynecological examination and it was found that there was no anatomical problem, after which therapy was initiated accordingly. Sexual therapy was performed on the patients in the presence of the same psychologist (N.B.) and obstetrician (S.Y.E.) and was completed after 8 sessions. To assess sexual function, the Female Sexual Function Scale (FSFI) and the International Erectile Function Form (IIEF) were employed, and to assess sexual satisfaction, the male and female forms of the Golombok-Rust Sexual Satisfaction Scale (GRISS) were utilized. Before and after therapy, patients' anxiety and depression levels were assessed using the Beck Depression and Anxiety Form.

For each patient, age, body mass index (BMI), work status, education level, presence of an unwanted child, previous sexual abuse, parental separation situation, smoking, drinking and drug habits, masturbation, premarital sexual experience, coital frequency, vulvodynia, vaginismus symptoms, and previous treatments were recorded. The Helsinki Declaration was followed in this study, which was authorized by the institutional review board (approval number: 27/12/2017/7). All participants provided verbal and written informed consent.

GRISS, a test developed by Rust and Golombok and approved in Turkey[8,9], is the first test we used. The test consists of 28 items and is used to assess sexual dysfunction in heterosexual couples. The form used for women contains scales with titles such as vaginismus, anorgasmia, female emotionality, and dissatisfaction. The form prepared for men contains several titles. Impotence, Premature Ejaculation, Frugality, Male Avoidance, Male Apathy, and Male Dissatisfaction are the symptoms. The index can have a maximum score of 9.0 and a minimum value of 1.0. Higher scores imply a worsening in sexual function and relationship quality.

FSFI; It is a test developed by Rosen et al.[10] to assess female sexuality. The scale assesses sexual function over the past four weeks using six subcategories. Sexual desire, arousal, lubrication, orgasm, satisfaction, and pain are examples of these. The smaller the loss of function, the better the score. On the scale, the maximum possible score is 36.0, and the lowest possible score is 2.0. The cut-off point is 26.55, and anything below implies sexual dysfunction. This test has been translated into Turkish.[11,12]

The International Index of Erectile Function (IIEF) is an erectile dysfunction questionnaire. Rosen et al. established the IIEF's overall dependability. The index's 15 items, which are divided into

five categories of sexual function (erectile function, orgasmic function, sexual desire, satisfaction with sexual intercourse, and general satisfaction), shown adequate validity, sensitivity, and specificity. The index can have a maximum score of 75.0 and a minimum value of 5.0. The smaller the loss of function, the higher the questionnaire score. Based on the scores, the IIEF scale categorizes erectile dysfunction as severe (1-10), moderate (11-16), moderate to mild (17-21), light (22-25), and no erectile dysfunction. (26-30).[13] The Turkish Andrology Society has validated the IIEF's validity and reliability.[14]

The Beck Depression Inventory is a 21-item questionnaire that examines depression's presence and severity.[15] The survey items were chosen to represent symptoms often linked with depression disorder, such as melancholy, pessimism, crying bouts, guilt, self-hatred and self-reproach, irritability, social withdrawal, work inhibition, sleep and eating disorders, and loss of libido. The Turkish version's validity and dependability were proved. The total score ranges from 0 to 63, with a cut-off number of 17.[16]

The Beck Anxiety Inventory is a self-report questionnaire with 21 items that largely measures somatic anxiety symptoms such as palpitations, uneasiness, inability to relax, and dizziness or light-headedness.[17] Thirteen items are graded on a four-point scale ranging from 0 (not at all) to 3 (very severe: I could hardly stand it). Ulusoy et al. 18 assessed the Turkish version's validity and reliability[18].

Statistical analysis

The SPSS 23.0 program was used for the statistical analysis of the investigation. To summarize the data, descriptive statistics were employed. The mean and standard deviation of categorical variables were reported. The Shapiro-Wilk test was used to determine the normal distribution of continuous variables. The paired sample t test was employed if the seasonal changes were regularly distributed. For nonparametric paired samples, the Wilcoxon signed rank test was utilized. For statistical significance, a p 0.05 significance level was chosen.

Result

Forty-one couples presenting to the sexual dysfunction outpatient clinic with a diagnosis of vaginismus were included in the study. The mean age was 26 (18-40) years in women and 27 (18-42) years in men. The mean BMI was 29.5±4.4 in the women and 29.7±2 in the men. 56.1% of women (n=23) and 12.2% of men were not employed, which was statistically significant (p=0.01). While the educational level of women was the highest (34.1%), the majority of men had a college degree (48.8%) (p=0.03). For both genders, 12.2% (n=5) had unwanted child status and 2.4% (n=1) had a history of sexual abuse. 48.8% of men (n=20) smoked statistically significantly more than women ($p < 0.01$). 87.8% (n=36) of men masturbated statistically significantly more than women, and 58.5% (n=24) had premarital sexual experiences ($p < 0.01$ and $p < 0.01$, respectively). Frequency of sexual intercourse was once per week or less in 61% (n=25). Vulvodynia was noted in 43.9% (n=18) of women and vaginismus in 100% (n=41). 70.7% (n=29) of women had not previously received treatment (Table 1). After 8 therapy sessions, 35 couples had vaginal penetration and 6 couples were encouraged to continue sessions.

Table 1. Sociodemographic and clinical characteristics of couples.

	Female n=41 (%)	**Male n=41 (%)**	**p**
Age (year, median (min-max))	26(18-40)	27(18-42)	1.0
BMI (kg/m2)	29.5 ±4.4	29.7±2	0.79
Working status			**0.01**
Working	23(56.1)	36(87.8)	
Not working	18(43.9)	5(12.2)	
Graduated, % (n)			0.03
Primary school	12(29.3)	7(17.1)	
Elementary school	14(34.1)	6(14.6)	
High school	6(14.6)	8(19.5)	
University	9(22)	20(48.8)	
Unwanted child	5(12.2)	5(12.2)	1.0
History of sexual abuse	1(2.4)	1(2.4)	1.0
Parents separate	5(12.2)	3(7.3)	0.71
Smoking habit	4(9.8)	20(48.8)	**<0.01**
Drinking habit	5(12.2)	7(17.1)	0.532
Recreational drug use	1(2.4)	1(2.4)	1.0
Masturbation	7(17.1)	36(87.8)	**<0.01**
Premarital sexual experience	2(4.9)	24(58.5)	**<0.01**
Coit frequency			
No coit	9(22)	-	
once week	25(61)	-	
≤ 3 a week	4(9.8)	-	
>3 a week	3(16.7)	-	
Vulvodynia	18(43.9)	-	
Vajinismus	41(100)	-	
Previous treatment	-		
No treatment	29(70.7)	-	
Vaginal examination	6(14.6)	-	
Psychotherapy	2(4.9)	-	
Botox application	3(7.3)	-	
Vaginal operations	1(2.4)	-	

Chi square test performed. BMI, Body mass index. Data is a given as mean± Standard deviation. Results were accepted as 95% confidence interval and p value <0.05 significant.

It was found that when sexual function was assessed using the FSFI score before and after therapy, there was a statistically significant change in desire, arousal, lubrication, orgasm, satisfaction, pain, and total FSFI score (respectively p < 0.01, p < 0.01, p < 0.01, p). =0.01, p < 0.01, p < 0.01, p < 0.01, Table 2). When assessing men's sexual function with the IIEF score before and after therapy, a statistically significant change was observed in erectile function, orgasmic function, sexual desire, satisfaction with sexual intercourse, overall satisfaction, and total IIEF score (respectively p < 0.01, p < 0.01, p < 0.01, p < 0.01, p < 0.01, p < 0.01, Table 2).

Table 2. Couples' depression, anxiety, sexual satisfaction and functional scores before and after therapy.

	Female before therapy (Mean± standard deviation)	Female after therapy (Mean± standard deviation)	Z	P	Male before therapy (Mean± standard deviation)	Male after therapy (Mean± standard deviation)	Z	P
FSFI score								
Desiree	2.85±1.71	3.8±1.6	-5.30a	**<0.01**	-	-	-	-
Arousal	2.5±1.4	3.7±1.7	-4.93a	**<0.01**	-	-	-	-
Lubrication	2.8±1.5	3.4±1.6	-3.88a	**<0.01**	-	-	-	-
Orgasm	3.2±1.5	3.8±1.8	-2.54a	**0.01**	-	-	-	-
Satisfaction	3.3±1.6	3.7±1.4	-316a	**<0.01**	-	-	-	-
Pain	2.7±1.6	3.7±1.4	-5.16a	**<0.01**	-	-	-	-
Total	21.04±3.8	29.8±3.8	-5.41a	**<0.01**	-	-	-	-
IIEF score								
EF	-	-	-	-	25.4±3.4	27.8±2.1	-5.27a	**<0.01**
OF	-	-	-	-	7.2±2.5	8.9±1.2	-5.08a	**<0.01**
SD	-	-	-	-	6.6±2.2	8.5±1.3	-5.306 a	**<0.01**
IS	-	-	-	-	10.3±3.08	13.1±1.6	-5.34 a	**<0.01**
OS	-	-	-	-	6.7±2.1	8.6±1.1	-5.302 a	**<0.01**
Total	-	-	-	-	49.9±7.0	52.3±7.2	-5.62 a	**<0.01**
GRISS score								
Infrequency	5.48±1.81	3.46±2.3	-3.6b	**<0.01**	5.7±1.9	4.5±5.1	-2.82b	**0.005**
Non-communication	4.78±1.87	4.70±1.9	-0.14b	0.88	4.8±2.0	4.2±1.8	-1.37b	0.171
Female/male dissatisfaction	4.46±1.97	4.78±1.4	-0.81a	0.41	5.1±2.0	4.2±1.5	-2.36b	**0.018**
Female/male avoidance	4.09±2.14	4.78±1.8	-1.52a	0.12	4.6±2.3	4.2±1.7	-1.06b	0.28
Female/male non-sensuality	4.63±1.85	4.63±2.2	-0.91b	0.92	4.9±1.9	4.1±2.1	-1.72b	0.85
Vaginismus/ Impotence	4.56±2.1	5.31±1.6	-1.87a	0.06	5.0±2.2	4.7±1.8	-0.48b	0.62
Anorgasmia /Premature ejaculation	4.4±1.7	5.6±1.9	-2.53a	**0.01**	5.2±1.9	4.9±2.1	-0.80b	0.42
Total	7.04±0.94	5.9±1.4	-3.87b	**<0.01**	7.1±1.0	5.5±1.5	-4.54b	**<0.01**
Beck depression score	24±16.3	8.6±5.26	-5.32b	**<0.01**	16.5±13.4	12.4±11.7	-3.209b	**0.01**
Beck anxiety score	14.8±9.9	11.5±9.1	-2.93b	**0.003**	11.8±8.7	10.3±7.2	-0.6 b	0.549

Summary of Wilcoxon signed rank test results. Results were accepted as 95% confidence interval and p value <0.05 significant. a based on negative ranks. b based on positive ranks. FSFI, Female Sexual Function Index; IIEF, International Index of Erectile Function; EF, erectile function; OF, orgasmic function; SD, sexual desire; IS, intercourse satisfaction; OS, overall satisfaction; GRISS, Golombok Rust Inventory of Sexual Satisfaction

When assessing sexual satisfaction with the women's GRISS score before and after therapy, a statistically significant change was found in frequency, anorgasmia, and GRISS total score (respectively p < 0.01, p=0.01, p < 0.01, Table 2). When assessing men's sexual satisfaction with the GRISS score before and after therapy, a statistically significant change was found in frequency, male dissatisfaction and GRISS total score (respectively p=0.005, p=0.018, p < 0.01, Table 2). It was found that there was a statistically significant change in the depression scores of women and men with the Beck depression score before and after therapy (respectively p < 0.01, p=0.01, Table 2). It was found that there was a statistically significant change in anxiety scores with the Beck Anxiety Score before and after therapy in females (p=0.003), although there was a decrease in the score in males, but it was not statistically significant (Table 2).

Discussion

This study objectively demonstrates the effectiveness of sex therapy and counseling in vaginismus patients. After therapy, there was a significant improvement in GRISS scores in both men and women, FSFI scores in women, and IIEF scores in men. Depression scores decreased significantly in both women and men. Anxiety scores also decreased significantly in women. When sex therapy was provided during treatment for vaginismus, men's sexual functioning improved compared to before treatment. This is a point that has not been mentioned in the literature before and is very important for couples who have problems with vaginismus.

When penetration is not attempted or expected in women with vaginismus, the normal female sexual response does not change. Many authors report that sexual functions such as pleasure, arousal, and orgasm are not affected, and sexual satisfaction is quite high.[19-21] In our study, scores for pleasure, arousal, lubrication, orgasm, satisfaction, and pain on the FSFI test were statistically higher after therapy than before. This objectively proves that therapy is effective for female sexual function. Sexual dysfunction, adequate and appropriate sex It is known that sexual problems are resolved with greater satisfaction thanks to counseling.[22] According to a study by Kabakçı et al, improvements in vaginismus, anorgasmia, frequency, communication, satisfaction and avoidance were observed in all GRISS subscale scores due to sex therapy.[23] In our study, there was a significant improvement in all GRISS scores for sexual satisfaction after therapy compared to before therapy, both in men and women.

It is known that IIEF scores improve during sex therapy for erectile dysfunction.[24] When sex therapy was given during treatment for vaginismus, this score improved compared to before therapy. This is a point that has not been mentioned in the literature before and is important for

couples who have problems with vaginismus. According to a study by Yıldırım et al, the prevalence of depression and anxiety was found to be higher in women with vaginismus than in the general population, suggesting that these patients are more vulnerable to psychiatric disorders.[25] In our study, a significant decrease in depression scores was found in both men and women after therapy in couples complaining of vaginismus. Anxiety scores in women also decreased significantly. This situation objectively demonstrates the importance of couples therapy and a holistic approach in the assessment of couples complaining of vaginismus.

Reissing et al [26] reported in a study comparing patients with vaginismus to healthy controls that in women with vaginismus, desire, arousal, and pleasure were impaired and masturbation rates were low. The fact that men masturbate statistically significantly more often than women and have more experience with premarital sex suggests that women are less knowledgeable and accepting of their own sexual organs. In this case, we assume that the cultural and geographic influence is quite large.

The fact that smoking is significantly more common in men than in women suggests that, contrary to popular belief, vaginismus is a stressor for both men and women, and that they are as obsessed as women. Therefore, it is entirely appropriate to treat vaginismus as a couple's problem in our clinic and to treat it as a couple.

One of the limitations of the study is that not all couples who registered in the outpatient clinic agreed to participate in the study, resulting in a small number of patients.

Conclusion

As a result, after sexual counseling and therapy, depression and anxiety were observed to decrease, while sexual satisfaction and sexual functioning improved in both men and women, Vaginismus is a couple's problem, and sex therapy is very important in this disease. Further studies on this topic are needed.

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RESEARCH ARTICLE

Association of Systemic Immune-Inflammation Index with the Presence and Severity of Obstructive Sleep Apnea Syndrome

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Abstract

Introduction: PThe systemic immune-inflammation (SII) index provides information about the inflammatory status. Therefore, in the present study, we aimed to show the role of the SII index in patients with OSAS.

Methods: Patients who were taken to a tertiary center for apnea, excessive daytime sleepiness, or snoring between May 2019 and December 2022 were analyzed. The SII index was calculated as follows: (neutrophil × platelet) / lymphocyte.

Results: The study included 300 OSAS patients with an apnea-hypopnea index (AHI) of over 5 according to PSG.A control group of 106 people with an AHI of less than 5 was also part of the study. OSAS patients were separated into three groups according to their AHI: mild (5 ≥ AHI < 15), moderate (15 ≥ AHI < 30), and severe (AHI ≥ 30). The SII index had a larger area under the ROC curve for the presence and severity of OSAS than other CBC parameters (AUC for AHI 5 = 0.733 and AHI 30 = 0.699). After adjustment, multivariable logistic regression analyses revealed that the SII index, age, and BMI were independent predictors of OSAS [ORs (CI 95%) = 1.053 (1.030-1.076); p<0.001, 1.009 (1.006-1.012); p<0.001 and 1.360 (1.244-1.487); p<0.001], respectively.

Conclusion: In our study, we showed that an increased SII index was associated with the presence and severity of OSAS. We believe that it can be used as a novel and important marker since the higher SII index provided relevant information regarding the presence and severity of OSAS patients.

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Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is defined by recurrent respiratory arrest brought on by repeated obstruction of the upper airway, resulting in a decrease in blood oxygen saturation during sleep.[1] It affects up to 5% of people.[2] The polysomnography (PSG) is the gold standard to determine OSAS patients.[3] OSAS is thought to have a role in the etiology of many systemic disorders, including neurologic and cardiovascular diseases.[4] The etiology of OSAS is yet unknown, but the role of inflammation in the upper airway is well-known.[5]

A simple and relatively cheap laboratory test, the complete blood count (CBC), is often used in routine clinical practice. This test is promising for learning more about a variety of diseases. In a number of studies, it has been observed that CBC parameters are helpful in order to assess inflammation and thrombotic risk. There are many studies investigating whether CBC indicators such as the neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), and white blood cell count/MPV ratio (WMR) alone or in any combination can be used to provide prognostic information for various diseases.[6-10] Furthermore, several CBC parameters, such as NLR, PLR, and WMR, were evaluated in OSAS patients and provided valuable information about the prognosis of the disease.[6, 7, 9, 10]

The systemic immune-inflammation (SII) index is a novel predictor of adverse outcomes in various cancers.[11-14] Recent studies also show that the SII index may be utilized to predict the prognosis of cardiovascular diseases.[15,16] In addition, it has been demonstrated that the SII index outperformed other CBC indicators in predicting the prognosis of cardiovascular diseases since it contains more information about the inflammatory status.[15,16]

The association between the SII index and the presence and severity of OSAS has not been shown. Therefore, in the present study, we aimed to show the role of the SII index in patients with OSAS.

Material and Methods

Study Cohort

In the current retrospective cohort study, we analyzed the data of 710 patients admitted to Ankara City Hospital with complaints of witnessed apnea, snoring, and excessive daytime sleepiness between May 2019 and December 2022. A total of 304 patients were excluded from the study due to the following reasons: diabetes mellitus (n=51), active infection (n=31), history of acute coronary syndrome (n=21), history of chronic obstructive pulmonary disease (n=14), history of autoimmune or rheumatologic diseases (n=13), malignancy (n=8), and missing data (166).

Blood Samples

All patients' age, sex and body mass index (BMI) were recorded. Patients whose complete blood count data were available were included in the study. An automated blood cell counter (Beckman Coulter analyzer, California, USA) was used for measuring CBC parameters. The parameters that were measured were: white blood cells; neutrophils; lymphocytes; monocytes; platelets; and eosinophils. NLR, PLR, LMR, and ELR values were calculated by dividing related values by each other. The SII index was calculated as follows: (neutrophil×platelet) / lymphocyte.

Polysomnography

During spontaneous sleep, a full-night PSG (Alice 6 Model PSG - Philips Respironics, The Netherlands) was performed under the control of a sleep technician in sleep laboratory. Parameters including minimum oxygen saturation, oxygen desaturation index, sleep efficiency, the time in minutes spent in sleep with oxygen saturation below 90%, and the ratio of time in rapid eye movement (REM) to total sleep time were recorded. All data were manually scored by at least two independent Ear, Nose, and Throat (ENT) physicians according to the standard criteria set by the American Academy of Sleep Medicine. Apnea was defined as a cessation of airflow at the nose and mouth lasting at least 10 seconds. Hypopnea was defined as a 30% decrease in airflow for 10 seconds accompanied by a 3% decrease in oxygen saturation or an arousal. AHI was measured as the number of apneas and hypopneas per hour in the sleep test (PSG) performed during nighttime sleep. In total, 300 patients with OSAS [> 5 AHI as assessed by PSG] were included in the study. Additionally, 106 individuals with less than 5 AHI were included in the study as a control group. OSAS patients were separated into three groups: mild ($5 \geq AHI < 15$), moderate ($15 \geq AHI < 30$), and severe ($AHI \geq 30$).

Statistical Analyses

All statistical analyses were performed using Stata (version 17.0 MP; StataCorp). After the appropria-

te tests for the assessment of distribution, continuous variables were presented as mean and standard deviation (SD), and categorical variables were presented as the number of individuals and their percentage. The Student's t-test was used for two different groups. The Pearson correlation test was used to evaluate the association between the SII and AHI indices. Receiver operating characteristics (ROC) curve analysis was used to demonstrate the discriminative value of CBC parameters, including NLR, PLR, LMR, ELR, and SII index, in predicting the presence and severity of OSAS (for AHI ≥ 5 and 30). The area under the curve (AUC) was calculated for each parameter. A univariate logistic regression model was used to show significant predictors of OSAS patients, and then those with $p < 0.05$ were tested using a multivariable logistic regression model. The results of multivariable logistic regression analysis were presented as odds ratios (OR) with lower and upper 95% confidence intervals (95% CIs) of independent predictors of OSAS patients. Finally, a nomogram containing significant predictors was plotted as a graph. A p-value of < 0.05 was considered significant in all the statistical analyses.

Results

As shown in Table 1, in total, the study population consisted of 406 individuals. A total of 300 patients consisted of 114 (38.0%) females and 186 males (62.0%) in the OSAS group. The control group consisted of 106 people, 34 (32.1%) of whom were female and 72 (67.9%) of whom were male. The mean (SD) ages of the patients and control groups were 49.2 (10.4) and 38.4 (12.6) years, respectively. While the mean BMI of the OSAS group was 30.8 (4.6), it was 26.5 (3.4) in the control group (p<0.001). Furthermore, when compared to the control group, neutrophil count, NLR, PLR, SII index, and ELR were significantly higher in the OSAS group (p = 0.002, p = 0.001, p = 0.001, p = 0.046, respectively).

Table 1. Baseline characteristics and laboratory markers of study population according to control and OSAS Patients

	Overall N=406	Control (<5) N=106	OSAS (≥5) N=300	p-value
Age, years	46.4 (12.0)	38.4 (12.6)	49.2 (10.4)	<0.001
Male, (%)	258 (63.5%)	72 (67.9%)	186 (62.0%)	0.28
Body Mass Index, kg/m2	29.7 (4.7)	26.5 (3.4)	30.8 (4.6)	<0.001
White Blood Cell, (mm3)	7814.0 (1856.7)	7530.2 (1627.0)	7914.3 (1923.8)	0.067
Neutrophil, (mm3)	4508.0 (1421.6)	4149.1 (1055.0)	4634.8 (1511.5)	0.002
Lymphocyte, (mm3)	2480.0 (639.3)	2549.1 (624.5)	2455.7 (643.8)	0.20
Monocyte, (mm3)	595.4 (338.0)	550.9 (106.2)	611.1 (387.1)	0.12
Eosinophil, (mm3)	205.3 (198.4)	188.7 (136.2)	211.1 (216.1)	0.32
Systemic Immune Inflammatory Index	486.7 (284.9)	391.2 (111.8)	520.5 (318.1)	<0.001
Neutrophil Lymphocyte Ratio	1.9 (0.8)	1.7 (0.4)	2.0 (0.9)	<0.001
Platelet Lymphocyte Ratio	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	<0.001
Lymphocyte Monocyte Ratio	4.5 (1.4)	4.7 (0.9)	4.5 (1.5)	0.24
Eosinophil Lymphocyte Ratio	0.1 (0.1)	0.1 (0.0)	0.1 (0.1)	0.046

Figure 1 shows a statistically significant and positive correlation was found between the SII index and AHI as well as the SII index and severity of OSAS (p < 0.001; r = 0.370 and p < 0.001; r = 0.298, respectively).

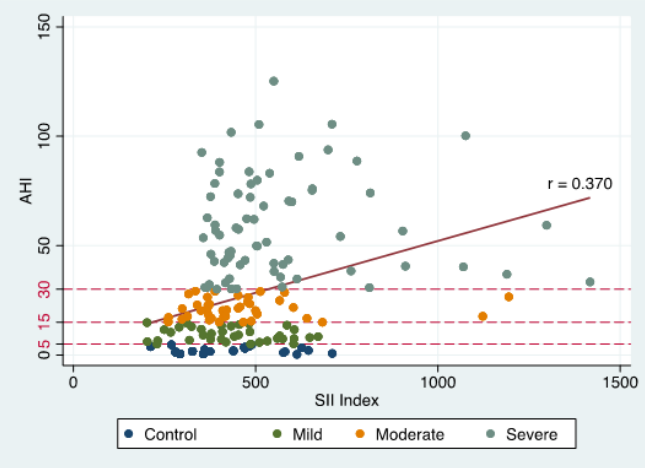


Figure 1. Correlation between the SII index and AHI

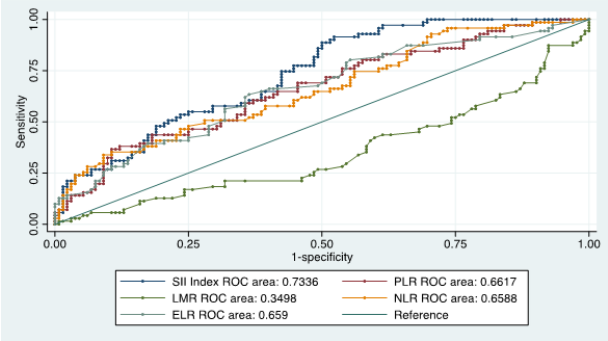
As shown in Table 2, 72 patients had mild OSAS, 86 patients had moderate OSAS, and 142 patients had severe OSAS. According to the severity of OSAS, age (p<001), BMI (p<001), WBC (p=0.008), neutrophil (p<001), monocyte (p<001), eosinophil (p<001), SII index (p<001), PLR (p<001), LMR (p<001), ELR (p<001) were statistically significantly increased with an increasing degree of disease.

Table 2. Baseline characteristics, laboratory and PSG markers of study population according to severity of OSAS Patients

	Mild N=72	Moderate N=86	Severe N=142	p-value
Age, years	45.0 (8.6)	49.3 (9.7)	51.3 (11.0)	<0.001
Male, (%)	38 (52.8%)	60 (69.8%)	88 (62.0%)	0.11
Body Mass Index, kg/m2	29.0 (3.8)	29.7 (4.0)	32.4 (4.9)	<0.001
White Blood Cell, (mm3)	7486.1 (1667.8)	7764.9 (1915.3)	8222.0 (2008.5)	0.008
Neutrophil, (mm3)	4234.7 (1222.1)	4466.3 (1368.6)	4939.7 (1664.5)	<0.001
Lymphocyte, (mm3)	2517.2 (672.8)	2524.9 (618.6)	2382.5 (640.3)	0.16
Monocyte, (mm3)	551.1 (159.9)	554.7 (197.6)	675.8 (522.9)	0.006
Eosinophil, (mm3)	153.3 (109.8)	171.9 (97.3)	264.2 (285.9)	<0.001
Systemic Immune Inflammatory Index	428.4 (132.6)	456.1 (184.9)	606.2 (413.3)	<0.001
Neutrophil Lymphocyte Ratio	1.8 (0.6)	1.8 (0.5)	2.2 (1.1)	<0.001
Platelet Lymphocyte Ratio	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	<0.001
Lymphocyte Monocyte Ratio	4.8 (1.3)	4.9 (1.8)	4.1 (1.4)	<0.001
Eosinophil Lymphocyte Ratio	0.1 (0.0)	0.1 (0.0)	0.1 (0.1)	<0.001
Minimum Oxygen Saturation	85.0 (4.0)	81.8 (5.7)	70.8 (13.4)	<0.001
Oxygen Desaturation Index, (%)	8.1 (7.5)	18.7 (7.9)	56.6 (25.0)	<0.001
Sleep efficiency, (%)	78.5 (18.7)	80.8 (18.1)	81.9 (12.8)	0.34
Sleep with oxygen saturation below 90%, (min)	7.9 (29.4)	10.2 (16.3)	83.6 (100.5)	<0.001
Ratio of REM, (%)	17.6 (6.5)	16.9 (6.8)	16.6 (13.8)	0.81

When compared to other CBC parameters such as PLR, NLR, LMR, and ELR, the SII index had the highest discriminative value for the presence and severity of OSAS (AUC for AHI 5 = 0.733 and AUC for AHI 30 = 0.699). (Figure 2 A and B).

A



B

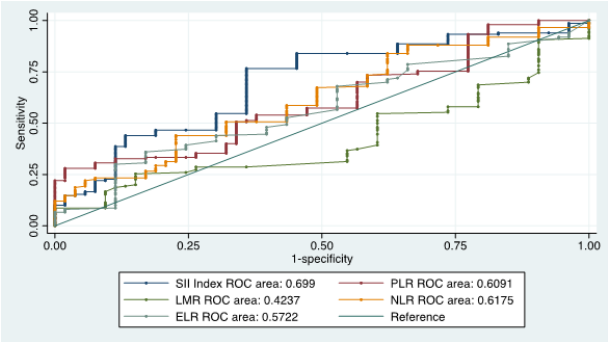


Figure 2. Receiver operating characteristics (ROC) curve analyses
2A Capable of discriminating the presence of OSAS (AHI ≥ 5)
2B Capable of discriminating the severity of OSAS (AHI ≥ 30

After adjustment, multivariable logistic regression analyses revealed that the SII index, age, and BMI were independent predictors of OSAS [ORs (CI 95%) = 1.053 (1.030-1.076), 1.009 (1.006-1.012), and 1.360 (1.244-1.487)], respectively. Using these parameters, we also created a new nomogram scale, as shown in Figure 3.

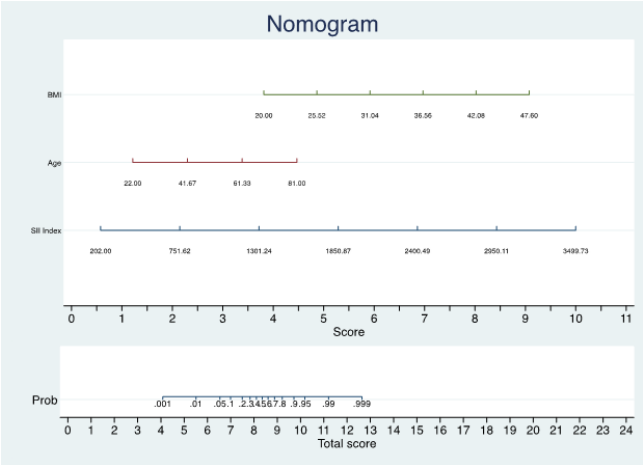


Figure 3. The nomogram of independently significant predictors of OSAS patients

Discussion

In this study, we found that the SII index, a routine marker that is easy to get and not too expensive, gave useful information about the presence and severity of OSAS in patients. Also, the SII index is better at telling people apart than CBC markers like PLR, NLR, LMR, and ELR.

OSAS is characterized by recurrent complete or partial collapse of the upper airway. Obstructions in the upper airway during sleep leading to hypoxemia, hypercapnia, autonomic nervous system changes, and sleep disruption are determinants in the development of OSAS. It can be said that genetic and environmental factors affect processes such as facial structure, collapsibility in the upper airway, body fat distribution, neurological control of the upper airway, central regulation of respiration, and the development of OSAS. The disease has a very complex pathophysiology, and the roles of contributing factors also vary among individuals with OSAS17.

Inflammation is increased in both the mucosal tissue and the muscular compartment in patients with OSAS. The vibration of snoring, intense activation of muscles during airway reopening, and increased oxidative stress associated with hypoxia-reoxygenation

are thought to be responsible for increased inflammation. In patients with OSAS, there is an increase in connective tissue, both in the upper respiratory tract mucosa and muscles. Changes in the connective tissue content in the upper respiratory tract cause changes in airway caliber and compliance18.

It has been suggested that inflammation plays a role in the development of many diseases19. Prior studies show stenosis in the uvulopalatal arch region in half of the patients with OSAS, and in the base of the tongue in the other half20. It has been shown by MRI that narrowing of the upper airway in patients with OSAS is associated with thickening of the lateral pharyngeal wall21. This wall thickening is characterized not only by an increase in pharyngeal fat tissue or an abnormality in the bony roof but also by an increase in soft tissue. Some of this swelling is edema due to inflammation.

In various studies, the increase in many biomarkers such as CRP, leptin, TNF-alpha, IL-6, vascular endothelial growth factor, and reactive oxygen radicals which are indicating that systemic inflammation is increased in OSAS22. In light of the above-mentioned, local and systemic inflammation have an important role in the development and severity of OSAS.

We speculate that several mechanisms may be responsible for the SII index being a stronger predictor of the presence and severity of OSAS than other CBC parameters. The SII index is more sensitive than neutrophils, lymphocytes, the NLR, and the PLR since it is caused by the combination of three different inflammatory parameters in a single combination. Single-component inflammatory markers, such as neutrophils, lymphocytes, or platelets, and two-component inflammatory markers, such as NLR or PLR, are relatively poor prognostic markers. Therefore, the SII index could be a more sensitive predictor of host immunological and inflammatory states.

In the current study, we found that BMI and age are also significant and independent predictors of the presence of OSAS23-24. Our findings were similar to prior studies. According to our multivariable logistic regression results, we created a nomogram using the SII index, age, and BMI. We believe that our nomogram can be used in routine clinical practice to predict the presence of OSAS, which can easily be used to provide prognostic information for ENT physicians.

Limitations

There are several limitations to the study. First, it is a retrospective and relatively single-center study. Second, alterations in parameters based on response were not analyzed. Finally, since the SII index is a novel biomarker in the field of OSAS, prospective, multicenter studies with a larger study population are needed.

Conclusions

In our study, we showed that an increased SII index was associated with the presence and severity of OSAS. There are few studies in the literature on this subject. In addition, we found that the SII index has a better informative value than other CBC parameters in patients with OSAS. We believe that it can be used as a novel and important marker since the higher SII index provided relevant information regarding the presence and severity of OSAS patients.

Ethics Statement:

Ankara City Hospital's local ethics committee approved the study. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki.

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Conflict of Interest: None

Ethical Approval: Approved, no: E2-23-128

Informed consent: Yes

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CASE REPORT

A Post-Rhinoplasty Complication: Nasal Abscess And Preseptal Cellulitis

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Abstract

Rhinoplasty is one of the most frequently performed cosmetic surgeries and it may cause serious complications. Although it is a non-sterile operation, infection develops in less than 1% of the cases due to the facial abundant blood flow. Herein, we present a case diagnosed with preseptal cellulitis accompanied with progressive edema and tenderness that developed in the nasal tip and nasal dorsum one week after the rhinoplasty operation. Group A ß hemolytic streptococcus was detected in the abscess culture, and the infection was treated successfully with antibiotics. Vital sequels and complications were prevented by early diagnosis and appropriate antibiotic treatment. The patient was discharged without any complications.

Article Info

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Introduction

Rhinoplasty is gaining more and more popularity in the last decades; nevertheless, the complications of the operation are overlooked by both the surgeons and the patients. There are various complications related to rhinoplasty operation, which can be grouped as infectious, traumatic, hemorrhagic, and systemic. Although those complications rarely occur, they can cause disastrous results by both aesthetical and functional means. Infection is a rare but severe complication and can be seen in 0.1-0.5% of all rhinoplasty cases.[1] Post rhinoplasty infection is believed to be developed due to devascularised bone spicules or hematoma.[2] In this case, we present a nasal dorsum abscess and bilateral periorbital cellulitis after rhinoplasty operation.

Case Report

A thirty-three-year-old male patient admitted to our clinic with the complaint of a nasal deformity due to a nasal trauma in his childhood. The patient had a dorsal hump, inadequate tip support, and inadequate rotation at the inspection.

Figure 1: The preoperative appearance of the patient.

Both airways were open and intact at the rhinoscopy. An open structural rhinoplasty under general anesthesia was planned with the diagnosis of nasal deformity. The preoperative complete blood count and coagulation parameters were in normal ranges, and viral markers were negative.

The patient was not given a prophylactic antibiotic or premedication prior to surgery. Intranasal hair removal was performed intraoperatively prior to initial incision. The nasal flap was elevated using V-shaped trans-columellar and intercartilaginous incisions. After the subperichondrial and subperiosteal dissections, the dorsal hump was excised using a rasp. There was no need for spreader flaps or grafts since the airway was patent. Only a caudal septal excision was made and the cartilage graft was used as a columellar strut. Then, paramedian and lateral osteotomies were performed. No bone spicules were observed on the nasal dorsum during the operation. Likewise, unusual or any kind of excessive bleeding problems were not encountered. Any kind of alloplastic material was not used, and a further septoplasty was not performed. Power-assisted devices like piezoelectric systems that can be considered potential damage sources to the nasal flap vasculature were not used during the surgery. Doyle silicone splints were placed and sutured after surgical corrections. A thermoplastic splint was used for nasal bone stabilization. The patient was discharged on the first postoperative day after scheduling the follow-up examinations.

The patient was prescribed oral antibiotic therapy which included 2 x 1000 mg Amoxicillin/clavulanic acid for 1 week. Nasal splints were removed on the third postoperative day.

Fifteen days after the surgery, the patient applied to our clinic with complaints of edema and pain in the nasal dorsum, bilateral lower eyelid and infraorbital area, and erythema on the skin.

Figure 2: The appearance of the patient on the postoperative 15th day.

Moderate purulent rhinorrhea was observed. A paranasal computed tomography (CT) scan was performed for the differential diagnosis of cellulitis and abscess. CT scan report was as follows; "Tissue augmentation in the frontal part of the nasal dorsum and central tissue collection was observed, abscess?". Since the mass in the nose was well-circumscribed, an abscess was considered instead of cellulitis as the initial diagnosis and no further radiologic investigations were made.

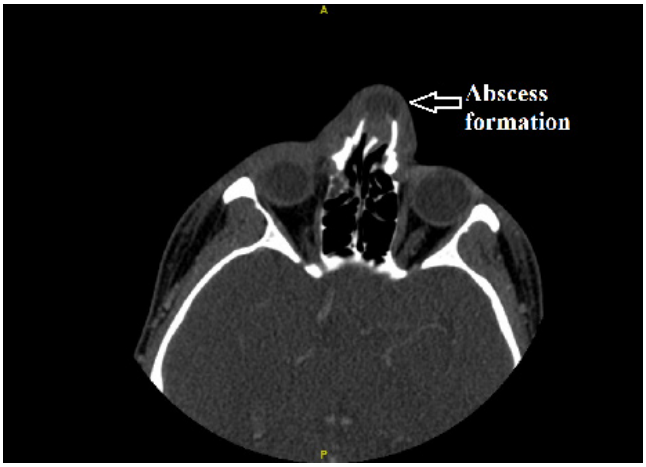

Figure 3: The CT scan of the patient.

In the complete blood count, leucocyte count was 15,000/mm3, the neutrophil ratio was 77%, and CRP was 57,2. Other biochemical laboratory results were in the normal ranges. Blood and throat cultures were negative. The patient was consulted with the infectious disease department; sulbactam-ampicillin 4 x 1,5 gr and metronidazole 3 x 500mg treatments were initiated empirically. The abscess in the nasal dorsum was drained percutaneously. Group A ß hemolytic streptococcus was shown in the culture of the drainage material. This result was reconsulted with the infectious diseases department. Ampicillin 4 x 1,5 gr IV treatment was maintained. No other additional treatment was given.

Clinical remission was observed in edema, pain, and skin erythema during the final treatment process. Leucocyte and neutrophil values were regressed. On the seventh day of the hospitalization, edema and all other symptoms were regressed, and the patient was discharged.

Figure 4: The appearance of the patient on the postoperative 22th day

Discussion

The high concentration of sebum releasing adipose tissue in the nose supports facultative anaerobic bacterias such as Propionibacterium acnes.[3] According to the study of Rudolph R, Slavin SA, Rees TD., pathogen bacterias Staphylococcus aureus and Streptococcus viridans were detected in nasal cultures of one-third of the rhinoplasty patients[4] Therefore, the nose is one of the most contaminated and most colonized regions in the body.

Sebben found that 20% of microorganisms on the skin remain in the regions where soaps and antiseptic solutions cannot reach.[5] Therefore the antiseptic choice is vital in septorhinoplasty operations.

The most commonly preferred antiseptics are alcohol-based (ethyl alcohol, propyl, or isopropyl alcohol), or iodine-based antiseptics (Povidone-Iodine), and chlorhexidine. Alcohol-based antiseptics are more effective on bacterias and viruses than other antiseptic types.[6] Rutala stated that alcohol-based antiseptics with 30 – 100 % concentration need a minimum of 10-15 seconds to gain bactericidal or virucidal effects.[7] Iodine-based antiseptics are routinely in use for rhinoplasty surgery in our clinic.

Postrhinoplastic infection may spread through skin, subcutaneous fascia, and muscle. The access points of microorganisms may be the areas where skin integrity is damaged, such as trauma lines, surgical incisions, and external osteotomy lines.

Vestibulitis and cellulitis are the most commonly occurring postoperative complications and can

be treated by a local antibiotic. If an abscess presence is seen, it should be drained. Also, in the cases of graft material implantation, the graft should be removed.

The most prevalent bacterial causes of post rhinoplasty infections are Staphylococcus and Streptococcus[8] However, there are other pathogens shown in the literature, such as Pseudomonas, Actinomyces, Haemophilus influenza, and non-tuberculous mycobacteria[8,9]

The presence of bone spicules on the lateral osteotomy lines and rhinoplasty accompanied by sinus surgery in the presence of purulent sinusitis are within the risk factors that might cause infection after rhinoplasty. In addition usage of acellular dermal matrix is another cause of nasal infections.[10]

There is no consensus in the literature on prophylactic antibiotherapy. Infection rates were found similar between the groups treated with and without prophylactic antibiotics in studies examining prophylactic antibiotic treatment. Prophylactic antibiotic treatment is suggested under the following conditions; active infection within the surgical area, keeping nasal tampons more than 24 hours, presence of hematoma, placing alloplastic implant, cases in which graft is used, revision surgeries, immunosuppression and, metabolic diseases.[11] The presented case was not given a prophylactic antibiotic.

Machida et al. reported a case of resistant face cellulitis after rhinoplasty, who had cord blood stem-cell transplantation.[12] It should be kept in mind that complications can arise after cosmetical surgery in immunosuppressed patients. Rhinoplasty can cause serious orbital and periorbital complications such as orbital bleeding, enophthalmos, exophthalmos, periorbital cellulitis, and blindness.[13] Orbital cellulitis is differentiated from preseptal cellulitis by ptosis, restriction of eye movements, and optic nerve damage. Orbital cellulitis is a potentially fatal emergent complication. Thus, these two complications should be differentiated, both clinically and radiologically such as using a CT scan. Since there was no ptosis and restriction of eye movements, this presented case was considered as preseptal cellulitis, which was also confirmed by a CT scan.

Additionally, since streptococcal periorbital necrotizing infection cases were reported, it is crucial to differentiate postoperative eyelid swelling and infective conditions. Systemic penicillin treatment prevents eyelid necrosis in those cases[2,13,14]

Toxic shock syndrome (TSS) is a rare post-rhinoplasty complication. Although the actual incidence of post rhinoplasty TSS is not precisely known, Jacobson JA, Kasworm EM reported that it is seen 16,5 in a million (15). Nasal pads/tampons are present in 98% of post-surgical TSS cases. Prodromal symptoms of TSS are fever, nausea, vomiting, erythroderma, and hypotension.[15] These symptoms were associated with Staphylococcus aureus, which releases exotoxins and exists on nasal pads/tampons.[5]

The area between the oral commissure and glabella covering the nose and maxilla is known as “The Triangle of Death." Infections occurring within this area can lead to cavernous sinus thrombosis in a retrograde way due to the deep anastomosis of the valve-free facial veins with superior orbital and pterygoid plexus. The occurrence of thrombosis may lead to complications such as blindness, facial nerve paralysis, meningitis, cerebritis, and brain abscess. If cavernous sinus thrombosis occurs, high dose intravenous antibiotic treatment must be initiated emergently[16]

Although bacteriemia after septorhinoplasty is seldom, it was detected in 3-12% of submucosal resection cases in which a nasal pad was used. Coursey reported a case that had staphylococcus endocarditis after septorhinoplasty.[17]

In conclusion, in this case we presented a nasal abscess and preorbital cellulitis, which are rare postoperative complications after a rhinoplasty operation. Vital sequels were prevented by early diagnosis and appropriate antibiotic treatment. In order to prevent this complication, the operation should be delayed in patients who have an active skin infection or purulent sinusitis. Bone dust, hematoma, and spicules remaining on osteotomy lines and dorsum after osteotomy should be removed. Although the desired cosmetic results were not fully achieved when the preoperative and postoperative photographs were examined, patient satisfaction was ensured and a secondary operation was not required.

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LETTER TO THE EDITOR

A Case of Pseudogout Successfully Treated with Prednisolone and Clarithromycin

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To the Editor pseudogout (PG) is an acute arthritis induced by calcium pyrophosphate dihydrate crystal deposition, and it frequently develops in the elderly population. Non-steroidal anti-inflammatory drugs and/or corticosteroids, such as prednisolone (PSL), administered either by local intra-articular injection or systemic therapy remain the mainstay of PG treatment.[1] Macrolide antibiotics (MACs), such as clarithromycin (CAM) and azithromycin (AZM) provide not only antibacterial activity but also anti-inflammatory properties. Several recent studies reported the successful treatment of rheumatoid arthritis[2] and polymyalgia rheumatica[3] using CAM as an anti-inflammatory agent. Herein, we describe a case of PG treated with PSL in combination with CAM, considering their anti-inflammatory properties. A 92-year-old female with Alzheimer's disease, hypertension and osteoporosis presenting with fever, arthralgia and articular swellings in her bilateral shoulders, elbows, and wrists, was referred to our hospital. At the age of 91, she was diagnosed with PG by an orthopedic doctor. So far, she has experienced two PG attacks. The laboratory findings on this visit were as follows: white blood cell count, 8,990/μL (basophils, 0.3%; eosinophils, 1.0%; neutrophils, 78.4%; lymphocytes, 12.7%; and monocytes, 7.6%); C-reactive protein (CRP), 11.81 mg/dL; rheumatoid factor, 5 IU/L; anti-cyclic citrullinated peptide antibody, 0.5 U/mL; and antinuclear antibody titer, 1:40. A blood culture yielded negative results. No abnormal findings suggestive of infection could be found in the systemic survey, including the chest roentgenogram and urinalysis. Bone roentgenogram revealed intra-articular calcification compatible with PG. The aforementioned symptoms were similar to those of the previous PG attacks; therefore, the patient was diagnosed with PG attack. Initially, she was treated with acetaminophen (800 mg/day), which was unsuccessful, although it was effective in the previous PG attacks. Therefore, she was treated with PSL (10 mg/day). Seven days after PSL treatment, fever and articular symptoms rapidly improved with a decreased CRP of 1.12 mg/dL. Therefore, the PSL dosage was decreased to 7.5 mg/day. A week later, fever and articular symptoms relapsed with an

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increased CRP of 16.01 mg/dL. The PSL dosage was again increased to 10 mg/day. Furthermore, she received CAM (400 mg/day), considering its anti-inflammatory properties. Ten days after CAM treatment, the symptoms improved with a decreased CRP of 0.2 mg/dL. Therefore, CAM was ceased and the PSL dosage was decreased to 9 mg/day. Thereafter, the PSL dosage could be gradually decreased to 5 mg/day without any recurrence of fever and articular symptoms. However, 2 weeks after receiving PSL (5 mg/day), articular symptoms relapsed with CRP increasing to 5.81 mg/dL. As an alternative to increasing the PSL dosage, she received CAM (400 mg/day) again. Two weeks after CAM retreatment, articular symptoms improved with CRP decreasing to 0.2 mg/dL. Thereafter, the PSL dosage could be gradually decreased to 2 mg/day. As stated above, MACs provide anti-inflammatory properties as well as antibacterial activity. MACs reportedly affect several pathways of the inflammatory process, including the production of proinflammatory cytokines. In fact, AZM inhibits the production of interleukin (IL)-1.[4] It has been reported that IL-1 is associated with PG attack[5]; therefore, the efficacy of CAM treatment in the present case might be because of its anti-inflammatory properties that inhibit the production of IL-1.

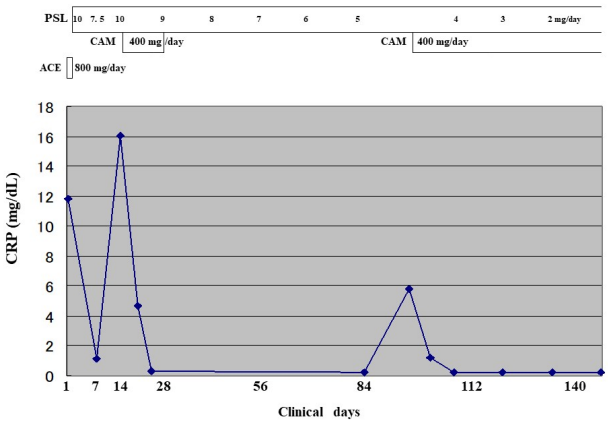

Figure 1. The laboratory data and prescribed agents on clinical days. ACE: acetaminophen, PSL: prednisolone, CAM: clarithromycin, CRP: C-reactive protein

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