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Revitalizing Sexual Function in Heart Failure patients: The Impact of Sodium-Glucose Co-Transporter 2 Inhibitors on Erectile Dysfunction

İlke Erbay, Yeşim Akın

Department of Cardiology, Karabük University Faculty of Medicine, Karabük, Türkiye

Abstract

BACKGROUND/AIMS: The prognosis of heart failure (HF) is closely related to the structural integrity of the endothelium. Endothelial dysfunction is observed as a characteristic feature of HF and it plays an important role in the development of erectile dysfunction (ED) in patients with HF. Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) have been shown to increase microvascular endothelial cell function through their pleiotropic effects. Therefore, we aimed to investigate the effects of SGLT-2i treatment on ED in patients with HF.

MATERIALS AND METHODS: Forty sexually active HF patients with reduced left ventricular ejection fraction [(LVEF) <40%] and ED were enrolled in this study. In all patients, their functional status was assessed according to the New York Heart Association functional classification, and erectile function was assessed by the Sexual Health Inventory for Men (SHIM) questionnaire at baseline and after three months of SGLT-2i treatment.

RESULTS: SGLT-2i treatment resulted in a significant improvement in the SHIM scores (12.7±5.6 vs. 15.4±5.5, p<0.001). Predictors of improved SHIM scores with SGLT-2i were assessed using multivariable regression. Age (p=0.002), baseline SHIM scores (p=0.042), and lower extremity peripheral vascular disease (p=0.002) were identified as negative predictors of improvements in SHIM scores, while changes in brain natriuretic peptide levels (p=0.035) emerged as a significant predictor of improvement in SHIM scores.

CONCLUSION: This cross-sectional study suggests that treatment by SGLT-2i could potentially provide advantages to patients with HF who also experience ED, enhancing their functional status.

Keywords: Heart failure, SGLT-2 inhibitors, SHIM score, sexual function, endothelial dysfunction

INTRODUCTION

Heart failure (HF) is a health concern which has a considerable impact on the adult population in developed nations, affecting around 1-2% of individuals.[1,2] The strong connection between endothelial dysfunction and shear stress significantly impacts the etiology of HF. Shear stress is frequently responsible for inducing the release of endothelial nitric oxide (NO). The reduction in shear stress which occurs in HF causes a concomitant reduction in endothelium-derived NO release, leading to an elevation in the oxidative stress.[3] Studies have shown that elevated levels of oxidative stress contribute to a reduction of NO bioavailability, impairing endothelial function.[4,5] This impairment may lead to decreased endothelium-dependent vasorelaxation[6,7] in penile endothelial cells, leading to erectile dysfunction (ED). Indeed, the incidence of ED may be as high as 84% in men with chronic compensated HF, the New York Heart Association (NYHA) class 1-3.[8]

Studies have shown that treatment with sodium-glucose cotransporter-2 inhibitors (SGLT-2i) reduces the likelihood of combined cardiovascular

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ORCID IDs of the authors: İ.E. 0000-0002-6817-4686; Y.A. 0000-0002-1238-7439.

Address for Correspondence: İlke Erbay
E-mail: ilkeerbay@karabuk.edu.tr
ORCID ID: orcid.org/0000-0002-6817-4686

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and all-cause mortality, first hospitalization, and hospitalization length in HF patients.[9,10] The physiological effects of SGLT-2i are thought to be mediated through antioxidant, anti-inflammatory, and anti-fibrotic pathways.[9,11,12] They also affect microvascular endothelial cell activity by increasing NO levels and endothelial bioavailability, thus improving endothelial dysfunction.[13] Although the positive effects of SGLT-2i on endothelial dysfunction have been established, their potential impact on ED in humans is currently unknown.

In line with all this evidence, this study evaluated the potential effects of SGLT-2i treatment on ED in patients diagnosed with HF with reduced ejection fraction (HFrEF).

MATERIALS AND METHODS

Study Population

The study was designed by the principles of the Declaration of Helsinki and the principles of Good Clinical Practice and did not violate the ethical rules of research involving human subjects. All participants provided their informed consent to participate in the study. Approval for the study was obtained from the Bioethics Committee of Karabük University (approval number: 2023/1258, date: 25.01.2023).

The present study was designed as a cross-sectional study. The study group consisted of HFrEF patients who continued to have symptoms despite receiving optimal medical therapy according to the 2021 European Society of Cardiology Guidelines for diagnosing and treating HF[9] and who were subsequently prescribed SGLT-2i as an adjunctive therapy. A total of fifty sexually active HF patients aged 30 to 70 years with reduced left ventricular ejection fraction [(LVEF) <40%] were recruited between January, 2021 and November, 2022 in the outpatient cardiology clinic of the faculty of medicine. Exclusion criteria included requiring positive inotropic medication, being admitted with acute decompensation, NYHA class 4, changes in their HF treatment during the study, having an end-stage renal disease requiring hemodialysis or peritoneal dialysis, malignancy, having undergone medical or surgical ED treatment, or having ED due to urogenital causes. Five patients did not complete the follow-up Sexual Health Inventory for Men (SHIM) questionnaire and withdrew from this study. Additionally, three patients were excluded due to hospitalization for acute HF, and two patients were excluded due to changes in their dosages of other HF treatments without modifications in medication. Therefore, the statistical analysis was performed with the remaining forty patients (Figure 1).

The demographic profiles of all of the patients, along with their medical history, NYHA functional class, comorbidities, and medication details, were meticulously documented. The patients were defined as being hypertensive if their blood pressure was >140/90 mmHg on two measurements or if they were receiving antihypertensive medications. The diagnosis of diabetes mellitus (DM) was determined based on a fasting blood glucose level equal to or higher than 126 mg/dL or the use of antidiabetic medications. Lower extremity peripheral vascular disease (PVD) was defined by symptoms such as leg pain, cramping, or weakness, accompanied by identifying stenosis or occlusion of 50% or more in the main arteries of the lower extremities using imaging modalities.

All patients underwent blood analysis and echocardiographic evaluation, under resting conditions at baseline. Circulating brain natriuretic peptide (BNP) levels were analyzed by an immunoassay technique (Elecsys®, Roche Diagnostics) in venous blood samples obtained from the antecubital vein using an ethylenediaminetetraacetic acid test tube.

Echocardiographic Evaluation

Baseline and three-month follow-up transthoracic echocardiography were performed on all patients using the Vivid 7, 2.5 MHz probe, and the results were interpreted by two independent cardiologists according to the guidelines of the American Society of Echocardiography[14]. In the patients, LVEF was evaluated using the modified Simpson technique on apical four-chamber imaging.

Assessment of Erectile Dysfunction

All patients provided written and verbal consent to complete the SHIM questionnaire.[15] Erectile function was assessed using the SHIM questionnaire at the beginning of this study. After an initial assessment, a follow-up evaluation was conducted three months after SGLT-2i treatment. This follow-up assessment included re-administering the SHIM questionnaire and evaluating the patient's clinical status, LVEF, NYHA functional classes, and current BNP levels. This timeframe was chosen based on previous reports suggesting that it takes 12-16 weeks for the effects of SGLT-2i to become noticeable.[16,17]

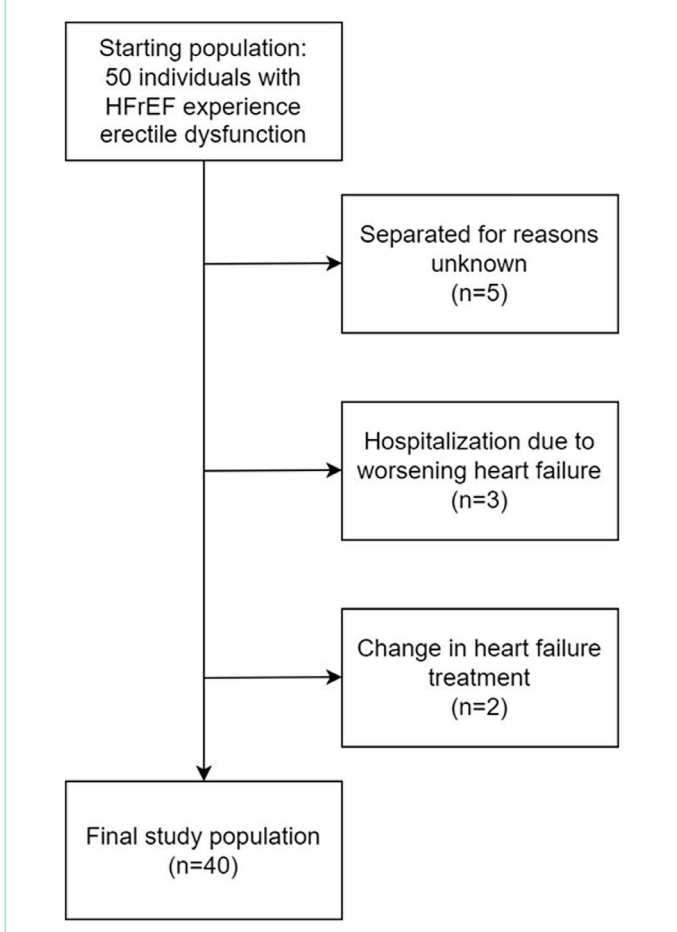

Figure 1. Study flowchart. The diagram describes the protocol used for the enrollment of patients with HFrEF in the present study.

HFrEF: Heart failure with reduced ejection fraction.

The SHIM questionnaire is a widely used scale for assessing ED in men. The total score of the questionnaire ranges from 1 to 25, with higher scores indicating better erectile function. Accordingly, the SHIM score is divided into five categories: severe ED (1-7), moderate ED (8-11), mild-moderate ED (12-16), mild ED (17-21), and non-ED (22-25).[15]

Statistical Analysis

All data were analyzed using the statistical package SPSS version 26.0 (SPSS Inc., Chicago, IL). Data visualizations were performed with the R version 4.0.2 (packages: tidyverse, ggsankey). The normality of the distributions of the parameters was assessed by the Kolmogorov-Smirnov test. Quantitative variables with a normal distribution are given as the mean ± standard deviation and those with non-normal distribution are given as median (minimum-maximum); categorical variables are given as number and percentage values. In order to compare repeated measurements, the statistical analysis utilized Student's t-test for paired samples. In cases where the data did not meet the assumptions of normality, Wilcoxon's test was employed as a non-parametric alternative. McNemar's chi-square test was used to compare the SHIM classes and NYHA functional classes before and after SGLT-2i treatment. Correlations were assessed using the Spearman's rank correlation coefficient. In order to evaluate the potential influence of confounding factors, a multivariable stepwise regression analysis was performed. A p-value <0.05 was considered statistically significant.

Sample Sizing

This study included 40 patients comparing their SHIM scores before and after SGLT-2i treatment. The statistical power of this study was determined using the G*Power program, which provided a power value of 0.56. Based on a prior study on changes in SHIM score,[18] an expected change of at least 5% over time, an 80% power, and an α level of 0.05, groups of at least eight subjects were required for the analysis.

RESULTS

The demographic and laboratory characteristics of the study population are presented in Table 1, with a mean age of 57.9±9.9 years and a mean duration of SGLT-2i treatment of 100±8 days. The majority of the patients (92.5%) received beta-blockers, while 33 patients (82.5%) were taking a mineralocorticoid receptor antagonist. All patients were treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or angiotensin-neprilysin inhibitors.

After a three-month follow-up, patients receiving SGLT-2i demonstrated a significant improvement in SHIM scores compared to their baseline values (15.4±5.5 vs. 12.7±5.6, p<0.001). However, no significant changes were observed in the transitions between ED groups (p>0.05) (Figure 2), and likewise, although there was a minimal increase in LVEF, it was not statistically significant (31.0±7.8% vs. 32.5±7.5%, p=0.068).

The findings regarding the effect of SGLT-2i on SHIM score, BNP, and NYHA functional classes before treatment are presented in Table 2. In order to investigate the potential age-related variability regarding the impact of SGLT-2i on ED, the patients were divided into two groups according to their age: under 50 years (n=10) and over 50 years (n=30).[19] Although the baseline SHIM scores were lower in the older group, both age groups showed a significant increase in SHIM scores after treatment with SGLT-2i (<50 years group: 16.5±3.8 vs. 19.2±3.5, p=0.010; ≥50 years group: 11.7±5.7 vs. 14.5±5.5, p<0.001).

Table 1. Demographic and laboratory characteristics of the patients (n=40)

Variables	n (%)	Mean ± SD
Age (year)		
BMI (kg/cm^2)		
SGLT-2 inhibitor duration (day)		
Left ventricular ejection fraction (%)		
Ischemic CMP, n (%)	27 (67.5)	
Hypertension, n (%)	23 (57.5)	
Diabetes mellitus, n (%)	20 (50.0)	
Lower extremity PVD, n (%)	6 (15.0)	
Hyperlipidemia, n (%)	31 (77.5)	
COPD, n (%)	11 (27.5)	
Atrial fibrillation, n (%)	17 (42.5)	
ICD, n (%)	17 (42.5)	
Smoking, n (%)	8 (20.0)	
Urea, (mg/dL)		43.2±11.4
Creatinine (mg/dL)		1.1±0.2
eGFR (mL/min/1.73 m^2)		71±19.8
Sodium (mEq/L)		139±2.7
Potassium (mEq/L)		4.4±0.5
Medications		
Antiplatelet, n (%)	21 (52.5)	
Anticoagulant, n (%)	17 (42.5)	
ACE inhibitor, n (%)	25 (62.5)	
ARB, n (%)	10 (25.0)	
ARNI, n (%)	5 (12.5)	
Beta blocker, n (%)	37 (92.5)	
CCB, n (%)	6 (15.0)	
MRA, n (%)	33 (82.5)	
Furosemide, n (%)	35 (87.5)	
Thiazide, n (%)	16 (40.0)	
Statin, n (%)	17 (42.5)	
Digoxin, n (%)	7 (17.5)	

SD: Standard deviation, BMI: Body mass index, SGLT-2i: Sodium-glucose co-transporter-2 inhibitors, CMP: Cardiomyopathy, PVD: Peripheral vascular disease, COPD: Chronic obstructive pulmonary disease, ICD: Implantable cardioverter defibrillator, eGFR: Estimated glomerular filtration rate, ACE: Angiotensin-converting enzyme, ARB: Angiotensin-2 receptor blockers, ARNI: Angiotensin receptor blocker-neprilysin inhibitor complex, CCB: Calcium channel blockers, MRA: Mineralocorticoid receptor antagonists.

The study patients were divided into two subgroups based on their diabetes status and smoking history,[20,21] as these factors have been associated with endothelial dysfunction and, consequently, ED. After treatment with SGLT-2i, both the diabetic (p<0.001) and the non-diabetic (p<0.001) patients showed a significant improvement in their SHIM scores. Although the smokers had lower baseline SHIM scores, they demonstrated a similar improvement in their SHIM scores as the non-smokers following the administration of SGLT-2i [10.5 (4-17) vs. 13 (7-22), p=0.010; 11.5 (4-22) vs. 16 (6-24), p<0.001, respectively].

Treatment with SGLT-2i was also associated with statistically significant reductions in BNP levels [483 pg/mL (98-2122) vs. 264 pg/mL (48-1297), p<0.001], as well as significant changes in the distribution of NYHA

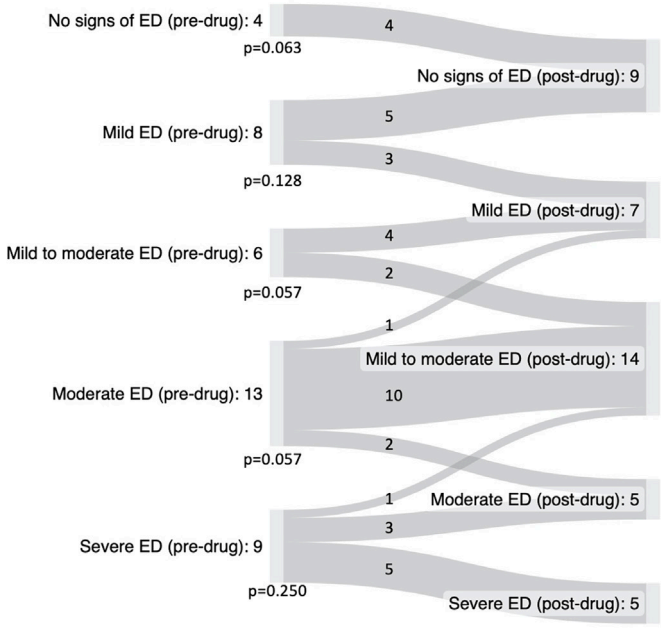

Figure 2. The transition of patients between ED groups after SGLT-2i treatment.

ED: Erectile dysfunction, SGLT-2i: Sodium-glucose co-transporter 2 inhibitor.

Table 2. Comparing pre- and post-treatment values of SHIM scores, BNP, and NYHA functional classes with the use of SGLT-2i

	Pre-SGLT-2i value	Post-SGLT-2i value	p
SHIM score	12.7±5.6	15.4±5.5	<0.001
50< years old (n=10)	16.5±3.8	19.2±3.5	0.010
≥50 years old (n=30)	11.7±5.7	14.5±5.5	<0.001
Non-smoker (n=32)	11.5 (4-22)	16 (6-24)	<0.001
Smoker (n=8)	10.5 (4-17)	13 (7-22)	0.010
DM (-) (n=20)	13.2±5.5	16.0±4.9	<0.001
DM (+) (n=20)	12.2±5.9	14.9±6.1	<0.001
Absence of lower extremity PVD (n=34)	13.4±5.6	16.3±5.3	<0.001
Presence of lower extremity PVD (n=6)	8.8±3.9	10.5±4.2	0.036
SHIM classification*			
Non-ED group, n (%)	4 (10.0)	9 (22.5)	0.006
Group with ED, n (%)	36 (90.0)	31 (77.5)	<0.001
Left ventricular ejection fraction (%)	31.0±7.8	32.5±7.5	0.068
BNP (pg/mL)	483 (98-2122)	264 (48-1297)	<0.001
NYHA class*			
NYHA 1, n (%)	-	21 (52.5)	-
NYHA 2, n (%)	30 (75.0)	18 (45)	0.043
NYHA 3, n (%)	10 (25.0)	1 (2.5)	0.004

*McNemar chi-square test was used. SHIM: Sexual Health Inventory for Men, BNP: Brain natriuretic peptide, NYHA: New York Heart Association, SGLT-2i: Sodium-glucose co-transporter 2 inhibitor, DM: Diabetes mellitus, PVD: Peripheral vascular disease, ED: Erectile dysfunction.

classes 2 (p=0.043) and 3 (p=0.004). Before SGLT-2i treatment, 75.0% of the patients were in NYHA class 2, and 25.0% were in NYHA class 3. After treatment with SGLT-2i, only 2.5% of the patients remained in NYHA class 3, whereas 45% were in NYHA class 2, and 52.5% were in NYHA class 1.

A multivariable stepwise regression analysis was conducted in order to identify predictors of improved SHIM scores in response to SGLT-2i treatment. The analysis considered several factors, including age, baseline SHIM scores, baseline LVEF, baseline BNP, lower extremity PVD, changes in BNP, diabetic status, and smoking status. Age (p=0.002), baseline SHIM scores (p=0.042), and lower extremity PVD (p=0.002) were identified as negative predictors of improvements in SHIM scores. In contrast, changes in BNP (p=0.035) emerged as a significant predictor of improvements in SHIM scores (Table 3).

DISCUSSION

Our study was the first to show that SGLT-2i treatment improves sexual function in patients with HFrEF. In addition, SHIM scores also indicated that SGLT-2i treatment decreased the number of patients diagnosed with ED.

Endothelial dysfunction plays an important role in the pathophysiology of ED and some cardiovascular diseases.[22,23] The imbalance between vasoconstriction and vasodilation caused by endothelial dysfunction leads to excessive systemic vasoconstriction and decreased peripheral tissue perfusion in HF patient.[24,25] Indeed, most HF patients may suffer from ED,[8,26] and in our study, 90% of HF patients were diagnosed with EDs of various severities.

Impaired NO production is one of the mechanisms underlying endothelial dysfunction. Increased vascular oxidative stress or reduced shear stress in HF leads to decreased vascular NO release and bioavailability.[26] NO has been reported to be the major neurotransmitter of non-adrenergic non-cholinergic neurons innervating the corpus cavernosum or erectile tissue in rabbits[27] and humans[28] and to play a significant role in the relaxation of the corpus cavernosum. Thus, improving the NO pathway will contribute to the treatment of ED.[29]

The physiological effects of SGLT-2i are thought to be mediated by antioxidant, anti-inflammatory, and anti-fibrotic pathways.[9,11,12] It has been reported that mitochondrial reactive oxygen species (ROS) production and cytoplasmic ROS accumulation decreased in empagliflozin-treated cardiac microvascular endothelial cells, increasing endothelial NO bioavailability.[30] Three months of SGLT-2i treatment was associated with increased levels of brachial artery flow-mediated dilatation in 22 patients with chronic HF and type 2 DM suggesting that the NO pathway is positively affected.[17] Indeed, in a rat model of type 2 DM, empagliflozin significantly improved erectile

Table 3. Predictors of improved SHIM scores with SGLT-2i treatment via multivariable stepwise regression analysis

	β	Std. Err	p
Age	-0.245	0.103	0.002
Baseline SHIM score	-0.078	0.037	0.042
Lower extremiy PVD	-1.685	0.496	0.002
Change in BNP levels	0.002	0.001	0.035

SHIM: Sexual Health Inventory for Men, SGLT-2i: Sodium-glucose co-transporter 2 inhibitor, β: Beta, PVD: Peripheral vascular disease, BNP: Brain natriuretic peptide.

responses, as evidenced by increased intracavernous pressure and mean arterial pressure, along with enhanced nitrergic relaxations of cavernosal strips.[31] Our finding that three months of SGLT-2i treatment led to a significant increase in SHIM scores in HFrEF patients may indicate improved endothelial function.

Sexual activity is known to be closely related to aerobic capacity and endurance. Jaarsma et al.[32] reported that the decline in exercise capacity due to chronic HF is associated with the level of sexual function. The same study also showed a weak but significant correlation between the NYHA functional class and sexual performance.[32] In our study, three months of SGLT-2i treatment significantly improved the NYHA functional class. Although the exercise tolerance of the patients was not assessed, it is possible that improvements in the NYHA class also positively affected the changes in the SHIM scores.

ED is known to be associated with age and many comorbidities, including DM, hypertension, and PVD.[33-36] Although they benefited from SGLT-2i treatment, regression analysis shows that age and lower extremity PVD attenuated improvements in SHIM scores. In addition, considering that hypertensive patients were 57.5% and diabetic patients were 50% in our patient group, the improvements in the SHIM scores observed in this study following SGLT2i treatment is significant and could be valuable.

Brain natriuretic peptide, a marker used in diagnosing and following various cardiovascular diseases, is known to be elevated in HF.[37,38] In our study, 92.5% of patients were receiving beta-blockers, while all patients were treated with ACE inhibitors, angiotensin receptor blockers, or angiotensin-neprilysin inhibitors. Although beta-blockers have been shown to decrease[39] and ACE inhibitors to increase BNP levels,[40] our results showed that three months of SGLT-2i treatment led to a significant decrease in serum BNP levels in the HFrEF patients.

Study Limitations

While our study provides valuable insights into the potential benefits of SGLT-2i towards improving sexual function in male patients with HF, the strict exclusion criteria applied to better understand the effects of these inhibitors on ED resulted in a small sample size which may limit the statistical power and generalizability of this study. Another limitation is that we did not have evaluations conducted by a urology specialist to assess erectile function before and after SGLT-2i treatment. Additionally, the evaluation of erectile function before and after SGLT-2i treatment using imaging methods such as penile Doppler ultrasonography could have provided more comprehensive insights into the impact of these inhibitors on erectile function. Moreover, our study was conducted at a single center, which may limit the generalizability of its findings.

CONCLUSION

Our study suggests that treatment by SGLT-2i improves the SHIM scores in patients with HFrEF.

MAIN POINTS

- The prognosis of heart failure is strongly associated with the integrity of the endothelium.
- Endothelial dysfunction is a prominent characteristic in heart failure patients and plays a significant role in the development of erectile dysfunction in these individuals.
- Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) have the potential to improve microvascular endothelial cell function due to their multifaceted effects.
- This study aims to investigate the impact of SGLT-2i treatment on erectile dysfunction in patients with heart failure.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Karabük University (approval number: 2023/1258, date: 25.01.2023).

Informed Consent: All participants provided their informed consent to participate in the study.

Authorship Contributions

Surgical and Medical Practices: İ.E., Y.A., Concept: İ.E., Y.A., Design: İ.E., Y.A., Data Collection and/or Processing: İ.E., Analysis and/or Interpretation: İ.E., Literature Search: İ.E., Y.A., Writing: İ.E., Y.A.

DISCLOSURES

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

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