Association Between Erectile Dysfunction and Fontaine Classification in Patients with Peripheral Artery Diseases: A Cross Sectional Study

Periferik Arter Hastalığı Olan Hastalarda Fontaine Sınıflaması ve Erektil Disfonksiyon Arasındaki İlişki: Kesitsel Çalışma

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ABSTRACT Objective: To identify the association between peripheral artery disease (PAD) and erectile dysfunction (ED) with using Fontaine classification (FC). **Material and Methods:** The present study was planned in a prospective manner between November 2020- April 2022, and male patients who admitted to cardiovascular surgery outpatient polyclinic were enrolled into the study. Severity of PAD and presence of ED were evaluated by FC and International Index of Erectile Function (IIEF) score, respectively. To clarify the correlation between ED and FC, patients were divided into 2 groups. Patients with IIEF score ≤11 were classified as Group 1 and patients with IIEF score ≥17 were categorized as Group 2. The groups were compared in terms of patient demographic characteristics, blood test outcomes, IIEF scores and GS scores. **Results:** Totally, 181 patients with mean age 55.9 years were enrolled in the study. Smoking rate and presence of diabetes mellitus was significantly lower in favor of patients without ED (69.1% vs 42.5%, p=0.001 and 54.4% vs 33.6%, p=0.006).Lower extremity ischemic scores according to FC were significantly better in favor of patients without ED (p=0.001). Multivariate regression analysis showed that higher body mass index (BMI), being a smoker and presence of diabetes mellitus were predictive factors for ED (p=0.001,p=0.034 and p=0.001, respectively). In addition, FC 3-4 were significantly associated with ED (7.132 times, p=0.001). **Conclusion:** The present study revealed for the first time that FC 3-4 increased risk of ED. Additionally, diabetes mellitus, smoking history, and higher BMI were predictive factors for ED.

Keywords: Body mass index; erectile dysfunction; low density lipoprotein; peripheral arterial disease

ÖZET Amaç: Fontaine sınıflandırmasını (FS) kullanarak periferik arter hastalığı (PAH) ve erektil disfonksiyon (ED) arasındaki ilişkiyi belirlemektir. **Gereç ve Yöntemler:** Bu çalışma, Kasım 2020-Nisan 2022 tarihleri arasında prospektif olarak planlanmış ve kardiyovasküler cerrahi polikliniğine başvuran erkek hastalar çalışmaya dâhil edilmiştir. PAH şiddeti ve ED varlığı sırasıyla FS ve Uluslararası Erektil Fonksiyon İndeksi [International Index of Erectile Function (IIEF)] skoru ile değerlendirildi. IIEF skoru ≤11 olan hastalar Grup 1, IIEF skoru ≥17 olan hastalar Grup 2 olarak sınıflandırıldı. Gruplar, hasta demografik özellikleri, kan testi sonuçları, IIEF skorları ve FS skorları açısından karşılaştırıldı. **Bulgular:** Çalışmaya, yaş ortalaması 55,9 yıl olan 181 hasta dâhil edildi. Sigara içme oranı ve diabetes mellitus varlığı, ED'si olmayan hastalar lehine anlamlı olarak daha düşüktü (%69,1'e karşı %42,5, p=0,001 ve %54,4'e karşı %33,6, p=0,006). Ortalama düşük yoğunluklu lipoprotein seviyesi, ED'li hastalarda daha yüksekti (p=0,012). FS'ye göre alt ekstremite iskemik skorları ED'si olmayan hastalar lehine anlamlı olarak daha iyiydi (p=0,001). Çok değişkenli regresyon analizi, yüksek beden kitle indeksi (BKİ), sigara kullanımı ve diabetes mellitus varlığının ED için öngörücü faktörler olduğunu gösterdi (p=0,001, p=0,034 ve p=0,001, sırasıyla). Ayrıca FS 3-4, ED ile anlamlı olarak ilişkiliydi (7.132 kez, p=0,001). **Sonuç:** Bu çalışma, ilk kez FS 3-4'ün ED riskini artırdığını ortaya koydu. Ek olarak, diabetes mellitus varlığı, sigara içme öyküsü ve daha yüksek BKİ, ED için öngörücü faktörlerdi.

Anahtar Kelimeler: Beden kitle indeksi; erektil disfonksiyon; düşük yoğunluklu lipoprotein; periferik arter hastalığı

Erectile dysfunction (ED) is simply described as the deficiency to reach and/or keep penile erection to allow satisfying sexual intercourse.[1] Although ED is not a life-threatening disease, previous reports demonstrated that ED is related to loss of self-confidence, depression, deterioration of social life and re-

lationships.[2,3] Prevalence of ED has a wide range in the literature due to many reasons including acceptance of this situation as normal, hesitation in consulting a doctor, and use of different evaluation techniques for ED diagnosis.[2] The underlying physiopathology of ED can be anatomical, hormonal, neurologic, psychogenic and vasculogenic. However, many studies emphasized that the most common cause of ED is vasculogenic and atherosclerosis (AT) is the most common reason for vasculogenic ED.[3] AT is also the main cause of peripheral artery diseases (PAD). Thus, the association between ED and PAD is closely monitored.

Prevalence of PAD is between 7% and 10%, and the prevalence is expected to increase by 2050, due to prolonged life expectancy, increased incidence of hypertension and AT.[4] Physical examination is the main diagnosis method for PAD, and the Fontaine classification (FC) was developed by the European Society of Cardiovascular Surgery to diagnose the presence of PAD and assess the seriousness of PAD. Hardman and colleagues stated that the most important advantage of FC is that it can diagnose only the patient's symptoms without requiring an additional invasive diagnostic method.[5] In another study, Mills et al. showed that higher scores for FC were associated with severe ischemic lower extremity pathologies, including non-healing ulcers, gangrene and amputation.[6]

Although previous studies discussed the correlation between PAD and ED, no study evaluated the connection between PAD and ED using FC. In this study, we aimed to identify the association between PAD and ED using FC.

MATERIAL AND METHODS

The present study was planned in a prospective manner between November 2020-April 2022, and male patients who were admitted to the cardiovascular surgery clinic with lower extremity pain were enrolled into the study. This study was approved by the Bezmiâlem Vakıf University Ethics Committee (date: February 19, 2020, no: 2020-318). After ethics committee approval was taken the study was planned in consistency with the Helsinki Declaration principles and informed consent was obtained from all participants. Patient erection status was evaluated with the International Index of Erectile Function (IIEF) questionnaire. To prevent an inhomogeneous group, patients who had lower extremity orthopedic disease(s), patients with history of PAD surgery, and patients with leg amputation were not included to the study. Also, unable to complete the IIEF, not having sexual intercourse for more than 4 weeks, being <18 years old, use of phosphodiesterase-5 inhibitors, history of penile implantation surgery, and presence of psychiatric disease were other exclusion criteria. Also, patients with ED score 12-16 (mild to moderate ED) were excluded from the study to avoid confusion.

Records of patient demographic characteristics were examined. Also, fasting glucose (FG), and blood lipid profile were noted. Additionally, severity of PAD and presence of ED were evaluated by FC and IIEF scores, respectively. FC was calculated by 2 different cardiovascular surgeons who were blinded to patient characteristics, serum blood results and IIEF scores.

FC

FC is a simple and easy-to-use clinical classification to determine the severity of PAD, which includes 5 subcategories.[7] Patients with sub-clinical PAD without any ischemic symptoms are classified as Group 1. Patients who face intermittent claudication after walking are categorized as FC 2 (2a: Intermittent claudication after walking ≥200 meters and 2b: intermittent claudication after walking <200 meters). Patients who have rest pain are categorized as FC 3 and patients who have ischemic ulcers and/or gangrene are classified as FC 4, respectively.

IIEF

The IIEF-5 includes 5 questions [scores between 1 (worst) and 5 (best)] to evaluate intercourse satisfaction, sexual desire, orgasmic function, and ED. Severity of ED was divided into 5 categories based on the scores: no ED (22-25), mild (17-21), mild to moderate (12-16), moderate (8-11), and severe (5-7).[8]

To clarify the correlation between ED and FC, patients were splitted into 2 groups. Patients with IIEF score ≤11 were classified as Group 1 and pa-

tients with IIEF score ≥17 were categorized as Group 2. The groups were compared in terms of patient demographic characteristics, blood test outcomes, IIEF scores and FC scores.

For statistical analyses, Statistical Package for the Social Sciences version 25 (SPSS IBM Corp., Armonk, NY, USA) program was used. Variable distribution was analyzed with the Shapiro-Wilk test. For comparison of parameters between groups, the independent student-t test or Mann-Whitney U test were used. Quantitative data are presented as mean±standard deviation values. Categorical parameters were classified and matched using the χ^2 test. Predictive factors for ED were examined with binary logistic regression analysis. The relationship between FC and ED was evaluated using the receiver operating characteristic (ROC) curve. p value of less than 0.05 was accepted as statistically significant. The data were evaluated at 95% confidence level.

RESULTS

In the end, 181 patients with mean age 55.9 years were recorded in the study. The mean body mass index (BMI) was 28.9 kg/m², and 95 of 181 (52.5%) patients were smokers. The mean systolic blood pressures and diastolic blood pressures were 144.6 mmHg and 89.2 mmHg, respectively. Diabetes mellitus was detected in 75 patients (41.4%). The mean FG level and low density lipoprotein (LDL) level were 110.1 mg/dL and 185.4 mg/mL, respectively. In total, 68 (37.6%) patients and 83 (45.9%) patients were grouped as FC 1 and FC 2. Also, 5 (2.7%) patients were classified as FC 4. The mean IIEF score was 17.4 in the study population. Patient characteristics and blood test results are listed in Table 1.

Comparison of patients without ED and with ED revealed that diastolic blood pressure, systolic blood pressure, and asset of hypertension were similar between the groups (p=0.436, p=0.290 and p=0.312). Additionally, blood tests including FG, total cholesterol, high density lipoprotein and triglyceride were similar (p=0.577, p=0.404, p=0.481 and p=0.199). In contrast, patients with ED were significantly older and had higher BMI (p=0.042 and p=0.001). Smoking rate and presence of diabetes mellitus was signif-

TABLE 1: Demographic characteristics of all patients.

	n=181
Age (years)*	55.9±6.4
Systolic BP (mmHg)*	144.6±8.5
Diastolic BP (mmHg)*	89.2±5.9
Body mass index (kg/m²)*	28.9±4.1
Fasting glucose (mg/dL)*	110.1±4.7
Total cholesterol (mg/dL)*	196.1±33.3
HDL (mg/dL)*	40.2±6.4
LDL (mg/dL)*	185.4±35.8
Triglycerides (mg/dL)*	184.3±7.6
Smoking, n (%)	95 (52.5%)
Hypertension, n (%)	160 (88.4%)
Diabetes mellitus, n (%)	75 (41.4%)
Fontaine score	
Class I	68 (37.6%)
Class IIa	51 (28.2%)
Class IIb	32 (17.7%)
Class III	25 (13.8%)
Class IV	5 (2.7%)
IIEF score*	17.4±8.3
Family history of stroke, n (%)	58 (32.0%)
Family history of CVD, n (%)	79 (43.6%)

*mean±standard deviation; IIEF: International Index of Erectile Function; BP: Blood pressure; HDL: High density lipoprotein; LDL: Low density lipoprotein; CVD: Cardiovascular disease.

icantly lower in favor of patients without ED (69.1% vs 42.5%, p=0.001 and 54.4% vs 33.6%, p=0.006). Mean LDL was 194.0 mg/dL in patients with ED and 180.2 mg/dL in patients without ED (p=0.012). Lastly, lower extremity ischemic scores according to FC were significantly better in favor of patients without ED (p=0.001) (Table 2).

Multivariate analysis demonstrated that age and LDL level were not associated with ED (p=0.206 and p=0.227). In contrast, higher BMI, being a smoker and presence of diabetes mellitus were predictive factors for ED (p=0.001, p=0.034 and p=0.001, respectively). In addition, FC 3-4 were significantly associated with ED (7.132 times, p=0.001) (Table 3). ROC analysis of FC and ED is presented in Figure 1.

DISCUSSION

Scoring systems are developed for better prediction of procedure outcomes, detailed patient counselling, and more objective scientific reporting. To analyze

TABLE 2: Comparison of groups according to patient IIEF values.			
	IIEF≤11 (n=68)	IIEF≥17 (n=113)	p value
Age (years)*	57.1±6.0	55.2±6.5	**0.042**
Systolic BP (mmHg)*	145.2±8.0	144.1±8.7	0.436
Diastolic BP (mmHg)*	89.8±5.8	88.8±6.0	0.290
Body mass index (kg/m²)*	30.5±4.0	27.9±4.0	**0.001**
Fasting glucose (mg/dL)*	111.0±18.2	109.5±16.9	0.577
Total cholesterol (mg/dL)*	193.4±32.4	197.7±33.8	0.404
HDL (mg/dL)*	39.7±7.1	40.4±5.9	0.481
LDL (mg/dL)*	194.0±37.6	180.2±33.9	**0.012**
Triglycerides (mg/dL)*	178.4±46.1	187.8±48.4	0.199
Smoking, n (%)	47 (69.1%)	48 (42.5%)	**0.001**
Hypertension, n (%)	58 (85.3%)	102 (90.3%)	0.312
Diabetes mellitus, n (%)	37 (54.4%)	38 (33.6%)	**0.006**
Fontaine score			**0.001**
Class I	11 (16.2%)	57 (50.4%)	
Class IIa	16 (23.5%)	35 (31.0%)	
Class IIb	19 (27.9%)	13 (11.5%)	
Class III	18 (26.5%)	7 (6.2%)	
Class IV	4 (5.9%)	1 (0.9%)	
IIEF score*	7.9±3.0	23.1±4.1	**0.001**
Family history of stroke, n (%)	22 (32.4%)	36 (31.9%)	0.945
Family history of CVD, n (%)	27 (39.7%)	52 (46.0%)	0.407

*mean±standard deviation; IIEF: International Index of Erectile Function; BP: Blood pressure; HDL: High density lipoprotein; LDL: Low density lipoprotein; CVD: Cardiovascular disease.

TABLE 3: Results of multivariate regression analysis.			
Variable	Odds ratio	CI 95%	p value
Age (<60 years vs ≥60 years)	1.488	0.691-3.206	0.310
Body mass index (<30 kg/m² vs ≥30 kg/m²)	2.696	1.301-5.586	0.008
LDL (<160 mg/dL vs ≥ 160 mg/dL)	1.640	0.734-3.665	0.227
Smoking (no vs yes)	3.609	1.732-7.519	0.001
Diabetes mellitus (no vs yes)	2.826	1.364-5.855	0.005
Fontaine score (I-IIa-IIb vs III-IV)	7.132	2.603-19.547	0.001

CI: Confidence interval; LDL: Low density lipoprotein.

the seriousness of PAD and to predict the treatment outcome, the FC was developed and externally validated.[9] The IIEF-5 questionnaire is used for objective assessment of ED and ED severity.[8] We found that ED was significantly related to the presence of diabetes mellitus, being a smoker, BMI≥30 kg/m², and FC 3-4.

Higher Fontaine scores indicate the severity of PAD. Dorros and et al. analyzed survival of 235 patients with critical lower extremity ischemia, and the authors concluded that patients in FC 3-4 had signif-

icantly worse survival rate in comparison to patients in FC 1-2.[10] In another study, Yuksel et al. explored the correlation between severity of PAD and overactive bladder syndrome. Yuksel and et al. found that the presence of Fontaine score ≥class 2b was a predictive factor for overactive bladder.[11] Pomeshkin et al., in their study on patients who underwent coronary artery bypass surgery (CABS), showed that ED occurs due to endothelial defect.[12] Also, Hizli et al. investigated the effect of extracorporeal circulation and cross-clamping time on ED in patients undergo-
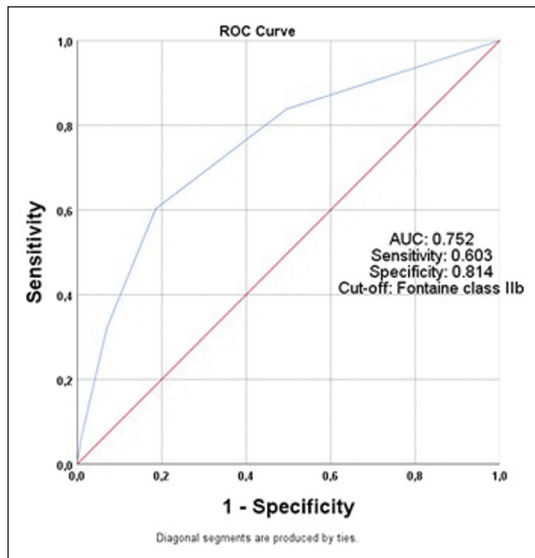
FIGURE 1: Roc analysis of Fontaine classification and erectile function. ROC: Receiver operating characteristic; AUC: Area under curve.

ing CABS and found that existing ED prior to surgery was the best predictor of postoperative ED.[13] In the present study, for the first time, we analyzed the relationship between FC and erectile status of men, and we found that being in FC 3-4 was a predictive factor for ED.

Previous reports demonstrated an inverse correlation between BMI and testosterone level. Moreover, lower level of sex hormone binding globulin in obese cases contributes to the lower free and total testosterone concentrations.[14] Kratzik and et al. researched the effect of BMI on ED, and the authors stated that increments in BMI by 1 kg/m² decreased IIEF-5 score by 0.141, independent of age.[15] In another study, Andersen et al. analyzed the erectile status of 863 men, and found BMI≥30 kg/m² was an independent risk factor for ED in patients aged 20-45 years.[16] In the present study, we observed significantly higher rate of ED in patients with higher BMI. However, we did not evaluate testosterone hormone levels in the present study, which can be included in another study.

Although the exact mechanism of how smoking causes ED is not known, there is a growing literature that shows significant relationships between smoking and ED. Gades and et al. analyzed the erection status of 2,115 men, and concluded that smoking increased ED risk by 1.42 times.[17] In a prospective study by the Massachusetts Male Aging Study Group, smokers had moderate and severe ED at rates twice as high in comparison with non-smokers. Additionally, in the same study group, being a smoker and passive exposure to cigarettes were associated with CAD.[18] Similarly, the smoking rate was significantly higher in patients with ED in the present study.

The presence of diabetes has strong correlation with ED, and previous studies reported up to 90% ED prevalence among diabetic men. Moreover, Feldman and et al. stated that ED was detected almost 15 years earlier in diabetic men in comparison with non-diabetic men.[19] Malavige et al. stated that diabetes mellitus causes deterioration in penile nerve stimulus, reduction in cavernosal smooth muscle relaxation, and disruption of nitric oxide synthesis.[20] Additionally, Sentell et al. found 28.7% diabetes mellitus prevalence in patients with ED and 2.8% prevalence in patients without ED, and the authors claimed that diabetes mellitus is a predictive factor for ED.[21] In parallel, we determined that the presence of diabetes mellitus increased ED risk by 2,468 times.

Our study has some limitations. This study included a relatively little patient number from a single academic center. Also, the present study has a cross-sectional nature, and we focused on short-term results of possible predictive factors for ED. Additionally, we did not evaluate the interval period between the beginning of PAD symptoms and ED, which may be the subject of another study. Lastly, we did not investigate the effect of FC on the success of ED treatment, we believe that this issue may be clarified in further studies.

CONCLUSION

The present study revealed for the first time that FC 3-4 increased risk of ED by 7,132 times. Additionally, the presence of diabetes mellitus, smoking history, and higher BMI were predictive factors for ED. Our study suggests that patients who are admitted to the cardiovascular outpatient clinic and have FC 3-4 should be examined in terms of ED to improve patient quality of life. The results of our study should be strengthened by prospective studies with larger number of patients.

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