

# Exploring the Link Between Diagonal Earlobe Crease (Frank's Sign) and the Severity of Erectile Dysfunction

## Diagonal Kulak Memesi Kıvrımı (Frank Belirtisi) ile Sertleşme Bozukluğu Şiddeti Arasındaki İlişkinin Araştırılması

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### Abstract

**Objective:** To investigate the relationship between Frank's sign (FS), a diagonal fold of the earlobe, and the severity of erectile dysfunction (ED), focusing on FS as a potential prognostic marker for ED, particularly its vascular components.

**Materials and Methods:** A prospective study was conducted on 114 male patients aged 18-80 years at the Andrology Clinic of Haydarpaşa Numune SUAM. Participants were stratified according to International Index of Erectile Function-5 (IIEF-5) scores. FS presence, body mass index (BMI), lipid profiles and inflammatory markers (NLR, PLR) were recorded. Statistical analyses assessed the association between FS, ED severity and cardiovascular risk factors.

**Results:** A significant correlation was found between FS and ED severity, especially for bilateral FS ( $p=0.000$ ). Patients with FS had higher BMI and LDL levels, indicating a strong association with cardiovascular risk factors. Atherogenic index and PLR were also significantly associated with ED ( $p=0.018$ ,  $p=0.003$ ).

**Conclusion:** FS, especially bilateral FS, is closely associated with ED severity and its vascular pathology, suggesting its potential use as a prognostic marker in the evaluation of ED. Further research is needed to confirm these findings and to explore the integration of FS into clinical practice.

**Keywords:** Frank's sign, erectile dysfunction, cardiovascular risk factors

### Özet

**Amaç:** Kulak memesindeki diagonal kıvrım olan Frank belirtisi (FB) ile erektil disfonksiyon (ED) şiddeti arasındaki ilişkiyi araştırmak, özellikle de FB'nin ED'nin vasküler bileşenleri için olası bir prognostik belirteç olarak kullanımını değerlendirmek.

**Gereçler ve Yöntemler:** Haydarpaşa Numune SUAM Androloji Kliniği'nde 18-80 yaş aralığındaki 114 erkek hasta üzerinde prospektif bir çalışma yapıldı. Katılımcılar, Uluslararası Erektile Fonksiyon İndeksi-5 (IIEF-5) skorlarına göre sınıflandırıldı. FB varlığı, beden kitle indeksi (BKİ), lipid profilleri ve inflamatuvar belirteçler (NLR, PLR) kaydedildi. İstatistiksel analizler, FB, ED şiddeti ve kardiyovasküler risk faktörleri arasındaki ilişkiyi değerlendirdi.

**Bulgular:** FB ile ED şiddeti arasında, özellikle bilateral FB'de anlamlı bir ilişki bulundu ( $p=0.000$ ). FB olan hastaların daha yüksek BKİ ve LDL seviyelerine sahip olduğu gözlemlendi, bu da kardiyovasküler risk faktörleriyle güçlü bir ilişki olduğunu gösterdi. Aterojenik indeks ve PLR de ED ile anlamlı şekilde ilişkiliydi ( $p=0.018$ ,  $p=0.003$ ).

**Sonuç:** FB, özellikle bilateral FB, ED şiddeti ve vasküler patolojisi ile yakından ilişkilidir ve ED'nin değerlendirilmesinde prognostik bir belirteç olarak kullanıma potansiyeline sahiptir. Bu bulguların doğrulanması ve FB'nin klinik uygulamaya entegrasyonu için daha fazla araştırmaya ihtiyaç vardır.

**Anahtar kelimeler:** Frank belirtisi, erektil disfonksiyon, kardiyovasküler risk faktörleri

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## Introduction

Erectile dysfunction (ED) is a multifactorial disorder that is common in men and has a significant impact on quality of life. Its pathophysiology is complex and includes neurogenic, psychogenic, endocrine and, most importantly, vascular components [1,2]. Vascular aetiologies have led to ED being frequently recognised as an early sign of cardiovascular disease (CVD). In this context, it has been suggested that ED may act as a subclinical indicator of CVD [2]. There is increasing evidence in the literature of the effects of inflammation and oxidative stress on erectile function. The study by Roumeguere et al. shows that elevated levels of IL-18 and myeloperoxidase-dependent oxidised LDL in the corpus cavernosum impair endothelial function by inhibiting e-NOS mRNA expression. These findings support the critical role of inflammation and oxidative stress in the pathophysiology of ED [3].

Frank's sign (FS), defined by Sanders T. Frank in 1973, is known as a diagonal fold in the earlobe and has been reported in the literature as a physical marker of cardiovascular disease [4]. This marker has attracted attention because of its association with coronary artery disease and other atherosclerotic conditions. Several studies have shown that FS is associated with endothelial dysfunction, inflammation and oxidative stress [5]; endothelial dysfunction and inflammation are factors that play a critical role in the pathogenesis of atherosclerosis and are among the basic pathophysiological mechanisms of ED. Metabolic syndrome is a cardiometabolic disorder consisting of components such as abdominal obesity, hypertension, dyslipidaemia and insulin resistance, and is strongly associated with ED [6].

The fact that FS is associated with these components of the metabolic syndrome raises the question of the usefulness of this physical marker in predicting ED. It has been reported in the literature that FS impairs endothelial function as an indicator of inflammation and oxidative stress in the vessel wall. Therefore, it is thought that FS may be a predisposing factor that may predispose to the development of ED. Indeed, the fact that ED and CVD share common risk factors makes it necessary to investigate the prognostic value of FS [6,7].

The aim of this article is to review the potential role of FS in the prediction of ED and its use in clinical practice. A comprehensive review of the existing literature will assess the relationship between FS and ED and CVD, its prognostic value and its place in clinical practice. This evaluation should contribute to the development of new approaches to the use of FS in the diagnosis and management of ED.

## Materials and Methods

Our study, which was approved by the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee on 19 June 2023 with decision number HNEAH-KAEK 2023/128, is a prospective study. Written informed consent was obtained from all participants. Men aged 18-80 years with ED as defined by the International Index of Erectile Function-5 (IIEF-5), scoring less than 22 points and with normal hormonal parameters were enrolled in the study between 1 May 2023 and 23 July 2023 at the SBU Haydarpaşa Numune SUAM Andrology Clinic. As a control group, 33 patients were enrolled

who had no complaints of ED or scored 22 points and above on the IIEF-5 and who met other inclusion criteria. Exclusion criteria included men with ED secondary to hormonal deficiency, those under 18 or over 80 years of age, and those who were unwilling to consent or unable to communicate effectively.

Each participant underwent a comprehensive physical examination and a detailed medical history was taken. Height, weight, body mass index (BMI), presence of diabetes mellitus (DM), and whether FS was unilateral or bilateral were recorded. Laboratory tests were performed on the morning after the clinic visit on an empty stomach, including glucose, lipid profile and complete blood count. Based on IIEF-5 scoring, patients were classified as having severe ED (scores 5-7), moderate ED (scores 8-11), mild-moderate ED (scores 12-16), mild ED (scores 17-21), and normal (scores 22-25). The neutrophil/lymphocyte and platelet/lymphocyte ratios, atherogenic index (LDL/HDL) and coronary risk index (total cholesterol/HDL) were calculated and recorded from the hemogram and lipid profile.

## Statistical Analysis

SPSS 25.0 (IBM, NY, USA) was used for statistical analysis. Normality tests were assessed using the Kolmogorov-Smirnov test. Descriptive statistical methods (mean, standard deviation, frequency, ratio, percentage) were used to evaluate the study data. Mann-Whitney U test and chi-squared test were used for paired groups. Statistically significant p-value was defined as  $<0.05$ .

## Results

Our study included 114 male patients, of whom 81 (71%) had ED complaints and 33 (29%) did not. FS was present in 57 of our patients and there was no FS in 57 of our patients. The age range of our patients was  $52.36 \pm 10.87$  years. The IIEF-5 score of our patients with ED was minimum 6 and maximum 21 ( $15.74 \pm 3.10$ ).

The mean age was  $52.22 \pm 10.66$  years in patients with ED and  $52.72 \pm 11.53$  years in patients without ED; there was no statistically significant difference in age between the two groups ( $p=0.743$ ). The mean BMI of patients with ED was  $29.03 \pm 4.90$ , whereas the mean BMI of patients without ED was  $26.19 \pm 3.66$ . This difference was statistically significant ( $p=0.002$ ). It shows that patients with ED had a higher BMI (**Table 1**).

When the lipid profile of our patients was evaluated, the VLDL values were  $34.25 \pm 22.45$  mg/dL in patients with ED and  $39.34 \pm 18.96$  mg/dL in patients without ED. This difference was not statistically significant ( $p=0.072$ ). LDL levels were  $128.48 \pm 68.49$  mg/dL in patients with ED and  $96 \pm 32.81$  mg/dL in patients without ED, and this difference in LDL levels was statistically significant ( $p=0.007$ ). HDL levels were  $45.30 \pm 17.46$  mg/dL in patients with ED and  $49.30 \pm 20.86$  mg/dL in patients without ED and this difference was not statistically significant ( $p=0.373$ ). The mean triglyceride level was  $175.86 \pm 123.86$  mg/dL in patients with ED and  $196.72 \pm 94.80$  mg/dL in patients without ED and this difference was not statistically significant ( $p=0.053$ ). Patients with ED had a total cholesterol level of  $190.58 \pm 36.69$  mg/dL and patients without ED had a total cholesterol level of  $183 \pm 38.42$  mg/dL. The difference in

**Table 1.** Demographic characteristics of patients non-ED and ED

	ED (n:81)	Non-ED (n:33)	P
Age	52.22±10.66	52.72±11.53	0.743*
BMI	29.03±4.90	26.19±3.66	<b>0.002*</b>
VLDL	34.25±22.45	39.34±18.96	0.072*
LDL	128.48±68.49	96±32.81	<b>0.007*</b>
HDL	45.30±17.46	49.30±20.86	0.373*
Trigliserid	175.86±123.86	196.72±94.80	0.053*
Total Kolesterol	190.58±36.69	183±38.42	0.219*
Coronary Risk Index	4.56±1.53	4.23±1.65	0.193*
Aterojenik Risk Index	3.19±2.54	2.29±1.07	<b>0.018*</b>
NLR	1.95±0.74	1.93±0.66	0.536*
PLR	107.20±35.84	125.27±32.72	<b>0.003*</b>

\*: Mann-Whitney U Test

cholesterol levels was not significant (p=0.219) (**Table 1**).

When the relationship between Coronary Risk Index (CRI) and Atherogenic Risk Index and ED was evaluated, the mean values were 4.56 ± 1.53 and 3.19 ± 2.54 in patients with ED and 4.23 ± 1.65 and 2.29 ± 1.07 in patients without ED, respectively. Although no statistically significant correlation was found between CRI and ED, a statistically significant correlation was found between Atherogenic Index and ED (p=0.193, p=0.018) (**Table 1**).

When the relationship between neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are inflammatory biomarkers, and ED was evaluated, NLR was found to be 1.95 ± 0.74 and PLR was 107.20 ± 35.84 in patients with ED. In patients without ED, NLR was 1.93 ± 0.66 and PLR was 125.27 ± 32.72. Although the relationship between NLR and ED was not statistically significant, the relationship between PLR and ED was statistically significant (p=0.536, p=0.003) (**Table 1**).

When the relationship between FS and ED was evaluated, 87.7% of patients with FS had ED complaints, but 45.7% of patients without FS did not have ED complaints. There is a statistically significant relationship between the presence of FS and ED (p=0.000) (**Table 2**).

When the relationship between FS subgroups and ED was evaluated, 22.8% of patients had ED in the unilateral presence of FS, whereas all patients had ED complaints in the bilateral presence. There is statistical significance between FS subgroup analysis and ED (p=0.000) (**Table 3**).

When FS and ED subgroup analysis was evaluated, 45.7% of patients without FS had no ED complaint and 29.8% of patients with FS had mild ED, 47.4% had mild-moderate ED, 8.7% had moderate ED and 1.7% had severe ED. The relationship between the severity of ED in patients with FS was statistically significant (p=0.000) (**Table 4**).

When analysing the FS subgroup and the ED subgroup, it was observed that ED was more severe in patients with bilateral FS than unilateral (p=0.000) (**Table 5**) (**Figure 1**).

**Table 2.** The relationship between the presence of frank's sign and ED

	Frank's Sign (+)	Frank's Sign (-)	P**
ED	50 (%87.7)	31 (%54.3)	<b>0.000</b>
Non-ED	7 (%12.3)	26 (%45.7)	
	57 (%100)	57 (%100)	

\*\* : Chi-Square test

**Table 3.** The relationship between frank's sign subgroup presence and ED

	Frank's Sign Subgroup			P**
	Frank's Sign (-)	Unilateral	Bilateral	
ED	31 (%54.3)	13 (%65)	37 (%100)	<b>0.000</b>
Non-ED	26 (%45.7)	7 (%35)	0	
	57 (%100)	20 (%100)	37 (%100)	

\*\* : Chi-Square test

**Table 4.** The relationship between the presence of frank's sign and ED subgroup

	Frank's Sign (+)	Frank's Sign (-)	P**
Severe	1 (%1.7)	1 (%1.7)	<b>0.000</b>
Moderate	5 (%8.7)	0 (%0)	
Mild to moderate	27 (%47.4)	8 (%14)	
Mild	17 (%29.8)	22 (%38.6)	
No ED	7 (%12.4)	26 (%45.7)	
	57 (%100)	57 (%100)	

\*\* : Chi-Square test

**Table 5.** The relationship between the presence of frank's sign subgroup and ED subgroup

	Frank's Sign Subgroup			P**
	Frank's Sign (-)	Unilateral	Bilateral	
Severe	1 (%1.7)	0 (%0)	1 (%2.7)	<b>0.000</b>
Moderate	0 (%0)	0 (%0)	5 (%13.5)	
Mild to Moderate	8(%14)	4 (%20)	23 (%62.2)	
Mild	22 (%38.1)	9 (%45)	8(%21.6)	
No ED	26(%45.7)	7 (%35)	0 (%0)	
	57 (%100)	20 (%100)	37 (%100)	

\*\* : Chi-Square test

## Discussion

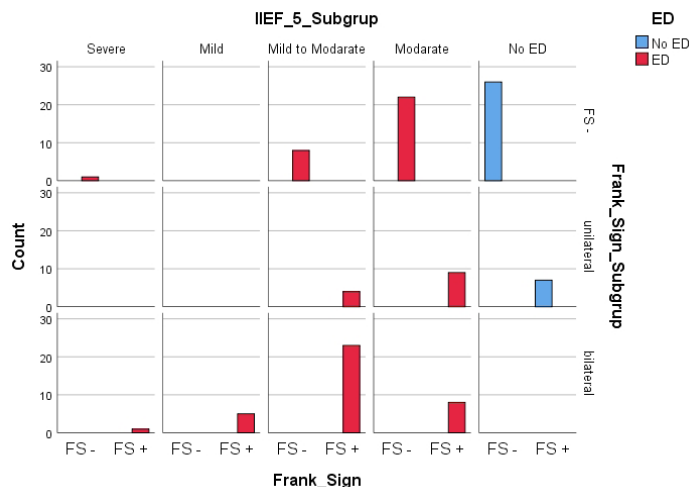
Our study is one of the first to investigate the relationship between FS and ED, and to examine in detail the link between this physical marker and the vascular component of ED. FS was first described by Sanders T. Frank in 1973 and has been associated with coronary artery disease (CAD) and other atherosclerotic conditions. FS has been accepted in the literature as a physical marker of cardiovascular disease, making the association of FS with vascular pathologies such as ED even more significant [4,8]. When the association of FS findings with the presence of chronic diseases in healthy young Turkish population and first degree relatives was evaluated, it was observed that chronic diseases including CAD, cerebrovascular disease and peripheral vascular disease were observed in first degree relatives of patients with Frank's sign findings [9].

Stoyanov et al., in their autopsy study, arterial fibrosis in the myocardium and fibrosis in deep tissues and nerves were observed in patients with Frank's sign, and it has been accepted as an indicator of vascular and neuronal dysfunction [10]. However, the association of FS with endothelial dysfunction and vascular inflammation plays an important role in understanding the mechanisms underlying the strong association of this physical marker with ED. When the relationship between FS and CAD was evaluated by Wang et al, more severe vessel obstruction was observed on coronary angiography in patients with bilateral FS findings (OR, 5.690; 95% CI (3.4-9.3),  $p \leq 0.001$ ) [11]. In line with our hypothesis, our study found a significant correlation between the presence of ED in patients with FS and its severity in bilateral cases.

There is a significant association between ED and metabolic syndrome. In recent years, an increased likelihood of ED has been reported in patients with metabolic syndrome [6]. Çulha et al., in the study evaluating the relationship between atherogenic index and ED, a significant correlation was found between ED and high atherogenic index, but no significant correlation was found between BMI and LDL levels [12]. Similarly, in our study, a significant correlation was found between the level of atherogenic index and ED, but a significant correlation was also found between BMI and LDL levels and ED.

The effect of haematological parameters on acute and chronic inflammation has recently been the subject of much debate. It has been observed that the value of haematological parameters in predicting CVD and ED may be similarly influenced by inflammation. Liao et al., in the study in which they evaluated the relationship between haematological parameters and cholesterol metabolism and ED, a statistically significant correlation was found between LDL, NLR, PLR values and ED, and a negative correlation was found with BMI [13]. In our study, a statistically significant correlation was observed between high LDL and PLR levels and ED.

This relationship between FS and ED severity may have important applications in clinical practice. In particular, the bilateral presence of FS may indicate conditions in which the vascular component of ED is more severe, and in these cases patients may need to be monitored more closely. In addition, the presence of FS may be used as an additional tool to determine the risk of CVD in individuals diagnosed with ED. This may help in the development of early diagnosis and treatment strategies to prevent vascular complications of ED.



**Figure 1.** The relationship between the presence of frank's sign subgroup and ED subgroup

## Conclusion

The presence of FS, especially in bilateral cases, shows a significant correlation with the severity of ED and the underlying vascular pathophysiology. The results of our study suggest that FS may be considered as a potential prognostic marker in the diagnosis and management of ED. Although the limitations of the study include the small sample size and single-centre design, it should be noted that these factors do not fully affect the clinical validity of our findings and provide important contributions to the existing literature. In addition, the lack of control for lifestyle factors such as smoking and physical activity are limitations that should be taken into account when considering the generalisability of the results. However, even with these limitations, it is believed that this study provides a valuable perspective on the clinical potential of FS in the diagnosis and treatment of ED.

**Ethics Committee Approval:** Ethical approval for this study was obtained from Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Approval number: HNEAH-KAEK 2023/128, Date: 19 June 2023).

**Informed Consent:** An informed consent was obtained from all the patients.

**Publication:** The results of the study were not published in full or in part in form of abstracts.

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