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Can the severity of erectile dysfunction be predicted by the change in plasma viscosity

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Abstract

Background: We aimed to contribute to the literature by exploring the possible relationship of PV with erectile dysfunction (ED), as in atherosclerosis-based vascular diseases. **Methods**: Between October 2021 and December 2022, 99 patients who applied to the urology polyclinic with a complaint of ED were included in the study (Group 1). Fifty-two patients who applied with a complaint other than ED constituted the control group (Group 2). **Results**: While 52 participants with normal erectile function were included as controls, 17 participants had mild ED, 24 had mild-moderate ED, 31 had moderate ED, and 27 had severe ED. PV ($p < 0.001$), age ($p < 0.001$), fasting blood glucose ($p < 0.001$), glycated hemoglobin level ($p < 0.001$), and rate of coronary artery disease ($p = 0.028$) were significantly higher in Group 1. High density lipoprotein (HDL) cholesterol was significantly lower in Group 1 ($p = 0.001$). A negative correlation was found between IIEF score and PV ($p < 0.001$), whereas a positive correlation was found between PV and age ($p = 0.023$). Logistic regression analyses revealed that plasma viscosity ($p < 0.001$) and age ($p < 0.001$) were predictive of ED. The cut-off value for PV was 1.12 mPas with area under the curve (AUC) of 0.808 (95% confidence interval (CI): 0.734–0.883) and it predicted ED with 72% sensitivity and 74% specificity. The cut-off value for age was 47.5 years and it predicted ED with 56% sensitivity and 90% specificity (AUC: 0.807, 95% CI: 0.738–0.877). **Conclusions**: According to the results of this study, PV is higher in patients with ED, negatively correlated with IIEF score, and predictive of ED. PV measurements may be useful in supporting the diagnosis of ED and evaluating its severity.

Keywords

Erectile dysfunction; International index of erectile function; Plasma viscosity

Puede predecirse la gravedad de la disfunción eréctil mediante el cambio en la viscosidad del plasma

Resumen

Antecedentes: Nuestro objetivo era contribuir a la literatura explorando la posible relación de la viscosidad plasmática (VP) con la disfunción eréctil (DE), como en las enfermedades vasculares basadas en la aterosclerosis. **Métodos**: Entre octubre de 2021 y diciembre de 2022, se incluyeron en el estudio 99 pacientes que solicitaron atención en la policlínica de urología con una queja de DE (Grupo 1). Cincuenta y dos pacientes que solicitaron atención con una queja relacionada con la DE constituyeron el grupo de control (Grupo 2). **Resultados**: Mientras que 52 participantes con función eréctil normal fueron incluidos como controles, 17 participantes tenían DE leve, 24 tenían DE leve-moderada, 31 tenían DE moderada y 27 tenían DE grave. VP ($p < 0.001$, edad ($p < 0.001$), glucemia en ayunas ($p < 0.001$), nivel de hemoglobina glucosilada ($p < 0.001$) y tasa de enfermedad arterial coronaria ($p = 0.028$) fueron significativamente mayores en el Grupo 1. El colesterol unido a lipoproteinas de alta densidad (HDL) fue significativamente menor en el Grupo 1 ($p = 0.001$). Se encontró una correlación negativa entre la puntuación IIEF y VP ($p < 0.001$), mientras que se encontró una correlación positiva entre VP y edad ($p = 0.023$). Los análisis de regresión logística revelaron que la viscosidad plasmática ($p < 0.001$) y la edad ($p < 0.001$) fueron predictivas de la DE. El valor de corte para VP fue de 1.12 mPas con área bajo la curva (AUC) de 0.808 (intervalo de confianza (IC) del 95%: 0.734–0.883) y predijo la DE con una sensibilidad del 72% y una especificidad del 74%. El valor de corte para la edad fue de 47.5 años y predijo la DE con una sensibilidad del 56% y una especificidad del 90% (AUC: 0.807, IC del 95%: 0.738–0.877). **Conclusiones**: Según los resultados de este estudio, la VP es mayor en pacientes con DE, se correlaciona negativamente con la puntuación del IIEF y es predictiva de la DE. Las mediciones de VP pueden ser útiles para respaldar el diagnóstico de la DE y evaluar su gravedad.

Palabras Clave

Disfunción eréctil; Índice internacional de la función eréctil; Viscosidad plasmática

1. Introduction

Erectile dysfunction (ED) is characterized as the failure to obtain and/or maintain a penile erection adequate for satisfactory sexual relations [1]. Due to the diffuse vasculature of the penis, vasculogenic causes are more common than other etiological causes, being responsible for 60–80% of ED cases [2]. The most important vasculogenic risk factors include cardiovascular disease (CVD), diabetes mellitus (DM), hypertension (HT), dyslipidemia, metabolic syndrome, obesity, smoking and sedentary lifestyle [3, 4]. A close association between ED and CVD has been shown, with many common risk factors [2, 4].

Various studies have shown that high blood and plasma viscosity increases the risk of CVD and plays a role in the pathophysiology of thrombosis and atherothrombosis [5, 6]. The association of plasma viscosity with cardiovascular events has been found to be at least as strong as its association with traditional risk factors such as smoking, diastolic blood pressure, and low density lipoprotein (LDL) cholesterol [7]. In this study, we aimed to contribute to the literature by exploring the possible relationship of plasma viscosity with ED, as in atherosclerosis-based vascular diseases.

2. Materials and methods

Patients admitted to the urology polyclinic between October 2021 and December 2022 due to ED were voluntarily enrolled in the study. The erectile function of the patients was evaluated using the 15-question International Index of Erectile Function (IIEF-15) form. Patients with IIEF erectile function scores of ≥26 (based on questions 1, 2, 3, 4, 5 and 15) were considered to have normal erectile function, while scores of 22–25 signified mild ED, scores of 17–21 signified mild-moderate ED, scores of 11–16 signified moderate ED, and scores of 0–10 signified severe ED. The control group included individuals who applied to the outpatient clinic for other reasons, received scores of ≥26 from the IIEF-15 form and thus had normal erectile function, did not meet any exclusion criteria, and volunteered to participate in the study. Patients in the ED group constituted Group 1 while the control group was Group 2.

Individuals younger than 18 years of age or older than 75 and those with endocrinological diseases other than DM (hyperprolactinemia, hypogonadism, hypo/hyperthyroidism, *etc.*), neurological diseases, hematological diseases, psychiatric disorders, concomitant malignancy, penile curvature/deformity, Peyronie's disease, history of pelvic surgery/trauma/radiotherapy, or chronic renal failure were excluded.

Detailed anamnesis was taken from all participants and physical examinations were performed. Participants were requested to complete the IIEF-15 form by themselves. Questions that were not understood were explained in detail and subsequently answered without further guidance. The height and weight of the participants were measured and recorded and then BMI was calculated. In addition, cigarette smoking in pack-years was also questioned and recorded.

Blood samples were collected from all participants between 07:00 and 11:00 AM following an 8-hour fasting period. Blood samples were used to evaluate complete blood count, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, total cholesterol, total protein, albumin, fibrinogen, sodium (Na), potassium (K), chlorine (Cl), cal-

cium (Ca), total testosterone, and thyroid-stimulating hormone (TSH). Prostate-specific antigen (PSA-total) was also evaluated for patients over 45 years of age.

In addition, 3 mL of blood was collected from all patients from the same venous route into purple-capped ethylenediamine tetraacetic acid (EDTA) tubes. The sample measurement guide prepared by the manufacturer of the device used for plasma viscosity measurements and previous studies on plasma viscosity measurements were taken as a basis for the measurement procedure [8–10]. Accordingly, blood samples were held at 4 °C for 30 minutes and then centrifuged at 3000 rpm for 15 minutes. After centrifugation, the separated plasma was collected in an Eppendorf tube and stored in a sealed cabinet at −80 °C until further study. Plasma viscosity was measured using a Brookfield DV3T Viscometer (DV3TLV 8735248, Brookfield Engineering, Middleboro, MA, USA), CPA-40Z spindle (V069.CPA-40Z, Brookfield Engineering, Middleboro, MA, USA), and Lauda Alpha RA8 circulating bath (Cooling thermostat 230 V; 50 Hz S180000983, Lauda Scientific, Lauda-Königshofen, BW, Germany) at 37 °C. Two viscosity values were calculated at 40 and 60 rpm, at shear rates of 300 and 450 1/s. These values were summed, divided by 2, and recorded as the average viscosity value.

IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. The Kolmogorov-Smirnov test was applied for each group of continuous variables to ensure accuracy. We presented the results as mean ± standard deviation (SD) and used the Student *t*-test for comparisons of normally distributed measurement data. Measurement data with non-normal distribution were presented using median (IQR) values and compared with the Mann-Whitney U test. Categorical variables were presented as numbers and percentages, and they were compared using chi-square and Fisher exact tests between groups. The relationships between the participants' plasma viscosity and other data were analyzed by Pearson correlation analysis. Parameters predicting ED were investigated by univariate analysis, while multivariate logistic regression analysis was used to detect independent predictors while correcting for possible interactions between parameters. Receiver operating characteristic (ROC) curve analysis was performed to calculate the sensitivity and specificity of independent predictive parameters and to determine cut-off values. Values of $p < 0.05$ were considered to be statistically significant.

3. Results

Power analysis was performed with the G*Power 3.1 program (Universitat Kiel, Kiel, SH, Germany) using a power value of 0.95, error level of 0.05, and effect size of 0.8 in line with data from the study conducted by Leschke [11]. This analysis revealed that 42 participants were enough for each group for statistical evaluation. However, we included more patients in Group 1, considering that differences could be seen among patients in the ED group according to their symptom scores. Thus, a total of 151 volunteering participants, with 99 ED patients in Group 1 and 52 controls without ED in Group 2, were included in the study. Participants were further categorized according to the scores obtained from their answers to questions 1, 2, 3, 4, 5 and 15 of the IIEF-15 form. Accordingly, the 52 (34.4%) participants in Group 2 were classified as having normal erectile function. In Group 1, 17 (11.3%) had mild ED, 24 (15.9%) had mild-moderate ED, 31 (20.5%) had moderate ED and 27 (17.9%) had severe ED.

Relationships between demographic characteristics, comorbid conditions, IIEF scores, and laboratory results of the ED patients (Group 1) and controls (Group 2) are shown in Table 1. Age, FBG, HbA1c level, plasma viscosity level, and rate of CVD were significantly higher in Group 1, while HDL cholesterol was significantly lower in Group 1. No significant difference was found between the two groups in terms of the other data presented in Table 1 ($p > 0.05$).

When participants were analyzed according to ED severity, statistically significant differences were found between the subgroups for HT ($p = 0.014$) and CVD ($p = 0.01$) (Table 2).

When the participants' plasma viscosity and other data were evaluated by correlation analysis, a significant positive correlation was found between age and plasma viscosity, while a significant negative correlation was found between IIEF score and plasma viscosity. No significant correlations were found between plasma viscosity and other considered parameters (Table 3).

Logistic regression analyses were performed to determine the factors predicting ED. In univariate analysis, age, smoking, FBG, HbA1c level, HDL cholesterol level, and plasma viscosity were found to be significant. When these data were analyzed by multivariate analysis, associations were observed between age and mean plasma viscosity and ED (Table 4).

Receiver operating characteristic (ROC) analysis was performed to find a cut-off value for plasma viscosity, which was found to be predictive of ED, since there is no relevant reference range for ED in the literature. The AUC was 0.808 (95% CI: 0.734–0.883; $p < 0.001$). The cut-off value for plasma viscosity was found to be 1.12 mPas and it predicted ED with 72% sensitivity and 74% specificity (Fig. 1).

When ROC analysis was performed for age, which was also found to be predictive of ED, the AUC was 0.807 (95% CI: 0.738–0.877; $p < 0.001$). The cut-off value for age was found to be 47.5 years and it predicted ED with 56% sensitivity and 90% specificity (Fig. 2).

4. Discussion

The major results of this prospective study were that plasma viscosity and age could predict ED of vasculogenic origin. When the previous literature is considered, this is the first study showing the association of ED with plasma viscosity. Plasma viscosity, age, FBG, and HbA1c were significantly higher in the ED group, while HDL cholesterol was significantly lower.

Various studies have shown that high blood and plasma viscosity increases the risk of CVD and plays a role in the pathophysiology of thrombosis and atherothrombosis [5–7]. Plasma viscosity is reported to be an independent risk factor for CVD [12]. The Edinburgh Artery Study by Lowe *et al.* [7] revealed that the association of plasma viscosity with cardiovascular events was at least as strong as the association with traditional risk factors (*i.e.*, smoking, diastolic blood pressure and LDL cholesterol). Since CVD and ED have several com-

TABLE 1. Comparison of data between the groups.

Variables	Group 1 (n = 99) Median (IQR)	Group 2 (n = 52) Median (IQR)	*p*
Age, yr	49 (40–58)	31 (27–44)	<0.001
BMI, kg/m^2	27.1 (25.2–30.4)	26.4 (25.3–28.0)	0.158
Smoking, pack-years	0 (0–25)	0 (0–10)	0.066
Hgb, g/dL	15.1 (14.1–15.8)	15.1 (14.6–15.7)	0.452
FBG, mg/dL	98 (87–119)	84 (75–96)	<0.001
HbA1c, %	5.7 (5.4–6.4)	5.3 (5.0–5.6)	<0.001
TG, mg/dL	143 (92–196)	115 (76–167)	0.069
Total cholesterol, mg/dL	186 (163.0–210.0)	195 (161.5–232.5)	0.129
HDL cholesterol, mg/dL	38.6 (35.1–47.8)	46.3 (38.5–54.2)	0.001
VLDL cholesterol, mg/dL	28.8 (18.4–39.2)	23.0 (15.0–33.0)	0.053
Total testosterone, ng/dL	457.7 (365.6–548.9)	417.5 (373.9–513.9)	0.577
Total PSA, ng/mL	0.78 (0.5–1.5)	0.48 (0.4–0.7)	0.069
Na, mmol/L	139 (137–140)	139 (138–141)	0.307
K, mmol/L	4.3 (4.1–4.6)	4.2 (4.0–4.4)	0.069
Cl, mmol/L	105 (103–106)	104 (102–106)	0.222
Ca, mg/dL	9.2 (9.0–9.4)	9.1 (8.8–9.3)	0.234
Plasma viscosity, mPas	1.170 (1.115–1.250)	1.050 (1.010–1.132)	<0.001
Variables	Mean ± SD	Mean ± SD	
LDL, mg/dL	111.27 ± 34.94	123.23 ± 36.82	0.052
Total protein, g/L	75.12 ± 3.60	74.79 ± 3.54	0.592
Albumin, g/L	46.74 ± 3.35	47.59 ± 2.91	0.125
Fibrinogen, mg/dL	307.68 ± 66.27	286.56 ± 60.33	0.057
Variables	n (%)	n (%)	
Hypertension	15 (15.2%)	2 (3.8%)	0.055
Diabetes mellitus	15 (15.2%)	4 (7.7%)	0.211
Cardiovascular disease	9 (9.1%)	0 (0%)	0.028

IQR: Inter quartile range; BMI: Body mass index; Hgb: Hemoglobin; FBG: Fasting blood glucose; HbAlc: Glycated hemoglobin; TG: Triglycerides; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; PSA: Prostate Specific Antigen; Na: Sodium; K: Potassium; Cl: Chlorine; Ca: Calcium.

TABLE 2. Frequency of comorbid conditions in ED subgroups.

Comorbidities	Normal (n = 52)	Mild ED (n = 17)	Mild-Moderate ED (n = 24)	Moderate ED (n = 31)	Severe ED (n = 27)	*p*
Hypertension, n (%)	2 (3.9%)	1 (5.9%)	1 (4.2%)	6 (19.4%)	7 (25.9%)	0.014
Diabetes mellitus, n (%)	4 (7.7%)	0 (0%)	4 (16.7%)	6 (19.4%)	5 (18.5%)	0.164
Cardiovascular disease, n (%)	0 (0%)	0 (0%)	1 (4.2%)	4 (12.9%)	4 (14.8%)	0.010

ED: Erectile dysfunction.

TABLE 3. Correlation analysis for plasma viscosity and other parameters.

	Pearson correlation coefficient (*r*)	*p*
Age, yr	+0.185	0.023
IIEF erectile function score	−0.445	<0.001

IIEF: International Index of Erectile Function.

TABLE 4. Predictors of ED by logistic regression analysis.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (yr)	0.900 (0.866–0.934)	<0.001	0.908 (0.863–0.956)	<0.001
Smoking (pack-years)	0.965 (0.938–0.992)	0.012	1.007 (0.962–1.055)	0.757
FBG (mg/dL)	0.968 (0.949–0.987)	0.001	0.977 (0.950–1.004)	0.097
HbA1c (%)	0.325 (0.169–0.623)	0.001	0.917 (0.364–2.311)	0.855
HDL cholesterol (mg/dL)	1.056 (1.019–1.094)	0.003	1.049 (0.992–1.109)	0.092
Plasma viscosity (mPas)	3.719 (3.030–4.408)	<0.001	0.115 (0.083–0.147)	<0.001

OR: Odds ratio; CI: confidence interval; FBG: Fasting blood glucose; HbAlc: Glycated hemoglobin; HDL: High density lipoprotein.

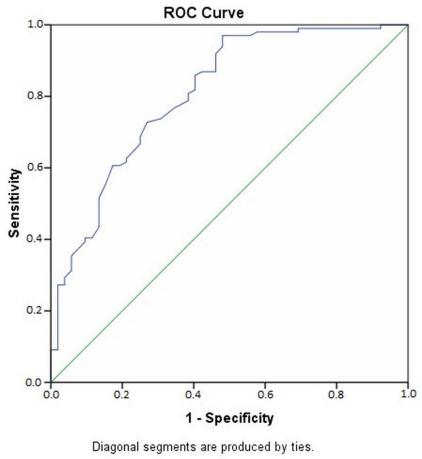

FIGURE 1. ROC curve analysis of plasma viscosity. ROC: Receiver operating characteristic.

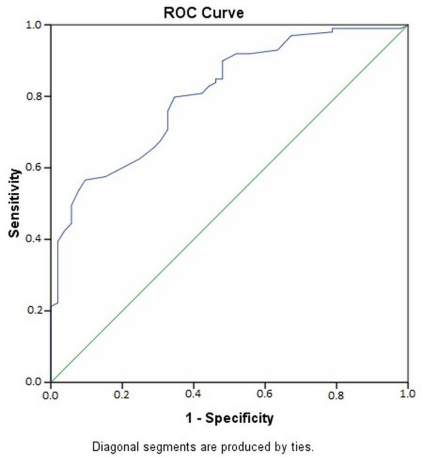

FIGURE 2. ROC curve analysis of age. ROC: Receiver operating characteristic.

mon risk factors and also share pathophysiological pathways, and as ED is accepted as foreshadowing vascular diseases caused by atherosclerosis, especially CVD, we investigated the relationship between plasma viscosity as an indicator of blood viscosity and ED in the present study. Plasma viscosity was significantly higher in Group 1, comprising ED patients, compared to the control group. Univariate and multivariate logistic regression analyses revealed that plasma viscosity was predictive of ED. When ROC analysis was performed, the cut-off value for plasma viscosity was found to be 1.12 mPas and it predicted ED with 72% sensitivity and 74% specificity. The cut-off value that we report supports the previous study conducted by Peters *et al.* [8], who suggested that plasma viscosity could be used to predict CVD and mortality. It also supports the results reported by Lowe *et al.* [7].

Plasma viscosity, determined by blood components, is an important parameter that reflects the fluidity and resistance of blood. For the provision of tissue perfusion, the pumping force of the heart, which creates pressure differences, and the geometry of the vessel, which contributes to flow resistance,

are extremely important together with fluid properties [13]. The more the viscosity increases, the more the flow in the vessel decreases. Decreased flow is a factor that affects both perfusion and the nutrition of the organ as well as erectile function. The results of our study support these findings as a negative correlation was revealed between IIEF score and plasma viscosity.

The viscosity of plasma is approximately 1.8 times that of water at the same temperature (37 °C). Plasma proteins (albumin, fibrinogen and globulins) are responsible for 98% of this difference, while electrolytes and glucose account for 2% [14]. Large proteins have a greater effect on plasma viscosity. Fibrinogen is one of the most important determinants of plasma viscosity with its high molecular weight and asymmetric structure [15]. In the present study, plasma glucose levels were significantly higher among the patients with ED. No significant difference was found for other blood parameters that might have an effect on plasma viscosity. However, fibrinogen and total protein levels were also higher in the ED group, although the differences did not reach the level of statistical significance. The main effective factors in the difference in plasma viscosity between the groups in this study may be the differences in fibrinogen, total protein, and blood glucose levels.

It is commonly recognized that there is a strong association between both ED and CVD, and any common risk factors [2, 4, 16, 17]. Some of the common factors that underlie ED and other vascular diseases, including the pathophysiology of CVD, are inflammation, atherosclerosis and endothelial dysfunction [4]. The hypothesis that vessels smaller in diameter will be more susceptible to similar vascular lesions leads to the conclusion that arteries in the penis will be less tolerant to similar amounts of atheroma plaque because they are smaller [2, 18]. Therefore, patients with endothelial dysfunction develop sexual symptoms first and ED is usually seen earlier than CVD [2, 18]. The available literature confirms that vascular ED may be a precursor of CVD, stroke, and peripheral arterial disease [18]. In many reports, the severity of ED has been associated with atherosclerotic CVD and it has been emphasized that more severe ED correlates with a higher risk of cardiovascular events [19, 20]. In our study, consistent with the literature, significantly higher rates of CVD were observed in the ED group and the frequency of CVD increased significantly as the severity of ED increased.

The association of ED with aging, the latter of which is accepted as a significant risk factor, has been reported many times. Many studies have clearly shown that the prevalence and severity of ED increases with age [21, 22]. Our results are consistent with previous reports as the mean age was found to be higher in the ED group compared to controls. Age was also found to be predictive of ED. When ROC analysis was performed, the cut-off value for age was found to be 47.5 years and it predicted ED with 56% sensitivity and 90% specificity. There was also a positive correlation between plasma viscosity and age. Many studies have shown that plasma viscosity increases with age and our findings support those studies [23, 24].

Many studies have shown that DM, HT, and dyslipidemia are important risk factors for ED [3, 25–31]. In our study, FBG and HbA1c levels were significantly higher in the ED group, consistent with the literature. Our findings support studies showing that the occurrence of HT and ED severity are correlated. In addition, HDL cholesterol levels were found to be significantly lower in the ED group, consistent with previous studies.

The focus of our study, plasma viscosity, can be easily measured in clinical practice with a viscometer. The cut-off value that we obtained reveals that plasma viscosity can provide important information to clinicians, supporting the diagnosis of ED. The demonstration of a negative correlation between IIEF scores and plasma viscosity may indicate that plasma viscosity constitutes a new, objective, and reproducible test that can be used in daily urology practice to evaluate the severity of ED. In addition, it should be kept in mind that ED may be a precursor to serious underlying CVD that has not yet shown clinical findings, especially in patients considered to have vasculogenic ED. Plasma viscosity measurements can provide information about ED in daily urology practice and may be beneficial in making decisions to refer patients with high levels to cardiology clinics for atherosclerosis and coronary artery disease. They may also be valuable in the early diagnosis of serious CVD that could lead to death in the future, and they could be applied for the follow-up of treatment and evaluation of patient responses.

In a previous study conducted by Mayer, it was reported that plasma viscosity decreased with anticoagulant treatment and that this could explain the relief of anginal pain in individuals with coronary heart disease [32]. Schabitz and Petri similarly stated that plasma viscosity decreased with heparin treatment [33]. In the literature, the positive effects of aspirin, prasugrel, and ticagrelor have been noted [34]. These positive effects of anticoagulant and antiaggregant agents on ED may be due to the decrease in plasma viscosity. However, studies targeting this relationship are needed. In addition, no study was found in the literature addressing the relationship between fibrinolytic agents and plasma viscosity, and future studies could accordingly evaluate the possible effects of these drugs on ED.

Our study has some limitations to be noted. It was conducted as a single-center, cross-sectional study and patients did not have specific durations of follow-up. The numbers of participants in the ED and control groups were relatively small. Participants were included in the study and categorized into groups based on only anamnesis and IIEF-15 scores; penile Doppler ultrasonography (USG) following intracavernosal injection of an agent was not performed because it is an invasive procedure. Finally, the numbers of participants with CVD, DM, HT, dyslipidemia and smoking habit were low.

5. Conclusions

In this study, the cut-off value for plasma viscosity in ED patients was found to be 1.12 mPas, predicting ED with 72% sensitivity and 74% specificity. In addition, a negative correlation was found between IIEF scores and plasma viscosity. To the best of our knowledge, this is the first study to address the relationship between plasma viscosity and ED and we believe that our findings constitute a valuable contribution to the literature. However, more comprehensive multicenter studies conducted with larger sample sizes are needed to support our

findings.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

MG and SZ—designed the Research study. SZ, MG, AG and MK—performed the Research. YK—provided assistance and advice on plasma viscosity measurement. AG, OE and CB—analyzed the data. SZ, AG, MK, OE, CB and DB—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted prospectively between 01 October 2021 and 01 December 2022 in accordance with the principles of the Declaration of Helsinki after obtaining approval from the Ethics Committee of Health Sciences University Bursa Yuksek Ihtisas Training and Research Hospital (Approval No. 2011-KAEK-25 2020/03-10). All participants were informed about the study and informed consent forms were signed by all participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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