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Erkek Cinsel Sağlığı

Monocyte-to-high-density lipoprotein-cholesterol ratio as a predictor and severity indicator of erectile dysfunction

Erektil disfonksiyonun belirleyicisi ve ciddiyet göstergesi olarak monosit - yüksek yoğunluklu lipoprotein kolesterol oranı

İbrahim Üntan[1], Ahmet Emin Doğan[2]

ABSTRACT

OBJECTIVES: Although increased inflammation causes endothelial dysfunction and the role of monocytes and high-density lipoprotein-cholesterol in inflammation has been demonstrated, there are surprisingly few publications examining the relationship between monocyte-to-high-density lipoprotein-cholesterol ratio and erectile dysfunction. In this study, we both summarized the actors of the inflammation process and examined the relationship between the monocyte-to-high-density lipoprotein-cholesterol ratio and erectile dysfunction in terms of whether it can be a prognostic or predictive marker.

MATERIAL and METHODS: Between January and September 2021, 143 patients with erectile dysfunction and 140 control patients who applied to the urology outpatient clinic and had no systemic disease were selected. Complete blood count, biochemical parameters, and hormone samples were obtained from all patients under appropriate conditions. Erectile dysfunction was diagnosed with the five-item version of the International Index of Erectile Function questionnaire. Statistical comparisons were made between the groups with the obtained data.

RESULTS: Age, height, white blood cell, platelet, lymphocyte, creatinine, fasting plasma glucose, triglyceride, follicle-stimulating hormone, luteinizing hormone, and total testosterone variables were indifferent among the groups. Body mass index, weight, total cholesterol, low-density lipoprotein-cholesterol, neutrophil count, monocyte-to-high-density lipoprotein-cholesterol ratio, and neutrophil-to-lymphocyte ratio variables were significantly high in the case group. International Index of Erectile Function - 5 scores and low-density lipoprotein-cholesterol levels were significantly high in the case group. A significant negative correlation was observed between the monocyte-to-high-density lipoprotein-cholesterol ratio and the International Index of Erectile Function - 5 score.

CONCLUSIONS: The monocyte-to-high-density lipoprotein-cholesterol represents inflammation and endothelial damage and can be used as a readily and inexpensive predictor or severity indicator of erectile dysfunction, caused by these impairments.

Keywords: endothelial dysfunction, erectile dysfunction, inflammation, monocyte, high-density lipoprotein-cholesterol

ÖZ

AMAÇ: Artan enflamasyonun endotel disfonksiyonuna neden olması ve monositlerin ve yüksek yoğunluklu lipoprotein kolesterolün enflamasyondaki rolü gösterilmesine rağmen, monosit - yüksek yoğunluklu lipoprotein kolesterol oranı ile erektil disfonksiyon arasındaki ilişkiyi inceleyen şaşırtıcı derecede az sayıda yayın bulunmaktadır. Bu çalışmada hem enflamasyon sürecinin aktörlerini özetledik hem de monosit - yüksek yoğunluklu lipoprotein kolesterol oranı ile erektil disfonksiyon arasındaki ilişkiyi prognostik veya prediktif bir belirteç olup olamayacağı açısından inceledik.

GEREÇ ve YÖNTEMLER: Ocak-Eylül 2021 tarihleri arasında üroloji polikliniğine başvuran ve herhangi bir sistemik hastalığı olmayan 143 erektil disfonksiyonlu hasta ve 140 kontrol hastası seçildi. Tüm hastalardan uygun koşullar altında tam kan sayımı, biyokimyasal parametreler ve hormon örnekleri alındı. Erektil disfonksiyon tanısı, Uluslararası Cinsel İşlev Endeksi anketinin beş maddelik versiyonuyla koyuldu. Elde edilen verilerle gruplar arasında istatistiksel karşılaştırmalar yapıldı.

BULGULAR: Yaş, boy, beyaz kan hücresi, trombosit, lenfosit, kreatinin, açlık plazma glukozu, trigliserit, folikül uyarıcı hormon, luteinizan hormon ve total testosteron değişkenleri gruplar arasında farksızdı. Vücut kitle endeksi, ağırlık, toplam kolesterol, düşük yoğunluklu lipoprotein kolesterol, nötrofil sayısı, monosit - yüksek yoğunluklu lipoprotein kolesterol oranı ve nötrofil-lenfosit oranı değişkenleri vaka grubunda anlamlı derecede yüksekti. Uluslararası Cinsel İşlev Endeksi - 5 skorları ve düşük yoğunluklu lipoprotein kolesterol değişkenleri vaka grubunda anlamlı derecede yüksekti. Monosit - yüksek yoğunluklu lipoprotein kolesterol oranı ile Uluslararası Cinsel İşlev Endeksi - 5 skoru arasında anlamlı negatif korelasyon gözlendi.

SONUÇ: Monosit - yüksek yoğunluklu lipoprotein kolesterol oranı, enflamasyonu ve endotel hasarını temsil eder ve bu bozuklukların neden olduğu erektil disfonksiyonun kolay ve ucuz bir öngörücüsü veya ciddiyet göstergesi olarak kullanılabilir.

Anahtar Kelimeler: endotel disfonksiyonu, erektil disfonksiyon, enflamasyon, monosit, yüksek yoğunluklu lipoprotein kolesterol

[1]*Department of Urology, Ahi Evran University, Training and Research Hospital, Kirsehir, Turkey*
[2]*Department of Urology, Etlik Integrated Health Campus, Ankara, Turkey*

Yazışma Adresi/ *Correspondence:*
Dr. Öğr. Üyesi İbrahim Üntan
Ahi Evran University, Training and Research Hospital, Department of Urology, Kervansaray Mah. 2019. Sok. No:1 40100 Kırşehir-Turkey
Tel: +90 386 415 45 15
E-mail: ibrahimuntan@erciyes.edu.tr

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INTRODUCTION

Erectile dysfunction (ED) is a frequent male sexual disorder. It is common in men over the age of 40. ED is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance. It affects more than half of men aged 40–70 years.[1] Several different factors are implicated in the pathophysiology of ED.[2] The most common and worth mentioning are neurogenic, endocrinologic,

vasculogenic, and psychogenic factors. Since the penis is an organ with a high blood flow, the most important factor seems to be the vasculogenic factor.[3]

Erectile dysfunction and cardiovascular diseases (CVD) often accompany each other. Endothelial dysfunction is held responsible for impaired blood flow, which is also effective in the pathogenesis of both diseases.[4] Due to endothelial dysfunction, which is commonly blamed in both diseases, ED appears to be both an independent risk factor for CVD and an early predictor of CVD as well.[5] Risk factors for CVD, particularly low levels of high-density lipoprotein-cholesterol (HDL-C), can affect and determine the severity of ED.[6] There are studies indicating that ED is resolved significantly in those receiving treatment for cardiovascular risk factors giving hints that CVD and ED have a common pathogenesis.[7]

Intact vascular endothelium which has an anti-inflammatory effect, regulates blood flow and fluidity in the absence of inflammation.[8] However, in the presence of inflammation, vascular endothelial function deteriorates, and oxidative stress increases. Various studies refer to the link between inflammation and endothelial dysfunction.[9] Contact of proinflammatory and prooxidant cytokines with vascular endothelial cells impairs vascular dilatation, which is one of the sine qua non of erection.[10] During the inflammation process, the cells most responsible for the release of these pro-oxidant and pro-inflammatory cytokines are the monocytes of inflamed tissue.[11] HDL-C has been shown to act as a barrier against the pro-oxidant and pro-inflammatory releasing behaviors of monocytes.[12] Moreover, HDL-C has been pointed to inhibit the proliferation and activation of monocytes and the differentiation of common progenitor cells towards monocytes.[13] In other words, both increased monocytes and decreased HDL-C concentrations act in favor of inflammation. Based on this information, it is argued that the monocyte-to-HDL-C ratio (MHR) may be a novel marker for CVD.[14] The association of markers obtained from inflammatory cells and their mediators with ED has been demonstrated before.[15] Similarly, the reason for the neutrophil-to-lymphocyte ratio (NLR) to have been accepted as a prospective biomarker of inflammatory conditions, which can lead to ED, is based on the above-mentioned relationship.[16] It seems reasonable to use this convenience and inexpensive ratio for ED, which shares a common pathogenesis with CVD. In our study, we tried to reveal the effects of MHR on ED. To the best of our knowledge, our study is the largest-scale study among little research among on this topic.

MATERIAL and METHODS

Participant Selection and Study Design

This study was designed after acquiring approval from the local research ethics committee. The study was planned as a single-center, retrospective study. The study included 283 patients. Of these, 143 patients were who applied to urology outpatient clinics and diagnosed as organic ED. Of these, 140 were included in the control group, who applied to the urology outpatient clinics and have neither ED nor any other systemic diseases. All participants were selected over the age of 40. They were all heterosexual and monogamous. Participants with malignancy, major psychiatric disorder, acute/chronic hepatobiliary disease anatomical deformity of the penis, Peyronie's disease, pelvic or spinal cord injury, adrenal and metabolic diseases, hematologic disorder, thyroid dysfunction, congestive heart failure, hyperprolactinemia, renal failure, pulmonary hypertension, and stroke were debarred from the work. Participants with an anamnesis of radical prostatectomy, pelvic major surgery, pelvic radiation, or any treatment related to ED. Anti-coagulants, β-blockers, spironolactone, alcohol, drugs, cigarettes, cigars, tobacco, corticosteroids, and testosterone supplements were other reasons for exclusion. Recent history of a chronic inflammatory or immunological disease, acute infection, and testosterone supplementation for hypogonadism also prevented inclusion.

Clinical Assessment

The complete medical and sexual histories recalled and recounted by the patients were noted.

Psychogenic and organic ED distinction was performed interrogating morning erections. Sociodemographic characteristics such as height, weight, age, and ED causes were recorded. Complete physical examinations including genital and neurologic examinations were administered. Body mass indexes were calculated using the weight (in kg) / height^2 (in m^2) formula.[17] A five-question version of the International Index of Erectile Function (IIEF-5) was utilized to score the erectile wellness of the participants.[18] All the participants marked the IIEF-5 questionnaires on their own. Participants who scored 21 or less in the IIEF-5 questionnaire were included in the study while others were deemed to have a normal erectile function.

Laboratory Tests

Peripheral blood samples were drawn from all the participants as fasting samples and the serum was separated. Then, serum samples were tested within two hours. Fasting plasma

glucose (FPG) was studied utilizing the hexokinase method. Triglyceride (TG) and total cholesterol (TC) were subjected to an enzymatic method. Low-density lipoprotein-cholesterol (LDL-C) and HDL-C were measured by direct quantitation also known as peroxidase scavenging. These biochemical parameters were tested by automatic biochemical detectors. Luteinizing hormone (LH) levels were obtained using a time-resolved immuno-fluorometric assay (Delfia, Wallac), total testosterone (TT) levels were measured by radioimmunoassay (Coat-a-Count), and follicle-stimulating hormone (FSH) measurements were performed by chemiluminescent immunoassay. The parameters of complete blood count were revealed with an automatic blood cell counter (Cobas 8000, Roche Diagnostics, Mannheim, Germany). The MHR ratio was found by dividing the monocyte count by the HDL-C level. The NLR ratio was found by dividing the neutrophil count by the lymphocyte count.

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) program version 24.0 (IBM Corp. Released 2013, SPSS for Windows, Version 24.0 Armonk, NY: IBM Corp.) was utilized for statistical analysis of the data. Shapiro-Wilk test was used to detect the normality of the data distribution. Subjects characteristics' were summarized using descriptive statistics. The numerical variables with a normal distribution were reflected as mean ± standard deviation (SD). Data that is not normally distributed were presented as median ± interquartile range (IQR). The minimum and maximum values are given in parentheses. Mann-Whitney U test and Student's t-test were used in the statistical analysis. Spearman correlation coefficient (ρ) was used to evaluate correlations between non-normal distributed data. The area under the curve (AUC) was extracted from the receiver operating characteristic (ROC) curve and utilized to evaluate MHR's diagnostic accuracy. The cut-off value of the ROC curve was forecasted with the maximum Youden index. The specificity, sensitivity, positive predictive value, and negative predictive value were assayed. A p-value below 0.05 was considered statistically significant. Two decimal points were placed for mean, SD, median, and IQR. One decimal point is placed for minimum and maximum. No decimals are set for integers.

RESULTS

Demographic Characteristics

The mean age of the ED patients (59.67±6.12 years) and the control participants (59.78±7.41 years) were similar (p=0.494). Body mass index comparison exhibited that ED patients (27.75±4.26 kg/m^2) were slightly overweight compared to control participants (25.75±4.71 kg/m^2)(p=0.001). Weight comparison displayed that ED patients (82.37±12.18 kg) were found to be heavier than the control participants (77.35±14.34 kg)(p=0.002). The mean height of the ED patients (172.46±6.01 cm) and the control participants (173.35±5.74 years) were indifferent (p=0.454). The comparison of the baseline laboratory assessments between groups imparted that, ED patients did not have significantly different white blood cell, platelet, and creatinine levels compared to the control subjects (Table 1).

Table 1. Baseline demographics and clinical characteristics

Variables	*Case (n=143)*	*Control (n=140)*	*p*
Age (year)	59.67±6.12 (41–76)	59.78±7.41 (40–76)	0.494[b]
BMI (kg/m^2)	27.75±4.26 (16.6–40)	25.75±4.71 (17.6–41)	0.001[b]
Weight (kg)	82.37±12.18 (51–123)	77.35±14.34 (50–123)	0.002[b]
Height (cm)	172.46±6.01 (155–187)	173.35±5.74 (160–189)	0.454[b]
FPG (mg/dl)	99.52±11.6 (70–104)	98.95±13.47 (67–102)	0.154[a]
Creatinine (mg/dl)	0.88±0.26 (0.4–1.4)	0.91±0.24 (0.6–1.5)	0.831[a]
WBC (x10^3/l)	7.26±2.08 (2.8–15.8)	7.68±1.99 (4.8–14.2)	0.212[b]
PLT (x10^3/l)	268.8±74.1 (134–583)	274.8±75.9 (346–950)	0.383[b]
LYM (10/µl)	187±39.99 (99–238)	229±45.21 (165–304)	0.198[b]
NEU (10/µl)	448±43.36 (361–534)	268±42.37 (101–395)	0.000[b]
FSH (mIU/ml)	6.22±5.29 (0.9–44.9)	5.78±2.59 (1.6–23.1)	0.086[a]
LH (mIU/ml)	6.54±4.56 (1.4–52.3)	6.79±2.63 (2.6–14)	0.164[a]
TT (ng/ml)	427.11±155.31 (116–1084)	433.02±129.81 (200–765)	0.802[a]

BMI: body mass index; **FPG:** fasting plasma glucose; **WBC:** white blood cell; **PLT:** platelet; **LYM:** lymphocyte; **NEU:** neutrophil; **FSH:** follicle-stimulating hormone; **LH:** luteinizing hormone; **TT:** total testosterone.
[a] Mann-Whitney U test.
[b] Student's t-test.

Erectile Dysfunction and MHR

As a natural consequence of grouping, IIEF-5 scores of ED patients were found to be significantly lower than that of the control participants. The mean IIEF-5 scores were; 9.85±3.21 in the case group and 23.25±1.01 in the control group (p<0.001).

Comparison of the blood parameters between groups disclosed that ED patients did not have significantly different FPS, TG, FSH, LH, TT levels, and lymphocyte count compared to the control subjects. TC level was significantly higher in ED patients (183.31±37.43) than in control participants (169.91±37.14)(p=0.003). LDL-C level was significantly higher in ED patients (119.56±32.1) than in control participants (106.01±34.41)(p=0.004). Monocyte count was significantly higher in ED patients (740±176) than in control participants (550±229)(p<0.001). HDL-C levels were significantly lower in ED patients (41.92±9.98) than in control participants (54.34±11.74)(p<0.001). Neutrophil count was significantly higher in ED patients (448±43.36) than in control participants (268±42.37) (p<0.001). MHR was significantly higher in ED patients (18.65±6.3) than in control participants (10.97±6.56) (p<0.001). NLR fractions were significantly higher in ED patients (2.08±1.14) than in control participants (1.28±0.62)(p<0.001)(Table 2).

Table 2. Assessment of erectile dysfunction and relevant parameters

Variable	*Case (n=143)*	*Control (n=140)*	*p*
IIEF-5 (point)	6±7* (5–15)	24±1* (22–25)	0.000[b]
Monocyte (/μL)	740±176 (350–1180)	550±229 (220–1510)	0.000[a]
TC (mg/dl)	183.31±37.43 (108–290.7)	169.91±37.14 (67.6–236.2)	0.003[a]
TG (mg/dl)	181.64±115.24 (35.2–770.2)	169±85.9 (33.8–444)	0.811[a]
HDL-C (mg/dl)	41.92±9.98 (23.9–76.2)	54.34±11.74 (27.6–76.6)	0.000[b]
LDL-C (mg/dl)	119.56±32.1 (52–205.5)	106±34.41 (11.2–159.8)	0.004[b]
MHR (10^2/μg)	18.65±6.3 (7.4–37.1)	10.97±6.56 (3.5–46.2)	0.000[a]
NLR	2.08±1.14 (0.5–9.3)	1.28±0.62 (0.4–3.9)	0.001[a]

IIEF: International Index of Erectile Function; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; MHR: monocyte to-HDL-C ratio; NLR: neutrophil-to-lymphocyte ratio.
* median±IQR.
[a] Mann-Whitney U test.
[b] Student's t-test.

Correlation Analysis

Spearman correlation analysis was performed for MHR and IIEF-5 in ED patients and control participants. A negative correlation was found with a ρ-value of -0.28 between MHR and IIEF-5 score indicating an positive correlation between MHR and ED (p<0.0001).

ROC curve

To interpret the diagnostic value of it, MHR was subjected to ROC curves in ED and control groups. The result pointed the AUC of MHR to be 0.675 (95% CI: 0.643–0.821; p<0.001). The cut-off value of the MHR was 1.8 according to the maximum Youden index. This value gave 58.4% sensitivity and 80.1% specificity when MHR is less than or equal to 1.8. Besides, the positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for this cut-off point are 2.93 and 0.53, respectively (Figure 1).

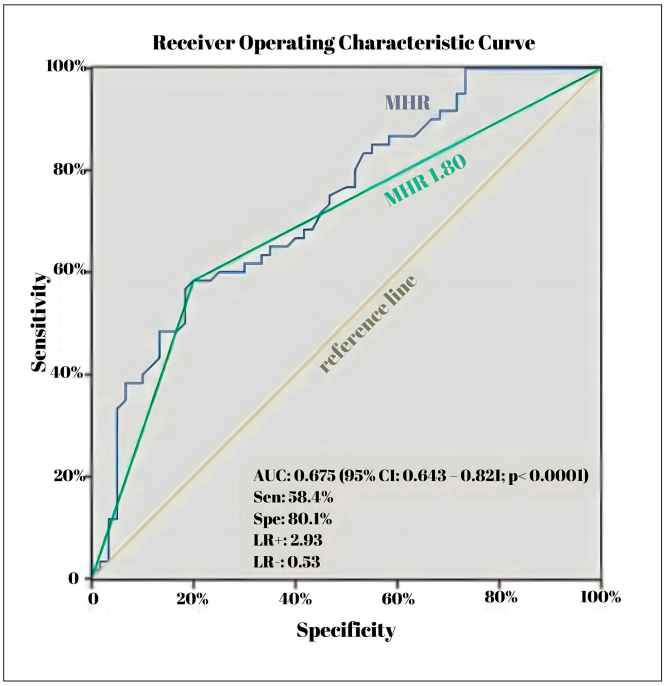

Figure 1. Receiver operating characteristic curve for the diagnosis of erectile dysfunction by monocyte-to-high-density lipoprotein-cholesterol.

DISCUSSION

As a novel inflammatory marker, the severity and presence of ED are related to MHR as well as other subclinical inflammatory mediators.[19] Based on this relationship, our study focused on the relationship between MHR and ED. To test the power of MHR as a marker for ED, we formed two groups of ED patients and healthy participants. In our study, MHR was significantly higher in patients with ED compared to healthy participants, and this supported the pathogenesis of inflammation in ED. Consistently, MHR also mirrored a negative correlation with IIEF-5 scores and

this revealed the correlation with ED severity. We indicated the MHR can be utilized as a marker of the presence or the severity of ED.

Erectile dysfunction and CVD are linked by their common pathophysiology, endothelial dysfunction.[20] Aging, obesity, smoking, sedentary lifestyle, diabetes mellitus, renal failure, dyslipidemia, and hypertension are risk factors for both ED and CVD and they all lead to endothelial dysfunction. ED is tightly associated with CVD as its predictor.[21]

The endothelial cells are not only mechanic barriers to blood flow but are also responsible for modulating vascular tone, regulating hemostasis and inflammation, and repairing local tissue injury.[22] Endothelial dysfunction plays a key role in ED where the vasoconstrictor and vasodilator balance is impaired.[23] The most important consequence of endothelial dysfunction is procrastination of vasodilatory processes and acceleration of vasoconstrictor processes.[24] When vasodilation in vascular structures is inhibited, the cavernous system cannot fully fill and cannot reach sufficient blood pressure, which causes ED.[25] In the presence of inflammation and oxidative stress, endothelial cells do not perform their normal anti-inflammatory functions. In the process of oxidative stress, the production of free radicals and peroxidation of lipids advance, and this leads to endothelial inflammation and dysfunction.[26] The pathophysiology of endothelial dysfunction can be summarized with this path. The association of the presence and severity of endothelial dysfunction and mediators of inflammation (CRP, fibrinogen, von Willebrand factor, interleukin 1b, interleukin 6, etc.) are revealed by several studies.[27]

Monocytes are inflammatory cells that originate from the bone marrow and pass into the bloodstream, they differentiate into macrophages or dendritic cells in tissues or lymphoid organs.[28] Secreted inflammatory cytokines trigger monocytes to endothelial adhesion and vessel wall migration.[29] HDL-C suppresses the inflammatory properties of monocytes in several stages by inhibiting activated monocytes, hindering migration, and interrupting macrophage differentiation.[30] HDL-C works against inflammation and oxidation diminishing adhesion for both endothelial cells and monocytes and reducing moleculer expression. HDL-C depresses the surface expression of integrin CD11b to down-regulate the transmigration of immune cells into the arterial wall.[31] HDL-C inhibits the oxidation of LDL-C and thus prevents inflammatory activation of LDL-C in endothelial cells.[32] HDL acts as a vasorelaxant by enhancing the expression of endothelial nitric oxide synthase.[33]

Consistent with studies that identified low HDL-C levels as a significant predictive factor for ED, we found the HDL-C levels of ED patients to be significantly lower than the others supporting the favorable effect of HDL-C on ED in our study.[34] In a 30-year-old study, While the likelihood of complete ED was 0% in those with HDL-C above 90 mg/dl, the likelihood rose to 7.2% when the level decreased to 60 mg/dl and to 16.1% when the level decreased to 30 mg/dl.[35]

Monocyte-to-high-density lipoprotein-cholesterol ratio is a new combined inflammatory marker that combines the inflammatory effect of monocytes and the anti-inflammatory effect of HDL-C under one roof. This ratio is superior to both the numerator and denominator in predicting CVD.[36] It has been shown that CVD prognosis is worse in patients with high MHR in chronic kidney disease.[37] A correlation has been shown between high MHR and coronary artery ectasia and obstructive CVD in terms of both presence and severity.[38] All studies agree that MHR is indicative of endothelial dysfunction and systemic inflammation. Consistent with these studies, we found higher monocyte count, higher MHR, and lower HDL-C levels in ED patients compared to control participants in our study. Our findings provide evidence for the link between MHR and the presence and severity of ED. The fact that high MHR refers to loss of erectile function is a conclusion that can be inferred from the strength of the negative correlation between MHR and IIEF-5 scores.

Having a retrospective design is the primary limitation of the study. However, MHR needs to be supported by further studies to become a reliable predictor. Another limitation is that although monocyte and HDL-C have been measured, the complex parameters involved in the interaction process between these two have not been assessed. Because the response behavior of monocytes varies and different types of monocytes perform different activities, another limitation is that we do not divide monocytes into subgroups.[39] Another limitation is that other inflammatory parameters which can be a confusing role between cytocines, monocytes, or HDL-C were not evaluated. The fact that Turkish people are not very enthusiastic about reading may have created a limitation in terms of the IIEF-5, which is a form filled out by reading.[40]

CONCLUSIONS

In our study, we found that MHR, a new inflammatory marker, was also significantly lower in ED patients and higher in control participants. This statistically significant difference suggests that this ratio, which is easy and inexpensive,

and often routinely studied, can give clues about the presence or severity of ED. However, MHR needs to be supported by further studies to become a reliable predictor.

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Availability of Data and Materials

The data that support the findings of this study are available on reasonable request from the corresponding author. There is no time limit on data sharing.

Ethics Committee Approval
The study was approved by Ankara Dışkapı Training and Research Hospital Ethics Committee. (date and number of approval: 20.09.2021/120-02).

Peer-review
Externally peer-reviewed.

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

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