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A Comparative Analysis of The Association Between Remnant Cholesterol and Erectile Dysfunction

Remnant Kolesterol ve Erektil Disfonksiyon Arasındaki İlişkinin Karşılaştırmalı Analizi

Salim ZENGİN[1] [ID], Abdullah GÜL[1] [ID], Özgür EKİCİ[2] [ID], Çağlar BOYACI[1] [ID]

[1]Department of Urology, Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences, Bursa, Türkiye.
[2]Department of Urology, Bursa City Hospital, University of Health Sciences, Bursa, Türkiye.

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Correspondence: Salim Zengin; MD., Department of Urology, Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences, Bursa, Türkiye. E-mail: salimmzengin@gmail.com

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Abstract

Considering that cardiovascular diseases (CVD) and erectile dysfunction (ED) have many common risk factors and pathophysiology, we aimed to determine whether remnant cholesterol (RC) is associated with ED. Patients who were diagnosed with ED and examined with any other andrological complaints between January 2022 and December 2023 in our outpatient clinic were retrospectively reviewed. The erectile function of the participants was evaluated using the International Index of Erectile Function (IIEF-15) form. Fasting blood glucose (FBS), hemoglobin A1c (HbA1c), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total testosterone, body mass index (BMI) and RC were calculated and recorded. Patients were categorized as having ED (Group 1) and not having ED (Group 2) according to the erectile function score of the IIEF-15 questionnaire. The mean age of the participants included in the study was 46.93±12.29 years. There were 160 (58.6%) patients in Group 1 and 113 (41.4%) patients in Group 2. Age, BMI, FBS and HbA1c levels were significantly higher in Group 1 (p=0.001; p=0.013; p=0.009; p=0.001, respectively). HDL cholesterol level was significantly lower in Group 1 (p=0.008). The mean RC level was 35.7±21.3 mg/dL in Group 1 and 31.8±19.4 mg/dL in Group 2 and was comparable between the two groups (p=0.123). In our study, although the RC level was found to be higher in the ED group, it did not reach a statistically significant level. Further prospective studies with larger sample size are needed.

Keywords: Erectile dysfunction, IIEF, Remnant cholesterol.

Özet

Kardiyovasküler hastalıklar (KVH) ve erektil disfonksiyonun (ED) çok sayıda ortak risk faktörüne ve patofizyolojiye sahip olduğunu göz önünde bulundurarak; remnant kolesterolün (RK) ED ile ilişkisinin olup olmadığını ortaya koymayı amaçladık. Kliniğimizde Ocak 2022 – Aralık 2023 tarihleri arasında ED tanısı konmuş ve herhangi bir başka androlojik yakınmalarla tetkik edilmiş hastalar geriye dönük olarak tarandı. Katılımcıların erektil fonksiyonları Uluslararası Erektil Fonksiyon İndeksi (IIEF-15) formu kullanılarak değerlendirilmiştir. Açlık kan şekeri (AKŞ), hemoglobin A1c (HbA1c), total kolesterol, yüksek yoğunluklu lipoprotein (HDL), düşük yoğunluklu lipoprotein (LDL), total testosteron, vücut kitle indeksi (VKİ) ve RK hesaplanarak kayıt altına

alınmıştır. Hastalar IIEF-15 formu erektil fonksiyon skoruna göre ED'si olan (Grup 1) ve olmayan (Grup 2) olarak kategorize edilerek kıyaslama yapılmıştır. Çalışmaya dahil edilen katılımcıların ortalama yaşı 46.93±12.29 yıl idi. Grup 1'de 160 (%58.6) hasta, Grup 2'de ise 113 (%41.4) hasta bulunmaktadır. Grup 1'de yaş, VKİ, AKŞ ve HbA1c düzeyi anlamlı olarak daha yüksek saptanmıştır (sırasıyla p=0.001; p=0.013; p=0.009; p=0.001). HDL kolesterol düzeyi Grup 1'de anlamlı olarak daha düşük saptanmıştır (p=0.008). RK düzeyi Grup 1'de ortalama 35.7±21.3 mg/dL ve Grup 2'de ortalama 31.8±19.4 mg/dL olup iki grup arasında istatistiksel anlamlı fark saptanmamıştır (p=0.123). Çalışmamızda, ED grubunda RK düzeyi daha yüksek saptanmasına rağmen, istatistiksel açıdan anlamlı seviyeye ulaşmamıştır. Geniş kapsamlı, prospektif ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Erektil disfonksiyon, Remnant kolesterol, IIEF.

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve and/or maintain a sufficient penile erection for satisfactory sexual intercourse [1]. Epidemiological data show that ED has a high prevalence and incidence worldwide [2-5]. ED is a symptom acting vasculogenic, neurogenic, endocrinological, iatrogenic, psychogenic, and anatomical factors in its pathophysiology [6,7]. Compared to other etiological factors, vasculogenic causes are more predominant and are responsible for the vast majority of all ED cases [7]. The main conditions causing vasculogenic ED are diabetes mellitus (DM), hypertension (HT), hyperlipidemia, cardiovascular diseases (CVD), obesity, metabolic syndrome, smoking, and sedentary life [7]. The common pathophysiological pathway underlying these vasculogenic risk factors is inflammation, atherosclerosis, and endothelial dysfunction resulting in decreased blood flow, arterial insufficiency, or arterial stenosis [7,8].

Many studies have emphasized that dyslipidemia is an important risk factor for ED [9,10]. Various studies have showed that high total cholesterol and LDL cholesterol levels increase the risk of ED, whereas high HDL cholesterol levels are protective against ED risk [3,11]. Fragments other than HDL and LDL cholesterol in total cholesterol content are called remnant cholesterol (RC) [12]. RC is mainly composed of very low-density lipoprotein (VLDL), intermediate- density lipoprotein (IDL), and chylomicron remnants [12,13]. Similar to LDL cholesterol, RC adheres to the intima of the arterial wall and causing endothelial dysfunction and atherosclerotic plaque development [12]. Numerous studies have demonstrated that high RC is associated with an increased risk of CVD [14-16]. In this study, considering that CVD and ED have many common risk factors and pathophysiology, we aimed to determine whether RC is associated with ED.

Material and Method

Participants were included in the study after the approval of the ethics committee numbered 2011-KAEK-25 2023/12-15 from the ethics committee of University of Health Sciences, Bursa Faculty of Medicine, Yuksek Ihtisas Training and Research Hospital, by the Principles of the Declaration of Helsinki. All the volunteers accepted to participate in study by signing of informed consent form. Patients who applied to the urology outpatient clinic of our hospital between January 2022 and December 2023 due to andrological complaints were retrospectively evaluated in this study. The erectile function of the patients was evaluated using the International Index of Erectile Function (IIEF-15) questionnaire [17]. Patients with an erectile function score in IIEF-15 form (questions 1,2,3,4,5 and 15) of 26 and above were considered healthy/normal, while those with a score below 26 were considered ED.

Exclusion criteria; Patients with any endocrinological disease other than type 2 DM such as hyperprolactinemia, hypogonadism and hypo/hyperthyroidism, neurological disease, hematological disease, accompanying malignancies, psychiatric disease, ED-related drug and addictive substance usage, collagen tissue disease, history of previous penile or pelvic surgery/ trauma/radiotherapy, history of spinal cord trauma, liver, and renal disorders. In addition, patients with missing data were excluded from the study.

IIEF-15 erectile function score, anamnesis and physical examination findings were obtained from archive records. It was ensured that the blood samples reached to the laboratory between 08:00-11:00 a.m. The results of FBS, HbA1c, total cholesterol, HDL, LDL, and total testosterone were recorded. Age and BMI of the patients were also calculated and recorded. The RC value was calculated by subtracting the sum of LDL and HDL cholesterol from the fasting total cholesterol level [18].

As a control group, patients who were examined due to an andrological reason other than ED (Peyronie's disease, ejaculation disorders, infertility, etc.) and who had an IIEF-15 erectile function score of 26 and above were included in the study. The patients were divided into two groups as ED (Group 1) and control/ no ED (Group 2).

Statistical analysis was performed using SPSS 21.0 (IBM SPSS for Windows, Armonk, NY IBM Corp.). The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Data are presented as mean, standard deviation, number, and percentage. Comparison between the two groups was performed by Student's t-test. Predictive parameters of ED were analyzed by multivariate logistic regression analysis. Statistical significance was accepted as $p<0.05$.

Results

The mean age of the 273 patients included in the study was 46.93±12.29 years. There were 160 (58.6%) patients in Group 1 and 113 (41.4%) patients in Group 2. The mean age of Group 1 was 49.4±11.4 years while it was 43.4±12.6 years in Group 2, which was significantly higher in Group 1 (p=0.001).

The mean BMI was 26.7±4.3 kg/m^2 in Group 1 and 25.5±3.2 kg/m^2 in Group 2 and was significantly higher in Group 1 (p=0.013). The mean FBG was 118±54.8 mg/dL in Group 1 and 103±30 mg/dL in Group 2 and the difference was significant between the groups (p=0.009). The mean HbA1c was higher in Group 1 (6.1±1.5%) than in Group 2 (5.5±0.8%) (p=0.001). The mean HDL cholesterol level was 39.8±8.7 mg/dL in Group 1 and 42.9±10.7 mg/dL in Group 2, which was significantly lower in Group 1 (p=0.008). The mean RC level was 35.7±21.3 mg/dL in Group 1 and 31.8±19.4 mg/dL in Group 2 and no significant difference was found between the two groups (p=0.123).

The data of all participants are presented in Table 1 and the comparison between Group 1 and Group 2 is presented in Table 2. As a result of regression analysis, age, BMI, HbA1c, and HDL cholesterol levels were found to be effective factors in ED (Table 3).

Table 1. Baseline characteristics of the participants.

Data	Mean±SD	Minimum	Maximum
Age (year)	46.93±12.29	24	72
BMI (kg/m^2)	26.23±3.94	17.60	42.52
Fasting Blood Glucose (mg/dL)	111.80±46.74	54	412
Glycolyzed Hemoglobin (HbA1c, %)	5.91±1.30	3.79	13.89
Triglycerides (mg/dL)	185.76±128.66	17	765
Total Cholesterol (mg/dL)	180.45±39.17	90	283
HDL Cholesterol (mg/dL)	41.11±9.74	15.60	77
LDL Cholesterol (mg/dL)	105.22±36.50	11.4	200
Remnant Cholesterol (mg/dL)	34.11±20.61	2.4	136
Total Testosterone (ng/dL)	459.80±127.06	300	1009

SD; Standard deviation. BMI; Body Mass Index.

Table 2. Comparison of data between Group 1 and Group 2.

Data	Group 1 (n:160) (mean±SD)	Group 2 (n:113) (mean±SD)	p-value
Age (year)	49.4±11.4	43.4±12.6	**0.001**
BMI (kg/m^2)	26.7±4.3	25.5±3.2	**0.013**
Fasting Blood Glucose (mg/dL)	118±54.8	103±30	**0.009**
Glycolyzed Hemoglobin (HbA1c, %)	6.1±1.5	5.5±0.8	**0.001**
Triglycerides (mg/dL)	190.3±128.3	179.3±129.3	0.487
Total Cholesterol (mg/dL)	178.3±37.4	183.4±41.4	0.282
HDL Cholesterol (mg/dL)	39.8±8.7	42.9±10.7	**0.008**
LDL Cholesterol (mg/dL)	102.7±36.9	108.7±35.7	0.185
Remnant Cholesterol (mg/dL)	35.7±21.3	31.8±19.4	0.123
Total Testosterone (ng/dL)	468±128	448±124	0.203

SD; Standard deviation.

Table 3. Multivariate logistic regression analysis.

Variables	OR	p value	Lower*	Upper*
Age (year)	1.033	**0.004**	1.011	1.056
BMI (kg/m^2)	1.083	**0.025**	1.010	1.161
Glycolyzed hemoglobin (HbA1c, %)	1.480	**0.005**	1.123	1.950
HDL Cholesterol (mg/dL)	0.963	**0.007**	0.937	0.990

*95% confidence interval (CI).

Discussion

The main findings of this retrospective study were that age, BMI, FBG and HbA1c levels were significantly higher in ED patients. HDL cholesterol was found to be significantly lower in the ED group. Age, BMI, HbA1c and HDL cholesterol levels were found to be associated with ED in regression analysis. No significant difference was observed in RC levels between the two groups.

The relationship between age and ED has been demonstrated by many studies [2-5,19]. In the Massachusetts Male Aging Study (MMAS), which included 1290 men aged 40-70 years in the USA, the prevalence of ED of any degree was 52%; the prevalence of mild, moderate, and severe ED was reported to be 17.2%, 25.2% and 9.6%, respectively [3]. In the National Health and Social Life Survey (NHSLS) study conducted in the USA with 1410 male participants aged 18-59 years, the prevalence of ED was reported as 7% in 18-29 years, 9% in 30-39 years, 11% in 40-49 years, and 18% in 50-59 years [4]. In 2010, in the European Male Ageing Study (EMAS), which was conducted in eight European Union countries with 3369 male participants with an average age of 60±11 years; while the prevalence of moderate or severe ED was reported in 30% of all participants, this rate was reported as 64% in men aged 70 years and over [2]. In another study published by Lewis et al. showing that the prevalence of ED increases with age, the prevalence was reported to be 1-10% under 40 years of age, 2-15% between 40-49 years of age, 20-40% between 60-69 years of age, and 50-100% over 80 years of age [5]. When the literature is analysed, it is seen that the prevalence and severity of ED increase in parallel with age. In our study, the mean age was found to be significantly higher in the ED group, similar to the literature.

DM causes sexual dysfunction in both men and women, and ED is one of the most important

dysfunction in men with DM [20]. Epidemiological studies show that the age of onset of ED in diabetic men is on average 10-15 years earlier than in non-diabetic men and that the duration of DM and ED are closely related [21]. According to a meta-analysis of 145 studies, the overall ED prevalence rate in men with DM was reported to be 52.5%, whereas the prevalence rates in patients with Type 1 and Type 2 DM were 37.5% and 66.3%, respectively [22]. Today, the concept of prediabetes, which is considered a metabolic state between normoglycemia and diabetes, has emerged [23]. According to the World Health Organisation, the definition of prediabetes is defined as an FBG of 110-125 mg/dL and an HbA1c level of 5.7-6.4% [24]. According to the meta-analysis published by Jin et al., compared with normoglycemic men, prediabetic men were reported to have a higher prevalence of ED (OR 1.62; 95% CI 1.28-2.07; p<0.001) [23]. The results reported in various studies support this situation [25,26]. Similarly, mean FBG and HbA1c levels were significantly higher in the ED group compared to the control group in the present study. Increasing evidence suggests that obesity may be a factor in the development of ED [27-29]. Individuals are considered overweight when their BMI is >25 kg/m^2 and obese when their BMI is >30 kg/m^2 [29]. Kratzik et al. reported in their study that each 1 kg/m^2 increase in BMI decreased 0.141 point in IIEF-5 score (p=0.005) by independent of age and that high BMI rates strongly contribute to the development of ED [27]. In a meta-analysis aiming to determine the relationship between BMI and ED, it was found that ED was significantly associated high BMI ratios [28]. In this context, the present study is consistent with the literature and BMI was found to be significantly higher in the ED group.

It is well known that LDL cholesterol plays a direct role in the pathogenesis of atherosclerosis-induced vascular diseases and the risk of atherosclerotic heart disease increases with high LDL cholesterol levels [30]. After LDL particles in plasma are oxidized, they are taken into the arterial wall by macrophages and foam cells, which are the basis of atherosclerotic plaques, are formed [31]. In contrast, the role of HDL cholesterol in mediating atherosclerotic heart disease is unclear but results from epidemiological studies suggest that low HDL cholesterol levels are an independent risk factor for atherosclerotic heart disease [30,32].

Similar to CVD, numerous studies have emphasized that dyslipidemia is a risk factor for ED [3,9,10]. Azadzoi and Tejeda concluded that hypercholesterolemia impairs endothelium-mediated relaxation in rabbit corpus cavernosum smooth muscle [33]. The MMAS study reported an inverse association between the likelihood of having an ED and a high HDL cholesterol level [3]. High serum cholesterol and low HDL cholesterol levels are associated with an increased risk of ED [34]. In another study conducted by Nikoobakht et al., it was emphasized that high total cholesterol and LDL cholesterol constitute a potential risk for ED [11]. Fragments other than HDL and LDL cholesterol in the total cholesterol content, called RC, are known to be atherogenic [12,16]. In some previous studies, high RC levels were found to be associated with increased CVD risk [35,36]. Devaraj et al. reported that RC levels were significantly higher in men with CVD compared to healthy controls [15]. In another study, it was reported that RC rather than LDL cholesterol was more strongly associated with the development of CVD in elderly patients and serum RC levels may serve as an appropriate and reliable index in the evaluation of CVD [16].

In the results of our study, although we could not detect a significant difference between the two groups, the RC level was found to be higher in the ED group than in the control group. HDL cholesterol was found to be significantly lower in the ED group compared to the control group and this result supports the studies reporting that HDL cholesterol is protective for ED.

Our study has some limitations. Firstly, it is a retrospective study. Secondly, LDL cholesterol levels were similar between the two groups in our cohort contrary to the literature. We think that the reason why RC was found to be similar between the two groups may be due to the similar LDL cholesterol levels between the groups and that our study may be a preliminary study that is pregnant for further studies. In addition, the smoking/alcohol/nutritional habits of the patients

included in the study, which might affect ED, could not be recorded and analysed due to lack of data.

Conclusion

In our study, although there was no statistical difference in RC levels between ED patients and the control group, an elevated level was found in the ED group. To the best of our knowledge, our study is the first study examining the relationship between ED and RC level and we think that it makes a valuable contribution to the literature. There is a need for more comprehensive, larger sample, prospective and multicenter studies to reveal the relationship of RC and ED.

Conflict of interest: The authors declare that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper. **Financial disclosure:** There is no financial support for this study.

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