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ANDROLOGY
Original Article

The impact of metabolic syndrome on retinal findings in patients with erectile dysfunction

Erektil disfonksiyonu olan hastalarda metabolik sendromun retinal bulgular üzerine etkisi

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ABSTRACT

Objective: In the present study, we investigated the association between metabolic syndrome (MS) and retinal findings in patients presenting with erectile dysfunction (ED) complaints.

Material and methods: A total of 102 patients with ED were included in this study. The patients were divided into two groups according to the National Cholesterol Education Program Adult Treatment Panel - III consensus definition: patients with MS (Group 1, n=62) and patients without MS (group 2, n=40). The severity of ED was determined according to the first five versions of the International Index of Erectile Function. A detailed fundus examination was performed to evaluate the patients for retinopathy. The patients' retinopathy grades were classified according to the Early Treatment Diabetic Retinopathy Study.

Results: The mean age of the patients was 51.4 years. Twenty-two patients (35.5%) in Group 1 and nine (22.5%) in group 2 had severe ED (p=0.241). Ten (16.1%) patients in group 1 and one (2.5%) patient in group 2 had any degree of retinopathy (p=0.047). The logistic regression analysis of the correlation between severe ED and MS risk factors revealed that a fasting glucose level (FBG) of >110 mg/dL increased the risk of severe ED by 2.5 times (95% CI 1-6.2, p=0.058). Additionally, the logistic regression analysis of metabolic risk factors showed that only the FBS level was strongly associated with retinopathy, with the relative risk increased to 10.6 (95% CI 1.2-93, p=0.033).

Conclusion: Our results showed that elevated FBG levels were the most critical MS component in the development of severe ED and retinopathy.

Key words: Erectile dysfunction; metabolic syndrome; retinopathy.

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ÖZET

Amaç: Erektil disfonksiyon (ED)'u olan hastalarda metabolik sendrom (MS) ve retinal bulgular arasındaki ilişkiyi incelemek.

Gereç ve yöntemler: Çalışmaya ED'si olan 102 hasta dahil edildi. Hastalar Ulusal Kolesterol Eğitim Programı Erişkin Tedavi Paneli - III konsensus tanımına göre MS'i olan (Grup 1, n=62) ve MS'i olmayan hastalar (Group 2, n=40) olmak üzere iki gruba ayrıldı. ED şiddeti Uluslararası erektil fonksiyon endeksinin ilk 5 (IIEF-5) sorusu ile belirlendi. Retinopati değerlendirmesi için detaylı fundus muayenesi yapıldı. Hastaların retinopati dereceleri Diyabetik Retinopati Erken Tedavi Çalışmasına göre sınıflandırıldı.

Bulgular: Hastaların ortalama yaşı 51.4 yıl idi. Grup 1'de 22 hastada (%35.5) ve Grup 2'de 9 hastada (%22.5) şiddetli ED (p=0.241) saptandı. Grup 1'de 10 (%16.1) hastada ve Grup 2'de 1 (%2.5) hastada herhangi bir derecede retinopati saptandı (p=0.047). MS risk faktörleri ile şiddetli ED arasındaki lojistik regresyon analizinde açlık kan şekerinin >110 mg/dL olmasının şiddetli ED riskini 2.5 (%95 CI 1-6.2, p=0.058) kat arttırdığı saptandı. Ayrıca, metabolik risk faktörlerinin lojistik regresyon analizinde sadece açlık kan şekerinin >110 mg/dL olması retinopati ile güçlü derecede ilişkiydi ve göreceli risk 10.6 (%95 CI 1.2-93, p=0.033) kat artmıştı.

Sonuç: Sonuçlarımız artmış açlık kan şekeri düzeyinin, şiddetli ED ve retinopati gelişimi için en kritik MS bileşeni olduğunu göstermektedir.

Anahtar sözcükler: Erektil disfonksiyon; metabolik sendrom; retinopati.

Introduction

Erectile dysfunction (ED) has been described as the inability to achieve and maintain an erection that is adequate for satisfactory sexual performance.[1] All epidemiological studies have indicated an association between ED and advanced age. Smoking, hypertension (HT), diabetes mellitus (DM), hypercholesterolemia, obesity and a sedentary lifestyle have all been implicated as major risk factors for ED.[2] The Massachusetts Male Aging Study conducted in the United States, which evaluated 1709 non-institutionalized men with respect to ED, showed that the prevalence for any degree of ED was 52.1% for men between the ages of 40 and 70 years.[3] A large-scale study conducted in Turkey in 2002 reported the combined ED prevalence to be 69.2%.[4]

The clinical findings described as metabolic syndrome (MS) were also reported as risk factors for ED.[5-8] These clinical findings share similar risk factors with cardiovascular disease (CVD).[9,10] Studies have reported that one-third of all middle-aged men suffer from MS, with more than half of these patients having some degree of ED.[7] Endothelial dysfunction is of significant importance in terms of ED pathophysiology.[11] Endothelial dysfunction is an early stage of vascular damage, which can lead to more severe atherosclerotic alterations in the systemic circulation. MS includes a number of risk factors for the development of endothelial dysfunction, which significantly leads to CVD and ED.[10] Urological studies have often used the carotid artery intimal-medial thickness and/or brachial artery flow-mediated dilatation to evaluate endothelial dysfunction.[12] The ocular fundus is the only location in the human body where the endothelium can be observed macroscopically. A condition, such as MS, that leads to endothelial dysfunction is likely to have a manifestation in the ocular fundus, such as generalized retinal arteriolar narrowing, arteriovenous nicking and retinal hemorrhages, microaneurysms and cotton wool spots.[13]

We investigated the association between MS and retinal findings in patients presenting with ED complaints in the present study.

Material and methods

A total of 102 male patients presenting at our outpatient clinic between September 2009 and April 2010 with complaints of ED were enrolled prospectively. The patients were divided into two groups according to National Cholesterol Education Program Adult Treatment Panel-III consensus definition: patients with MS (Group 1, n=62) and patients without MS (Group 2, n=40). The study was approved by the Institutional Review Board of Ankara Numune Research and Training Hospital, and all of the subjects provided proper informed consent. A detailed anamnesis, including risk factors such as trauma, surgery, DM, HT, dyslipidemia, atherosclerosis and coronary artery disease, was recorded. The exclusion criteria were a urogenital system malignancy, high-risk CVD, use of nitrates or nitrate derivatives, chronic hepatic or renal failure, history of pelvic surgery and history of drug use (e.g., tiazid, 5-α-reductase inhibitors and β-blockers) that could lead to ED as well as, given the design of the study, a history of ocular surgery, corneal problems that could impair the fundus examination, lens opacity, a high degree myopia and treatment with drugs that are known to be toxic to the retina (e.g., chloroquine, hydroxychloroquine, tamoxifen, fenotiazin and ethambutol).

The severity of the ED was established according to the first 5-question version of the International Index of Erectile Function (IIEF-5). Therefore, an IIEF-5 score of ≤ 7 was interpreted as indicating severe ED, and an IIEF-5 score of 8-21 represented mild to moderate ED. Following a detailed physical examination, height and weight measurements were performed, and body mass index (BMI) (weight/height^2) was calculated. Waist circumference (WC) measurements were performed by the same physician (M.B.) with a tape measure in the morning before breakfast above the iliac crest at the umbilicus level after removing the clothing. All patients were evaluated in terms of serum high molecular weight lipoprotein (HDL), triglyceride (TG), total testosterone (TT), glycosylated hemoglobin (HbA1c) and fasting blood glucose (FBG) levels.

The diagnosis for MS was established according to the criteria set in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III).[9] Therefore, the presence of at least three of the factors listed below was required for a positive MS diagnosis.

- WC ≥ 102 cm
- TG level ≥150 mg/dL
- HDL cholesterol level <40 mg/dL
- Systolic blood pressure ≥130/85 mmHg
- FBG >110 mg/dL or presence of type 2 DM (T2DM)

The patients' ocular fundus examination was conducted by the same physician (B.B.) at the Ophthalmology Clinic of our hospital. The patients underwent a complete ophthalmological examination comprising visual acuity testing, intraocular pressure measurement and biomicroscopy. The detailed fundus examination was performed to evaluate the patients for retinopathy using a 90 diopter lens after ensuring pupillary dilation with 2.5% phenylephrine and 1% tropicamide. A fundus fluorescein angiography was used when required to establish the diagnosis.

The Early Treatment Diabetic Retinopathy Study (ETDRS) classification, the most commonly utilized classification system

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to evaluate microangiopathy, was used to assess the retinopathy. [14] Therefore, the patients were classified as follows:

- Grade 0: No Diabetic Retinopathy (DRP)
- Grade 1: Nonproliferative DRP
  a. Mild-moderate (Background DRP)
  b. Moderate-severe (Preproliferative DRP)
- Grade 2: Proliferative DRP
  a. Early DRP
  b. High-Risk DRP

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 13.0 software was used for the statistical analyses. The descriptive statistics of the groups were calculated. Age, duration of DM, duration of ED, WC, BMI and serum measurement parameters were presented as the mean±standard deviation. Comparisons were performed using the *t-test* and *Mann-Whitney* test. *Correlation analyses* between the MS presence and age and between the retinopathy risk and IIEF-5 score were performed using *Pearson's correlation analysis*. The patients were classified with respect to the presence of MS into either Group 1 (patients with MS) or Group 2 (patients without MS). The correlation between the presence of retinopathy and severe ED in the groups was analyzed using the *chi-square* test. The correlation between the MS criteria and the presence of retinopathy and severe ED was evaluated using *Logistic Regression Analysis*. *P* values of <0.05 were considered to indicate statistical significance.

Results

The mean age of the patients was 51±8 (range, 25 to 67) years. The values for the mean durations of ED and DM were established as 20.6±26.2 (range, 6 to 180) and 20.8±42.3 (range, 0 to 180) months, respectively. The values for the median durations of ED and DM were established as 12 (range; 6 to 180) and 0 (range; 0 to 180) months, respectively. The mean values for BMI, WC, FBG, HDL, TG, HbA1C, TT and IIEF-5 were 27.8±4.1 (range, 18.6 to 47) kg/m^2, 102.7±11.5 (range, 68 to 144) cm, 73.9±13.2 (range, 70 to 400) mg/dL, 36.3±14.9 (range, 20 to 70) mg/dL, 163.8±89.9 (range, 36 to 552) mg/dL, 6.9±1.9% (range, 4.7 to 13.6%), 3.4±1.1 (range, 1 to 7) ng/mL and 9.3±4.4 (range, 5 to 20), respectively.

Among the patients, 47 (46.1%) had DM, and 46 (45.1%) had HT. In addition, 62 (60.8%) were classified as having MS. Although the differences between the groups in terms of age, IIEF-5 score, ED duration and TT levels were not significant, the differences with respect to the DM duration, BMI, WC, FBG, HDL, TG and HbA1c levels were significant (Table 1).

Severe ED was observed in 22 patients (35.5%) in Group 1 and in 9 patients (22.5%) in Group 2 (p=0.241).

The logistic regression analysis of the correlation between severe ED and the MS risk factors revealed that a fasting glucose level of >110 mg/dL increased the risk for severe ED by 2.5 times (95% CI 1-6.2, p=0.058). The Backward Stepwise method demonstrated that a fasting glucose level of >110 mg/dL increased the risk by 2.7 times (95% CI 1.1-6.6, p=0.034). However, the other risk factors were determined to not have a significant impact (Table 2).

Of the patients, 11 (10.8%) were diagnosed with retinopathy (9 with Grade 1 and the remaining 2 with Grade 2). Of those, 10 (90.9%) patients were found to have MS. Retinopathy was observed in 16.1% (n=10/62) of the patients in Group 1 and in 2.5% (n=1/40) of the patients in Group 2 (OR=7.5, 95% CI 0.9-61, p= 0.047).

The evaluation of the association between the presence of retinopathy and the MS risk factors using logistic regression analysis revealed that a fasting glucose level of >110 mg/dL increased the presence of retinopathy by 10.6 times (95% CI 1.2-93, p=0.033) (Table 3).

Of the 11 patients with retinopathy, 10 had DM, and 7 had HT. T2DM was noted in 38 patients (61.3%) in Group 1 and in 9

Table 1. Demographic characteristics of the study population

Parameters	Group 1 (n=62)	Group 2 (n=40)	p value
Age (year)	52.3±6.6	49.2±9.7	0.068*
Duration of ED (month)	22.8±24.8	17.3±28.4	0.105#
Duration of Diabetes (month)	29.9±49.3	6.6±22.5	<0.001*
BMI (kg/m^2)	28.9±4.1	26.4±3.4	<0.001*
WC (cm)	106±10.6	97.4±11.1	<0.001*
HDL (mg/dL)	32±7.0	42.9±20.7	<0.001*
TG (mg/dL)	196.6±89.9	112.8±62.5	<0.001*
FBG (mg/dL)	150.6±80.9	101.1±48.7	<0.001#
HbA1c (%)	7.5±2.2	6.1±1.2	<0.001*
TT (ng/mL)	3.3±0.9	3.6±1.3	0.217*
IIEF-5	8.7±4.0	10.3±4.7	0.245*

BMI: Body mass index, BP: Blood pressure, ED: Erectile dysfunction, FBG: Fasting blood glucose, HbA1c: Glycosylated hemoglobin, HDL: High-density lipoprotein, IIEF-5: First 5-question version of the International Index of Erectile Function, TG: Triglycerides, TT: Total testosterone, WC: Waist circumference
*t Test
#Mann-Whitney Test

Table 2. Logistic regression analysis of the metabolic risk factors for severe erectile dysfunction. Variables were entered as categorical variables, except for age and waist circumference

Risk factors	Beta coefficiency	p value	OR	95% CI
Age (year)	0.1000	0.746	1.0	0.9-1.1
WC (cm)	-0.009	0.668	1.0	0.9-1.0
Systolic blood pressure ≥130/85 mmHg	-0.108	0.814	0.9	0.4-2.2
HDL (mg/dL)	-0.375	0.479	0.7	0.2-1.9
TG (mg/dL)	0.670	0.163	2	0.8-5.0
FBG (mg/dL)	0.900	0.058	2.5	1.0-6.2
FBG (mg/dL)*	0.978	0.034	2.7	1.1-6.6

CI: Confidence interval, FBG: Fasting blood glucose, HDL: High-density lipoprotein, OR: Odds ratio, TG: Triglycerides, WC: Waist circumference
*Backward Stepwise method

Table 3. Logistic regression analysis of the metabolic risk factors for retinopathy. Variables were entered as categorical variables, except for age and waist circumference

Risk factors	Beta coefficiency	p value	OR	95% CI
Age (year)	-0.006	0.906	1.0	0.9-1.1
WC (cm)	-0.038	0.318	1.0	0.9-1.0
Systolic blood pressure ≥130/85 mmHg	0.791	0.271	2.2	0.5-9.0
HDL (mg/dL)	1.5	0.178	4.5	0.5-39.8
TG (mg/dL)	0.298	0.683	1.3	0.3-5.6
FBG (mg/dL)	2.362	0.033	10.6	1.2-93.0

CI: Confidence interval, FBG: Fasting blood glucose, HDL: High-density lipoprotein, OR: Odds ratio, TG: Triglyceride, WC: Waist circumference

patients (22.5%) in Group 2. Of the patients with retinopathy, 8 (72.7%) had HbA1c levels of >7 (p=0.003). The presence of T2DM increased the risk for MS by 5.5 times (95% CI 2.2-13.4, p<0.001).

The risk for retinopathy was found to have a weak positive correlation with the presence of MS and with age, whereas it had a weak negative correlation with the IIEF-5 score ($r_{ms\text{-}age}$=0.190, $p_{ms\text{-}age}$=0.056; $r_{ms\text{-}retinopathy}$=0.215, $p_{ms\text{-}retinopathy}$=0.030; $r_{ms\text{-}IIEF\text{-}5}$=-0.176, $p_{ms\text{-}IIEF\text{-}5}$=0.076). The higher the number of MS risk factors, the lower the IIEF-5 score was observed to be ($r_{MS\ risk\text{-}IIEF\text{-}5}$=-0.169, $p_{MS\ risk\text{-}IIEF\text{-}5}$=0.089). The patients' retinal findings are shown in Figure 1.

Discussion

ED and MS are common health issues throughout the world, and their prevalences increase with age.[4,6] Syndrome X, insulin resistance syndrome, polymetabolic syndrome, the deadly four and civilization syndrome are different terms used to describe MS, which is a cluster of risk factors that are linked with diabetes and CVD. Metabolic syndrome was described in a number of different ways by various organizations, such as the World Health Organization in 1998, the European Group for the Study of Insulin Resistance in 1999, ATP-III in 2001, the American College of Endocrinology in 2003, the International Diabetes Federation in 2005, the American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHL/NHLBI). However, certain factors were common among these different descriptions, including insulin resistance or impaired glucose tolerance, elevated blood pressure levels, elevated TG levels, decreased HDL cholesterol levels and central obesity.[9]

The MS prevalence, together with ED, increases with age. Two major studies have been conducted in the United States to investigate the prevalence of metabolic syndrome as defined by the NCEP ATP-III criteria. The first study, conducted by Ford et al. [15], reported the prevalence of MS to be 6.7% among participants aged 20 through 29 years but 43.5% and 42.0% among participants aged 60 through 69 years and aged at least 70 years, respectively. The other study, conducted by Alexander and co-workers, concluded that 44% of the U.S. population over the age of 50 years met the criteria for MS.[16] Similarly, the prevalence of MS was established to be 39.9% for the Turkish population aged 40 through 70 years.[7]

Many studies demonstrated a strong correlation between MS and ED.[5-8] Heidler and associates reported the prevalence of MS to be 33.8% for the male population between the ages of 30 and 69 years, with some degree of ED present in 68.4% of the patients with MS younger than 50 years and in 74.8% of the men with MS older than 50 years. The same study concluded that MS was significantly associated with ED pathogenesis in men older than 50 years.[6] A study by Yeh et al. [8] evaluated 103 patients with ED, with 41.1% having severe ED, and found that 36.9% of these patients had MS. Bal et al.[7] reported the overall incidence of ED to be 79% in their patients with MS and the incidence of severe ED to be 24.8%. In the present study, 62 patients (60.8%) were classified with MS, and 31 patients (30.4%) were found to have severe ED. Although not significant, the patients with severe ED in the current study were more likely to have MS (35.5% vs. 22.5%). Furthermore, a drop in the IIEF-5 score was noted as the number of risk factors for MS increased. We attribute these conflicting results to the differences in the study designs, various IIEF questionnaires used to classify ED, different diagnostic criteria for MS and social differences.

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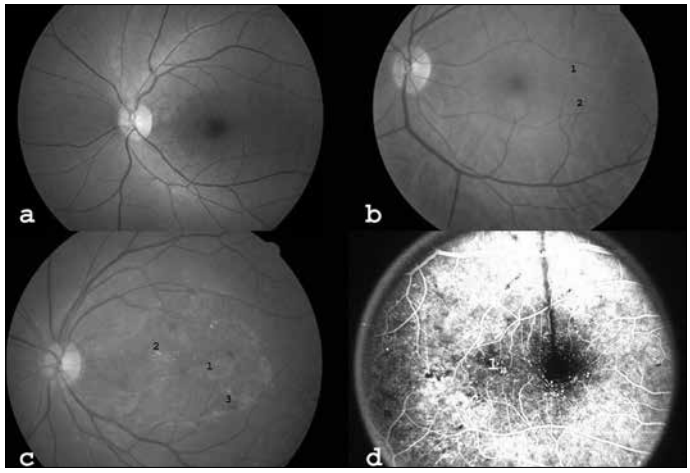

Figure 1. a. Appearence of normal fundus. b. Nonproliferative diabetic retinopathy (Grade 1); (1) Hard exudates (2) Focal arteriolar narrowing. c. Proliferative Diabetic Retinopathy (Grade 2); (1) Macular edema, (2) Drusen and (3) Retinal haemorrhages. d. Microaneurysms in retinal angiography

Endothelial dysfunction has been suggested to be a common pathophysiology in ED and MS. Moreover, this particular pathogenesis is at the center of the proposed hypothesis regarding the association between ED and CVD.[17] There is general consensus regarding the observation that DM, dyslipidemia, smoking and HT trigger endothelial dysfunction. Oxidative stress has been proposed to damage the vascular and sinusoidal endothelia of the penile veins, leading to atherosclerosis, thrombosis, inflammation and vasoconstriction in this mechanism.[18] However, demonstrating endothelial dysfunction in the penis and elucidating the association between ED and MS are necessary. Studies have indicated the reduced bioavailability of nitric oxide (NO), which is the primary vasodilator and consequently the most significant homeostatic regulatory agent in the penis, as a factor in the process. The impaired response of the erectile tissue as a result of vascular disease as well as the reduced production, increased degradation or inactivation of the mediator also play a role in the process. Endothelial NO production decreases following endothelial cell damage. However, the inactivation of endothelial nitric oxide synthetase (eNOS), its synthesizing enzyme, or the decreased functioning of this enzyme can also lead to endothelial cell damage. Experimental studies demonstrated that the structurally active form of eNOS played a major role in inducing the erectile response and that aging and diabetes had unfavorable effects on it.[19] Similarly, a reduction in eNOS may be associated with the increased effect of vasoconstrictive mechanisms, such as RhoA/Rho-kinase, similar to that observed in patients with diabetic ED.[20]

Diabetes is associated with an earlier onset and increased severity of urological symptoms, such as ED and hypogonadism. McCulloch et al. found a positive association of poor glycemic control and the 5-year incidence of ED in men with diabetes mellitus.[21] The duration of diabetes and systolic blood pressure is positively associated with DR. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) revealed that the prevalence of any retinopathy was 8% at 3 years and 25% at 5 years.[22]

Studies have demonstrated that diabetic patients with MS experienced microvascular complications earlier and more often compared with diabetic patients without MS.[23-26] Diabetes is known to induce endothelial dysfunction and is a major risk factor leading to microangiopathy. Other MS criteria have also been reported to increase endothelial dysfunction and thus accelerate the inflammatory process.[27] A number of studies have demonstrated MS to be associated with macrovascular and microvascular complications.[23,28] Cuspidi et al.[28] investigated the prevalence of MS in patients with vascular, cardiac and renal organ damage by utilizing the NCEP criteria. They established the prevalence of MS in patients with three-organ damage to be 2.3 times as high as that in patients without organ damage. Although the incidence of two or three-organ damage was 53% in patients with MS, this incidence was 33% in patients without MS. A population-based screening study that employed the AHA/NHLBI metabolic syndrome criteria revealed that patients with T2DM and those with CVD, neuropathy and nephropathy complications were more likely to have MS. The same study reported that although the incidence of MS was 75.3% in patients with T2DM and retinopathy complications, this incidence was 24.7% in patients without MS.[23]

Retinal vascular alterations, independent of elevated blood pressure and cardiovascular risk factors, were established to be associated with subclinical and clinical stroke, cognitive impairments, renal dysfunction and cardiovascular mortality. This particular relationship suggests that select patients with retinal vascular alterations may benefit from careful systemic evaluations and risk reduction therapies.[13] The number of studies in the medical literature demonstrating the association between MS and retinal findings is rather limited.[23-26] Wong and co-workers established that MS led to retinal vascular pathologies and increased the risk of retinopathy by 1.68 times. The same study also reported that elevated blood pressure and FBG levels were the most critical risk factors for the development of retinopathy.[25] Another retrospective study demonstrated that MS components led to different retinal vascular alterations and that the presence of MS independently increased the risk for retinopathy by 1.64 times.[26] The study conducted by Abdul-Ghani et al.[24] on 415 patients with diabetes established that patients with MS were 3.42 times more likely to have retinopathy compared with patients without MS (9.6% vs. 4.1%). Although a separate study established a significant relationship between MS and retinopathy (OR=2.23), it failed to demonstrate the same correlation in the sub-group without diabetes (OR=1.23).[29]

In the present study, ED patients were evaluated for retinopathy by an ocular fundus examination to investigate the association between endothelial dysfunction and MS. Of the 11 patients diagnosed with retinopathy, 10 (90.9%) had MS. Retinopathy was established in 16.1% of the patients with MS and in 2.5% of the patients without MS. The presence of MS increased the risk for retinopathy by 7.5 times. The logistic regression analysis revealed that of the MS criteria, only FBG levels >110 mg/dL led to a 10.6-fold increased risk. The risk for retinopathy in this study was established as being higher than previously reported. However, given the design of the current study, the study population consisted of patients with ED, which is a known consequence of endothelial dysfunction; therefore, our high results may be attributed to that particular condition.

Our previously published study evaluating MS components in our country reported that patients with FBG levels >100 mg/dL and/or with T2DM had a 7.1-fold higher risk of being diagnosed with severe ED compared with MS patients with normal blood glucose levels. Similarly, FBG levels >110 mg/dL were established as a major risk factor for ED in this study.[5] Good glycemic control (HbA1c<7) has been found to have positive effects on decreasing microvascular and macrovascular complications.[30] Of the patients observed with retinopathy in the present study, 72.7% had HbA1c levels >7 and poor glycemic control.

In conclusion, to the best of our knowledge, this study is the first prospective study investigating MS and retinal findings in patients with ED. The results of this study revealed that elevated FBG levels were the most critical MS component in the development of severe ED and retinopathy.

We maintain that patients diagnosed with retinopathy during a routine eye examination, especially if they are diabetic, should undergo a thorough examination regarding their systemic circulation and should be referred to a urologic assessment for possible ED. Moreover, an ocular fundus examination may reflect endothelial dysfunction in patients with ED. The findings of the present study should be supported with further prospective studies with larger study samples and longer follow-up periods.

Conflict of interest

No conflict of interest was declared by the authors.

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