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Association between severity of lower urinary tract symptoms, erectile dysfunction and metabolic syndrome

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Abstract

Introduction. The purpose of this study was to investigate the association between severity of lower urinary tract symptoms (LUTS), erectile dysfunction (ED) and metabolic syndrome.

Methods. Our study population included a consecutive series of 190 patients with LUTS (International Prostate Symptom Score-IPSS >7) with or without manifestations of the metabolic syndrome. The diagnoses of diabetes mellitus and hypertension were obtained from the patient's medical history. Data on blood pressure, waist measure, body height and weight were collected and body mass index were calculated. Patients were assessed based on the International Index of Erectile Function (IIEF) for ED and IPSS and IPSS-Quality of Life for LUTS. Blood samples were drawn from fasting patients to determine, fasting blood glucose (FBG), triglycerides, HDL-cholesterol and serum total testosterone levels.

Results. In severe LUTS patient group, IIEF erectile function domain scores were significantly lower than moderate LUTS patient group ($p < 0.05$). Multiple logistic regression analysis confirmed that presence of ED was the most predictor of severe LUTS. The prevalence of metabolic syndrome was higher in patients with severe LUTS (26% *vs.* 46%, $p = 0.009$). The severe form of the LUTS was significantly correlated with waist circumference >102 cm ($p < 0.05$), blood pressure $\geq 130/85$ mmHg ($p < 0.05$) and FBG >110 mg/dl ($p < 0.01$).

Conclusion. Obesity, high plasma level of FBG and hypertension constitute risk factors for the development of severe LUTS. Metabolic syndrome may play a key role in the pathogenesis in both ED and LUTS. Presence of ED is the most predictor of severe LUTS.

Keywords: *Erectile dysfunction, metabolic syndrome, lower urinary tract symptoms*

Introduction

There has been dramatic worldwide increase in the elderly population during the 20th Century. Thus, in recent years symptoms and complaints of aging men have found increasing scientific attention. Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are the most common complaints in elderly men [1]. Epidemiological studies provide strong association between LUTS and ED that are strongly linked [1–4]. Recent publications confirm the correlation between these conditions, suggesting a possible common pathophysiology [5]. However, a causal relationship between LUTS and sexual dysfunction cannot be understood clearly, as the underlying pathophysiological mechanisms need to be determined.

There is growing evidence establishing that LUTS and ED can also be caused by various similar conditions affecting the neurovascular system such as diabetes mellitus, dislipidemia, hypertension and obesity [6–8]. These disorders constitute the metabolic syndrome, associated with hypothesis that explains the pathomechanism linking between LUTS and ED.

Diabetes mellitus and obesity are common conditions which are components of the metabolic syndrome [9]. Other features of this syndrome are hypertension and dyslipidemia including high triglyceride and low high density lipoprotein (HDL) serum levels. Any of three existences out of five factors is defined as metabolic syndrome [9]. Increasing evidence recently has pointed towards a relationship between LUTS and the presence of metabolic syndrome [10]. The components of this syndrome are also proposed as risk factors for the development of benign prostate hyperplasia (BPH); therefore, it is thought that metabolic syndrome may play a role in LUTS related to BPH aetiology [11].

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It has also been reported the association between metabolic syndrome and LUTS, metabolic syndrome and ED. However, the association between these three disorders has not been well studied in patients with LUTS. The aim of the present study was to determine the association between metabolic syndrome and ED among urologic patients with moderate to severe LUTS in patients aged >40 years.

Methods

The study population consisted of 190 male patients aged >40 years who had been in a steady sexual relationship for the past 6 months and were admitted to urology clinics with the complaints of LUTS (International Prostate Symptom Score-IPSS >7). In this prospective multicentre cross-sectional study, patients were recruited from four different institutions of Aegean Region of Turkey that had similar patients profile. The exclusion criteria included severe genital anatomic deformities that affect erectile function; psychological or social problems that made it impossible for the patient to participate in the study; a history of major pelvic surgery; patients taking medications including 5-α reductase inhibitor; patients with a diagnosis of congestive heart failure, bronchial asthma, coronary heart disease, malignancy, liver cirrhosis, known malignant disease, including prostate cancer or chronic renal failure.

All men who agreed to participate in the study provided written informed consent. The patients were questioned about their medical history, including systemic diseases, chronic use of drugs, cigarette smoking and previous prostate surgery. Drug treatment history for hypertension and diabetes mellitus was also taken. Patients underwent physical examination, including systemic blood pressure, weight and height measurement. The waist circumference (WC) was measured using a standard measurement strip with the patient standing and breathing normally. The measurement location was just above the iliac crest at the level of the umbilicus.

Blood samples were drawn between 8:00 am and 10:00 am from overnight-fasting patients. Plasma levels of the fasting blood glucose (FBG), triglyceride, HDL-cholesterol and total testosterone were measured for each patient. The diagnosis of metabolic syndrome was made according to the most recent consensus report of the National Cholesterol Education Program's Third Adult Treatment Panel (NCEP ATP III) [9]. Patients were diagnosed with metabolic syndrome when the occurrence of at least three of five risk factors. The five factors are abdominal obesity (WC >102 cm), blood pressure ≥130/85 mmHg (or current use of antihypertensive medication), FBG ≥110 mg/dl (or current use of oral diabetes medication or insulin), triglyceride >150 mg/dl and HDL-cholesterol <40 mg/dl [9].

Patients were assessed based on the International Index of Erectile Function (IIEF) for ED and IPSS and IPSS-Quality of Life (IPSS-QoL) for LUTS. The erectile function (EF) domain consists of questions 1–5 and 15 aimed to assess erectile function. ED was diagnosed when total of IIEF-EF domain scores <26 point. LUTS were classified as moderate (IPSS of 8–9) or severe (IPSS of 20 or more). At the end of data collection, the patients are divided into two groups according to LUTS severity.

Statistical analysis

The patient characteristics and metabolic risk factors for metabolic syndrome were compared using the independent Student t test. The Pearson χ^2 test was exploited to test the association of each risk factor with LUTS, and crude odds ratios are given. The relationship between IPSS and IIEF was compared by Pearson-correlation test. A multivariate logistic regression analysis was performed to determine the effects of ED and other metabolic risk factors and metabolic syndrome on severity of LUTS. Multivariate model was made using the 'enter model'; results were expressed as adjusted OR with 95% CI. Adjustments were made for potential confounding factors such as age, and smoking duration. Statistical significance was defined as $p < 0.05$. The data were analysed using the Statistical Package for Social Sciences, version 11.0 (SPSS, Chicago, IL) software program.

Results

Of the 190 patients, 55 (29%) had severe LUTS. Twelve (6.3%) patients were treated with oral antidiabetic drugs, 36 (18.9%) patients were treated with anti-hypertensive drugs and 13 (6.3%) patients were treated with both of these drugs. Of the patients, 37.9% never smoked, 20.5% former smokers and 41% current smokers.

Table I shows the characteristics of the groups. Waist circumference, smoking duration, plasma level of FBG, sexual intercourse frequency, presence of metabolic syndrome and all domains of IIEF score except sexual desire domain score were significantly different between patients with moderate LUTS and severe LUTS (Table I).

Mean age, systolic and diastolic blood pressure; anthropometric factors including weight, height and BMI, plasma triglyceride and HDL-cholesterol levels were not significantly different between groups.

Although plasma total testosterone levels were not statistically different between moderate and severe LUTS groups (Table I), significant differences were detected between patients with metabolic syndrome and patients without metabolic syndrome (403.3 ± 149.7 *vs.* 460.1 ± 176.8 ng/dl, $p < 0.05$).

ED was diagnosed in 88 (65.2%) patients with moderate LUTS and 45 (81.8%) patients with severe

LUTS based on the IIEF-EF domain score. A statistically significant association was determined between the presence of ED and LUTS severity (Pearson χ^2-test; $p < 0.05$; OR, 2.4; 95% CI 1.1–5.2). The correlation analysis revealed that IIEF-EF domain scores and total IPSS score ($p < 0.05$; $r = -0.169$) and QoL ($p < 0.05$; $r = -0.148$) were significant but slightly correlated.

The presence of ED, metabolic syndrome and each metabolic risk factor were cross-tabulated with LUTS severity (Table II). According to those ratios, there were significant associations between severe LUTS and presence of ED, metabolic syndrome and its components including abnormal WC, high blood pressure and abnormal FBG.

A multiple logistic regression analysis was performed with the presence of moderate/severe LUTS as the dependent variable and the following as predictive variables: age, hypertension (≥135/85 mmHg or antihypertensive treatment versus <135/85 mmHg), smoking duration, WC (>102 cm *versus* ≤102 cm), triglycerides (≥150 mg/dl versus <150 mg/dl), HDL (<40 mg/dl *versus* ≥40 mg/dl), FBG (≥110 mg/dl *versus* <110 mg/dl) and ED (IIEF-EF scores ≥26 *versus* <26). Analysis showed that presence of ED (OR: 2.3; 95%

Table I. Demographic, laboratory and questionnaire data of patients according to LUTS severity.

	LUTS severity		
	Moderate	Severe	*p*
N	135	55	–
Age (years)	59.7 ± 8.4	59.6 ± 7.4	0.907
Cystolic blood pressure (mmHg)	125.7 ± 15.4	128.9 ± 18.3	0.220
Diastolic blood pressure (mmHg)	78.9 ± 9.3	80.5 ± 8.7	0.274
Height (cm)	169.4 ± 6.5	170.4 ± 5.1	0.563
Weight (kg)	78.2 ± 12.1	80.6 ± 14.8	0.263
Waist circumference (cm)	98.9 ± 9.9	102.8 ± 13.8	0.033
Smoking duration (packet/yıl)	12.9 ± 18.1	17.6 ± 24.5	0.016
BMI (kg/m^2)	27.2 ± 3.6	27.8 ± 4.7	0.326
LUTS duration (month)	23.1 ± 31.5	28.7 ± 30	0.262
IPSS	12.2 ± 3.5	24.1 ± 3.6	–
QoL	2.9 ± 1.1	4.3 ± 0.7	<0.001
FBG (mg/dl)	106.9 ± 37.8	120.0 ± 49.7	0.050
Triglyceride (mg/dl)	130.5 ± 74.6	147.1 ± 135.9	0.284
HDL cholesterol (mg/dl)	43.8 ± 11.7	43.4 ± 12.1	0.823
Testosterone (ng/dl)	443.6 ± 179.7	438.7 ± 145.8	0.860
Sexual intercourse (per moth)	4.4 ± 4.0	3.2 ± 2.6	0.036
IIEF-EF	19.2 ± 9.3	16.2 ± 9.5	0.049
IIEF-OF	7.1 ± 3.3	5.9 ± 3.6	0.031
IIEF-SD	6.2 ± 2.2	5.5 ± 2.2	0.069
IIEF-IS	8.4 ± 4.3	6.9 ± 4.5	0.037
IIEF-OS	6.6 ± 2.7	5.6 ± 2.7	0.023
Metabolic syndrome (%)	25.9	45.5	0.009

LUTS, lower urinary tract symptoms; BMI, body mass index, IPSS, international prostate symptom score; QoL, quality of life; FBG, fasting blood glucose; HDL, high density lipoprotein; MFR, maximum flow rate; AFR, average flow rate; IIEF-EF, international index of erectile function-erectile function; IIEF-OF, international index of erectile function-orgasmic function; IIEF-SD, international index of erectile function-sexual desire; IIEF-IS, international index of erectile function-intercourse satisfaction; IIEF-OS, international index of erectile function-overall satisfaction.

Table II. Frequency of patients according to the severity of LUTS and the presence of the metabolic risk factor.

	Moderate LUTS	Severe LUTS	OR	*p*⋆
HT (≥130/85 mmHg)	78 (57.8%)	41 (74.5%)	2.1 (1.07–4.29)	0.030
FBG (≥110 mg/dl)	33 (24.4%)	25 (45.5%)	2.6 (1.33–4.98)	0.004
TG (>150 mg/dl)	37 (27.4%)	15 (27.3%)	0.99 (0.49–2.01)	0.985
HDL (<40 mg/dl)	47 (34.8%)	22 (40%)	1.24 (0.67–2.38)	0.500
WC (>102 cm)	52 (38.5%)	30 (54.5%)	1.9 (1.02–3.61)	0.043
Presence of MS	35 (25.9%)	25 (45.5%)	2.4 (1.24–4.59)	0.009
Presence of ED	88 (65.2 %)	45 (81.8 %)	2.4 (1.11–5.20)	0.023

⋆Probability values were calculated using χ^2 tests.
LUTS, lower urinary tract symptoms; OR, odds ratio; HT, hypertension; FBG, fasting blood glucose; TG, triglyceride; HDL, high density lipoprotein; WC, waist circumference.

CI: 1.01–5.27 was the only significant predictors of severe LUTS (Table III).

Discussion

In this multicentre cross-sectional analysis of LUTS, metabolic syndrome and ED, we observed that patients with severe LUTS were more likely to have ED and metabolic syndrome compared with patients with moderate LUTS. The abnormality of WC, FBG and high blood pressure and the presence of metabolic syndrome are important risk factors for development of severe LUTS. Furthermore, the presence of ED is the most predictor of severe LUTS.

It has been clearly demonstrated that aging and LUTS are the most important risk factors for ED. Also severity and prevalence of ED was correlated with LUTS severity. The most recent and important study to date is the Multinational Survey of the Aging Male [1]. In that study, the incidence of ED increased progressively with LUTS severity (mild: 43%, moderate: 65.8%, severe: 82.5%). Concordant with previous studies, our results revealed that the prevalence of ED was associated with LUTS severity in elderly men independent with age. Although many theories have been proposed for clarifying the association between ED and LUTS, pathological mechanism between two disorders has remained unclear till now. McVary has proposed that four leading theories supporting biological plausibility currently exists: the nitric oxide synthase (NOS)/NO theory; the autonomic hyperactivity and metabolic syndrome hypothesis; the Rho-kinase activation/endothelin pathway and pelvic atherosclerosis [12]. Most of these hypotheses have been supported by recent findings. In a recent experimental study, it has been established that adrenergic contractility of human corpus cavernosum is increased in the presence of bladder outlet obstruction and inhibition of Rho-kinase pathway generates effective relaxation of cavernosal smooth muscle [5]. In addition, Berger et al. demonstrated an association between an age-related impairment of blood supply to the lower urinary tract and pathogenesis of BPH [13]. In that study, it has been reported that in diabetics and men with peripheral arterial occlusive disease the mean prostate volume was greater than in healthy controls and men with coronary artery disease. In a previous clinical study, McVary et al. demonstrated an association between autonomic nervous system overactivity and LUTS and BPH measures [14]. Nevertheless, further studies are required to clarify the underlying pathomechanism between LUTS and ED.

In our study, regression analyses showed that the presence of ED is the most predictor of severe LUTS. This relationship remains significant after controlling for comorbidities such as age, hypertension, smoking duration and abnormal levels of WC, triglycerides, HDL, FBG and presence of metabolic syndrome. Thus, the presence of ED is an independent predictor of severe LUTS in older men. Why the presence of ED exists as such a strong predictor of LUTS as determined by IPSS is uncertain. ED has been demonstrated to share a common profile of risk factors with LUTS related to BPH. As the penile arteries are similar with the pelvic arteries and common branch with prostate, they may be more prone to cause ED and LUTS with even comparatively small amounts of atherosclerosis. Another possibility is that ED is a barometer of global vascular impairment. Kaiser et al. demonstrated that patients with ED exhibit a widespread peripheral vascular defect in both endothelium-dependent and endothelium-independent vasodilatation that appears to precede the onset of clinically overt coronary artery disease [15].

Our results show that severity of LUTS is associated with high prevalence of metabolic syndrome. On the basis of our findings, men suffering from abdominal obesity, high blood pressure levels or treated hypertension and high FBG levels or treated diabetes had more severe LUTS than men without these disorders. It may suggests the possibility that hyperinsulinemia is related to the development of LUTS secondary to BPH as most of these conditions are associated with hyperinsulinemia. It has been

Table III. Multiple logistic regression analysis risk factors for LUTS severity.

Risk factors	Beta Coefficient	S.E.	OR	95% CI	*P*
Age	−0.02	0.02	0.98	0.94–1.02	0.394
Smoking (packet/year)	0.01	0.01	1.01	0.99–1.03	0.148
Abnormal WC	0.27	0.42	1.31	0.58–2.99	0.516
Abnormal TA	0.52	0.42	1.67	0.74–3.80	0.218
Abnormal FPG	0.74	0.41	2.09	0.93–4.67	0.074
Abnormal Tg	−0.35	0.45	0.71	0.29–1.71	0.706
Abnormal HDL	0.11	0.43	1.11	0.48–2.60	0.806
Presence of ED	0.84	0.42	2.31	1.01–5.27	0.048
Prescence of MS	0.24	0.63	1.28	0.37–4.37	0.698

OR, odds ratio; CI, confidence interval; WC, waist circumference; FBG, fasting blood glucose; TG, triglyceride; HDL, high density lipoprotein; ED, erectile dysfunction; TA, tension arterial; MS, metabolic syndrome.

supposed that hyperinsulinemia, insulin resistance and autonomic hyperactivity are important aetiologic links between metabolic syndrome and increased LUTS secondary to BPH risk [10]. Our results are concordant with previous studies that investigated the association between BPH and metabolic syndrome [16]. In the study conducted by Hammarsten and Hogstedt, it has been found significantly larger prostate volumes and faster annual BPH growth rates in men with non-insulin-dependent diabetes mellitus, treated hypertension, and obesity than in men without these conditions [16]. In another cohort of 258 men with LUTS, the results revealed that men with fast-growing BPH had a higher prevalence of NIDDM, treated hypertension and obesity (measured by BMI, waist measurement, hip measurement and waist to hip ratio) [11]. The relationship between obesity and BPH/LUTS may be attributed to the transformation of androgen in adipose tissue into estrogens in obese men patients [17].

In this study, we found an association between smoking duration and LUTS severity. Our results, similar to previous studies, have shown a higher risk of BPH among smokers [18,19]. In a previous study, it has been hypothesised that smoking can also influence plasma steroid hormone levels by raising the testosterone and androstenedione levels and consequently the generation of BPH/LUTS [20]. In addition, nicotine can stimulate the sympathetic nervous system and irritate bladder function, and these changes may cause LUTS [21].

In this study, we did not find significant association between LUTS severity and plasma testosterone levels. Although the importance of androgens for prostate development, growth and maintenance is well established, there is no consensus on their possible effect on LUTS. In their recent study, Rohrmann et al. did not find consistent association with LUTS as was seen for testosterone, free testosterone or sex hormone binding globulin concentrations, in accordance with our results [22]. In addition, Miwa et al. also did not find significant association between IPSS and serum total testosterone levels [23]. Furthermore, in recent studies it has been established that there were significant association between free testosterone and LUTS, whereas testosterone concentrations were not associated with LUTS [23,24]. In our study, we did not evaluate the free testosterone and other sex hormones level. This might be the limitation of our study; however, the measurements of all sex hormone levels were beyond the scope of our study.

Although no association was seen between LUTS and serum testosterone levels, low serum levels of testosterone was significantly associated with the presence metabolic syndrome. Recently, several studies have noted a strong association between low serum testosterone levels and metabolic syndrome. Laaksonen et al. reported that low testosterone levels correlate strongly with metabolic syndrome and thus might be an early marker for endothelial dysfunction [25]. It has been shown that sex steroid hormones, in particular testosterone, play an important role in the regulation of body composition, fat metabolism, glucose regulation and restoring and maintaining the penile trabecular smooth muscle and structure [26–29]. Low testosterone levels may cause insulin resistance, increase in abdominal obesity and dyslipidemia. All of these diseases are the components of metabolic syndrome and cause endothelial dysfunction. As mentioned in the review of Makhsida et al., low testosterone levels in the middle-aged men predict the development of metabolic syndrome later in life [30].

The limitations of our study should be mentioned. First, our study was targeted on patients who were admitted to hospital with the complaints of LUTS and not representative of the general population. Another possible limitation concerns the use of self-report questionnaires for assessing LUTS and ED. This introduces a potential for response bias, as respondents may inaccurately report their urinary or sexual dysfunction symptoms. However, the questionnaires selected for this study have all been previously validated in clinical and non-clinical samples and are widely used in various studies. It can also be quarrelled that LUTS and ED are intrinsically subjective in nature, and that patient self-report should be the primary measure of these disorders. A study with large sample size and objective diagnostic indicators would be required for definitive conclusions about the causal link between LUTS, ED, metabolic syndrome and its' components.

Obesity, high plasma level of FBG or treated diabetes and high blood pressure or treated hypertension constitutes risk factors for the development of severe LUTS. Metabolic syndrome as a collection of abnormalities might play a key role in the pathogenesis in both ED and severe LUTS. Presence of ED is the most predictor of severe LUTS.

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