

Original Article

Are age, anthropometry and components of metabolic syndrome-risk factors interrelated with lower urinary tract symptoms in patients with erectile dysfunction? A prospective study

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Abstract

Aim: To evaluate the effects of metabolic profiles on lower urinary tract symptoms (LUTS) in men with erectile dysfunction (ED). **Methods:** A total of 75 impotent men aged 25–75 years old (mean 58.1 years) were included in the study on a prospective basis. Patients were evaluated with a complete history, physical examination, anthropometry and metabolic profiles. LUTS were assessed using the International Prostate Symptom Score (IPSS). **Results:** Overall, there was no correlation between the IPSS and continuous parameters. However, when continuous variables were categorized, some parameters were significantly associated with LUTS. Patients with triglyceride level of 150 mg/dL or higher had more severe symptoms than those with triglyceride levels less than 150 mg/dL (19.4 ± 2.4 vs. 14.3 ± 1.1 , $P = 0.033$). When 40 mg/dL was chosen as the high-density lipoprotein (HDL)-cholesterol cut-off level, the IPSS was significantly different between the two groups divided by 40 mg/dL (19.4 ± 2.6 for HDL-cholesterol < 40 mg/dL vs. 14.4 ± 1.0 for HDL-cholesterol ≥ 40 mg/dL, $P = 0.042$). The area under the receiver operating characteristic curve (AUROCC) of triglyceride was 65.7% (95% confidence interval [CI], 52.6%–82.3%; $P = 0.034$) for severe LUTS. However, the AUROCC for ‘HDL-cholesterol’ was not significant (area, 65.4%; 95% CI, 48.2%–82.7%; $P = 0.062$). No other factors were determined to be significant in this regard. **Conclusion:** The results of the present study indicate that some metabolic profiles might influence LUTS in men with ED. (*Asian J Androl* 2007 Mar; 9: 213–220)

Keywords: lower urinary tract symptoms; erectile dysfunction; metabolic syndrome; body mass index; testosterone

1 Introduction

According to National Cholesterol Education Program, a patient with metabolic syndrome has three

or more risk factors consisting of the disorder of lipid storage, insulin resistance and hypertension [1]. Esposito *et al.* [2] reported that compared with age- and weight-matched control subjects, patients with metabolic syndrome had increased prevalence of erectile dysfunction (ED); moreover, there was an increase in prevalence of ED as the number of components of metabolic syndrome increased, suggesting that the cumulative burden of cardiovascular risk might be central to the pathogenesis of ED. Conversely, ED can be considered a risk marker of metabolic syndrome and its associated conditions [3, 4].

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Both lower urinary tract symptoms (LUTS) and ED are common within a similar gender and age distribution in older men, but there is little evidence to support a link between LUTS and ED. However, many community-based studies reported a statistically significant association between LUTS and ED [5–11]. Furthermore, recent studies suggested that benign prostatic hyperplasia (BPH) is a component of the metabolic syndrome and that BPH patients might share the same metabolic abnormality with patients of metabolic syndrome [12–14]. In addition, Poulakis *et al.* [15] reported that risk factors for the occurrence of postoperative, newly reported ED were diabetes and intraoperative capsular perforation.

Therefore, we suspected that metabolic profiles might affect LUTS of impotent men. To our knowledge, however, it is unknown which profiles impact LUTS in patients suffering from ED because previously such effects on LUTS have not been systemically investigated. The present study was designed to evaluate the effects of metabolic profiles on LUTS in men with ED.

2 Materials and methods

2.1 Patients

ED patients admitted urology outpatient clinic between January and December 2004 were recruited. Patients who were eligible and willing to participate in the study were assessed. The eligibility criteria included: aged 20 years or older and married with a stable and heterosexual relationship in at least the past 6 months. The exclusion criteria of this study included the use of medications for the control of bladder symptoms, bladder tumors, bladder stones, urethral strictures, neurogenic bladder dysfunction and restricted mobility. Patients were also excluded from the analysis if they had a documented history or clinical symptoms of prostatitis, prostate cancer, or prostatic intraepithelial neoplasia on biopsy, serum prostate-specific antigen (PSA) levels in excess of 20 ng/mL, history of prostate surgery or radiotherapy, acute urinary retention or an indwelling catheter, evidence of acute urinary infection (pyuria and bacteriuria) on urinalysis, or if they had ever taken 5 α -reductase inhibitors. A total of 75 men of 25–75 years old (mean age 58.1 years) were included in the study on a prospective basis.

2.2 Methods

At the initial visit, patients' complete medical history

was evaluated, with a physical examination consisting of digital rectal examination and standard blood test, including serum PSA, serum fasting glucose level and lipid profiles, such as concentrations of total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol and triglyceride. Patients of 50 years or older with suspicious results of digital rectal examination and/or elevated PSA levels in excess of 4 ng/mL also underwent systemic sextant biopsies under transrectal ultrasonographic guidance, using an 18-gauge needle fitted to an automatic biopsy gun. Hypoechoic lesions detected on ultrasonography and areas corresponding to palpable abnormalities on digital rectal examinations were also biopsied. Blood samples were separated, and then frozen at –80°C until used for analysis. The body size of patients, including height and body weight, was determined using an automatic instrument. The body mass index (BMI) of each patient was calculated as the body weight in kilograms divided by the square of the height in meters. Information on demographic characteristics was collected by questionnaire. LUTS and symptom-specific quality of life were assessed using the International Prostate Symptom Score (IPSS) and the IPSS quality of life scores. ED was defined as a consistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance. Documented evidence of ED included a medical history of at least 6-month duration, physician records and objective testing, if available. Baseline sexual function was also evaluated using the self-administered International Index of Erectile Function (IIFE) [16]. The severity of ED was confirmed on the six-item erectile function domain (Erectile Function domain score 6–25) [17].

2.3 Statistical analysis

Data are presented as mean \pm SE or percentages, according to the variables. Correlations among continuous variables (age, anthropometry and blood tests) and the IPSS were determined using the Pearson correlation test. Statistical comparisons of continuous data were performed using paired *t*-test or one-way analysis of variance (ANOVA) and the Armitage test for categorical data. We assessed whether clinical parameters, including age, anthropometry and metabolic profiles, are discriminative for severe LUTS (IPSS = 20) using the area under the receiver operating characteristic curve (AUROCC). The area under the curve is a suitable parameter to summarize the overall discriminative or diagnostic value of a

model and can range from 0.5 (flipping a coin, a useless model) to 1.0 (perfect discrimination). The larger the AUROCC approached 100% (i.e. the more the receiver operating characteristic [ROC] curve approached the upper-left corner), the greater the predictive power. The level of statistical significance was defined as $P < 0.05$ and all statistical tests were two-sided. Statistical analyses were performed using a commercially available analysis program, SPSS version 10.0 (SPSS, Chicago, IL, USA).

3 Results

The mean age of the studied patients was 58.1 years, and their mean PSA level was 1.6 ng/mL. All the patients enrolled in this study had ED (IIEF-EF domain score 6–25). Basic characteristics of patients are shown in Table 1. The results of Pearson's correlation analysis in 75 studied patients with ED are summarized in Table 2. Overall, there was no correlation between IPSS scores and continuous parameters. When continuous variables were categorized, some parameters were significantly associated with LUTS. Patients with triglyceride levels of 150 mg/dL or higher had more severe symptoms than those with triglyceride levels of less than 150 mg/dL (19.4 ± 2.4 vs. 14.3 ± 1.1 , $P = 0.033$). When 40 mg/dL was chosen as the HDL-cholesterol cut-off level, the IPSS were significantly different between the two groups divided by this level (19.4 ± 2.6 for HDL-cholesterol < 40 mg/dL vs. 14.4 ± 1.0 for HDL-cholesterol ≥ 40 mg/dL, $P = 0.042$) (Table 3). Figure 1 presents the area under the receiver operating characteristic curves for the discriminative value of clinical parameters on severe LUTS. The AUROCC of triglyceride was 65.7% (95% CI, 52.6%–82.3%; $P = 0.034$) for severe LUTS. However, the area under the receiver operating characteristics curve for "HDL-cholesterol" was not significant (area, 65.4%; 95% CI, 48.2%–82.7%; $P = 0.062$) (data not shown). No other factors were determined to be significant in this regard (data not shown). The performance of sensitivity and specificity at various triglyceride levels are shown in Table 4. Using the standard cut-off of 150 mg/dL, sensitivity of 44.4% and specificity of 85.0% were observed.

4 Discussion

With the growing life expectancy and absolute number of the elderly, studies on age-related diseases are

becoming increasingly important. Therefore, the association between LUTS and sexual dysfunction has been investigated. In 2 011 French men aged 50–80 years, Macfarlane *et al.* [5] found that the probability of sexual dissatisfaction increased with the severity of LUTS. Among 423 British men aged 40 years or older, Frankel *et al.* [6] observed that sexual dysfunction was associated with a wide range of LUTS. Terai *et al.* [18] also reported that ED is highly prevalent among Japanese men with LUTS and is significantly associated with the severity of LUTS after controlling for age. Several other community-based studies using the IPSS and various male sexuality questionnaires showed that a moderate to severe IPSS is significantly associated with ED, with reported age-adjusted odds ratios (OR) of 2.11 [7], 1.8–7.5 [8], 1.39 [9], 2.25 [10] and 2.05–5.75 [11], depending on the severity of IPSS.

Therefore, ED and LUTS might have a common causative factor. Although the mechanism underlying the relationship between lower urinary tract function and ED remains unknown, four leading theories of how these diseases interrelated are suggested: the nitric oxide (NO) synthase/NO [19], autonomic hyperactivity effects on LUTS and ED [20], increased Rho-kinase activation/downregulation of endothelin-B receptor sites [21], and prostate and penile atherosclerosis [22]. However, it is unclear whether sexual dysfunction in older men is causally related to BPH or only a consequence of aging. Blanker *et al.* [8] revealed that urinary flow rate and prostate enlargement have no independent influence on ED. Green *et al.* [23] also showed that ED is not associated with prostate volume or maximal flow rate.

ED is more prevalent in men with metabolic syndrome [2]. Metabolic syndrome represents a constellation of risk factors for cardiovascular disease. Strong epidemiological evidence links the subsequent risk of ED to the presence of well-recognized risk factors for coronary disease, such as increased body weight, diabetes, cardiovascular disease, hypertension and dyslipidemia [24–26]. All the major risk factors for cardiovascular disease are associated with increased production of superoxide radicals and other reactive oxygen species (ROS), which, in turn, decrease NO bioavailability [27]. Abnormalities of this vasodilator system play an important role in the pathophysiology of ED, as it is now recognized that vascular disease of the penile arteries is the most common cause of ED, accounting for up to 80% of cases [28]. Therefore, the earliest events in the

Table 1. Patient characteristics. Data were presented as mean \pm SE (5th–95th percentiles) or numbers (%). P values are calculated by one-way analysis of variance (continuous variables) or Armitage test (categorical variables). LUTS, lower urinary tract symptoms; BMI, body mass index; PSA, prostate-specific antigen; HDL, high density lipoprotein; LDL, low density lipoprotein; IPSS, International Prostate Symptom Score.

	Total n = 75			Mild LUTS n = 13		Moderate LUTS n = 42		Severe LUTS n = 20		P value
	Mean \pm SE	(5th–95th percentiles)	n (%)	Mean \pm SE	(5th–95th percentiles)	Mean \pm SE	(5th–95th percentiles)	Mean \pm SE	(5th–95th percentiles)	
Age (years)	58.1 \pm 1.0	(39.4–70.4)		61.2 \pm 1.9	(53.0–75.0)	57.6 \pm 1.4	(38.5–69.0)	57.2 \pm 2.3	(35.3–71.9)	0.390
Height (cm)	168.4 \pm 0.7	(159.7–179.0)		166.4 \pm 1.4	(158.0–174.0)	168.8 \pm 1.0	(159.2–179.0)	168.9 \pm 1.1	(160.1–182.6)	0.444
Weight (kg)	69.9 \pm 1.1	(54.7–88.0)		68.1 \pm 2.4	(52.0–81.0)	69.8 \pm 1.5	(54.1–88.0)	71.2 \pm 2.4	(56.1–92.8)	0.681
BMI (kg/m ²)	24.6 \pm 0.4	(18.7–30.4)		24.7 \pm 1.0	(18.2–30.9)	24.5 \pm 0.5	(18.7–30.9)	24.9 \pm 0.7	(19.9–30.0)	0.884
PSA (ng/mL)	1.6 \pm 0.3	(0.2–7.4)		2.5 \pm 1.3	(0.5–8.8)	1.6 \pm 0.4	(0.2–7.3)	1.0 \pm 0.3	(0.2–4.3)	0.314
Fasting glucose (mg/dL)	107.4 \pm 3.8	(84.9–147.1)		102.6 \pm 4.2	(92.0–136.0)	108.6 \pm 6.0	(82.3–185.0)	108.1 \pm 4.9	(86.0–146.0)	0.845
Triglyceride (mg/dL)	123.4 \pm 9.5	(50.5–294.9)		107.0 \pm 13.7	(71.0–196.0)	114.1 \pm 14.2	(31.4–324.8)	147.4 \pm 16.1	(64.0–259.0)	0.229
HDL-cholesterol (mg/dL)	57.8 \pm 9.0	(29.9–95.5)		50.7 \pm 3.3	(38.0–68.0)	66.1 \pm 16.5	(35.2–279.8)	47.3 \pm 5.0	(28.0–105.0)	0.622
LDL-cholesterol (mg/dL)	112.0 \pm 4.2	(71.9–161.0)		120.4 \pm 8.5	(103.0–143.0)	106.1 \pm 5.7	(47.2–161.0)	119.1 \pm 7.6	(74.0–182.0)	0.294
Total cholesterol (mg/dL)	183.1 \pm 4.1	(129.5–237.3)		193.5 \pm 5.7	(170.0–225.0)	176.8 \pm 6.1	(105.8–241.1)	189.9 \pm 7.4	(131.0–267.0)	0.221
Smoking, n (%)										0.632
None-smoker	38	(50.7)		6	(46.2)	24	(57.1)	8	(40.0)	
Ex-smoker	22	(29.3)		3	(23.1)	13	(31.0)	6	(30.0)	
Smoker	15	(20.0)		4	(30.8)	5	(11.9)	6	(30.0)	0.797
Alcohol, n (%)										
< One bottle/week	40	(53.3)		8	(61.5)	21	(50.0)	11	(55.0)	
\geq One bottle/week	35	(46.7)		5	(38.5)	21	(50.0)	9	(45.0)	0.673
Cardiovascular disease, n (%)										
No	67	(89.8)		12	(92.3)	36	(85.7)	19	(95.0)	
Yes	8	(10.2)		1	(7.7)	6	(14.3)	1	(5.0)	0.305
Hypertension, n (%)										
No	44	(58.7)		7	(53.8)	23	(54.8)	14	(70.0)	
Yes	31	(41.3)		6	(46.2)	19	(45.2)	6	(30.0)	0.256
Diabetes mellitus, n (%)										
No	60	(80.0)		12	(92.3)	33	(78.6)	15	(75.0)	
Yes	15	(20.0)		1	(7.7)	9	(21.4)	5	(25.0)	
IPSS	14.9 \pm 0.9	(3.0–27.0)		3.6 \pm 0.4	(1.0–6.0)	13.9 \pm 0.5	(10.0–19.0)	24.3 \pm 0.7	(20.0–32.9)	< 0.001
IPSS quality of life index	3.3 \pm 0.2	(1.0–5.0)		1.4 \pm 0.3	(0.0–3.0)	3.4 \pm 0.2	(1.0–4.9)	4.3 \pm 0.2	(3.0–6.0)	< 0.001

Table 2. Pearson's correlation analyses. IPSS: International Prostate Symptom Score; BMI, body mass index; PSA, prostate-specific antigen; HDL, high density lipoprotein; LDL, low density lipoprotein.

	IPSS	
	Correlation coefficient	P value
Age (years)	-0.175	0.132
Height (cm)	0.168	0.159
Weight (kg)	0.089	0.455
BMI (kg/m ²)	-0.014	0.906
PSA (ng/mL)	-0.286	0.063
Fasting glucose (mg/dL)	0.099	0.467
Triglyceride (mg/dL)	0.216	0.103
HDL-cholesterol (mg/dL)	-0.018	0.891
LDL-cholesterol (mg/dL)	-0.020	0.894
Total cholesterol (mg/dL)	-0.048	0.704

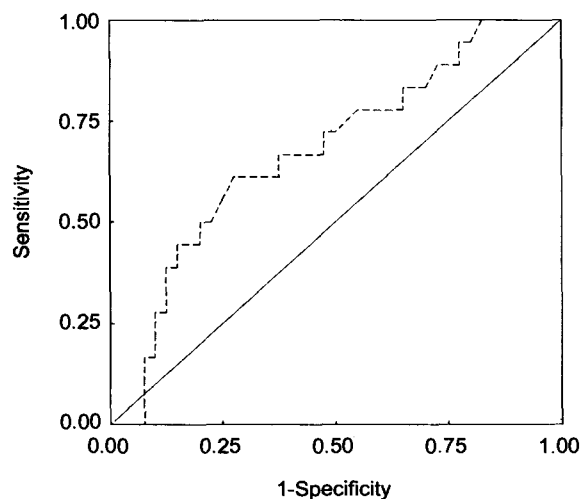


Figure 1. Ability of 'triglyceride' to predict 'severe lower urinary tract symptoms (LUTS) (International Prostate Symptom Score [IPSS] = 20)'. Solid line indicates a reference line. Dashed line indicates 'triglyceride'. Area under the receiver operating characteristics curve for 'triglyceride' was 65.7% (95% confidence interval, 52.6% to 82.3%; $P = 0.034$).

development of atherosclerosis (endothelial dysfunction) are similar to the earliest events in the development of ED.

Recently, several investigators have examined the association of components of the metabolic syndrome with BPH. Previous studies [12–14] demonstrated that the prostate gland volume is related to components of the metabolic syndrome, including non-insulin-dependent

Table 3. International Prostate Symptom Score (IPSS) according to clinical parameters. P values are calculated by one-way analysis of variance (smoking) or paired t -test (others). Data presented are means \pm SE or numbers (%). BMI, body mass index; PSA, prostate-specific antigen; HDL: high density lipoprotein, LDL: low density lipoprotein.

	Mean IPSS	P value
Age (years)		0.702
< 55	15.2 \pm 1.1	
\geq 55	14.5 \pm 1.3	
Height (cm)		0.492
< 170	14.5 \pm 1.1	
\geq 170	15.7 \pm 1.4	
Weight (kg)		0.992
< 70	15.1 \pm 1.1	
\geq 70	15.0 \pm 1.4	
BMI (kg/m ²)		0.679
< 25	14.7 \pm 1.0	
\geq 25	15.5 \pm 1.6	
PSA (ng/mL)		0.053
< 1.5	16.1 \pm 1.3	
\geq 1.5	11.1 \pm 2.0	
Fasting glucose (mg/dL)		0.208
< 110	13.4 \pm 1.1	
\geq 110	16.2 \pm 2.0	
Triglyceride (mg/dL)		0.033
< 150	14.3 \pm 1.1	
\geq 150	19.4 \pm 2.4	
HDL-cholesterol (mg/dL)		0.042
< 40	19.4 \pm 2.6	
\geq 40	14.4 \pm 1.0	
LDL-cholesterol (mg/dL)		0.748
< 100	16.7 \pm 1.2	
\geq 100	16.0 \pm 1.6	
Total cholesterol (mg/dL)		0.701
< 200	15.4 \pm 1.2	
\geq 200	14.7 \pm 1.6	
Smoking		0.846
Non-smoker	14.7 \pm 1.0	
Ex-smoker	14.8 \pm 1.5	
Smoker	16.0 \pm 2.7	
Alcohol		0.842
< One bottle/week	15.3 \pm 1.2	
\geq One bottle/week	14.9 \pm 1.3	
Cardiovascular disease		0.366
No	15.0 \pm 1.0	
Yes	11.2 \pm 1.2	
Hypertension		0.303
No	15.6 \pm 1.1	
Yes	13.8 \pm 1.4	
Diabetes mellitus		0.479
No	14.7 \pm 1.0	
Yes	16.2 \pm 1.9	

Table 4. Calculation of sensitivity and specificity using various concentrations of the triglyceride levels.

Cut-off (mg/dL)	Sensitivity (%)	Specificity (%)
50	100.0	5.0
75	83.3	30.0
100	66.7	52.5
125	50.0	77.5
150	44.4	85.0
175	38.9	85.0
200	27.8	87.5
225	22.2	90.0
250	11.1	92.5

diabetes mellitus, hypertension, obesity, low HDL-cholesterol levels and high insulin levels. These findings suggested that metabolic profiles constitute risk factors for the development of BPH and generate a hypothesis of a causal relationship between metabolic profiles and the development of BPH and of an increased sympathetic nerve activity in men with BPH. Furthermore, in the Third National Health and Nutrition Examination Survey [29], history of diabetes (OR, 1.67; 95% CI, 0.72 to 3.86) and hypertension (OR, 1.76; 95% CI, 1.20 to 2.59) was positively associated with LUTS and men classified as having three or more components of the metabolic syndrome had increased odds of LUTS (OR, 1.80; 95% CI, 1.11 to 2.94). These findings support the role for metabolic perturbations in the etiology of LUTS.

The main aim of this study was to evaluate the role of metabolic profiles in LUTS in patients with ED. In our study, some metabolic parameters, such as triglyceride and HDL-cholesterol levels, were associated with LUTS and were the discriminative factors for severe LUTS. To our knowledge, this finding has not been described previously. The pathophysiological mechanisms remain unclear, but there are several possible explanations for our results. Men with low HDL-cholesterol levels have a larger prostate gland than those without this condition [12] and men with fast-growing prostate glands had lower HDL-cholesterol levels than those with slow-growing prostate glands [13, 14]. In a recent study, serum triglycerides emerged as the main determinants of prostate gland volume in subjects with prostate hypertrophy [30]. Furthermore, Lee *et al.* [31] reported that the serum level of HDL-cholesterol showed a biphasic association with moderate to severe LUTS. In a rabbit model, hypercholesterolemia

resulted in thickening and fibrosis of the prostate, changing its mechanical properties, and also impaired neurogenic relaxation in the prostate, although to a lesser extent than chronic ischemia [32]. In addition, the effects of impaired lipid metabolism on the contractile and relaxation response of smooth muscles or smooth muscle cell degeneration are well known [33, 34]. However, because these studies were performed on subjects without sexual dysfunction, further research is needed to clarify the underlying mechanisms involved.

Limitations affecting our current findings must be considered. First, our study included only Korean men. The population within each country differs culturally and sociodemographically. The results of studies of urinary symptoms in specific countries might not be generally applicable in other countries, because different countries have different cultural backgrounds and specific health-care delivery systems [35]. Second, using cross-sectional methods might not allow definitive conclusions about the causal link between the severity of ED and the investigated variables. In addition, our study was not a community-based study. Data from general practice settings might have been preferable, although other biases might also present in these populations (e.g. the volunteer bias). In the absence of general practice data, the results from clinical trials were used as the next best available information. Third, because this was a pilot study, the sample size was small. In our study, although a trend of influence of some metabolic profiles on LUTS was observed, no statistical significance was observed. The lack of statistical significance might be a result of the relatively small number of patients. Therefore, further study with larger sample size is necessary. Finally, the study did not include all demographic variables. Because other sociodemographic and health status variables, such as marital status and work situation, might affect urinary symptoms, additional studies including these variables are needed. Also, some factors that could be important causes of severe LUTS have not been included in this study.

In this study, we found that some metabolic profiles in patients with ED might influence LUTS. These findings suggest that early detection or correction of these metabolic profiles might reduce the prevalence of LUTS in men with ED. However, although our study provides some descriptive information on LUTS in patients suffering from ED, the findings need to be confirmed in larger epidemiological studies.

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