

Evaluation of the Association between Lower Urinary Tract Symptoms and Erectile Dysfunction, Considering its Multiple Risk Factors

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ABSTRACT

Aim. To investigate the relationship between lower urinary tract symptoms (LUTS) and erectile dysfunction (ED), while considering multiple risk factors for ED, including an anthropometric evaluation of central obesity.

Methods. A cross-sectional study was carried out with 192 consecutive male subjects (≥ 40 years old). Conditions clearly associated with ED, other than obesity and age, were considered exclusion criteria. Men were evaluated routinely for clinical history, received a physical examination, and were subjected to blood analysis for fasting serum glucose, lipid profile, and serum testosterone. Patients with previous known history of diabetes mellitus or hypertension were excluded. Anthropometric measures taken included body mass index (general obesity) and waist circumference, waist-hip index, and sagittal abdominal diameter (visceral obesity). Analyses were performed using bivariate and multivariate models (multiple logistic regression). Age, education, alcohol consumption, smoking, sedentary lifestyle, fasting blood glucose level, dyslipidemia, hypogonadism, general obesity, and visceral obesity were taken into account as potential confounding factors.

Main Outcome Measures. All men completed the International Index of Erectile Function and International Prostate Symptom Score (IPSS).

Results. IPSS scores were low, intermediate, and high in 89 (46.4%), 76 (39.6%), and 27 (14.1%) men, respectively. Overall IPSS scores were significantly associated with ED ($P = 0.002$). In addition, an association between the severity of ED and LUTS was observed ($P = 0.008$). The mean quality of life assessment in the IPSS revealed a statistically significant difference between individuals with varying degrees of ED ($P = 0.008$). The logistic regression analyses showed that IPSS scores and ED remained independently associated even after the control for confounding factors (odds ratio = 1.07, 95% CI = 1.02–1.13, $P = 0.01$).

Conclusion. This study suggests that LUTS are independently associated with ED, taking into account various risk factors for ED, including visceral obesity. **Rhoden EL, Riedner CE, Fornari A, Fuchs SC, and Ribeiro EP. Evaluation of the association between lower urinary tract symptoms and erectile dysfunction, considering its multiple risk factors. J Sex Med 2008;5:2662–2668.**

Key Words. Erectile Dysfunction; Obesity; Sexual Dysfunction; Lower Urinary Tract Symptoms; LUTS

Introduction

Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) are common urologic conditions that are seen in the aging male,

with estimated prevalences of 56% and 40%, respectively, in men >40 years old [1]. The high prevalence of these conditions may explain the coincidence of LUTS and ED in older men: in one study [2], 77% of men diagnosed with ED

presented with LUTS. Until recently, little evidence was available to support a consistent relationship between LUTS and ED. Recent epidemiological studies have demonstrated that these two clinical conditions are independently related, despite the effect of other recognized risk factors for both conditions, such as age, systemic hypertension, dyslipidemia, cardiovascular diseases, and lifestyle factors [3,4]. Thus, LUTS is now considered an important risk factor for sexual dysfunction [5], and a potential common cause has been suggested [6].

Recently, various theories have been proposed regarding the common pathophysiology between LUTS and ED, including autonomic hyperactivity, the presence of pelvic atherosclerosis, reduced production of nitric oxide in the pelvic organs including the prostate and penis, increased RHO-kinase activation and endothelin activity, and influences of a metabolic syndrome which affects both voiding and erectile function. However, a mechanistic association between ED and LUTS has not been definitively established [2,3,5–10].

To determine the relationship between LUTS and ED, a careful epidemiological analysis, including other risk factors for ED, must be conducted. Previous work has only considered the contribution of general obesity, measured by body mass index [9]. However, a recent report suggested a strong independent association between central obesity and ED [11].

Aims

In the present study we have investigated the association between LUTS and ED, while considering the multiple risk factors for ED, including an anthropometric evaluation of central obesity.

Methods

Between August 2003 and July 2004, a total of 1,981 patients were seen at a large state outpatient clinic for primary health care and urologic center in the city of Porto Alegre, southern Brazil. From this population, all men aged ≥ 40 years (total = 623) were eligible for inclusion, regardless of their reason for consultation. Exclusion criteria included previous diagnosis of diabetes mellitus (17.66%), systemic arterial hypertension (15.25%), previous radiotherapy (1.61%) or chemotherapy (1.44%), pelvic or orthopedic surgery (3.53%), heart or peripheral vascular diseases (10.43%), psychiatric disease (2.41%), use of psy-

chotropic medications, anxiolytic agents, or mood stabilizers (11.24%), current or previous treatment for ED (5.14%), or use of medications that may affect the levels or action of androgens (0.48%). In total, 192 men were included in the study. The study was approved by our institution's Committee on Ethics in Research.

Erectile function was evaluated by the International Index of Erectile Function (IIEF), with the questionnaire being completed by the subject or, if required, by a certified interviewer. Answers to questions 1–5 and 15 provided the score for the erectile domain, and the cases were classified as without ED (score > 25 points) or with any intensity of ED (score ≤ 25 points). Cases were also classified according to intensity: mild ED (score: 17–25), moderate ED (score = 11–16), and severe ED (score ≤ 10 points).

LUTS were evaluated with the International Prostate Symptom Score (IPSS). The sum of the score for the first seven questions allowed to classify the subjects into the low score range (0–7), intermediate score range (8–19), and high score range (20–35). The eighth question, regarding the subject's quality of life (QoL), was considered separately, with a score range from 1 to 6.

A single investigator performed the standardized anthropometry in triplicate, and was blinded to the IIEF and IPSS outcomes. Four variables were selected, one for general obesity (body mass index) and three for visceral obesity (waist circumference, waist-hip index, and sagittal abdominal diameter). Body mass index was calculated as the ratio between weight (kg) and the height squared (m^2). Normal values ranged from $20 \text{ kg}/m^2$ to $24.9 \text{ kg}/m^2$, overweight values from $25.0 \text{ kg}/m^2$ to $29.9 \text{ kg}/m^2$, and obese values were $\geq 30 \text{ kg}/m^2$. Circumference values were obtained from the perpendicular plane along the body axis, in scales of 0.5 cm. The waist circumference measurement was obtained from the midpoint between the iliac crest and the costal margin; values greater than the 85th percentile (102 cm) were considered central obesity. The waist-hip index was calculated using the ratio between the waist and hip (taken at the level of the femoral trochanters) circumferences, with the 10th percentile (0.91) as a cut-off for central obesity. Sagittal abdominal diameter was assessed in dorsal decubitus position, using the distance from the exam table to the highest point of the subject's abdomen. Sagittal diameter > 24.5 cm (the 75th percentile) was also used as cut-off for central obesity.

During the same interview, confounding factors associated with ED were investigated, including age [12], formal education <8 years of school, smoking [12,13], sedentary lifestyle [12–14] (<120 minutes/week of physical activity, independent of the intensity [12]), and abusive consumption of alcoholic beverages [13] (≥ 350 g/week of ethanol or a daily consumption of at least 3.5 glasses of wine, two bottles of beer, or two doses of spirits [12]).

A fasting blood sample was obtained from all subjects, and glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and total testosterone (radioimmunoassay, normal range: 300–1,000 ng/dL) were determined, all in the same laboratory. The presence of dyslipidemia was defined by serum levels of total cholesterol > 240 mg/dL, LDL > 130 mg/dL, triglycerides > 150 mg/dL and/or HDL ≤ 40 mg/dL, and hypogonadism as serum levels of total testosterone < 300 ng/dL. The presence of dyslipidemia [14], hypogonadism [15], and fasting blood glucose [14] were also considered potential confounding factors.

The presence and degree of LUTS were analyzed and correlated with the presence and degree of ED, with statistical significance assessed by Pearson's Chi-square using SPSS[®] v.12 software (SPSS Inc., Chicago, IL, USA). Student's *t*-test or the Wilcoxon-Mann-Whitney test were used as appropriate for means or ranks comparison. *P* values < 0.05 were considered statistically significant. The QoL means were analyzed with the three-degree of IPSS as covariates, using one-way ANOVA with Tukey post hoc analysis. The IPSS

scores (taken as a continuous variable) and QoL scores were analyzed for correlation with IIEF, using Pearson's coefficient.

Associations between the LUTS and ED were tested using logistic regression, adjusted for history and laboratory confounding factors (including age, education, sedentary lifestyle, smoking, abusive consumption of alcohol, fasting blood glucose, dyslipidemia, and hypogonadism) and for anthropometry: body mass index (general obesity) and waist circumference, waist-hip index, and sagittal abdominal diameter (visceral obesity). Crude and adjusted odds ratios and 95% confidence intervals were obtained for LUTS as a predictor of ED (IIEF ≤ 25 points). This model was initially tested in the entire subject population using IPSS as a continuous variable. Thereafter, the same model was tested by including the IPSS score as a categorical variable, with the 2nd, 3rd, and 4th quartiles compared to the 1st, in order to determine whether the last three quartiles odds ratio serve as predictors of ED.

Results

All 192 recruited subjects agreed to participate in the study. The demographic, socioeconomic, behavioral, and clinical characteristics for all subjects are presented in Table 1. The participants' ages ranged from 40 to 81 years (mean = 57.8 ± 9.1 years); 2.6% were illiterate, 67.2% attended school for <8 years, 19.3% for 9–11 years, and 11% for >11 years; 15.1% exhibited excessive consumption of alcoholic beverages; 69.8% were sedentary and 17.7% were smokers.

Table 1 Demographic, socioeconomic, behavioral, and clinical characteristics of the study population—overall and stratified by the presence of ED (N and %, mean \pm standard deviation or (median [25%–75%])

Characteristics	Total	Men with ED (IIEF < 25) N = 147
White skin color	159 (82.8%)	123 (83.7%)
Education (8 years or less at school)	155 (80.7%)	117 (79.6%)
Smoking	34 (17.7%)	28 (19%)
Sedentary life style	134 (69.8%)	98 (66.7%)
Alcohol consumption	29 (15.1%)	24 (16.3%)
Total testosterone (ng/dL)	472.7 (381–614.8)	481.8 (378–620)
Triglycerides (mg/dL)	118 (87.2–160.5)	117 (82.0–161.0)
Total cholesterol (mg/dL)	203.6 \pm 40.5	202.2 \pm 39.5
HDL-cholesterol (mg/dL)	44.6 \pm 11.1	44.3 \pm 11.1
LDL-cholesterol (mg/dL)	130.7 \pm 34.6	130.7 \pm 34.1
Fasting blood glucose (mg/dL)	94 (84.0–106.8)	95 (84.0–111.0)
Waist circumference (cm)	92.9 \pm 9.2	92.4 \pm 9.3
Sagittal abdominal diameter	22.7 \pm 3.7	22.6 \pm 3.8
Waist-hip index	0.95 \pm 0.03	0.95 \pm 0.38
Body mass index ≥ 30 kg/m ²	46 (24.0%)	63 (42.9%)
Body mass index 25–29.9 kg/m ²	87 (45.3%)	35 (23.8%)

ED = erectile dysfunction; IIEF = International Index of Erectile Function; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2 Presence and degree of erectile dysfunction according to the International Prostate Symptom Score intensity (N and %)

		Erectile dysfunction				Total
		No (IIEF > 25)	Mild (IIEF 17–25)	Moderate (IIEF 11–16)	Severe (IIEF < 11)	
International	0–7	31 (34.8%)	33 (37.1%)	9 (10.1%)	16 (18%)	89
Prostate Symptom	8–19	10 (13.2%)	31 (40.8%)	21 (27.6%)	14 (18.4%)	76
Score	>19	4 (14.8%)	9 (33.3%)	7 (25.9%)	7 (25.9%)	27
Total	45 (23.4%)	73 (38%)	37 (19.3%)	37 (19.3%)	192	

Pearson Chi-squared: 17.52; $P = 0.008$ (df: 6).
IIEF = International Index of Erectile Function.

Overall prevalence of ED was 76.6%, with a mean of IIEF score of 18.5 ± 7.8 .

In the study population, the reported IPSS scores were in the lower range (0–7 points) in 89 (46.4%) subjects, intermediate range (8–19 points) in 76 (39.6%) subjects, and in the high range (20–35 points) in 27 (14.1%) subjects. An analysis of IPSS quartiles indicated that scores of 3, 8, and 15 fell into the 25th, 50th, and 75th percentiles, respectively.

The association between LUTS and ED is shown in Table 2. In men with mild symptoms of LUTS, the prevalence of ED was 65.2% (58 of 89 men), but when moderate and severe symptoms of LUTS were considered, the rates of ED were 86.8% (66 of 76 men) and 85.2% (23 of 27 men), respectively ($P = 0.002$). In addition, a significant association between the severity of ED and LUTS was observed (Table 2). It is interesting to note that in men with normal erectile function (IIEF > 25) the occurrence of mild urinary symptoms were more common (68.9%) than moderate (22.2%) or severe (8.9%) symptoms. Thus, among men with scores of the IIEF in the ED range (≤ 25 points) there is a tendency toward an increased prevalence of moderate and severe LUTS, with a decreased frequency of mild urinary symptoms. This was also suggested too by the significant negative correlation between IIEF and IPSS ($r = -0.23$, $P = 0.01$).

The QoL measurements revealed a significant difference between the various degrees of ED ($P = 0.008$), with post hoc analysis indicating that moderate ED was significantly different in QoL scores than both mild ED and no ED ($P = 0.04$ and $P = 0.007$, respectively, Figure 1). The negative correlation between these two variables is significant ($r = -0.21$, $P = 0.003$).

After controlling for confounding variables, including central obesity, a significant and independent association between urinary symptoms (IPSS) and ED was observed ($P = 0.01$; Table 3).

We noted that, in men in the 3rd and 4th quartiles for IPSS scores, relative to the 1st quartile the calculated odds ratio for ED was 3.45 (95% CI = 1.22–9.77) and 3.76 (95% CI = 1.29–11.00), respectively (Table 3). Based on these analyses, the IPSS scores equal to or above eight represented a significant increase in the risk (odds ratio) for the presence of ED in this study population.

Discussion

The present study identified an independent association between LUTS and ED as well as a significant association between the intensity of both conditions. We also observed an independent effect of IPSS in predicting ED, regardless of the adjustment for confounding factors such as age,

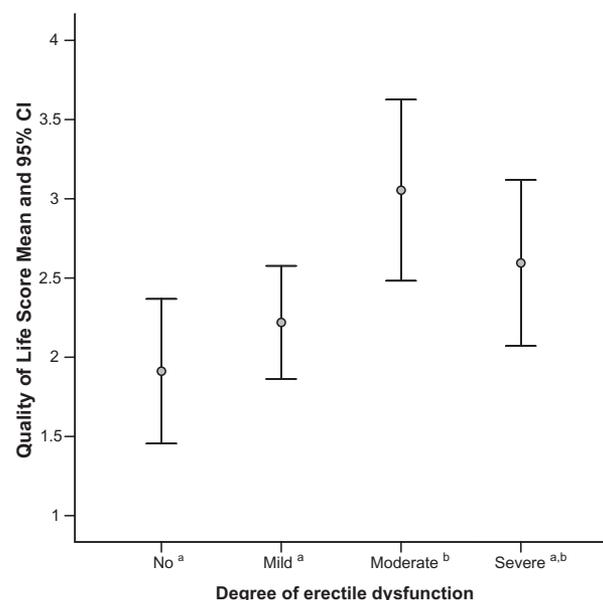


Figure 1 Quality of life assessment from the International Prostate Symptom Score, considering the presence and degree of erectile dysfunction. ANOVA $F: 4.08$, $df: 3$, $P = 0.008$. a, b: Post hoc analysis (Tukey), $P < 0.05$.

Table 3 Effect of IPSS as a predictor of erectile dysfunction, with total score range and IPSS quartile (reference: 1st quartile)

	β Coefficient	β Standard error	Adjusted odds ratio (95% CI)*
All score range	0.07	0.03	1.07 (1.02–1.13) [†]
IPSS quartile			
Score 3–8 (2nd quartile)	0.37	0.48	1.44 (0.56–3.70)
Score 8–15 (3rd quartile)	1.24	0.53	3.45 (1.22–9.77)
Score >15 (4th quartile)	1.33	0.55	3.76 (1.29–11.00)

* $P = 0.01$.

[†]Odds ratio adjusted for age, education, excessive consumption of alcoholic beverages, smoking, sedentary lifestyle, fasting blood glucose, dyslipidemia, hypogonadism, general obesity (body mass index), and visceral obesity (waist-hip index, sagittal abdominal diameter, and waist circumference).
IPSS = International Prostate Symptom Score.

education, excessive consumption of alcoholic beverages, smoking, sedentary lifestyle, fasting blood glucose, dyslipidemia, hypogonadism, general obesity (body mass index), and visceral obesity (waist-hip index, sagittal abdominal diameter, and waist circumference). Moreover, the odds ratios for ED were 3.45 (95% CI = 1.22–9.77) and 3.76 (95% CI = 1.29–11.00) for men in the 3rd and 4th quartiles of IPSS, respectively, relative to the 1st quartile. To the best of our knowledge, this is a novelty in the assessment of the association between LUTS and ED and establishes visceral obesity as a meaningful confounding factor in this relationship.

The prevalence of LUTS varies internationally [16], and is reported to occur in 45% of men in Sweden [8] and 75% in Egypt [2]. Specifically, Glina et al. [1] reported a prevalence of 56% of moderate and severe LUTS scores in men 40 years old or older. Despite this large country-to-country variation, a significant increase in LUTS with age has been reported by several authors [16].

Nevertheless, the high prevalence of ED and LUTS in older men has stimulated research concerning their comorbidity, because both conditions significantly reduce quality of life reports [6]. Aslan et al. [4] reported a significant negative correlation between IIEF and IPSS scores, after controlling for confounding factors such as age and other known ED risk factors. Similarly, numerous others authors [1,4,5,9] reported a strong independent association between LUTS and ED. In particular, a correlation between the severity of LUTS and ED has been described [2,9,10]. For example, Shiri et al. [9] reported an adjusted odd ratio for ED of 2.6 when IPSS scores were between 11–19 points and 4.4 for IPSS scores ≥ 20 points. The adjusted odds ratio calculated from the present data are consistent with the results of Shiri and colleagues, since an odds ratio greater than three was demonstrated for IPSS scores in the 3rd

(8–15 points) and 4th (scores >15) quartiles relative to the 1st (1–3 points) quartile, indicative of a severity relationship of IPSS and ED.

This statistically significant association, described in the literature, has led to four hypotheses concerning the possible common pathophysiology of LUTS and ED. The theory of autonomic hyperactivity highlights the effects of a metabolic syndrome and its components, such as hypertension, obesity, and hyperinsulinemia, which are associated with autonomic activation. According to this theory, these alterations give rise to ED and also effects in the bladder and urethra, which underlie LUTS pathogenesis [3,6,7]. The nitric oxide theory is based on the finding that conditions such as aging, hypertension, smoking, hypercholesterolaemia, and diabetes, which are also risk factors for ED, can decrease the release of nitric oxide in the pelvic organs, including the prostate and penis. This in turn increases smooth muscle cells' contractile forces at the corpus cavernosum, bladder neck, and prostate urethra, resulting in an increase of the bladder outlet resistance as well as venous leakage from the penis associated with poor smooth muscle relaxation [3,6,7]. The theory of increased Rho-kinase activation and endothelin activity has been suggested by experimental studies, which have demonstrated an increase in Rho-kinase activity (and consequently increased calcium sensitivity of the contractile machinery) in the detrusor as well as in the corpus cavernosum of rabbits with partial bladder outlet obstruction. Since the actions of several factors aside from norepinephrine (e.g., endothelin-1 and angiotensin II), which may be involved in the increased smooth muscle activity in both LUTS and ED, are dependent on Rho-kinase activity that acts downstream from these receptors, it has been suggested that the common link between these two conditions is increased Rho-kinase

activity [7]. The fourth theory suggests a common vascular pathway, since low peak systolic velocity of the cavernosal arteries and poor response to intracorporeal injection were observed in individuals with LUTS and arteriogenic and neurogenic ED [17].

These theories of common causality have been contested in the literature [6,7,18], and some authors have argued against the presence of an established basis of causality, despite the ever-increasing number of epidemiological studies. In this respect, Stromberg et al. [8] cited a significant but weak association between ED and LUTS (correlation coefficient of -0.29 , $P < 0.001$) and recommended further studies to better understand the possible causal relationship. This weak effect is consistent with the present findings of a low odds ratio of 1.07 (95% CI = 1.02–1.13) for ED when all IPSS values were considered (continuous variable). Similarly, the correlation coefficients detected for IPSS or QoL and IIEF ($r = -0.23$ and $r = -0.21$, respectively), although significant, are weak. Thus, in our analysis, a significant relationship could be observed, but this effect is diminished by the low magnitude of the effect. However, these findings added strength to a common causality theory for both conditions.

Previous analyses of the relationship between LUTS and ED were controlled for factors known to be associated with ED, such as smoking [12,13], education [19], excessive consumption of alcohol [13], hyperglycemia [14], dyslipidemia [14,20], hypogonadism, [15], and sedentary lifestyle [12–14]. In all these studies, only general obesity was considered and controlled as confounding factor. The importance of central obesity, evaluated by anthropometry, in predicting ED has been recently reviewed by Rhoden et al. [11]. In this study, an independent association between ED and central obesity was demonstrated, despite controlling for the effects of various confounding factors, including general obesity (body mass index). This result highlights the importance of obesity assessment due to the age-related redistribution of body fat. The evaluation of central obesity is mandatory when evaluating confounding factors that may interact in LUTS and ED.

Some limitations of the present study could be attributed to the population size and the source of participants' recruitment—a urologic center—that explains the high prevalence of ED. However, the test of hypothesis required such selection of participants in order to assess the

association between these conditions. The alternative—to select men from a general population—would require a very large sample size and it might be less cost-effective. On the other hand, the aim of the article was not to provide prevalence rate of ED for a general population. In addition, the rigid eligibility criteria allowed excluding participants with diabetes and hypertension and the measurements were conducted in an appropriate environment. Finally, the multivariate analyses adjusting for confounding factors strengthened the role of central obesity as the novelty of this study.

Conclusion

In conclusion, the data from the present study showed that ED and LUTS are associated clinical conditions and that LUTS is independently associated with ED even when confounding risk factors for the latter condition are taken into account, including visceral obesity. The possibility of a common causal relationship between LUTS and ED requires further epidemiological investigation.

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Statement of Authorship

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(b) Acquisition of Data

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