A Possible Relationship Between Testosterone and Lower Urinary Tract Symptoms in Men

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Purpose: In this study we searched for possible associations between serum testosterone levels and the severity of lower urinary tract symptoms in men.

Materials and Methods: In 278 patients with a mean age of 62 years blood levels of total testosterone, albumin, sex hormone-binding globulin, fasting glucose, fasting insulin and high sensitivity C-reactive protein were measured. Free testosterone, bioavailable testosterone and homeostasis model assessment of insulin resistance were calculated. Prostate volume was measured by transrectal ultrasonography and the severity of lower urinary tract symptoms was assessed using the International Prostate Symptom Score.

Results: Calculated free testosterone and bioavailable testosterone were negatively related to International Prostate Symptom Score total scores and subscores (voiding symptoms) after adjusting for age, prostate volume, high sensitivity C-reactive protein and homeostasis model assessment of insulin resistance ($p < 0.05$). In addition, calculated free testosterone and bioavailable testosterone were significantly related to the presence of severe lower urinary tract symptoms (International Prostate Symptom Score 20 or greater) using unadjusted and adjusted models ($p < 0.05$), although the odds ratio of bioavailable testosterone was lower than that of calculated free testosterone on multivariate analysis. High sensitivity C-reactive protein was negatively correlated with serum total testosterone ($r = -0.128$, $p = 0.038$) and bioavailable testosterone ($r = -0.126$, $p = 0.041$), and homeostasis model assessment of insulin resistance was negatively correlated with serum total testosterone ($r = -0.236$, $p < 0.001$), calculated free testosterone ($r = -0.179$, $p = 0.003$) and bioavailable testosterone ($r = -0.162$, $r = 0.007$). However, no significant correlation was found between high sensitivity C-reactive protein or homeostasis model assessment of insulin resistance, and International Prostate Symptom Score total scores, voiding symptoms scores and storage symptoms scores.

Conclusions: Our findings support the favorable role of endogenous testosterone in lower urinary tract function and suggest that testosterone deficiency may be a pathophysiological mechanism connecting lower urinary tract symptoms and the metabolic syndrome in men.

Key Words: testosterone, insulin resistance, urinary tract, signs and symptoms

Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

BT = bioavailable testosterone

FT = calculated free testosterone

HOMA-IR = homeostasis model assessment of insulin resistance

hsCRP = high sensitivity C-reactive protein

I-PSS = International Prostate Symptom Score

LUTS = lower urinary tract symptoms

NOS = nitric oxide synthase

PSA = prostate specific antigen

QOL = quality of life

SHBG = sex hormone-binding globulin

TT = total testosterone

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In the last decade it has become clear that many of the age related health problems of men, until now treated using different medical disciplines, are actually interrelated and require a more integrative approach in the aging male. Lower urinary tract symptoms may serve as an example.

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The prevalence of LUTS increases from 8% in the fourth decade of life to more than 70% in the seventh decade, and benign prostatic hyperplasia is the most common cause of LUTS in middle-aged and elderly men.[1] The 2 factors that are generally accepted to have a role in the etiopathogenesis of BPH are aging and androgens.[1–3] While serum testosterone steadily decreases after age 40 years it has been demonstrated that 5α-reductase activity[4] and androgen receptor levels[5] increase with aging. Thus, prostatic cells may gradually become more sensitive to dihydrotestosterone during aging, which stimulates cell replication in the prostate. However, LUTS can also occur in aging men without BPH and, furthermore, the severity of LUTS secondary to BPH is not necessarily correlated with prostate volume.[6]

Recent studies have suggested that LUTS may comprise the same metabolic abnormalities as the metabolic syndrome.[7–10] One explanation for LUTS not being correlated with prostate volume is that insulin resistance, a hallmark of the metabolic syndrome, is associated with overactivity of the autonomic nervous system, which has a key role in the severity of LUTS.[7,8] Another explanation is that the presence of the metabolic syndrome might be associated with increased C-reactive protein, an indicator of intraprostatic inflammation in symptomatic BPH.[9,10] Recently testosterone deficiency has attracted attention because it is a possible risk factor for the metabolic syndrome and because preliminary evidence indicates that men with LUTS benefit from treatment with testosterone. In this study we investigated the possible association between the severity of LUTS and blood testosterone levels in men.

MATERIALS AND METHODS

A total of 278 men who visited the outpatient clinic at Chung-Ang University Hospital (Seoul) from October 2004 to July 2008 were recruited for this study. Participants were all provided informed consent in advance. Men younger than 50 years, with a malignancy or liver cirrhosis, who were taking hormones, antiandrogen agents, antifungal agents, or steroidal agents, or who had undergone surgical or medical therapy for BPH were excluded from study.

Blood samples were taken between 8:00 and 11:00 am to minimize the confounding effects of diurnal variations in serum testosterone. The blood level of serum albumin was measured with the dye binding bromocresol green method using HR II BCG kit (Wako Pure Chemical, Osaka, Japan), high sensitivity C-reactive protein by turbidimetric immunoassay using Latex Olympus System Reagent kit (Olympus Diagnostics GmbH, Hamburg, Germany) and fasting glucose by hexokinase method using Hexokinase Olympus System Reagent Kit (Olympus Diagnostics GmbH) on the same automated analyzer (AU 5421, Olympus Corp., Tokyo, Japan). Insulin and TT were measured with a chemiluminescence immunoassay kit (Siemens Healthcare Diagnostics, Los Angeles, California) on the same automated analyzer (ADVIA Centaur®). Sex hormone-binding globulin was measured by radioimmunoassay using IRMA count SHBG kit (Siemens Medical Solutions Diagnostics, Los Angeles, California) and PSA by electrochemiluminescence immunoassay using Total PSA Elecsys kit (Roche, Indianapolis, Indiana). Calculated free testosterone and bioavailable testosterone were determined using the formula derived by the International Society for Study of the Aging Male (available at www.issam.ch).

Insulin sensitivity was calculated using the homeostasis model assessment-insulin resistance index.[11] The HOMA-IR is calculated using the equation, $(I_f \times G_f/22.5)$, where I_f is fasting insulin and G_f is fasting glucose. As insulin secretion is pulsatile, we used the mean of 3 samples taken every 5 minutes after an overnight fast to measure the fasting insulin.

Demographic information and detailed medical histories, particularly of systemic diseases such as diabetes mellitus and hypertension, were obtained from all patients. The International Prostate Symptom Score, a validated 8-item questionnaire, was used to assess LUTS. The first 7 items have an ordered categorical response that can be scored from 0 to 5, with an overall score of 0 to 35. The severity of symptoms was classified as mild (7 or less), moderate (8 to 19) or severe (20 or greater). Storage symptoms scores were evaluated by summing responses to I-PSS questions 2 (frequency), 4 (urgency) and 7 (nocturia). Voiding symptoms scores were evaluated by summing responses to I-PSS questions 3 (intermittency), 5 (weak stream) and 6 (straining). Question 8 (QOL) assessed the degrees of bother and dissatisfaction associated with the symptoms with responses scored from 0 to 6.

All patients underwent digital rectal examination. Prostate length, width and height were measured with transrectal ultrasonography using a 7.5 MHz transducer (Voluson 730, ultrasound scanner A00595, transducer 14843, General Electric, Milwaukee, Wisconsin). Prostate volume was calculated using the formula for a prostate ellipsoid, $[(\pi/6) \times$ (width in maximal transverse dimension) $\times$ (length in maximal anteroposterior dimension) $\times$ (height in maximal superoinferior dimension)]. Patients with abnormal serum PSA (ie greater than 4.0 ng/ml) were referred for prostate biopsy to exclude the possibility of prostate cancer.

Correlations between parameters were first estimated using Pearson correlation coefficients. Multivariate linear regression models were then constructed to assess associations between I-PSS or voiding symptoms scores, and serum TT, FT, BT and SHBG levels, with adjustments for other covariates such as age, prostate total volume and transitional zone volume, HOMA-IR and hsCRP. We compared the 3 I-PSS severity groups with respect to age, total prostate volume, transitional zone volume, PSA, TT, FT, BT, SHBG, hsCRP and HOMA-IR using ANOVA. Associations of TT, FT, BT and SHBG with severe LUTS were analyzed by logistic regression analysis. Multivariate logistic regression models were constructed to assess associations of the presence of severe LUTS with serum TT, FT, BT and SHBG levels with adjustment for other covariates such as age, total prostate volume, transitional