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ORIGINAL ARTICLE

Prostate Disease

Association between benign prostatic hyperplasia, body mass index, and metabolic syndrome in Chinese men

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Previous studies have showed that men suffering from diabetes mellitus, metabolic syndrome (MetS) and obesity have a higher risk of benign prostatic hyperplasia (BPH). The present study aimed to examine the association between BPH, obesity, and features of MetS among men of the Hunan area of China. For this cross-sectional study, 904 males (aged 50–59 years) were included. MetS parameters, International Prostate Symptom Score (IPSS), prostate-specific antigen (PSA) levels, total prostate volume (TPV), postvoid residual volume (PVR) and maximum urine flow rate (Qmax) were measured. Results showed that MetS was associated with TPV ($P = 0.048$), PVR ($P = 0.004$) and IPSS ($P = 0.011$), but not with other indicators of BPH progression such as PSA levels or Qmax. MetS was associated with the voiding symptoms score ($P < 0.05$), but not with the storage symptom score. In addition, body mass index and fasting blood glucose positively correlated with TPV ($r = 0.416$, $P < 0.001$; and $r = 0.310$, $P = 0.011$, respectively). In conclusion, results suggest that MetS is associated with higher prostatic volume, prostate symptom score and voiding symptoms, but not with other features of prostatic hyperplasia such as PSA levels or Qmax. Changes in lifestyle factors, including physical activity and prevention of MetS, might be useful to prevent BPH and its progression, but further studies are needed.
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Keywords: benign prostatic hyperplasia; International Prostate Symptom Score; metabolic syndrome; obesity; postvoid residual; prostate volume

INTRODUCTION

Benign prostate hyperplasia (BPH) mostly affects men >45 years old and is the most common benign neoplasm in aging males, with a prevalence of about 50% in men 70–79 years old.[1] Androgens and chronic inflammation are involved in its pathogenesis.[2] BPH leads to lower urinary tract symptoms (LUTS) such as voiding symptoms, storage symptoms, and dribbling.[1,3] There are increasing evidence from clinical studies suggesting associations between LUTS and major chronic illnesses such as heart diseases, diabetes, and metabolic syndrome (MetS).[4] These evidence motivated interest in the contribution of factors outside of the urinary tract to urological symptoms, the so-called beyond-the-bladder hypothesis.[5,6]

Metabolic syndrome is a chronic systemic condition associated with a chronic inflammatory state and an increased risk of a number of diseases, including cardiovascular diseases and cancers.[7] Diagnosis of MetS is made in patients presenting a waist circumference of >90 cm and at least two of following conditions: hypertension, hyperglycemia, low high-density lipoprotein cholesterol (HDL-C) levels and/or high triglyceride (TG) levels.[7] The Third National Health and Nutrition Examination Survey[8] has indicated that men presenting three or more components of the MetS had increased odds of LUTS. Data from Sweden[9] have showed that men suffering from diabetes mellitus and obesity had a larger prostate. Men with BPH combined with MetS had a higher median annual total prostate growth rate and median annual growth rate of the transitional zone compared with BPH patients without MetS.[10] These studies suggest that MetS increases the risk of LUTS and BPH. Indeed, Gacci *et al.*[11] have suggested that MetS could be regarded as a new determinant of prostate inflammation and BPH progression. A recent meta-analysis have showed that obesity, dyslipidemia, and older age were determinants of BPH.[12]

The present study aimed to examine the association between features of MetS and BPH among men of the Hunan area of China. Using data from the Hunan area health survey, we examined the relative risk of men having three or more components of MetS as a function of the presence of BPH. Although body mass index (BMI) is not included in the definition of MetS,[7] studies have showed that obesity increases the risk of BPH.[9,13–15] Therefore, the association between components of MetS, BMI, and total prostate volume (TPV) was analyzed in the present study. A better understanding of these relationships could lead to a better prevention of prostate diseases.

MATERIALS AND METHODS

Study subjects

Between January and June 2012, 904 men (aged between 50 and 59 years) who underwent routine health examinations provided for by their employer at the Second Xiangya Hospital and Hunan People

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Hospital were included in this cross-sectional study. Patients with a history of urological disease, including urological malignancy or neurogenic bladder or urinary infection, were excluded. The study was approved by the Institutional Ethical Committee of each hospital. All included patients provided a written informed consent.

Diagnostic criteria

Patients were diagnosed with BPH according to the 2011 Chinese Guidelines for the diagnosis and treatment of prostate hyperplasia. Criteria for BPH diagnosis were: (1) males over 50 years of age; (2) complaint of urinary tract symptoms; (3) evidence of prostate enlargement on digital rectal examination; and (4) B-mode ultrasound showing a prostate volume ≥31 ml.[16]

Metabolic syndrome was diagnosed in patients presenting a waist circumference of >90 cm and at least two of the following conditions: (1) blood pressure >130/85 mmHg and/or receiving antihypertensive medications; (2) fasting blood glucose (FBG) of >100 mg dl^{-1} (5.6 mmol l^{-1}) or diagnosed with diabetes mellitus; (3) HDL-C <40 mg dl^{-1} (1.03 mmol l^{-1}) and/or receiving cholesterol-reducing medication; and/or (4) TGs >150 mg dl^{-1} (1.7 mmol l^{-1}) and/or receiving TG-reducing reducing medication.[7]

Questionnaires

The Chinese version of the International Prostate Symptom Score (IPSS) and the quality-of-life score table was used. The Chinese version of the IPSS was administered to evaluate urinary symptoms. Physical activities, alcohol consumption, smoking (pack-years), and medication for LUTS were also assessed. The questionnaires were administered by personnel specialized in urinary healthcare. The questionnaires were filled by the patients themselves. The investigators were blinded to the patient's clinical information such as TPV and other urinary symptoms.

Physical examination

A digital rectal examination was performed in all patients to detect enlargement of the prostrate. MetS assessment was made using the mean of two measures of blood pressure taken 5 min apart using a mercury sphygmomanometer on the right arm. The waist circumference was measured midway between the lowest ribs and the iliac crest to the nearest 0.1 cm. Body weight and height were measured, and BMI was calculated.

Evaluation index of prostate hyperplasia

The evaluation index of prostate hyperplasia included IPSS, serum prostate-specific antigen (PSA) levels, TPV, residual urine volume, and maximum urine flow rate (Qmax). TPV and postvoid residual (PVR) urine volume were assessed using transrectal ultrasonography. TPV was calculated as: 0.52 × anteroposterior diameter × transverse diameter × longitudinal diameter. The Qmax was assessed by uroflowmetry, voiding volume more than 150 ml.

Whole blood samples were collected in the morning (7:00AM) after an overnight fast. PSA levels were determined using radioimmunoassay. Other biochemical analyses included serum glucose, total cholesterol (TC), TGs, low-density lipoprotein cholesterol (LDL-C), and HDL-C, and were performed using an automatic biochemical analyzer.

Predicting risk factor of indicators of benign prostatic hyperplasia progression

According to the 2011 version "Guideline for urological diseases diagnosis and treatment in China,"[16] we defined the indicators of BPH progression as a TPV of ≥31 cm^3, PSA levels of ≥1.6 ng ml^{-1}, Qmax <10.6 ml s^{-1}, PVR of ≥39 ml, and IPSS ≥7.

Statistical analysis

Statistical analysis was performed using SPSS 11.0 (SPSS, Inc., Chicago, IL, USA). Patients were first divided into two groups according to the presence or absence of MetS, and then according to the number of MetS components (0, 1–2, 3, or 4–5). Chi-square tests were performed to determine whether the proportions of patients who were positive for the indicators of BPH progression were increased in the MetS groups. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were estimated using logistic regression methods to investigate the magnitude of the association between indicators of BPH progression and MetS components. Two-tailed $P < 0.05$ were considered statistically significant.

RESULTS

The demographic and baseline characteristics of participants are presented in **Table 1**. There were no differences in age, TC levels, LDL-C levels and PSA levels ($P > 0.05$). BMI, waist circumference, blood pressure, FBG, postprandial blood glucose, TG levels, and frequency of low HDL-C levels were different between subjects with/without MetS (all $P < 0.05$).

Association between metabolic syndrome and indicators of benign prostatic hyperplasia progression

The percentage of participants with TPV ≥31 cm^3 was higher in the MetS group compared with the non-MetS group (32.4% *vs* 19.5%, $P < 0.001$). In addition, the proportions of patients with PVR ≥39 ml and IPSS ≥7 were also higher in the MetS group (PVR: 28.1% *vs* 19.2%, $P = 0.004$; IPSS: 28.5% *vs* 20.6%, $P = 0.011$). However, there were no differences between the two groups for risk factors of BPH progression such as PSA ≥1.6 ng ml^{-1} and Qmax <10.6 ml s^{-1} (**Table 2**).

Correlations

Results of correlation analyses are presented in **Table 3**. IPSS was correlated with systolic blood pressure ($r = 0.257$, $P = 0.027$), waist circumference ($r = 0.288$, $P = 0.013$), BMI ($r = 0.402$, $P < 0.001$) and fasting plasma glucose (FPG) ($r = 0.552$, $P < 0.001$). TPV was correlated with diastolic blood pressure ($r = 0.226$, $P = 0.018$), BMI ($r = 0.416$, $P < 0.001$), HDL-C ($r = -0.220$, $P = 0.018$) and

Table 1: Demographic characteristics of the participants

Variable	*Value*		*P*
	Non-MetS	*MetS*	
Age (year)	54.5±6.1	55.1±5.8	0.783
BMI (kg m^{-2})	24.1±2.6	27.3±3.1	<0.05
Waist circumference (cm)	85.4±5.2	92.5±6.7	<0.05
Blood pressure			
Systolic (mmHg)	132±18	148±21	<0.05
Diastolic (mmHg)	81±12	85±16	0.058
Blood chemistry panel			
FBG (mmol l^{-1})	5.4±1.0	6.9±1.3	<0.05
2 hBG (mmol l^{-1})	6.8±2.1	7.3±2.5	<0.05
TG (mmol l^{-1})	1.8±0.7	2.3±1.1	<0.05
TC (mmol l^{-1})	4.7±1.2	5.3±1.1	0.873
HDL-C (mmol l^{-1})	1.3±0.4	1.0±0.3	<0.05
LDL-C (mmol l^{-1})	2.9±0.7	3.2±0.5	0.726
PSA (ng ml^{-1})	0.95±0.4	1.16±0.3	0.805

Data are presented as mean±s.d. BMI: body mass index; FBG: fasting blood glucose; 2 hBG: 2 h postprandial blood glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PSA: prostate-specific antigen; MetS: metabolic syndrome; s.d.: standard deviation; TG: triglyceride; TC: total cholesterol

FPG (r = 0.310, P = 0.011). PVR was correlated with systolic blood pressure (r = 0.278, P = 0.017), diastolic blood pressure (r = 0.266, P = 0.022), waist circumference (r = 0.318, P = 0.006), BMI (r = 0.424, P < 0.001), and FPG (r = 0.553, P < 0.001).

Association between the number of metabolic syndrome components and urological variables

International Prostate Symptom Score >7 was not correlated with the number of MetS components after adjustment for age (OR = 1.136, 95%CI: 0.811–1.726) or for age and testosterone levels (OR = 1.141, 95% CI: 0.824–1.733). However, TPV ≥31 ml and PVR ≥39 ml were associated with the number of metabolic abnormalities (P = 0.011 and 0.005, respectively) (**Table 4**). In addition, the age-adjusted ORs increased with the number of MetS components for TPV ≥30 ml (0: OR = 1.00; 1–2: OR = 1.583, 95%CI: 1.021–2.166; 3: OR = 1.746, 95%CI: 1.033–2.476; and 4–5: OR = 2.962, 95%CI: 1.785–4.126) and for PVR ≥39 ml (0: OR = 1.00; 1–2: OR = 1.519, 95%CI: 1.002–2.208; 3: OR = 1.906, 95%CI: 1.112–2.517; and 4–5: OR = 2.806, 95%CI: 1.562–4.375). Similar ORs were observed after adjustment for age and testosterone levels.

Table 2: Association between BPH progression predictors and MetS

Predictors of clinical BPH	*No MetS (n=651)*	*MetS (n=253)*	*P*
IPSS≥7, *n* (%)	134 (20.6)	72 (28.5)	0.011*
PSA≥1.6 ng ml^{-1}, *n* (%)	81 (12.4)	32 (12.6)	0.418
TPV≥31 cm^3, *n* (%)	127 (19.5)	82 (32.4)	<0.001*
Qmax<10.6 ml s^{-1}, *n* (%)	62 (9.5)	26 (10.3)	0.732
PVR≥39 ml, *n* (%)	125 (19.2)	71 (28.1)	0.004*

*P<0.05. MetS: metabolic syndrome; BPH: benign prostate hyperplasia; IPSS: International Prostate Symptom Score; PSA: prostate-specific antigen; TPV: total prostate volume; Qmax: maximum flow rate; PVR: postvoid residual

DISCUSSION

The aim of the present study was to assess the association between features of obesity and MetS and BPH among men of the Hunan area of China. The present study showed that MetS was associated with TPV, PVR, and IPSS. However, there was a lack of association between MetS and other indicators of BPH progression such as PSA or Qmax. An association was observed between MetS and the voiding symptom score, but not with the storage symptom score. In addition, BMI and FPG were positively correlated with TPV.

Rohrmann *et al.*[8] have defined LUTS as the presence of at least three of the following urinary symptoms: nocturia, incomplete bladder emptying, weak stream, and hesitancy; OR for LUTS was elevated in men with at least four MetS components (OR: 1.6; 95%CI: 1.0–2.6) compared with men who had fewer MetS components. Kupelian *et al.*[17] have reexamined the relationship between MetS and LUTS in 1899 men who participated in the Boston Area Community Health Survey: increased odds of MetS were observed in men with mild to severe urinary symptoms, primarily for incomplete emptying, intermittency and nocturia. These associations were stronger in men younger than 60 years compared with men aged 65 years or older. Results from the present study showed a similar association between MetS and voiding symptoms.

Possible pathophysiological mechanisms explaining the relationship between voiding symptoms and MetS include the influence of hyperinsulinemia on sympathetic activity and of hyperglycemia on the viability of parasympathetic neurons. Indeed, hyperinsulinemia is associated with increased sympathetic activity via enhanced glucose metabolism in ventromedial hypothalamic neurons.[18] This may contribute to an increased activation of the α-adrenergic pathway, which may in turn increase smooth muscle contraction in the

Table 3: Relationship of metabolic factors and BMI with a benign prostate hyperplasia progression

	SP (mmHg)	*DP (mmHg)*	*Waist (cm)*	*BMI (kg m^{-2})*	*TG (mmol l^{-1})*	*TC (mmol l^{-1})*	*HDL-C (mmol l^{-1})*	*LDL-C (mmol l^{-1})*	*FPG (mmol l^{-1})*
IPSS									
r	0.257	0.021	0.288	0.402	0.115	0.139	–0.080	0.027	0.552
P	0.027*	0.067	0.013*	<0.001**	0.329	0.238	0.498	0.817	<0.001**
TPV									
r	0.190	0.226	0.126	0.416	0.030	0.029	–0.220	0.076	0.310
P	0.090	0.018*	0.138	<0.001**	0.873	0.785	0.018*	0.565	0.011*
PVR									
r	0.278	0.266	0.318	0.424	0.096	0.119	–0.085	0.040	0.553
P	0.017*	0.022*	0.006**	<0.001**	0.415	0.312	0.473	0.732	<0.001**

*P<0.05; **P<0.01. IPSS: International Prostate Symptom Score; PVR: postvoid residual; TPV: total prostate volume; SP: systolic blood pressure; DP: diastolic blood pressure; TG: triglyceride; TC: total cholesterol; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose

Table 4: Relationship of a benign prostate hyperplasia progression with the number of components of MetS components

Variables	*No MetS[a] (n=651)*		*MetS[a] (n=253)*		*P*
	0 (n=112)	*1–2 (n=539)*	*3 (n=156)*	*4–5 (n=97)*	
IPSS≥7, *n* (%)	23 (20.6)	153 (28.4)	45 (28.8)	34 (35.1)	0.136*
OR1	1.000	1.136 (0.811–1.726)	1.257 (0.933–1.862)	1.656 (0.985–2.326)	0.133$^{\Delta}$
OR2	1.000	1.141 (0.824–1.733)	1.261 (0.938–1.873)	1.668 (0.993–2.348)	0.128$^{\Delta}$
TPV≥31 cm^3, *n* (%)	22 (19.6)	162 (30.1)	51 (32.7)	40 (41.2)	0.011*
OR1	1.000	1.583 (1.021–2.166)	1.746 (1.033–2.476)	2.962 (1.785–4.126)	0.010$^{\Delta}$
OR2	1.000	1.589 (1.018–2.171)	1.741 (1.038–2.473)	2.956 (1.779–4.118)	0.008$^{\Delta}$
PVR≥39 ml, *n* (%)	22 (19.6)	131 (24.3)	49 (31.4)	37 (38.1)	0.005*
OR1	1.000	1.519 (1.002–2.208)	1.906 (1.112–2.517)	2.806 (1.562–4.375)	0.003$^{\Delta}$
OR2	1.000	1.526 (1.008–2.216)	1.933 (1.106–2.541)	2.804 (1.569–4.432)	0.001$^{\Delta}$

[a]Number of components of MetS; *Chi-square test; $^{\Delta}$Logistic analysis. OR1: adjusted for age; OR2: adjusted for age and testosterone. MetS: metabolic syndrome; IPSS: International Prostate Symptom Score; OR: odds ratio; TPV: total prostate volume; PVR: postvoid residual

prostate, bladder neck, and urethra.[19] Hyperglycemia is associated with decreased parasympathetic activity via neuronal apoptosis.[20] An imbalance of sympathetic and parasympathetic activity may result in increased bladder neck obstruction and reduced the bladder power. The Rho kinase system plays an important role in prostate contractility[21] by modifying the calcium sensitivity of the contractile muscles.[22] Higher levels of interleukin (IL)-8 and of the vasoconstrictor endothelin-1, which are usually observed in men with MetS, may lead to an increased activity of the Rho kinase system that in turn may result in prostate contractility, inducing voiding symptoms.[23–25]

Enlargement of the prostate has been proposed as a possible link between MetS and voiding symptoms. Hammarsten *et al.*[9] have reported that men with MetS had a larger prostate volume (mean: 49.0 *vs* 28.5 ml) and a higher annual BPH growth rate (1.01 *vs* 0.69 ml per year) compared with men without MetS. Hyperinsulinemia results in an increase in insulin-like growth factor, a known prostatic mitogen, and induces a reduction in proapoptotic cascades in the prostate.[13] MetS has been associated with elevated levels of C-reactive protein as well as other inflammatory markers.[26,27] A recent study has suggested that fat and insulin increased inflammation and contributed to BPH.[28] This may reduce nitric oxide (NO) synthesis in endothelial cells.[29] The reduced prostatic NO/nitric oxide synthase activity may lead to increased smooth muscle proliferation and enlargement of the prostate. All of these changes contribute to prostate growth and increase the risk of LUTS.

Data from the present study show an association between BMI, FPG, and TPV. Possible mechanisms to explain the BMI and FPG contribution to TPV include insulin resistance, obesity-induced prostate inflammation, and sexual hormonal changes. Vikram *et al.*[15] have suggested that hyperinsulinemia-induced prostate growth could be attributed to the enhanced mitogenic activity of insulin, altered steroidal hormonal activity, increased sympathetic tone and/or perturbed endocrine levels in the prostate. Obesity induces adipose cell enlargement and chemokine release, leading to macrophage infiltration of adipose tissue.[30] Macrophage infiltration further perpetuates the proinflammatory state and may account for the adipose secretion of adipokines such as IL-1, IL-6, and IL-8.[31–33] Indeed, IL-6 and IL-8 are elevated in MetS, and may contribute to inflammation in BPH/LUTS as both can be secreted by stromal cells under cytokine stimulation, and both result in the proliferation of prostatic tissues.[34]

Obesity, particularly abdominal obesity, is associated with increased BPH risk. Abdominal obesity can affect the androgen-to-estrogen conversion process, so that the estrogen levels are increased while testosterone levels are reduced,[35] finally leading to an increased risk of occurrence of BPH. The study by Parsons *et al.*[14] have confirmed that BMI is positively correlated with TPV and that for each additional unit of BMI (1.0 kg m^{-2}), TPV increases by 0.41 ml. Furthermore, obese patients have an increased probability of prostate enlargement compared with individuals with a BMI <25 kg m^{-2}. Two large-scale studies have showed that insulin resistance and obesity were associated with PSA levels in healthy men,[36,37] underlining the fact that the MetS and obesity are associated with an increased risk of prostate diseases. Another study showed that the obesity was associated with LUTS in Korean patients with BPH.[38]

Despite the best efforts, there are limitations to the present study. First, a potential selection bias may exist because the data were collected from one area. This could be corrected in the future by performing a multicenter study. Second, we did not evaluate testosterone levels and insulin resistance indexes. This would have added a deeper understanding of the association between MetS and BPH. Third, this was a cross-sectional study. A longitudinal study would provide more answers about the influence of obesity and development of MetS on BPH.

This study strongly suggests that MetS is associated with increased TPV, prostate symptom scores, and voiding symptoms, but without association with other features of prostatic hyperplasia such as PSA or Qmax. MetS was associated with voiding symptom score but not with storage symptom score. BMI and FPG were found to be predictors of TPV >31 cm^3. Changes in lifestyle factors and physical activity might be useful and cost-effective approaches for the prevention of BPH and its progression, but further longitudinal studies are needed.

AUTHOR CONTRIBUTIONS

ZY supervised the design of the study and coordination. WS and KQZ carried out data acquisition. JMR and ZY performed data analysis. JRY provided expert assistance in andrology for data acquisition and analysis. All authors participated in manuscript drafting. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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