# Relationship between Metabolic Syndrome and Predictors for Clinical Benign Prostatic Hyperplasia Progression and International Prostate Symptom Score in Patients with Moderate to Severe Lower Urinary Tract Symptoms

Sicong Zhao,[1] Chao Chen,[1] Zongping Chen,[1] Ming Xia,[1] Jianchun Tang,[2] Sujun Shao,[3] Yong Yan[1]*

**Purpose:** To investigate the association between metabolic syndrome (MetS) and the predictors of the progression of benign prostatic hyperplasia (BPH) and the corresponding frequency and severity of lower urinary tract symptoms (LUTS).

**Materials and Methods:** A total of 530 men with moderate to severe International Prostate Symptom Score (IPSS) > 7 were recruited in the present study. The predictors for clinical BPH progression were defined as the total prostate volume (TPV) ≥ 31 cm3, prostate-specific antigen level (PSA) ≥ 1.6 ng/mL, maximal flow rate (Qmax) < 10.6 mL/s, postvoid residual urine volume (PVR) of ≥ 39 mL, and age 62 years or older. LUTS were defined according to the IPSS and MetS with the National Cholesterol Education Program-Adult Treatment Panel III guidelines. The Mantel-Haenszel extension test and the multivariate logistic regression analyses were used to statistically examine their relationships.

**Results:** The percentage of subjects with ≥ 1 predictors for clinical BPH progression, the percentage of subjects with a TPV ≥ 31 $cm^3$, the percentage of subjects with a PVR ≥ 39 mL, and the percentage of subjects with a Qmax < 10.6 mL/s increased significantly with the increasing in the number of MetS components (all $P < .05$). After adjusting for age and serum testosterone level, the MetS were independently associated with the presence of TPV ≥ 31 cm3 (OR = 17.030, 95% CI: 7.495-38.692). Moreover, MetS was positively associated with the severity of LUTS ($P < .001$) and voiding scores ($P < .001$), and each individual MetS component appeared as an independent risk factor for severe LUTS (IPSS > 19, all $P < .001$).

**Conclusion:** Our data have shown that the MetS significantly associated with the predictors for clinical BPH progression and the frequency and severity of LUTS, especially the voiding symptoms. The prevention of such modifiable factors by promotion of dietary changes and regular physical activity practice may be of great importance for public health.

**Keywords:** metabolic syndrome X/complications; prostatic hyperplasia/pathology; humans; male; prostate/pathology; urination.

## INTRODUCTION

Benign prostatic hyperplasia (BPH) and secondary lower urinary tract symptoms (LUTS) are high prevalence public health problems that have been well described in elderly men. BPH, which is characterized by enlargement of prostatic glandular tissue and narrowing of the urethra, affects 70% of US men at the age of 60-69 years and 80% of those at the age of 70 years.[(1)] The clinical progression of BPH could results in acute urinary retention, renal insufficiency, recurrent urinary tract infection, urinary incontinence, and the need for BPH-related surgery.[(2,3)] Apparently these complications can affect the quality of life and increase the medical expenses of the elderly.

Metabolic syndrome (MetS) is a cluster of metabolic disorders that increased the risk of cardiovascular diseases and type 2 diabetes mellitus, which associated with central obesity, dyslipidemia, hyperglycemia, elevated blood pressure, and insulin resistance.[(4)] Recent years, emerging studies have suggested that MetS is correlated with BPH/LUTS in different countries.[(5,6)] To date, a positive correlation between MetS and prostate volume

[1] Department of Urology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China.

[2] Department of Cardiology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China.

[3]Department of Physical Examination Center, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China.

*Correspondence: Department of Urology, Beijing Shijitan Hospital, Capital Medical University, 10 Tieyi Road, Haidian District, Beijing 100038, China.

Tel: +86 010 63926667. Fax: +86 010 60298651. E-mail: yyshijitan@126.com.

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growth rate has been emphasized in clinical series.[7,8] However, little is known about the relationship between MetS and the progression of BPH. Furthermore, most studies exclusively focused on the correlation between MetS and prostate volume or prostate growth rate, without exploring the corresponding frequency and severity of LUTS with MetS. A recent systematic review identified eight eligible studies showing the role of MetS in the development of BPH.[9] Unfortunately, only the correlation between MetS and prostate volume has been assessed, without strong available evidence regarding the severity of LUTS.

In order to investigate the association between MetS and the predictors of the progression of BPH and the corresponding frequency and severity of LUTS, we carefully assessed the relationship between MetS and the predictors for clinical BPH progression and the overall IPSS in patients with moderate to severe LUTS in Chinese male population. We believe a better understanding of these relationships could lead to a better prevention of prostate diseases.

## MATERIALS AND METHODS

### *Study Subjects*

The institutional review board of the Beijing Shijitan Hospital approved the present study in September 2014. From October 2014 to December 2014, 871 community elderly male residents who had an International Prostate Symptom Score (IPSS) > 7, and had consecutively participated in prostate health examinations at the Beijing Shijitan Hospital were recruited in the present study. To minimize potential confounding factors and bias, the participants who had a former history of prostate or urethral surgery and those who had been diagnosed with urologic diseases, including urethral stricture, urologic infections, malignancy, or neurogenic bladder or who had been administrated drugs including anticholinergics, 5α-reductase inhibitors, phosphodiesterase-5 inhibitors and hormone replacement therapy, were excluded from the study. In summary, 86 men suffered one or several of the above conditions. Sixteen men refused to undergo a transrectal ultrasound examination of the prostate. Eleven men did not finish the IPSS questionnaire. Moreover, 196 patients taking BPH-related medications and 32 patients were diagnosed with prostate cancer by prostate biopsy. Finally, the remaining 530 participants were included in the present study. The dedicated informed consents were obtained from all subjects before enrolling.

### *BPH/LUTS Assessment*

The subjects' medical histories were collected using a standardized structured questionnaire. The Chinese version of the International Prostate Symptom Score (IPSS) was administered to the subjects to evaluate urinary symptoms. As proposed in the Boston Area Community Health (BACH) survey,[5] IPSS was both considered as a continuous and categorical variable, stratifying subjects as none/mild (0-7), moderate[8-19], and severe (20-35). LUTS were further categorized as voiding (incomplete emptying, weak stream, intermittency, straining) and storage (frequency, urgency and nocturia) and dichotomized as 5 or greater vs. less than 5 for voiding and 4 or greater vs. less than 4 for storage. The postvoid residual urine volume (PVR) and total prostate volume (TPV) were measured using transrectal ultrasonography, and TPV was calculated using the prolate ellipse formula (transverse × anteroposterior × cephalocaudal diameter × π/6). The maximum urinary flow rate (Qmax) was determined by uroflowmetry at a voided volume of > 150 mL. The serum prostate-specific antigen (PSA) levels were collected in the morning after an overnight fast and determined using radioimmunoassay. The serum testosterone was determined by automatic electrochemiluminescence immunoassay. All subjects underwent digital examinations of the rectum to exclude palpable prostatic nodules. According to results from the placebo-arm study of the Medical Therapy of Prostatic Symptoms study (MTOPS),[10] the defined predictors for clinical BPH progression including a TPV ≥ 31 $cm^3$, Qmax < 10.6 mL/s, PSA ≥ 1.6 ng/mL, PVR ≥ 39 mL and age 62 years or older.

### *Definition of Metabolic Syndrome*

Anthropometric measurements were measured by trained nurses using a standardized protocol. The waist circumference (WC) was measured from midway between the lowest rib and the iliac crest to the nearest 0.1 cm. Two blood pressure (mm Hg) measurements were obtained 5 minutes apart using a mercury sphygmomanometer on the right arm and the values were averaged. Body weight (kg) and height (cm) were measured. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of height (m). Blood specimens were obtained with the subjects in the fasting state at the same time as PSA and serum testosterone levels. The biochemical analyses included fasting plasma glucose (FPG), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC). All laboratory parameters were measured on fresh serum obtained after a 12-hour overnight fast, when the patient had been sedentary in a sitting or supine position for 15 minutes. The MetS was diagnosed using the 2005 National Cho-

**Table 1.** Patients' characteristics according to the presence or absence of metabolic syndrome.

| Variables | Overall (n = 530) | MetS (n = 200) | Non-MetS (n = 330) | *P* Value |
|---|---|---|---|---|
| Age (yeas) | 65 (58-75) | 61 (54-73) | 67 (60-76) | < .001* |
| Testosterone (ng/mL) | 3.4 (3.2-3.7) | 3.2 (3.0-3.3) | 3.6 (3.4-3.8) | < .001* |
| BMI (kg/m2) | 25.1 (23.3-27.1) | 27.2 (25.3-29.0) | 24.0 (22.2-25.6) | < .001* |
| Waist (cm) | 88 (82-94) | 94 (90-99) | 85 (80-89) | < .001* |
| SBP (mmHg) | 136 (126-147) | 139 (131-149) | 134 (122-146) | < .001* |
| DBP (mmHg) | 81 (74-87) | 84 (76-90) | 79 (72-84) | < .001* |
| FPG (mg/dL) | 96.5 (89.3-109.8) | 104.6 (94.4-116.3) | 93.4 (88.2-101.5) | < .001* |
| Triglycerides (mg/dL) | 110.3 (81.9-169.6) | 180.5 (124.6-234.7) | 93.5 (69.7-122.8) | < .001* |
| HDL-C (mg/dL) | 47.2 (40.0-55.2) | 39.6 (35.3-46.0) | 51.8 (44.8-59.6) | < .001* |
| LDL-C (mg/dL) | 110.5 (88.1-131.8) | 114.0 (94.3-132.8) | 109.2 (86.2-131.1) | .167 |
| TC (mg/dL) | 183.0 (158.6-204.6) | 186.7 (165.0-204.6) | 181.3 (156.0-204.1) | .347 |
| MetS (%) | 37.7 (200/530) | - | - | - |
| TPV (cm3) | 26.6 (23.1-31.2) | 32.6 (28.4-36.8) | 23.9 (22.1-26.4) | < .001* |
| IPSS | | | | |
| Total score | 13 (11-16) | 16 (13-17) | 12 (11-14) | < .001* |
| 8-19 (%) | 94.2 (499/530) | 85.5 (171/200) | 99.4 (328/330) | < .001 |
| 20-35 (%) | 5.8 (31/530) | 14.5 (29/200) | 0.6 (2/330) | - |
| Voiding | 8 (6-12) | 11 (8-13) | 7 (5-9) | < .001* |
| ≥ 5 (%) | 89.2 (473/550) | 97.0 (194/200) | 84.5 (279/330) | < .001 |
| Storage | 5 (3-7) | 5 (3-7) | 5 (3-7) | .912 |
| ≥ 4 (%) | 68.7 (364/550) | 67.5 (135/200) | 69.4 (229/330) | .649 |
| Qmax (mL/s) | 16.9 (7.7-18.8) | 17.1 (7.7-18.8) | 16.8 (7.7-18.8) | .763 |
| PSA (ng/mL) | 0.73 (0.43-1.06) | 1.16 (1.00-1.58) | 0.50 (0.34-0.68) | < .001* |
| PVR (mL) | 34.6 (29.5-40.5) | 37.8 (31.7-42.5) | 32.6 (27.2-39.5) | < .001* |

**Abbreviations:** BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; MetS, metabolic syndrome; TPV, total prostate volume; IPSS, International Prostate Symptom Score; Qmax, maximum urinary flow rate; PSA, prostate-specific antigen; PVR, postvoid residual urine volume; AUR, acute urinary retention.

* Kruskal-Wallis 1-way analysis of variance.

•chi-squared test.

*P* value < .05 was considered statistically significant.

lesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria for Asian Americans.[11] The modified NCEP-ATP III has defined the MetS as the simultaneous occurrence of at least 3 of the following 5 risk factors: (1) waist circumference ≥ 90 cm, (2) triglycerides ≥ 150 mg/dL or drug treatment for elevated triglycerides, (3) high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL or drug treatment for reduced HDL-C, (4) blood pressure ≥130/85 mmHg or antihypertensive drug treatment with a history of hypertension, (5) fasting plasma glucose (FPG) ≥ 100 mg/dL or drug treatment for elevated glucose.

### *Statistical Analysis*

Evaluation of data distribution showed a skewed distribution of the data set. Differences between groups of subjects in medians (IQR) for quantitative variables and differences in distributions for categorical variables were tested with the Kruskal-Wallis 1-way analysis of variance and chi-square tests. We stratified subjects into 6 groups according to the number of metabolic components they met (0, 1, 2, 3, 4 and 5). The Mantel-Haenszel extension and chi-square tests were introduced to determine whether the percentage of subjects who were positive of predictors for clinical BPH progression increased with the increasing in the number of metabolic components. Multivariate logistic regression analyses adjusted for potential confounders (age and serum testosterone level) were performed to

**Table 2.** Association between number of metabolic components and predictors for clinical BPH progression.

| Predicators | Overall | Components of Metabolic Syndrome (n) | | | | | | *P* Value* |
|---|---|---|---|---|---|---|---|---|
| | (n = 530) | 0 (n = 49) | 1 (n = 148) | 2 (n = 133) | 3 (n = 121) | 4 (n = 55) | 5 (n = 24) | |
| ≥ 1 predictor (%) | 89.4 | 73.5 | 81.1 | 91.7 | 96.7 | All | All | < .001† |
| Age ≥ 62 years (%) | 58.9 | 63.3 | 57.4 | 57.9 | 59.5 | 63.6 | 50.0 | .865 |
| TPV ≥ 31 cm3 (%) | 25.7 | 12.2 | 16.2 | 18.8 | 37.2 | 40.0 | 58.3 | < .001† |
| Qmax <10.6 mL/s (%) | 31.5 | 18.4 | 26.4 | 33.8 | 33.9 | 41.8 | 41.7 | .032† |
| PSA ≥ 1.6 ng/mL (%) | 9.2 | None | None | None | 28.9 | 23.6 | 16.7 | .410 |
| PVR ≥ 39 mL (%) | 33.8 | 6.1 | 10.8 | 26.3 | 56.2 | 63.6 | 91.7 | < .001† |

**Abbreviations:** TPV, total prostate volume; Qmax, maximum urinary flow rate; PSA, prostate-specific antigen; PVR, postvoid residual urine volume.
* Mantel-Haenszel extension test.
† Statistically significant difference ($P < .05$).

assess the association of MetS and its components with each predictor for clinical BPH progression, and the association between each individual MetS component and the severity of LUTS and the specific risk of voiding and storage symptoms. Multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were simultaneously estimated by logistic regression analyses. Differences were considered statistically significant by a two-tailed *P* value of < 0.05. Statistical analyses were performed using Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 13.0 for windows (SPSS Inc., Chicago, IL, USA).

## RESULTS

### *Patients Characteristics*

The characteristics of our study population are listed in **Table 1**. The median age was 65 years (IQR, 58-75 years), and the median serum testosterone level was 3.4 ng/mL (IQR, 3.2-3.7 ng/mL). The median BMI was 25.1 kg/m2 (IQR, 23.3-27.1 kg/m2) and approximately 16.2% (86/530) were obese (BMI ≥ 28 kg/m$^2$). Of the 530 patients, 37.7% (200/530) had MetS. LUTS were considered as moderate and severe in 94.2% (499/530) and 5.8% (31/530) of subjects, respectively. The median voiding and storage scores were 8 (IQR, 6-12) and 5 (IQR, 3-7), respectively. BMI, IPSS, TPV, PVR, and PSA levels were higher and serum testosterone levels were lower in the MetS group than in the non-MetS group (all $P < .001$). We found a strong positive association between the present of MetS and LUTS severity for overall IPSS and voiding scores. The median IPSS was greater by approximately 4 points in subjects with MetS, and men more frequently had severe LUTS symptoms in subjects with MetS ($P < .001$). Voiding scores were increased by 57% in subjects with MetS as compared with those without MetS, and men more frequently had a voiding score ≥ 5 in subjects with MetS ($P < .001$). However, there were no statistically significant association between MetS and Qmax and storage scores.

### *Association between Number of Mets Components and Predictors for Clinical BPH Progression*

As shown in **Table 2**. A total of 474 patients (89.4%) had at least 1 predictors of the risk of clinical progression of BPH. The percentage of subjects with ≥ 1 predictors for clinical BPH progression, the percentage of subjects with a TPV ≥ 31 cm$^3$ and the percentage of subjects with a PVR ≥ 39 mL, all significantly increased as the number of MetS components increased (All $P < .001$). On the other hand, although the median Qmax was not associated with the presence of MetS, the percentage of subjects with a Qmax < 10.6 mL/s also increased significantly with the increase in the number of MetS components (P = .032). Notably, even for patients who did not meet the criteria of MetS diagnosis (with < 3 MetS components), a significant difference in the percentage of subjects with ≥ 1 predictors for clinical BPH progression was also observed among patients with 1 or 2 components compared with those without any components of MetS (0 vs. 1-2, 73.5% vs. 86.1%; chi-square test, $P = .025$; data not shown). However, the percentage of subjects with a PSA ≥ 1.6 ng/mL or age ≥ 62 years did not associated with the number of MetS components.

Association of Mets and Its Components with Each Predictor for Clinical BPH Progression

After adjusting for age and serum testosterone level, the MetS, waist circumference and FPG level were independently associated with the presence of TPV ≥ 31 cm3 (OR = 17.030, 95% CI: 7.495-38.692; OR = 1.101, 95% CI: 1.014-1.195; and OR = 1.011, 95% CI: 1.001-1.021, respectively, (**Table 3**). In addition, the presence of PVR ≥ 39 mL showed an independent positive asso-

**Table 3.** Association of metabolic syndrome and its components with each predictor for clinical benign prostatic hyperplasia progression.

| | TPV ≥ 31 cm$^3$ | | | Qmax 10.6 mL/s | | | PSA ≥ 1.6 ng/mL | | | PVR ≥ 39 mL | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Factors | OR | 95% CI | *P* value* | OR | 95% CI | *P* value* | OR | 95% CI | *P* value* | OR | 95% CI | *P* value* |
| WC | 1.101 | 1.014-1.195 | .021† | 1.010 | 0.950-1.074 | .748 | 0.968 | 0.882-1.061 | .485 | 1.075 | 1.009-1.145 | .025† |
| SBP | 1.008 | 0.987-1.028 | .458 | 1.007 | 0.992-1.022 | .369 | 1.004 | 0.981-1.029 | .712 | 1.002 | 0.987-1.017 | .775 |
| DBP | 1.002 | 0.974-1.031 | .875 | 0.983 | 0.961-1.005 | .119 | 0.975 | 0.941-1.010 | .164 | 1.005 | 0.983-1.027 | .659 |
| FPG | 1.011 | 1.001-1.021 | .031† | 0.999 | 0.992-1.007 | .864 | 0.988 | 0.986-1.011 | .815 | 1.003 | 0.996-1.010 | .447 |
| TG | 1.000 | 0.998-1.002 | .998 | 0.999 | 0.997-1.002 | .496 | 1.000 | 0.996-1.004 | .970 | 1.000 | 0.998-1.002 | .978 |
| HDL-C | 0.980 | 0.951-1.009 | .172 | 0.997 | 0.978-1.016 | .752 | 1.008 | 0.980-1.038 | .571 | 0.998 | 0.979-1.018 | .837 |
| MetS | 17.030 | 7.495-38.692 | <.001† | 0.998 | 0.572-1.742 | .995 | 0.473 | 0.192-1.161 | .102 | 1.670 | 0.962-2.900 | .068 |

**Abbreviations:** OR, odds ratio; CI, confidence interval; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; Qmax, maximum flow rate; TPV, total prostate volume; PSA, prostate-specific antigen; PVR, postvoid residual urine volume.

* Multivariate logistic regression analysis, adjusted for age and serum testosterone.

† Statistically significant difference ($P < .05$).

ciation with waist circumference (OR = 1.075, 95% CI: 1.009-1.145).

### *Association of Each Mets Component with the Severity of LUTS*

The association between each individual component of MetS and LUTS is shown in Table 4. There was a positive association between each individual MetS component and the presence of severe LUTS (IPSS>19, all $P < .001$). Moreover, blood pressure and FPG level were independently associated with a voiding scores ≥ 5 (OR = 2.993, 95% CI: 1.539-5.820; and OR = 3.074, 95% CI: 1.419-6.657, respectively) in multivariate logistic regression analyses. However, there was no statistically significant association between any individual MetS component and a storage scores ≥ 4.

## DISCUSSION

This is the first study to investigate the association between MetS and the predictors for clinical BPH progression and overall IPSS in patients with moderate to severe LUTS in Chinese male population. We found that the percentage of subjects with predictors for the progression of BPH significantly increased as the number of MetS components increased, and the specific MetS component were independently associated with predictors of BPH progression after adjusting for age and serum testosterone level. We also found a strong positive association between the present of MetS and LUTS severity for overall IPSS and voiding scores, and there was a positive association between each MetS component and the presence of severe LUTS. Moreover, blood pressure and FPG level were independently associated with a voiding scores ≥ 5.

MetS is a complex and widespread epidemic disorder with a high socio-economic impact, due to its association with increased morbidity and mortality. To date, a positive link between MetS and prostate volume growth rate has been emphasized in clinical series.[7,8] Although the exact pathophysiology linking MetS and BPH/LUTS remains unknown, there are several hypotheses were introduced to depict this association, including the insulin growth factor pathway, leading to prostate cells growth and proliferation, the chronic prostatic inflammation, leading to the development of BPH nodules, and pelvic atherosclerosis, leading to chronic ischemia of the bladder and prostate, which can result in structural and functional impairment.[12] These mechanisms might still exist after BPH/LUTS development and could continuously affect the clinical progression of BPH. Therefore, it is important to identify whether and how the MetS-related events contribute to the clinical progression of BPH.

In the present study, we found that fasting glucose level and central obesity (waist circumference) were associated with a TPV ≥ 31 cm3. These results are in close agreement with numerous former studies. Initially, Hammarsten and colleagues[13] found correlations between the annual prostate growth rates, MetS, and fasting plasma insulin levels and concluded that BPH might be an insulin resistance-related disorder, and this founding is supported by the study of Dahle and colleagues,[14] that a high correlation was found between hyperinsulinemia and the median prostate growth rate in a 280 patients' cohort. A recent report demonstrated that diet-induced insulin resistance and compensatory elevated plasma insulin resulted in increased cellular proliferation, prostate enlargement and reduced prostate

**Table 4.** Association of each metabolic syndrome component with the severity of LUTS.

| Variables | Waist Circumference ≥ 90 cm | | | SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg | | | Fasting Plasma Glucose ≥ 100 mg/dL | | | Triglycerides ≥ 150 mg/dL | | | High-Density Lipoprotein Cholesterol < 40 mg/dL | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Yes, % | No, % | *P* value• | Yes, % | No, % | *P* value• | Yes, % | No, % | *P* value• | Yes, % | No, % | *P* value• | Yes, % | No, % | *P* value• |
| IPSS | | | < .001† | | | < .001† | | | < .001† | | | < .001† | | | < .001† |
| 8-19 | 88.2 | 98.7 | | 91.8 | 100 | | 89.4 | 97.4 | | 86.1 | 97.8 | | 83.3 | 97.5 | |
| 20-35 | 11.8 | 1.3 | | 8.2 | 0 | | 10.6 | 2.6 | | 13.9 | 2.2 | | 16.7 | 2.5 | |
| Voiding | OR = 1.926 | | | OR = 2.993 | | | OR = 3.074 | | | OR = 2.508 | | | OR = 0.945 | | |
| ≥ 5* | 95% CI: 0.762-4.870 | | | 95% CI: 1.539-5.820 | | | 95% CI: 1.419-6.657 | | | 95% CI: 0.951-6.611 | | | 95% CI: 0.388-2.298 | | |
| | *P* = .166 | | | *P* = .001† | | | *P* = .004† | | | *P* = .063 | | | *P* = .900 | | |
| Storage | OR = 0.725 | | | OR = 1.076 | | | OR = 0.862 | | | OR = 1.150 | | | OR = 1.192 | | |
| ≥ 4* | 95% CI: 0.402-1.307 | | | 95% CI: 0.689-1.680 | | | 95% CI: 0.568-1.308 | | | 95% CI: 0.681-1.941 | | | 95% CI: 0.713-1.993 | | |
| | *P* = .285 | | | *P* = .747 | | | *P* = .485 | | | *P* = .601 | | | *P* = .04 | | |

**Abbreviations:** OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; IPSS, International Prostate Symptom Score.
• chi-squared test.
* Multivariate logistic regression analysis, adjusted by age, serum testosterone level, body mass index, total prostate volume, postvoid residual urine volume and serum prostate-specific antigen level.
† Statistically significant difference (*P* < .05).

atrophy and apoptosis in rats.[15] As considered to be the core pathophysiology of MetS, insulin resistance leads to secondary hyperinsulinemia in order to maintain glucose homeostasis. Increased fasting glucose levels are likely to be accompanied by hyperinsulinemia which stimulates the liver and then, results in an increase in free biologically active IGF-1 (insulin-like growth factor, a known prostatic mitogen) levels and induces a cluster of disorders such as central obesity, increased IGF-1 favor prostate gland growth and lead to prostatic enlargement.[16] On the other hand, central obesity may play a key role in the pathogenesis of MetS. Although the pathophysiology is incompletely understood, the role of fatty adipose tissue has been assumed by the fact that an excess of fatty acids and cytokines may induce insulin resistance and compensatory hyperinsulinemia. In a retrospective study of 409 men aged ≥ 40 years, as the waist circumference increased from < 90 cm to 90-99 cm to ≥ 100 cm, the likelihood of an increased prostate volume was greater after adjusting for age (OR = 1.39, *P* = .01).[17] Moreover, Parsons and colleagues(18) have confirmed that men above the 50th percentile of waist circumference (i.e. 96.5 cm) had increased risk of prostate enlargement compared with those below this threshold (OR = 1.58; 95% CI: 1.06-2.36), in addition, they also found that men with increased fasting glucose levels were three times more likely to have prostate enlargement than those with normal levels. In accordance with the aforementioned results, our data confirms that insulin resistance is an important etiologic link between MetS and the increased risk of BPH.

Additionally, we found that central obesity (waist circumference) correlated with a PVR ≥ 39 mL. A recent epidemiological study[19] from Europe of 4666 participants showed a positive correlation between waist circumference and IPSS. However, no data concerning the PVR were included in that study. To our knowledge, this is the first study suggesting an association between waist circumference and PVR. There is a pathophysiology known to be associations between central obesity and PVR. Central obesity can affect the androgen-Estrogen conversion process, so that obese patients often have relatively lower levels of testosterone.[20] Ehrén and colleagues[21] has suggested that nitric oxide may influence the dilation of the bladder neck. Testosterone modulates nitric oxide (NOS) activity; thus we can speculate that low levels of testosterone may possibly inhibit bladder neck dilation by regulating the NOS metabolism. Consequently, this mechanism might influence the relationship between central obesity and a PVR ≥ 39 mL in patients with moderate to severe LUTS in the present study. Recent data[22,23] have, indeed, suggested that low testosterone might be an additional MetS component that induces urinary tract diseases, and this hypothesis is also supported by our data (3.2 vs. 3.6 ng/mL, *P* < .001; Kruskal-Wallis 1-way analysis of variance).

Unfortunately, despite the importance of the public

health impact of these two pathologies, correlation between MetS and BPH/LUTS has not been thoroughly studied. A recent systematic review identified eight eligible studies showing the role of MetS in the development of BPH,[9] whereas only the correlation between MetS and prostate volume has been assessed, without strong available evidence regarding the frequency and severity of LUTS. Theoretically LUTS are considered as a substitute for the course of BPH and often resulting from an enlarged prostate and heightened tone of the prostate and bladder smooth muscle. To our knowledge, we have firstly evaluated the relationship between MetS and the overall IPSS in patients with moderate to severe LUTS. In addition we also investigated the role of each individual MetS component in this potential relationship. In the present study, participants with MetS had a higher IPSS score and voiding score ($P < .001$; $P < .001$, respectively), and there was a positive association between each individual MetS component and the presence of severe LUTS (IPSS > 19, all $P < .001$). Moreover, blood pressure and fasting glucose level were independently associated with a voiding score ≥ 5 (OR = 2.993, 95% CI: 1.539-5.820; and OR = 3.074, 95% CI: 1.419-6.657, respectively). In the Third National Health and Nutrition Examination Study (NHANES III),[24] where of 2372 male participants, those with at least 3 components of MetS were at 80% increased risk for LUTS defined as a report of 3 or 4 urologic symptoms in men aged ≥ 60 years compared with those without any components (OR = 1.6; 95% CI: 1.0-2.6). Similarly, BACH survey(5) showed a statistically significant association between MetS and mild to severe LUTS (multivariate OR = 1.68, 95% CI: 1.21-2.35), the prevalence of MetS were lowest (about 20%) for men reporting no symptoms or 1 symptom and increased with mild LUTS (AUA-SI) to approximately 40%, and a statistically significant association was also observed between MetS and a voiding score ≥ 5 (multivariate OR = 1.73, 95% CI: 1.06-2.80) but not for a storage score ≥ 5 (multivariate OR = 0.94, 95% CI: 0.66-1.33). Results of the present study strengthen the evidences that MetS correlates with the severity of LUTS, especially the voiding symptoms.

Possible pathophysiological mechanisms to explain the relationship between MetS and LUTS include the influence of sustained hyperglycemia on the viability of parasympathetic neurons in the pelvic ganglion. Animal studies have shown that long-term increased serum glucose induces neuronal apoptosis that favors parasympathetic neuron compared to sympathetic neuron.[25] Such an unbalanced loss of autonomic neurons might induce an oversupply of sympathetic tone compared to parasympathic efferent activity. In addition, hypertension is also known to be associated with increased sympathetic tone and α1-adrenoceptor function.[26,27] Therefore, it is presumed that an increased sympathetic tone may result in increased bladder neck obstruction and reduced bladder power. Taken together, these changes could collaboratively culminate in increased voiding symptoms as reported in the present study. In addition, the Rho kinase system plays an important role in prostate contractility by modifying the calcium sensitivity of the contractile muscles.[28,29] 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, including voiding symptoms.[30-32] In a former clinical study, doxazosin, an α-blocker used for symptomatic prostatic hyperplasia treatment, was shown to increase insulin sensitivity and reduce insulin levels.[33]

However, a few studies do not support the association between MetS and LUTS. Gao and colleagues[34] retrospectively evaluated the effect of MetS on the severity of LUTS with data from a healthy and examination survey project in China, they concluded that no significant were found in the severity of LUTS in men with or without MetS. However, their study is difficult to compare with our results as they took the whole man population as the study objects, regardless of whether or not there was a concomitant BPH existed, and their subjects are younger (median age were 39 vs. 65 of the present study) and less symptomatic (92.1% participants with mild LUTS). Even so, their study found moderate or severe storage symptoms were inversely correlated with MetS. The same considerations are also valid for similar studies performed in an Asian population where no significant differences were found in the severity of LUTS between the MetS and non-MetS group.[35]

Our finding certainly need further confirmatory studies, but once confirmed, would raise a number of questions regarding the different components of MetS such as central obesity, diabetes and hypertension, multiple serum hormone alterations including testosterone, and insulin resistance that may promote the development and progression of BPH and specifically the voiding symptoms in patients with moderate to severe LUTS. Our data suggests that improved clinical attention, including finding the BPH progression, prescribing a combination of α-blockers and 5α-reductase inhibitors to reduce BPH progression, and more detailed counseling concerning the prognosis of BPH/LUTS, is needed for

patients with the MetS and BPH/LUTS. The sixth national census of China in 2010 showed that 13.26% of the Chinese population was older than 60 years. With the arriving of aging society, the predicted increase in the proportion of elderly people in future years means that the prevalence of BPH/LUTS and costs of treatment will continue to increase, thus Chinese urologists confronted with challenges of applying early intervention or cost-effective approaches for urinary tract diseases at a relatively low medical expenses. A recent meta-analysis of eleven studies found that physical activity decreases the risk of BPH by as much as 25% relative to a sedentary lifestyle.[36] Indeed, Gacci and colleagues[37] have suggested that MetS could be regarded as a new determinant of BPH/LUTS.

Despite the best efforts, some potential limitation in the present study should be considered. First, we acknowledge that the results of our study are only hypotheses generated, and we have already organized a multicenter longitudinal confirmatory study with other urology centers involved in China. Second, a potential selection bias was present because our study included only subjects from a single institution, which could also be improved by performing the multicenter study in the future, which is in progress indeed, as conducted by the Department of Urology Research Institute of Peking University. Another possible limitation was the use of self-report IPSS questionnaires for assessing the severity of LUTS. This may introduce a potential response bias, as respondents may inaccurately report their urinary symptoms. However, the questionnaires selected for this study have all been formerly validated in clinical and nonclinical samples and are used worldwide. Finally, we did not evaluate insulin levels and insulin resistance indexes, while former studies have suggested a significant association of insulin resistance or hyperinsulinemia with the prostate volume.[6,33]

## CONCLUSIONS

At the present of time, this is the largest contemporary prospective series evaluating the association between MetS and the predictors for clinical BPH progression and the overall IPSS in patients with moderate to severe LUTS. We found that MetS significantly associated with the predictors for clinical BPH progression and the corresponding frequency and severity of LUTS, especially the voiding symptoms. The prevention of such modifiable factors by promotion of dietary changes and regular physical activity practice may be of great importance for public health. Further investigations with long-term follow-up are needed to better understand the role of MetS as a potential risk factor for BPH/LUTS progression and to identify new possible therapeutic targets and open novel strategies for the management of BPH/LUTS.

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## CONFLICT OF INTEREST

None declared.

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