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Impact of Metabolic Syndrome on Benign Prostatic Hyperplasia in Elderly Chinese Men

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Key Words

Benign prostatic hyperplasia · Metabolic syndrome · Lower urinary tract symptoms · Prostate volume · Insulin resistance

Abstract

Objective: The aim of the present study was to evaluate the impact of metabolic syndrome (MetS) on benign prostatic hyperplasia (BPH) in elderly Chinese men. ***Methods:*** A total of 401 elderly BPH patients were divided into the without or with MetS group to assess the associations of MetS and components of MetS with BPH. Urologic evaluation included prostate volume, International Prostate Symptom Score, serum prostate-specific antigen, duration of concomitant lower urinary tract symptoms (LUTS) and maximum flow rate. ***Results:*** Body mass index (BMI), waist circumference, fasting glucose, glycosylated hemoglobin, triglyceride, fasting insulin (FINS), insulin resistance assessed by homeostasis model assessment (HOMA-IR) were greater and high-density lipoprotein cholesterol (HDL-C) was lower in BPH patients with MetS than in those without MetS. The patients with MetS showed a significantly larger prostate volume ($p = 0.000$) and longer duration of LUTS ($p = 0.006$) than those without MetS. Prostate volume was positively correlated with BMI ($p = 0.000$), FINS ($p = 0.001$), HOMA-IR ($p = 0.003$) and inversely correlated with HDL-C ($p = 0.000$). Multiple linear regression analysis showed that prostate volume was significantly correlated with HOMA-IR ($p = 0.015$). ***Conclusions:*** Our results suggest that MetS, BMI, low HDL-C level, increased serum insulin and especially insulin resistance are considered risk factors for prostate enlargement in elderly Chinese men.

Introduction

Benign prostatic hyperplasia (BPH) and concomitant lower urinary tract symptoms (LUTS) are obvious public health problems with a high prevalence that have been well described in older 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 or older [1]. LUTS can induce irritative and obstructive symptoms and are generally regarded as indirect measures of clinical BPH. The etiology of BPH caused by nonmalignant cell proliferation in the prostate gland is not well understood. The known etiologic factors of BPH are aging and androgen metabolism [2]. There is also evidence that metabolic disorders play a role in promoting the development of pathological and clinical prostatic hyperplasia [3–7]. Metabolic syndrome (MetS) is a cluster

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of metabolic disorders increasing the risk of cardiovascular diseases and type 2 diabetes mellitus, associated with obesity, dyslipidemia, hyperglycemia, elevated blood pressure and insulin resistance. The prevalence of MetS increases with age, and people aged 70–79 years are 2–4 times more likely to have MetS compared with those aged 30–39 years [8]. Some studies have demonstrated a further increase in prostate growth or larger prostate volume in BPH patients with MetS [3–5]. Metabolic disorders are associated with an increased risk of LUTS secondary to ensuing clinical prostatic enlargement [6, 7].

At present, the impacts of MetS on BPH remain unknown in elderly Chinese men. The aim of the present study was to investigate the possible associations among BPH, LUTS and MetS in elderly Chinese patients.

Patients and Methods

Study Patients

From February 2009 to March 2012, 761 BPH patients older than 60 years who admitted to our geriatrics outpatient clinic were enrolled in our investigation. BPH was defined as a prostate volume >20 ml. Patients who had a previous history of prostate or urethral surgery and those with other conditions, such as prostate cancer, bladder cancer, bladder stone, Parkinson's disease, acute or chronic inflammation, serious liver and kidney dysfunction, serious cardiovascular disease and insulin use, were excluded from the study. 97 men suffered from one or several of these conditions. 70 patients refused to undergo a transrectal ultrasound examination of the prostate gland, and 14 patients did not finish the International Prostate Symptom Score (IPSS) questionnaire. In addition, 179 patients taking medications for BPH were not selected. The remaining 401 patients were included in this study.

Data Collection

A physical examination with the assessment of height, weight, waist circumference and blood pressure was performed. The body mass index (BMI) was calculated as body weight in kilogram divided by the square of body height in meters. Blood samples were drawn from patients after fasting for 10 h to determine the levels of serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting insulin (FINS), glycosylated hemoglobin (HbA1c), fasting glucose and prostate-specific antigen (PSA). Testosterone and estradiol were determined by automatic electrochemiluminescence immunoassay with cobas e411 (Hitachi High-Technologies Corporation, Tokyo, Japan). A detailed medical history and the self-reported duration of LUTS were recorded. The symptoms of LUTS were assessed using the IPSS. Each subject was asked to complete the IPSS questionnaire, which includes seven questions covering frequency, nocturia, weak urinary stream, hesitating, intermittency, incomplete emptying and urgency. The IPSS is the sum of all seven scores with a range from 0 to 35; the higher the score, the severer the symptoms. All patients underwent digital rectal examination and transrectal ultrasound for determination of prostate volume. Maximum flow rate was detected by a Laborie urodynamic detector when the patients felt their bladder was full. Patients with an elevated PSA level of ≥4.0 ng/ml and/or abnormal nodules by digital rectal examination underwent a prostate biopsy. Insulin resistance assessed by homeostasis model assessment (HOMA-IR) was calculated using the following formula [9]: HOMA-IR = (FINS × fasting glucose)/22.5.

Definition of MetS

Central obesity was defined as a waist circumference ≥90 cm, based on the data provided by the WHO-Western Pacific Region and the International Association for the Study of Obesity for Asian populations in 2000, which was included in the modified ATP III guidelines. MetS was defined by the National Cholesterol Education Program's Third Adult Treatment Panel (NCEP ATP III) [10] guidelines as the presence of three or more of the following findings: circumference ≥90 cm, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, TG >150 mg/dl (1.7 mmol/l), HDL-C <40 mg/dl (1.03 mmol/l), fasting plasma glucose ≥110 mg/dl (6.1 mmol/l) or undergoing treatment for hyperglycemia.

Statistical Analysis

The SPSS17.0 statistics package (SPSS, Inc., Chicago, Ill., USA) was applied to analyze the data. Descriptive data were presented as mean ± standard deviation. Non-normally distributed variables, such as waist circumference, HDL-C and PSA levels, and IPSS value were transformed into logarithms for the data analysis. The statistical analyses were performed using the one-sample t test, approximate t test, Pearson's correlation analysis and linear multiple regression analysis with two-sided p values <0.05 considered statistically significant.

Results

Clinical and Prostate Characteristics of the Subjects

All of the 401 BPH patients were divided into a without (n = 179) or a with MetS (n = 222) group according to the definition of MetS. As shown in table 1, there were no significant differences in age, systolic blood pressure, diastolic blood pressure, LDL-C, TC, testosterone, estradiol, PSA levels, IPSS values and maximum flow rate between the two groups. In contrast, waist circumference, BMI, fasting glucose, HbA1c, TG, FINS, HOMA-IR and prostate volume were significantly greater, the duration of LUTS was longer and HDL-C was lower in BPH patients with MetS than in those without MetS.

Correlation between Prostate Volume and MetS Components

The correlations between prostate volume and waist circumference, BMI, levels of fasting glucose, HbA1c, FINS, HDL-C, LDL-C, TG, TC and HOMA-IR were determined using the Pearson correlation analysis. It showed that prostate volume was positively correlated

Table 1. Comparison of clinical and prostate characteristics of the two groups

	BPH patients with MetS (n = 222)	BPH patients without MetS (n = 179)
Age, years	76.93±5.85	77.75±5.78
Waist circumference, cm	97.98±8.47*	87.69±9.84
BMI, kg/m^2	26.18±2.78*	23.45±2.50
Fasting glucose, mmol/l	6.56±1.73#	5.58±0.79
HbA1c, %	6.09±0.92*	5.43±0.73
FINS, μIU/ml	12.54±8.19*	6.46±3.84
Systolic blood pressure, mm Hg	141.14±11.38	137.84±19.39
Diastolic blood pressure, mm Hg	78.91±7.79	78.13±10.44
HDL-C, mmol/l	1.05±0.25*	1.31±0.35
LDL-C, mmol/l	2.38±0.71	2.22±0.70
TG, mmol/l	2.06±1.16#	1.09±0.66
TC, mmol/l	4.27±0.94	4.13±0.86
HOMA-IR	3.76±2.78*	1.60±0.96
Testosterone, ng/ml	5.39±1.50	5.61±1.47
Estradiol, pg/ml	34.68±13.86	34.22±17.91
Prostate volume, ml	51.19±25.64*	38.34±13.67
PSA level, ng/ml	2.71±2.09	2.35±2.01
IPSS	11.18±7.52	11.20±7.96
Duration of LUTS, years	14.46±6.32#	11.51±6.32
Maximum flow rate, ml/s	12.33±3.70	12.58±3.47

*Compared with BPH patients without MetS, $p < 0.001$. #Compared with BPH patients without MetS, $p < 0.05$.

Table 2. Correlation of prostate volume with MetS components

	r	p
Waist circumference	0.140	0.164
BMI	0.459	0.000
Fasting glucose	0.091	0.364
HbA1c	0.153	0.127
FINS	0.421	0.001
HDL-C	–0.378	0.000
LDL-C	0.031	0.757
TG	0.006	0.951
TC	–0.071	0.483
HOMA-IR	0.490	0.003

Table 3. Multiple regression analysis of the correlation of prostate volume with MetS components

	Partial regression coefficient	Standard error	Standardized regression coefficient	t	p
Constant	13.52	21.159		0.639	0.524
BMI	1.698	0.785	0.225	2.162	0.033
HDL-C	–15.589	5.991	–0.228	–2.602	0.011
HOMA-IR	3.162	1.275	0.347	2.48	0.015

with BMI (r = 0.459, p = 0.000), FINS (r = 0.421, p = 0.001) and HOMA-IR (r = 0.490, p = 0.003) and inversely correlated with HDL-C (r = –0.378, p = 0.000) (table 2). Furthermore, stepwise multiple linear regression analysis was performed to evaluate the linear dependencies between prostate volume as a dependent variable and MetS components as independent variables. It still showed prostate volume positively correlated with BMI and HOMA-IR, while it was inversely correlated with HDL-C. The greatest standardized regression coefficient (0.347) was between prostate volume and HOMA-IR (table 3), which implied that among the components of MetS, insulin resistance had the greatest impact on prostate enlargement.

Discussion

Our study found that MetS, which describes the combination of several metabolic abnormalities, was associated with BPH in elderly Chinese men and furthermore that MetS specifically contributed to enlarged prostate volume and longer LUTS duration. Many studies have demonstrated the association between MetS and BPH in other countries. Ozden et al. [11] confirmed these findings in a Turkish population, presenting a significantly higher median annual prostate growth rate in patients with MetS than those without MetS. Hammarsten et al. [12] found that men with individual components of MetS had significantly larger prostate volumes and faster annual BPH growth rates in a cohort of 158 patients with LUTS secondary to BPH in Sweden. A Korean investigation of 1,357 men showed that the total prostate volume and transitional zone volume were significantly larger in MetS men than in non-MetS men [13]. Similar to these reports, our results showed that the BPH patients with MetS had a significantly larger prostate size than the BPH patients without this syndrome. Furthermore, we found that BMI, low HDL-C, FINS and HOMA-IR were risk factors of prostate enlargement but that waist circumference, fasting glucose, HbA1c, LDL-C, TG and TC were not. The patients' prostates enlarged as BMI and FINS

levels increased, HDL-C levels decreased and insulin resistance aggravated. Emerging studies also have suggested that these components of MetS are risk factors of prostatic hyperplasia. Parsons et al. [14] reported that BMI was positively associated with prostate volume: for each 1 kg/m^2 increase in BMI, the prostate volume increased by 0.41 ml (95% CI –0.15 to 0.84; p = 0.06). They also found that men with increased fasting glucose levels were three times more likely to have prostate enlargement than those with normal levels. Hammarsten and Högstedt [4] observed that a high diastolic blood pressure, BMI and FINS level and a low HDL-C level were significantly correlated with a larger prostate volume and a faster annual BPH growth rate. Another survey [3] showed that fasting serum insulin, HOMA-IR, TC and LDL-C were significantly higher and HDL-C was significantly lower in BPH patients compared with controls. The components of MetS obviously affected the prostate volume and accelerated the development of BPH.

Among the components of MetS, our findings indicated that insulin resistance had the greatest impact on prostate enlargement, which confirms that insulin resistance is an important etiologic link between MetS and the increased risk of BPH. Convincing evidence of the association between insulin resistance and BPH was provided in previous experimental and clinical reports [4, 15]. A sequential study of 307 patients with LUTS investigated the association of different components of MetS and fasting plasma insulin level with prostate volume and annual BPH growth rate, and the results supported a hypothesis that hyperinsulinemia was causally related to the progression of BPH [4]. A recent report [15] demonstrated that diet-induced insulin resistance and compensatory elevated plasma insulin resulted in increased cellular proliferation, prostate enlargement and reduced prostate atrophy and apoptosis in rats. Hyperinsulinemia associated with insulin resistance also was an independent risk factor for the development of BPH in non-diabetes mellitus men [3].

Insulin resistance, which is at the center of MetS, should be considered as the underlying factor that determines the other components of the syndrome, including obesity, glucose intolerance, hypertension, dyslipidemia and diabetes [16]. The mechanisms by which insulin resistance may lead to prostate hyperplasia are not fully understood. It was demonstrated that insulin resistance may contribute to prostate hyperplasia through sympathetic nerve activity, the insulin-like growth factor (IGF) axis, sex hormones and the growth-stimulating effect of insulin [15]. Hyperinsulinemia-associated hyperglycemia is sensed by the ventromedial hypothalamus, which ultimately regulates the sympathetic nervous system [17], and involved in reducing sex hormone-binding globulin, leading to an increase in the estrogen/androgen ratio, a confirmed risk factor of BPH [18]. An animal experiment emphasized the role of the autonomic nervous system in prostatic growth [19]. IGF-1 had been shown to induce hyperplasia in the prostate in a transgenic mouse model that specifically expresses human IGF-1 in prostate epithelial cells [20]. Insulin resistance activates the mitogenic signaling of insulin, which has growth-promoting activity, and thus can increase prostate cellular proliferation [15]. Therefore, insulin resistance and hyperinsulinemia play a major role in BPH development.

In addition, chronic inflammation has been proposed recently as a candidate mechanism at the crossroad between MetS and BPH. Accumulating evidence suggests that inflammation is a significant etiologic factor in BPH. Clinical trials have indicated a positive correlation between inflammation and the symptomatic progression of BPH [21]. Histologic studies have found acute and chronic inflammation in BPH specimens [22]. MetS can broadly be considered a systemic inflammatory state and has been associated with elevated levels of inflammation cytokines such as IL-6 and tumor necrosis factor. Two recent studies demonstrated the existence of an association among MetS features, prostate enlargement and prostate inflammation. Fats and insulin were shown to have a detrimental effect on prostate health and to boost prostate inflammation; inflammatory infiltrate score in prostatectomy specimens showed a significant positive correlation with the presence of MetS and a stepwise association with the number of MetS factors present in histologically proven BPH patients [23, 24]. This illustrates that MetS can induce remarkable intraprostatic inflammation and drive BPH progression, and it can be regarded as a new determinant of prostate inflammation and BPH progression.

The majority of studies [25, 26] have shown that the metabolism of androgen and estrogen were factors in the persistent stimulation of BPH with age. Recent data [27, 28] have, in fact, suggested that low testosterone might be an additional MetS component that induces urinary tract disease. One investigation [29] indicated that BPH and the components of MetS shared the same endocrine aberration, which included an increased level of free estradiol, and also showed that a reduced testosterone level was not linked to the same endocrine aberration in the two diseases. However, our findings suggested there was no significant difference in the testosterone or androgen levels

between the two groups. Our study suggested that testosterone and androgen may not be links between MetS and BPH.

Theoretically LUTS, 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, may have a causative relationship with BPH. MetS is associated with an increased prostate volume and may induce a severer LUTS. However, there have been conflicting reports about the associations between MetS and LUTS. Several large-scale surveys [30, 31] showed that MetS and its components were correlated with LUTS. Out of 2,372 men in the NHANES III study [30], the participants with no components of MetS had 80% decreased odds of having LUTS compared with those with at least three components. In the Boston Area Community Health Survey [31] that examined 1,899 male participants, the data showed that increased risks for MetS were observed in men with mild to severe symptoms compared with men with an American Urological Association symptom index score of 0 or 1. Conversely, in our study, although prostate volume was significantly greater in BPH patients with MetS than in those without, MetS was only related to a longer duration of LUTS, but not associated with maximum urinary flow rate (one of the factors used to estimate the urethral obstruction grade and detrusor contractility grade in men with LUTS) or IPSS value. Several studies [32, 33] investigating the male population in China reported that the presence of any components of MetS was not related to LUTS as assessed by the IPSS, which was similar to our result. LUTS, in addition to causing physical obstruction from prostatic hyperplasia, can be influenced by multiple factors, such as vascular, neurological, muscular abnormalities of the bladder, altered bladder neck compliance and tone, prostate and pelvic floor, aging and lifestyle factors, in a complex interplay [34, 35]. As a consequence, the relationship between the severity of BPH and the degree of LUTS is not simple or linear; the development of LUTS is to some extent independent of prostate size. This may contribute to the larger prostate volume in MetS patients without any difference in maximum urinary flow rate or IPSS value with respect to the presence or absence of MetS in our study.

The limitations affecting our current findings should be considered. The duration of LUTS was self-reported, which may have introduced a non-differential observational bias into our analysis that then masked any true associations of the duration of LUTS with MetS. Moreover, cigarette smoking, alcohol intake, physical exercise and diet have not been evaluated as risk factors for BPH and LUTS [36] which may affect the outcome regarding the relationship of MetS with BPH and LUTS.

In conclusion, BPH patients with obesity, low levels of HDL-C, elevated FINS and insulin resistance are at increased risk of an enlarged prostate. Among the components of MetS, insulin resistance is the major risk factor in prostate enlargement. MetS has an effect on the development of BPH, but the association between MetS and LUTS is still unclear and needs further investigation.

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Disclosure Statement

The authors have no disclosures to make.

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