

Impact of metabolic syndrome on lower urinary tract symptoms in patients with benign prostate hyperplasia

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ABSTRACT

BACKGROUND Studies evaluating the relationship between metabolic syndrome (MetS) and lower urinary tract symptoms (LUTS) in men with benign prostate hyperplasia (BPH) are lacking in Indonesia. This study aimed to discover the association of LUTS and MetS in men with BPH.

METHODS Subjects who underwent biopsy were recruited from Cipto Mangunkusumo Hospital, Jakarta, Indonesia from January 2014 to January 2018, but only men who had biopsy-proven BPH were included. Body mass index, waist circumference, fasting blood glucose, triglyceride, high-density lipoprotein, prostate volume (PV), and international prostate symptom score (IPSS) were collected before the biopsy. MetS criteria were based on the National Cholesterol Education Program Adult Treatment Panel III. IPSS was assessed for LUTS and consisted of irritative and obstructive symptoms and quality of life (QoL). Independent t-test or Mann–Whitney test was used to analyze numerical data.

RESULTS Of 227 men with biopsy-proven BPH, 87 (38.3%) were diagnosed with MetS. PV was similar in men with or without MetS (54.4 [20.3–100] versus 49.9 [19.5–100] cm³, $p = 0.239$). Men with MetS generally had more LUTS (15 [1–30] versus 11 [0–35], $p = 0.005$), more irritative symptoms (8 [0–20] versus 6 [0–20], $p = 0.007$), and lower QoL (4 [0–6] versus 3 [0–6], $p = 0.018$).

CONCLUSIONS BPH patients with MetS had greater LUTS, particularly irritative symptoms and QoL score.

KEYWORDS benign prostate hyperplasia, lower urinary tract symptoms, metabolic syndrome

Benign prostate hyperplasia (BPH) is a major cause of lower urinary tract symptoms (LUTS).¹ BPH is diagnosed clinically with prostate enlargement and histologically with simple micronodular hyperplasia, resulting in nodular enlargement that leads to bladder outlet obstruction.² The lifetime prevalence of BPH worldwide is estimated at 26% and increases with age.³

Approximately, 25% of men had metabolic syndrome (MetS), which also a rising health problem.⁴

A recent data from Indonesia showed that low high-density lipoprotein (HDL) cholesterol, hypertension, and central obesity were the most frequent components found in the prevalence of MetS with a percentage of 21.7%.⁵ A recent meta-analysis showed that in contrast to the international prostate symptom score (IPSS), BPH patients with MetS had a significantly higher prostate growth rate and larger prostate volume (PV). It has been known that MetS

would increase estrogen and decrease androgen in men, and this would promote prostate enlargement and also increase the sympathetic nervous system resulting in LUTS.^{2,6}

The identification of the relationship between LUTS and MetS is essential in delaying the progression of BPH to maintain the quality of life (QoL). However, the impact of MetS toward LUTS in Indonesian patients with BPH had not been studied before. Therefore, this study aimed to evaluate the association of LUTS with MetS in Indonesian men with BPH.

METHODS

This cross-sectional study was conducted from January 2014 to January 2018. Subjects who had undergone prostate biopsy in the operating room at Cipto Mangunkusumo Hospital, Jakarta, Indonesia, were recruited consecutively. The eligibility criterion was biopsy-proven BPH. Subjects with prostate malignancy, previous medication with either/both alpha-blockers and 5-alpha reductase inhibitors, neurogenic bladder dysfunction, history of recurrent urinary tract infection (UTI) or bladder stone, acute or chronic prostatitis within the previous 3 months, and any previous prostate-related surgical procedure were excluded. The institutional review board (the Ethics Committee of the Faculty of Medicine Universitas Indonesia) approved the protocol (No: 447/UN2.F1/ETIK/V/2017), and the written informed consent was obtained from each subject.

Laboratory examinations were performed along with the preparation for prostate biopsy a week before surgery. Fasting blood glucose (FBG), triglyceride (TG), and HDL were evaluated after asking the subjects to fast for 8 hours. Blood pressure was evaluated in the operating room before the prostate biopsy. Anthropometry measurements, including height and weight, and waist circumference were performed by the same nurse using a digital scale and tapeline (calibrated according to the company's manual). Waist circumference was measured using the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared.

Transrectal ultrasound was performed by a urologist before the biopsy to determine the PV.

All subjects independently completed the validated Indonesian self-questionnaire IPSS, including QoL, as part of the questionnaire to evaluate LUTS in BPH patients.⁷ IPSS is a seven-part questionnaire that evaluated LUTS, and questions were answered using a Likert scale, from 1 (not at all) to 5 (almost always). Questions about frequency, urgency, and nocturia were summed to get irritative scores, whereas questions about incomplete emptying, intermittency, weak stream, and straining were summed to get obstructive scores. QoL also used a six-Likert scale: the higher the score is, the poorer the QoL concerning LUTS. Total IPSSs were categorized into two groups, namely mild (0–7) and moderate-severe (8–35), whereas PV was classified into ≤ 30 and >30 cm.³

Criteria from the National Cholesterol Education Program Adult Treatment Panel III were used to diagnose MetS. MetS was diagnosed if three or more of the following five criteria were met: waist circumference >90 cm, blood pressure $>130/85$ mmHg, TG level >150 mg/dl, HDL cholesterol level <40 mg/dl, and FBG >100 mg/dl.⁸

Data were presented as median (minimum–maximum) or mean (standard deviation). Independent t-test was used to analyze mean difference of age, body weight, BMI, TG, and HDL between men with and without MetS. The odds ratio was used to calculate the risk of MetS for LUTS. Statistical software (SPSS version 23 for Macintosh, IBM Corp., USA) was used. A p-value of <0.05 was considered statistically significant.

RESULTS

Of 353 patients underwent biopsy at the center during the period, 126 patients were excluded because 31 patients had prostate cancer, 26 patients had a previous prostate medication (alpha-blocker and/or 5-alpha reductase inhibitor), 15 patients had a neurogenic bladder dysfunction, 49 patients had a bladder stone and/or recurrent UTIs, and 5 patients had prostatitis history. A total of 227 subjects with BPH were included in this study (Table 1). Irritative symptoms, total IPSS, and QoL scores were found to be worse in MetS patients ($p<0.05$). The odds ratio of MetS patients having moderate to severe LUTS were 17.04 (95% confidence interval [CI]: 8.72–33.3) compared with mild symptoms.

Table 1. Patient characteristics

Variable	All men, median (min–max) (N = 227)	MetS, median (min–max) (N = 87)	Non-MetS, median (min–max) (N = 140)	<i>p</i>
Age (year), mean (SD)	66.6 (7.5)	67.5 (6.6)	66.08 (8.1)	0.157*
Height (cm)	165 (145–180)	165 (153–175)	165 (145–180)	0.923 [†]
Body weight (kg), mean (SD)	64.2 (10.7)	67.3 (10.4)	62.4 (10.5)	0.001*
BMI (kg/m ²), mean (SD)	23.7 (3.5)	24.8 (3.5)	23.1 (3.3)	<0.001*
Waist circumference (cm)	87 (60–130)	92 (72–130)	85 (60–126)	<0.001[†]
SBP (mmHg)	130 (100–182)	135 (100–182)	130 (100–179)	0.04[†]
DBP (mmHg)	80 (60–122)	80 (60–110)	80 (60–122)	0.41 [†]
TG (mg/dl), mean (SD)	144.3 (53.9)	179.6 (58.2)	122.3 (36.8)	<0.001*
HDL (mg/dl), mean (SD)	44.3 (9.4)	39.4 (9.5)	48.0 (8.1)	<0.001*
FBG (mg/dl)	95 (59–237)	109 (59–237)	9 (61–163)	<0.001[†]
IPSS				
Irritative score	7 (0–20)	8 (0–20)	6 (0–20)	0.007[†]
Obstructive score	6 (0–20)	6 (0–16)	5 (0–20)	0.15 [†]
QoL score	4 (0–6)	4 (0–6)	3 (0–6)	0.018[†]
Total score	12 (0–35)	15 (1–30)	11 (0–35)	0.005[†]
IPSS (category), n (%)				0.039
Mild	52 (22.9)	16 (18)	36 (25.7)	
Moderate–severe	175 (77.1)	71 (82)	104 (74.2)	
Prostate volume (cm ³)	51.9 (19.5–100)	54.4 (20.3–100)	49.9 (19.5–100)	0.239 [†]

BMI=body mass index; DBP=diastolic blood pressure; FBG=fast blood glucose; HDL=high-density lipoprotein; IPSS=international prostate symptom score; MetS=metabolic syndrome; SBP=systolic blood pressure; TG=triglycerides; QoL=quality of life

*Independent t-test; [†]Mann–Whitney test

DISCUSSION

LUTS, as measured qualitatively by IPSS and QoL, were often used to determine the severity subjectively. Previous studies had concluded that men with MetS had worse LUTS, therefore poorer QoL.^{9–11} Our results showed that men with MetS had more irritative than obstructive symptoms. Obstructive symptoms were mainly affected by PV, whereas irritative symptoms were more complex and involved both intra- and extra-bladder components.¹² This might happen because there was no difference in PV between men with and without MetS. A recent meta-analysis showed that PV was greater in men with MetS; however, it was different among regions (Asia and Europe).¹³ This discrepancy might be due to multifactorial causes of prostate enlargement, such as age,¹⁴ inflammation,⁶ testosterone level,¹⁵ diet, and metabolism.¹⁶

LUTS (total IPSS score) and irritative symptoms were more severe in men with MetS. The fact that the increase in smooth muscle contraction of the male genitourinary tract structures (e.g., prostate, bladder

neck, and the urethra) was caused by an increase in alpha-adrenergic pathway activation may explain this result.¹⁷ Along with that, men with MetS would have lower testosterone levels (due to the increase of adipose stores, which decreased plasma levels) that might affect the progression of LUTS.¹⁸ In the National Health and Nutrition Examination Survey III study, LUTS was more severe in men having lower androstanediol glucuronide levels (a parameter of androgen in the circulation) and molar estradiol/testosterone ratios.¹⁹ On the other hand, a recent study by Hammarsten et al²⁰ showed no association between testosterone and LUTS; thus, this would involve a lot further complex interrelationship of sex hormones. In alignment with a previous study, this study showed that patients with MetS had more severe irritative symptoms than those without MetS.²¹ The following mechanisms might explain this result: patients with MetS had higher intra-abdominal pressure (IAP) (bladder pressure and intravesical pressure), surged in estrogen to androgen ratio (fat tissue expressing enzyme P450 aromatase), and intensified microvascular disease and

inflammation (contributing to ischemia and oxidative stress); all of which had the hypothetical cause to aggravate and worsen LUTS.⁶

Of all the above causes on MetS might also be explained through a mechanism of obesity in causing LUTS. MetS is related to obesity as shown by higher BMI in men with MetS. Obesity increases IAP, which subsequently increases bladder and intravesical pressure, and can exacerbate and worsen LUTS.²² Obesity also promotes microvascular disease and inflammation, which would cause ischemia and oxidative stress and create an intraprostatic environment favorable to BPH.²² Another possibility explaining no association between PV and MetS was a small difference in BMI in groups with and without MetS in this study as the mean BMI of both groups belongs to the “at risk of obesity” category. Hence, although the men had no MetS, they already had obesity. This result may be different between men without MetS and obesity and men with MetS or obesity. In addition, waist circumference is another method to determine obesity status.²³ This parameter was also accounted as a component of MetS and thought to reflect central obesity. It has been known that central fat contains different types of adipose tissue that promote more inflammatory and angiogenic cytokines than peripheral fat.²⁴

Men with MetS were found to have poorer QoL compared with those without MetS. There has been a growing body of evidence that shows a significant association between MetS and QoL worsening.²⁵ In addition to MetS, patients with higher IPSS score have even lower QoL due to more limitations in their daily activities and a decrease in physical and mental well-being.^{14,26} Both obstructive and irritative symptoms may decrease QoL, but patients with both symptoms have even lower QoL.²⁷ However, the relationship between QoL, MetS, and LUTS could not be specifically identified due to different cultures and lifestyles. Nevertheless, the improvement of MetS components consistently decreases LUTS severity and increases QoL.^{25,28}

Several limitations of this study include not controlling other potential biases, such as sex hormone level, androgen level, and insulin resistance due to limited resource. Moreover, most of the men in this study had obesity, although they did not have MetS. Furthermore, there should be further research evaluating the exact physiologic and molecular

relationship between LUTS severity and each MetS component.

In this study, we confirmed that although MetS had a limited impact on LUTS (mainly irritative symptoms, total IPSS, and QoL) in Indonesian men with BPH, the association and increase risk of LUTS were seen in patients with central obesity. This shows that lifestyle modification (including nutritional intake and physical exercise) might be a valuable additional therapy in men with MetS and LUTS. However, a more constant and uniform definition is needed regarding these conditions.

Conflict of Interest

Agus Rizal Ardy Hariandy Hamid is the editor-in-chief of this journal but was not involved in the review or decision process of the article.

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