

# Impact of metabolic syndrome-related factors on the development of benign prostatic hyperplasia and lower urinary tract symptoms in Asian population

Jee Soo Park, MD<sup>a</sup>, Kyo Chul Koo, MD, PhD<sup>a</sup>, Hye Kyung Kim, MD<sup>b</sup>, Byung Ha Chung, MD, PhD<sup>a</sup>, Kwang Suk Lee, MD<sup>a,b,\*</sup>

## Abstract

This study aimed to investigate the metabolic syndrome-related risk factors for the development of benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) in healthy men.

A total of 4880 healthy men who underwent transrectal ultrasonography at our hospital during routine health examinations were included in this study. Those who had undergone a prior biopsy or surgery for prostate disease, were suspected of having urinary tract infection, or were taking BPH/LUTS or metabolic syndrome medications were excluded. BPH/LUTS was defined as an International Prostate Symptom Score (IPSS) of  $\geq 8$  and a prostate volume (PV) of  $\geq 30$  cm<sup>3</sup>.

The subjects had a mean age of 54.1 years, PV of 29.2 cm<sup>3</sup>, prostate-specific antigen (PSA) level of 1.20 ng/mL, and IPSS of 9.2. The annual PV growth rate was 0.48 cm<sup>3</sup>/year. Age, body mass index (BMI), PSA, basal metabolic rate, apolipoprotein A-1, fasting blood glucose, high-density lipoprotein (HDL) cholesterol levels were significant predictive factors for PV. Age, PSA, apolipoprotein B, fasting blood glucose, cholesterol, HDL, and low-density lipoprotein (LDL) levels were predictors of BPH/LUTS at the initial health examination. A decreased fat mass and LDL level were a significant risk factor for the development of BPH/LUTS within 5 years in men without a BPH/LUTS diagnosis at the initial examination.

Metabolic syndrome-related variables were strongly associated with BPH/LUTS and by decreasing fat mass and LDL levels, development of BPH/LUTS could be prevented within 5 years in healthy Korean men.

**Abbreviations:** BMI = body mass index, BPH = benign prostatic hyperplasia, CI = confidence interval, HDL = high-density lipoprotein, IPSS = international prostate symptom score, LDL = low-density lipoprotein, LUTS = lower urinary tract symptoms, OR = odds ratio, PNI = prognostic nutritional index, PSA = prostate-specific antigen, PV = prostate volume, TRUS = transrectal ultrasonography.

**Keywords:** benign prostatic hyperplasia, lower urinary tract symptoms, metabolic syndrome

Editor: Vito Mancini.

All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

The authors have no conflicts of interest to disclose.

<sup>a</sup>Department of Urology, Yonsei University College of Medicine, <sup>b</sup>Health Promotion Center, Gangnam Severance Hospital, Seoul, Korea.

\*Correspondence: Kwang Suk Lee, Department of Urology, Yonsei University College of Medicine, 211 Eonjuro, Gangnam-gu, 135-720 Seoul, Korea (e-mail: calmenow@yuhs.ac).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Park JS, Koo KC, Kim HK, Chung BH, Lee KS. Impact of metabolic syndrome-related factors on the development of benign prostatic hyperplasia and lower urinary tract symptoms in Asian population. *Medicine* 2019;98:42(e17635).

Received: 9 July 2019 / Received in final form: 5 September 2019 / Accepted: 24 September 2019

<http://dx.doi.org/10.1097/MD.0000000000017635>

## 1. Introduction

Benign prostatic hyperplasia (BPH) occurs in aging men, characterized by the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.<sup>[1]</sup> The enlarged gland contributes to several lower urinary tract symptoms (LUTS), including nocturia, incomplete voiding, urgency, and hesitancy. The natural history of BPH and the risk factors for LUTS progression have been evaluated in community-based studies,<sup>[2,3]</sup> and with data from the placebo arms of several clinical trials.<sup>[4,5]</sup> However, most of these studies have been conducted in Caucasian men.<sup>[6,7]</sup> Although several studies have reported a relationship between prostate volume (PV) and prostate-specific antigen (PSA) level in men with BPH/LUTS in Asia,<sup>[8,9]</sup> there are no studies that investigated the risk factors for BPH/LUTS in Asian men.

Previous studies have reported several risk factors for the development and progression of BPH/LUTS, and interestingly, other than PV and PSA level, metabolic syndromes were found out to be important determinants in both the development and progression of LUTS.<sup>[10–12]</sup> Therefore, by maintaining healthy lifestyle, including stop smoking and alcohol consumption, and increase in exercise which leads to normalization of blood glucose, cholesterol levels, etc, which eventually would decrease in metabolic syndromes, could alleviate voiding symptoms. Thus,

in this study, we aimed to evaluate whether the risk factors for metabolic syndromes, including lifestyle variables, are related to the predictors of BPH/LUTS at initial diagnosis and for the development of BPH/LUTS within a 5-year follow-up in a large-scale health program.

## 2. Materials and methods

### 2.1. Study population and data collection

This is the retrospective study approved by the institutional review board (3–2016–0233). Among individuals who presented at our hospital for routine health examinations between April 2006 and May 2016, healthy men who underwent at least one transrectal ultrasonography (TRUS) examination were enrolled. Data on characteristics of the 4880 subjects, including age at the health examination, body mass index (BMI), medical history, previous diagnosis of cancer, surgical history, medication types, smoking status, alcohol drinking status, exercise status, PV, PSA level, International Prostate Symptom Score (IPSS), and blood and urine laboratory results, were collected.

Men who had undergone a prior biopsy or surgical treatment for prostate disease, those who were suspected of having urinary tract infection on the basis of a urine test revealing  $>10$  white blood cells/ $\mu\text{L}$ , those with metabolic syndrome, and those who were taking treatment for BPH or metabolic syndrome were excluded from the analysis. After applying the exclusion criteria, a total of 4880 men were included for analysis.

### 2.2. Assessments of clinical variables

BMI was calculated as the weight in kilograms divided by the height in meters squared. The serum PSA level was assayed using a chemiluminescence method and commercially available kits. PV was calculated by substituting the formula for an ellipsoid, i.e.,  $\pi/6 \times \text{height} \times \text{length} \times \text{width}$ , with the height, length, and width of the prostate measured by TRUS. For 1459 men who underwent two or more serial TRUS examinations, the annual PV growth rate was calculated as the PV at the latest TRUS minus the PV at the first TRUS, divided by the time elapsed in years between the two measurements.

### 2.3. Nutrition status evaluation

To evaluate the effect of nutrition status, the prognostic nutritional index (PNI) was assessed. The PNI values were calculated using data from blood and urine laboratory results. On the basis of a previous study, the PNI was calculated as  $10 \times$

serum albumin (g/dL) +  $0.005 \times$  total lymphocyte count (per  $\text{mm}^3$ ).<sup>[13]</sup> A PNI value of at least 50 was defined as normal, whereas  $<50$  was considered mild malnutrition,  $<45$  was considered moderate-to-severe malnutrition, and  $<40$  was considered serious malnutrition.<sup>[14]</sup> In this study, clinically significant malnutrition was defined as a PNI cut-off value of  $<50$ .

### 2.4. Statistical analysis

BPH/LUTS was defined as an IPSS of  $\geq 8$  points concomitant with a PV of  $\geq 30 \text{ cm}^3$ . The patients were categorized according to the level of smoking (non-smoker/ex-smoker vs current smoker), alcohol consumption (non-drinker/intermittent drinker vs current drinker), and exercise (non-exerciser/intermittent exerciser vs current exerciser). Pearson's chi-square test was used to compare the distributions of categorical baseline clinical characteristics. For continuous variables, means and standard deviations were compared with Student's *t*-test. Additionally, simple and multiple logistic regression analyses with forward stepwise procedures were used. Statistical analyses were performed with the SPSS 23.0 (Chicago, IL, USA). All tests were two sided, and significance was set at  $P < .05$ .

## 3. Results

### 3.1. Demographic characteristics

The baseline characteristics of the subjects are shown in Table 1. A total of 4880 subjects were available at baseline, with a mean age, PV, and PSA levels were  $54.1 \pm 8.6$  years,  $29.2 \pm 14.3 \text{ cm}^3$ , and  $1.20 \pm 1.47 \text{ ng/mL}$ , respectively. The mean IPSS was  $9.2 \pm 6.6$ . The PSA level and PV significantly increased with age, however, there was no significant association between total IPSS and age. The mean annual PV growth rate was  $0.48 \text{ cm}^3/\text{year}$ . The annual PV growth rate increased with increasing age, especially from age  $>70$  years.

### 3.2. Predictors of BPH/LUTS at the initial health examination

Among 4880 subjects, men with BPH/LUTS ( $n=3529$ , 72.3%) were significantly older than men without BPH/LUTS ( $n=1351$ , 27.7%) ( $P < .001$ ) at the initial health examination (Table 2). The PSA levels, PV, total IPSS, and quality of life score were significantly higher in those with BPH/LUTS. For metabolic factors, basal metabolic rate, apolipoprotein B, cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL)

**Table 1**  
Baseline characteristics of the study group.

	Total	Age 40–49 years	Age 50–59 years	Age 60–69 years	Age > 70 years	P-Value
No. of subjects	4880	1753 (35.9)	1992 (40.8)	883 (18.1)	252 (5.2)	
Age (years)	$54.1 \pm 8.6$	$45.6 \pm 2.8$	$54.5 \pm 2.8$	$64.2 \pm 2.8$	$74.2 \pm 3.8$	$<.001$
BMI ( $\text{kg}/\text{m}^2$ )	$24.4 \pm 2.8$	$24.6 \pm 2.9$	$24.5 \pm 2.7$	$24.1 \pm 2.7$	$23.6 \pm 2.9$	$<.001$
PSA level (ng/mL)	$1.20 \pm 1.47$	$0.99 \pm 1.19$	$1.13 \pm 1.17$	$1.56 \pm 2.05$	$2.02 \pm 2.31$	$<.001$
PV ( $\text{cm}^3$ )	$29.2 \pm 14.3$	$26.2 \pm 6.9$	$28.8 \pm 8.1$	$33.9 \pm 27.6$	$36.6 \pm 17.3$	$<.001$
Total IPSS	$9.2 \pm 6.6$	$9.3 \pm 6.7$	$9.2 \pm 6.6$	$8.8 \pm 6.5$	$9.2 \pm 7.0$	.468
PV growth rate ( $\text{cm}^3/\text{year}$ )	$0.48 \pm 3.28$	$0.45 \pm 4.16$	$0.47 \pm 2.47$	$0.46 \pm 2.62$	$0.67 \pm 4.52$	.324

Data are presented as n (%) or as mean  $\pm$  standard deviation.

BMI=body mass index, IPSS=International Prostate Symptom Score, PSA=prostate-specific antigen, PV=prostate volume, TV=transitional zone volume.

**Table 2**  
**Characteristics of subjects stratified into groups with and without BPH/LUTS at the initial health examination.**

	Total	BPH/LUTS (+)	BPH/LUTS (-)	P-Value
No. of subjects	4880	3529 (72.3)	1351 (27.7)	
Age (years)	54.0 ± 8.6	54.7 ± 8.6	52.6 ± 8.2	<.001
BMI (kg/m <sup>2</sup> )	24.4 ± 2.8	24.4 ± 2.7	24.4 ± 2.8	.622
PSA level (ng/mL)	1.20 ± 1.47	1.29 ± 1.58	1.11 ± 0.97	<.001
PV (cm <sup>3</sup> )	29.2 ± 14.3	31.5 ± 16.2	23.5 ± 4.2	<.001
Total IPSS	9.2 ± 6.6	11.4 ± 6.3	3.3 ± 2.5	<.001
Quality of life	2.6 ± 1.4	2.8 ± 1.2	1.8 ± 1.3	<.001
Basal metabolic rate (kcal/day)	1311.7 ± 139.9	1308.5 ± 139.6	1319.8 ± 140.3	.023
Fat mass (kg)	16.6 ± 4.8	16.6 ± 4.7	16.5 ± 5.0	.449
Apolipoprotein A-1 (mg/dL)	140.9 ± 22.8	140.4 ± 22.1	142.5 ± 24.3	.124
Apolipoprotein B (mg/dL)	100.9 ± 24.8	99.4 ± 24.4	104.5 ± 25.3	<.001
Fasting blood glucose (mg/dL)	103.3 ± 23.4	102.9 ± 22.3	104.5 ± 26.1	.304
Triglyceride (mg/dL)	142.0 ± 91.8	140.5 ± 89.3	145.6 ± 97.5	.076
Cholesterol (mg/dL)	195.9 ± 36.0	194.9 ± 35.9	198.3 ± 36.2	.003
HDL (mg/dL)	48.0 ± 11.1	47.6 ± 10.8	48.9 ± 11.9	.006
LDL (mg/dL)	125.5 ± 33.2	124.1 ± 32.8	129.1 ± 33.9	<.001
PNI	47.1 ± 2.7	47.0 ± 2.7	47.2 ± 2.7	.018
PNI <50	3811 (78.1)	2769 (78.5)	1042 (77.1)	.028
Smoking (current)	1574 (32.3)	1140 (32.3)	434 (32.1)	.024
Alcohol (current)	2557 (52.4)	1783 (50.5)	774 (57.3)	.062
Exercise (current)	455 (9.3)	229 (6.5)	226 (16.7)	.173

Data are presented as n (%) or as mean ± standard deviation.

BMI=body mass index, BPH=benign prostatic hyperplasia, HDL=high-density lipoprotein cholesterol, IPSS=International Prostate Symptom Score, LDL=low-density lipoprotein cholesterol, LUTS=lower urinary tract symptoms, PNI=prognostic nutritional index, SA=prostate-specific antigen, PV=prostate volume.

were significantly lower in men with BPH/LUTS. The proportion of patients with PNI <50 (considered malnutrition status) was higher among men with BPH/LUTS than among those without BPH/LUTS. Among lifestyle variables, only smoking status were significantly associated between those with and without BPH/LUTS.

In the multivariate logistic regression analysis of BPH/LUTS diagnosis at the initial health examination, age (odds ratio [OR]=1.04, 95% confidence interval [CI] 1.023–1.053;  $P < .001$ ), PSA (OR=1.26, 95% CI 1.083–1.461;  $P = .003$ ), apolipoprotein B (OR=0.98, 95% CI 0.972–0.995;  $P = .006$ ),

fasting blood glucose (OR=0.99, 95% CI 0.988–0.998;  $P = .005$ ), cholesterol (OR=1.04, 95% CI 1.025–1.046;  $P < .001$ ), HDL (OR=0.96, 95% CI 0.946–0.973;  $P < .001$ ), and LDL (OR=0.97, 95% CI 0.962–0.978;  $P < .001$ ) were identified as significant variables (Table 3).

### 3.3. Predictors of the development of BPH/LUTS within a 5-year follow-up of men without BPH/LUTS at baseline

Among men without a BPH/LUTS diagnosis at the initial examination, 262 (33.8%) were diagnosed as having BPH/LUTS

**Table 3**  
**Results of univariate and multivariate logistic regression analyses for predictors of BPH/LUTS at the initial health examination.**

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-Value	Odds ratio (95% CI)	P-Value
Age	1.03 (1.022–1.038)	<.001	1.04 (1.023–1.053)	<.001
BMI	1.01 (0.952–1.029)	.656		
PSA level	1.42 (1.301–1.554)	<.001	1.26 (1.083–1.461)	.003
Basal metabolic rate	5.47 (0.999–1.000)	<.001	1.00 (1.000–1.002)	.118
Fat mass	1.00 (0.989–1.016)	.751		
Apolipoprotein A-1	1.00 (0.991–1.000)	.075		
Apolipoprotein B	0.99 (0.988–0.996)	<.001	0.98 (0.972–0.995)	.006
Fasting blood glucose	1.00 (0.995–1.000)	.042	0.99 (0.988–0.998)	.005
Triglyceride (mg/dL)	1.00 (0.999–1.000)	.069		
Cholesterol	1.00 (0.996–0.999)	.004	1.04 (1.025–1.046)	<.001
HDL	0.99 (0.984–0.995)	<.001	0.96 (0.946–0.973)	<.001
LDL	1.00 (0.994–0.997)	<.001	0.97 (0.962–0.978)	<.001
PNI	0.98 (0.952–0.999)	.039	1.01 (0.969–1.062)	.544
Smoking (current)	0.83 (0.707–0.975)	.024	0.85 (0.652–1.097)	.206
Alcohol (current)	0.94 (0.696–1.009)	.063		
Exercise (current)	1.31 (0.888–1.933)	.173		

Data are presented as mean ± standard deviation. Only variables found to be significant in the univariate analysis were included in the multivariate analysis.

BMI=body mass index, BPH=benign prostatic hyperplasia, CI=confidence interval, IPSS=International Prostate Symptom Score, LUTS=lower urinary tract symptoms, PNI=prognostic nutritional index, PSA=prostate-specific antigen, PV=prostate volume.

**Table 4**  
**Results of univariate and multivariate logistic regression analyses for predictors of the development of BPH/LUTS during a 5-year follow-up of men without BPH/LUTS at baseline.**

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	P-Value	Odds ratio (95% CI)	P-Value
Age	1.01 (0.996–1.032)	.134		
BMI	0.95 (0.900–1.000)	.050		
PSA level	1.02 (0.905–1.156)	.714		
Basal metabolic rate	0.84 (0.999–1.001)	.800		
Fat mass	0.97 (0.940–0.998)	.038	0.93 (0.879–0.984)	.012
Apolipoprotein A-1	1.01 (0.997–1.017)	.185		
Apolipoprotein B	0.99 (0.975–0.996)	.009	1.00 (0.971–1.020)	.710
Fasting blood glucose	1.00 (0.989–1.002)	.182		
Triglyceride (mg/dL)	1.00 (0.999–1.000)	.078		
Cholesterol	1.00 (0.991–0.999)	.017	1.03 (1.009–1.041)	.002
HDL	1.00 (0.986–1.013)	.918		
LDL	0.99 (0.989–0.999)	.010	0.97 (0.950–0.983)	<.001
PNI	0.97 (0.917–1.021)	.230		
Smoking (current)	0.96 (0.658–1.407)	.841		
Alcohol (current)	1.64 (1.004–2.671)	.048	1.14 (0.582–2.222)	.707
Exercise (current)	1.93 (0.802–4.633)	.143		

Data are presented as mean  $\pm$  standard deviation. Only variables found to be significant in the univariate analysis were included in the multivariate analysis.

BMI=body mass index, BPH=benign prostatic hyperplasia, CI=confidence interval, IPSS=International Prostate Symptom Score, LUTS=lower urinary tract symptoms, PNI=prognostic nutritional index, PSA=prostate-specific antigen, PV=prostate volume.

within 5 years. Men who developed BPH/LUTS during the follow-up period had a significantly lower fat mass, apolipoprotein B, cholesterol, LDL, and higher alcohol drinking status at the initial examination.

In the multivariate analysis, fat mass (OR=0.93, 95% CI 0.879–0.984;  $P=.012$ ), cholesterol (OR=1.03, 95% CI 1.009–1.041;  $P=.002$ ), and LDL (OR=1.14, 95% CI 0.950–0.983;  $P<.001$ ) were significant risk factors for the development of BPH/LUTS within 5 years (Table 4).

#### 4. Discussion

In this study, we investigated the risk factors for BPH/LUTS of 4880 healthy men without prostate cancer, urinary tract infection, BPH/LUTS medication, or metabolic syndrome at baseline. The various variables including metabolic syndrome components, such as apolipoprotein B, fasting blood glucose, cholesterol, HDL, and LDL levels, were significantly associated with BPH/LUTS at initial diagnosis. Among the metabolic syndrome variables, decreased fat mass and LDL level were predictive factors for the development of BPH/LUTS within 5 years in men who did not have these conditions at baseline. Smoking, alcohol consumption, and exercise were not identified as preventive factors for the development of BPH/LUTS.

Several reports have investigated the normal reference ranges for PV, PSA level, and annual PV change rates in men, using a nationwide screening population.<sup>[15,16]</sup> The mean PV in each 10-year age group was similar to that reported in studies in Japanese<sup>[16]</sup> and Korean<sup>[9,17]</sup> populations, but lower than that in studies on Caucasians<sup>[15]</sup> and African Americans.<sup>[18]</sup> We found that the serum PSA level in our study population was slightly higher than that reported in another Korean population.<sup>[8]</sup> In our screening population, the estimated annual PV growth rate was 0.48 cm<sup>3</sup>/year, which was similar to the rates reported in previous community-based studies (0.3–0.6 cm<sup>3</sup>/year).<sup>[3,15,17]</sup>

Previous studies reported that age, BMI, PSA level, and the presence of metabolic syndrome were significant factors

associated with PV.<sup>[17,19,20]</sup> In a small case-control study, HDL level was shown to be negatively associated with prostate enlargement.<sup>[21]</sup> In a meta-regression analysis, the major metabolic syndrome-related determinant of BPH was HDL level.<sup>[22]</sup> After evaluating the parameters associated with PV, including those suggested in previous studies, we found that age, BMI, PSA, basal metabolic rate, apolipoprotein A-1, fasting blood glucose, and HDL were statistically significant factors associated with PV. Similar to previous study, HDL level was negatively associated with PV. In particular, apolipoprotein A-1, as the major protein in HDL which plays an important role during the process of reverse cholesterol transport,<sup>[23]</sup> was found to be positively associated with PV with significance.

In contrast to the findings of association of several metabolic syndrome-related factors with PV, different metabolic syndrome-related factors were found out to be associated with BPH/LUTS. Among metabolic syndrome-related factors, apolipoprotein B, fasting blood glucose, cholesterol, HDL, and LDL were significantly associated with BPH/LUTS at initial diagnosis in multivariate analysis. Basal metabolic rate and apolipoprotein A-1, which were associated with PV, were not found to be associated with BPH/LUTS, however, apolipoprotein B, cholesterol, and LDL were found out to be associated with BPH/LUTS. Notably, apolipoprotein B is known to regulate metabolic syndrome. Apolipoprotein B is a high molecular weight protein that is strongly correlated with the values of total cholesterol and HDL.<sup>[24]</sup> High apolipoprotein B levels predict atherogenic alterations, based on the known association between apolipoprotein B level and cardio-cerebrovascular complications. Moreover, evidence has shown significant associations between apolipoprotein B level and chronic degenerative complications.<sup>[25,26]</sup> Therefore, it is presumed that apolipoprotein B level may be associated with vascular disease of the organ involved in urination and voiding.

Pan et al reported that weight; levels of fasting blood glucose, HDL, total cholesterol, and total glycerides; BMI; systolic and diastolic blood pressure; residual urine volume; total PV; and

annual PV growth rate were significantly different between men with moderate LUTS and those with severe LUTS.<sup>[27]</sup> The results of our analysis of subjects stratified into groups with and without BPH/LUTS at the initial health examination were similar to the findings of this previous report (Table 2). Notably, current smoking was significantly associated with a lower risk of BPH/LUTS diagnosis at the initial health examination. However, smoking had no effect on decreasing the risk of BPH/LUTS development. Although smoking is a known risk factor of several disorders, the relationship between smoking and BPH/LUTS remains controversial. Nicotine in cigarettes has been shown to lead to increased dihydrotestosterone level in the prostate and increased sympathetic nervous system activity, contributing greatly to BPH and LUTS.<sup>[28,29]</sup> However, Platz et al concluded that smoking decreases prostate enlargement to a degree, and even argued for a protective effect of smoking against prostate enlargement.<sup>[30]</sup> In this way, smoking increases the bladder activity through the sympathetic nervous system and may potentially aggravate overactive bladder symptoms. It was presumed that the autonomic muscle relaxation was caused by nicotine, with the first sphincter being autonomic. Therefore, further studies are needed to investigate the effect of smoking on BPH/LUTS.

In this study, exercise was not found to be significantly associated with BPH/LUTS. However, there is a growing body of evidence supporting a protective role for exercise in reducing the risk of developing BPH/LUTS.<sup>[31]</sup> Several hypotheses have been proposed, and favorable changes in hormonal milieu (androgen levels, insulin, and metabolic syndrome) could be associated. Other hypotheses include decreased resting sympathetic tone in the prostate and reduction in prostatic inflammation by decreasing oxidative damage.<sup>[31]</sup> However, for any of these, causal relationships have not been established. Moreover, most studies have described an inverse relationship between exercise and BPH/LUTS, although some have not clearly demonstrated a positive role for exercise on BPH/LUTS and have provided conflicting results. We think that this may be due to differences in defining exercise and BPH/LUTS and that the age of starting exercise may warrant consideration.<sup>[31]</sup>

Published reports about predictors of BPH/LUTS development are scarce. Dahle et al suggested that risk factors reflecting metabolic syndrome, such as the waist-to-hip ratio, influence the development of BPH/LUTS.<sup>[32]</sup> Interestingly, the present study found that a decreased LDL level was a significant predictor of BPH/LUTS development within a 5-year follow-up period in men without BPH/LUTS. Among the metabolic syndrome components, we predicted HDL as a major factor in the development of BPH/LUTS because increasing HDL showed a negative effect on both PV and IPSS, which is in agreement with the results of previous studies.<sup>[22]</sup> Therefore, maintaining a high HDL level has been considered a preventive strategy against BPH/LUTS. However, the predictor of the development of BPH/LUTS was LDL, not HDL. To interpret these results, we further evaluated nutrition status; however, we did not identify any obvious findings. We assumed that this is because of the intercorrelation between each metabolic syndrome component, although this theory requires further validation.

BPH/LUTS is common among older adult men; however, it may be linked to malignant disease of the prostate. A large recent population-based European study established a clear association between LUTS and the subsequent risk of prostate cancer.<sup>[33]</sup> A recent study by Cormio et al attempted to identify cheap and

non-invasive clinical parameters with which to accurately predict prostate cancer risk, since imaging has not significantly increased the accuracies of prostate cancer risk prediction models.<sup>[34]</sup> We believe that incorporating BPH/LUTS as a parameter for predicting prostate cancer would be interesting and might help increase the accuracy of predicting prostate cancer risk. Therefore, for future study, we are planning to investigate associations for newly diagnosed prostate cancer in men with and without BPH/LUTS.

This study has several limitations. First, the study was conducted at a single institution and may have been subject to selection bias. Most of those screened at our hospital are healthy people who undergo routine health examinations. Moreover, the data were not derived from a community-based population. Further large-scale studies in the general population will be necessary to confirm our results. Second, although the IPSS is a validated patient-administered questionnaire that is useful to quantify the severity of LUTS, IPSS should not be used alone. The quality of life score is more important than IPSS.<sup>[35]</sup> However, our criteria of BPH/LUTS, such as the various definitions of BPH/LUTS by many international guidelines and local studies, did not include the quality of life score as a component of the definition. This might indicate that a higher quality of life score has a preventive effect against the development of BPH/LUTS. Future studies are needed to validate our findings.

In conclusion, metabolic syndrome-related variables, including fat mass, apolipoprotein B, fasting blood glucose, cholesterol, HDL, and LDL levels, are significantly associated with development of BPH/LUTS, and increasing fat mass and LDL levels appear to be important to preventing the development of BPH/LUTS. Further studies investigating the intercorrelation between each metabolic syndrome component are warranted to validate the results of the present study.

## Acknowledgments

None.

## Author contributions

**Conceptualization:** Jee Soo Park, Byung Ha Chung, Kwang Suk Lee.

**Data curation:** Jee Soo Park, Kyo Chul Koo, Kwang Suk Lee.

**Formal analysis:** Kwang Suk Lee.

**Investigation:** Jee Soo Park, Kwang Suk Lee.

**Methodology:** Kyo Chul Koo, Hye Kyung Kim, Kwang Suk Lee.

**Project administration:** Byung Ha Chung, Kwang Suk Lee.

**Supervision:** Byung Ha Chung, Kwang Suk Lee.

**Validation:** Hye Kyung Kim, Kwang Suk Lee.

**Writing – original draft:** Jee Soo Park, Kwang Suk Lee.

**Writing – review & editing:** Jee Soo Park, Kyo Chul Koo, Byung Ha Chung, Kwang Suk Lee.

Kwang Suk Lee orcid: 0000-0002-7961-8393.

## References

- [1] Lee C, Kozlowski JM, Grayhack JT. Intrinsic and extrinsic factors controlling benign prostatic growth. *Prostate* 1997;31:131.
- [2] Lepor H. Pathophysiology of lower urinary tract symptoms in the aging male population. *Rev Urol* 2005;7(Suppl 7):S3.
- [3] Loeb S, Kettermann A, Carter HB, et al. Prostate volume changes over time: results from the Baltimore Longitudinal Study of Aging. *J Urol* 2009;182:1458.

- [4] Marberger MJ, Andersen JT, Nickel JC, et al. Prostate volume and serum prostate-specific antigen as predictors of acute urinary retention. Combined experience from three large multinational placebo-controlled trials. *Eur Urol* 2000;38:563.
- [5] Roehrborn CG, McConnell J, Bonilla J, et al. Serum prostate specific antigen is a strong predictor of future prostate growth in men with benign prostatic hyperplasia. PROSCAR long-term efficacy and safety study. *J Urol* 2000;163:13.
- [6] Hochberg DA, Armenakas NA, Fracchia JA. Relationship of prostate-specific antigen and prostate volume in patients with biopsy proven benign prostatic hyperplasia. *Prostate* 2000;45:315.
- [7] Mochtar CA, Kiemeny LA, van Riemsdijk MM, et al. Prostate-specific antigen as an estimator of prostate volume in the management of patients with symptomatic benign prostatic hyperplasia. *Eur Urol* 2003;44:695.
- [8] Yuan XD, Dong ZG, Zhang H, et al. Distribution of serum prostate-specific antigen in Chinese healthy men: a population-based study. *Chin Med J (Engl)* 2011;124:1189.
- [9] Chung BH, Hong SJ, Cho JS, et al. Relationship between serum prostate-specific antigen and prostate volume in Korean men with benign prostatic hyperplasia: a multicentre study. *BJU Int* 2006;97:742.
- [10] Vignozzi L, Gacci M, Maggi M. Lower urinary tract symptoms, benign prostatic hyperplasia and metabolic syndrome. *Nat Rev Urol* 2016;13:108.
- [11] Yang TK, Hsieh JT, Chen SC, et al. Metabolic syndrome associated with reduced lower urinary tract symptoms in middle-aged men receiving health checkup. *Urology* 2012;80:1093.
- [12] Kim JH, Doo SW, Yun JH, et al. Lower likelihood of having moderate-to-severe lower urinary tract symptoms in middle-aged healthy Korean men with metabolic syndrome. *Urology* 2014;84:665.
- [13] Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi* 1984;85:1001.
- [14] Migita K, Takayama T, Saeki K, et al. The prognostic nutritional index predicts long-term outcomes of gastric cancer patients independent of tumor stage. *Ann Surg Oncol* 2013;20:2647.
- [15] Rhodes T, Girman CJ, Jacobsen SJ, et al. Longitudinal prostate growth rates during 5 years in randomly selected community men 40 to 79 years old. *J Urol* 1999;161:1174.
- [16] Masumori N, Tsukamoto T, Kumamoto Y, et al. Japanese men have smaller prostate volumes but comparable urinary flow rates relative to American men: results of community based studies in 2 countries. *J Urol* 1996;155:1324.
- [17] Park J, Lee DG, Suh B, et al. Establishment of reference ranges for prostate volume and annual prostate volume change rate in Korean adult men: analyses of a nationwide screening population. *J Korean Med Sci* 2015;30:1136.
- [18] Sarma AV, Jaffe CA, Schottenfeld D, et al. Insulin-like growth factor-1, insulin-like growth factor binding protein-3, and body mass index: clinical correlates of prostate volume among Black men. *Urology* 2002;59:362.
- [19] Gupta A, Aragaki C, Gotoh M, et al. Relationship between prostate specific antigen and indexes of prostate volume in Japanese men. *J Urol* 2005;173:503.
- [20] Rohrmann S, Smit E, Giovannucci E, et al. Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III). *Int J Obes (Lond)* 2005;29:310.
- [21] Nandeesh H, Koner BC, Dorairajan LN, et al. Hyperinsulinemia and dyslipidemia in non-diabetic benign prostatic hyperplasia. *Clin Chim Acta* 2006;370:89.
- [22] Gacci M, Corona G, Vignozzi L, et al. Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis. *BJU Int* 2015;115:24.
- [23] Mei X, Atkinson D. Lipid-free Apolipoprotein A-I Structure: Insights into HDL Formation and Atherosclerosis Development. *Arch Med Res* 2015;46:351.
- [24] Motta M, Bennati E, Cardillo E, et al. The significance of apolipoprotein-B (Apo-B) in the elderly as a predictive factor of cardio-cerebrovascular complications. *Arch Gerontol Geriatr* 2009;49:162.
- [25] Talmud PJ, Hawe E, Miller GJ, et al. Nonfasting apolipoprotein B and triglyceride levels as a useful predictor of coronary heart disease risk in middle-aged UK men. *Arterioscler Thromb Vasc Biol* 2002;22:1918.
- [26] Sung KC, Hwang ST. Association between insulin resistance and apolipoprotein B in normoglycemic Koreans. *Atherosclerosis* 2005;180:161.
- [27] Pan JG, Liu M, Zhou X. Relationship between lower urinary tract symptoms and metabolic syndrome in a Chinese male population. *J Endocrinol Invest* 2014;37:339.
- [28] Rohrmann S, Crespo CJ, Weber JR, et al. Association of cigarette smoking, alcohol consumption and physical activity with lower urinary tract symptoms in older American men: findings from the third National Health and Nutrition Examination Survey. *BJU Int* 2005;96:77.
- [29] Allen NE, Appleby PN, Davey GK, et al. Lifestyle and nutritional determinants of bioavailable androgens and related hormones in British men. *Cancer Causes Control* 2002;13:353.
- [30] Platz EA, Rimm EB, Kawachi I, et al. Alcohol consumption, cigarette smoking, and risk of benign prostatic hyperplasia. *Am J Epidemiol* 1999;149:106.
- [31] Sea J, Poon KS, McVary KT. Review of exercise and the risk of benign prostatic hyperplasia. *Phys Sportsmed* 2009;37:75.
- [32] Dahle SE, Chokkalingam AP, Gao YT, et al. Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia. *J Urol* 2002;168:599.
- [33] Mancini V, Balzarro M, Illiano E, et al. Lower urinary tract symptoms in elderly men: a simple yet comprehensive approach. *J Gerontol Geriatr* 2008;66:245.
- [34] Cormio L, Cindolo L, Troiano F, et al. Development and internal validation of novel nomograms based on benign prostatic obstruction-related parameters to predict the risk of prostate cancer at first prostate biopsy. *Front Oncol* 2018;8:438.
- [35] Tan HY, Choo WC, Archibald C, et al. A community based study of prostatic symptoms in Singapore. *J Urol* 1997;157:890.