

## Original Research Article

# Association of metabolic syndrome with intravesical prostatic protrusion and international prostatic severity symptoms score in patients with benign prostatic enlargement

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## ABSTRACT

**Background:** Intravesical prostatic protrusion (IPP), a morphological change resulting from enlarged lateral and median lobe of prostate. It could be for assessment of BOO (Bladder outlet obstruction). MetS is one of the causative factors for the development of Benign Prostatic Enlargement (BPE) and associated LUTS. The aim of this study is to assess the association of components of MetS and MetS with IPP, TPV and International Prostatic Severity Symptoms Score (IPSS).

**Methods:** This is a single centre cross-sectional study in Department of Urology, GMCH, Guwahati, Assam, India between March 2016 and May 2018, 114 consecutive men aged >50 years presenting with LUTS suggestive of BPE (PSA 0-4ng/ml). MetS was defined according to International Diabetes Federation criteria. We have analysed IPSS and IPP of these patients. Patients were classified into 3 groups each for IPSS and IPP (IPSS: group I - 0-7, II -8-19, III ->20 and IPP: Group I- <5 mm, II- 5-10 mm, III- >10 mm).

**Results:** We have correlated these groups with each component of MetS and MetS. IPSS group III had significant correlation with hyperglycaemia (HG), hypertriglyceridemia (HTG), hypertension (HTN) and HDL cholesterol (HDL), group II had significant correlation with HG, HTN and HDL and group I had significant correlation with HTN ( $p<0.001$ ). Similarly, IPP group III had significant correlation with HG, HTG, HTN, obesity and HDL, group II had significant correlation with HG, HTN and obesity and group I had significant correlation with HTN only ( $p<0.001$ ).

**Conclusions:** We found that patients with higher IPSS and IPP had significant correlation with MetS components.

**Keywords:** Benign prostatic enlargement, Intravesical prostatic protrusion, International prostatic severity symptoms score, Metabolic syndrome, Lower urinary tract symptoms

## INTRODUCTION

It is known benign prostatic enlargement (BPE) gives rise to LUTS and bladder outlet obstruction (BOO).<sup>1</sup> Prostate enlargement is also manifested by the development of intravesical prostatic protrusion (IPP), a morphological change resulting from enlarged lateral lobes and median

lobe.<sup>2</sup> It has also been suggested that a prostatic mass with greater protrusion causes more severe voiding dysfunction by causing more serious BOO.<sup>3</sup> Many investigators have made efforts to evaluate the severity of BOO or overactive bladder in a non-invasive manner; for example, by using transabdominal ultrasonography to estimate bladder weight, surface area, bladder wall

thickness and IPP.<sup>4,5</sup> Multiple reports have examined the utility of IPP as a marker of BOO (which should be confirmed by urodynamic or video-urodynamics studies) and IPP has been reported to be a useful anatomical measure for the assessment of BOO.<sup>4</sup> IPP is useful in evaluating BOO because of its good correlation with conventional pressure flow study and with detrusor function.<sup>6</sup> According to previous studies, IPP is significantly correlated with increased total prostate volume (TPV), greater obstructive symptoms, decreased maximum urinary flow rate (peak flow), and increased post-void residual urine volume (PVR), which suggests that IPP may have clinical usefulness in predicting the need for treatment.<sup>7</sup>

The aetiology and pathogenesis of LUTS/BPE remains unclear. Well-designed studies are needed to assess the effect of morphological features of BPE on LUTS according to the presence of MetS and to determine whether there is a significant correlation between LUTS (IPSS), TPV and IPP with MetS. The aim of this study is to assess the association of MetS and its components with IPP, TPV, and IPSS.

## METHODS

This is a single centre cross-sectional study in Department of Urology, GMCH, Guwahati, Assam, India between March 2016 to May 2018, 114 consecutive men aged >50 years presenting with lower urinary tract symptoms (LUTS) suggestive of BPE (PSA 0-4ng/ml) were recruited to this single centre cross-sectional observational study with informed consent.

The exclusion criteria included: 5- $\alpha$  reductase inhibitor therapy, neurogenic bladder dysfunction, history of prostatic and/or urethral surgery, history of bladder cancer, gross haematuria and urinary infection, PSA >4 ng/mL and diagnosis of prostate cancer, previous lower urinary tract or pelvic surgery and radiation therapy. Men with incomplete data were excluded from the statistical analysis.

Evaluation of the participants in the study included DRE, IPSS, and USG KUBP. Each participant completed the IPSS questionnaire and PSA values were obtained. TPV and IPP were measured using USG KUBP. IPP was assessed by measuring the vertical distance from the tip of the protrusion to the circumference of the bladder at the base of the prostate gland and classified as grade I (<5 mm), II (5-10 mm) and III (>10 mm). TPV was automatically calculated in mm<sup>3</sup> after the measurement of their largest antero-posterior (height, H), transverse (width, W), and cephalocaudal (length, L) diameters, using the formula  $H \times W \times L \times 0.52$ . All measurements were carried out with the bladder containing approximately 150 ml of urine, which was confirmed after ultrasonography by measuring voided urine. Blood samples were drawn from the participants after an overnight fast, and serum PSA, fasting blood glucose,

high-density lipoprotein (HDL), triglyceride levels and blood pressure were recorded. LUTS were evaluated by culturally and linguistically validated versions of IPSS. LUTS severity was classified as mild (IPSS 0-7), moderate (IPSS 8-19) and severe (IPSS 20-35).

International diabetes federation criteria were used to define MetS in the presence of central obesity (defined as waist circumference  $\geq 94$  cm for European ethnic group) and two or more of the four characteristics: triglycerides  $\geq 150$  mg/dl or treatment for hypertriglyceridaemia; HDL cholesterol <40 mg/dl or treatment for reduced HDL cholesterol; blood pressure  $\geq 130/85$  mmHg or current use of antihypertensive medications and fasting blood glucose >100 mg/dl or previous diagnosis of type 2 diabetes mellitus. All the MetS components were considered individually (single variables above vs below defined thresholds) and combined, according to MetS (presence or absence). Poor response to medication has been considered as the lack of a decrease of 35% in IPSS after 12 weeks of  $\alpha$ -blocker therapy.

## Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS, Cary, NC, USA). Continuous variables are presented as median (interquartile range) and differences between groups were tested using Student's independent t-test or the Mann-Whitney U-test according to their normal or non-normal distribution, respectively (normality of variables' distribution was tested by Kolmogorov-Smirnov test). Age-adjusted linear regression models were performed to verify factors associated with IPP and TPV. Multivariate logistic regression models were constructed to identify predictive factors of IPP and TPV by including all collected variables.

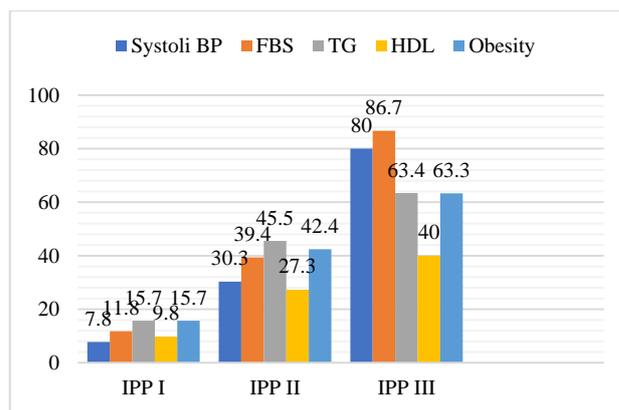
## RESULTS

Characteristics of participants in terms of age, PSA value, TPV, IPSS, IPP grade, systolic BP, Fasting blood sugar, Triglycerides, HDL cholesterol, obesity and their correlation with MetS shown in Table 1. Medications taken by the participants were as follows: 94 (82.4%) were on  $\alpha$ -blocker therapy and 102 underwent surgery (89.4%). MetS was present in 36 out of 114 participants (31.5%) with average age 71.3 years old. Patient with MetS had average TVP 64.6 gms. Figure 1 showing Correlation of systolic blood pressure, fasting blood sugar, triglycerides, high density lipoprotein and obesity with IPSS group with highest proportion of hypertensive (65.2%), diabetic (71.7%), hyperlipidemic (58.7%), low HDL (34.8%) and obese (56.5%) patients in IPSS III group. Lowest proportion of patients in IPSS I group, hypertensive (7.1%), while no diabetic, hyperlipidemic, obese patients, and no patient with low HDL. Significant difference between IPSS I, II and III group in terms of above mentioned parameters (<0.001). Figure 2 showing that MetS significantly associated with IPSS (<0.001) with

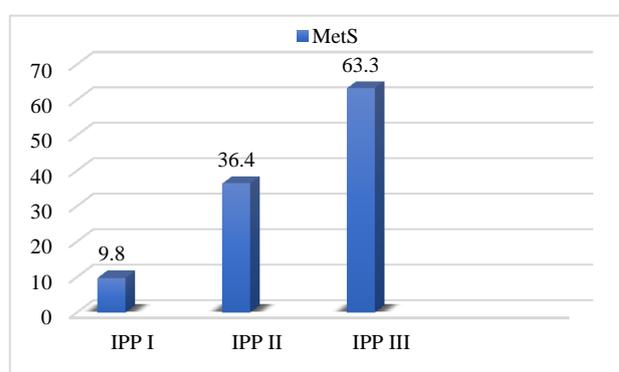
highest numbers of patients in group III (54.3%) and MetS was not present in group I. Correlation of systolic blood pressure, fasting blood sugar, triglycerides, high density lipoprotein and obesity with IPP group shown in Figure 3. Highest proportion of hypertensive (80%), diabetic (86.7%), hyperlipidemic (63.4%), low HDL (40.0%) and obese (63.3%) patients in IPP III group. Lowest proportion of patients in IPP I group, hypertensive (7.8%), diabetic (11.8%), hyperlipidemic (15.7%), low HDL (9.8%) and obese (15.7%) patients. Significant difference between IPP I, II and III group in terms of above mentioned parameters (<0.001).

**Table 1: Characteristics in terms of age, PSA value, TPV, IPSS, IPP grade, systolic BP, fasting blood sugar, triglycerides, HDL cholesterol and obesity.**

Characteristics	No MetS (n=78)	Met S (n=36)	P value
Age	71.3	71.4	0.937
PSA	1.8 (0.6-2.8)	1.5 (1.0-3.2)	0.34
TPV	62.82	64.50	0.642
IPSS	17.54	25.83	<0.001
IPP	6.18	11.53	<0.001
Systolic BP	124.95	150.61	<0.001
Fasting blood glucose	89.27	167.42	<0.001
Triglycerides	139.18	179.69	<0.001
HDL cholesterol	52.27	36.53	<0.001
Obesity (n)	5	36	



**Figure 3: Correlation of systolic BP, FBS, TG, HDL and obesity with IPP group.**



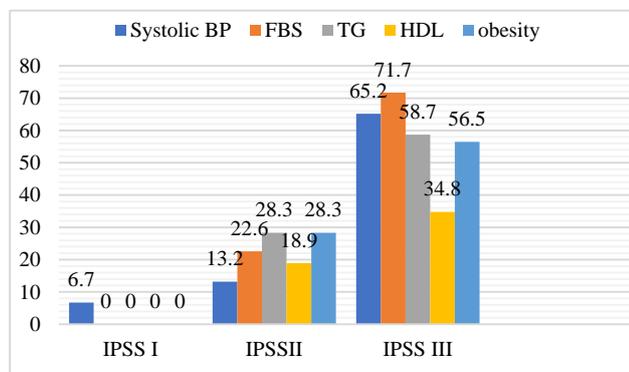
**Figure 4: Correlation of MetS with IPP group.**

Figure 4 is showing that MetS significantly associated with IPP (<0.001) with highest proportion of patients in group III (63.3%) and lowest proportion of MetS in group I (9.8%).

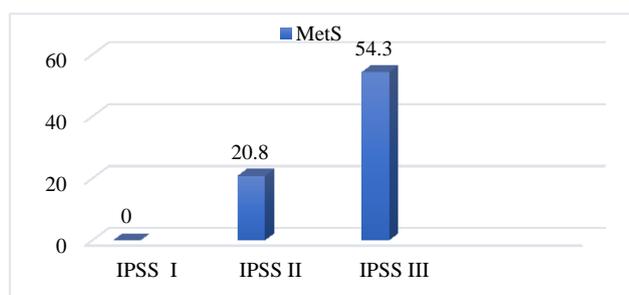
**DISCUSSION**

In present study, we investigated the correlation of hypertension, hyperglycaemia, hyperlipidaemia, low HDL and obesity with IPSS and IPP groups. It has been found that MetS was not only associated with increase in prostate size, but also with increasing grade of IPSS and IPP, supporting the association between metabolic alterations and clinical increase in prostate volume. MetS was significantly associated with IPSS (<0.001) with highest numbers of patients in group III (54.3%) and IPP (<0.001).

Russo et al found an association between MetS and BPE, demonstrating a relationship with IPP. They analysed 224 patients aged >50 years presenting with lower urinary tract symptoms (LUTS) suggestive of BPE. MetS was present in 46 out of 224 participants, and found that MetS was significantly associated with IPP ≥10 mm (p<0.01), TZV ≥20 ml (p<0.01) and TPV ≥40 ml (p=0.03). Further, IPP ≥10 mm and MetS were associated with greater risk



**Figure 1: Correlation of systolic BP, FBS, TG, HDL and obesity with IPSS group.**



**Figure 2: Correlation of MetS with IPSS group.**

of having IPSS  $\geq 20$  ( $p < 0.05$ ).<sup>9</sup> Their results correlated with our study.

Gacci et al showed a significant difference in MetS-dependent prostate growth in men with a prostate volume  $>30$  ml or  $<30$  ml (3.4 ml vs 1.99 ml, respectively). Moreover, their meta-regression analysis suggested obese, dyslipidaemic and elderly patients were more at risk of MetS being a determinant of their increased prostate size. Present study also suggested that obese and dyslipidemic patients had high IPSS and IPP.<sup>10</sup> They also found that MetS-induced differences in prostate volumes were greater in patients with metabolic disorders. This inference correlated well with our study which also showed that MetS patients had IPSS III in 54.3% and IPP III in 63.3% patients.

The features of MetS that represent the trigger causes associated with BPE/LUTS are central obesity, lipid disorder and hyperinsulinaemia.<sup>11</sup> These alterations include an increase in the activity of the sympathetic nervous system and muscle tone of the prostate, resulting in more severe LUTS independent of prostate enlargement.<sup>12,13</sup> Furthermore, reduced HDL cholesterol and increased triglyceride levels were significantly related to higher prostatic inflammation by secreting interleukin-8 in response not only to oxidated LDL, but also to insulin, indicating that different MetS features could synergistically boost inflammation and tissue remodelling in BPH/LUTS.<sup>14,15</sup>

Lotti et al showed that waist size and reduced HDL cholesterol level were significantly associated with prostate volume. In addition, similarly to the TPV results, TZV was significantly associated with reduced HDL cholesterol levels (hazard ratio 1.15).<sup>13</sup> Similar correlation was found in our study.

St Sauver et al in a retrospective population-based cohort study in 2447 men aged 40–79 years, showed that statin therapy was associated with a 6.5 to 7 year delay in the new onset of moderate/severe LUTS/BPE.<sup>14</sup> Dyslipidaemia could have a detrimental effect on prostate cells, boosting prostate inflammation, a key factor in the development and progression of BPH/LUTS.

Recently, IPP has been studied as a non-invasive test in diagnosing BOO in men with LUTS.<sup>4,7</sup> A systematic review of the overall literature reported that five studies used a threshold of 10 mm to define BOO and found similar diagnostic accuracy for uroflowmetry alone with a median sensitivity of 67.8% and specificity of 74.8%. A positive predictive value of 73.8% and a negative predictive value of 69.3%.<sup>16</sup>

Kyung et al in a longitudinal analysis during a 5-year period, showed that changes in weight and MetS status were significantly associated with the prostate growth rate. Moreover, MetS diagnosis affected the prostate growth rate could be decreased by controlling for MetS.<sup>17</sup>

It could be speculated that the counteracting release of inflammatory mediators by adipose tissue, increasing HDL cholesterol and decreasing triglyceride levels, could reverse the prostate volume increase. New evidence suggests that metformin could also have the effect of reducing metabolic stress conditions and activating lipophagy mechanisms through activation of AMPK-independent mechanisms.<sup>14</sup> We are still far from this application in patients affected by BPH/LUTS, but the targeting of coexisting inflammation is crucial for this condition.<sup>14,18</sup> The present study has several limitations. Firstly, we did not investigate the role of cytokines and inflammatory markers in patients with IPP or their relationship with MetS. Secondly, the study was cross-sectional and we are yet to demonstrate the impact of metabolic alterations on the onset of IPP in a longitudinal model. Thirdly, we did not adjust for the use of statins or metformin. We did, however, determine that MetS is associated with an increase in IPP together with an increase in prostate volume, explaining the lack of response to medical therapy in those patients with metabolic alterations and LUTS/BPE.

## CONCLUSION

We found that metabolic alterations, including low HDL cholesterol, hypertension, high triglycerides, hyperglycaemia and obesity are associated with increased risk of IPP  $\geq 10$  mm and IPSS  $\geq 19$ . Moreover, an IPP  $\geq 10$  mm and IPSS  $\geq 19$  were associated with MetS and a lack of satisfaction with therapy. These results offer new insights into the link between metabolic alterations and BPE.

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