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Association between metabolic syndrome and intravesical prostatic protrusion in patients with benign prostatic enlargement and lower urinary tract symptoms (MIPS Study)

Giorgio I. Russo*, Federica Regis*, Pietro Spatafora†, Jacopo Frizzi†, Daniele Urzì*, Sebastiano Cimino*, Sergio Serni†, Marco Carini†, Mauro Gacci† and Giuseppe Morgia*

*Urology Section, Department of Surgery, University of Catania, Catania, Italy, and †Department of Urology, University of Florence, Florence, Italy

Objective

To investigate the association between metabolic syndrome (MetS) and morphological features of benign prostatic enlargement (BPE), including total prostate volume (TPV), transitional zone volume (TZV) and intravesical prostatic protrusion (IPP).

Patients and Methods

Between January 2015 and January 2017, 224 consecutive men aged >50 years presenting with lower urinary tract symptoms (LUTS) suggestive of BPE were recruited to this multicentre cross-sectional study. MetS was defined according to International Diabetes Federation criteria. Multivariate linear and logistic regression models were performed to verify factors associated with IPP, TZV and TPV.

Results

Patients with MetS were observed to have a significant increase in IPP ($P < 0.01$), TPV ($P < 0.01$) and TZV ($P = 0.02$). On linear regression analysis, adjusted for age and metabolic factors of MetS, we found that high-density lipoprotein (HDL) cholesterol was negatively associated with IPP ($r = -0.17$), TPV ($r = -0.19$) and TZV ($r = -0.17$), while hypertension was positively associated with IPP ($r = 0.16$), TPV ($r = 0.19$) and TZV ($r = 0.16$). On multivariate logistic regression analysis adjusted for age and factors of MetS, hypertension (categorical; odds ratio [OR] 2.95), HDL cholesterol (OR 0.94) and triglycerides (OR 1.01) were independent predictors of TPV ≥ 40 mL. We also found that HDL cholesterol (OR 0.86), hypertension (OR 2.0) and waist circumference (OR 1.09) were significantly associated with TZV ≥ 20 mL. On age-adjusted logistic regression analysis, MetS was significantly associated with IPP ≥ 10 mm (OR 34.0; $P < 0.01$), TZV ≥ 20 mL (OR 4.40; $P < 0.01$) and TPV ≥ 40 mL (OR 5.89; $P = 0.03$).

Conclusion

We found an association between MetS and BPE, demonstrating a relationship with IPP.

Keywords

metabolic syndrome, lower urinary tract symptoms, benign prostatic enlargement, prostate volume, intravesical prostatic protrusion

Introduction

It is known that LUTS secondary to benign prostatic enlargement (BPE) develop through BOO [1]. Chia et al. [2] suggested that prostate enlargement is also manifested by the development of intravesical prostatic protrusion (IPP), a morphological change resulting from enlarged lateral lobes and median lobe. It has thus also been suggested that a prostatic mass with greater protrusion causes more severe voiding dysfunction by causing more serious BOO [3]. 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 [4,5]. Prostatic protrusion into the bladder often occurs as a result of morphological changes during an individual's lifetime [6]. Multiple reports have examined the utility of IPP as a marker of BOO in men (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 [7]. IPP is useful in evaluating BOO because of its good

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correlation with conventional pressure flow study and with detrusor function.

According to previous studies, IPP is significantly correlated with increased total prostate volume (TPV), increased transitional zone volume (TZV), 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 [2,8].

The aetiology and pathogenesis of LUTS/BPE remain unclear, but it has been established that metabolic syndrome (MetS) is one of the causative factors for the development of BPE in aging men [9] and MetS is associated with TPV and TZV [10,11]. 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 IPP and MetS in men with BOO. The aim of the present study, therefore, was to analyse the association between MetS and morphological features of BPE.

Patients and Methods

Between January 2015 and January 2017, 224 consecutive men aged >50 years presenting with LUTS (IPSS ≥ 8) secondary to BPE were recruited to this multicentre cross-sectional study.

All participants received a detailed description of the study protocol and completed the informed consent process. The protocol was approved by the internal institutional review board (Ethics Committee Approval #90/2015). Evaluation of the study participants included DRE, IPSS, uroflowmetry and TRUS of the prostate. Before the undergoing TRUS, each participant completed the IPSS questionnaire, and PSA values and uroflowmetry results, showing the peak flow value, were obtained. For uroflowmetry, the voided volumes had to be >150 mL to avoid bias.

The main diameters of the prostate, TPV, TZV and IPP were measured using TRUS. 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. TPV was automatically calculated in mm by Ultrasonography after the measurement of their largest antero-posterior (height, *H*), transverse (width, *W*), and cephalocaudal (length, *L*) diameters, using the formula $H^*W^*L^*0.52$.

During this examination, similar methods were also used to determine the TZV, based on a previous publication [12].

All measurements were carried out with the bladder containing 100–150 mL of urine, which was confirmed after ultrasonography by measuring voided urine. Blood samples were drawn from participants after an overnight fast, and serum PSA, fasting blood glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol, and triglyceride levels 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 [13] in the presence of central obesity (defined as waist circumference ≥94 cm for European ethnic group) and two or more of the four characteristics: triglycerides ≥150 mg/dL or treatment for hypertriglyceridaemia; HDL cholesterol <40 mg/dL or treatment for reduced HDL cholesterol; blood pressure ≥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 or lack of at least a 1.6-mL/s improvement in the maximum urinary flow rate after 12 weeks of α-blocker therapy.

The exclusion criteria included: maximum urinary flow rate >20 mL/s; IPSS < 8; 5-α 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.

Statistical analysis

Statistical analysis was performed using SPSS version 10.5 (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, TZV and TPV. Multivariate logistic regression models were constructed to identify predictive factors of IPP, TZV and TPV by including all collected variables.

All tests were completed using SPSS v. 19 software (SPSS Inc., IBM Corp, Somers, NY, USA). *P* values of < 0.05 were taken to indicate statistical significance.

Results

Table 1 lists the characteristics of participants at time of enrolment. Medications taken by the participants were as

Table 1 Baseline characteristics of patients.

Age, years	61.0 (55.0–67.0)
PSA, ng/mL	1.6 (0.8–3.2)
IPSS, mg/dL	17.0 (11.0–20.0)
IPSS: storage	8.0 (5.0–10.0)
IPSS: voiding	8.0 (6.0–12.0)
Fasting glucose, mg/dL	105.0 (95.0–108.0)
HDL cholesterol, mg/dL	47.0 (41.0–50.0)
Triglycerides, mg/dL	170.0 (147.0–202.0)
Waist circumference, mg/dL	94.0 (90.0–105.0)
Duration of therapy, months	6.0 (0.0–24.0)
IPP, mg/dL	7.0 (4.0–16.0)
TPV, mg/dL	48.0 (40.0–68.0)
TZV, mg/dL	15.0 (13.0–22.0)
Q_{max}, mL/s	11.2 (9.7–14.5)
PVR, mL	50.0 (30.0–60.0)
Hypertension, *n* (%)	142 (63.4)
Diabetes, *n* (%)	44 (19.6)
MetS, *n* (%)	46 (20.5)

Data are median (interquartile range), unless otherwise indicated. BMI, body mass index; HDL, high-density lipoprotein; IPP, intravesical prostatic protrusion; MetS, metabolic syndrome; PVR, post-void residual urinve volume; Q_{max}, peak flow rate; TPV, total prostate volume; TZV, transitional zone volume.

follows: 90 (40.2%) were on α-blocker therapy, six (2.7%) were on phytotherapy and 128 (57.1%) were treatment-naïve. MetS was present in 46 out of 224 participants (20.5%). Table 2 shows the comparison of included variables according to the presence of MetS. In particular, we found significant differences when considering IPP ($P < 0.01$), TPV ($P < 0.01$) and TZV ($P = 0.02$). Figure 1 shows that IPP was significantly greater with increasing number of MetS components.

Linear regression analysis, adjusted for age and metabolic components of MetS, showed significant negative associations between HDL and IPP ($r = -0.17$; $P = 0.01$), TPV ($r = -0.19$; $P < 0.01$) and TZV ($r = -0.17$; $P = 0.01$), while hypertension was significantly positively associated with IPP ($r = 0.16$; $P = 0.02$), TPV ($r = 0.19$; $P < 0.01$) and TZV ($r = 0.16$; $P = 0.02$). In addition, the number of MetS components was significantly associated with IPP ($r = 0.23$; $P < 0.01$ [Fig. 1]).

Multivariate logistic regression analysis, adjusted for age and components of MetS, showed that hypertension (categorical; odds ratio [OR] 2.95; $P < 0.01$), HDL cholesterol (OR 0.94; $P < 0.01$) and triglycerides (OR 1.01; $P < 0.05$) were independent predictors of TPV ≥ 40 mL. We also found that HDL cholesterol (OR 0.86; $P < 0.01$), hypertension (OR 2.0; $P < 0.05$) and waist circumference (OR 1.09; $P = 0.01$) were significantly associated with TZV ≥ 20 mL.

Finally, hypertension (categorical; OR 2.70; $P < 0.01$), HDL cholesterol (OR 0.92; $P < 0.05$) and waist circumference (OR 1.04; $P < 0.05$) were independently associated with IPP ≥ 10 mm. Serum glucose level was not significantly associated with TPV, IPP or TZV (Table 3).

On age-adjusted logistic regression analysis, MetS was significantly associated with IPP ≥ 10 mm (OR 34.0; $P < 0.01$), TZV ≥ 20 mL (OR 4.40; $P < 0.01$) and TPV ≥ 40 mL (OR 5.89; $P = 0.03$). Furthermore, IPP ≥ 10 mm and MetS were associated with greater risk of having an IPSS ≥ 20 (OR 2.22; $P < 0.05$) and a poor response to medication (OR 3.72; $P < 0.01$) when compared with presence of MetS only.

Discussion

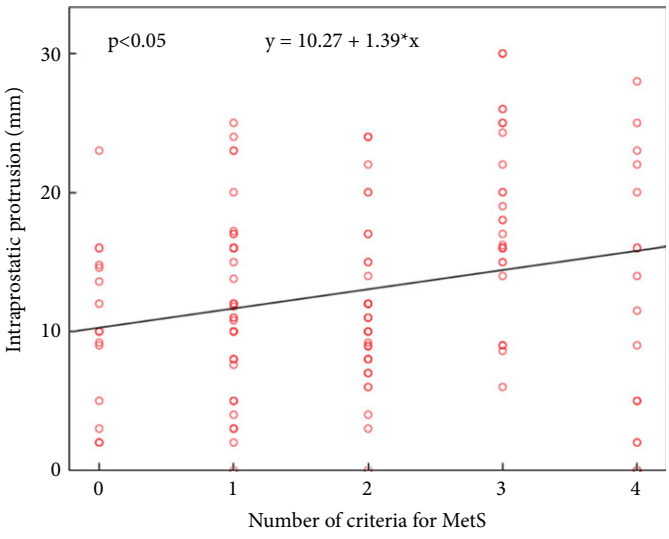
In the present study, we showed that MetS was associated with increases in prostate size, but also with TZV and IPP, supporting the association between metabolic alterations and clinical increase in prostate volume.

Table 2 Characteristics of patients according to the presence of metabolic syndrome.

	No MetS (*n* = 178)	MetS (*n* = 46)	*P*
Age, years	65.0 (55.0–70.0)	56.5 (51.25–60.25)	0.19
PSA, ng/mL	1.8 (0.6–2.8)	1.5 (1.0–3.2)	0.34
IPSS, mg/dL	14.0 (11.0–20.0)	20.0 (17.75–21.50)	0.45
IPSS: storage	8.0 (5.0–11.0)	7.5 (5.5–8.0)	0.82
IPSS: voiding	12.0 (12.0–13.5)	18.0 (13.0–20.0)	0.62
Fasting glucose, mg/dL	96.0 (95.0–105.0)	131.5 (113.0–135.0)	<0.01
HDL cholesterol, mg/dL	48.0 (43.0–51.0)	39.0 (35.25–43.50)	<0.01
Tryglicerides, mg/dL	150.0 (145.0–197.0)	202.5 (170.0–244.75)	<0.01
Waist circumference, mg/dL	93.0 (87.0–96.0)	125.5 (105.5–136.5)	<0.01
Duration of therapy	6.0 (0.0–24.0)	12.0 (0.0–33.0)	<0.01
IPP, mg/dL	5.0 (4.0–10.0)	18.0 (15.25–23.75)	<0.01
TPV, mg/dL	45.0 (39.0–50.0)	69.0 (53.0–74.5)	<0.01
TZV, mg/dL	15.0 (12.0–20.0)	29.0 (14.5–26.5)	0.02
Q_{max}, mL/s	12.8 (9.7–15.7)	11.15 (7.65–12.02)	0.25
PVR, mL	50.0 (30.0–60.0)	65.0 (35.0–87.5)	0.04
Hypertension, *n* (%)	102 (57.3)	40 (87.0)	<0.01
Diabetes, *n* (%)	24 (13.5)	20 43.5)	<0.01

Data are median (interquartile range), unless otherwise indicated. BMI, body mass index; HDL, high-density lipoprotein; IPP, intravesical prostatic protrusion; MetS, metabolic syndrome; PVR, post-void residual urinve volume; Q_{max}, peak flow rate; TPV, total prostate volume; TZV, transitional zone volume.

Fig. 1 Linear regression analysis between intraprostatic protrusion and number of metabolic syndrome components ($P < 0.05$).



Although several studies have shown the link between metabolic alterations and increases in prostate volume, we still do not know the impact of MetS and morphological changes in the prostate gland with regard to middle lobe protrusion or IPP.

A recent meta-analysis by Gacci et al. [9] 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.

Moreover, Gacci et al. [9] found that MetS-induced differences in prostate volumes were greater in patients with metabolic disorders. Hence, obese, dyslipidaemic and elderly patients were more at risk of having MetS as a determinant of their increased prostate size [9].

The features of MetS that represent the trigger causes associated with BPE/LUTS are central obesity, lipid disorder and hyperinsulinaemia. These alterations include an increase in the activity of the sympathetic nervous system and muscle tone of the prostate, resulting in more severe LUTS independently of prostate enlargement [14,15]. 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 [16–18], indicating that different MetS features could synergistically boost inflammation and tissue remodelling in BPH/LUTS [19,20].

Prostatic growth may, however, develop with different patterns and morphological changes. In a study in 379 patients with LUTS, Gacci et al. showed that, in age-adjusted multivariate analyses, systolic blood pressure, serum HDL levels and number of MetS components were still statistically significantly correlated to calculated prostate volume [21]. Moreover, the number of MetS components, was directly associated with calculated prostate volume ($r = 0.244$, $P = 0.001$), and with antero-posterior ($r = 0.231$, $P = 0.002$), cranio-caudal ($r = 0.192$, $P = 0.009$) and latero-lateral prostate diameters ($r = 0.171$, $P = 0.020$ [Fig. 1]).

With regard to morphological increase in prostate diameter, Lotti *et al.* showed that waist size and reduced HDL cholesterol level were significantly associated with prostate volume and that TZV also increased as a function of an increasing number of MetS components. In addition, similarly to the TPV results, TZV was significantly associated with reduced HDL cholesterol levels (hazard ratio 1.15) [22].

Dyslipidaemia could have a detrimental effect on prostate cells, boosting prostate inflammation, a key factor in the development and progression of BPH/LUTS. Interestingly, 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 [23].

Recently, IPP has been studied as a non-invasive test in diagnosing BOO in men with LUTS [24]. A systematic review of the overall literature reported that five studies used a threshold of 10 mm to define BOO, and found similar

Table 3 Age-adjusted multivariate logistic regression for significant predictors of benign prostatic enlargement features.

Predictors	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Waist circumference (cm)	1.04 (1.00–1.07)	<0.05	1.09 (1.02–1.15)	<0.05	1.00 (0.97–1.02)	0.58
Serum glucose (mg/dL)	1.00 (0.99–1.01)	0.27	1.00 (0.99–1.02)	0.39	1.01 (0.99–1.02)	0.54
HDL (mg/dL)	0.92 (0.89–0.96)	<0.05	0.86 (0.75–0.94)	<0.05	0.94 (0.90–0.98)	<0.01
Triglycerides (mg/dL)	1.01 (1.00–1.02)	0.22	1.00 (0.98–1.04)	0.83	1.01 (1.00–1.02)	<0.05
Hypertension (categorical)	2.70 (1.50–5.25)	<0.05	2.00 (1.20–3.80)	<0.05	2.95 (1.50–5.80)	<0.01

Model 1: IPP ≥ 10 mm (independent variables); Model 2: TZV ≥ 20 mL (independent variables); Model 3: TPV ≥ 40 mL (independent variables). IPP, intravesical prostatic protrusion; TZV, transitional zone volume; TPV, total prostate volume.

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% [24].

The presence of median lobe enlargement implies that dyskinetic smooth muscle contraction occurs during micturition [25]. Kyung et al. [26], 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 [26].

Despite the aforementioned links between MetS and increase in prostate volume in men with MetS, the mechanism that may determine the onset of IPP in patients with BPE is not entirely clear. Although we did not investigate the pathogenesis of this process, we showed that metabolic alterations, including low HDL cholesterol, hypertension and high triglycerides, are associated with increased risk of IPP $\geq$ 10 mm. Moreover, an IPP $\geq$ 10 mm together with MetS was associated with a greater risk of having an IPSS $\geq$ 20 and a lack of satisfaction with therapy among patients when compared with the presence of only MetS.

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 [27]. We are still far from this application in patients affected by BPH/LUTS, but the targeting of coexisting inflammation is crucial for this condition [17,18].

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 have 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.

In conclusion, MetS showed a correlation with morphological features of BPE, demonstrating a relationship with IPP. These results offer new insights into the link between metabolic alterations and BPE.

Conflict of Interest

Each author declares no conflict of interest.

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Correspondence: Giorgio Ivan Russo, Urology Section, Department of Urology, University of Catania, Catania 95125, Italy.

e-mail: giorgioivan@virgilio.it

Abbreviations: BPE, benign prostatic enlargement; HDL, high-density lipoprotein; HDL, high-density lipoprotein; IPP, intravesical prostatic protrusion; LDL, low-density lipoprotein; MetS, metabolic syndrome; OR, odds ratio; PVR, post-void residual urine volume; TPV, total prostate volume; TZV, transitional zone volume.