

Central obesity is predictive of persistent storage lower urinary tract symptoms (LUTS) after surgery for benign prostatic enlargement: results of a multicentre prospective study

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Objective

To evaluate the impact of components of metabolic syndrome (MetS) on urinary outcomes after surgery for severe lower urinary tract symptoms (LUTS) due to benign prostatic enlargement (BPE), as central obesity can be associated with the development of BPE and with the worsening of LUTS.

Patients and Methods

A multicentre prospective study was conducted including 378 consecutive men surgically treated for large BPE with simple open prostatectomy (OP) or transurethral resection of the prostate (TURP), between January 2012 and October 2013. LUTS were measured by the International Prostate Symptom Score (IPSS), immediately before surgery and at 6–12 months postoperatively. MetS was defined according the USA National Cholesterol Education Program-Adult Treatment Panel III.

Results

The improvement of total and storage IPSS postoperatively was related to diastolic blood pressure and waist

circumference (WC). A WC of >102 cm was associated with a higher risk of an incomplete recovery of both total IPSS (odds ratio [OR] 0.343, $P = 0.001$) and storage IPSS (OR 0.208, $P < 0.001$), as compared with a WC of <102 cm. The main limitations were: (i) population selected from a tertiary centre, (ii) Use exclusively of IPSS questionnaire, and (iii) No inclusion of further data.

Conclusions

Increased WC is associated with persistent postoperative urinary symptoms after surgical treatment of BPE. Obese men have a higher risk of persistent storage LUTS after TURP or OP.

Keywords

benign prostatic enlargement, benign prostatic hyperplasia, lower urinary tract symptoms, metabolic syndrome, waist circumference

Introduction

Excess bodyweight has progressively increased since the 1980s, rapidly becoming a worldwide epidemic disorder with a remarkable socioeconomic impact, due to its association with increased morbidity and mortality [1].

Central obesity is also considered an early step in the development and progression of metabolic syndrome (MetS), a cluster of several medical conditions in addition to abdominal obesity, including diabetes, dyslipidaemia (high

triglycerides and low high-density lipoprotein [HDL] cholesterol), autonomic hyperactivity and arterial hypertension [2]. In particular, visceral adipose tissue secretes various bioactive substances that can induce inflammatory responses and have proinflammatory effects. The progressive development of inflammation in men with MetS may explain the emerging link between MetS, benign prostatic enlargement (BPE) and LUTS [3–5].

In 1985, Glynn et al. [6] noted that in the Veterans Administration Normative Aging Study, only body mass

index (BMI) was a significant predictor of a clinical diagnosis of BPH. Giovannucci et al. [7], 20 years ago, described the association between obesity (measured as waist circumference, WC) and BPH in a population of men followed for incidence of prostatectomy, suggesting that central obesity could worsen urinary symptoms and increase the risk of prostatic surgery. These data have recently been confirmed in a retrospective study showing that in patients with a larger WC there was an enhanced prevalence of MetS components, with the consequence of worsened voiding function [8].

The aim of the present multicentre prospective study was to evaluate the impact of the components of MetS on urinary outcomes after simple open prostatectomy (OP) or TURP for severe LUTS due to BPE.

Patients and Methods

Between January 2012 and September 2013, 378 consecutive men treated with simple OP or TURP for large BPE, were prospectively enrolled in two tertiary referral centres. In both high-volume referral centres, all patients included in this trial were managed by surgeons skilled in the diagnosis and treatment of BPE. The study did not require any deviation of the Good Clinical Practice and was conducted in accordance with the principles expressed in the Declaration of Helsinki. Inclusion criteria were: prostatectomy (TURP or OP) for moderate-to-severe LUTS due to BPE refractory to medical treatment, and ability to communicate and comply with study requirements. Exclusion criteria were: history of preceding prostate surgery, chronic medication for prostatitis and/or urinary infection or bladder stone, and known malignant disease including prostate cancer.

LUTS were measured by the IPSS and categorised as storage and voiding symptoms, immediately before surgery and at 6–12 months postoperatively. The total IPSS score was categorised into 0–7, 8–19, 20–35; storage subscore into 0–5, 6–9 and 10–15; voiding subscore into 0–6, 7–13 and 14–20 as mild, moderate and severe, respectively. For all IPSS (total, storage and voiding) the percentage of recovery of urinary symptoms after the operation (total-, storage- and voiding- Δ IPSS) was calculated using the following method: $([\text{Preoperative IPSS} - \text{Postoperative IPSS}]/\text{Preoperative IPSS})$, expressed as a percentage: the full recovery of lower urinary tract function was considered as $\Delta = 100\%$.

The PSA level and prostate volume (by ultrasound) were measured before hospitalisation. OP and TURP were performed as previously reported [9,10].

MetS Parameters

MetS was defined according the USA National Cholesterol Education Program (NCEP)-Adult Treatment Panel III,

which requires at least three of the following five components: central obesity (WC of >102 cm), elevated triglycerides (≥ 1.7 mmol/L or 150 mg/dL), elevated blood pressure (BP $\geq 130/85$ mmHg), elevated fasting glucose (≥ 6.1 mmol/L or 110 mg/dL) and reduced HDL cholesterol (<1.03 mmol/L or 40 mg/dL) [11].

WC and BP were measured by trained personnel using a standardised protocol. In particular, WC was measured midway between the lowest rib and the iliac crest, to the nearest 0.1 cm. Blood samples were drawn in the morning, after an overnight fast, for determination of blood glucose, total cholesterol, HDL cholesterol and triglycerides, 7–30 days preoperatively.

Statistical Analyses

The differences between men with MetS and without MetS were assessed by unpaired *t*-test (if normal) or with Mann–Whitney test (in the remaining cases). The correlations between all the recorded items and the improvement of urinary symptoms (total-, storage- and voiding- Δ IPSS) were calculated by a Spearman correlation analysis; significant data were included in a multivariate logistic regression analysis. Moreover, we included significant data in a binary logistic model to evaluate the odds ratio (OR) based on full recovery of lower urinary tract function (Δ IPSS = 100%) vs partial recovery (Δ IPSS $<100\%$). All the analyses were done with SPSS statistics 17.0 version for windows XP and a $P < 0.05$ was considered to indicate statistical significance.

Results

In all, 378 unselected consecutive men were recruited in two tertiary referral centres for surgical treatment of BPE. Overall, 191 patients (50.5%) presented moderate LUTS, while 187 (49.5%) had severe LUTS. According to the IPSS subscores, 53 (14.3%), 211 (55.7%) and 114 (30%) patients presented with mild, moderate or severe voiding LUTS, respectively. In addition, 80 (21.2%), 149 (39.4%) and 149 (39.4%) presented with mild, moderate or severe storage LUTS, respectively. Preoperative patient's characteristics, stratified according to MetS diagnosis, are reported in Table 1. As expected, there was a significant difference between the population according to weight and BMI (both $P < 0.001$). Patients with MetS showed milder preoperative voiding symptoms and worse postoperative storage symptoms as compared with those without MetS (Table 1). In addition, an increasing number of MetS components resulted in increased postoperative storage IPSS scores (age-adjusted Wald 1.090, $P = 0.009$; Fig. 1).

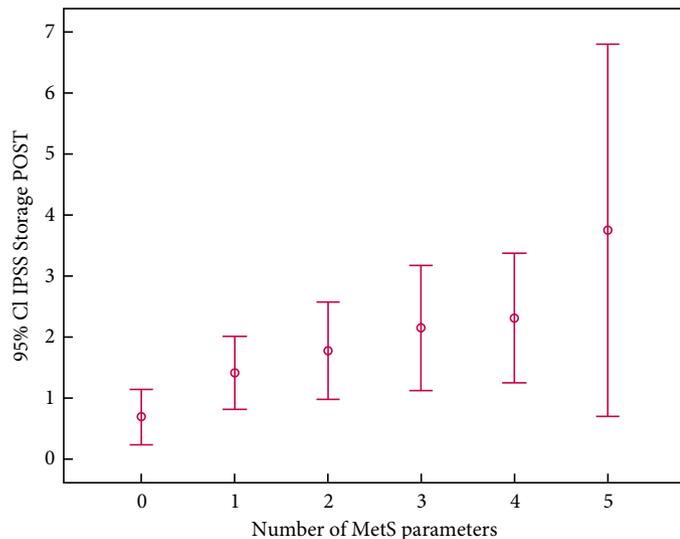
Overall, 220 patients (58.2%) reported a complete recovery of their lower urinary tract function (total- Δ IPSS 100%), while the remaining 158 (41.8%) had an incomplete recovery; in particular, 222 men (58.7%) reported a complete recovery of

Table 1 Descriptive statistics of population of men included in the study, stratified according to their MetS profile.

Patients (n = 378)	With MetS (n = 140) Mean (SD)	Without MetS (n = 238) Mean (SD)	P
Demographic			
Age, years	69.7 (7.4)	68.5 (8.8)	0.187
Weight, kg	81.5 (12.0)	77.3 (8.5)	0.000
Height, m	1.72 (0.1)	1.73 (0.1)	0.136
BMI, kg/m ²	27.4 (3.5)	25.7 (2.3)	<0.001
Prostate features			
Prostate volume, mL	79.1 (42.3)	88.6 (58.2)	0.110
PSA level, ng/mL	2.6 (3.0)	1.9 (1.9)	0.143
Preoperative uroflowmetry			
Q _{max} , mL/s	8.9 (3.5)	8.8 (3.6)	0.905
Q _{ave} , mL/s	5.5 (2.4)	5.2 (2.2)	0.438
Voided volume, mL	248 (46.5)	257 (58.3)	0.398
Preoperative IPSS			
Total	20.0 (5.7)	20.5 (4.8)	0.454
Voiding	11.1 (4.2)	12.3 (4.1)	0.024
Storage	8.9 (3.7)	8.7 (3.2)	0.603
Postoperative IPSS			
Total	2.2 (3.8)	1.5 (3.3)	0.077
Voiding	0.5 (1.7)	0.6 (1.1)	0.413
Storage	2.3 (3.6)	1.3 (2.5)	0.015

Q_{ave}, average urinary flow rate; Q_{max} maximum urinary flow rate.

Fig. 1 The mean and 95% CI of the mean of postoperative IPSS storage score, stratified according to the number of MetS parameters (age-adjusted Wald 1.090, P = 0.009).



their storage symptoms and 293 (77.5%) of their voiding symptoms. According to the postoperative IPSS subscores, 355 (93.9%), 20 (5.3%) and three (0.8%) patients had mild, moderate or severe LUTS, respectively. Categorising for voiding and storage IPSS, 372 (98.4%) and six (1.6%) patients, had mild or moderate voiding LUTS, while 350 (92.7%), 13 (3.5%) and 15 (3.8%) patients presented mild, moderate or severe storage LUTS, respectively. Moreover,

Table 2 Multivariate regression analysis adjusted for age, PSA level, volume, smoking history, to evaluate the impact of number of MetS parameters and each component on the improvement of total IPSS (total Δ IPSS).

IPSS total	B (non-standardised coefficient)	Lower limit	Upper limit	P
MetS (0–5)	−0.047	−0.095	0.001	0.052
WC	−0.008	−0.013	−0.003	0.003
Diastolic BP	−0.013	−0.022	−0.005	0.003
Systolic BP	−0.005	−0.010	0.000	0.057
Glycaemia	0.000	−0.002	0.002	0.955
Triglyceride	0.000	−0.002	0.001	0.708
HDL-cholesterol	−0.002	−0.008	0.004	0.547

Table 3 Multivariate regression analysis adjusted for age, PSA, volume, smoking history, to evaluate the impact of number of MetS parameters and each component on the improvement of storage IPSS (storage-Δ IPSS).

IPSS storage	B (non-standardised coefficient)	Lower limit	Upper limit	P
MetS (0–5)	−0.130	−0.240	−0.020	0.021
WC	−0.021	−0.033	−0.009	0.001
Diastolic BP	−0.027	−0.046	−0.008	0.006
Systolic BP	−0.010	−0.022	0.001	0.074
Glycaemia	0.001	−0.005	0.006	0.742
Triglyceride	0.000	−0.004	0.003	0.895
HDL-cholesterol	−0.005	−0.018	0.009	0.518

Table 4 Multivariate regression analysis adjusted for age, PSA, volume, smoking history, to evaluate the impact of number of MetS parameters and each component on the improvement of voiding IPSS (voiding-Δ IPSS).

IPSS voiding	B (non-standardised coefficient)	Lower limit	Upper limit	P
MetS (0–5)	0.001	−0.03	0.031	0.973
WC	−0.003	−0.006	0.001	0.112
Diastolic BP	−0.009	−0.014	−0.004	0.001
Systolic BP	−0.003	−0.006	0.000	0.077
Glycaemia	0.001	−0.001	0.002	0.336
Triglyceride	0.000	−0.001	0.001	0.962
HDL-cholesterol	−0.001	−0.005	0.003	0.700

patients with MetS reported a lower recovery in total and storage IPSS as compared with those without MetS (63.2 vs 81.7, P = 0.015 and 19.6 vs 63.6, P = 0.013, respectively).

Improvements in the total and storage IPSS were related to WC and diastolic BP (Tables 2 and 3), while improvement in voiding IPSS was only related to diastolic BP (Table 4), after adjustment for age, smoking history, PSA level and prostate volume. These data were confirmed after further adjustment for the numbers of MetS factors (data not shown).

In the binary logistic model, adjusted for age, smoking history, PSA level, prostate volume, presence of MetS and surgical procedure, men with a WC of >102 cm had a higher risk of an incomplete recovery of lower urinary tract function,

Fig. 2 OR based on full recovery of lower urinary tract function (total- Δ IPSS 100%) vs partial recovery (total- Δ IPSS <100%), as derived from a logistic regression model adjusted for: Age, PSA level, prostate volume, smoking history, surgical procedure (TURP or OP), presence of MetS. LL, lower limit; UL, upper limit.

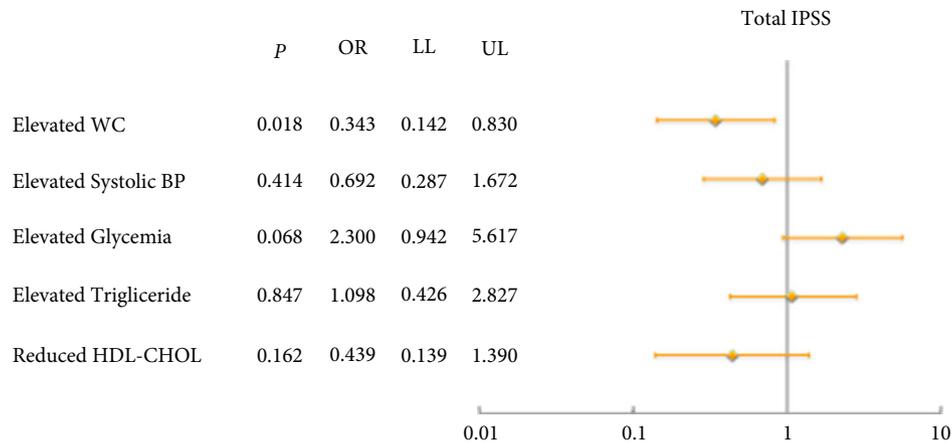
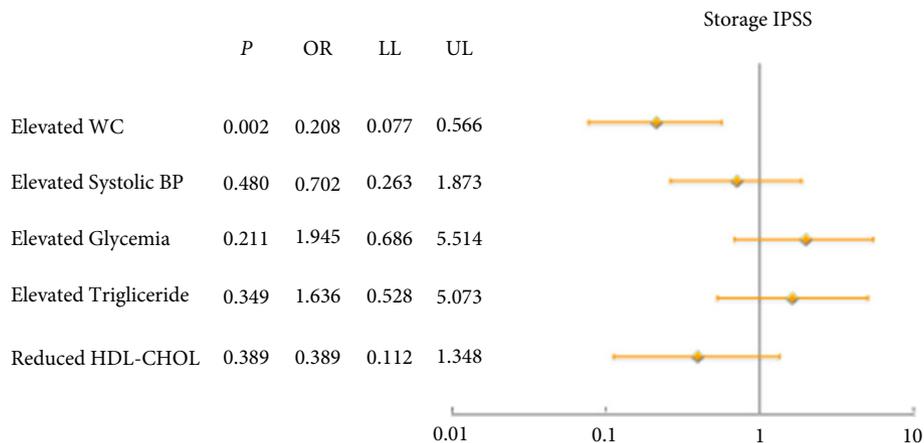


Fig. 3 OR based on full recovery of lower urinary tract function (storage- Δ IPSS 100%) vs partial recovery (storage- Δ IPSS <100%), as derived from a logistic regression mode adjusted for: Age, PSA level, prostate volume, smoking history, surgical procedure (TURP or OP), presence of MetS. LL, lower limit; UL, upper limit.



measured with total IPSS (OR 0.343, $P = 0.018$; Fig. 2) and storage IPSS (OR 0.208, $P = 0.002$; Fig. 3), as compared with those with a WC of <102 cm. No MetS parameter could be identified as a determining factor for full recovery of voiding function (Fig. 4).

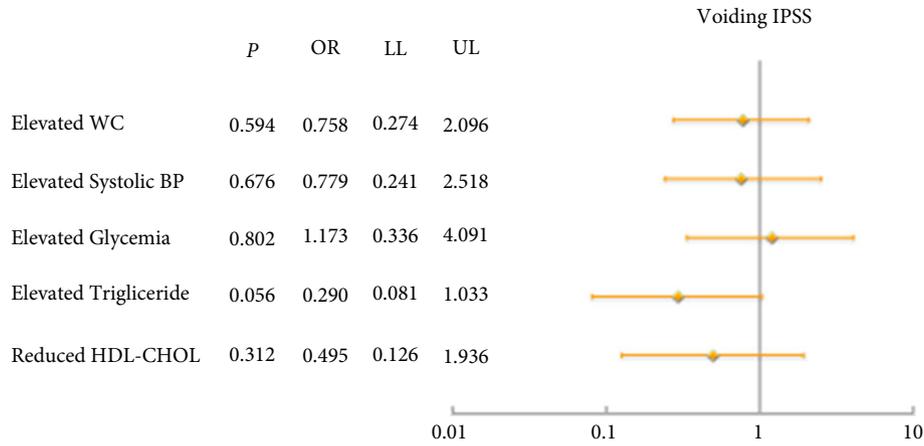
Discussion

Central obesity and MetS are becoming critical topics in urology due to their global epidemic diffusion and strong relationship with several urological diseases [12]. In the 'Multicenter Italian Report on Radical prostatectomy: Outcome and Research' (MIRROR) study, based on data from men treated with radical prostatectomy for prostate cancer in 25 urological departments across the whole Italian territory, we have previously shown a significant positive

correlation between WC and post-prostatectomy incontinence severity; the risk of needing at least two pads/day is 2.5-times greater in men with a WC of ≥ 102 cm than those with a WC of <102 cm [13].

While following 5 667 men in the Prostate Cancer Prevention Trial placebo arm, investigators noted the predictors for progression were age, baseline LUTS severity, an elevated hip-waist ratio, as well as ethnic background. Specifically they noted the risk of LUTS worsening (defined as 2 points worse on the IPSS) increased by 4% ($P < 0.001$) with each additional year of age. Additional risks for worsening LUTS were 41% higher for Black ($P < 0.03$) and Hispanic men ($P < 0.06$) compared with White men, and for severe LUTS these increases were 68% ($P < 0.01$) and 59% ($P < 0.03$), respectively. Each 0.05 increase in waist-hip ratio (a measure

Fig. 4 OR based on full recovery of lower urinary tract function (voiding-Δ IPSS 100%) vs partial recovery (voiding-Δ IPSS <100%), as derived from a logistic regression mode adjusted for: Age, PSA level, prostate volume, smoking history, surgical procedure (TURP or OP), presence of MetS. LL, lower limit; UL, upper limit.



of abdominal obesity) was associated with a 10% increased risk of overall LUTS progression ($P < 0.003$) and severe LUTS ($P < 0.02$). They noted that weight loss might be helpful for the treatment and prevention of LUTS [14]. A cohort of men undergoing TURP were noted to have a higher waist-hip ratio than controls; relative to men in the lowest waist-hip ratio quartile (<0.856) those in the highest quartile (>0.923) were at 2.4-fold risk of BPH (OR 2.42, 95% CI 1.34–4.37, test for trend $P = 0.01$) [15].

Recently, several studies have focused on the impact of MetS parameters on LUTS due to BPE [15–17]. We have recently shown that MetS can lead to an increase in prostate volume. In particular, our meta-regression analysis showed that the overall prostate volume and the transitional zone increment were significantly greater in older and obese men, and in those with low serum HDL cholesterol levels [18].

Moreover, as reported by Lee et al. [8], an increased WC was associated with worsened voiding function. In particular, the multivariate logistic regression analysis of urological parameters with WC showed that as WC increased from <90 to 90–99 to ≥ 100 cm, there was a greater likelihood for prostate volume growth (OR 1.39, $P = 0.01$).

In the present study, we report a unique finding, where the worse outcomes after surgery for BPH/LUTS were in men with increased WC. Men with a WC of ≥ 102 cm had three-fold risk of an incomplete recovery of LUTS and a five-fold risk of having persistent storage symptoms after surgery. In our unselected consecutive cross-sectional population, men with MetS presented similar baseline IPSS storage scores (8.9 vs 8.7) as compared with men without MetS; nevertheless, postoperatively they presented significantly worse IPSS storage scores than those without MetS (2.3 vs 1.3). A comparable correlation between the number of components of MetS and the severity of urinary symptoms has been

recently reported in a prospective cross-sectional study of men aged 50–59 years who had participated in a hospital health examination [19]. The authors reported that the number of men with LUTS (IPSS >7), enlarged prostate volume (total prostate volume ≥ 30 mL) and/or reduced maximum urinary flow rate ($Q_{\max} < 15$ mL/s) significantly increased with an increasing number of metabolic abnormalities. These results corroborated our preclinical data, suggesting that MetS could have a detrimental effect on prostate health, boosting inflammation, and finally inducing the concomitant enlargement of the prostatic gland and the decline of storage LUTS [20].

We recently suggested that hormonal, inflammatory and metabolic derangements might have a permissive or causative role in determining BPH. In particular, MetS could induce or maintain an inflammatory state within the prostate that could even be exacerbated by a relative hyperoestrogenism [21] or by androgen deficiency [22,23], medical conditions often associated to MetS and in particular to increased WC [24,25].

In the present study, diastolic BP emerges as a negative predictive factor for both voiding and storage urinary symptoms, while WC seems to have a negative impact exclusively on storage symptoms (Tables 2, 3 and 4). Interestingly, these data are consistent to those reported in a recently published observational study on police officers in their 50s with moderate-to-severe LUTS (IPSS >7) [26]. Their logistic regression analysis showed that only WC and hypertension among the MetS components were determinants of progression of BPH (OR 1.034, $P = 0.021$ and OR 1.511, $P = 0.009$, respectively). Moreover, the clinical impact of BP on persistent storage LUTS after TURP has been recently highlighted by a prospective study on patients treated with TURP for BOO due to BPH, based on the use of pulsed wave colour Doppler ultrasonography. The author showed that

persistent detrusor overactivity, 1 year after TURP, was associated with increased vascular resistance of the bladder vessels with subsequent reduced perfusion and hypoxia [27].

We recently showed in an experimental animal model of high fat diet-induced MetS, that MetS was associated with severe vascular damage in the whole of the LUT. In particular, we observed severe inflammation, running in parallel with hypoxia and tissue remodelling, both in prostatic and bladder tissue [22,28].

The binary logistic model showed that in cases of severe LUTS due to large BPE, the full recovery of LUTS and especially that of storage symptoms, can be more easily achieved in men with a WC of <102 cm compared with those with WC of ≥ 102 cm. Moreover, central obesity, as with other MetS parameters, seems to have no detrimental effect on the recovery of voiding activity, as measured by the IPSS. Thus surgical removal of central adenomatous tissue allows one to largely reverse flow-related symptoms, regardless of MetS features.

Our present prospective study has several limitations. We included men treated exclusively in tertiary referral centres for BPE surgery; this population of men with large prostates (≥ 80 mL), and a pronounced reduction in urinary flow ($Q_{\max} < 9$ mL/s) may be very different to that of the general community. Furthermore, we evaluated the population exclusively with the IPSS. The use of other validated questionnaires, such as the Short Form-12 to evaluate overall health (including physical and mental health), might have provided additional insight. Moreover, data from preoperative and postoperative pressure/flow studies were not available. Finally, we did not adjust our present data for additional parameters, such as physical activity and comorbidities, which can influence the development of LUTS or alter clinical outcomes after any surgical procedure.

In conclusion, our present study demonstrated that increased WC is associated with worse urinary symptoms recovery after surgical treatment of BPE. In particular, obese men have a higher risk of persistent storage LUTS after TURP or OP. Further prospective studies are needed to confirm our present data.

Conflicts of Interest

No sources of funding were used to assist in the preparation of this article. The Authors have no conflict of interest for this study.

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Abbreviations: BMI, body mass index; BP, blood pressure; BPE, benign prostatic enlargement; HDL, high-density lipoprotein; MetS, metabolic syndrome; OR, odds ratio; Q_{max} , maximum urinary flow rate; WC, waist circumference.