# Metabolic syndrome and lower urinary tract symptoms: the role of inflammation

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ORIGINAL ARTICLE

# Metabolic syndrome and lower urinary tract symptoms: the role of inflammation

M Gacci[1,6], L Vignozzi[2,6], A Sebastianelli[1], M Salvi[1], C Giannessi[1], C De Nunzio[3], A Tubaro[3], G Corona[4], G Rastrelli[4], R Santi[5], G Nesi[5], S Serni[1], M Carini[1] and M Maggi[2]

**BACKGROUND:** Epidemiological data indicate that lower urinary tract symptoms (LUTS)/BPH can be associated with metabolic syndrome (MetS). Chronic inflammation has been proposed as a candidate mechanism at the crossroad between these two clinical entities. Aim of study is to examine the correlation among pre-operatory LUTS/BPH severity, MetS features and inflammatory infiltrates in prostatectomy specimens.

**METHODS:** A total of 271 consecutive men treated with simple prostatectomy were retrospectively selected for this study in two tertiary referral centers for LUTS/BPH. Prostate diameters and volume were measured by transrectal ultrasound, LUTS scored by International Prostate Symptom Score (IPSS) and obstruction by uroflowmetry. The International Diabetes Federation and American Heart Association and the National Heart, Lung and Blood Institute was used to define MetS. The inflammatory infiltrate was investigated combining anatomic location, grade and extent of flogosis into the overall inflammatory score (IS); the glandular disruption (GD) was used as a further marker.

**RESULTS:** Eighty-six (31.7%) men were affected by MetS. Prostatic volume and anterior-posterior (AP) diameter were positively associated to the number of MetS components. Among MetS determinants, only dyslipidaemia (increased serum triglycerides and reduced serum high-density lipoprotein) was associated with an increased risk of having a prostatic volume $>60\,cm^3$ (hazard ratio (HR) $= 3.268$, $P < 0.001$). A significant positive correlation between the presence of MetS and the IS was observed. MetS patients presented lower uroflowmetric parameters as compared with those without MetS (Maximum flow rate ($Q_{max}$): 8.6 vs 10.1, $P = 0.008$ and average flow rate ($Q_{ave}$): 4.6 vs 5.3, $P = 0.033$, respectively), and higher obstructive urinary symptoms score ($P = 0.064$). A positive correlation among both IS–GD and IPSS Score was also observed (adjusted $r = 0.172$, $P = 0.008$ and adjusted $r = 0.128$, $P = 0.050$).

**CONCLUSIONS:** MetS is associated with prostate volume, prostatic AP diameter and intraprostatic IS. The significantly positive association between MetS and prostatic AP diameter could support the observation that MetS patients presented lower uroflowmetric parameters. In conclusion, MetS can be regarded as a new determinant of prostate inflammation and BPH progression.

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**Keywords:** BPH; prostate; metabolic syndrome; MetS; LUTS; lower urinary tract symptoms

## INTRODUCTION

Lower urinary tract symptoms (LUTS) and BPH are highly prevalent diseases in adult male.[1] Historically, male LUTS were thought to be merely related to benign prostatic enlargement. However, a simplistic causal relationship linking prostatic overgrowth, progressive urethral obstruction, urinary retention and LUTS, has been challenged, based on the incomplete overlap of prostatic enlargement with symptoms.[2] In fact, investigations into the relation of LUTS, prostate volume and urodynamic parameters failed to identify a causative relationship between parameters of BPH severity and symptoms, suggesting that other factors may intervene in determining LUTS.[3]

Although age remains the best-recognized risk factor for LUTS, LUTS may reflect other systemic derangements.[4] Emerging data indicate nowadays that a spectrum of age-related disorders, such as metabolic syndrome (MetS), type 2 diabetes, cardiovascular disease, hypogonadism or a combination thereof, have a heretofore unrecognized, negative impact on LUTS.

MetS was proposed as an umbrella term to include subjects affected by cardiovascular and metabolic risk factors, such as visceral obesity, hypertension, hyperglycemia, low high-density lipoprotein cholesterol (HDL-C) and hypertriglyceridemia, in the effort to identify a diagnostic category able to predict cardiovascular-metabolic complications. Several MetS components have been closely associated with BPH, suggesting that MetS has very heterogeneous clinical ramifications.[5–9]

Although the exact nature and origins of the association between LUTS/BPH and MetS are still poorly understood,[10] finding that men with metabolic alterations show a faster-developing BPH[5] or are more likely to undergo BPH surgery[8] support the intriguing hypothesis that pathological alterations characterizing

[1]Department of Urology, Careggi Hospital, University of Florence, Florence, Italy; [2]Department of Clinical Physiopathology, University of Florence, Florence, Italy; [3]Department of Urology, Sant'Andrea Hospital, University 'La Sapienza', Rome, Italy; [4]Endocrinology Unit, Maggiore-Bellaria Hospital, Bologna, Italy and [5]Department of Pathology, University of Florence, Florence, Italy. Correspondence: Dr M Gacci, Department of Urology, University of Florence, Viale Pieraccini 18, Florence 50139, Italy or Professor M Maggi, Department of Clinical Physiopathology, University of Florence, Viale Pieraccini 18, Florence 50139, Italy.
E-mail: maurogacci@yahoo.it or m.maggi@dfc.unifi.it
[6]These authors contributed equally to this work.
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MetS also predispose to the development and progression of BPH/LUTS. Chronic inflammation has been proposed as a candidate mechanism at the crossroad between these two clinical entities. MetS can broadly be considered a systemic inflammatory state and a chronic inflammation-driven tissue remodeling, and overgrowth is recognized to have a causative role in BPH/LUTS.[11]

The aim of the present study is to retrospectively examine the correlation among pre-operatory LUTS/BPH severity, MetS features and inflammatory infiltrates in prostatectomy specimens of men with BPH.

## MATERIALS AND METHODS

### Study population and design

Between January 2010 and September 2011, 271 consecutive patients treated with simple prostatectomy for BPH, with signed informed consent, were retrospectively selected in two tertiary referral centers for LUTS/BPH. The study did not required any deviation of the current clinical practice and was conducted in accordance with the principles of research involving human subjects as expressed in the Declaration of Helsinki and with Good Clinical Practice.

Inclusion criteria were: prostatectomy for moderate to severe LUTS because of BPH not responding to conventional medical treatment, ability to communicate, understand and comply with study requirements. Exclusion criteria were: history of preceding prostate surgery, previous catheterization for acute urinary retention, chronic medication for prostatitis and/or urinary infection or bladder stone, known malignant disease including prostate cancer, chronic renal failure.

Height, weight, waist circumference and blood pressure, were measured by trained personnel using a standardized protocol. Body mass index was calculated by dividing the weight (kg) by the square of height (m). Waist circumference was measured midway between the lowest rib and the iliac 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-C and triglycerides, 7–30 days preoperatively.

Open transvesical prostatectomy and TURP were performed as previously reported.[12,13] Surgical specimens (taken by at least three different randomly selected sites of the adenomatous tissue) were collected with sterile procedure and used for both conventional histological examination and inflammatory pattern definition.

### Assessment of LUTS and BPH features

LUTS were measured by the International Prostate Symptom Score (IPSS) immediately before surgery and further evaluated and categorized as storage (irritative) and voiding (obstructive) symptoms respectively.

All patients had digital rectal examination, uroflowmetry, abdominal ultrasound and transrectal ultrasound of the prostate. The main diameters of the prostate (AP: antero-posterior; CC: cranio-caudal; LL: latero-lateral) were measured by transrectal ultrasound and the prostate volume was calculated using the prostate ellipsoid formula ($AP \times CC \times LL \times \pi/6$).

Maximum flow rate ($Q_{max}$) and average flow rate ($Q_{ave}$) were collected preoperatively. Uroflowmetry data were analyzed only if voided volume exceeded 150 ml.

### Definition of MetS

MetS was defined by the International Diabetes Federation (IDF) and American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI).[14,15] The IDF and AHA/NHLBI criteria defined MetS in the presence of three or more of the five characteristics of (1) waist circumference $>102$ cm; (2) triglycerides $\geqslant 150$ mg/dl or treatment for hypetrygliceridemia, (3) HDL-C $<40$ mg dl$^{-1}$ or treatment for reduced HDL-C, (4) blood pressure $\geqslant 130/85$ mm Hg or current use of antihypertensive medications, and (5) fasting blood glucose $>100$ mg dl$^{-1}$ or previous diagnosis of type 2 diabetes mellitus.

All the above mentioned items of MetS were considered individually (single parameters above vs below cut-off points), as sum of continuous variables (one if the single parameter is positive for MetS, zero if the single parameter is negative), and combined according to MetS (present or absent).

### Pathological characterization of prostatic inflammatory infiltrates

All surgical specimens were examined on hematoxylin and eosin-stained sections by two independent pathologists (GN, RS), blinded of any clinical information. Samples were investigated for the presence of an inflammatory infiltrate, according to the standardized classification system of chronic prostatitis of the National Institutes of Health (NIH).[16] The resulting parameters were defined and scored as follows: prevalent anatomical location (stromal,[1] periglandular,[2] glandular[3]), grade (mild,[1] moderate,[2] severe[3]) and extent (focal, $<10\%$;[1] multifocal, 10–50%;[2] diffuse, $>50\%$[3]) of inflammatory infiltrates.

The grading methods was based on an '*inflammatory score*' (IS), combining all the above mentioned histological parameters, ranging from three (mild inflammatory infiltrate) to nine (severe inflammatory infiltrate). Moreover, the resulting destruction of the glandular epithelium, due to the massive inflammatory infiltration, was considered as a further marker of flogosis: '*glandular disruption*' (GD) present or absent, see Figure 1.

### Statistical analysis

Differences between more than two groups were assessed with one-way ANOVA or Kruskal–Wallis test, whenever appropriate. For continuous variables, correlations were assessed using Pearson's or Spearman's method whenever appropriate. Stepwise multiple linear or logistic analysis were used for multivariate analyses whenever appropriate.

All analyses were carried out with SPSS 18.0.1. (SPSS, Armonk, NY) statistical package and a $P<0.05$ was considered statistically significant.

## RESULTS

Overall, 271 patients treated with simple prostatectomy for BPH were enrolled. Patient characteristics are summarized in Table 1. One-hundred fifty-five men (57.2%) underwent open transvesical prostatectomy, and 116 (42.8%) TURP: 204 (75.3%) were previously treated with alpha-blockers alone, none with 5$\alpha$-reductase inhibitors alone and 67 (24.7%) with combined therapy. Thirty-two men with MetS (31.6%) and 35 without MetS (20.6%) were previously treated with 5$\alpha$-reductase inhibitors.

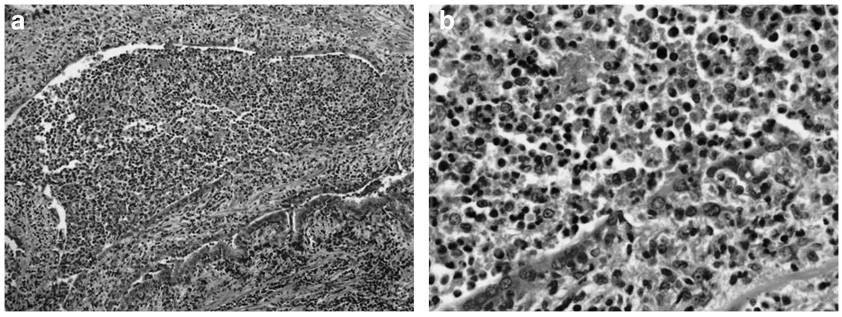


**Figure 1.** Representative images of intraprostatic inflammation in BPH specimen. (**a**) Severe acute and chronic inflammatory cell infiltrate with glandular and periglandular distribution (H&E stain, original magnification $\times 5$). (**b**) Epithelium disruption at higher magnification (hematoxylin and eosin stain, original magnification $\times 20$).

Of 271 men with BPH, 86 (31.7%) were affected by MetS. In particular, 46 (17.0%) presented with 3/5 parameters of MetS, 34 (12.5%) 4/5 and 6 (2.2%) 5/5. The complete analysis of the inflammatory infiltrate, including anatomic location, extent, grade, and the determination of the GD, was available in 245/271 (90.4%) patients; 26 men (9.6%) were excluded by the pathologists for the lacking of an adequate sampling from different sites of the adenomatous tissue. Mean IS, was $4.8 \pm 1.5$, and GD has been detected in 77/245 (31.4%) of cases.

Prostatic volume and AP diameter were significantly and positively associated with the number of MetS parameters (see Figures 2a and b), even after adjustment for age and 5α-reductase inhibitor's consumption (adjusted $r = 0.151$, $P = 0.023$ and adjusted $r = 0.267$, $P < 0.0001$, respectively). No correlation between MetS and the other diameters was observed (CC: $P = 0.198$; LL: $P = 0.757$). Patients fulfilling criteria for MetS ($\geqslant 3$ factors) have, on average, prostate volume $> 60\,cm^3$ and AP diameter $> 45\,mm$. Moreover, men with MetS presented lower uroflowmetric parameters as compared with those without MetS ($Q_{max}$: 8.6 vs 10.1, $P = 0.008$ and $Q_{ave}$: 4.6 vs 5.3, $P = 0.033$, respectively), and more severe obstructive urinary symptoms, even if this difference was not statistically significant (IPSS obstructive: 12.3 vs 11.4, $P = 0.064$).

**Table 1.** Patient characteristics

| *Patients* | *With MetS mean ± s.d.* | *Without MetS mean ± s.d.* |
|---|---|---|
| *Demographic* | | |
| Age (years) | 69 ± 7.4 | 68 ± 7.5 |
| Weight (Kg) | 81 ± 12.0 | 79 ± 9.9 |
| Height (m) | 1.73 ± 0.1 | 1.73 ± 0.1 |
| BMI ($Kg\,m^{-2}$) | 27.4 ± 3.5 | 25.4 ± 3.6 |
| *Prostate features* | | |
| AP diameter (mm) | 47 ± 11.2 | 42 ± 10.7 |
| CC diameter (mm) | 51 ± 9.6 | 48 ± 9.4 |
| LL diameter (mm) | 55 ± 8.5 | 52 ± 8.9 |
| Prostate volume (cc) | 63 ± 27.39 | 58 ± 27.9 |
| *LUTS/BPH* | | |
| IPSS overall | 22.5 ± 5.7 | 20.9 ± 5.7 |
| IPSS obstructive | 13.7 ± 3.8 | 12.3 ± 3.0 |
| IPSS irritative | 9.0 ± 3.0 | 8.6 ± 3.0 |
| $Q_{max}$ | 8.7 ± 3.5 | 9.4 ± 3.2 |
| $Q_{ave}$ | 4.3 ± 1.7 | 4.9 ± 1.8 |

Abbreviations: AP, antero-posterior; BMI, body mass index; CC, cranio-caudal; IPSS, International Prostate Symptom Score; LL, latero-lateral; LUTS, lower urinary tract symptoms; MetS, metabolic syndrome; $Q_{ave}$, average flow rate; $Q_{max}$, maximum flow rate.

Among MetS parameters, only increased serum triglycerides and reduced serum HDL-C levels were associated with an increased risk of having a prostatic volume $> 60\,cc$ (see Figure 3; hazard ratio (HR) = 3.268, 95% confidence interval: 1.810–5.901, $P < 0.001$). In addition, high serum triglycerides and low serum HDL-C levels were significantly associated with prostate volume, even after adjustment for age and 5α-reductase inhibitors consumption (adjusted $r = 0.273$, $P < 0.001$ and adjusted $r = -0.245$, $P < 0.001$, respectively; see Figures 4a and b).

A significant positive correlation between the presence of MetS and the IS was observed (age and 5α-reductase inhibitor–adjusted HR: 1.250 (1.001–1.1561), $P = 0.049$). The association retains significance even after introducing AP diameter as a further covariate (HR = 1.295 (1.005–1.670), $P = 0.046$).

Both IS and GD were correlated with total IPSS score, even after adjusting for age and BPH medical therapies (adjusted $r = 0.172$, $P = 0.008$, and adjusted $r = 0.128$, $P = 0.050$, respectively, see Figures 4a and b). In particular, a significant association between obstructive IPSS sub-scores and both IS (adjusted $r = 0.166$, $P = 0.011$) and GD (adjusted $r = 0.152$, $P = 0.020$) was observed, while irritative sub-scores were not correlated either with IS and GD. Prostate volume was not correlated with IS and GD, while AP diameter was correlated with IS, after adjusting for age (adjusted $r = 0.133$, $P = 0.053$). Finally, preoperative $Q_{max}$ was negatively correlated with the IS (adjusted $r = -0.212$, $P = 0.018$), but not with GD (adjusted $r = -0.044$, $P = 0.630$), after the adjustment for age and therapies for BPH.

## DISCUSSION

Our study demonstrated the existence of an association among MetS features, prostate enlargement (in particular AP diameter) and prostate inflammation. We speculate that this pathological network can have a relevant impact on LUTS severity in men with histologically proven BPH.

The progressive growth of prostatic in men with BPH, with the consequent modification of glandular profile into an oval, rounded shape, is mainly dependent on the increase of AP diameter.[17] The AP diameter is usually the shorter one, as compared with others diameters (CC and LL) (Aarnink *et al.*[18] and present series). We assumed $60\,cm^3$ and 45 mm as cut-off points for prostate volume and AP diameter, respectively, as previously performed by other authors,[19,20] even if both these arbitrary thresholds have been not internationally recognized. However, prostate with a volume below $60\,cm^3$ or an AP diameter below 45 mm are conventionally considered 'small prostate'. In our population of BPH men treated with simple prostatectomy for severe LUTS, both prostate volume and AP diameters were progressively increasing as a function of MetS components. Interestingly, the fulfilling of the diagnosic criteria for MetS

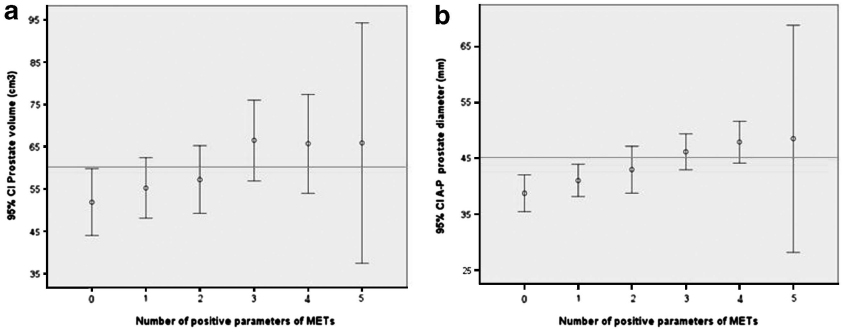


**Figure 2.** Prostate volume (**a**) and AP diameter (**b**) as a function of the number of MetS (AHA/NHLBI criteria) components obtained in a sample of 271 BPH subjects. Data are expressed as means ± s.e.m. Red lines indicate cut-off points for both prostate volume ($60\,cm^3$) and AP diameter (45 mm), respectively. The color reproduction of this figure is available on the *Prostate Cancer and Prostatic Disease* journal online. AP, antero-posterior.

(simultaneous presence of at least three components) was associated with a pathological prostate volume and/or a AP diameter, because resulted, on average, higher than the aforementioned thresholds (see Figure 2). The strong and unique association between MetS and the AP (but not CC and LL) diameter suggests that MetS is associated not only to an increased size, but also to a modification of its shape, which can finally lead to a compression of the prostatic urethra, with the consequent deterioration of the voiding function.

As showed in Figure 3, prostate volume was significantly associated with dyslipidaemia (HDL and triglycerides), while other MetS parameters were not. In accordance with our results, Hammarsten *et al.*[5,21] has previously reported that low HDL-C is a risk factor for the development of BPH.[5,21] The inconsistency of the correlation between waist circumference and prostate volume, reported in our study, is in agreement with other previously reported experiences,[22] while a recent clinical trial on obesity and LUTS reported a significant and positive correlation between waist circumference and prostate volume.[23] It should be noted that the association between prostate volume and hypertension resulted very close to the level of MetS significance (HR = 1.962, 95% confidence interval: 0.996–3.864, $P = 0.055$, see Figure 3), suggesting that this component may be a potential contributor for the growth of prostate volume, as reported by other Authors.[5,21,23]

A wealth of recent epidemiological and histopatological studies have clearly indicated that prostate chronic inflammation is not only a common finding in BPH,[24,25] but also has a primary role in triggering prostatic cells overgrowth.[26,27] Potential causes for inflammation and immune dysregulation in the prostate include exposure to dietary factors, and metabolic variations. This notion mainly stems from preclinical studies, which have provided a great deal of information about an association between metabolic diseases and LUT alterations.[28,29] Our laboratory has developed, over the last few years, an animal model of MetS by feeding adult male rabbits a high-fat diet for twelve weeks.[28–31] Interestingly, high-fat diet induced not only the classical features of MetS (overt dyslipidaemia, hypertension, hyperglycemia, insulin resistance and increased visceral adiposity), but also a marked inflammation and stromal derangement in the whole of the LUT, including the prostate[28] and bladder.[29]

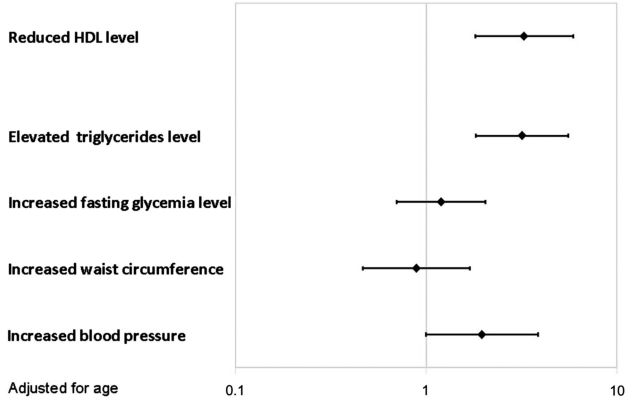


**Figure 3.** Hazard ratio (HR; 95% confidence interval; adjustment for age) for prostate volume as detected by logistic regression analysis considering MetS components as putative predictors (AHA/NHLBI criteria). HDL, high-density lipoprotein; MetS, metabolic syndrome.

From a pathophysiological standpoint, dyslipidemia is the best-recognized pro-inflammatory factor among all the others MetS features, leading to inflammation and pro-atherogenic remodeling of the vascular wall. Hence, studies aimed at investigating the potential pro-inflammatory effects of lipids on human prostatic cells are needed.

Interestingly, in our study population, MetS was not only associated with an increased prostate volume and AP diameter, but also with a severe intraprostatic inflammation. These observations substantiate the intriguing hypothesis that MetS could boosts a chronic inflammation-driven prostate overgrowth. This is particularly relevant given that MetS is an emergent epidemic, and a potentially preventable or reversible, health condition. Hence, if it could be definitively demonstrated that it is causally linked to BPH/LUTS, then treating MetS would represent a strategy not only for cardio-metabolic, but also urological sequelae prevention.

All patients included in our study were affected by severe LUTS (mean preoperative IPSS: 20), refractory to medical treatment, thus requiring a surgical procedure. In particular, an IPSS score above 20 represents the worst-case scenario with regards of BPH progression.[32] As showed in Figure 5, men with IPSS scores $>20$ were characterized by remarkable intraprostatric inflammation.

A statistically significant association between chronic inflammation and IPSS variables has been previously reported by Nickel *et al.*[26] in the REDUCE trial. Moreover, in the MTOPS study, prostatic inflammation within BPH tissue resulted a relevant risk factor for disease progression and in particular for the development of episodes of acute urinary retention and the needing of surgery.[33] Accordingly, in our population of obstructed men requiring a surgical procedure, only the presence of a severe inflammatory pattern, leading to the disruption of the normal glandular arrangement, is determinant for the worsening of LUTS. As reported in the PLESS study, histologic features, such as chronic inflammation, basal cell hyperplasia and transitional cell metaplasia, were not different between men treated with 5α-reductase inhibitors and placebo groups. In particular, the overall incidence on chronic inflammation is very similar between those treated with or without finasteride (16% vs 19%, respectively).[34] However, 5α-reductase inhibitors can induce a regression of prostatic glandular tissue, the specific area where the prostatic

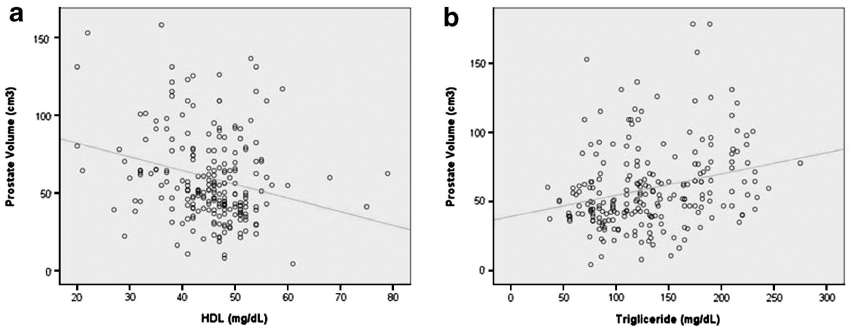


**Figure 4.** Relationship between HDL (**a**) or triglycerides (**b**) level and prostate volume (ordinate) as derived from univariate Spearman's regression analysis. The relative adjusted *r* and level of significance (*P*) are reported in the text. HDL, high-density lipoprotein.

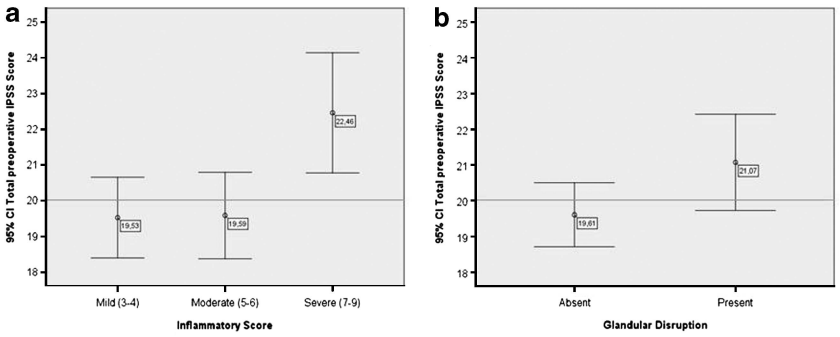


**Figure 5.** IPSS as a function of inflammatory score (**a**), grouped as mild (3–4), moderate (5–6) or severe (7–9) or presence/absence of GD (**b**), in a sample of 271 BPH subjects. Data are expressed as means ± s.e.m. Red lines indicate cut-off points for IPSS 20 (severe LUTS). The color reproduction of this figure is available on the *Prostate Cancer and Prostatic Disease* journal online. IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms.

inflammation is located, that can lead to a regression of prostatic inflammation.[35] In our study we adjusted the correlations between MetS and IS for the use of 5α-reductase inhibitors to avoid this potential bias.

Our study has several limitations. Mainly, the retrospective design of the study; however, the number of patients was adequate and patients were enrolled consecutively. Moreover, prostate volume and diameters were measured only by transrectal ultrasound, symptoms severity exclusively by assessing IPSS and grade of obstruction just by uroflowmetry: however, all these methods are conventionally performed in daily clinical practice for the work up of LUTS/BPH. Theoretically, a population of untreated men could be suitable to avoid potential confounding biases related to previous treatments.

The strengths of the study are: the multicenter scheme and the blinded assessment of preoperative data (MetS parameters, IPSS) the use of standardized classification (IDF and AHA/NHLBI for MetS and NIH for inflammation).

## CONCLUSION

In conclusion, the presence of MetS is associated with a substantial increase of prostate volume and a concomitant modification of prostatic shape, associated with a selective increase of anterior-posterior diameter. The significantly positive association between MetS and prostatic AP diameter could support the observation that MetS patients presented lower uroflowmetric parameters. In conclusion, MetS can be relevant for the development of a remarkable intraprostatic inflammation that could be a predictor, or even a driver, of BPH progression.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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