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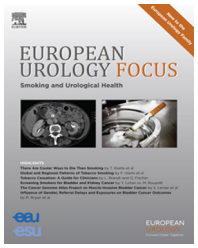

Review – Benign Prostatic Enlargement

Current Status of the Relationship Between Metabolic Syndrome and Lower Urinary Tract Symptoms

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Abstract

Although the exact nature of the association between metabolic syndrome (MetS) and lower urinary tract symptoms (LUTS) is still not completely understood, findings that men with metabolic alterations experience faster-developing LUTS or are more frequently candidates for benign prostatic enlargement (BPE) surgery support the hypothesis that metabolic and pathological derangements characterizing MetS can promote the development and progression of BPE and LUTS. The strong evidence that MetS is associated with larger prostate size supports a role for metabolic derangements in the development and progression of BPE. However, the relationship between MetS and LUTS is currently based on conflicting results. Most of the US and European population-based studies demonstrate a positive association between MetS and LUTS, but Asian studies often show opposite results. These findings indicate that ethnicity, diet and lifestyle could represent a central issue for the association between MetS and LUTS.
Patient summary: The strong evidence that metabolic syndrome is associated with greater prostate size supports a role for metabolic derangements in the development and progression of benign prostatic enlargement. Ethnicity, diet, and lifestyle could represent central issues for the association between metabolic syndrome and lower urinary tract symptoms.

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Emerging data indicate that a spectrum of age-related disorders, such as type 2 diabetes (T2DM), cardiovascular disease, hypogonadism, and a combination of these conditions such as metabolic syndrome (MetS) have a detrimental impact on lower urinary tract symptoms (LUTS). Indeed, MetS components have been closely associated with benign prostatic enlargement (BPE) and LUTS, suggesting that MetS has very heterogeneous clinical ramifications.

Traditionally, male LUTS were thought to be merely caused by BPE linked to aging. However, a simplistic causal relationship linking prostatic overgrowth, bladder outlet obstruction, and LUTS has been rejected because of the heterogeneity of LUTS and their associations with systemic disorders.

Although the exact nature of the association between MetS and LUTS is still not completely understood, findings that men with metabolic alterations experience faster-developing LUTS or are more frequently candidates for BPE surgery [1] support the hypothesis that metabolic and pathological derangements characterizing MetS can promote the development and progression of BPE and LUTS.

Moreover, MetS can be considered a “systemic inflammatory state”: chronic inflammation-driven tissue

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remodeling and overgrowth of prostatic tissue are recognized as playing a causative role in BPE and related LUTS. Visceral adipose tissue secretes several proinflammatory bioactive substances that can induce a low-grade chronic inflammatory response that could even be exacerbated by relative hyperestrogenism or by androgen deficiency [2].

In a prospective study of patients undergoing surgery for BPE [3], a number of MetS parameters and MetS itself were associated with higher calculated prostate volume (PV). Interestingly, different MetS features were associated with specific prostate diameters: the anteroposterior diameter was mainly correlated with low high-density lipoprotein (HDL) cholesterol, the craniocaudal diameter with high triglycerides, and the laterolateral diameter with high systolic blood pressure. However, on binary regression, low HDL cholesterol was the only significant determinant for enlargement of all the diameters and consequently of the whole PV. These findings have been confirmed by a recent meta-analysis. Patients with MetS had a significantly higher total PV (+1.8 ml; $p < 0.001$) and meta-regression analysis showed that waist circumference and low HDL cholesterol were the strongest features correlated with greater PV.

Evidence of an association between MetS and LUTS is mainly derived from epidemiological studies in populations from the US and Asia with conflicting results. The BACH survey [4] used the Adult Treatment Panel III Report criteria created by the National Education Program (NCEP-ATPIII) to define MetS and the American Urologic Association symptom index (AUA SI) to quantify LUTS. The authors reported a trend of increasing prevalence of MetS with increasing AUA SI. Specifically, the prevalence of MetS was 40% higher among men with mild to severe symptoms (AUA-SI 2–35 vs AUA-SI 0–1). Interestingly, a significant association was observed only between MetS and a voiding symptom score of $\geq$5, but not a storage symptom score of $\geq$4. Similarly, the NHANES III survey found that men who fulfilled MetS criteria had a significantly greater risk of LUTS compared to control subjects [5]. Conversely, a negative correlation between MetS and LUTS has been described in some Eastern Asia studies.

MetS was not directly associated with LUTS in a study in Japan. In particular, MetS was significantly inversely correlated with storage symptoms in middle-aged men (50–64 yr) [6]. Moreover, a South Korean study including 33 841 men aged $\geq$30 yr showed a negative association between MetS and LUTS. Similarly, lower total International Prostate Symptom Score (IPSS) and voiding subscores were found for Taiwanese men with MetS compared to control subjects.

In 2015, a meta-analysis specifically designed to evaluate MetS and LUTS relationships [7] was published. The researchers did not find a significant difference in total IPSS or voiding or storage subscores between men with and without MetS. In addition, the presence of MetS was not significantly associated with the risk of having moderate to severe LUTS [8]. By contrast, some of the components of MetS, such as hypertriglyceridemia, elevated fasting glucose, and/or T2DM, were significantly associated with a higher risk of LUTS.

Further studies specifically designed to evaluate the association between MetS and LUTS have recently been published and describe a positive correlation between MetS and LUTS. A population-based European study [9] demonstrated a strong positive association between MetS (defined using NCEP-ATPIII criteria) and LUTS severity. The presence of MetS was correlated not only with total IPSS score but also with voiding and storage subscores, as well as each single question of the IPSS questionnaire. Moreover, higher IPSS scores were positively associated with each component of MetS, and a higher risk of LUTS treatment was associated with MetS severity. Indeed, the presence of two components was associated with a 51% higher risk of being treated for LUTS, rising to nearly 250% when all five components were present. In particular, men with a waist circumference $\geq$102 cm were 39% more likely to report a voiding IPSS subscore $\geq$5 and 40% more likely to report a storage IPSS subscore $\geq$4. Accordingly, MetS (defined using NCEP-ATPIII criteria) was the only independent parameter associated with a risk of IPSS storage subscores $\geq$4 on multivariate analysis in a single-centre Italian cohort study in 431 men with BPE-related LUTS.

Comparable correlation between the number of MetS components and LUTS severity has also been reported in a prospective cross-sectional study of males aged 50–59 yr [10]. The authors demonstrated that the number of men with LUTS (IPSS >7), an enlarged prostate (total PV $\geq$30 ml), and/or lower urinary flow rate (Q_{max} <15 ml/s) significantly increased with the number of metabolic abnormalities.

The conflicting results on the relationship between MetS and LUTS could be explained by the heterogeneity of the study populations. Most of the US and European population-based studies demonstrated a positive association between MetS and LUTS, but Asian studies often show opposite results. These findings indicate that ethnicity, diet, and lifestyle could represent central issues for the association between MetS and LUTS. The differences could also be related to the multiple separate definitions of MetS and its components. Furthermore, most of the studies evaluated LUTS using IPSS. However, IPSS measures the subjective perception of LUTS, which can be associated with other variables, such as race or ethnic background, age, overall health, and socioeconomic status, as well as quality of life. By contrast, the strong evidence that MetS is associated with greater prostate size, in particular for the transition zone, supports a role for metabolic derangements in the development and progression of BPE.

In conclusion, lifestyle modification, including diet and physical activity, together with treatment of MetS and MetS-related diseases could represent a novel intriguing therapeutic approach to prevent or mitigate LUTS due to BPE. Further prospective studies are needed to confirm this hypothesis.

Conflicts of interest: Mauro Gacci has received consulting fees, honoraria, and research support from Lilly, Bayer, Pfizer, Ibsa, GSK, Astellas, Pierre Fabre, and Konpharma. Arcangelo Sebastianelli has nothing to disclose.

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