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Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis

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Objective

To summarise and meta-analyse current literature on metabolic syndrome (MetS) and benign prostatic enlargement (BPE), focusing on all the components of MetS and their relationship with prostate volume, transitional zone volume, prostate-specific antigen and urinary symptoms, as evidence suggests an association between MetS and lower urinary tract symptoms (LUTS) due to BPE.

Methods

An extensive PubMed and Scopus search was performed including the following keywords: 'metabolic syndrome', 'diabetes', 'hypertension', 'obesity' and 'dyslipidaemia' combined with 'lower urinary tract symptoms', 'benign prostatic enlargement', 'benign prostatic hyperplasia' and 'prostate'.

Results

Of the retrieved articles, 82 were selected for detailed evaluation, and eight were included in this review. The eight studies enrolled 5403 patients, of which 1426 (26.4%) had MetS defined according to current classification. Patients with MetS had significantly higher total prostate volume when compared with those without MetS (+1.8 mL, 95% confidence interval [CI] 0.74–2.87; $P < 0.001$). Conversely, there were no differences between patients with or without MetS for International Prostate Symptom Score total or LUTS subdomain scores. Meta-regression analysis showed that differences in total prostate volume were significantly higher in older (adjusted $r = 0.09$; $P = 0.02$), obese patients (adjusted $r = 0.26$; $P < 0.005$) and low serum high-density lipoprotein cholesterol concentrations (adjusted $r = -0.33$; $P < 0.001$).

Conclusions

Our results underline the exacerbating role of MetS-induced metabolic derangements in the development of BPE. Obese, dyslipidaemic, and aged men have a higher risk of having MetS as a determinant of their prostate enlargement.

Keywords

metabolic syndrome, MetS, benign prostatic hyperplasia, BPH, lower urinary tract symptoms, LUTS

Introduction

Metabolic syndrome (MetS) is a complex and worldwide epidemic disorder with a high socioeconomic impact, due to its association with increased morbidity and mortality [1]. MetS is a cluster of medical conditions, including abdominal obesity, impaired glucose metabolism, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol and arterial hypertension, which increase the odds for type 2 diabetes mellitus (T2DM) and cardiovascular (CV) diseases [2–8]. Besides T2DM and CV diseases, several other pathological conditions are also associated with MetS, e.g. non-alcoholic fatty liver disease, polycystic ovarian syndrome, obstructive sleep apnoea, lipodystrophy and microvascular disease [3]. In addition, in males, hypogonadism, erectile dysfunction, infertility, and psychological disturbances are often considered factors comorbid with MetS [5,9,10]. Although the association among the aforementioned conditions and MetS is generally accepted, the pathogenetic link still needs to be elucidated.

A significant amount of epidemiological evidence indicates a possible association between MetS and prostatic diseases, including LUTS [11,12]. LUTS and BPE are highly prevalent

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conditions in men [13] and LUTS related to BPE are among the 10 most prevalent and most costly diseases in Western countries [14]. Historically, male LUTS were thought to be merely related to the progressive prostate overgrowth; however, relationships between prostatic growth, BOO, urinary retention and LUTS have recently been challenged [15,16]. LUTS, due to BPE, affects 15–60% of men aged ≥40 years and are associated with an increased risk of falls, fractures, bothered/decreased quality of life and depression, all of which alter daily life activities [17,18].

Recently, preclinical and clinical studies have provided evidence of a possible role of metabolic derangements in the development of BPE, prostate growth and worsening LUTS [12,13,19,20]. In particular, after a very early trial in 1966, suggesting a role for diabetes or hypertension in the pathogenesis of prostatic enlargement [21], Nandeesha et al. [22] showed that insulin and HDL-cholesterol levels were positive and negative independent predictors of prostate enlargement, respectively. In another prospective study on men with no obesity related morbidities (e.g. diabetes, impaired fasting glucose, hypertension, or dyslipidaemia), body mass index and waist circumference were positively correlated with prostate volume [23]. These data have recently been confirmed in the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial [24].

In 1998, Hammarsten et al. [25] performed the first prospective study evaluating the relationship between prostate volume and individual MetS components in 158 men with BPH showing that diabetes, arterial hypertension, obesity, high fasting insulin levels and low HDL-cholesterol levels were all risk factors for prostatic enlargement. Thereafter, even if contribution of individual components of MetS have been analysed within clinical trials, only some additional studies, based on the concept of the MetS construct, have been published. In particular, in the last few years, only five Authors have investigated the link between MetS and PSA; however, results have been controversial [26–30]. Nevertheless, both prostate volume and PSA were shown to be the most powerful predictors of BPE progression, including the risk of acute urinary retention or need for surgery for BPE in comparison with LUTS score, urinary flow rate, or post-void residual urine volume [31].

The emerging interest in the relationship between MetS and prostate volume suggests that modifiable factors, e.g. abdominal obesity, dyslipidaemia and hyperglycaemia, should be investigated as new targets for disease prevention, diagnosis, and treatment of BPE [32]. The aim of the present systematic review is to summarise and meta-analyse the current literature on the association of MetS and BPE, focusing on all the components of MetS, including glucose intolerance, hypertension, waist circumference and dyslipidaemia (HDL and triglyceride), and their relationships with prostate volume, transitional zone volume, PSA, and urinary symptoms.

Materials and Methods

An extensive PubMed and Scopus search was performed including the following keywords: 'metabolic syndrome', 'obesity', 'diabetes', 'hypertension' and 'dyslipidaemia' combined with 'benign prostatic enlargement (BPE)', 'benign prostatic hyperplasia (BPH)', 'prostate' and 'lower urinary tract symptoms (LUTS)'. Additionally, reference lists of relevant articles were hand-searched to identify other articles, and the related articles function in PubMed was used. The search which gathered data until October 2013 was restricted to articles in the English language and human studies.

In the vast majority of the studies analysed, MetS was defined according the USA National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATPIII), which requires at least three of the following five components: central obesity (waist circumference of >102 cm), elevated triglycerides (≥1.7 mmol/L or 150 mg/dL), elevated blood pressure (≥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) [13]. Previous diagnosis of hypertension and T2DM were included as evidence of raised blood pressure or fasting glucose. We also included one study based on the revised MetS criteria proposed by the International Federation of Diabetes and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI criteria). The latter essentially differs in its reduced threshold of hyperglycaemia of 6.0 mmol/L (or 100 mg/dL) and in considering possible ethnic differences in the waist circumference threshold [6].

The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by two authors and conflicts resolved by a third investigator. The quality of studies was individually assessed by using the Cochrane criteria [33].

Heterogeneous studies were assessed using the I^2 statistics for prostate volume. Considering that heterogeneity could not be excluded ($I^2 = 78.98$), mean differences in total prostate volume and in transitional zone prostate volume between patients with or without MetS were calculated using a random effect model. Meta-regression analysis was used to test the effect of age and waist circumference on total prostate volume differences between patients with or without MetS. In addition, a linear age- and PSA-adjusted regression analysis, weighting each study for the number of patients enrolled, was used to verify the independent effect of MetS components on total prostate volume. All analyses were performed using Comprehensive Meta-analysis Version 2, Biostat, (Englewood,

NJ, USA). Multivariate analyses were performed on SPSS (Statistical Package for the Social Sciences; Chicago, USA), version 17.1.

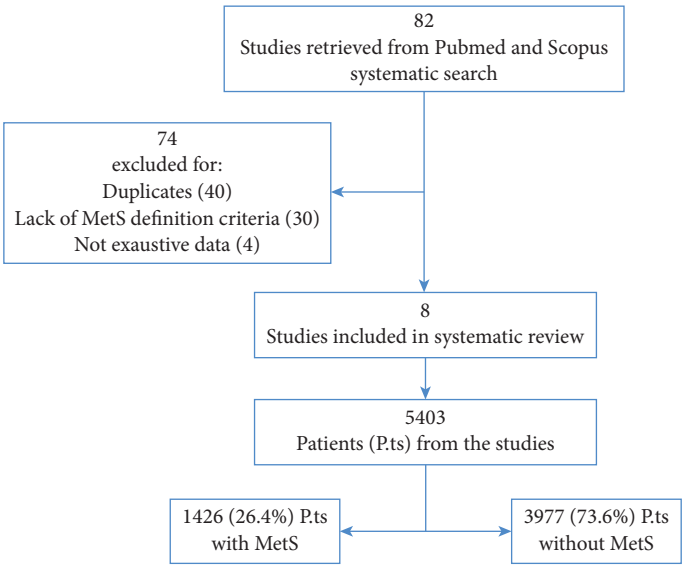
Results

Study Characteristics

Of the retrieved articles, 82 were selected for detailed evaluation, and eight (9.7%) were included in this review. Details of the literature search and identification of relevant studies are shown in Fig. 1.

Characteristics of trials included in the meta-analysis are summarised in Table 1 [19,30,34–39]. The eight studies enrolled a total of 5403 patients, of which 1426 (26.4%) had MetS defined according to current classification. All the studies included prostate volume differences between patients with or without MetS but data on transitional prostate volume were only available in four studies.

Fig. 1 Flowchart of literature searches and results.



Total Prostate Volume Differences

The Begg-adjusted rank correlation test (Kendall's tau [τ] 0.11; $P = 0.71$), calculated based on total prostate volume differences between patients with or without MetS, suggested no major publication bias.

The combination of results of trials showed that patients with MetS have significantly higher total prostate volume vs those without MetS (+1.8 mL, 95% CI 0.74–2.87; $P < 0.001$; Fig. 2A) [19,30,34–39]. Similar results were seen when a threshold of 30 mL in mean prostate volume was introduced (+2.13 mL, 95% CI 0.34–3.91; $P = 0.02$; Fig. 2A). Differences in prostate volume between patients with or without MetS were confirmed when only studies based on NCEP-ATPIII criteria were considered (+1.73 mL, 95% CI 0.66–2.81; $P < 0.002$) and were even higher when transitional zone prostate volume was introduced into the analysis (+3.67 mL 95% CI 1.31–6.03; $P < 0.001$; Fig. 2B). Conversely, there were no differences between patients with or without MetS for total IPSS and its storage or voiding sub-scores (not shown).

Meta-regression analysis showed that differences in total prostate volume were significantly higher in older and obese patients and in those with low serum HDL-cholesterol levels (Fig. 3A–C). In contrast, no significant relationships were found for increased glycaemia and triglyceride levels. No further meta-regression analyses were performed for systolic or diastolic blood pressure, due to insufficient data.

The relationship between total prostate volume differences and waist circumference or HDL cholesterol were confirmed in a linear, age- and PSA-adjusted, multivariate model, weighing each study for the number of patients enrolled (adjusted $r = 0.275$ and adj. $r = -0.651$, respectively; both

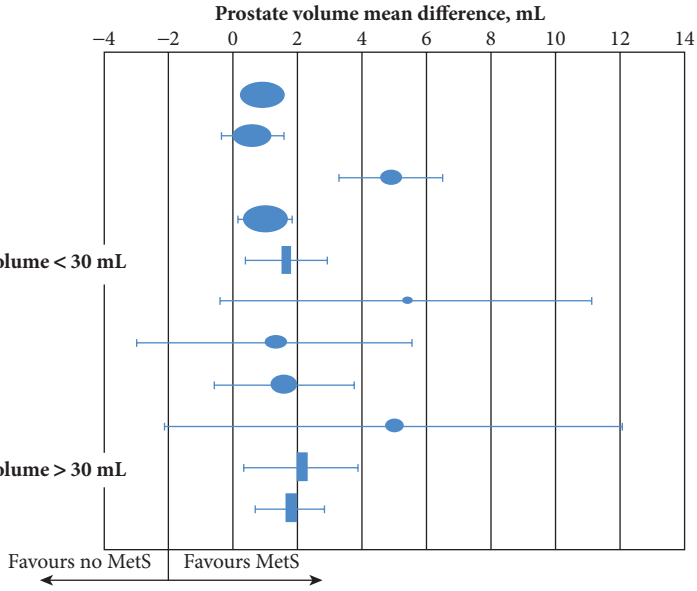
Table 1 Characteristics of the studies included in the present meta-analysis.

Overall population				Men with MetS			Men without MetS		
Reference	Level of evidence USPSTF	Number of patients	Mean (SD) age, years	Number of patients	Mean IPSS	Mean prostate volume, mL	Number of patients	Mean IPSS	Mean prostate volume, mL
Ozden et al. 2007 [34]	II-2	78	60 (0)	38	22.0	37.4	40	20	32.0
Park et al. 2008 [35]	II-2	348	74 (8.1)	102	11.1	41.7	246	12.3	40.4
Jeong et al. 2011 [36]	II-2	1506	46.4 (8.4)	354	6.8	20.6	1003	6.5	19.7
Yim et al. 2011 [37]	II-2	848	41.4 (5.2)	140	–	18.4	708	–	17.8
Yang et al. 2012 [38]	II-2	708	55.6 (9.7)	209	6.8	31.4	499	7.9	29.8
Byun et al. 2012 [30]	II-2	420	53.8 (6.9)	142	–	30.1	278	–	25.2
Park et al. 2013 [39]	II-2	1224	54 (2.0)	355	10.0	26.0	869	10.0	25.0
Gacci et al. 2013 [19]	II-2	271	68 (7.8)	86	22.5	63.0	185	20.9	58.0

USPSTF, USA Preventive Services Task Force.

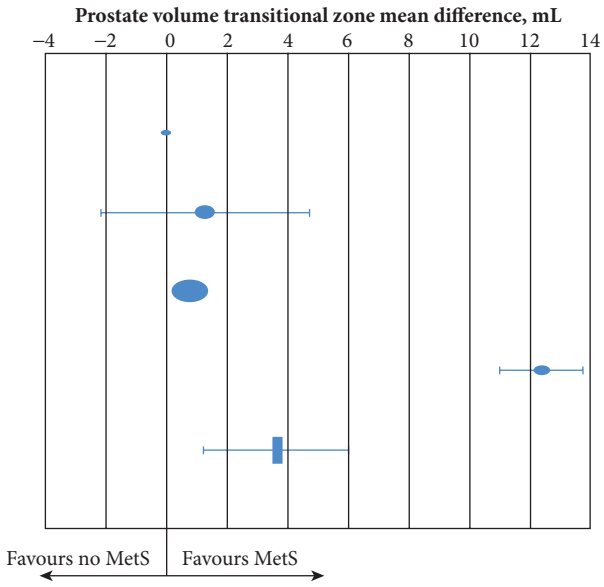
Fig. 2 (**A**) Weighted differences (with 95% CIs) of total prostate volume mean differences (mL) between patients with or without MetS. LL, lower level; UL, upper level. (**B**) Weighted differences (with 95% CIs) of prostate volume transitional zone mean differences (mL) between patients with or without MetS [19,30,34–39].

A



Source	Diff. in mean	LL, 95% CI	UL, 95% CI	P
Jeong *et al.* 2011 [51]	0.90	0.28	1.52	0.00
Yim *et al.* 2011 [52]	0.60	−0.37	1.57	0.22
Byun *et al.* 2012 [54]	4.90	3.29	6.51	0.00
Park *et al.* 2013 [55]	1.00	0.16	1.84	0.02
Overall mean prostate volume < 30 mL	1.66	0.38	2.94	0.01
Ozden *et al.* 2007 [49]	5.40	−0.36	11.16	0.07
Park *et al.* 2008 [50]	1.30	−2.99	5.59	0.55
Yang *et al.* 2012 [53]	1.60	−0.58	3.78	0.15
Gacci *et al.* 2013 [19]	5.00	−2.09	12.09	0.17
Overall mean prostate volume > 30 mL	2.13	0.34	3.91	0.02
Overall	1.80	0.74	2.87	0.00

B



Source	Diff. in mean	LL, 95% CI	UL, 95% CI	P
Ozden *et al.* 2007 [49]	0.00	0.00	0.00	0.05
Park *et al.* 2008 [50]	1.30	−2.13	4.73	0.46
Jeong *et al.* 2011 [51]	0.80	0.45	1.15	0.00
Gacci *et al.* 2013 [19]	12.40	11.06	13.74	0.00
Overall	3.67	1.31	6.03	0.00

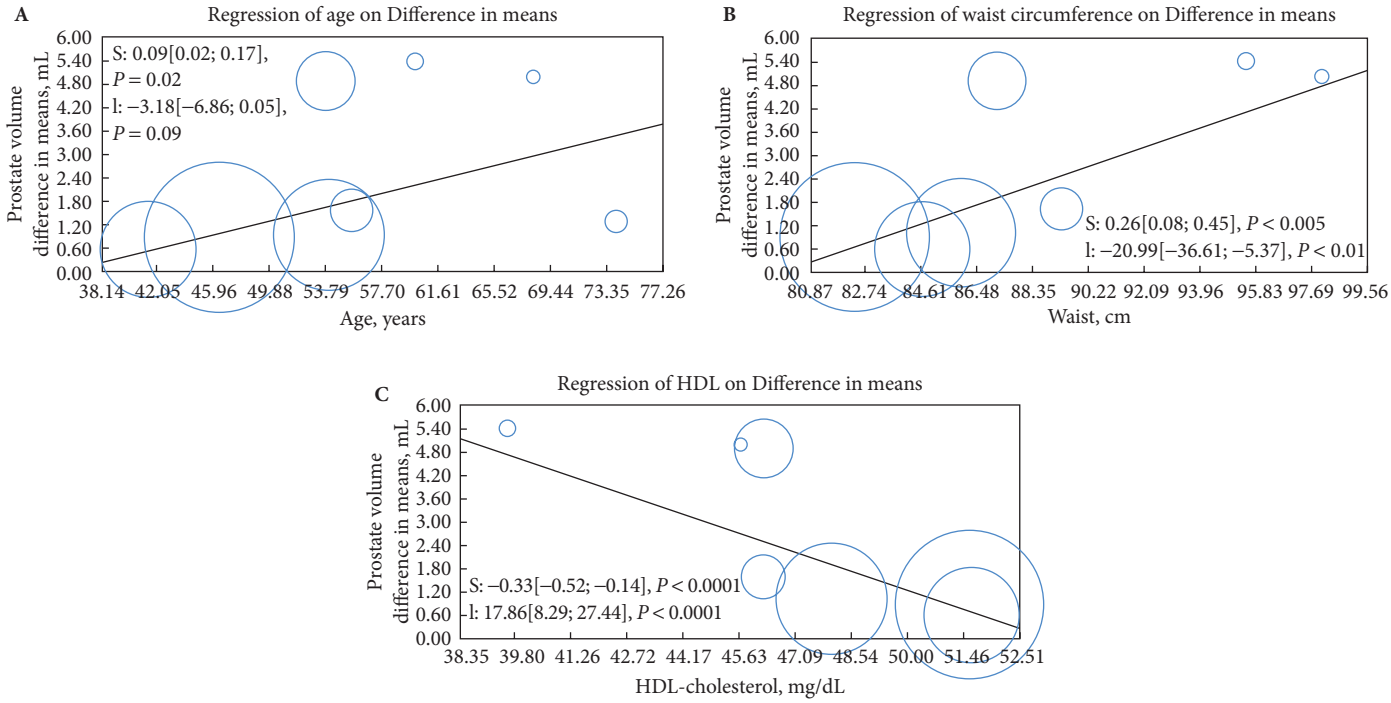
$P < 0.001$). When the significant contributing factors to MetS-associated prostate volume difference, as derived from the previous analysis (waist circumference, and serum HDL cholesterol), were simultaneously introduced in a further multivariate model as covariates, both covariates were independently associated with MetS-associated volume difference (adjusted $r = 0.401$ and $r = -0.378$ for waist circumference and HDL cholesterol, respectively; both $P < 0.001$).

Discussion

The present study indicates that MetS is associated with increased prostate size, in particular of the transitional zone, supporting a positive role for metabolic derangements in the progression of BPE.

As reported in the Baltimore Longitudinal Study of Aging, prostate growth rate is strictly dependent on both age and baseline prostatic volume [40]; in particular, men aged ≥65

Fig. 3 Influence of (**A**) age, (**B**) waist circumference, and (**C**) serum HDL cholesterol on prostate volume.



years with a larger prostate had a doubled rate of prostatic growth, compared with those with smaller prostates (2 vs 1 mL/year). Interestingly, we identified in the present meta-analysis, a similar difference in MetS-dependent prostate growth in men with prostate volume above or below 30 mL (3.4 vs 1.99, respectively), suggesting that, in elderly men with a larger prostate, the occurrence of MetS could represent a major contributing factor in BPE progression.

Meta-regression analysis suggested that MetS-induced differences in prostate volumes were almost equally weighted as a factor of age, waist circumference or serum HDL concentration. Hence, obese, dyslipidaemic and aged patients are more at risk of having MetS as a determinant of their increased prostate size. When waist and HDL-cholesterol levels were introduced in multivariate modelling, along with PSA level and age as further covariates, they both retained an independent ability to explain prostate volume variations. Considering the slope of the meta-regression analyses, the major MetS-related determinant of BPE was HDL cholesterol. In contrast, hyperglycaemia and increased triglyceride levels were not significantly associated with prostate enlargement. The contribution of hypertension was not specifically addressed by meta-regression, due to insufficient data.

The finding that HDL cholesterol is an important contributor to MetS-associated prostate enlargement is not surprising. We recently showed that lipids (oxidised low-density lipoprotein, LDL) increase *in vitro* the secretion of growth (VEGF, b-FGF) and pro-inflammatory factors (interleukin 6 [IL-6], IL-8, and IL-7) by human stromal BPH cells in culture [41]. In contrast, other metabolic factors such as insulin, IGF-1 and advanced glycosylated end products were less potent [41,42]. In experimental animal models, feeding a high cholesterol diet was enough to induce prostate enlargement [43] or inflammation [20]. In clinical studies, Nandeesha et al. [22] reported that HDL cholesterol was lower and total and LDL cholesterol higher in patients with symptomatic BPH than in controls. However, other studies did not confirm the association between dyslipidaemia and BPE [44–46]. In the Rancho Bernardo cohort study, Parsons et al. [47] found a four-fold increased risk of BPH among diabetic men with LDL cholesterol in the highest tertile, but not in the overall cohort. This observation suggests that dyslipidaemia per se is not sufficient enough to induce prostate enlargement, but the concomitant presence of other metabolic derangements, such as T2DM or those concurring with the MetS construct, favours the process [47]. A role for cholesterol in BPE progression was also suggested by retrospective intervention studies. In fact, in a cohort of 791 patients with BPH treated with specific medications, the addition of statin therapy increased prostate volume reduction by almost 15 times [48].

Increased central adiposity, as reflected by waistline, is another MetS-related factor that significantly contributes to variation in prostate enlargement. This finding is consistent with most previous studies, the meta-analysis of which indicates that obesity (as detected by body mass index) is associated with a 28% increased risk of having BPH [49]. Prospective data of the Health Professionals Follow-up Study (HPFS), on >18 000 men without LUTS at baseline, recently showed that men with higher total and abdominal adiposity or who gained weight at follow-up were more likely to develop LUTS or experience progressive LUTS [50].

However, the major contribution of the present meta-analytic survey is underlying the concept that the syndromic presence of several metabolic derangements, recapitulated in the MetS construct, more than the individual contribution of some of its components, might drive prostate enlargement. Considering that lifestyle changes are the universally recognised first-line intervention for facing LUTS/BPH (European Association of Urology, EAU), the present findings pave the way for introducing physical activity and diet intervention as a rational strategy for treating BPE at a first glance, as already recommended by guidelines (EAU). In 2002, Suzuki et al. [51] first reported that men with high energy intakes and particularly with high consumption of protein and polyunsaturated fatty acid were at a greater risk of developing BPH. Similar results were later reported in two Italian studies [52]. In a meta-analysis that enrolled 43 083 male patients, intensity of exercise was related to reduction of risk of prostate enlargement. Compared with the sedentary group, the risk for BPH or LUTS was significantly reduced with odds ratios of 0.70, 0.74, and 0.74 for men engaging in light, moderate, and heavy physical activity, respectively [53]. Whether or not lifestyle change-induced prostate size improvements are mediated by smoothing MetS severity is a matter for further studies. It is worthwhile to note that in a recent study on male partners of infertile couples, we noticed that the relationship between MetS severity and prostate enlargement, but not symptoms, was evident even in young subjects. Also in the present meta-analysis, the relationship between MetS and LUTS was not evident, suggesting that other factors, besides metabolic derangements, are necessary to elicit symptoms.

The present study has several limitations; primarily only eight trials were included in the meta-analysis; however, these data were gathered in 5403 men, 1426 of which had MetS. Moreover, there was heterogeneity in the definition of MetS applied in the different studies, although most Authors used the NCEP-ATPIII 2001 definition [54] and when only the latter were considered the association between MetS and prostate enlargement was confirmed. Finally, relevant data about serum testosterone levels, uroflowmetry parameters, and LUTS treatments were not available.

Conclusions

The present results suggest that the MetS construct, and in particular dyslipidaemia and central obesity, is specifically associated with a greater overall (and transitional) prostate volume increment. Considering that MetS is essentially composed of a cluster of modifiable conditions, acting on these conditions might represent a new strategy to combat BPE. In addition, because MetS represents a well-known risk factor not only for prostate enlargement, but also for T2DM and CV disease, a holistic approach in considering the morbidities of ageing men is strongly encouraged.

Conflict of Interest

None declared.

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Abbreviations: BPE, benign prostatic enlargement; CV, cardiovascular; EAU, European Association of Urology; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; MetS, metabolic syndrome; NCEP-ATPIII, USA National Cholesterol Education Program – Adult Treatment Panel III; T2DM, type 2 diabetes mellitus.

