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Review Article

Emerging links between non-neurogenic lower urinary tract symptoms secondary to benign prostatic obstruction, metabolic syndrome and its components: A systematic review

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Abbreviations & Acronyms
AHA/NHLBI = American Heart Association and the National Heart, Lung, and Blood Institute
BMI = body mass index
BPH = benign prostatic hyperplasia
BPO = bladder outlet obstruction
DRE = digital rectal examination
FINS = fasting insulin
FPG = fasting plasma glucose
FR/PVR = flow rate/post-void residual
HbA1c = glycosylated hemoglobin
HDL = high-density lipoprotein
HO = hemeoxygenase
IGF = insulin-like growth factor
IPSS = International Prostate Symptom Score
IR = insulin resistance
LDL = low-density lipoprotein
LUTS = lower urinary tract symptoms
MetS = metabolic syndrome
NCEP–ATPIII = USA National Cholesterol Education Program – Adult Treatment Panel III
PSA = prostate-specific antigen
PV = prostate volume
PVR = post-void residual
TP = total prostate
TPV = total prostate volume
TZ = transitional zone
WC = waist circumference

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Abstract: We carried out a systematic review in order to determine the connection between lower urinary tract symptoms secondary to bladder outlet obstruction and metabolic syndrome with its components. We searched the Cochrane Central Register of Controlled Trials, PubMed, EMBASE, the Cochrane Database of Systematic Review and Web of Science from their inception until January 2015 to identify all eligible studies on the effect of metabolic syndrome (or component factors) on the presence or severity of lower urinary tract symptoms/bladder outlet obstruction in men. This analysis was carried out according to the STrengthening the Reporting of OBservational studies in Epidemiology guidelines. In total, 19 studies were identified as eligible for this systematic review. The quality assessment score was ≥50% in more than half of the studies (11/19). The evidence synthesis showed a positive association between metabolic syndrome, number of components and lower urinary tract symptoms/bladder outlet obstruction. In particular, the major endocrine aberrations of this connection are central obesity and hypertriglyceridemia. The links between insulin resistance and lower urinary tract symptoms/bladder outlet obstruction should be better investigated. Ethnic disparities in all examined studies showed a different impact of metabolic syndrome on lower urinary tract symptoms/bladder outlet obstruction severity and such influence still remain unclear. The relationship between metabolic syndrome and lower urinary tract symptoms/bladder outlet obstruction open the way for introducing physical activity and diet as recognized first-line interventions for treating lower urinary tract symptoms. However, this connection should be investigated in two different ethnic cohorts (i.e. Asian *vs* Caucasian) in order to better understand the impact of ethnic disparities on metabolic syndrome and lower urinary tract symptoms/bladder outlet obstruction severity.

Key words: age, benign prostatic hyperplasia, insulin resistance, lower urinary tract symptoms, metabolic syndrome, non-alcoholic fatty liver disease.

Introduction

LUTS secondary to BPO is one of the most common disease of the aging male.[1] It is considered a chronic disease with early initiation and slow progression. The exact molecular mechanisms underlying the development of LUTS/BPO are mainly secondary to the occurrence of BPH that starts as a simple micronodular hyperplasia and evolves into a macroscopic nodular enlargement that gradually results in BPO, causing LUTS. Recent studies have shown that chronic inflammation represents a crucial component in the pathogenesis of BPH, probably determining the hyperplasia of prostate cells. The inflammatory cells, in fact produce growth factors, which can support the fibromuscular growth in BPH.[2]

In the past years, many studies have provided emerging evidence of a role of MetS and its components in LUTS/BPO. MetS is considered a worldwide epidemic with a high socioeconomic cost; it is characterized by a systemic inflammatory state and a chronic inflammation driven tissue remodeling that derives from the combination of several metabolic abnormalities.[3]

A great deal of evidence suggests that glucose homeostasis, hyperinsulinemia and IR might increase the risk of BPH.[4] Hyperinsulinemia is also associated with an increase in the activity of the sympathetic nervous system, and this could contribute to increased muscle tone of the

prostate, resulting in more severe LUTS/BPO independently of prostate enlargement. Recent studies suggest that the severity of LUTS/BPO is associated with an increase in the number of components of MetS (hypertension, obesity, IR and high dyslipidemia).[5] However, discordant results are still present in the literature arising inconsistencies about the connections between MetS, LUTS/BPO and ethnic disparities.

The aim of the present systematic review was to evaluate new and emerging links between LUTS related to bladder outlet obstruction secondary to clinical BPH and MetS with its components.

Methods

Eligibility criteria

The present analysis was carried out according to the STrengthening the Reporting of OBservational studies in Epidemiology guidelines.[6]

We defined MetS according to the NCEP–ATPIII, which requires at least three of the following five components: (i) central obesity (waist circumference of ≥102 cm); (ii) elevated triglycerides (≥1.7 mmol/L or 150 mg/dL); (iii) elevated blood pressure (≥130/85 mmHg); (iv) elevated fasting glucose (≥6.1 mmol/L or 110 mg/dL); and (v) reduced HDL cholesterol (<1.03 mmol/L or 40 mg/dL). Previous diagnosis of hypertension and type 2 diabetes mellitus were included as evidence of raised blood pressure or fasting glucose. We also included studies based on the revised MetS criteria proposed by the International Federation of Diabetes and the AHA/NHLBI criteria. The latter essentially differs in its reduced threshold of hyperglycemia of 6.0 mmol/L (or 100 mg/dL) and in considering possible ethnic differences in the waist circumference threshold.[7]

Eligible studies included published journal articles that provided quantitative data on LUTS secondary to BPO, and assessed by the validated IPSS.

We also aimed to evaluate the impact of MetS components on LUTS/BPO.

Information source

We carried out a systematic literature search of PubMed, EMBASE, Cochrane, and Academic OneFile databases using Medical Subject Headings indexes, keyword searches and publication types until December 2014. The search was limited to English-language articles. The search terms included prostate, benign prostatic hyperplasia, benign prostatic enlargement, benign prostatic obstruction, metabolic syndrome, PV, IR, obesity, hypertension, triglycerides, cholesterol and LUTS.

Study selection

Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy. References of the included papers were hand-searched to identify other potential relevant studies. Studies were reviewed by two independent reviewers (GIR and DU); differences in opinion were discussed in consultation with the last author (GM).

Data extraction and quality assessment

The quality of these eligible citations was assessed using the Newcastle–Ottawa quality assessment scale quality scoring system;[8] two authors scored independently. Risk of bias assessment included randomization, incomplete outcomes data, selective outcomes reporting and other biases.

Data synthesis and analysis

We constructed evidence tables detailing study characteristics, outcome measures, MetS definition and study quality. We compared and contrasted studies reporting the connection between MetS and LUTS, summarizing patient characteristics and evidenced results.

Results

Figure 1 shows the flowchart of included studies. In total, 151 studies were identified from the online databases and relevant references. After evaluating the title and abstract of each study, 75 studies were excluded, as they did not meet the inclusion criteria. Subsequently, we carefully read the full texts of the remaining 76 studies, and thus 19 studies (Table 1) were identified as eligible for the present systematic review and including 22 540 patients. The quality assessment score was ≥50% in more than half of the studies (11/20). Of 19 included studies, 10 examined the link between MetS and LUTS/BPO, eight examined links between MetS and PV, and LUTS/BPO, and three examined links between LUTS/BPO and diabetes mellitus or IR.

LUTS/BPO and MetS

A link between MetS and LUTS/BPO was first proposed by Hammarsten *et al.* in 1998.[9] Thereafter, many authors have

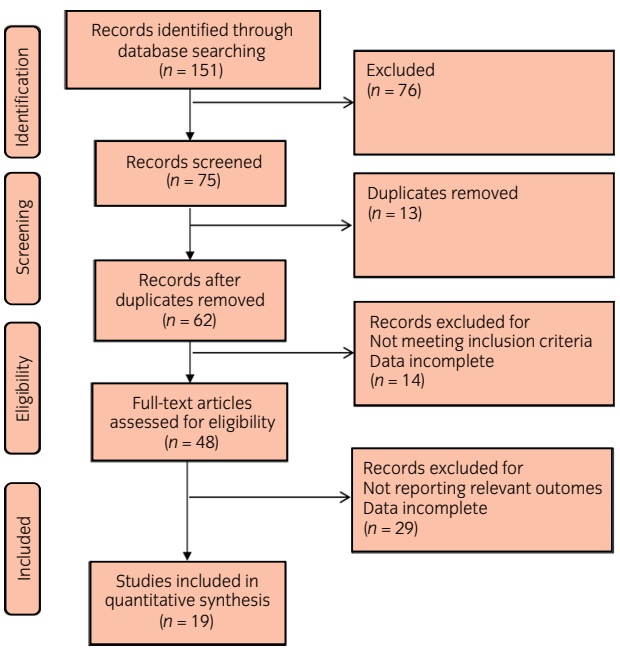

Fig. 1 Flow diagram of included studies.

Table 1 Studies on the association between MetS components and LUTS

Year	Authors	Country	Number of samples	BPH definition	MetS components definition	MetS features and BPH findings	PSA	Prostate volume	IPSS	IPSS storage	IPSS voiding	MetS yes *n* (%)	MetS no *n* (%)	Urodynamic exam	Therapy	NOS quality score
2014	Zhang *et al.*	China: cross-sectional	394	LUTS (IPSS); PSA; TRUS; PV	FPG (≥110 mg/dL)	PV was correlated with FINS (r = 0.421, P = 0.001), but no FPG (r = 0.091, P = 0.364) or HbA1c levels (r = 0.153, P = 0.127)	MetS 2.71 ± 2.09 No MetS 2.35 ± 2.01	MetS 51.19 ± 25.64 No MetS 38.34 ± 13.67	MetS 11.18 ± 7.52 No MetS 11.20 ± 7.96	Not valuable	Not valuable	222 (55.36%)	179 (44.63%)	No	No	5
2014	Russo *et al.*	Italy: cross-sectional	544	LUTS (IPSS); PSA; TRUS; PV	IDF	IR was an independent predictor of severe LUTS (IPSS ≥ 20) (OR = 2.0, 95% CI 1.20–3.34)	2.51 (0.96–5.86)	40 (30.0–57.0)	17 (6.0–22.0)	5.5 (2.0–9.0)	10.0 (5.0–14.0)	104 (19.1%)	440 (80.9%)	No	No	5
2014	Pashootan *et al.*	France: observational	4413	LUTS (IPSS); PSA; PV	NCEP ATP III	MetS was positively correlated with the severity of the LUTS (P < 0.001) for overall IPSS and both voiding and storage scores (P < 0.001). Each component of MetS (except HDL) was an independent risk factor of high IPSS and of LUTS.	MetS 3.3 No MetS 2.7	Not valuable	MetS 9.62 No MetS 7.45	MetS 4.39 No MetS 3.52	MetS 5.23 No MetS 3.93	2273 (51.59%)	2136 (48.61%)	No	No	5
2014	De Nunzio *et al.*	Italy: observational	431	LUTS (IPSS); PSA; PV	NCEP ATP III	On multivariate analysis, the presence of MetS was associated with an increased risk of an IPSS storage subscore ≥4 (OR 1.782; P = 0.03)	MetS 3.2 ± 1.6 No MetS 3.4 ± 1.8	MetS 45.9 ± 5.1 No MetS 49.2 ± 9.6	MetS 9.7 ± 6.8 No MetS 9.6 ± 7.2	MetS 4.8 ± 3.1 No MetS 4.1 ± 3.4	MetS 4.9 ± 4.7 No MetS 5.5 ± 4.7	103 (23.8%)	328 (76.2%)	–	–	5
2014	Kim *et al.*	Korea: retrospective	4076	LUTS (IPSS); PSA; PV	NCEP ATP III	In the larger PV group (≥28 mL), the age-adjusted OR for having moderate-to-severe LUTS was significantly lower in subjects with MetS (OR 0.666; P < 0.01) and in subjects with MetS having 4 or 5 risk factors (OR 0.612; P < 0.05)	Not valuable	Not valuable	MetS 8.03 ± 5.72 No MetS 8.32 ± 6.10	MetS 2.88 ± 2.47 No MetS 3.02 ± 2.47	MetS 5.15 ± 4.04 No MetS 5.30 ± 4.27	756 (18.5%)	3320 (81.5%)	No	No	4
2013	Gacci *et al.*	Italy: cross-sectional	271	Prostatectomy for moderate/severe LUTS due to BPH	AHA/NHLBI criteria or previous diagnosis of type 2 diabetes	Inflammatory score (P = 0.049), lower uroflowmetric parameters (P = 0.0008) IPSS (P = 0.064)	Not valuable	MetS 63 ± 27.39 No MetS 58 ± 27.9	MetS 22.5 ± 5.7 No MetS 20.9 ± 5.7	MetS 13.7 ± 3.8 No MetS 12.3 ± 3.0	MetS 9.0 ± 3.0 No MetS 8.6 ± 3.0	81 (31.7%)	190 (68.3%)	No	Yes (alpha-blockers, 5a-reductase inhibitors)	5
2013	Park *et al.*	Korea: retrospective	1224	PV, IPSS, LUTS	NCEP ATP III	IPSS, TPV>30 mL, and PVR>50 mL significantly increased with an increasing of number of MetS components (P < 0.001)	0.8 (0.5–1.1)	25.5 (21.0–31)	10 (5.0–15.0)	–	–	355 (29.0%)	869 (71%)	–	–	4
2012	Byun *et al.*	Korea: retrospective	420	PV, IPSS, LUTS	NCEP ATPIII AHA/NHLBI	PSA and PV was correlated with MetS and with number of MetS components (P < 0.001)	MetS 1.29 ± 0.9 No MetS 0.8 ± 0.5	MetS 30.1 ± 9.8 No MetS 25.2 ± 6.8	Not valuable	Not valuable	Not valuable	278 (66.19%)	142 (33.81%)	No	No	4
2012	Yang *et al.*	Taiwan: prospective	708	IPSS, PSA, DRE, PV	NCEP ATP III	MetS group has lower IPSS score (P = 0.05). The negative association between voiding score, severity of LUTS, and MetS became higher as the number of MetS increased (P < 0.01).	MetS 1.55 ± 2.10 Non-MetS 1.44 ± 1.57	MetS 31.4 ± 14.4 Non-MetS 29.8 ± 13.1	MetS 6.85 ± 6.52 Non-MetS 7.89 ± 6.63	MetS 3.14 ± 2.68 Non-MetS 3.47 ± 2.71	MetS 3.68 ± 4.44 Non-MetS 4.37 ± 4.59	209 (29.5%)	499 (70.5%)	No	No	4
2012	Gao *et al.*	China: cross-sectional	3103	LUTS (IPSS); PSA; PV	NCEP ATP III	The presence of MetS was not associated with the severity of LUTS (OR 0.97), but its subcategories of moderate or severe storage symptoms were inversely related to MetS (OR 0.64)	–	–	Not valuable	Not valuable	Not valuable	464 (14.95%)	2639 (85.1%)	No	No	5

Table 1 (Continued)

Year	Authors	Country	Number of samples	BPH definition	MetS components definition	MetS features and BPH findings	PSA	Prostate volume	IPSS	IPSS storage	IPSS voiding	MetS yes *n* (%)	MetS no *n* (%)	Urodynamic exam	Therapy	NOS quality score
2011	Ohgaki *et al.*	Japan: observational	900	LUTS (IPSS); PSA; PV	NCEP ATP III; IDF; JASSO	In the younger and older men, LUTS was observed equally in those with and without the MetS	MetS 1.22 ± 1.08 Non-MetS 1.3 ± 1.29	Not valuable	Not valuable	MetS 1.86 ± 1.68 Non-MetS 2.07 ± 1.93	MetS 1.66 ± 2.59 Non-MetS 2.00 ± 2.79	150 (16.7%)	750 (83.3%)	No	No	4
2011	Yim *et al.*	Korea: retrospective	848	TRUS, PSA, DRE	NCEP ATP III	PV is not significantly larger in the MetS group (18.4 *vs* 17.8 cc; $P = 0.225$), but in pt. with elevated FPG and WC is ($P = 0.001$)	MetS 18.4 (14.3–23.1) No MetS 17.8 (13.6–21.6)	Not valuable	Not valuable	Not valuable	Not valuable	Not valuable	Not valuable	No	No	4
2011	Jeong *et al.*	Korea: retrospective	1357	IPSS, PSA, DRE, TRUS	NCEP on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults guidelines	PV and BPE is higher in MetS pt. ($P < 0.001$). No differences in IPSS or voiding or storage subscore were noted. Diabetes and obesity are risk factors for BPE ($P < 0.001$).	MetS 0.8 ± 0.4 No MetS 0.9 ± 0.5	MetS 20.6 ± 5.4 No MetS 19.7 ± 5.0	MetS 6.8 ± 5.6 No MetS 6.5 ±4 .7	MetS 2.8 ± 2.5 No MetS 2.7 ± 2.0	MetS 3.9 ± 3.7 No MetS 3.7 ± 3.3	354 (26.09%)	1003 (73.91%)	No	No	4
2009	Wang *et al.*	Taiwan: case-control convenience sample from diabetes clinic and health fair. Age <45	409	IPSS; FR/PVR	DM defined by American Diabetes Association criteria	IPSS (6.1 *vs* 4.1, $P = 0{,}0001$), storage symptoms (2.7 *vs* 2.0, $P = 0.02$), voiding symptoms (3.5 *vs* 2.1, $P < 0.001$)	Not valuable	Not valuable	MetS 6.1 (5.8) Non-MetS 4.1 (4.6)	MetS 2.7 (2.7) Non-MetS 2.0 (2.2)	MetS 3.5 (4.2) Non-MetS 2.1 (3.1)	226 (55.26%)	183 (44.74%)	No	No	5
2009	Kupelian *et al.*	USA: observational	1899	IPSS; PV; PSA	NCEP ATP III	Increased odds of the MetS were observed in men with mild to severe LUTS (OR 1.68). A statistically significant association was observed betweenthe MetS and a voiding symptom score of 5 or greater (OR 1.73) but not for a storage symptom score of 4 or greater (OR 0.94).	MetS 1.55 ± 2.10 Non-MetS 1.44 ± 1.57	MetS 31.4 ± 14.4 Non-MetS 29.8 ± 13.1	MetS 6.85 ± 6.52 Non-MetS 7.89 ± 6.63	MetS 3.14 ± 2.68 Non-MetS 3.47 ± 2.71	MetS 3.68 ± 4.44 Non-MetS 4.37 ± 4.59	613 (29.0%)	1286 (71%)	No	Yes	5
2008	Park *et al.*	Korea: retrospective (KLoSHA)	348	IPSS, PV, PSA	NCEP ATP III	No significant differences in IPSS score ($P > 0.05$)	MetS 2.16 ± 2.82 Non-MetS 2.03 ± 2.70	MetS 41.7 ± 16.4 Non-MetS 40.4 ± 19.4	MetS 11.1 ± 8.2 Non-MetS 12.3 ± 8.8	MetS 5.0 ± 3.6 Non-MetS 5.4 ± 3.5	MetS 4.7 ± 4.3 Non-MetS 5.3 ± 4.6	102 (29.3%)	246 (70.7%)	No	No	4
2007	Ozden *et al.*	Turkey: prospective	78	PSA, TP, TZ	NCEP ATP III	Higher BMI, FPG, serum triglyceride, PSA levels, lower serum HDL-C, compared with pt. without MetS ($P < 0.05$). TP growth rate and TZ growth rate higher in pt. MetS (0.64 mL/year and 0.93 mL/year, $P < 0.05$).	MetS 1.73 (0.5–3.9) Non-MetS 1.46 (0.2–4.0)	MetS 37.4 (23–109.4) Non-MetS 32.04 (21.6–63.1)	MetS 22 (10–32) Non-MetS 20 (10–33)	Not valuable	Not valuable	38(%)	40(%)	No	No	5
2006	Parsons *et al.*	USA: cross-sectional	422	LUTS, PSA, AUA symptom score	BMI, WC, FPG	PV is higher for BMI≥35 ($P = 0.01$). Men with elevated FPG have a higher PV ($P = 0.01$).	Not valuable	Not valuable	Not valuable	Not valuable	Not valuable	Not valuable	Not valuable	No	No	5
2005	Rohrmann *et al.*	USA: cross-sectional	878	LUTS	NCEP ATP III	Diabetes, hypertension and HbA1c are positively associated with LUTS. No statistically significant associations between FPG and LUTS.	Not valuable	Not valuable	Not valuable	Not valuable	Not valuable	Not valuable	Not valuable	No	No	5

investigated the link between MetS and BPH; however, the results have been controversial, probably secondary to the racial differences of the analyzed cohorts. In fact, before commenting on the MetS contribution in LUTS/BPO disease, it could be important to consider what population is affected by. As reported in the Baltimore Longitudinal Study of Aging, prostate growth rate is strictly dependent on both age and baseline prostatic volume; in particular, men aged ≥65 years with a larger prostate had a doubled rate of prostatic growth, compared with those with smaller prostates (2 *vs* 1 mL/year).[10] Furthermore, Ford *et al.* showed that the frequency of MetS increased with age.[11] In a Japanese study, 105 men with MetS and LUTS/BPO were evaluated. The prevalence of LUTS/BPO was dependent on age, but not the prevalence of MetS. Moreover, an association between MetS and LUTS/BPO was not found. Furthermore, in an age-matched autopsy series, the prevalence and severity of histological BPH were similar in Caucasian and Southeast Asian men, despite very different diets and lifestyle.[12] These findings are in contrast to previous observations where, compared with the Western population, Japanese men are less likely to develop a progression to BPH owing to differences in the Asian diet, lifestyle and environment, which can differently impair abdominal obesity, commonly associated with the development of vascular diseases, IR and associated complications. In fact, the incidence of BPH has been reported to be much lower in Chinese and Japanese men living in Asia than in white populations. In this context, Asian reports have evidenced an absent or even negative association between LUTS/BPO and MetS.[13–17]

Data on the racial background of the patients with surgically treated BPH in Hawaii have provided evidence for a relatively greater incidence of BPH in Japanese-American men who ate beef.[18]

In a different study, Chinese men living in China had smaller PV than age-matched non-Chinese men living in Australia. However, no differences were found in the PV between native-born Chinese men who had immigrated to Australia and non-Chinese men living in Australia.[19] Thus, these studies imply that prostate growth could accelerate after exposure to a Western diet, lifestyle and environment.

In 2002, Suzuki *et al.* 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.[20]

The influence of dietary fat on LUTS/BPO has been linked to specific fatty acids. An excess of fatty acids and cytokines could induce IR and compensatory hyperinsulinemia. Many of the hormones, growth factors, cytokines, and other mediators associated with obesity and MetS enable cross-talk between macrophages, adipocytes, endothelial cells and epithelial cells, which is implicated in carcinogenesis and tissue growth. Rahman *et al.* found that rats fed a high-fat diet, leading to hyperlipidemia, developed prostate enlargement and bladder overactivity.[21]

Byun *et al.* found that MetS components were associated with larger PV and higher serum PSA level. Patients with more than one metabolic component were significantly more likely to have a larger PV and higher serum PSA level. The serum PSA level and PV were increased in a similar manner with the increasing sum of MetS components ($P < 0.0001$).[22]

This strong association between LUTS and MetS have been widely shown. The severity of voiding score and LUTS became particularly pronounced as the number of MetS factors increased.[23,24]

Conversely, in a series of 968 participants, PV was not significantly larger in the MetS group. Instead patients with abnormal FPG and WC had larger PV than normal groups.[25]

In a recent and very interesting meta-analysis on the associations between MetS and BPE, the authors found that MetS-induced differences in PV were almost equally weighted as a factor of age, WC or serum HDL concentration. Hence, obese, dyslipidemic and aged patients are at higher risk of having MetS as a determinant of their increased prostate size. Furthermore, increased central adiposity, as reflected by waistline, was another MetS-related factor that significantly contributed to variation in prostate enlargement.[7]

Rohrmann *et al.* observed a statistically significant elevated odds of LUTS in men with at least three components of MetS. However, the odds ratio was elevated in men with at least four components of MetS compared with men with fewer components.[26] In the Rancho Bernardo cohort study, Parsons *et al.* found a fourfold increased risk of BPH among diabetic men with LDL cholesterol, but not in the overall cohort. This observation suggests that dyslipidemia is not sufficient enough to induce prostate enlargement, but the concomitant presence of other metabolic derangements, such as diabetes mellitus type 2 or those concurring with the MetS construct, favors the process.[27] Therefore, in any patient presenting with LUTS/BPO, the possible presence of non-insulin-dependent diabetes mellitus, hypertension, obesity, high insulin and low HDL cholesterol levels should be considered.[28] Conversely, in patients suffering from these conditions, the possibility of a clinical LUTS/BPO should be taken into account.[9] The Baltimore Longitudinal Study of Aging showed that diabetic men are twofold more likely to have an enlarged prostate.[29] Recently, in a population-based sample of African-American men aged 40–79 years, Joseph *et al.* reported that men with a diagnosis of diabetes mellitus or hypertension had higher odds of having moderate to severe LUTS/BPO.[30]

A reason for this aspect could be increased IR that accompanies increasing numbers of MetS components, and its positive effect on BPH, TPV ≥30 mL and PVR ≥50 mL.[31]

Furthermore, the occurrence rate of prostate enlargement (≥30 mL) could significantly increase in men with one to two components of MetS, even though they do not have clinically diagnosed MetS.

There is also evidence that storage and voiding symptoms might be susceptible to different risk factors of MetS, yet the majority of studies examined potential associations with total LUTS only.

The significant association between storage symptoms and MetS suggests the possible role of the autonomic nervous system. MetS is known to cause autonomic sympathetic overactivity, through a complex and incompletely elucidated mechanism. The activation of the parasympathetic nervous

system can cause detrusor muscle contraction, and could therefore contribute to detrusor overactivity, which is characteristic of the prevalence of storage symptoms.[3]

The variability in the prevalence of MetS between Eastern and Western countries is also observed in voiding and storage LUTS.

In a Korean study of MetS, IR and the accompanying hyperinsulinemia could have favorable effects on LUTS in the early compensatory stage, especially voiding symptoms. However, advanced diabetes can have unfavorable effects on LUTS, especially storage symptoms. Rather, high HbA1c was strongly and positively associated with storage symptoms.[32] De Nunzio *et al.* observed that MetS is associated with an increased risk of storage symptoms in patients with BPE. These subjects presented a higher IPSS storage subscore ($P \leq 0.002$). Patients with an IPSS storage subscore ≥4 presented a higher BMI and a higher WC when compared with the less symptomatic patients. Instead, MetS was not associated with an increased risk of IPSS and IPSS voiding subscore ≥5.[33]

An Australian study confirmed this positive effect of abdominal fat mass percentage on storage LUTS ($P = 0.046$), but there was no effect of BMI. An elevated FPG was a predictor of storage LUTS ($P = 0.05$). There was also an association between lowered plasma HDL cholesterol and storage symptoms ($P = 0.05$).[34] In a previous study of 45–79-year-old Scandinavian men, a positive association was also observed between waist-to-hip ratio and frequency of urination, nocturia and urgency.[35]

Nocturia is a serious problem that is characterized with sleep disturbances, daytime fatigue and a lower level of general well-being in LUTS/BPO patients. Repeated awaking and voiding attacks lead to sleep disturbances during the night. This condition increases the sympathetic activity, and might damage blood pressure rhythmicity. Meigs *et al.* showed that LUTS are positively associated with coronary heart disease.[36] MetS is not only linked with LUTS/BPO, but also with bladder alterations, including fibrosis (reduced muscle/fiber ratio), hypoxia-increased leukocyte infiltration and inflammatory markers.[37] We have recently shown a relationship between MetS, IR and the presence of moderate to severe LUTS, in particular with voiding symptoms.[38] These results could be explained by the increased sympathetic tone as a result of IR associated with obesity that could result in LUTS and subjective voiding complaints.[39]

All these contributions strongly confirm and strengthen the hypothesis of a close link between MetS and LUTS/BPO, conditions that should be considered as new pathologies of aging.

LUTS/BPO and IR

The major endocrine aberration in connection with MetS is hyperinsulinemia and IR.[38,40] Metabolic disturbances can promote BPH. Recently, some metabolic-related growth factors, such as IGF and higher serum concentrations of insulin and IGF-1, are considered important mediators of the stromal–epithelial interaction. These factors regulate physiology at the cellular and the whole organism levels. High glucose concentrations increase oxidative stress, leading to a higher risk of IR.[4] IR leads to secondary hyperinsulinemia in order to maintain glucose homeostasis. Hyperinsulinemia determines the reduction of IGF-binding protein and an increase in the bioavailability of IGF inducing a cluster of disorders.[41] IR might change the risk of BPH through several biological pathways. The most obvious pathway is by the insulin itself. As a mitogen and a growth factor for prostate epithelial cells, and also as an anti-apoptotic agent, insulin directly mediates its mitogenic effect on prostate cells through signal transduction mechanisms.[42] In addition, insulin has a stimulating effect on the ventromedial hypothalamic nucleus, increasing sympathetic nerve activity through its sympatho-excitatory effect and enhances plasma catecholamine concentrations. The consequence is the increase of prostate smooth muscle tone and of the bladder muscles.[38] In this context, Wang *et al.* showed the connection between diabetes mellitus and LUTS/BPO, demonstrating that diabetic patients had a greater odds ratio of having moderate to severe LUTS (OR 1.78; $P < 0.01$).[43]

A link between hyperinsulinemia and prostatic hyperplasia was suggested in a series of 158 men with LUTS where those men with larger prostates had increased incidence of diabetes, hyper tension and obesity, while also having lower levels of LDL and higher serum insulin levels. This study showed that there was a larger prostate gland in men with non-insulin-dependent diabetes mellitus ($P = 0.0058$), treated hypertension ($P = 0.0317$), obesity ($P < 0.0001$), low HDL cholesterol levels ($P = 0.0132$) and high insulin levels ($P < 0.0001$) than in men without these conditions.[9] These findings suggested that BPH is a facet of MetS, and generated a hypothesis of a causal relationship between high insulin levels and the development of LUTS/BPO. Dahle *et al.* found that the median prostate growth rate was significantly higher in men with high insulin levels.[44] Taken as a whole, these results show that elevated fasting glucose, increased fasting insulin, IR and diabetes could be considered risk factors for LUTS/BPO.

In contrast, several studies have suggested that the IR is not associated with LUTS. In a Korean study of MetS, IR and the accompanying hyperinsulinemia might have favorable effects on LUTS in the early compensatory stage, especially voiding symptoms. However, advanced diabetes could have unfavorable effects on LUTS, especially storage symptoms.[26,32] This unexpected result is confirmed in other studies in which LUTS failed to show a significant association with fasting glucose, fasting insulin and homeostasis model of assessment index.[26,42] A reason for the wide variability in the results could be owing to the large intraindividual variation. Another study has also suggested that the presence of diabetes might be more closely associated with the dynamic components of lower urinary tract function rather than with BPH progression.[45] These inconsistencies might be caused by the clinical overlap between the presence of BPH and LUTS.

LUTS/BPO and central obesity

IR can also lead to dyslipidemia characterized by high triglyceride and low HDL cholesterol levels.[46] Reduced HDL

cholesterol and high triglyceride levels are common denominators of dysregulated lipid metabolism, and can induce and sustain an inflammatory response in the human prostate. Nandeesha *et al.* reported that HDL cholesterol was lower, and total and LDL cholesterol higher in patients with symptomatic LUTS/BPO than in the control group.[47]

Several studies reported that larger WC (>102 cm) and an increase in BMI were positively correlated with increased LUTS.[48] Dahle *et al.* showed that men with higher waist-to-hip ratios were more likely to undergo BPH surgery.[44] In another prospective study of men with no obesity-related morbidities, such as diabetes, impaired fasting glucose, hypertension or dyslipidemia, BMI and WC were positively correlated with PV.[48] These data have recently been confirmed in the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial.[49]

Rohrmann *et al.* examined the association between obesity (especially central adiposity) and the frequency of LUTS in a cross-sectional study in 2797 men aged ≥60 years. The results suggested that being overweight in young adulthood might be associated with a lower prevalence of LUTS later in life, but that weight gain and central adiposity in adulthood were possibly associated with a greater prevalence of LUTS.[26]

Recently, significant emphasis has been placed on associations between chronic inflammation, obesity and BPH. Excessive visceral and subcutaneous fat increase oxidative stress, and simultaneously decrease the expression and activity of key cytoprotective enzymes, including the HO system. A recent study evaluated the components of the HO system in patients with higher levels of glucose, WC, BMI and triglyceride, and lower HDL cholesterol in MetS cases compared with those in controls. The resulted metabolic changes were associated with alterations in the HO cytoprotective system. HO-1 and HO-2 prostatic levels were significantly reduced in group A of specimens (HDL cholesterol level ≥40 mg/dL and triglyceride level <150 mg/dL) than in group B (HDL cholesterol level <40 mg/dL and triglyceride level ≥150 ng/mL; $P \leq 0.05$), with a consequent increase of oxidative stress and remodeling of prostate tissue.[50]

BPH/LUTS, MetS and flogosis

Recently Vignozzi *et al.* found an association not only between MetS and an increased PR, but also with severe intraprostatic inflammation. These observations underlined the new hypothesis that MetS, and hyperinsulinemia-related increase, could boost a chronic inflammation-driven prostate overgrowth.[51]

Among MetS features, reduced HDL and increased triglyceride levels are significantly related to higher prostatic inflammation by secreting interleukin-8. In addition, reduced HDL and increased triglyceride levels are significantly related to higher prostatic inflammation by secreting interleukin-8 in response not only to oxidized low-density lipoprotein, but also showing that different MetS features could synergistically boost inflammation and tissue remodeling in BPH/LUTS.[52,53]

Discussion

The findings of the present systematic review suggest that the presence of MetS is related to LUTS/BPO severity. However, some discordant data on the connection between both diseases are still present among included studies.

In this heterogeneous context, ethnic disparities seems to play an important role. First of all, the definition of MetS substantially differs in relation to ethnic group, varying in Europeans, Americans or Asians. In particular, the parameter that is more influenced by the definitions is WC. In our opinion, this variety might disorient the direct link between MetS and LUTS/BPO. We would also point out that MetS and LUTS/BPO have often been considered as a normal consequence of aging in men, with low onset and progression.

In fact, although several basic studies have shown the role of MetS in LUTS/BPO, probably as a result of an increase in the activity of the sympathetic nervous system and muscle tone of the prostate,[2,54–56] clinical studies have reported conflicting results. In this regard, cross-sectional studies or retrospective epidemiological studies should have been carried out in a select cohort of patients. Men aged older than their 60s and with contextual comorbidities seem the most appropriate. Furthermore, ethnic disparities might a play a significant role secondary to the MetS definition, different lifestyle and dietary patterns. In fact, Asians included in studies reported an absent or negative association between MetS and LUTS/BPO if compared with those from different geographical areas. In this regard, the attributable question about these differences might be referred to the previous biases.

The present review identified a link between MetS and LUTS/BPO severity secondary to several mechanisms including increase of WC, serum triglycerides and IR.

It has been also shown that MetS influences LUTS/BPO at an intraprostatic level. Gacci *et al.* recently reported that MetS was associated not only with an increased PV, but also with severe intraprostatic inflammation. These observations strengthened the new hypothesis that MetS and hyperinsulinemia-related increase, could boost a chronic inflammation-driven prostate overgrowth. In addition, reduced HDL and increased triglyceride levels are significantly related to higher prostatic inflammation by secreting interleukin-8 in response to oxidized LDL, but also showing that different MetS features could synergistically boost inflammation and tissue remodeling in BPH/LUTS.[52,53]

Among MetS features, reduced HDL 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,[52] indicating that different MetS features could synergistically boost inflammation and tissue-remodeling in LUTS/BPO.[57]

These findings are also supported by Cantiello *et al.*, who showed that peri-urethral prostate specimens from patients with MetS more frequently had an inflammatory infiltrate than those from men without MetS secondary to the reduction of elastic content and an increase of collagen peri-urethral amount both in patients with BPH or prostate cancer. Thus, they speculated that peri-urethral fibrosis secondary to MetS-related prostate chronic inflammation could cause

LUTS through a decreased urethral flexibility; this would eventually compromise the ability of the prostatic urethra to enlarge itself and to adequately accommodate urinary flow during micturition.[58,59]

Recently, Gharaee-Kermanid *et al.* showed that mice fed a high-fat diet developed obesity-induced diabetes concurrent with urinary voiding dysfunction associated with pronounced prostatic and urethral tissue fibrosis, and the common biological link between obesity/diabetes and lower urinary tract fibrosis was the inflammation.[60]

In addition, age, MetS and LUTS/BPO also share a variety of other risk factors, such as obesity, high FPG levels, hypertension and androgen deficiency, showing a common link.[61] We would breakdown this view and unveil that also the progression of this condition could be prevented by modifying previous metabolic factors.

In fact, LUTS/BPO are the primary clinical manifestation of BPH, but they also represent a syndrome generated by a host of bladder-related etiologies that may or may not coexist with true pathological BPH. Although a substantial proportion of the existing literature supports an association between diabetes and LUTS/BPO, the failure to differentiate LUTS from BPH has contributed to some controversy.

In our opinion, LUTS/BPO might be considered as a complex disorder that can be also be diagnosed in an earlier stage.

In this context, longitudinal studies investigating the impact of MetS and the onset of LUTS/BPO have not been yet carried out. Furthermore, intraprostatic flogosis should also be considered not as a bystander, but a target point.

"Primum non nocere" (first do no harm) should always be kept in mind, and therefore urologists should contrast the development of LUTS/BPO.

Conclusion

Patients affected by LUTS/BPO and MetS are continuously arising, and emerging links have been confirmed. However, the current literature is limited to having found a relationship between these two diseases of aging, without significant perspective about preventive and therapeutic strategies aimed to counteract the detrimental effect of MetS on LUTS/BPO severity. This connection should be investigated in two different ethnic cohorts (i.e. Asian *vs* Caucasian) in order to better understand the impact of ethnic disparities on MetS and LUTS/BPO severity.

The next challenges of urological research should identify how to decrease the occurrence of IR, dyslipidemia, flogosis and benign prostatic enlargement in order to achieve a well-being in the elderly.

Physical activity that promotes correct dietary intake, eating behaviors and consequent unaltered metabolic parameters could represent optimal strategies.

Finally, longitudinal studies focused on drugs (i.e. metformin, statins) given to patients at high risk of developing LUTS/BPO might set up future therapeutic programs.

Conflict of interest

None declared.

References

1 De NC, Autorino R, Bachmann A *et al.* The diagnosis of benign prostatic obstruction: development of a clinical nomogram. *Neurourol. Urodyn.* 2014; doi: 10.1002/nau.22705

2 Morgia G, Cimino S, Favilla V *et al.* Effects of Serenoa repens, selenium and lycopene (Profluss(R)) on chronic inflammation associated with benign prostatic hyperplasia: results of "FLOG" (Flogosis and Profluss in Prostatic and Genital Disease), a multicentre Italian study. *Int. Braz. J. Urol.* 2013; **39**: 214–21.

3 Kirby MG, Wagg A, Cardozo L *et al.* Overactive bladder: is there a link to the metabolic syndrome in men? *Neurourol. Urodyn.* 2010; **29**: 1360–4.

4 Turkseven S, Kruger A, Mingone CJ *et al.* Antioxidant mechanism of heme oxygenase-1 involves an increase in superoxide dismutase and catalase in experimental diabetes. *Am. J. Physiol. Heart Circ. Physiol.* 2005 Aug; **289**: H701–7.

5 Gacci M, Eardley I, Giuliano F *et al.* Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur. Urol.* 2011; **60**: 809–25.

6 Liberati A, Altman DG, Tetzlaff J *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009; **6**: e1000100.

7 Gacci M, Corona G, Vignozzi L *et al.* Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis. *BJU Int.* 2015; **115**: 24–31.

8 Wells GA, Shea B, O'Connell D *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2012. [Cited 12 July 2015.] Available from URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

9 Hammarsten J, Hogstedt B, Holthuis N, Mellstrom D. Components of the metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis.* 1998; **1**: 157–62.

10 Loeb S, Kettermann A, Carter HB, Ferrucci L, Metter EJ, Walsh PC. Prostate volume changes over time: results from the Baltimore Longitudinal Study of Aging. *J. Urol.* 2009; **182**: 1458–62.

11 Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002; **287**: 356–9.

12 Zlotta AR, Egawa S, Pushkar D *et al.* Prevalence of inflammation and benign prostatic hyperplasia on autopsy in Asian and Caucasian men. *Eur. Urol.* 2014; **66**: 619–22.

13 Kim JH, Doo SW, Yun JH, Yang WJ. Lower likelihood of having moderate-to-severe lower urinary tract symptoms in middle-aged healthy Korean men with metabolic syndrome. *Urology* 2014; **84**: 665–9.

14 Ohgaki K, Hikima N, Horiuchi K, Kondo Y. Association between metabolic syndrome and male lower urinary tract symptoms in Japanese subjects using three sets of criteria for metabolic syndrome and International Prostate Symptom Score. *Urology* 2011; **77**: 1432–8.

15 Gao Y, Wang M, Zhang H *et al.* Are metabolic syndrome and its components associated with lower urinary tract symptoms? Results from a Chinese male population survey. *Urology* 2012; **79**: 194–201.

16 Jeong JH, Kim ET, Kim DK. Association of metabolic syndrome and benign prostate enlargement in young Korean males. *Korean J. Urol.* 2011; **52**: 757–62.

17 Park HK, Lee HW, Lee KS *et al.* Relationship between lower urinary tract symptoms and metabolic syndrome in a community-based elderly population. *Urology* 2008; **72**: 556–60.

18 Chyou PH, Nomura AM, Stemmermann GN, Hankin JH. A prospective study of alcohol, diet, and other lifestyle factors in relation to obstructive uropathy. *Prostate* 1993; **22**: 253–64.

19 Jin B, Turner L, Zhou Z, Zhou EL, Handelsman DJ. Ethnicity and migration as determinants of human prostate size. *J. Clin. Endocrinol. Metab.* 1999; **84**: 3613–9.

20 Suzuki S, Platz EA, Kawachi I, Willett WC, Giovannucci E. Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia. *Am. J. Clin. Nutr.* 2002; **75**: 689–97.

21 Rahman NU, Phonsombat S, Bochinski D, Carrion RE, Nunes L, Lue TF. An animal model to study lower urinary tract symptoms and erectile dysfunction: the hyperlipidaemic rat. *BJU Int.* 2007; **100**: 658–63.

22 Byun HK, Sung YH, Kim W, Jung JH, Song JM, Chung HC. Relationships between prostate-specific antigen, prostate volume, and components of metabolic syndrome in healthy Korean men. *Korean J. Urol.* 2012; **53**: 774–8.

23 Yang TK, Hsieh JT, Chen SC, Chang HC, Yang HJ, Huang KH. Metabolic syndrome associated with reduced lower urinary tract symptoms in middle-aged men receiving health checkup. *Urology* 2012; **80**: 1093–7.

24 Pashootan P, Ploussard G, Cocaul A, de Gouvello A, Desgrandchamps F. Association between metabolic syndrome and severity of lower urinary tract symptoms (LUTS): an observational study in a 4666 European men cohort. *BJU Int.* 2015; **116**: 124–30.

25 Yim SJ, Cho YS, Joo KJ. Relationship between metabolic syndrome and prostate volume in Korean men under 50 years of age. *Korean J. Urol.* 2011; **52**: 390–5.

26 Rohrmann S, Smit E, Giovannucci E, Platz EA. Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III). *Int. J. Obes. (Lond)* 2005; **29**: 310–6.

27 Parsons JK, Bergstrom J, Barrett-Connor E. Lipids, lipoproteins and the risk of benign prostatic hyperplasia in community-dwelling men. *BJU Int.* 2008; **101**: 313–8.

28 Zhang X, Zeng X, Liu Y, Dong L, Zhao X, Qu X. Impact of metabolic syndrome on benign prostatic hyperplasia in elderly Chinese men. *Urol. Int.* 2014; **93**: 214–9.

29 Parsons JK, Carter HB, Partin AW *et al.* Metabolic factors associated with benign prostatic hyperplasia. *J. Clin. Endocrinol. Metab.* 2006; **91**: 2562–8.

30 Joseph MA, Harlow SD, Wei JT *et al.* Risk factors for lower urinary tract symptoms in a population-based sample of African-American men. *Am. J. Epidemiol.* 2003; **157**: 906–14.

31 Park YW, Kim SB, Kwon H *et al.* The relationship between lower urinary tract symptoms/benign prostatic hyperplasia and the number of components of metabolic syndrome. *Urology* 2013; **82**: 674–9.

32 Eom CS, Park JH, Cho BL, Choi HC, Oh MJ, Kwon HT. Metabolic syndrome and accompanying hyperinsulinemia have favorable effects on lower urinary tract symptoms in a generally healthy screened population. *J. Urol.* 2011; **186**: 175–9.

33 De Nunzio C, Cindolo L, Gacci M *et al.* Metabolic syndrome and lower urinary tract symptoms in patients with benign prostatic enlargement: a possible link to storage symptoms. *Urology* 2014; **84**: 1181–7.

34 Martin SA, Haren MT, Marshall VR, Lange K, Wittert GA. Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. *World J. Urol.* 2011; **29**: 179–84.

35 Andersson SO, Rashidkhani B, Karlberg L, Wolk A, Johansson JE. Prevalence of lower urinary tract symptoms in men aged 45–79 years: a population-based study of 40 000 Swedish men. *BJU Int.* 2004; **94**: 327–31.

36 Meigs JB, Mohr B, Barry MJ, Collins MM, McKinlay JB. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. *J. Clin. Epidemiol.* 2001; **54**: 935–44.

37 Morelli A, Comeglio P, Filippi S *et al.* Testosterone and farnesoid X receptor agonist INT-747 counteract high fat diet-induced bladder alterations in a rabbit model of metabolic syndrome. *J. Steroid Biochem. Mol. Biol.* 2012; **132**: 80–92.

38 Russo GI, Cimino S, Fragala E *et al.* Insulin resistance is an independent predictor of severe lower urinary tract symptoms and of erectile dysfunction: results from a cross-sectional study. *J. Sex. Med.* 2014; **11**: 2074–82.

39 McVary KT, Rademaker A, Lloyd GL, Gann P. Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J. Urol.* 2005; **174**: 1327–433.

40 Russo GI, Cimino S, Fragala E *et al.* Relationship between non-alcoholic fatty liver disease and benign prostatic hyperplasia/lower urinary tract symptoms: new insights from an Italian cross-sectional study. *World J. Urol.* 2015; **33**: 743–51.

41 Roberts RO, Jacobson DJ, Girman CJ *et al.* Insulin-like growth factor I, insulin-like growth factor binding protein 3, and urologic measures of benign prostatic hyperplasia. *Am. J. Epidemiol.* 2003; **157**: 784–91.

42 Giovannucci E. Nutrition, insulin, insulin-like growth factors and cancer. *Horm. Metab. Res.* 2003; **35**: 694–704.

43 Wang CC, Chancellor MB, Lin JM, Hsieh JH, Yu HJ. Type 2 diabetes but not metabolic syndrome is associated with an increased risk of lower urinary tract symptoms and erectile dysfunction in men aged <45 years. *BJU Int.* 2010; **105**: 1136–40.

44 Dahle SE, Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Hsing AW. Body size and serum levels of insulin and leptin in relation to the risk of benign prostatic hyperplasia. *J. Urol.* 2002; **168**: 599–604.

45 Burke JP, Jacobson DJ, McGree ME *et al.* Diabetes and benign prostatic hyperplasia progression in Olmsted County, Minnesota. *Urology* 2006; **67**: 22–5.

46 Russo GI, Castelli T, Privitera S *et al.* Increase of Framingham cardiovascular disease risk score is associated with severity of lower urinary tract symptoms. *BJU Int.* 2015; doi: 10.1111/bju.13053.

47 Nandeesha H, Koner BC, Dorairajan LN, Sen SK. Hyperinsulinemia and dyslipidemia in non-diabetic benign prostatic hyperplasia. *Clin. Chim. Acta* 2006; **370**: 89–93.

48 Lee S, Min HG, Choi SH *et al.* Central obesity as a risk factor for prostatic hyperplasia. *Obesity (Silver Spring)* 2006; **14**: 172–9.

49 Muller RL, Gerber L, Moreira DM *et al.* Obesity is associated with increased prostate growth and attenuated prostate volume reduction by dutasteride. *Eur. Urol.* 2013; **63**: 1115–21.

50 Vanella L, Russo GI, Cimino S *et al.* Correlation between lipid profile and heme oxygenase system in patients with benign prostatic hyperplasia. *Urology* 2014; **83**: 1444. e7–13.

51 Vignozzi L, Rastrelli G, Corona G, Gacci M, Forti G, Maggi M. Benign prostatic hyperplasia: a new metabolic disease? *J. Endocrinol. Invest.* 2014; **37**: 313–22.

52 Gacci M, Vignozzi L, Sebastianelli A *et al.* Metabolic syndrome and lower urinary tract symptoms: the role of inflammation. *Prostate Cancer Prostatic Dis.* 2013; **16**: 101–6.

53 Vignozzi L, Cellai I, Santi R *et al.* Antiinflammatory effect of androgen receptor activation in human benign prostatic hyperplasia cells. *J. Endocrinol.* 2012; **214**: 31–43.

54 Lee YC, Huang SP, Liu CC *et al.* The association of eNOS G894T polymorphism with metabolic syndrome and erectile dysfunction. *J. Sex. Med.* 2012; **9**: 837–43.

55 Porst H, Roehrborn CG, Secrest RJ, Esler A, Viktrup L. Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia and on erectile dysfunction in sexually active men with both conditions: analyses of pooled data from four randomized, placebo-controlled tadalafil clinical studies. *J. Sex. Med.* 2013; **10**: 2044–52.

56 Weinberg AE, Eisenberg M, Patel CJ, Chertow GM, Leppert JT. Diabetes severity, metabolic syndrome, and the risk of erectile dysfunction. *J. Sex. Med.* 2013; **10**: 3102–9.

57 Vignozzi L, Gacci M, Cellai I *et al.* PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE5 inhibitors in LUTS. *Prostate* 2013; **73**: 1391–402.

58 Cantiello F, Cicione A, Salonia A *et al.* Metabolic syndrome correlates with peri-urethral fibrosis secondary to chronic prostate inflammation: evidence of a link in a cohort of patients undergoing radical prostatectomy. *Int. J. Urol.* 2014; **21**: 264–9.

59 Cantiello F, Cicione A, Salonia A *et al.* Periurethral fibrosis secondary to prostatic inflammation causing lower urinary tract symptoms: a prospective cohort study. *Urology* 2013; **81**: 1018–23.

60 Gharaee-Kermani M, Rodriguez-Nieves JA, Mehra R, Vezina CA, Sarma AV, Macoska JA. Obesity-induced diabetes and lower urinary tract fibrosis promote urinary voiding dysfunction in a mouse model. *Prostate* 2013; **73**: 1123–33.

61 Fusco F, D'Anzeo G, Sessa A *et al.* BPH/LUTS and ED: common pharmacological pathways for a common treatment. *J. Sex. Med.* 2013; **10**: 2382–93.