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Review

Metabolic syndrome and benign prostatic hyperplasia: An update

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Abstract Metabolic syndrome (MetS) is a cluster of metabolic abnormalities related to central adiposity and insulin resistance. Its importance is increasingly recognized as it associates with increased risks of metabolic and cardiovascular diseases. These metabolic aberrations of MetS may lead to development of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) in men. A 26.5%–55.6% prevalence of MetS in men with LUTS was reported in worldwide studies. Although the exact biological pathway is not clear yet, insulin resistance, increased visceral adiposity, sex hormone alterations and cellular inflammatory reactions played significant roles in the related pathophysiological processes. Clinician should recognize the cardiovascular and metabolic impacts of MetS in men with LUTS, early risk factors optimization and use of appropriate medical therapy may possibly alter or slower the progression of LUTS/BPH, and potentially avoid unnecessary morbidities and mortalities from cardiovascular and metabolic diseases for those men.

1. Introduction

Recognized since the early 1920s, metabolic syndrome (MetS) encompasses a cluster of interrelated cardiovascular risk factors, namely insulin resistance, central obesity, dyslipidaemia and hypertension. It warrants every clinician's attention as the clinical impact is related to the increased risks of coronary heart diseases, cardiovascular disease and mortality in men with MetS [1].

There are few closely related terminology related to male lower urinary tract symptoms (LUTS). Benign prostate enlargement (BPE) means enlarged size of prostate gland with benign nature. Benign prostatic obstruction (BPO) is defined by urodynamic finding of bladder outlet obstruction

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related to BPE. Benign prostatic hyperplasia (BPH), indeed, refers to histological diagnosis.

There are increasing evidence for MetS and inflammation being important elements in men having LUTS related to development of BPH [2]. The understanding of the relationship of MetS and LUTS/BPH would better define our management approach in men with LUTS, not only limited to the relief of urological symptoms, but also be holistic and provide appropriate advice and management on cardiovascular risk factors optimization in men with MetS.

2. MetS — the definition

There has been a plethora of definitions for MetS. The consultation group on the definition of diabetes for the World Health Organization (WHO) was the first to define MetS where insulin resistance was a mandatary criterion [3]. It was not popularized as measurement of insulin resistance was difficult to apply in both epidemiological studies and clinical practices [4].

The European Group for the Study of Insulin Resistance (EGIR) believed that insulin resistance is the major cause of MetS and derived slightly different criteria by adopting fasting insulin to measure insulin resistance and using waist circumference (WC) as a measure of central obesity [5].

The US National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) devised the newer definition on MetS [6]. Men having any three or more of the five components (central obesity, hypertriglyceridaemia, reduced high density lipoprotein cholesterol (HDL-C), raised blood pressure and raised fasting plasma glucose) will be regarded as having MetS. Each component carries equal importance, and no mandatory component has to be present for establishing the diagnosis of MetS. It was updated by the American Heart Association and the National Heart Lung and Blood Institute in 2005, with major modification in reducing the threshold for impaired fasting glucose (IFG) [7,8].

The International Diabetes Federation (IDF) aimed to develop a new set of practical worldwide criteria to better define the nature of MetS as well as for epidemiological and clinical uses. This definition considered central obesity as an essential component, taking into consideration on the ethnic differences in WC and reduction of the hyperglycemic threshold [9].

Among these definitions, central obesity remains the important components of MetS. Understanding that increased visceral adipose tissue is associated with a range of metabolic abnormalities, decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles, all of which are risk factors for type 2 diabetes and cardiovascular diseases [10,11].

To better characterize obesity while defining MetS, WC is adopted in favor of body mass index (BMI). It is not surprising to have significantly different body fat composition between different ethnic populations for a given BMI. Asian has a higher level of body fat and abdominal adipose tissue [12—14]. Chinese, Japanese and South Asian men have more visceral adipose tissue for a given WC than European [15,16]. Therefore, the recommended cut-off values of WC have to be country- or population-specific, the commonly adopted WC using were $\geq$94 cm for Europid men, $\geq$90 cm for Asian men and $\geq$102 cm for men in US [9].

A number of expert groups have established different diagnostic criteria for MetS. Table 1 summarized four most commonly used definitions.

3. Epidemiology of MetS in men with BPH: the current situation

It was almost two decades ago when the researchers observed the relationship of MetS in men with BPH. Hammarsten et al. [17] reported the first prospective study showing the correlation between prostate volume and individual MetS components in men with BPH. One large cross-sectional epidemiological study of the US population based on 2372 Third National Health and Nutrition Examination Survey (NHANES III) male participants, supporting the intermingled relationship of metabolic diseases and the etiology of LUTS [18]. The study showed that men having three or more components of the MetS had increased risks of LUTS and there are strong positive associations between glycosylated haemoglobin, history of hypertension and low HDL-C, and LUTS. In this study, however, LUTS was defined as three or more of the four American Urological Association Symptom Index (AUA-SI) and only men aged 60 years or more were included. The result from another large scale population based epidemiological study in US, known as Boston Area Community Health (BACH) Survey, was later published [19]. Men aged 30—79 years were enrolled, LUTS was assessed with sub-categorized AUA-SI as none (0—1), mild (2—7) and moderate or severe (8—35). The MetS was defined using modified NCEP-ATP III guidelines. It is noted that prevalence of MetS was increased up to approximately 40% with mild LUTS, but not further increased with moderate to severe LUTS group. This pattern of relationship was also observed for individual voiding symptoms, but not in storage symptoms. These associations were stronger in younger men (age less than 60 years). Recently, a prevalence of 26.5% of men with BPH having MetS was reported from a large cross-sectional epidemiological study from UK [20]. Comparing with the matched controls without clinical BPH, the risk of having MetS in men with clinical BPH is increased by 37%.

The worldwide prevalence of LUTS is expected to be increasing in near future, including Asia [21]. Such prevalence in Asia was estimated as 44.8% and 45.5% in 2008 and 2018 respectively. Together with the observation on the increasing trend of BMI, fasting blood glucose and systolic blood pressure level in Asian men, the impact on the prevalence and regional burden of MetS in Asian men should not be underestimated.

Table 2 tabulated the available Asian studies [22—25] reporting the prevalence of MetS in men with BPH, ranging from 26.7% to 55.4%. On the contrary, the Korean Longitudinal Study on Health and Aging investigated on Korean elderly population aged 65 years or older, and found no significant difference observed in mean International Prostate Symptoms Scores (IPSS) or Quality of Life (QoL) scores in men with or without MetS [26]. In another Korean study on younger Korean males aged between 30 and 60 years, similarly, no difference was found in the IPSS voiding

Table 1 WHO, EGIR, NCEP-ATP III and IDF definitions of the metabolic syndrome.

	WHO 1999 [4]	EGIR 1999 [5]	NCEP-ATP III 2005 [6—8]	IDF 2005 [9]
Criteria	T2DM or IGT or insulin resistance plus ≥ 2 of the following:	Hyperinsulinaemia, plus ≥ 2 of the following:	Any ≥ 3 of the following:	Central obesity plus ≥ 2 of the following:
Central obesity	BMI > 30 kg/m^2 or WHR > 0.9 (M) or > 0.85 (F)	WC ≥ 94 cm (M),WC ≥ 80 cm (F)	WC ≥ 102 cm (M), WC ≥ 88 cm (F)	WC-ethnic specific or BMI > 30 kg/m^2
Dyslipidaemia	TG ≥ 150 mg/dL or HDL-C <35 mg/dL(M), <39 mg/dL(F)	TG ≥ 177 mg/dL or HDL-C <39 mg/dL	TG ≥ 150 mg/dL or medication	TG ≥ 150 mg/dL or medication
Dyslipidaemia			HDL-C: < 40 mg/dL (M), <50 mg/dL (F), or medication	HDL-C: <40 mg/dL (M), <50 mg/dL (F), or medication
Blood pressure	≥140/90 mmHg	≥140/90 mmHg or medication	Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or medication	Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or medication
Other	Microalbuminuria: albumin excretion ≥ 20 μg/min		Fasting plasma glucose: ≥ 100 mg/dL or medication	Fasting plasma glucose: ≥ 100 mg/dL or previously diagnosed T2DM

WHO, World Health Organization; EGIR, European Group for the Study of Insulin Resistance; NCEP-ATP, National Cholesterol Education Program Adult Treatment Panel; IDF, International Diabetes Federation; T2DM, type 2 diabetes mellitus; IGT, impaired glucose tolerance; BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; M, male; F, female.

and storage subscores and QoL scores [27]. In the same study, a higher prevalence of BPE (54.0% *vs.* 38.1%) is observed in men with MetS.

Japanese researchers found no relationship between LUTS severity and MetS despite using three different diagnostic criteria (Japan Society for the Study of Obesity (JASSO) criteria 2005, NCEP-ATP III criteria, and IDF criteria) in both young (<50 years) and older age (>65 years) groups [28]. Interestingly, they found that the rate of moderate or severe storage symptoms was less in middle age (50—64 years) group men with MetS no matter which MetS criteria are adopted.

Favorable effects of MetS on LUTS in middle age men were echoed in another study from Taiwan, China [29]. Those men with MetS (mean age 56.4 years) were shown to have less voiding and storage symptoms, in particular in men with larger prostates and/or higher prostate-specific antigen (PSA).

According to the recently published meta-analyses, men with MetS tended to have higher total prostate volume, by difference of 1.8—10.2 mL [30—32]. Higher annual prostate growth rate in men with MetS was also reported in one of the meta-analysis [32]. However, there was no significant difference demonstrated regarding the IPSS or subdomain scores in men with or without MetS [30,31], and presence of individual MetS components were not shown to correlate with the risk of having moderate-to-severe LUTS [31].

4. Biologic pathophysiology of MetS and BPH

Although there are epidemiological evidence suggesting the link of MetS and BPH/LUTS, the exact biological pathways are still unclear yet. Several key factors have been identified and postulated to be responsible in such pathophysiological processes.

a. Insulin resistance

Insulin is a well-known mitogen and growth factor for prostatic epithelial cells [33,34]. Hyperinsulinaemia directly, or indirectly through obesity and its altered hormone metabolism, may increase transcription of genes involved in sex hormone metabolism [35]. It is also associated with lower sex hormone-binding globulin, thus increasing the amount of androgen and estrogen entering prostatic cells, thereby increasing the risk of BPH [36].

Insulin-like growth factor 1 (IGF-1) has been shown to promote prostate epithelial growth [37]. IGF-1 was found to be associated with risk of BPH in two epidemiological studies [38,39]. Insulin receptor has homology with IGF receptor. Insulin can bind to IGF receptor and activate the IGF signaling pathway to promote prostatic growth. In addition, insulin lowers with insulin-like growth factor binding protein 1 (IGFBP-1) and further increases IGF-1 bioavailability [37].

Hyperglycaemia may increase cytosolic-free calcium in smooth muscle cells and neural tissues, leading to sympathetic nervous system activation. This activation may contribute to the increased smooth muscle tone of the prostate and may eventually worsen LUTS [18,40]. Furthermore, hyperinsulinemia increases plasma and tissue

Table 2 Prevalence of MetS in men with LUTS in Asian countries.

City of study	Numbers of men with BPH/LUTS	Participants characteristics	MetS criteria	Definition of obesity	Prevalence (%)
Seoul, South Korea [22]	778	Median age 54 years; IPSS > 7; police	NCEP-ATP III	WC ≥ 90 cm	26.7
Istanbul, Turkey [23]	78	Mean age 61.8 years	NCEP-ATP III	WC > 102 cm	34.6
Guangzhou, China [24]	1052	BPH inpatients; Mean age 70.1 years	NCEP-ATP III	BMI > 30 kg/m^2	39.7
Changsha, China [25]	401	Age > 60 years	NCEP-ATP III	WC ≥ 90 cm	55.4

MetS, metabolic syndrome; LUTS, lower urinary tract symptoms; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptoms Scores; NCEP-ATP, National Cholesterol Education Program Adult Treatment Panel; WC, waist circumference.

catecholamines [41], and may have a trophic effect on prostate cell growth [42].

Although early-stage hyperinsulinaemia might have a beneficial effect on men with LUTS [43], chronic hyperinsulinaemia induces prostate inflammation and overgrowth, and has been shown to be associated with LUTS deterioration [44,45].

Nandeesha et al. [46] found that fasting plasma insulin was an independent risk factor for increased prostate gland volume. Patients who had fasting plasma insulin levels less than 7 mU/mL, had an annual BPH growth rate of 0.84 mL per year while those had fasting plasma insulin levels >13 mU/mL was 1.49 mL per year ($p = 0.015$), suggesting that insulin is a promoter of BPH [42].

In those with BPH, diabetes doubled the risk of moderate-severe LUTS [47]. Second population-based Norwegian Nord-Trøndelag Health (HUNT) Study and BACH Survey also provided similar data and further confirmed this association [48,49].

b. Increased visceral adiposity

Obesity results in an increased aromatase activity, leading to increased estradiol production, which further inhibits gonadotropin secretion and the production of testosterone. This hypogonadal obesity cycle results in a progressive enhanced estrogen to androgen ratio, resulting in hypogonadal state [50].

Visceral adipose tissues secrete various bioactive substances known as adipocytokines, which can induce insulin resistance and related proinflammatory and proatherogenic effects. The reduction of adiponectin upon visceral fat accumulation stimulates glucose metabolism and fatty acid oxidation in the muscle, also enhances insulin sensitivity [51—53].

In Baltimore Longitudinal Study of Aging, each kg/m^2 increase in BMI corresponded with a 0.41 mL increase in prostate volume. Obese patients had a 3.5-fold increased risk of an enlarged prostate compared to non-obese participants [54].

The relationship between obesity and LUTS has been controversial until the result of Health Professionals Follow-up Study available. It was a large population-based prospective study; enrolling 51 529 US men aged 40—75 years, with a follow-up duration of more than 16 years. It showed that increased adiposity and weight gain since youth were significantly associated with the incidence and progression of LUTS [55].

Recently, a multi-center prospective study also suggested that central obesity (WC > 102 cm) was the main determinant of persistent storage symptoms after surgical treatment for BPH [56].

c. Sex steroid

Low androgen and high estrogen levels were found in men with LUTS and BPH, like those with MetS [57,58]. The lowered dihydrotestosterone (DHT) level in the transition zone of the prostate promotes smooth muscle hyperplasia [59].

Hyperinsulinaemia may cause BPH indirectly by its effect on obesity and sex hormones. In turn, abdominal obesity alters levels of insulin and sex hormones [60]. Sex hormones are involved with androgenic actions within the prostate, which activate DNA synthesis and cellular proliferation, increase the risk of BPH [60,61]. In the canine study by Johns Hopkins, estrogen was found to synergize androgen effects, inducing more than four-fold increase in total prostate weight [62].

d. Dyslipidaemia

Nandeesha et al. [46] reported that the level of HDL-C was lower, while level of total cholesterol and low density lipoprotein cholesterol (LDL-C) were higher in patients with symptomatic BPH than in controls. In a case-control study performed in Taiwan, China, dyslipidaemia was significantly associated with BPE compared with controls [64].

In the Florey Adelaide Male Ageing Study, men with hypertriglyceridaemia had a lower chance of storage LUTS improvement and those with greater abdominal fat mass was associated with storage LUTS progression. Lower HDL-C level was associated with worsening of voiding LUTS [63].

A prospective community-based cohort study from Parsons et al. [65] showed no significant association between total cholesterol, HDL-C, triglycerides, triglyceride to HDL-C ratio and the risk of BPH. Interestingly, only in the subset analysis of diabetic men with increased LDL-C, they were shown to have greater risk of having BPH.

Increased triglyceride level was not significantly associated with prostate enlargement from meta-analysis [66], yet was found significantly associated with risk of LUTS (odds ratio (OR) = 1.31, 95% confidence interval (CI):

1.01—1.71) from another meta-analysis by US Preventive Services Task Force [67].

e. Chronic low grade pro-inflammatory state

MetS has been associated with a state of chronic low grade inflammation, with elevated levels of inflammation markers such as C-reactive protein (CRP) as well as pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-8, IL-6, and IL-1p [68—70]. T-cell activities in prostate inflammatory infiltrates may result in stimulation of stromal and epithelial cell proliferation that is sustained by an autoimmune mechanism. Tissue damages and the subsequent chronic process of repetitive wound healing induced by chronic inflammation may lead to the development of BPH nodules [71—73].

Finding of inflammation in prostate biopsy in MTOPS study is associated with BPH progression [74]. In addition, increased serum levels of CRP have been associated with an increased risk of overall LUTS [49,75] and storage LUTS [76—78].

MetS is related to arteriosclerosis. Pelvic arterial tree is not an exception. In animal model, this pelvic arteriosclerosis had been shown to cause ischaemia, resulting in thickening and fibrosis of the prostate. Neurogenic relaxation in the prostate was also impaired [79].

f. Three-hit mechanism

Vignozzi et al. [80,81] proposed a three-hit hypothesis on the pathogenesis of BPH under metabolic influence. An induced prostatic inflammation (first hit) could be auto-sustained by metabolic alterations (second hit) and sex steroid abnormalities (third hit). This combined actions of these two or three hits, may result in overexpression of Toll-like receptors, transformation of prostatic cells into antigen-presenting cells, activation of resident human prostate-associated lymphoid tissue andover production of growth factors, therefore contributing to the prostate remodeling and enlargement [80].

5. Implication/importance of recognizing MetS in men with BPH—Cardiovascular concern of MetS

LUTS seem to have an inextricable relationship with major adverse cardiac events in the male population. Men with moderate to severe LUTS have shown an increased risk of major acute cardiac events [82]. The Framingham Risk score, expressed in percentage, is a gender-specific risk assessment tool in estimating the 10-year atherosclerotic cardiovascular risk of an individual. Patients with BPH-related LUTS showed a five-fold increase of having a Framingham cardiovascular disease risk score of $\geq$10% in men with moderate-severe LUTS [83].

As MetS and LUTS/BPH are closely linked, even though men got only one or two risk factors of MetS, they were shown to have increased risks of mortality from cardiovascular disease and coronary heart disease [1]. Therefore, lifestyle modification and optimization of such metabolic and cardiovascular risk factors would be considered as a sensible approach in order to avoid potential cardiovascular death.

6. Role of lifestyle modifications and weight loss

6.1. Obesity, exercise and weight reduction

Central obesity, an integral part of metabolic syndrome, is predictive of severity of LUTS [84]. Meta-analyses have shown a positive relationship between MetS and BPH/LUTS in men across different ethnic origins, in both Caucasians and Chinese populations despite very diversified lifestyle and diet [30,82,85]. Epidemiological data repeatedly show a favorable relationship between increased physical activity and weight loss with decreased risks and progression of BPH and LUTS [86,87]. In a recent Korean prospective longitudinal cohort study, men with low physical activity (defined by an average $<$140 kcal of daily energy consumption during leisure time and physical activity) experienced more severe exacerbation of LUTS [88]. Similarly, men who reported higher levels of physical activity are half less likely to report LUTS, when compared to those reporting low levels of physical activity in the Massachusetts Male Aging Study [89].

Analyses from a large population based study of 106 435 Australian men aged $\geq$45 years, demonstrated that the adjusted OR of severe LUTS decreased with increasing physical activities (high *vs.* low, OR = 0.83, 95%CI: 0.76—0.91) [90].

A meta-analysis of eight studies (n = 35 675) stratified the physical levels of activities into light, moderate, and vigorous categories, with a sedentary category as reference. When compared with the sedentary group, the pooled OR for BPH or LUTS were 0.70 (95%CI: 0.44—1.13, p = 0.14), 0.74 (95%CI: 0.60—0.92, p = 0.005), and 0.74 (95%CI: 0.59—0.92, p = 0.006) for men engaging in light, moderate, and heavy physical activity, respectively. The investigators concluded that moderate to vigorous physical activity may reduce up to 25% risk of BPH or LUTS, compared to a sedentary lifestyle [91].

Increased central adiposity, as reflected by WC, is another factor of metabolic syndrome that significantly contributes to BPH. In 2015, a meta-regression analysis of eight studies (n = 5403), revealed that the differences in total prostate volume were significantly higher in older and obese patients [26]. When WC, an indicator of central obesity, was introduced together with age and PSA level as further covariates, it still stands as an independent factor in association with overall and transitional zone prostatic volume increment [26]. This is concordance with previous meta-analysis that reported obesity (as measured by BMI) increased 28% risk of having BPH [92].

6.2. Diet and micronutrients

Few studies evaluated the association between diet and LUTS, results have been heterogeneous and inconclusive.

Focusing on the role of fruit and vegetable on prostate health, 2000 Southern Chinese elderly men were prospectively followed up through 4 years [93]. High levels of fruit and vegetables ($>$350 g/1000 kcal/day) were significantly associated with reduced IPSS score, relative to the moderate groups (250—350 g/1000 kcal/day). High intake of dark and

leafy vegetables (>50 g/1000 kcal/day) significantly reduced the risk of LUTS progression by 37.2% (OR = 0.628, 95%CI: 0.466—0.848, $p = 0.002$) and risk of symptomatic BPH by 34.3% (OR = 0.657, 95%CI: 0.442—0.976, $p = 0.038$) after 4 years compared with the moderate group (25—50 g/1000 kcal/day). Consumption of fruit and vegetables rich in β-carotene, lutein and vitamin C was inversely related to BPH [94]. Interestingly, consumptions of such micronutrients must be via diet and not supplements [95]. Alcohol consumption of seven drinks or more per week is independently associated with increased risk of moderate to severe LUTS in Chinese men [96].

Lifestyle factors emerge as a novel opportunity for the prevention and treatment of BPH and LUTS. Randomized controlled trials are yet to be carried out to ascertain the association between exercise, diet and weight loss on the prevention, development or progression of LUTS. Despite so, promotion of healthy lifestyle is definitely beneficial in the context of MetS and cardiovascular disease. Time will tell their impact on BPH and LUTS.

7. Role of statin

The use of statin-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors has been associated with a 6.5- to 7-year delay in the new onset of moderate/severe LUTS reported by St Sauver et al. [97]. This cholesterol synthesis inhibitor may provide a dualistic benefit in prevention of coronary heart disease events and LUTS progression.

A recently published meta-analysis has demonstrated the connection between triglycerides and LUTS severity. The pooled OR (95%CI) of patients with triglycerides level ≥ 150 mg/dL having moderate-to-severe LUTS was 1.31 (1.01—1.71) [98—100].

After adjusting possible metabolic syndrome related confounding factors, men across all age groups taking statin reported a lower incidence of moderate to severe LUTS compared to those not taking statin [97]. Results from the BACH Survey also confirmed that use of statin is associated with lower incidence of LUTS in older men [101]. The lengthiest duration of statin usage was associated with the lowest risk of developing moderate to severe LUTS [97].

Simvastatin and atorvastatin significantly reduced prostate volume, improved LUTS, and slowed the clinical progression of BPH possibly by lowering cholesterol and anti-inflammatory factors [102,103]. The decrease in prostate volume was more significant in those receiving simvastatin than those receiving atorvastatin; in the obese than in the normal weight patients; and in the hyperlipidaemia patients than in the normal-lipid patients following the statin interventions [102]. The reduction in prostate volume was positively related to the decreases in the levels of total cholesterol and IL-6 and to the increase in the level of HDL-C [102]. A small intervention studies investigating the efficacy of lovastatin [104] provided contradicting data, where usage of lovastatin showed no effects on LUTS. The only randomized control trial by Mills et al. [105] also found no difference between atorvastatin and placebo mean IPSS change after 6 months in men with BPH.

The large prospective Health Professionals Follow-up Study ($n = 51\ 529$) added onto existing conflicting data. Statin use was unlikely beneficial on the incidence or progression of LUTS. Participants were relatively affluent in this study population, authors suggested they may be healthier men with better access to healthcare and hence less need for statin medication, this may account for difference [106].

Majority of the existing studies are limited by small sample sizes, inability to control for confounding, cross-sectional designs and short follow-up interval. This raises our attention to the need of high-powered studies with longer follow-up interval to define the preventive and therapeutic role of statin in BPH/LUTS.

8. Role of biguanide

Metformin is an oral biguanide class anti-hyperglycemic agent and insulin sensitizer which inhibits hepatic gluconeogenesis and enhances peripheral glucose uptake [107]. It also possesses anti-neoplastic activity through induction of apoptotic signaling and cell cycle arrest. In basic science research conducted, metformin has been shown to attenuate the proliferation of prostate epithelial cells [108,109].

Since insulin resistance is shown to be an independent predictor of severe LUTS [110], reducing insulin resistance may serve as a means to prevent LUTS.

Using the Olmsted County Study of Urinary Symptoms and Health Status among Men and the Flint Men's Health Study, Sarma et al. [111] looked into the use of oral hypoglycemics and its relationship with LUTS and BPH. The odds of moderate or severe LUTS was found significantly greater in men with diabetes (age- and race-adjusted OR = 1.37, 95%CI: 1.00—1.87) compared with men without diabetes. For the men suffering from diabetes, those not taking medication had greater odds of moderate or severe LUTS than those taking medication. However, prostate volume and PSA level were not significantly associated with diabetes treatment. Authors suggest that the presence of diabetes and subsequent poor glycemic control might be less related to prostate growth and more to the dynamic components of lower urinary tract function.

However, a small population-based study of African American men aged 40—79 years did not show significant associations between hyperglycemia, hyperinsulinemia, and insulin resistance and burden and progression of BPH after adjustment for age and BMI [112].

Additional evaluations of the associations between glycemic control and BPH progression are warranted.

9. Conclusion

LUTS/BPH are linked with chronic inflammation, where MetS played an important role in the pathogenesis. Clinician should be alert in identifying MetS and understanding the associated cardiovascular risks in men with LUTS. Lifestyle modification and optimization of cardiovascular and metabolic risk factors may possibly alter or slower the progression of LUTS/BPH, and potentially avoid unnecessary morbidities and mortalities from cardiovascular and metabolic diseases for those men.

Conflicts of interest

The authors declared no conflict of interest.

References

[1] Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004;110:1245—50.

[2] De Nunzio C, Aronson W, Freedland SJ, Giovannucci E, Parsons JK. The correlation between metabolic syndrome and prostatic diseases. Eur Urol 2012;61:560—70.

[3] Department of Noncommunicable Disease Surveillance. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Geneva: World Health Organization; 1999. p32—3.

[4] Zimmet P, Alberti KGM, Ríos MS. A new international diabetes federation worldwide definition of the metabolic syndrome: the rationale and the results. Rev Esp Cardiol 2005;58:1371—6.

[5] Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 1999;16:442—3.

[6] Expert Panel on Detection. Evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the national Cholesterol Education Program (NCEP) expert Panel on Detection, Evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III). JAMA 2001;285:2486—97.

[7] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an american heart association/national heart, lung and blood Institute scientific statement. Circulation 2005;112:2735—52.

[8] Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al. Expert committee on the diagnosis and classification of diabetes mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160—7.

[9] Alberti KG, Zimmet P, Shaw J. IDF epidemiology task force consensus group. The metabolic syndrome-a new worldwide definition. Lancet 2005;366:1059—62.

[10] Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hipratio as predictors of cardiovascular risk—a review of the literature. Eur J Clin Nutr 2010;64:16—22.

[11] Seidell JC. Waist circumference and waist/hip ratio in relation to all-cause mortality, cancer and sleep apnea. Eur J Clin Nutr 2010;64:35—41.

[12] Diaz VA, Mainous 3rd AG, Baker R, Carnemolla M, Majeed A. How does ethnicity affect the association between obesity and diabetes? Diabet Med 2007;24:1199—204.

[13] Obesity in Asia Collaboration, Huxley R, Barzi F, Lee CM, Lear S, Shaw J, et al. Waist circumference thresholds provide an accurate and widely applicable method for the discrimination of diabetes. Diabetes Care 2007;30:3116—8.

[14] Huxley R, James WP, Barzi F, Patel JV, Lear SA, Suriyawongpaisal P, et al. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. Obes Rev 2008;9(Suppl 1):53—61.

[15] Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). Am J Clin Nutr 2007;86:353—9.

[16] Kagawa M, Binns CB, Hills AP. Body composition and anthropometry in Japanese and Australian Caucasian males and Japanese females. Asia Pac J Clin Nutr 2007;16(Suppl 1):31—6.

[17] Hammarsten J, Högstedt B, Holthuis N, Mellström D. Components of the metabolic syndrome—risk factors for the development of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 1998;1:157—62.

[18] 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.

[19] Kupelian V, McVary KT, Kaplan SA, Hall SA, Link CL, Aiyer LP, et al. Association of lower urinary tract symptoms and the metabolic syndrome: results from the Boston area community health survey. J Urol 2009;182:616—25.

[20] DiBello JR, Ioannou C, Rees J, Challacombe B, Maskell J, Choudhury N, et al. Prevalence of metabolic syndrome and its components among men with and without clinical benign prostatic hyperplasia: a large, cross sectional, UK epidemiological study. BJU Int 2016;117:801—8.

[21] Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. BJU Int 2011;108:1132—8.

[22] Park HK, Lee HW, Lee KS, Byun SS, Jeong JS, Hong SK, et al. Relationship between lower urinary tract symptoms and metabolic syndrome in a community-based elderly population. Urology 2008;72:556—60.

[23] 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.

[24] 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.

[25] 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.

[26] Gacci M, Corona G, Vignozzi L, Salvi M, Serni S, De Nunzio C, et al. Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis. BJU Int 2015;115:24—31.

[27] Russo GI, Castelli T, Urzì D, Privitera S, Fragalà E, La Vignera S, et al. Connections between lower urinary tract symptoms related to benign prostatic enlargement and metabolic syndrome with its components: a systematic review and meta-analysis. Aging Male 2015;18:207—16.

[28] Zou C, Gong D, Fang N, Fan Y. Meta-analysis of metabolic syndrome and benign prostatic hyperplasia in Chinese patients. World J Urol 2016;34:281—9.

[29] Kwon H, Kang HC, Lee JH. Relationship between predictors of the risk of clinical progression of benign prostatic hyperplasia and metabolic syndrome in men with moderate to severe lower urinary tract symptoms. Urology 2013;81:1325—9.

[30] Doğan Y, Uruç F, Aras B, Şahin A, Kıvrak M, Ürkmez A, et al. The relationships between metabolic syndrome, erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia. Turk J Urol 2015;41:7—12.

[31] Pan JG, Jiang C, Luo R, Zhou X. Association of metabolic syndrome and benign prostatic hyperplasia in Chinese patients of different age decades. Urol Int 2014;93:10—6.

[32] 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.
[33] Barnard RJ, Aronson WJ, Tymchuk CN, Ngo TH. Prostate cancer: another aspect of the insulin-resistance syndrome? Obes Rev 2002;3:303—8.
[34] Giovannucci E. Nutrition, insulin, insulin-like growth factors and cancer. Horm Metab Res 2003;35:694—704.
[35] Haffner SM. Sex hormones, obesity, fat distribution, type 2 diabetes and insulin resistance: epidemiological and clinical correlation. Int J Obes Relat Metab Disord 2000;24(Suppl 2): S56—8.
[36] Hautanen A. Synthesis and regulation of sex hormone-binding globulin in obesity. Int J Obes Relat Metab Disord 2000; 24(Suppl 2):S64—70.
[37] Peehl DM, Cohen P, Rosenfeld RG. The role of insulin-like growth factors in prostate biology. J Androl 1996;17:2—4.
[38] Chokkalingam AP, Gao YT, Deng J, Stanczyk FZ, Sesterhenn IA, Mostofi FK, et al. Insulin-like growth factors and risk of benign prostatic hyperplasia. Prostate 2002;52: 98—105.
[39] Stattin P, Kaaks R, Riboli E, Ferrari P, Dechaud H, Hallmans G. Circulating insulin-like growth factor-I and benign prostatic hyperplasia: a prospective study. Scand J Urol Nephrol 2001; 35:122—6.
[40] Sarma AV, Parsons JK, McVary K, Wei JT. Diabetes and benign prostatic hyperplasia/lower urinary tract symptoms—what do we know? J Urol 2009;182(6 Suppl):S32—7.
[41] Landsberg L. Diet, obesity and hypertension: an hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Q J Med 1986;61:1081—90.
[42] Hammarsten J, Hogstedt B. Hyperinsulinaemia as a risk factor for developing benign prostatic hyperplasia. Eur Urol 2001;39:151—8.
[43] 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.
[44] Lotti F, Corona G, Vignozzi L, Rossi M, Maseroli E, Cipriani S, et al. Metabolic syndrome and prostate abnormalities in male subjects of infertile couples. Asian J Androl 2014;16: 295—304.
[45] Vignozzi L, Gacci M, Santi R, Corona G, Morelli A, Rastrelli G, et al. Fat boosts, while androgen receptor activation counteracts, BPH-associated prostate inflammation. Prostate 2013;73:789—800.
[46] Nandeesha H, Koner BC, Dorairajan LN, Sen SK. Hyperinsulinemia and dyslipidaemia in non-diabetic benign prostatic hyperplasia. Clin Chim Acta 2006;370:89—93.
[47] Joseph MA, Harlow SD, Wei JT, Sarma AV, Dunn RL, Taylor JM, 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.
[48] Seim A, Hoyo C, Ostbye T, Vatten L. The prevalence and correlates of urinary tract symptoms in Norwegian men: the HUNT study. BJU Int 2005;96:88—92.
[49] Kupelian V, Araujo AB, Wittert GA, McKinlay JB. Association of moderate to severe lower urinary tract symptoms with incident type 2 diabetes and heart disease. J Urol 2015;193: 581—6.
[50] Cohen PG. Abdominal obesity and intra-abdominal pressure: a new paradigm for the pathogenesis of the hypogonadal-obesity-BPH-LUTS connection. Horm Mol Biol Clin Investig 2012;11:317—20.
[51] Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech 2009;2:231—7.
[52] Reaven GM. The metabolic syndrome: time to get off the merry go-round? J Intern Med 2011;269:127—36.
[53] Duvnjak L, Duvnjak M. The metabolic syndrome—an ongoing story. J Physiol Pharmacol 2009;60(Suppl 7):19—24.
[54] Parsons JK, Carter HB, Partin AW, Windham BG, Metter EJ, Ferrucci L, et al. Metabolic factors associated with benign prostatic hyperplasia. J Clin Endocrinol Metabol 2006;91: 2562—8.
[55] Mondul AM, Giovannucci E, Platz EA. A prospective study of obesity, and the incidence and progression of lower urinary tract symptoms. J Urol 2014;191:715—21.
[56] Gacci M, Sebastianelli A, Salvi M, De Nunzio C, Tubaro A, Vignozz L, et al. Central obesity is predictive of persistent storage lower urinary tract symptoms (LUTS) after surgery for benign prostatic enlargement: results of a multicentre prospective study. BJU Int 2015;116:271—7.
[57] Gorbachinsky I, Akpinar H, Assimos DG. Metabolic syndrome and urologic diseases. Rev Urol 2010;12:157—80.
[58] Rohrmann S, Nelson WG, Rifai N, Kanarek N, Basaria S, Tsilidis KK, et al. Serum sex steroid hormones and lower urinary tract symptoms in Third National Health and Nutrition Examination Survey (NHANES III). Urology 2007;69:708—13.
[59] Shibata Y, Ito K, Suzuki K, Nakano K, Fukabori Y, Suzuki R, et al. Simultaneous quantitative analysis of prostate sex steroids and comparison with human prostatic histological composition. Prostate 2000;42:45—55.
[60] Sciarra F, Toscano V. Role of estrogens in human benign prostatic hyperplasia. Arch Androl 2000;44:213—20.
[61] Hsing AW. Hormones and prostate cancer: what's next? Epidemiol Rev 2001;23:42—58.
[62] Walsh PC, Wilson JD. The induction of prostatic hypertrophy in the dog with and rostanediol. J Clin Invest 1976;57: 1093—7.
[63] Martin S, Lange K, Haren MT, Taylor AW, Wittert G. Members of the Florey Adelaide Male Ageing Study. Risk factors for progression or improvement of lower urinary tract symptoms in a prospective cohort of men. J Urol 2014;191:130—7.
[64] Chiu YL, Kao S, Lin HC, Liu SP, Huang CY. Benign prostatic enlargement is not associated with diabetes: a population-based study. Andrology 2015;3:933—6.
[65] 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.
[66] Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, et al. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with α-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 2012;61:994—1003.
[67] Russo GI, Castelli T, Urzì D, Privitera S, Fragalà E, La Vignera S, et al. Connections between lower urinary tract symptoms related to benign prostatic enlargement and metabolic syndrome with its components: a systematic review and meta-analysis. Aging Male 2015;18:207—16.
[68] Penna G, Mondaini N, Amuchastegui S, Degli Innocent S, Carini M, Giubilei G, et al. Seminal plasma cytokines and chemokines in prostate inflammation: interleukin-8 as a predictive biomarker in chronic prostatitis/chronic pelvic pain syndrome and benign prostatic hyperplasia. Eur Urol 2007;51:524—33.
[69] Devaraj S, Singh U, Jialal I. Human C-reactive protein and the metabolic syndrome. Curr Opin Lipidol 2009;20:182—9.
[70] Rohrmann S, De Marzo AM, Smit E, Giovannucci E, Platz EA. Serum C-reactive protein concentration and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey (NHANES III). Prostate 2005;62: 27—33.
[71] Alcaraz A, Hammerer P, Tubaro A, Schröder FH, Castro R. Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. Eur Urol 2009;55:864—73.

[72] De Nunzio C, Kramer G, Marberger M, Montironi R, Nelson W, Schröder F, et al. The controversial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation. Eur Urol 2011;60:106—17.
[73] Briganti A, Capitanio U, Suardi N, Gallina A, Salonia A, Bianchi M, et al. Benign prostatic hyperplasia and its aetiologies. Eur Urol Suppl 2009;8:865—71.
[74] Crawford ED, Wilson SS, McConnell JD, Slawin KM, Lieber MC, Smith JA, et al. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. J Urol 2006;175:1422—6.
[75] Schenk JM, Kristal AR, Neuhouser ML, Tangen CM, White E, Lin DW, et al. Biomarkers of systemic inflammation and risk of incident, symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. Am J Epidemiol 2010;171:571—82.
[76] Liao CH, Chung SD, Kuo HC. Serum C-reactive protein levels are associated with residual urgency symptoms in patients with benign prostatic hyperplasia after medical treatment. Urology 2011;78:1373—8.
[77] Hung SF, Chung S, Kuo HC. Increased serum C-reactive protein level is associated with increased storage lower urinary tract symptoms in men with benign prostatic hyperplasia. PLoS One 2014;9:e85588.
[78] Kim JH, Doo SW, Yang WJ, Song YS, Kwon SS. Association between high-sensitivity C-reactive protein and lower urinary tract symptoms in healthy Korean populations. Urology 2015;86:139—44.
[79] Kozlowski R, Kershen RT, Siroky MB, Krane RJ, Azadzoi KM. Chronic ischaemia alters prostate structure and reactivity in rabbits. J Urol 2001;165:1019—26.
[80] 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.
[81] Vignozzi L, Gacci M, Maggi M. Lower urinary tract symptoms, benign prostatic hyperplasia and metabolic syndrome. Nat Rev Urol 2016;13:108—19.
[82] Gacci M, Corona G, Sebastianelli A, Serni S, De Nunzio C, Maggi M, et al. Male lower urinary tract symptoms and cardiovascular events: asystematic review and meta-analysis. Eur Urol 2016;70:788—96.
[83] Russo GI, Castelli T, Privitera S, Fragala E, Favilla V, Reale G, et al. Increase of Framingham cardiovascular disease risk score is associated with severity of lower urinary tract symptoms. BJU Int 2015;116:791—6.
[84] Lee RK, Chung D, Chughtai B, Te AE, Kaplan SA. Central obesity as measured by waist circumference is predictive of severity of lower urinary tract symptoms. BJU Int 2012;110:540—5.
[85] Zou C, Gong D, Fang N, Fan Y. Meta-analysis of metabolic syndrome and benign prostatic hyperplasia in Chinese patients. World J Urol 2016;34:281—9.
[86] Penson DF, Munro HM, Signorello LB, Blot WJ, Fowke JH. Urologic Diseases in America Project. Obesity, physical activity and lower urinary tract symptoms: results from the Southern Community Cohort Study. J Urol 2011;186:2316—22.
[87] Parsons JK, Messer K, White M, Barrett-Connor E, Bauer DC, Marshall LM, et al. Obesity increases and physical activity decreases lower urinary tract symptom risk in older men: the Osteoporotic Fractures in Men study. Eur Urol 2011;60:1173—80.
[88] Choo MS, Han JH, Shin TY, Ko K, Lee WK, Cho ST, et al. Alcohol, smoking, physical activity, protein, and lower Urinary tract symptoms: prospective longitudinal cohort. Int Neurourol J 2015;19:197—206.
[89] Maserejian NN, Kupelian V, Miyasato G, McVary KT, McKinlay JB. Are physical activity, smoking and alcohol consumption associated with lower urinary tract symptoms in men or women? Results from a population based observational study. J Urol 2012;188:490—5.
[90] Smith DP, Weber MF, Soga K, Korda RJ, Tikellis G, Patel MI, et al. Relationship between lifestyle and health factors and severe lower urinary tract symptoms (LUTS) in 106,435 middle-aged and older Australian men: population-based study. PLoS One 2014;9:e109278.
[91] Parsons JK, Kashefi C. Physical activity, benign prostatic hyperplasia, and lower urinary tract symptoms. Eur Urol 2008;53:1228—35.
[92] Wang S, Mao Q, Lin Y, Wu J, Wang X, Zheng X, et al. Body mass index and risk of BPH: a meta-analysis. Prostate Cancer Prostatic Dis 2012;15:265—72.
[93] Liu ZM, Wong CK, Chan D, Tse LA, Yip B, Wong SY. Fruit and vegetable intake in relation to lower urinary tract symptoms and erectile dysfunction among Southern Chinese elderly men: a 4-year prospective study of Mr OS Hong Kong. Med Baltim 2016;95:e2557.
[94] Rohrmann S, Giovannucci E, Willett WC, Platz EA. Fruit and vegetable consumption, intake of micronutrients, and benign prostatic hyperplasia in US men. Am J Clin Nutr 2007;85:523—9.
[95] Maserejian NN, Giovannucci EL, McVary KT, McKinlay JB. Dietary, but not supplemental, intakes of carotenoids and vitamin C are associated with decreased odds of lower urinary tract symptoms in men. J Nutr 2011;141:267—73.
[96] Wong SY, Woo J, Leung JC, Leung PC. Depressive symptoms and lifestyle factors as risk factors of lower urinary tract symptoms in Southern Chinese men: a prospective study. Aging Male 2010;13:113—9.
[97] St Sauver JL, Jacobsen SJ, Jacobson DJ, McGree ME, Girman CJ, Nehra A, et al. Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms. BJU Int 2011;107:443—50.
[98] Russo GI, Castelli T, Urzi D, Privitera S, Fragala E, La Vignera S, et al. Connections between lower urinary tract symptoms related to benign prostatic enlargement and metabolic syndrome with its components: a systematic review and meta-analysis. Aging Male 2015;18:207—16.
[99] Gao Y, Wang M, Zhang H, Tan A, Yang X, Qin X, 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.
[100] Kupelian V, McVary KT, Kaplan SA, Hall SA, Link CL, Aiyer LP, et al. Association of lower urinary tract symptoms and the metabolic syndrome: results from the Boston Area Community Health Survey. J Urol 2009;182:616—25.
[101] Hall SA, Chiu GR, Link CL, Steers WD, Kupelian V, McKinlay JB. Are statin medications associated with lower urinary tract symptoms in men and women? Results from the Boston Area Community Health (BACH) Survey. Ann Epidemiol 2011;21:149—55.
[102] Zhang X, Zeng X, Dong L, Zhao X, Qu X. The effects of statins on benign prostatic hyperplasia in elderly patients with metabolic syndrome. World J Urol 2015;33:2071—7.
[103] Lee SH, Park TJ, Bae MH, Choi SH, Cho YS, Joo KJ, et al. Impact of treatment with statins on prostate-specific antigen and prostate volume in patients with benign prostatic hyperplasia. Korean J Urol 2013;54:750—5.
[104] Stamatiou KN, Zaglavira P, Skolarikos A, Sofras F. The effects of lovastatin on conventional medical treatment of lower urinary tract symptoms with finasteride. Int Braz J Urol 2008;34:555—62.
[105] Mills IW, Crossland A, Patel A, Ramonas H. Atorvastatin treatment for men with lower urinary tract symptoms and benign prostatic enlargement. Eur Urol 2007;52:503—9.
[106] Mondul AM, Giovannucci E, Platz EA. A prospective study of statin drug use and lower urinary tract symptoms in older men. Am J Epidemiol 2013;178:797—803.

[107] Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci Lond 2012;122:253—70.
[108] Mosli HH, Esmat A, Atawia RT, Shoieb SM, Mosli HA, Abdel-Naim AB. Metformin attenuates testosterone-induced prostatic hyperplasia in rats: a pharmacological perspective. Sci Rep 2015;5:15639.
[109] Wang Z, Olumi AF. Diabetes, growth hormone-insulin-like growth factor pathways and association to benign prostatic hyperplasia. Differentiation 2011;82:261—71.
[110] Russo GI, Cimino S, Fragala E, Privitera S, La Vignera S, Condorelli R, 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.
[111] Sarma AV, St Sauver JL, Hollingsworth JM, Jacobson DJ, McGree ME, Dunn RL, et al. Diabetes treatment and progression of benign prostatic hyperplasia in community-dwelling black and white men. Urology 2012;79:102—8.
[112] Wallner LP, Hollingsworth JM, Dunn RL, Kim C, Herman WH, Sarma AV, et al. Hyperglycemia, hyperinsulinemia, insulin resistance, and the risk of BPH/LUTS severity and progression over time in community dwelling black men: the Flint Men's Health Study. Urology 2013;82:881—6.