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Metabolic Syndrome, Inflammation and Lower Urinary Tract Symptoms – Possible Translational Links

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Abstract

Background—Epidemiological data suggest that lower urinary tract symptoms (LUTS) may be associated with metabolic syndrome (MetS). Inflammation has been proposed as a candidate mechanism at the crossroad between these two clinical entities. The aim of this review article is to evaluate the role of MetS-induced inflammation in the pathogenesis and progression of LUTS.

Methods—A systematic review was conducted using the keywords ‘metabolic syndrome AND lower urinary tract symptoms’ within the title search engines including PubMed, Web of Science, and the Cochrane Library for relevant research work published between 2000 and January 2015. The obtained literature was reviewed by the primary author (QH) and was assessed for eligibility and standard level of evidence.

Results—Total of 52 articles met the eligibility criteria. Based on database search during the past 15 years and our systematic review of prospective and retrospective cohorts, case-control trials, observational studies and animal data identified a possible link between MetS-induced inflammation and LUTS including benign prostatic hyperplasia, bladder outlet obstruction, overactive bladder, urinary incontinence and others possible urinary tract abnormalities.

Conclusions—There is convincing evidence to suggest that MetS and inflammation could be important contributors to LUTS in men, particularly in the development of benign prostatic

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hyperplasia. However, the role of MetS-induced inflammation remains unclear in overactive bladder, urinary incontinence and etiology of LUTS progression.

Keywords

Benign prostate hyperplasia; Overactive bladder; Urinary incontinence; Metabolic syndrome; Intraprostatic inflammation

1. Introduction

In recent decades, there has been a dramatic increase in obesity around the world and nearly half of the elderly population in the United States will be obese by 2030[1]. It can be predicted that in the aging baby boomer population, a dramatic rise in the incidence of obesity-related diseases (including cardiovascular and cerebrovascular diseases) will occur, which will have a significant impact on the American economy and healthcare system[2,3]. There is growing evidence that obesity may be one of the key etiological factor of metabolic syndrome-induced inflammation and other severe health problems[3-6]. Metabolic syndrome (MetS) is a term proposed to encompass a variety of cardiovascular and metabolic risk factors, such as visceral obesity (increasing body mass and waist circumference), hypertension, hyperglycemia, low levels of high-density lipoprotein cholesterol (HDL-C) and hypertriglyceridemia, in an effort to identify a diagnostic category able to predict cardiovascular-metabolic complications[2,4-6]. Although the correlations between the aforementioned disorders and MetS have been widely accepted, the patho-genetic links still needs to be elucidated.

A significant amount of epidemiological evidence indicates a possible association between MetS and Lower Urinary Tract Symptoms (LUTS). LUTS used to be generally considered a hallmark of benign prostatic hyperplasia (BPH) and its related bladder dysfunction, resulting from an intertwined contribution of static (prostate enlargement), dynamic (α-adrenergic receptor-mediated muscle tension) and inflammatory determinants[7,8]. Historically, male LUTS was thought to be merely related to benign prostatic hyperplasia, however, a simplistic causal relationship linking prostatic overgrowth, progressive urethral obstruction, urinary retention and LUTS, has been challenged, based on the incomplete overlap of prostatic enlargement with symptoms[8-10]. In fact, investigations into the relationships between LUTS, prostate volume and urodynamic parameters failed to identify a causative relationship between parameters of BPH severity and symptoms, suggesting that other factors may interfere in determining LUTS. Now LUTS is recognized to be a non–sex-specific, non–organ-specific and global term that encompasses all urinary symptoms, including storage, voiding, and post-micturition symptoms with a significant negative impact on patients' quality of life[11].

Previous epidemiological studies and meta-analysis have already demonstrated an association between LUTS and obesity/MetS[12-15], and also the pathogenesis has been attributed to systemic inflammation and oxidative stress associated with MetS[16-18]. Chronic inflammation has been proposed as a candidate mechanism at the crossroad between BPH/LUTS and MetS. In fact, MetS can broadly be considered a systemic inflammatory state and

a chronic inflammation-driven tissue remodeling, and overgrowth is recognized to have a causative role in BPH/LUTS[19]. Mets-induced pro-inflammation states have been reported in female overactive bladder, urinary tract infection and urinary incontinence, although there is limited data to support such assertions[20–22]. The aim of the present review is to evaluate recent literature regarding associations between MetS-induced inflammation and various disorders of the lower urinary tract. Through the database search performed on National Center for Biotechnology Information (NCBI) PubMed, Web of Science, and the Cochrane Library for relevant research work published between 2000 and January 2015 combining the following terms: metabolic syndrome, inflammation, lower urinary tract symptoms and/or benign prostatic hyperplasia, urinary incontinence, overactive bladder, nocturia. A list of records involving human subjects and studies involving animals and cell culture were assessed for eligibility and standard level of evidence (Supplemental Figure 1).

2. MetS-induced inflammation associated with BPH/Bladder outlet obstruction

Several studies have demonstrated that components of MetS such as type 2 diabetes (T2DM), hypertension, hyperinsulinemia and dyslipidemia directly correlate with pro-inflammatory state, oxidative stress and pro-fibrosis[23,24]. Biomarker studies on MetS have shown to be associated with elevated levels of C-reactive protein (CRP), a nonspecific marker of inflammation, as well as pro-inflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α)[25–27]. One etiology may be the presence of inflamed adipose tissue. Obesity induces adipose cell enlargement and chemokine release, leading to macrophage infiltration of adipose tissue[23,28]. Mounting evidence suggests the ability of IL-8 to stimulate prostatic growth, and a significant and stepwise correlation between various MetS components and seminal IL-8 (sIL-8) has been proposed as a surrogate marker of prostate inflammation[27,29,30]. IL-8 is a pro-inflammatory chemokine secreted by several cell types that contributes to inflammation by acting in concert with IL-1β and IL-6. Of all kinds of cytokines and chemokines, sIL-8 seems to be the most reliable and predictive surrogate marker of prostatitis[27,29]. Higher IL-8 levels have been reported in the expressed prostatic secretions of subjects with BPH, bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)[31,32]. IL-8 has been shown to be actively involved in BPH-associated chronic inflammation and mediates epithelial and stromal cell proliferation[33–35]. In clinical BPH-prostate tissue studies, epithelial and stromal cells were analyzed to secrete IL-8 actively in response to various stimuli, including the pro-inflammatory cytokines interferon (IFN) γ and IL-17, which are produced by prostate-infiltrating Th1 and Th17 cells, respectively[36,37]. Human stromal prostatic cells actively contribute to the organ-specific inflammatory process by acting as targets of bacterial or viral toll-like receptors agonists and as antigen-presenting cells capable of activating antigen-specific CD4+ T cells. In BPH, toll-like receptor activation leads to the production of pro-inflammatory cytokines (IL-6) and chemokines (IL-8 and CXCL10) capable of recruiting CXCR1 and CXCR2-positive leukocytes and CD15+ neutrophils[35]. Moreover, secretion of IL-8 has been shown to induce the expression of fibroblast growth factor (FGF)-2, a potent stromal and epithelial growth factor that promotes abnormal proliferation of prostatic cells[38]. In addition, CXCL5, CXCL1, CXCL6, and CXCL12-induced proliferative responses have been observed in both

epithelial and stromal prostate cells in vitro[38]. CXC-type chemokines, which comprise inflammatory proteins and known to be highly expressed in the aging prostate, can efficiently and completely mediate myofibroblast phenotype conversion thereby promoting fibrotic changes in prostate tissue architecture associated with the development and progression of lower urinary tract dysfunctions[39]. Our previous studies conducted in mice showed that continuous consumption of high-fat diet (HFD) induces oxidative stress and inflammation in the mouse prostate. High-fat diet intake increases expression of IL-6, PKC, and p-Akt (Ser473) in the prostate, followed by activation of Stat-3 and NF-κB/p65 transcription factors, and their sustained interaction is associated with increased prostatic inflammation[40,41]. Moreover, Vignozzi and colleagues have shown that rabbits exposed to high-fat diets resulted in marked decrease in the mRNA expression of several pro-inflammatory cytokines (IL8, IL6, IL1β, and TNFα), T lymphocyte (CD4, CD8, T-bet, Gata3, and RORγt), macrophage (TLR2, TLR4, and STAMP2), neutrophil (lactoferrin), inflammation (COX2 and RAGE) and fibrosis/myofibroblast activation (TGFβ, SM22α, αSMA, RhoA, and ROCK1/ROCK2) markers after Tadalafil treatment[42,43].

The majority of observational clinical studies suggest that inflammation is linked to the development of BPH and LUTS. Clinical BPH/LUTS specimens contain about 70% T lymphocytes, 15% B cells, and 15% macrophages, as well as a smaller subpopulation of mast cells. Most of the patients had inflammatory cells infiltrating BPH tissues: 81% had T-lymphocytes markers (CD3), 52% had B-lymphocytes markers (CD20), and 82% had macrophages markers (CD163)[40]. In prostate tissue, T-lymphocytes actively secrete a diverse array of chemokines into the surrounding microenvironment. Immuno-histochemical studies examining the histopathology of BPH have reported the presence of inflammatory infiltrates containing leucocytes associated with acute and/or chronic inflammation[44,45]. Neutrophilic or lymphocytic infiltrates were identified in 90% of transurethral resections of the prostate (TURP) specimens from 80 patients with BPH/LUTS but with no history of prostatitis or prostatic infection[46,47]. Patients with chronic inflammatory infiltrate had larger prostate volumes and were more likely to experience clinical progression and acute urinary retention than those with no evidence of inflammation. In another study[48], BPH was found in 93 of 167 patients who underwent autopsy; 75% of these glands contained inflammatory infiltrates (predominantly associated with chronic inflammation) compared with 50% of glands without signs of BPH and 55% of glands with evidence of cancer. The level of inflammation has been directly correlated with prostatic volume and IPSS. Prostatic inflammation was strongly associated with LUTS severity, and patients with chronic inflammation had higher IPSS than those without inflammation (21 *versus* 12, respectively; $P = 0.02$). Moreover, prostate volume was significantly higher in patients with more pronounced inflammation (77 *versus* 62 mL; $P = 0.002$). Patients in the highly-inflamed group more commonly underwent open prostatectomy than those with less pronounced inflammation. This finding may also be related to the association between prostate volume and chronic intraprostatic inflammation. Patients included in the highly-inflamed group more commonly underwent TRUS-guided prostate biopsy than those with less pronounced inflammation (37.6 *versus* 23.9%; $P < 0.02$)[44]. Similar conclusions have been reported in other large clinical studies[49–51]. In a small prospective trial, chronic inflammation was shown to induce fibrotic changes in 30 peri-urethral prostate tissues from retro-pubic radical

prostatectomy. Fibrosis in this region is alleged to promote urethral stiffness and LUTS[52]. A comprehensive summary and the evidence level of these studies are shown in table 1.

3. MetS-induced inflammation associated with Overactive bladder/Urinary incontinence

Overactive bladder (OAB) is the other major clinical manifestation of LUTS, typically characterized by urinary urgency, frequency, and urge incontinence adversely affecting patients' quality of life having an increasing prevalence with age[53]. It was now recognized that chronic low-level inflammation and activation of the immune system are involved in the pathogenesis of obesity-related insulin resistance[54]. Insulin resistance caused by obesity is a significant component of MetS and is regarded as a pro-inflammatory state. Tissue inflammation results in tissue fibrosis, which is supposed to represent an inflammation-initiated, aberrant wound-healing process characterized by myofibroblast accumulation, collagen deposition, extracellular matrix (ECM) remodeling, and increased tissue stiffness[39,55–57]. A few studies have investigated possible associations between MetS-induced inflammation and overactive bladder or urinary incontinence (UI). Some investigators have studied the role of urinary cytokines in patients with OAB[58,59]. Tyagi *et al.* have shown 10-fold increase in the levels of monocyte chemotactic protein-1 (MCP-1) and CD40 ligand , whereas 5-fold elevations were detected in macrophage inflammatory protein (MIP-1β), IL-12p70/p40, IL-5, epidermal growth factor (EGF), and growth-related oncogene GRO-α compared to controls[60]. Significant 3-fold elevation was also noticed in the urine levels of sIL-2Rα, and IL-10 in OAB patients. Another study demonstrated that C-reactive protein (CRP) was significantly higher in women with OAB associated with urgency incontinence, (n = 30, 0.12 mg/dl) as compared to women with bladder oversensitivity (n = 68, 0.075 mg/dl, P = 0.008) and nerve growth factor (NGF), IL-1β, IL-6, IL-8, and TNF-α levels were higher than the control group[58,59]. Further analysis revealed that body mass index and maximum flow rate were two independent factors that affected CRP levels. The area under the receiver-operating characteristic curve for using CRP to predict OAB wet was 0.55, and the most predictive cutoff point for CRP was 0.15 mg/dl (sensitivity 43.5%; specificity 72.7%). Chung and colleges[61] conducted a similar study and found that the patients of OAB associated with urgency incontinence had higher serum CRP level than patients without urge incontinence. Indications of tissue remodeling and inflammation-induced fibrosis have been reported in several animal studies. Lenis *et al.* found that vaginal distention up-regulated urethral expression of CCL7 immediately after injury in virgin and postpartum rats[62]. Hypoxia inducible factor-1α and vascular endothelial growth factor were up-regulated only in virgin rats immediately after vaginal distention. CD191 expression was immediately up-regulated in postpartum rats without vaginal distention compared to virgin rats without vaginal distention. CD195 was up-regulated in virgin rats 3 days after vaginal distention compared to virgin rats without vaginal distention. CD193 and CXCR4 showed delayed up-regulation in virgin rats 7 days after vaginal distention. CXCL12 was up-regulated in virgin rats 3 days after vaginal distention compared to successive vaginal distention. IL-8 and CD192 exhibited no differential expression. Remodeling of urethral connective tissue has also been detected in rodent stress urinary incontinence (SUI) models[63,64]. Inflammatory and fibrosis markers, TGF-β1, fibronectin

and type I collagen expressions were observed to be significantly increased 6 months post-surgical induction of OAB in a rat model[65]. Recently, increasing emphasis has been focused on the role of neurotrophines, including nerve growth factors and brain-derived neurotrophic factors (BDNF) to evaluate OAB and bladder dysfunction[66,67]. Elevated levels of NGF or BDNF have been associated with OAB and other conditions, including urinary tract infection, stones and tumors[68].

Numerous clinical studies have shown association between the components of MetS and OAB[62,64,66,67]. The onset of OAB is significantly associated with obesity[69]. Link *et al.* investigated for an association between visceral obesity (waist circumference, hip circumference, waist-to-hip ratio and body mass index) with OAB (urinary frequency and urgency) and whether the association varies by gender or age[70], and noted distinct patterns by gender for the association of various adiposity measures with OAB. The prevalence of OAB increased as waist (OR adjusted for other confounders 1.10/10cm increase) or hip circumference (OR 1.12/10cm increase) or body mass index (OR 1.03/kg/m^2 increase) increased in women; whereas in men the prevalence of OAB decreased as adiposity increased (OR 0.65/10cm increase in waist circumference, OR 0.71/10 cm increase in hip circumference and OR 0.87/kg/m^2 in body mass index) but only to a certain point (waist circumference 100cm, hip circumference 115 cm and body mass index 27.5 kg/m^2). At that point the prevalence of OAB increased with increasing adiposity (OR 1.19/10cm increase in waist circumference, OR 1.16/10cm increase in hip circumference and OR 1.08/kg/m^2 in body mass index), suggesting gender-specific relationship between adiposity and OAB. In our previous meta-analysis which combined 12 BPH/UI/LUTS studies[71], a positive association was observed between waist circumference (WC) and LUTS at an OR of 1.49, (95% CI: 1.34–1.64) and a 10 cm increase in waist circumference was associated with a statistically-significant 2.5% increase in the risk of LUTS; when separated by gender, that is 1.8% increase in LUTS risk in male and a 2.8% increase in female. A cross-sectional study from Taiwan assessed 371 women with the Incontinence-Quality of Life (I-QOL) questionnaire, and noted that stress urinary incontinence (SUI) was the most frequent subtype reported (28.6%), followed by mixed (24.5%) and urge (16.2%) incontinence and obesity (OR 3.38, 95% CI 1.94–6.98) and postmenstrual status (OR 2.17, 95% CI 1.35–3.50) were found to be risk factors of incontinence ($P < 0.001$)[72]. Hakki Uzun *et al.* demonstrated that serum insulin levels were higher in female patients with OAB (11.5 ± 6.2 μU/mL) relative to controls (6.4 ± 2.1 μU/mL, P=0.036). Insulin resistance was significantly higher in the OAB group, 2.86 (0.76 to 17.04) in comparison to controls, (1.32; 0.67 to 224, P=0.018). High-density lipoprotein cholesterol levels (HDL-c) were significantly lower in females with OAB[73]. There is lack of strong evidence and inconclusiveness to estimate the potential association between MetS and OAB/UI. A comprehensive summary and the evidence level of these studies are shown in table 2.

4. Inflammation, infection and their association with LUTS

Inflammation and inflammatory damage to the lower urinary tract may result from bacterial prostatitis and urinary tract infection (UTI). Several studies have documented an association between prostatitis/UTI and subsequent development of LUTS. Data from the Health Professionals Follow-up Study showed a significant association between a history of

gonorrheal infection or young-onset (aged <30 years) prostatitis and later development of LUTS[74]. Combined data from five studies involving a total of 10,617 men suggest that men reporting a history of prostatitis have a substantially increased risk of developing BPH, LUTS, and prostate cancer[75]. UTIs are also associated with male lower urinary tract dysfunction (LUTD). In a study of 208 patients with bacteriuria, 54% were diagnosed with UTIs and these patients demonstrated voiding dysfunction manifested by higher rates of dysuria (P = 0.0001), urgency (P = 0.0001), and frequency (P = 0.0001)[76]. Lee *et al.* developed an animal model of bacterial uropathogenic *E. coli—1677* induced isolated prostatic inflammation and examined the effect of prostatic inflammation on voiding behavior in adult C57BL/6J mice[77]. Mice with prostatic inflammation showed significantly increased voiding frequency and decreased volume per void, compared to mice instilled with saline. Linked analysis of voiding frequency and voided volumes revealed an overwhelming preponderance of high frequency, low volume voiding in mice with prostatic inflammation, suggesting that prostatic inflammation may be causal for symptoms of urinary frequency and nocturia. Another study demonstrated an increase in lipocalin 2 (LCN2) expression in the bladder, ureters, and kidneys of mice with *Escherichia coli* strain H9049. LCN2 is an innate immunity protein that binds to bacterial siderophores and starves them for iron, thus representing a novel host defense mechanism to infection. LCN2 was protective with higher bacterial numbers retrieved from bladders of Lcn2-deficient mice than from wild-type mice infected with the LCN2-sensitive *E. coli*. This study further demonstrates that a human cohort of women with recurrent *E. coli* UTIs, urine LCN2 levels are associated with UTI episodes and with evidence of bacteriuria[78]. Other recent studies have suggested that MetS-induced inflammation and altered lipid metabolism were common occurrence during bladder and kidney stone formation which might result in increasing incidence of LUTS[79–81].

5. Limitation of the work

This review has certain limitations. Definitions of LUTS is not uniform in the literature and this impedes proper comparisons. This review may have a publication bias in the choice of the reviewed studies. Although an attempt was made to retrieve and review all existing published data, but some studies may have been overlooked, and adequate emphasis may not have not been provided to some study designs.

6. Conclusion and future direction

A number of studies support MetS as a complex disorder consisting of numerous interrelated pathophysiologic entities including obesity, dyslipidemia, hyperglycemia/IR, all of which are thought to promote endothelial and smooth muscle dysfunction, which may contribute to the pathogenesis and progression of various conditions associated with LUTS. There is sufficient evidence to suggest that inflammation is an important predictor of LUTS in men, particularly in BPH and bladder outlet obstruction, while its association remains unclear in OAB/UI and other lower urinary tract disorders. Knowledge of these associations may assist urologists in their clinical management of patients with LUTS. In studies involving academic and translational medicine, a better understanding of the inflammatory pathways in MetS, might be helpful to identify and develop new forms of treatment for LUTS-associated disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

LUTS	lower urinary tract symptoms
BPH	benign prostate hyperplasia
MetS	metabolic syndrome
OAB	overactive bladder
UI	urinary incontinence
BOO	Bladder outlet obstruction
UTI	urinary tract infection
CRP	C-reactive protein
IL	interleukin
TNF-α	tumor necrosis factor-α
CP	chronic prostatitis
CPPS	chronic pelvic pain syndrome
IFN	interferon
FGF	fibroblast growth factor
PKC	protein kinase C
TLR	toll-like receptor
RhoA	RAS homolog gene family member A
ROCK	Rho-associated protein kinase
αSMA	α-smooth muscle actin
MCP	monocyte chemotactic protein
EGF	epidermal growth factor
NGF	nerve growth factor

LUTD	lower urinary tract dysfunction
LCN	lipocalin

References

1. King D. The future challenge of obesity. The Lancet. 2011; 378(9793):743–744.
2. Alberti K, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the Metabolic Syndrome A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120(16):1640–1645. [PubMed: 19805654]
3. Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW. Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. The Journal of Clinical Endocrinology & Metabolism. 2009; 94(6):1853–1878. [PubMed: 19494161]
4. Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006; 444(7121):881–887. [PubMed: 17167477]
5. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. The Lancet. 2005; 365(9468):1415–1428.
6. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. The Journal of Clinical Endocrinology & Metabolism. 2004; 89(6):2595–2600. [PubMed: 15181029]
7. Donnell RF. Benign prostate hyperplasia: a review of the year's progress from bench to clinic. Current opinion in urology. 2011; 21(1):22–26. [PubMed: 21171199]
8. Moul S, McVary KT. Lower urinary tract symptoms, obesity and the metabolic syndrome. Current opinion in urology. 2010; 20(1):7–12. [PubMed: 19904208]
9. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. Standardisation Subcommittee of the International Continence Society. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002; 21(2):167–178. [PubMed: 11857671]
10. Nickel J. Prostatic inflammation in benign prostatic hyperplasia-the third component? The Canadian journal of urology. 1994; 1(1):1–4. [PubMed: 12834558]
11. Welch G, Weinger K, Barry MJ. Quality-of-life impact of lower urinary tract symptom severity: results from the Health Professionals Follow-up Study. Urology. 2002; 59(2):245–250. [PubMed: 11834396]
12. 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 international. 2015; 115(1):24–31. [PubMed: 24602293]
13. De Nunzio C, Cindolo L, Gacci M, Pellegrini F, Carini M, Lombardo R, et al. Metabolic Syndrome and Lower Urinary Tract Symptoms in Patients With Benign Prostatic Enlargement: A Possible Link to Storage Symptoms. Urology. 2014; 84(5):1181–1187. [PubMed: 25443931]
14. Bhindi B, Margel D, Trottier G, Hamilton RJ, Kulkarni GS, Hersey KM, et al. Obesity is associated with larger prostate volume but not with worse urinary symptoms: analysis of a large multiethnic cohort. Urology. 2014; 83(1):81–87. [PubMed: 24044911]
15. Parsons JK, Sarma AV, McVary K, Wei JT. Obesity and benign prostatic hyperplasia: clinical connections, emerging etiological paradigms and future directions. The Journal of urology. 2013; 189(1):S102–S106. [PubMed: 23234610]
16. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. Journal of Clinical Investigation. 2004; 114(12):1752–1761. [PubMed: 15599400]
17. Kasturi S, Russell S, McVary KT. Metabolic syndrome and lower urinary tract symptoms secondary to benign prostatic hyperplasia. Current Prostate Reports. 2006; 4(3):127–131.
18. Ozden C, Ozdal OL, Urgancioglu G, Koyuncu H, Gokkaya S, Memis A. The correlation between metabolic syndrome and prostatic growth in patients with benign prostatic hyperplasia. European urology. 2007; 51(1):199–206. [PubMed: 16806666]

19. 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. European urology. 2011; 60(1):106–117. [PubMed: 21497433]
20. Bunn F, Kirby M, Pinkney E, Cardozo L, Chapple C, Chester K, et al. Is there a link between overactive bladder and the metabolic syndrome in women? A systematic review of observational studies. International journal of clinical practice. 2014
21. Tai H-C, Chung S-D, Ho C-H, Tai T-Y, Yang W-S, Tseng C-H, et al. Metabolic syndrome components worsen lower urinary tract symptoms in women with type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism. 2010; 95(3):1143–1150. [PubMed: 20103655]
22. Uzun H, Zorba OÜ. Metabolic syndrome in female patients with overactive bladder. Urology. 2012; 79(1):72–75. [PubMed: 22014972]
23. Devaraj S, Singh U, Jialal I. Human C-reactive protein and the metabolic syndrome. Current opinion in lipidology. 2009; 20(3):182. [PubMed: 19369869]
24. Fagerberg B, Behre CJ, Wikstrand J, Hultén LM, Hulthe J. C-reactive protein and tumor necrosis factor-alpha in relation to insulin-mediated glucose uptake, smoking and atherosclerosis. Scandinavian Journal of Clinical & Laboratory Investigation. 2008; 68(7):534–541. [PubMed: 19378424]
25. Greenfield JR, Campbell LV. Relationship between inflammation, insulin resistance and type 2 diabetes:'cause or effect'? Current diabetes reviews. 2006; 2(2):195–211. [PubMed: 18220627]
26. Powell K. Obesity: the two faces of fat. Nature. 2007; 447(7144):525–527. [PubMed: 17538594]
27. Fibbi B, Penna G, Morelli A, Adorini L, Maggi M. Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. International journal of andrology. 2010; 33(3):475–488. [PubMed: 19508330]
28. Kalyani RR, Dobs AS. Androgen deficiency, diabetes, and the metabolic syndrome in men. Current Opinion in Endocrinology, Diabetes and Obesity. 2007; 14(3):226–234.
29. Penna G, Mondaini N, Amuchastegui S, Degli Innocenti 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. European urology. 2007; 51(2):524–533. [PubMed: 16905241]
30. Lotti F, Maggi M. Interleukin 8 and the male genital tract. Journal of reproductive immunology. 2013; 100(1):54–65. [PubMed: 23611586]
31. Hochreiter WW, Nadler RB, Koch AE, Campbell PL, Ludwig M, Weidner W, et al. Evaluation of the cytokines interleukin 8 and epithelial neutrophil activating peptide 78 as indicators of inflammation in prostatic secretions. Urology. 2000; 56(6):1025–1029. [PubMed: 11113752]
32. Liu L, Li Q, Han P, Li X, Zeng H, Zhu Y, et al. Evaluation of interleukin-8 in expressed prostatic secretion as a reliable biomarker of inflammation in benign prostatic hyperplasia. Urology. 2009; 74(2):340–344. [PubMed: 19464042]
33. 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 journal of andrology. 2014; 16(2):295. [PubMed: 24435050]
34. Lotti F, Corona G, Vitale P, Maseroli E, Rossi M, Fino M, et al. Current smoking is associated with lower seminal vesicles and ejaculate volume, despite higher testosterone levels, in male subjects of infertile couples. Human Reproduction. 2015:deu347.
35. Penna G, Fibbi B, Amuchastegui S, Cossetti C, Aquilano F, Laverny G, et al. Human benign prostatic hyperplasia stromal cells as inducers and targets of chronic immuno-mediated inflammation. The Journal of Immunology. 2009; 182(7):4056–4064. [PubMed: 19299703]
36. Adorini L, Penna G, Fibbi B, Maggi M. Vitamin D receptor agonists target static, dynamic, and inflammatory components of benign prostatic hyperplasia. Annals of the New York Academy of Sciences. 2010; 1193(1):146–152. [PubMed: 20398021]
37. Penna G, Fibbi B, Amuchastegui S, Corsiero E, Laverny G, Silvestrini E, et al. The vitamin D receptor agonist elocalcitol inhibits IL-8-dependent benign prostatic hyperplasia stromal cell proliferation and inflammatory response by targeting the RhoA/Rho kinase and NF-kB pathways. The Prostate. 2009; 69(5):480–493. [PubMed: 19107880]

38. Giri D, Ittmann M. Interleukin-8 is a paracrine inducer of fibroblast growth factor 2, a stromal and epithelial growth factor in benign prostatic hyperplasia. The American journal of pathology. 2001; 159(1):139–147. [PubMed: 11438462]
39. Gharaee-Kermani M, Kasina S, Moore BB, Thomas D, Mehra R, Macoska JA. CXC-type chemokines promote myofibroblast phenoconversion and prostatic fibrosis. PLoS One. 2012; 7(11):e49278. [PubMed: 23173053]
40. Shankar E, Vykhovanets EV, Vykhovanets OV, MacLennan GT, Singh R, Bhaskaran N, et al. High-fat diet activates pro-inflammatory response in the prostate through association of Stat-3 and NF-κB. The Prostate. 2012; 72(3):233–243. [PubMed: 21604287]
41. Vykhovanets EV, Shankar E, Vykhovanets OV, Shukla S, Gupta S. High-fat diet increases NF-κB signaling in the prostate of reporter mice. The Prostate. 2011; 71(2):147–156. [PubMed: 20632379]
42. Vignozzi L, Filippi S, Comeglio P, Cellai I, Morelli A, Maneschi E, et al. Tadalafil Effect on Metabolic Syndrome-Associated Bladder Alterations: An Experimental Study in a Rabbit Model. The journal of sexual medicine. 2014; 11(5):1159–1172. [PubMed: 24612540]
43. Morelli A, Sarchielli E, Comeglio P, Filippi S, Vignozzi L, Marini M, et al. Metabolic syndrome induces inflammation and impairs gonadotropin-releasing hormone neurons in the preoptic area of the hypothalamus in rabbits. Molecular and cellular endocrinology. 2014; 382(1):107–119. [PubMed: 24064031]
44. Robert G, Descazeaud A, Nicolaïew N, Terry S, Sirab N, Vacherot F, et al. Inflammation in benign prostatic hyperplasia: a 282 patients' immunohistochemical analysis. The Prostate. 2009; 69(16): 1774–1780. [PubMed: 19670242]
45. Delongchamps NB, de la Roza G, Chandan V, Jones R, Sunheimer R, Threatte G, et al. Evaluation of prostatitis in autopsied prostates—is chronic inflammation more associated with benign prostatic hyperplasia or cancer? The Journal of urology. 2008; 179(5):1736–1740. [PubMed: 18343414]
46. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. New England Journal of Medicine. 2003; 349(25):2387–2398. [PubMed: 14681504]
47. Nickel J, Downey J, Young I, Boag S. Asymptomatic inflammation and/or infection in benign prostatic hyperplasia. BJU international. 1999; 84:976–981. [PubMed: 10571623]
48. Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, Kido M, et al. Prevalence of inflammation and benign prostatic hyperplasia on autopsy in Asian and Caucasian men. European urology. 2014; 66(4):619–622. [PubMed: 25012523]
49. Kwon YK, Choe MS, Seo KW, Park CH, Chang HS, Kim BH, et al. The effect of intraprostatic chronic inflammation on benign prostatic hyperplasia treatment. Korean journal of urology. 2010; 51(4):266–270. [PubMed: 20428430]
50. Mishra VC, Allen DJ, Nicolaou C, Sharif H, Hudd C, Karim O, et al. Does intraprostatic inflammation have a role in the pathogenesis and progression of benign prostatic hyperplasia? BJU international. 2007; 100(2):327–331. [PubMed: 17617139]
51. Nickel JC, Roehrborn CG, O'Leary MP, Bostwick DG, Somerville MC, Rittmaster RS. The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial. European urology. 2008; 54(6):1379–1384. [PubMed: 18036719]
52. Cantiello F, Cicione A, Salonia A, Autorino R, Tucci L, Madeo I, et al. Periurethral fibrosis secondary to prostatic inflammation causing lower urinary tract symptoms: a prospective cohort study. Urology. 2013; 81(5):1018–1024. [PubMed: 23608423]
53. Stewart W, Van Rooyen J, Cundiff G, Abrams P, Herzog A, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World journal of urology. 2003; 20(6):327–336. [PubMed: 12811491]
54. Heilbronn LK, Campbell LV. Adipose tissue macrophages, low grade inflammation and insulin resistance in human obesity. Current pharmaceutical design. 2008; 14(12):1225–1230. [PubMed: 18473870]

55. Biernacka A, Dobaczewski M, Frangogiannis NG. TGF-β signaling in fibrosis. Growth factors. 2011; 29(5):196–202. [PubMed: 21740331]
56. Liu Y. Cellular and molecular mechanisms of renal fibrosis. Nature Reviews Nephrology. 2011; 7(12):684–696. [PubMed: 22009250]
57. Rodriguez-Nieves JA, Macoska JA. Prostatic fibrosis, lower urinary tract symptoms, and BPH. Nature Reviews Urology. 2013; 10(9):546–550. [PubMed: 23857178]
58. Kuo H-C, Liu H-T, Shie J-H. Potential urine and serum biomarkers for patients with overactive bladder and interstitial cystitis/bladder pain syndrome. Tzu Chi Medical Journal. 2013; 25(1):13–18.
59. Hsiao S-M, Lin H-H, Kuo H-C. The role of serum C-reactive protein in women with lower urinary tract symptoms. International urogynecology journal. 2012; 23(7):935–940. [PubMed: 22422219]
60. Tyagi P, Barclay D, Zamora R, Yoshimura N, Peters K, Vodovotz Y, et al. Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study. International urology and nephrology. 2010; 42(3):629–635. [PubMed: 19784793]
61. Chung SD, Liu HT, Lin H, Kuo HC. Elevation of serum c-reactive protein in patients with OAB and IC/BPS implies chronic inflammation in the urinary bladder. Neurourology and urodynamics. 2011; 30(3):417–420. [PubMed: 21284020]
62. Lenis AT, Kuang M, Woo LL, Hijaz A, Penn MS, Butler RS, et al. Impact of parturition on chemokine homing factor expression in the vaginal distention model of stress urinary incontinence. The Journal of urology. 2013; 189(4):1588–1594. [PubMed: 23022009]
63. Chen H-Y, Lin Y-N, Chen Y-H, Chen W-C. Stress urinary incontinence following vaginal trauma involves remodeling of urethral connective tissue in female mice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2012; 163(2):224–229. [PubMed: 22572217]
64. Chen H-Y, Chen C-J, Lin Y-N, Chen Y-H, Chen W-C, Chen C-M. Proteomic analysis related to stress urinary incontinence following vaginal trauma in female mice. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013; 171(1):171–179. [PubMed: 24054828]
65. Juan YS, Chuang SM, Lee YL, Long CY, Wu TH, Chang WC, et al. Green tea catechins decrease oxidative stress in surgical menopause-induced overactive bladder in a rat model. BJU international. 2012; 110(6b):E236–E244. [PubMed: 22639915]
66. Wang, L-w; Han, X-m; Chen, C-h; Ma, Y.; Hai, B. Urinary brain-derived neurotrophic factor: a potential biomarker for objective diagnosis of overactive bladder. International urology and nephrology. 2014; 46(2):341–347. [PubMed: 23982767]
67. Agilli M, Aydin FN, Kurt YG, Cayci T. A potential biomarker for objective diagnosis of overactive bladder: urinary nerve growth factor. International urology and nephrology. 2014:1–2.
68. Bhide AA, Cartwright R, Khullar V, Digesu GA. Biomarkers in overactive bladder. International urogynecology journal. 2013; 24(7):1065–1072. [PubMed: 23314226]
69. Dallosso H, McGrother C, Matthews RJ, Donaldson M. The association of diet and other lifestyle factors with overactive bladder and stress incontinence: a longitudinal study in women. BJU international. 2003; 92(1):69–77. [PubMed: 12823386]
70. Link CL, Steers WD, Kusek JW, McKinlay JB. The association of adiposity and overactive bladder appears to differ by gender: results from the Boston Area Community Health survey. The Journal of urology. 2011; 185(3):955–963. [PubMed: 21247604]
71. He Q, Wang H, Yue Z, Yang L, Tian J, Liu G, et al. Waist circumference and risk of lower urinary tract symptoms: a meta-analysis. The Aging Male. 2014; 17(4):223–229. [PubMed: 25295871]
72. Tsai Y-C, Liu C-H. Urinary incontinence among Taiwanese women: an outpatient study of prevalence, comorbidity, risk factors, and quality of life. International urology and nephrology. 2009; 41(4):795–803. [PubMed: 19199071]
73. Uzun H, Yilmaz A, Kemik A, Zorba OU, Kalkan M. Association of insulin resistance with overactive bladder in female patients. International neurourology journal. 2012; 16(4):181–186. [PubMed: 23346484]
74. Sutcliffe S, Giovannucci E, De Marzo AM, Willett WC, Platz EA. Sexually transmitted infections, prostatitis, ejaculation frequency, and the odds of lower urinary tract symptoms. American journal of epidemiology. 2005; 162(9):898–906. [PubMed: 16177142]

75. Krieger JN, Lee SWH, Jeon J, Cheah PY, Liong ML, Riley DE. Epidemiology of prostatitis. International journal of antimicrobial agents. 2008; 31:85–90. [PubMed: 18054206]

76. Colodner R, Eliasberg T, Chazan B, Raz R. Clinical significance of bacteriuria with low colony counts of Enterococcus species. European Journal of Clinical Microbiology and Infectious Diseases. 2006; 25(4):238–241. [PubMed: 16596356]

77. Lee S, Yang G, Bushman W. Prostatic inflammation induces urinary frequency in adult mice. PLoS One. 2015; 10(2):e0116827. [PubMed: 25647072]

78. Steigedal M, Marstad A, Haug M, Damås JK, Strong RK, Roberts PL, et al. Lipocalin 2 Imparts Selective Pressure on Bacterial Growth in the Bladder and Is Elevated in Women with Urinary Tract Infection. The Journal of Immunology. 2014; 193(12):6081–6089. [PubMed: 25398327]

79. Eynard AR, Navarro A. Crosstalk among dietary polyunsaturated fatty acids, urolithiasis, chronic inflammation, and urinary tract tumor risk. Nutrition. 2013; 29(7):930–938. [PubMed: 23594581]

80. Jou Y-C, Tsai Y-S, Fang C-Y, Chen S-Y, Chen F-H, Huang C-H, et al. Mass Spectrometric Study of Stone Matrix Proteins of Human Bladder Stones. Urology. 2013; 82(2):295–300. [PubMed: 23896093]

81. Keddis MT, Rule AD. Nephrolithiasis and loss of kidney function. Current opinion in nephrology and hypertension. 2013; 22(4):390. [PubMed: 23736840]

Table 1

Studies on MetS-induced inflammation associated with benign prostatic hyperplasia/ bladder outlet obstruction.

Author/Year	Study	Country	Sample size	Biomarkers	Comments	Evidence level
Fibbi B; 2010 [27]	BS	Italy	-	IL-8, Th1, Th17	Prostate growth-promoting chemokine IL-8, induced in BPH stromal cells by a combination of Th1 and Th17 cell-derived inflammatory cytokines.	d
Penna G; 2007 [29]	Cohort	Italy	83 men	IL-1α, IL-1β, IL-6, 10, IL12p70, CCL1,3,4, CXCL8/IL-8	IL-8 appears to be the most reliable and predictive surrogate marker to diagnose prostate inflammatory conditions.	2b
Hochreiter WW; 2000 [31]	Cohort	USA	63 men	IL-8, ENA-78	IL-8 and ENA-78 were elevated in the prostatic secretions of men.	2b
Liu, L; 2009 [32]	Cohort	China	44 men	IL-8	IL-8 expressed prostatic secretion can serve as a reliable biomarker in identifying BPH with chronic prostatitis from simple BPH.	2b
Lotti F; 2014 [33]	Cohort	Italy	171 men	sIL8,	Insulin levels increased as a function of MetS components ($P < 0.0001$). MetS is positively associated with prostate enlargement, biochemical (sIL8) and ultrasound-derived signs of prostate inflammation.	2b
Giri D; 2001 [38]	BS	USA	-	IL-8, FGF2	IL-8 can induce FGF2 and promote abnormal proliferation of the prostatic transition zone.	d
Gharaee-Kermani M; 2012 [39]	BS	USA	-	TGF-β1, CXCL5, CXCL8, or CXCL12	Prostate stromal fibroblasts are induced to express collagen 1 and 3 and αSMA gene transcripts and proteins to undergo complete functional myofibroblast pheno-conversion in response to CXC-type chemokines, even in the absence of exogenous TGF-β1.	d
Shankar; 2012 [40,41]	BS	USA	C57BL/6 mice	IL-1ß, IL-6, IL-17, TNFα, NF-κB, Stat-3, Akt, PDK1, PKCε	High-Fat Diet activates Stat-3 and NF-κB/p65 in the prostate, and their interaction is associated with increased inflammation in the prostate.	d
Vignozzi L; 2014 [42,43]	BS	Italy	rabbits	GLUT4 ,IL-6, RhoA/ROCK	Tadalafil dosing reduced RhoA/ROCK signaling and smooth muscle over-activity in an animal model of MetS-associated bladder alterations.	d
Robert G; 2009 [44]	RS	France	282 patients	CD3, CD4, CD8, CD2, CD163	Prostate enlargement due to chronic inflammatory process may lead to BPH progression.	1b
Delongchamps NB; 2008 [45]	RS	USA	167 prostates	-	Chronic inflammation was a common finding in autopsied prostates.	1b
McConnell JD; 2003 [46]	RCT	USA	3047 men	-	Combination therapy and finasteride alone reduce long-term risk of acute urinary retention and the need for invasive therapy.	1a

Author/Year	Study	Country	Sample size	Biomarkers	Comments	Evidence level
Zlotta AR; 2014 [48]	Cohort	Canada	320 prostate glands	-	Chronic inflammation in >70% of men on autopsy. Increased chronic inflammation was associated with more BPH.	1b
Mishra VC; 2007 [50]	RS	UK	406 patients	-	70% of men with urinary retention had acute and/or chronic intraprostatic inflammation (ACI), vs 45% of those with LUTS ($P < 0.001$). The association of TURP for retention with ACI was stronger than that with prostate weight.	2b
Nickel JC; 2008 [51]	RCT	Canada	8224 men	-	Weak correlations were found between average and maximum chronic inflammation and IPSS variables.	1a
Cantiello F, 2013 [52]	Cohort	Italy	30 patients	-	Patients experiencing prostate-related LUTS could benefit from anti-inflammatory therapies, used alone or combined with the currently prescribed regimen.	2b

BS, basic study; RCT, random control trial; RS, retrospective study

Table 2

Studies on MetS-induced inflammation associated with overactive bladder/urinary incontinence.

Author/Year	Study	Country	Sample size	Biomarkers	Comments	Evidence level
Hsiao S-M; 2012 [59]	Cohort	China	197 women	CRP	High serum CRP levels were found in women with OAB wet, and was related to lower maximum urinary flow rates and higher body mass indices in non-SUI LUTD.	2b
Tyagi P; 2010 [60]	Cohort	USA	17 women midstream urine	MCP-1, IL-12p70/p40, IL-5, EGF	The presence of elevated levels in urine of inflammatory biomarkers involved in inflammation and tissue repair suggests a role for inflammation in OAB.	3b
Chung SD; 2011 [61]	Cohort	China	70 women	NGF, CRP	Serum CRP levels were significantly higher in subjects with OAB, chronic inflammation associated with OAB or IC/BPS.	3b
Lenis AT; 2013 [62]	BS	USA	72 rats	CCL7, CXCL12, CD191, CD193 and CXCR4	Pregnancy and parturition in rats contributes to the expression of chemokines and receptors after vaginal distention.	d
Chen H-Y; 2013 [63,64]	BS	China	18 mice	LOX	SUI following vaginal trauma involves over-expression of LOX and decrease synthesis of extracellular matrix components or increased proteolysis in the urethra.	d
Wang L-W; 2014 [66]	Cohort	China	90 women	BDNF, NGF	Urinary BDNF/Cr levels are elevated in women with OAB and are significantly associated with symptom severity.	2b
Dallosso H; 2003 [69]	Cohort	UK	7,046 women	-	Causal associations with obesity, smoking and carbonated drinks are confirmed for bladder disorders associated with incontinence, and additional associations with diet are suggested.	1b
Link CL; 2011 [70]	Cohort	USA	5,503 participants	-	Relationship between adiposity and overactive bladder varies by gender.	1b
He Q; 2014 [71]	MA	USA	83,304 cases	-	Large waist circumference is associated with increased risk of LUTS. A 10 cm increase in WC corresponded to a 1.8% increase in LUTS risk in male and a 2.8% risk in female.	1b
Tsai Y-C; 2009 [72]	Cohort	China	551 women		Obesity (OR 3.38, 95% CI 1.94-6.98) and postmenstrual status (OR 2.17, 95% CI 1.35-3.50) were found to be risk factors of incontinence ($P < 0.001$).	2b
Uzun H; 2012 [73]	Cohort	Turkey	122 patients	-	Insulin resistance can be associated to overactive bladder and may play significant role in pathogenesis.	2b

BS, basic study; MA, meta-analysis