REVIEW

Metabolic syndrome, inflammation and lower urinary tract symptoms: possible translational links

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BACKGROUND: Epidemiological data suggest that lower urinary tract symptoms (LUTSs) 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. On the basis of 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 BPH, bladder outlet obstruction, overactive bladder, urinary incontinence and other 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 BPH. However, the role of MetS-induced inflammation remains unclear in overactive bladder, urinary incontinence and etiology of LUTS progression.

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INTRODUCTION

In recent decades, there has been a marked 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 marked 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.2–5 There is growing evidence that obesity may be one of the key etiological factor of metabolic syndrome (MetS)-induced inflammation and other severe health problems.2–5 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 (WC)), hypertension, hyperglycemia, low levels of high-density lipoprotein cholesterol and hypertriglyceridemia, in an effort to identify a diagnostic category able to predict cardiovascular-metabolic complications.2–4 Although the correlations between the aforementioned disorders and MetS have been widely accepted, the patho-genetic links still need to be elucidated.

A significant amount of epidemiological evidence indicates a possible association between MetS and lower urinary tract symptoms (LUTSs). LUTS used to be generally considered a hallmark of 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 BPH; however, a simplistic causal relationship linking prostatic overgrowth, progressive urethral obstruction, urinary retention and LUTS has been challenged, on the basis of 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-inflammatory states have been reported in female overactive bladder (OAB), urinary tract infection (UTI) and urinary incontinence (UI), although there is
and proliferation. Moreover, Vignozzi and colleagues have shown that rabbits exposed to high-fat diets resulted in marked decrease in the messenger RNA expression of several pro-inflammatory cytokines (IL-8, IL-6, IL1β and tumor necrosis factor-α). T lymphocyte (CD4, CD8, T-bet, Gata3 and RORγt), macrophage (TLR2, TLR4 and STAMP2), neutrophil (lactoferin), inflammation (COX2 and RAGE) and fibrosis/myofibroblast activation (TGFβ, SM22α, αSMA, RhoA and ROCK1/ROCK2) markers after Tadalafil treatment. 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-lymphocyte markers (CD3), 52% had B-lymphocyte markers (CD20) and 82% had macrophage markers (CD163). 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 leukocytes associated with acute and/or chronic inflammation. Neutrophilic or lymphocytic infiltrates were identified in 90% of TURP specimens from 80 patients with BPH/LUTS but with no history of prostatitis or prostatic infection. 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, 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 International Prostate Symptom Score. Prostatic inflammation was strongly associated with LUTS severity, and patients with chronic inflammation had higher International Prostate Symptom Score than those without inflammation (21 vs 12, respectively; P = 0.02). Moreover, prostate volume was significantly higher in patients with more pronounced inflammation (77 vs 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 transrectal ultrasonography-guided prostate biopsy than those with less pronounced inflammation (37.6% vs 23.9%; P < 0.002). Similar conclusions have been reported in other large clinical studies. In a small prospective trial, chronic inflammation was shown to induce fibrotic changes in 30 peri-urethral prostate tissues from retropubic radical prostatectomy. Fibrosis in this region is alleged to promote urethral stiffness and LUTS. A comprehensive summary and the evidence level of these studies are shown in Table 1. METS-INDUCED INFLAMMATION ASSOCIATED WITH OAB/UI 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. 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. 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 remodeling and increased tissue with increased prostatic inflammation.

METS-INDUCED INFLAMMATION ASSOCIATED WITH BPH/BLADDER OUTLET OBSTRUCTION Several studies have demonstrated that components of MetS such as type 2 diabetes, hypertension, hyperinsulinemia and dyslipidemia directly correlate with pro-inflammatory state, oxidative stress and pro-fibrosis. 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. 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. 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. 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 prostate inflammation. 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. IL-8 has been shown to be actively involved in BPH-associated chronic inflammation and mediates epithelial and stromal cell proliferation. 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-γ and IL-17, which are produced by prostate-infiltrating Th1 and Th17 cells, respectively. 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. Moreover, secretion of IL-8 has been shown to induce the expression of fibroblast growth factor-2, a potent stromal and epithelial growth factor that promotes abnormal proliferation of prostatic cells. In addition, CXCL5-, CXCL1-, CXCL6- and CXCL12-induced proliferative responses have been observed in both epithelial and stromal prostate cells in vitro. 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. Our previous studies conducted in mice showed that continuous consumption of high-fat diet 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-kB/p65 transcription factors, and their sustained interaction is associated with increased prostatic inflammation.

Association between MetS, inflammation and LUTS Q He et al
A few studies have investigated possible associations between MetS-induced inflammation and OAB or UI. Some investigators have studied the role of inflammatory cytokines in patients with OAB.58,59 Tyagi et al.60 have shown 10-fold increase in the levels of monocyte chemotactic protein-1 and CD40 ligand, whereas fivefold elevations were detected in macrophage inflammatory protein-1β, IL-12p70/p40, IL-5, epidermal growth factor and growth-related oncogene GRO-α compared with controls. Significant threefold elevation was also noticed in the urine levels of sIL-2Ra, and IL-10 in OAB patients. Another study demonstrated that CRP was significantly higher in women with OAB associated with urgency incontinence, \( n = 30, 0.12 \text{ mg dl}^{-1} \) as compared with women with bladder oversensitivity \( (n = 68, 0.075 \text{ mg dl}^{-1}, P = 0.008) \), and nerve growth factor (NGF), IL-1β, IL-6, IL-8 and tumor necrosis factor-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\(^{-1}\) (sensitivity 43.5%; specificity 72.7%). Chung et al.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.62 found that vaginal

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**Table 1. Studies on MetS-induced inflammation associated with BPH/bladder outlet obstruction**

| Author            | Study | Country | Sample size | Biomarkers           | Comments                                                                 | Evidence level |
|-------------------|-------|---------|-------------|----------------------|--------------------------------------------------------------------------|---------------|
| Fibbi B et al.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. IL-8 appears to be the most reliable and predictive surrogate marker to diagnose prostate inflammatory conditions. | d             |
| Penna G et al.29  | Cohort| Italy   | 83 men      | IL-1α, IL-1β, IL-6, IL-12p70, CCL1,3,4, CXCL8/IL-8 | IL-8 and ENA-78 were elevated in the prostatic secretions of men. IL-8 expressed prostatic secretion can serve as a reliable biomarker in identifying BPH with chronic prostatitis from simple BPH. | 2b            |
| Hochreiter WW et al.31 | Cohort| USA     | 63 men      | IL-8, ENA-78         | IL-8 and ENA-78 were elevated in the prostatic secretions of men. IL-8 expressed prostatic secretion can serve as a reliable biomarker in identifying BPH with chronic prostatitis from simple BPH. | 2b            |
| Liu, L et al.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 et al.33  | Cohort| Italy   | 171 men     | sIL-8                | Insulin levels increased as a function of MetS components \( (P < 0.0001) \). MetS is positively associated with prostate enlargement, biochemical (sIL-8) and ultrasound-derived signs of prostate inflammation. IL-8 can induce FGF2 and promote abnormal proliferation of the prostatic transition zone. 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-β. High-fat diet activates Stat-3 and NF-κB/p65 in the prostate, and their interaction is associated with increased inflammation in the prostate. | 2b            |
| Giri D et al.38   | BS    | USA     | –           | IL-8, FGF2           | IL-8 can induce FGF2 and promote abnormal proliferation of the prostatic transition zone. 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-β. 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             |
| Gharaei-Kermani M et al.39 | BS    | USA     | –           | TGF-β1, CXCL5, CXCL8, or CXCL12 | IL-8 can induce FGF2 and promote abnormal proliferation of the prostatic transition zone. 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-β. High-fat diet activates Stat-3 and NF-κB/p65 in the prostate, and their interaction is associated with increased inflammation in the prostate. Prostate enlargement due to chronic inflammatory process may lead to BPH progression. | d             |
| Shankar et al.40,41 | BS    | USA     | C57BL/6 mice | IL-1β, IL-6, IL-17, TNFα, NF-κB, Stat-3, Akt, PDK1, PKcε, GLUT4, IL-6, RhoA/ROCK | IL-8 can induce FGF2 and promote abnormal proliferation of the prostatic transition zone. 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-β. High-fat diet activates Stat-3 and NF-κB/p65 in the prostate, and their interaction is associated with increased inflammation in the prostate. Prostate enlargement due to chronic inflammatory process may lead to BPH progression. | d             |
| Vignozzi L et al.42,43 | BS    | Italy   | rabbits     | –                   | Tadalafli dosing reduced RhoA/ROCK signaling and smooth muscle over-activity in an animal model of MetS-associated bladder alterations. | d             |
| Robert G et al.44  | RS    | France  | 282 patients | CD3, CD4, CD8, CD2, CD163 | Chronic inflammation was a common finding in autopsied prostates. Combination therapy and finasteride alone reduce long-term risk of acute urinary retention and the need for invasive therapy. Increased chronic inflammation was associated with more BPH. 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. | 1b            |
| Delongchamps NB et al.47 | RS    | USA     | 167 prostates | –                   | Chronic inflammation was a common finding in autopsied prostates. Combination therapy and finasteride alone reduce long-term risk of acute urinary retention and the need for invasive therapy. Increased chronic inflammation was associated with more BPH. 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. | 1b            |
| McConnell JD et al.46 | RCT   | USA     | 3047 men    | –                   | Chronic inflammation was a common finding in autopsied prostates. Combination therapy and finasteride alone reduce long-term risk of acute urinary retention and the need for invasive therapy. Increased chronic inflammation was associated with more BPH. 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. | 1a            |
| Zlotta AR et al.48 | Cohort| Canada  | 320 prostate glands | –                   | Chronic inflammation in >70% of men on autopsy. Increased chronic inflammation was associated with more BPH. 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            |
| Mishra VC et al.50 | RS    | UK      | 406 patients | –                   | Chronic inflammation in >70% of men on autopsy. Increased chronic inflammation was associated with more BPH. 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. | 1b            |
| Nickel JC et al.51 | RCT   | Canada  | 8224 men    | –                   | Weak correlations were found between average and maximum chronic inflammation and International Prostate Symptom Score variables. Patients experiencing prostate-related LUTS could benefit from anti-inflammatory therapies, used alone or combined with the currently prescribed regimen. | 1a            |
| Cantiello F52     | Cohort| Italy   | 30 patients | –                   | Chronic inflammation in >70% of men on autopsy. Increased chronic inflammation was associated with more BPH. 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            |

Abbreviations: BS, basic study; FGF2, fibroblast growth factor-2; IL, interleukin; LUTS, lower urinary tract symptom; MetS, metabolic syndrome; RCT, random control trial; RS, retrospective study; TNFα, tumor necrosis factor-α.
distention upregulated urethral expression of CCL7 immediately after injury in virgin and postpartum rats. Hypoxia inducible factor-1α and vascular endothelial growth factor were upregulated only in virgin rats immediately after vaginal distention. CD191 expression was immediately upregulated in postpartum rats without vaginal distention compared with virgin rats without vaginal distention. CD195 was upregulated in virgin rats 3 days after vaginal distention compared with virgin rats without vaginal distention. CD191 and CD193 and CD195 were upregulated in virgin rats immediately after vaginal distention. CD191 and CD193 and CD195 were upregulated in virgin rats immediately after vaginal distention. CD191 and CD193 and CD195 were upregulated in virgin rats immediately after vaginal distention. CD191 and CD193 and CD195 were upregulated in virgin rats immediately after vaginal distention.

Table 2. Studies on MetS-induced inflammation associated with overactive bladder/urinary incontinence

| Author               | Study   | Country | Sample size | Biomarkers | Comments                                                                 | Evidence level |
|----------------------|---------|---------|-------------|------------|---------------------------------------------------------------------------|----------------|
| Hsiao S-M et al.     | Cohort  | China   | 197 women   | CRP        | High serum CRP levels were found in women with OAB, wet, and were related to lower maximum urinary flow rates and higher body mass indices in non-SUI LUTD. | 2b             |
| Tyagi P et al.       | Cohort  | USA     | 17 women    | 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 et al.      | Cohort  | China   | 70 women    | NGF, CRP   | Serum CRP levels were significantly higher in subjects with OAB, chronic inflammation associated with OAB or IC/Bladder cancer (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). | 3b             |
| Lenis AT et al.      | BS      | USA     | 72 rats     | CCL7, CXCL12, CD191, CD193, CXCR4, LOX | Pregnancy and parturition in rats contribute to the expression of chemokines and receptors after vaginal distention. | d              |
| Chen H-Y et al.      | BS      | China   | 18 mice     | –          | oric following vaginal trauma involves overexpression of LOX and decrease synthesis of extracellular matrix components or increased proteolysis in the urethra. | d              |
| Wang L-W et al.      | Cohort  | China   | 90 women    | BDNF, NGF  | Causal associations with obesity, smoking and carbonated drinks are confirmed for bladder disorders associated with incontinence, and additional associations with diet are suggested. | 2b             |
| Dallosso H et al.    | Cohort  | UK      | 7046 women  | –          | Relationship between adiposity and overactive bladder varies by gender. | 1b             |
| Link CL et al.       | Cohort  | USA     | 5503 patients| –         | 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             |
| He Q et al.          | 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. | 2b             |
| Tsai Y-C et al.      | 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 et al.        | Cohort  | Turkey  | 122 patients| –         | Insulin resistance can be associated to overactive bladder and may have a significant role in pathogenesis. | 2b             |

Abbreviations: BS, basic study; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; EGF, epidermal growth factor; IL, interleukin; LUTD, lower urinary tract dysfunction; MA, meta-analysis; MCP-1, monocyte chemotactic protein-1; NGF, nerve growth factor; OAB, overactive bladder; SUI, stress urinary incontinence; WC, waist circumference.
be risk factors of incontinence \( (P < 0.001) \).\(^2\) Hakki Uzun \textit{et al.} demonstrated that serum insulin levels were higher in female patients with OAB \( (11.5 \pm 6.2 \mu \text{U ml}^{-1}) \) relative to controls \( (6.4 \pm 2.1 \mu \text{U ml}^{-1}, P = 0.036) \). Insulin resistance was significantly higher in the OAB group, \( 2.86 \) \((0.76–17.04)\) in comparison with controls, \(1.32; 0.67–22.4, P = 0.018\). High-density lipoprotein cholesterol levels were significantly lower in females with OAB.\(^3\) There is lack of strong evidence and inconclusiveness to estimate the potential association between MetS and OAB/UI.

**CONCLUSION AND FUTURE DIRECTION**

A number of studies support MetS as a complex disorder consisting of numerous interrelated pathophysiologic entities including obesity, dyslipidemia and 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, whereas 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.

**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.

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**REFERENCES**

1. King D. The future challenge of obesity. \textit{Lancet} 2011; \textbf{378}: 743–744.
2. Alberti K, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA \textit{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. \textit{Circulation} 2009; \textbf{120}: 1640–1645.
3. Golden SH, Robinson KA, Saldana I, Anton B, Ladenson PW. Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. \textit{J Clin Endocrinol Metab} 2009; \textbf{94}: 1853–1878.
4. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. \textit{Nature} 2006; \textbf{444}: 881–887.
5. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. \textit{Lancet} 2005; \textbf{365}: 1415–1428.
6. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. \textit{J Clin Endocrinol Metab} 2004; \textbf{89}: 2595–2600.
7. Donnell RF. Benign prostate hyperplasia: a review of the year’s progress from bench to clinic. \textit{Curr Opin Urol} 2011; \textbf{21}: 22–26.
8. Moul S, McVary KT. Lower urinary tract symptoms, obesity and the metabolic syndrome. \textit{Curr Opin Urol} 2010; \textbf{20}: 7–12.
9. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U \textit{et al.} The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. \textit{Neurourology and Urodynamics} 2002; \textbf{21}: 167–178.
10. Nickel J. Prostatic inflammation in benign prostatic hyperplasia—the third component? \textit{Can J Urol} 1994; \textbf{1}: 1–4.
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. \textit{Urology} 2002; \textbf{59}: 245–250.
12. Gacci M, Corona G, Vignozzi L, Salvi M, Serni S, De Nunzio C \textit{et al.} Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis. \textit{BJU Int} 2015; \textbf{115}: 24–31.
13. De Nunzio C, Cindolo L, Gacci M, Pellegrini F, Carini M, Lombardo R \textit{et al.} Metabolic syndrome and lower urinary tract symptoms in patients with benign prostatic enlargement: a possible link to storage symptoms. \textit{Urology} 2013; \textbf{84}: 1181–1187.
14. Bhindi B, Margel D, Trottier G, Hamilton RJ, Kulkarni GS, Hersey KM \textit{et al.} Obesity is associated with larger prostate volume but not with worse urinary symptoms: analysis of a large multietnic cohort. \textit{Urology} 2014; \textbf{83}: 81–87.
15. Parsons JK, Sarma AV, McVary K, Wei JT. Obesity and benign prostatic hyperplasia: clinical connections, emerging etiological paradigms and future directions. \textit{J Urol} 2013; \textbf{189}: S102–S106.
Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* 2004; 114: 1752–1761.

Kasturi S, Russell S, McVary KT. Metabolic syndrome and lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Curr Prostate Rep* 2006; 4: 127–131.

Ozawa M, Ozal OL, Urgancioglu G, Koyuncu H, Gokkaya S, Mensis A. The correlation between metabolic syndrome and prostatic growth in patients with benign prostatic hyperplasia. *Eur Urol* 2007; 51: 199–206.

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: 106–117.

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. *Int J Clin Pract* 2014; 69: 199–217.

Penna G, Fibbi B, Amuchastegui S, Corsiero E, Laverny G, Silvestrini E et al. Prostatic inflammation and/or infection in benign prostatic hyperplasia: a 282 patients’ immunohistochemical analysis. *Prostate* 2009; 69: 1774–1780.

Delongchamps NB, de la Roza G, Chandan V, Jones R, Sunheimer R, Threette G et al. Evaluation of prostatitis in autopsied prostates—is chronic inflammation more associated with benign prostatic hyperplasia or cancer? *J Urol* 2008; 179: 1736–1740.

McConnell JD, Roehrborn CG, Bautista OM, Androlicle 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. *N Engl J Med* 2003; 349: 2387–2398.

Nickel J, Downey J, Young I, Boag S. Asymptomatic inflammation and/or infection in benign prostatic hyperplasia. *BJU Int* 1999; 84: 976–981.

Zlotta AR, Egawa S, Pushkar D, Gavoretov A, Kimura T, Kidd M et al. Prevalence of inflammation and benign prostatic hypertrophy on autopsy in Asian and Caucasian men. *Eur Urol* 2014; 66: 619–622.

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 J Urol* 2010; 51: 266–270.

Mishra VC, Allen DJ, Nicolaou C, Shanif H, Hudd C, Karim O et al. Does intraprostatic inflammation have a role in the pathogenesis and progression of benign prostatic hyperplasia? *BJU Int* 2007; 100: 327–331.

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. *Eur Urol* 2008; 54: 1379–1384.

Cantello F, Ciccone A, Salonia A, Autorino R, Tucci L, Madeo I et al. Periurethral fibrosis secondary to prostatic inflammation causing lower urinary tract symptoms: a prospective study. *Urology* 2013; 81: 1018–1024.

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 J Urol* 2003; 20: 327–336.

Heilbronn LK, Campbell LV. Adipose tissue macrophages, low grade inflammation and insulin resistance in human obesity. *Curr Pharm Des* 2008; 14: 1225–1230.

Bieracka A, Dobaczewski M, Frangogiannis NG. TGF-β signaling in fibrosis. *Growth Factors* 2011; 29: 196–202.

Liu Y. Cellular and molecular mechanisms of renal fibrosis. *Nat Rev Nephrol* 2011; 7: 684–696.

Rodriguez-Nieves JA, Macojska JA. Prostatic fibrosis, lower urinary tract symptoms, and BPH. *Nat Rev Urol* 2013; 10: 546–550.

Kuo H-C, Liu H-T, Shie J-I. Potential urinary and serum biomarkers for patients with overactive bladder and interstitial cystitis/bladder pain syndrome. *Tai Chi Med J 2013;* 5: 13–18.

Hsiao S-M, Lin H-H, Kuo H-C. The role of serum C-reactive protein in women with lower urinary tract symptoms. *Int Urogynecol J* 2012; 23: 935–940.

Tyagi P, Barclay D, Zamora R, Yoshimura N, Peters K, Vodovoz Y et al. Urine cytokines suggest an inflammatory response in the overactive bladder: a pilot study. *Int Urol Nephrol* 2010; 42: 629–635.

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. *Neurolour Urodyn* 2011; 30: 417–420.

Lenis AT, Kuang M, Woo LL, Hijazi A, Penn MS, Butler RS et al. Impact of parturition on chemokine homing factor expression in the vaginal distention model of stress urinary incontinence. *J Urol* 2013; 189: 1588–1594.

Hinrichs JH, Hinrichs YH, Hinrichs WC. Stress urinary incontinence following vaginal trauma involves remodeling of urethral connective tissue in female mice. *Eur J Obstet Gynecol Reprod Biol* 2012; 163: 224–229.

Chen HY, Chen CJ, Lin Y-N, Chen Y-H, Chen WC, Chen CM. Proteomic analysis related to stress urinary incontinence following vaginal trauma in female mice. *Eur J Obstet Gynecol Reprod Biol* 2013; 171: 171–179.

Juan YS, Chuang SM, Lee YL, Long CY, Wu TH, Chang WC et al. Green tea catechins decrease relative stress in surgical menopause-induced overactive bladder in a rat model. *BJU Int* 2012; 110: E234–E244.

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. *Int Urol Nephrol* 2014; 46: 341–347.
67 Agilli M, Aydin FN, Kurt YG, Cayci T. A potential biomarker for objective diagnosis of overactive bladder: urinary nerve growth factor. Int Urol Nephrol 2014; 47: 317–318.
68 Bhide AA, Cartwright R, Khullar V, Digesu GA. Biomarkers in overactive bladder. Int Urogynecol J 2013; 24: 1065–1072.
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 Int 2003; 92: 69–77.
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. J Urol 2011; 185: 955–963.
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. Aging Male 2014; 17: 223–229.
72 Tsai Y-C, Liu C-H. Urinary incontinence among Taiwanese women: an outpatient study of prevalence, comorbidity, risk factors, and quality of life. Int Urol Nephrol 2009; 41: 795–803.
73 Uzun H, Yilmaz A, Kemik A, Zorba OU, Kalkan M. Association of insulin resistance with overactive bladder in female patients. Int Neurol J 2012; 16: 181–186.
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. Am J Epidemiol 2005; 162: 898–906.
75 Krieger JN, Lee SWH, Jeon J, Cheah PY, Liong ML, Riley DE. Epidemiology of prostatitis. Int J Antimicrob Agents 2008; 31: 85–90.
76 Colodner R, Eliasberg T, Chazan B, Raz R. Clinical significance of bacteriuria with low colony counts of Enterococcus species. Eur J Clin Microbiol Infect Dis 2006; 25: 238–241.
77 Lee S, Yang G, Bushman W. Prostatic inflammation induces urinary frequency in adult mice. PLoS One 2015; 10: e0116827.
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. J Immunol 2014; 193: 6081–6089.
79 Eynard AR, Navarro A. Crosstalk among dietary polyunsaturated fatty acids, urolithiasis, chronic inflammation, and urinary tract tumor risk. Nutrition 2013; 29: 930–938.
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: 295–300.
81 Keddis MT, Rule AD. Nephrolithiasis and loss of kidney function. Curr Opin Nephrol Hypertens 2013; 22: 390.

Supplementary Information accompanies the paper on the Prostate Cancer and Prostatic Diseases website (http://www.nature.com/pcan)