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Review Article

Causative significance of bladder blood flow in lower urinary tract symptoms

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Abbreviations & Acronyms
BBF = bladder blood flow
BOO = bladder outlet obstruction
BPH = benign prostatic hyperplasia
CDUS = color Doppler ultrasonography
DO = detrusor overactivity
ED = erectile dysfunction
H_2O_2 = hydrogen peroxide
LUTD = lower urinary tract dysfunction
LUTS = lower urinary tract symptoms
MetS = metabolic syndrome
mRNA = messenger ribonucleic acid
OAB = overactive bladder
PDE5 = phosphodiesterase 5
PV = prostate volume
RI = resistive index
SHR = spontaneously hypertensive rats
TURP = transurethral resection of the prostate
VV = voiding volume

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Abstract: The association between metabolic syndrome and lower urinary tract symptoms has been attracting enormous interest and attention. This enthusiasm is based on the presence of many common risk factors being involved in both metabolic syndrome and lower urinary tract symptoms, as shown by various epidemiological studies. Metabolic syndrome and lower urinary tract symptoms have many pathophysiological features in common, particularly overactive bladder. Herein, we analyze the pathophysiological relationship between metabolic syndrome and lower urinary tract symptoms with a special emphasis on bladder blood flow. We also propose a new treatment strategy for treating lower urinary tract symptoms from the viewpoint of bladder blood flow.

Key words: bladder blood flow, lower urinary tract symptoms, metabolic syndrome.

Common features of MetS and LUTS

The MetS describes the combination, or clustering, of several metabolic abnormalities or risk factors, including central obesity, dyslipidemia, hypertension, insulin resistance with compensatory hyperinsulinemia and glucose intolerance (type 2 diabetes, impaired glucose tolerance or impaired fasting glycemia).[1] Considerable evidence suggests a relationship between LUTS, BPH, OAB, ED and MetS. It has been reported that LUTS score becomes higher as the individual has more risk factors of MetS, such as hypertension, abnormal serum lipid levels and high blood glucose.[2] Numerous basic and clinical studies have focused on the relationships between these risk factors and LUTS/BPH. A recent retrospective study of the association between visceral fat accumulation (a major criterion for the diagnosis of MetS) and LUTS showed a significant correlation of visceral fat accumulation with storage symptoms in 233 patients with BPH.[3] Hypertension, one of the diseases constituting to MetS, deserves to be mentioned with relevance to LUTS. MetS is known to cause autonomic sympathetic overactivity through complex mechanisms.[1] Many basic studies examining the role of the autonomic nervous system in the pathophysiology of LUTD used SHR. SHR are known to show a significantly lower bladder capacity and VV.[4] SHR voided three times more frequently than normotensive rats, and cystometrograms showed spontaneous bladder contractions and lower VV in SHR.[5] We previously reported stroke-prone SHR voided more frequently than SHR.[6] Furthermore, SHR have enhanced activity of the sympathetic nervous system and increased prostate size.[7] Interestingly, regression of the prostate after blockade of the sympathetic nervous system is observed in SHR.[8] In a prospective clinical study involving 1709 men who were followed for 9 years, it was shown that the risk for development of LUTS/BPH or the necessity of its treatment were higher in individuals with a history of cardiac disease or a-blocker therapy.[9] Sympathetic nervous system activity is associated with increased prostatic smooth muscle tone and LUTS. Platz *et al*. showed that more physically active men have fewer LUTS, thereby resulting in a reduced risk for prostate surgery.[10] Taken together, it seems that in men with MetS, contractility of prostatic smooth muscles is enhanced through sympathetic overactivity, and atherosclerotic lesions induce ischemia of the lower urinary tract, leading to

further enhancement of sympathetic nervous activity and then the appearance of storage symptoms. Enhancement of sympathetic nervous activity also stimulates the proliferation of prostatic cells, thereby increasing PV and resulting in BOO and the appearance of voiding symptoms. However, it is difficult to entirely explain the underlying mechanisms of LUTS based on the involvement of the sympathetic nervous system alone. It is now considered that a combination of various factors, including environmental and genetic factors, is involved in a complex manner in the development of LUTS.

Disturbed BBF as a cause of LUTS

Pathophysiological conditions of MetS, such as hypertension, involve enhanced sympathetic nervous activity and possibly elevate the risk for atherosclerotic disease. These conditions might aggravate systemic vascular factors and cause disturbed blood flow through the lower urinary tract, thus leading to the onset of LUTS. In an animal study, bladder fibrosis and bladder dysfunction were more remarkable in rabbits with experimentally-induced atherosclerosis than in rabbits with hypercholesterolemia alone.[11] Moderate bladder ischemia resulted in enhanced DO, whereas severe bladder ischemia was associated with impaired detrusor contraction.[11] In a study using rabbits with hyperlipidemia accompanied by progressive atherosclerosis, reduction in BBF was associated with DO and urinary frequency.[12] In a clinical study using transrectal color Doppler ultrasonography that was designed to evaluate lower urinary tract blood flow in patients with LUTS, chronic ischemia of the lower urinary tract was shown to be involved in the development of LUTS.[13] In an analysis of intrapelvic blood flow using dynamic contrast-enhanced magnetic resonance imaging, men with coronary artery disease had lower intrapelvic blood flow than normal men, showing correlations of intrapelvic blood flow with parameters such as LUTS and ED.[14] In a recent clinical study in patients with LUTS/BPH as a result of BOO, the bladder vascular RI was analyzed using enhanced CDUS (ProSound SSD-5500; ALOKA, Mitaka-Shi, Japan, equipped with a 5.0-MHz probe) before and after TURP. The measurement of RI is described later. CDUS was carried out during the storage phase without urge to void with bladder volume between 100 and 150 mL. After the administration of ultrasound contrast agent (Levovist; Bayer, Osaka, Japan), arterial blood flow of the lateral bladder wall was examined by transabdominal ultrasonography. RI ([Vmax-Vmin]/Vmax) of right and left bladder vessels was measured and calculated. High bladder vascular RI is considered to implicate low BBF. RI significantly correlated with PV and the severity of obstruction by Schaffer nomogram, and overall RI was significantly reduced after TURP.[15] In 24 patients with BPH whose symptoms were poorly controlled by an α_1-blocker, the abdominal aorta calcification score significantly correlated with visceral fat accumulation, as well as objective voiding parameters (VV on uroflowmetry and detrusor pressure at maximum flow), PV and postvoid residual.[16] Although there was no significant correlation between abdominal aortic calcification score and RI, RI significantly correlated with visceral fat accumulation and objective voiding parameters.[16] Thus, many previous reports have shown that LUTS and LUTD can develop if underlying diseases, such as MetS, cause atherosclerotic lesions and disturb BBF.

BBF could be disturbed by the state of bladder distension, even in the absence of underlying bladder pathology or atherosclerosis. In animal studies designed to evaluate the influence of bladder distension on BBF, no substantial changes in the bladder wall or vessels were noted when the bladder was undistended (filling to 5% of bladder capacity), whereas slight distension of the bladder (filling to 25% of bladder capacity) compressed the bladder wall and vessels (Fig. 1).[17,18] Bladder wall thickness decreased more than
50% at 25% of bladder capacity, and by an additional 125% of bladder capacity (overdistension state).[17] CD31 immunohistochemistry was used to characterize the bladder wall vascularity. At 5% of bladder capacity, all vessels were open, and at 25% of bladder capacity most veins appeared collapsed and the arteries remained open, whereas with increasing volumes, the vessels showed additional compression.[18] Bladder distension significantly reduced pressure generation in response to field stimulation only, showing that distension reduced the effectiveness of synaptic transmission without altering muscarinic receptor function or membrane depolarization.[17] Thus, bladder distension affects a significant influence on bladder morphology and BBF, and impairs detrusor function. We developed a rat model of bladder overdistension/empting-induced bladder overactivity.[19] The rat bladder was distended with 2 mL of saline under anesthesia for 2 h (overdistension) and then emptied (emptying).[19] Bladder overdistension/emptying increased voiding frequency, and decreased VV and intercontraction interval without affecting micturition pressure, threshold pressure or postvoid residual in the cystometry study. Reduction in BBF was also observed by bladder overdistension, with partial recovery after emptying.[19] These results suggest that even in normal micturition, repetition of bladder distension can modify BBF and that BBF might be disturbed in the aging bladder because of long-term repetition of the micturition cycle. Therefore, in the presence of atherosclerotic disease as a result of MetS associated with aging, BBF is likely to be reduced more markedly and has a greater impact on LUTS.

It is known that not only reduced BBF (bladder ischemia), but also oxidative stress as a result of free radicals, which are formed by reperfusion after bladder ischemia, can cause bladder damage. Reperfusion injury is more severe than the

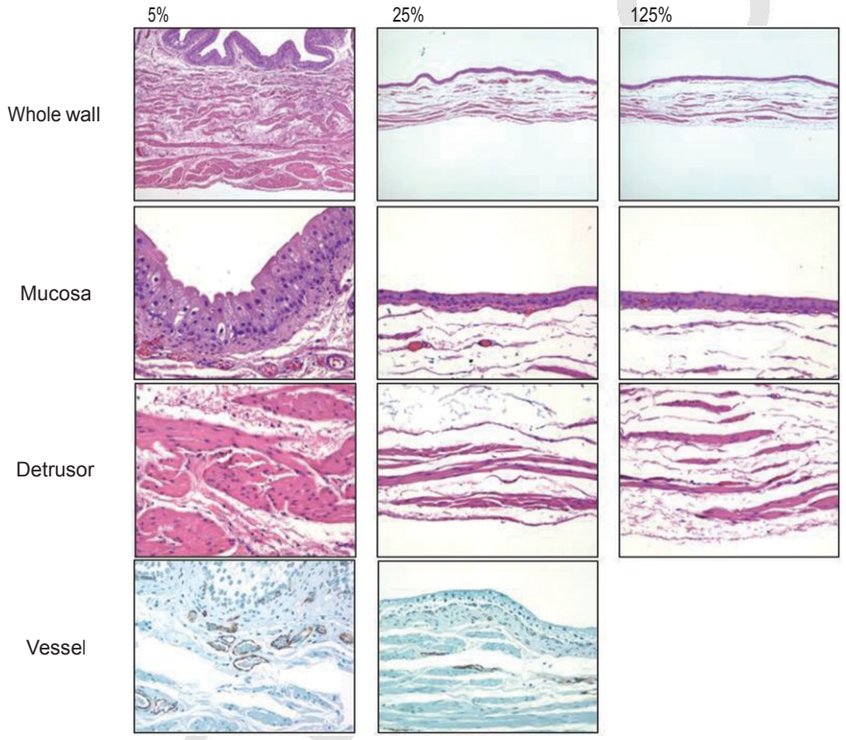

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Fig. 1 Changes in normal rabbit bladder wall (whole wall, mucosa, muscle, detrusor) and bladder blood vessels after different states of bladder distension.

ated bladder dysfunction caused by oxidative stress injury that was induced by exposure of bladder sections to H_2O_2, and showed reduced contractility of bladder smooth muscle in a manner dependent on the H_2O_2 concentration.[21] In another study involving injection of H_2O_2 into the bladder, the afferent c-fiber pathway was activated by the damage as a result of oxidative stress, resulting in the induction of DO and frequency of urination.[22] Thus, aggravation of systemic vascular factors as a result of MetS can affect BBF. Bladder ischemia reduces energy metabolism and inhibits ATPase-mediated uptake of calcium in mitochondria and sarcoplasmic reticulum, resulting in injury of autonomic nerves, smooth muscles and other membranous structures in the body. Reperfusion injury induces damage as a result of oxidative stress (free radical injury), resulting in further aggravation of bladder ischemia.

Mild to moderate bladder ischemia damages the urothelium and intramural nerves, and induces DO, resulting in the appearance of storage symptoms as represented by OAB. If bladder ischemia intensifies and persists for a long time, damage to the urothelium and nerves becomes apparent, and tissue damage is further advanced after bladder ischemia and reperfusion injury, resulting in a reduction of bladder smooth muscle contractility and development of a condition called underactive bladder. It seems that these changes progress in parallel or in association with each other, and that bladder function is initially compensated and preserved (compensation status), but eventually reaches a state of decompensated/irreversible damage (decompensation status) (Fig. 2).

Treatment strategy for LUTS from the aspect of BBF

Needless to say, priority should be given to treating the underlying condition responsible for MetS or LUTS. When dealing with cases in which the influence of disturbed BBF (bladder ischemia) on LUTS is likely, two treatment approaches are available: (i) intervention aimed at improving the reduced BBF (bladder ischemia); and (ii) intervention aimed at reducing the elevated oxidative stress during reperfusion. In practice, improvement of LUTS is expected after an increase in BBF or removal of oxidative stress (Fig. 3).[19,21,23–33]

Drugs used to increase BBF include antihypertensive agents (vasodilators). α_1-Blockers, which are often used for treatment of LUTS/BPH, are first considered for this purpose. A decrease in BBF associated with BOO has been reported in rats,[23] rabbits[34] and pigs.[35] When a rat BOO model was treated with doxazosin, a non-selective α_1-blocker, BBF increased in comparison with the untreated group, accompanied by suppression of the reduction in bladder smooth muscle contractility.[23] In other rat models of BOO[24] and bladder overdistension/emptying- induced bladder overactivity,[19] treatment with tamsulosin resulted in an increase in BBF, accompanied by improved bladder overactivity through improvement of BBF as compared with the untreated group. In a clinical study, tamsulosin was shown to increase bladder capacity and BBF in patients with LUTS/BPH.[25] These findings suggest that not only BOO, but also

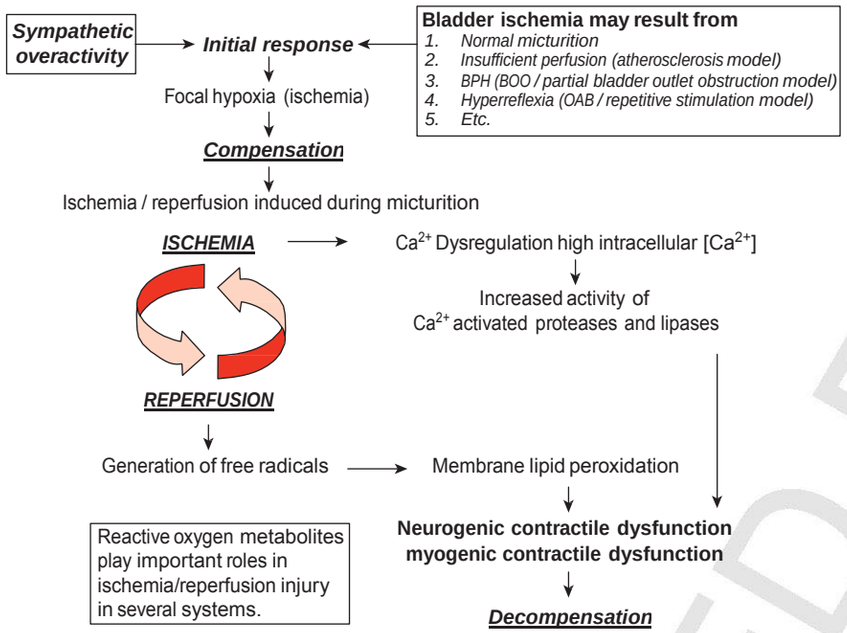

Fig. 2 Serial changes in bladder function after bladder ischemia and reperfusion.

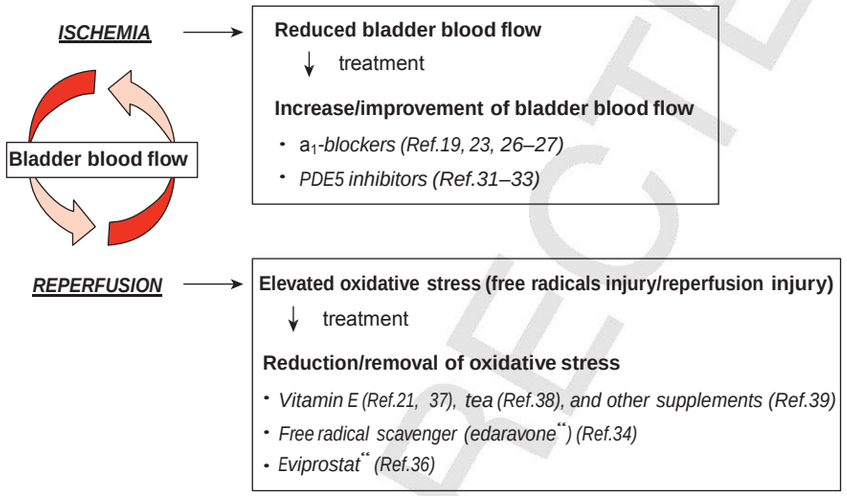

Fig. 3 Treatment strategy for improving bladder blood flow and reducing oxidative stress.

chronic ischemia of the bladder, are involved in LUTS/BPH, and that a_1-blockers can improve both BOO and BBF.

PDE5 inhibitors are the most widely used drugs for ED. PDE5 inhibitors are candidates for increasing BBF. Fibbi *et al*. showed PDE5 expression in vascular smooth muscle and endothelial cells of the human prostate and bladder in smooth muscle of the human prostatic urethra.[36] From a preclinical perspective, it is reported that PDE5 mRNA is expressed in the rat bladder at much higher level than in the penis, and that PDE5 inhibitors dose-dependently dilated rat bladder strips in an organ bath assay.[37] PDE5 inhibitors are clinically expected to serve as a means of treating LUTS/BPH.[38] Andersson *et al*. reviewed the published literature describing the pathophysiology of male LUTS, with an emphasis on mechanisms that might be modulated or improved by PDE5 inhibition, and showed that PDE5 inhibitors have shown beneficial effects on smooth muscle relaxation, smooth muscle and endothelial cell proliferation, nerve activity, and tissue perfusion that might impact on LUTS in men.[26] They explained that one possibility of the effect of PDE5 inhibitors for LUTS is that PDE5 inhibitors increase pelvic blood perfusion and reduce lower urinary tract chronic ischemia.[26] It has been reported that chronic treatment with a PDE5 inhibitor, vardenafil, prevented and improved bladder dysfunction in a rat BOO model.[27] Interestingly, chronic treatment with vardenafil increased the contractile force of normal bladder strips in rats.[28] These findings seem to be attributable to the increased blood flow in the lower urinary tract by PDE5 inhibitors.

Regarding drugs aimed at removing oxidative stress during bladder reperfusion, anti-oxidants and other neuroprotective medications might have a therapeutic benefit in patients with LUTS/BPH, as well as in older adults with acute and possibly chronic urinary retention. Edaravone, a newly developed radical (oxidative stress) scavenging agent used for protection against ischemia and reperfusion injury in patients with cerebral infarction, has been reported to prevent and improve bladder dysfunction by inhibiting the induction of lipid peroxidation.[32] Eviprostat, a phytotherapeutic agent used for treatment of BPH in Japan and Germany, is known to have anti-oxidative and anti-inflammatory activity.[39] Chronic treatment with Eviprostat improved micturition parameters and reduced the urinary levels of oxidative stress maker 8-ydroxy-2′-deoxyguanosine significantly in rabbits with BOO and humans with LUTS/BPH.[33] Anti-oxidant vitamin E preparations, tea and other supplements have also been reported to be useful in the treatment of bladder dysfunction as a result of ischemia and reperfusion injury.[21,29–31]

In conclusion, these treatment strategies designed to increase and improve BBF, and to reduce oxidative stress are promising for the treatment of LUTS and LUTD. Needless to say, correction of lifestyle, which can aggravate MetS, is indispensable not only for the treatment of LUTS, but also for improvement of overall health.

Conflict of interest

None declared.

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