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Review Article

Potential urine biomarkers in bladder outlet obstruction-related detrusor underactivity

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Abstract

Detrusor underactivity (DU), an important but under-researched issue, is thought to be complex and multifactorial in etiology, pathophysiology, and diagnosis. Bladder outlet obstruction (BOO) is one of the important known etiologies of DU, with significant morphologic and physiologic changes of the urothelium, suburothelium, and detrusor muscle in the urinary bladder. Chronic urinary bladder ischemia and repeated cycles of ischemia and reperfusion injury cause excessive oxidative stress, and it is thought to be responsible for the development of DU. DU might be the late phase or decompensated status of BOO, with the possible mechanisms of afferent nervous dysfunction, increased inflammation, denervation of the detrusor muscle, and myogenic failure. Prostaglandin E2 (PGE2) involves in the physiological detrusor contraction, and might provide the prognostic value for the recoverability of DU. Neurotrophins, including nerve growth factor and brain-derived neurotrophic factor, involve in the neuroplastic changes in many inflammatory bladder diseases, including BOO and DU. Oxidative stress biomarkers, including 8-hydroxy-2-deoxyguanosine, F2-isoprostane, and the involved pro-inflammatory cytokines, have been applied in BOO due to their involvements in chronic bladder ischemia. PGE2, neurotrophins, inflammatory cytokines, and oxidative stress biomarkers are the potential urine biomarkers in BOO-related DU.

Keywords: *Bladder outlet obstruction, Detrusor underactivity, Neurotrophin, Oxidative stress, Urine biomarker*

Introduction

Definition and clinical characteristics of detrusor underactivity

Detrusor underactivity (DU) is an important and gradually emphasized issue. DU is defined as "a contraction of reduced strength or duration resulting in prolonged or incomplete emptying of the bladder or both" by the International Continence Society [1]. DU is an urodynamic diagnosis, however, there is no consensus about the specific thresholds of "reduced strength or duration" or "prolonged or incomplete emptying" in urodynamic studies. The lack of standardized definition hinders the advancement in the clinical research of DU, which becomes an important but under-researched issue. In the elderly population (age over 65-year-old), DU is a common etiology of lower urinary tract symptoms, in 40.2% of men and 13.3% of women [2]. Underactive bladder (UAB) is a symptom complex suggestive of DU, and is defined by slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete bladder emptying and sometimes with storage symptoms [3]. In general, DU is a urodynamic term, and UAB is its clinical correlate. UAB might be received as the symptom of DU, although not all DU patients may have UAB symptoms. The correlation between DU and UAB is analogous to detrusor overactivity (DO) and overactive bladder (OAB) [4].

Currently, both DU and UAB are thought to be complex and multifactorial in etiology, pathophysiology, and diagnosis. Several causes of DU/UAB have been reported, including aging [5], diabetes mellitus (DM) [6], bladder outlet obstruction (BOO) [7], peripheral nervous system disorders (e.g., pelvic surgery, pelvic fracture, spinal stenosis, and herpes zoster), and central nervous system disorders (e.g., cerebrovascular accident, traumatic brain injury, Parkinson's disease, spinal cord injury, and multiple sclerosis) [8-10].

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DU is a status of a contraction of reduced strength or duration in urodynamic study. However, it is an intuitive but incorrect linkage to "detrusor muscle failure." Up to present, the pathophysiology of DU has included afferent nervous dysfunction, efferent nervous dysfunction, and myogenic failure, and the role of afferent nervous dysfunction in DU is increasingly recognized [9,11]. Several causes, contributing factors, and diverse pathophysiology of DU have been reported, and BOO is one of the important etiologies of DU. The understanding of progressive bladder remodeling in BOO [12] is more clear than other etiologies of DU, which makes BOO to be a better research model and encourages the further research in DU.

Pathophysiology of bladder outlet obstruction

LUTS is highly prevalent and affects >60% of men aged over than 40 years [13]. BOO is the most common cause (69.6%) of male LUTS, and benign prostatic hyperplasia/benign prostatic obstruction is the most common etiology (46.8%) of BOO [14]. BOO might lead to progressive bladder tissue remodeling and subsequent serious impairments of upper urinary tract [12,15].

The general urodynamic state of BOO is high detrusor pressure and low urinary flow rate during voiding phase [16]. Increased detrusor voiding pressure may result in the reduction of blood flow and chronic ischemia in urinary bladder [17]. Such ischemia status during voiding is followed by an increase in bladder blood flow after micturition, which induces the next step of reperfusion injury. Such cyclic ischemia-reperfusion injury may give rise to the increased oxidative stress and hypoxia-related inflammation, which result in the structural and functional damages of urinary bladder thereafter [12,15]. In BOO, available evidences demonstrate that the effects of hypoxia involve in not only increased inflammation, but also the alternations on human bladder smooth muscle cells (HBSMC) proliferation and differentiation [12]. Hypoxia induces a time-dependent increased expression of inflammatory cytokines, including transforming growth factor-beta (protein and mRNA), interleukin (IL) -1β, IL-6, and tumor necrosis factor alpha (TNFα) (mRNA), and decreased expression of anti-inflammatory cytokines IL-10. In addition, hypoxia inhibits the proliferation of HBSMC, induces the de-differentiation of HBSMC with increased αSMA, vimentin, and desmin, and elicits the profibrotic changes with a time-dependent increase of total collagen proteins [18]. In summary, the hypoxic cascade of HBSMC results in a potent inflammation, de-differentiation of smooth muscle cells, and increased extracellular matrix expression.

Pathophysiology of bladder outlet obstruction related detrusor underactivity

BOO is one of the important known etiologies of DU, with significant morphologic and physiologic changes of the urothelium, suburothelium, and detrusor muscle in the urinary bladder [7,15]. Chronic urinary bladder ischemia and repeated cycles of ischemia and reperfusion injury cause excessive oxidative stress, and it is thought to be responsible for the development of DU [19].

A hypothesis of 3 morpho-functional stages for BOO-induced bladder remodeling in human has been proposed recently [12]. The 3 phases comprise hypertrophy, compensation, and decompensation. Increased intravesical pressure during bladder voiding is considered as the "primum movens." Hypertrophy and hyperplasia of HBSMC, mediated by the increased of muscarinic receptor expression, are induced by increased hydrostatic pressure [20,21]. Subsequently, tissue hypoxia intervenes as the next critical stress factor. Compensatory response to hypoxia includes hypoxia induced pathway with hypoxia-inducible factor and vascular endothelial growth factor. Persistent hypoxia inhibits HBSMC proliferation with the transition from hypertrophy to compensation phase, and promotes the progression of extracellular matrix deposition. High levels of extracellular matrix deposition with the alternations of mechanical properties of bladder, resulting in decreased bladder compliance and contractility, characterizes the transition from compensation to decompensation phase. The histological and molecular characteristics in decompensation phase include urothelial dysfunction, neuron degeneration, and smooth muscle cell degeneration. DU is thought to be the decompensation phase or late phase of BOO related bladder dysfunction.

In BOO, urothelial dysfunction with low expression of E-cadherin, increased suburothelial inflammation, and increased cellular apoptosis are noted in the bladder urothelium of male BOO patients [7]. In addition, alternations of sensory proteins with increased expressions of P2X3 and M2 muscarinic receptors, and decreased expressions of M3 muscarinic receptors are explored, which indicates the prominent bladder dysfunction secondary to BOO. In patients with BOO related DU, increased expressions of β3 adrenoreceptors and lower expressions of inducible nitric oxide synthase are detected, which reflects the impaired sensory transduction [7]. In DU, decreased bladder urothelial-afferent signaling has an important role in its pathophysiology and accounts for the clinical presentation of hyposensitivity of DU [22]. In summary, DU might be the late phase or decompensated status of BOO, with the possible mechanisms of afferent nervous dysfunction (urothelial dysfunction and alternations of sensory proteins) [7], increased inflammation, denervation of the detrusor muscle [23], and myogenic failure [9].

Potential urine biomarkers of bladder outlet obstruction related detrusor underactivity

Until now, the relationship about the levels of the selected target between bladder tissue and urine is still under-researched. Nevertheless, noninvasive approach to urine cytokine analysis might provide important information regarding the different pathological bladder conditions without the invasive bladder biopsy procedures. Potential urine biomarkers of BOO-related DU are summarized in Table 1.

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Table 1: Summary of potential urine biomarkers in bladder outlet obstruction related detrusor underactivity

Target	Source of study	Evidence	Reference
PGE2	Human	↓urine PGE2 level in OAB with DU (vs. OAB without DU)	[24]
	Human	↑urine PGE2 level in DU with bladder function recovery (vs. DO, vs. control)	[25]
	Rat	↓urine PGE2 level in DM reduced UAB (vs. control)	[26]
NGF	Human	↑urine NGF level in female BOO before treatment (vs. control)	[27]
		↓urine NGF level after BOO treated (vs. before treatment)	
	Human	↑urine NGF level in BOO with OAB/DO (vs. control), with normal urine NGF level after successful OAB treatment	[28]
	Human	↑urine NGF level in DU (vs. control)	[25]
	Rat	↑urine NGF level in DM reduced UAB (vs. control)	[26]
BDNF	Human	↑urine BDNF level in DU (vs. control)	[25]
		↑urine BDNF level in DU with bladder function recovery (vs. DU without bladder function recovery, vs. control)	
8-OHdG	Human	↓urine 8-OHdG level after BOO treated (vs. before treatment)	[29]
	Rabbit	↑urine 8-OHdG level in partial BOO (vs. control), with normal level after the reversal of BOO	[30]
F2-isoprostane	Mice	↑bladder tissue F2-isoprostane level in partial BOO	[31]

8-OHdG: 8-hydroxy-2-deoxyguanosine, BDNF: Brain-derived neurotrophic factor, BOO: Bladder outlet obstruction, DO: Detrusor overactivity, DU: Detrusor underactivity, NGF: Nerve growth factor, OAB: Overactive, PGE2: Prostaglandin E2, UAB: Underactive bladder, DM: Diabetes mellitus

Prostaglandin E2

Prostaglandin E2 (PGE2), one of the prostanoids, is synthesized by COX-1 and COX-2 locally in urothelium, interstitial cells, and smooth muscle, and released during detrusor contraction/and under basal physiological conditions [32]. PGE2 is believed to be responsible for the spontaneous detrusor contractions necessary for potentiating afferent transmission.

Benign prostatic hyperplasia patients with OAB symptoms have significantly higher urinary PGE2 levels than those without OAB symptoms and normal controls, and urinary PGE2 level decreases with the relief of the OAB symptoms after treatment [33]. In OAB patients, urinary PGE2 level is higher than in controls with positive correlation to both the volume at first desire to void and maximum cystometric capacity [34]. However, urinary PGE2 level is decreased in OAB patients with concurrent DU compared with those without concurrent DU [24]. Lower urinary PGE2 level with upregulation of the associated EP1 and EP3 receptors in DM-induced hyposensitive UAB is recently revealed in a rat study [26]. Therefore, replenishing PGE2 is thought to be one of the treatment strategies to UAB/DU, and experimental instillation of PGE2 into urinary bladder has been tried [35,36].

DU, a dynamic bladder condition, may change with time or after treatment. In our recent study, DU patients with bladder function recovery after treatment had significantly higher urine PGE2 levels than DO patients and controls at baseline [25]. However, DU patients without bladder function recovery had low urine PGE2 levels, which were similar to controls. It suggested that urine PGE2 level might provide the prognostic value and have a potential role for the recoverability of DU. PGE2 involves in the physiological detrusor contraction, and it might be the core urine biomarker of DU.

Neurotrophins and inflammatory cytokines

Neurotrophins including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) have attracted considerable attention in the urologic community, because of the recognition of their ability to induce plastic changes of the neuronal circuits that govern bladder function [37]. Urinary neurotrophins have been considered as putative and important urinary biomarkers for bladder dysfunction [38]. In many inflammatory bladder diseases, such as OAB and interstitial cystitis, urinary symptoms reflect abnormal activity of bladder sensory afferents that results from neuroplastic changes, which indicates the important role of neurotrophins and their link to the inflamed bladder [37]. Recently, impaired urothelial signaling, increased suburothelial inflammation, and altered sensory transduction pathways are also observed in the urinary bladder of BOO with different bladder dysfunctions [7] and DU [22]. Accordingly, neurotrophins are considered to be have important roles in the pathophysiology of BOO with bladder dysfunctions and even DU.

In urinary bladder, NGF and BDNF are expressed in the urothelium, suburothelial tissue, and bladder smooth muscles, and function as governing innervation during development, growth, and injury, which influences urinary symptoms in bladder diseases [38]. Also, increased NGF and BDNF levels can eventually be founded in urine. In female patients with BOO resulting from pelvic organ prolapse, urine NGF levels significantly increased before treatment and then decreased after surgical treatment for BOO [27]. In BOO patients with OAB symptoms or DO, urine NGF levels significantly increased compared with controls, and these levels returned to normal levels after successful medical treatment of OAB symptoms [28]. It suggested that urine NGF level was a potential biomarker of BOO with OAB or DO, and it might be applied to the future investigation of DU, the late phase of BOO related bladder dysfunction.

In a recent study in rats, DM induced hyposensitive UAB is characterized by increased inflammatory reaction and apoptosis, lower bladder NGF level, and increased urine NGF level [26]. In our recent study, DU patients had significantly higher urine NGF and BDNF levels than controls [25]. More importantly, urine baseline BDNF level was significantly

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higher in DU patients with bladder function recovery after treatment, but not in those without recovery compared with that in controls. However, there was no difference in urine NGF levels between DU patients with and without bladder function recovery. It suggested that different neurotrophins might have the important but varied roles in DU, and urine BDNF level probably had more prognostic value than urine NGF level. Chronic bladder inflammation is an important pathophysiology of BOO-related bladder dysfunctions and DU, and the analysis of neurotrophins and inflammation-related cytokines and proteins in urine might be with the potential to monitoring the diseased status and the activity of the inflammation in bladder tissue in a non-invasive approach.

Oxidative stress biomarkers in bladder outlet obstruction and bladder outlet obstruction-related detrusor underactivity

Excessive oxidative stress and hypoxia-related inflammation resulting from cyclic ischemia-reperfusion injury are thought to play important and critical roles in BOO progression and the associated bladder dysfunctions, including DU [12,39].

Reactive oxygen species (ROS) are by-products of aerobic metabolism and can induce pathologic conditions by damaging lipids, proteins, and DNA [40]. In addition, ROS serve as signaling molecules to regulate biological and physiological processes [41]. However, excessive production of ROS can cause oxidative stress that may damage cellular lipids, proteins, and DNA, thereby changing the structure and function of target tissue [42-44]. Oxidative stress is regulated by the balance between pro-oxidative and anti-oxidative factors, and endogenous anti-oxidants act as scavengers under physiologic conditions. Cyclic ischemia-and-reperfusion injury in BOO generates ROS, that induce the elevation of oxidative stress and play important roles in bladder dysfunctions [19,45]. Numerous oxidative stress biomarkers are reported [46,47], and some are used to evaluate the degree of oxidative stress in BOO, including 8-hydroxy-2-deoxyguanosine (8-OHdG), F2-isoprostane, and malondialdehyde [39]. Various endogenous anti-oxidative defense systems protect against harmful activities caused by oxidative stress, and total antioxidant capacity reflect the cumulative effect of all antioxidants [39,48]. At present, the evidence from many animal studies discloses the application of oxidative stress and antioxidant biomarkers in BOO [39], and these targets might also become the potential biomarkers in human BOO related DU.

Eight-OHdG, a stable end product of DNA oxidation, is the mostly used oxidative marker, and the levels are not influenced by a long-term storage of urine specimen at −20°C [47,49]. In an animal study with rabbits, the levels of 8-OHdG in urine, plasma, and tissue were all increased under partial BOO, and all of them returned toward the control levels after the reversal of obstruction [30]. In addition, plasma total antioxidant capacity levels decreased under partial BOO and returned toward control levels after the reversal of obstruction. The results suggested that the imbalance of increased oxidative stress and decreased antioxidant capacity of the plasma and urine was detected in BOO, and it was reversible if early reversal happens. However, there was scarce evidence of 8-OHdG in human BOO subjects, which merely demonstrated the reverse of urinary levels of 8-OHdG after medical treatment [29].

F2-isoprostane, formed by free radical-induced peroxidation of arachidonic acid, is also a reliable indicator of oxidative stress [47,50]. F2-isoprostatne is chemically stable compounds, sensitive, not affected by dietary intake of lipids, and detectable in all normal biological fluids, and tissue. In the animal study with mice, the levels of F2-isoprostanes significantly elevated in bladder tissue after partial BOO, which suggested the usefulness of F2-isoprostanes as an oxidative stress biomarker of BOO [31].

ROS is required for the release of pro-inflammatory cytokines (IL-1β, TNFα, IL-6, IL-8, interferon beta) to affect an appropriate immune response [40]. In an BOO rat model, bladder weight, the levels of oxidative stress biomarkers in urine (8-OHdG), and the levels of proinflammatory cytokine (IL-1β, and TNFα) in tissue all increased in BOO and these changes were suppressed after Eviprostat treatment [51]. It suggested that oxidative stress and the related pro-inflammatory cytokines were responsible for BOO, and antioxidant and anti-inflammatory activities (from Eviprostat) might contribute to the protection of bladder function. In a rat model of atherosclerosis-induced chronic bladder ischemia, bladder oxidative stress biomarkers (8-OHdG in urine, and malondialdehyde in bladder tissue) and proinflammatory cytokines (TNFα, IL-6, and IL-8) were significantly higher in study group [52]. It indicated that oxidative stress and inflammation might be the key factors in the development of bladder dysfunction in chronic bladder ischemia.

Tissue hypoxia plays the critical role in the disease progression of BOO, and is essential to the pathophysiology of BOO related DU. Oxidative stress biomarkers including 8-OHdG, F2-isoprostane, and the involved pro-inflammatory cytokines have the potential of clinical application in BOO-related DU.

Conclusions

BOO is one of the important known etiologies of DU. Chronic urinary bladder ischemia and repeated cycles of ischemia and reperfusion injury cause excessive oxidative stress, and it is thought to be responsible for the development of DU. PGE2, neurotrophins, inflammatory cytokines, and oxidative stress biomarkers are the potential urine biomarkers in BOO-related DU.

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Conflicts of interest

Dr. Yuan-Hong Jiang, Dr. Yung-Hsiang Hsu, Dr. Han-Chen Ho, and Dr. Hann-Chorng Kuo are editoiral board members at *Tzu Chi Medical Journal*, had no roles in the peer review process of or decision to publish this article. The other author declared no conflict of interest in writing this paper.

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