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VOIDING DYSFUNCTION EVALUATION (B BRUCKER AND B PEYRONNET, SECTION EDITORS)

Molecular Characteristics of Underactive Bladder

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Abstract

Purpose of Review Underactive bladder (UAB) is a common urological problem in elderly patients presenting with urinary retention and lower urinary tract symptoms. UAB causes chronic urinary retention or a large post-void residual urine which is usually difficult to manage. Treatment of UAB is a challenge to urologists. The underlying pathophysiology has not been completely elucidated. Molecular diagnosis for the clinical characteristics of UAB is important for us to understand the pathogenesis and develop new therapeutic modalities.

Recent Findings The urodynamic finding of UAB might be detrusor acontractility of low contractility and is often termed detrusor underactivity. UAB is frequently encountered in elderly patients with chronic medical or neurological diseases. The pathophysiology of UAB may involve neurogenic, myogenic, and bladder outlet pathologies. Recent studies also reveal that increased suburothelial inflammation and altered sensory protein expressions in bladder mucosa were prominent in patients with UAB. Impaired urothelial signaling and sensory transduction pathways might be associated with impaired bladder sensation as well as impaired detrusor contractility. In addition, the bladder outlet obstruction, inflammation, or bladder ischemia-induced oxidative stress might also decrease the energy of the detrusor and result in UAB. Neurogenic inhibition, myogenic factor, and psychogenic inhibition might also be the causes for UAB.

Summary This article reviews recent researches on the pathophysiology and molecular characteristics of UAB. Neurogenic, myogenic, urotheliogenic, bladder outlet, and psychogenic factors might all contribute to UAB. Comprehensive clinical investigations and basic researches may provide a better understanding and effective treatment for this common but difficult bladder disorder.

Keywords Detrusor underactivity · Urinary retention · Neurogenic bladder · Diagnosis · Treatment

Introduction: Definition of Underactive Bladder and Detrusor Underactivity

Detrusor underactivity (DU), a urodynamic diagnosis, is a gradually emphasized issue and has been defined by International Continence Society, as "a contraction of reduced strength and/ or duration, resulting in prolonged bladder emptying and/ or a failure to achieve bladder emptying within a normal time span" [1]. Underactive bladder (UAB) is a symptom complex suggestive of DU and is recently redefined as slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms [2•]. UAB is a clinical diagnosis by symptoms and is not always associated with the urodynamic status of DU. Vice versa, not all DU patients may experience UAB symptoms [3]. Patients with UAB usually have a diminished sensation of bladder fullness or urgency and cannot contract the detrusor sufficiently to complete bladder emptying. DU is a urodynamic term, and UAB is its clinical correlate.

In general, the main urodynamic finding of UAB is DU with impaired detrusor contractility causing bladder emptying symptoms, although the related parameters in urodynamics are not clearly defined. Urodynamic study of UAB may be characterized by a non-contractile detrusor, low pressure, or poorly sustained detrusor contraction in association with a poor flow rate with or without a large post-void residual (PVR) volume [4]. Patients with UAB usually void with abdominal straining and an intermittent flow pattern is noted. The bladder sensation may be normal or reduced in sensing a first sensation or urge sensation [5]. Some patients with

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UAB may have both detrusor hyperactivity and inadequate contractility (DHIC), resulting in urgency incontinence and a large PVR [6]. In patients with UAB, the intrinsic detrusor contraction speed is more compromised than intrinsic strength [7]. These urodynamic findings are also found in women with idiopathic UAB [8]. The underlying pathophysiology for each group might be different and can be attributed to varying detrusor muscle contractility and bladder outlet resistance in individual patients.

Clinical Etiologies of UAB/DU

Both UAB and DU are complex, multifactorial, and under-researched condition in epidemiology, diagnosis, and treatment [3, 9•, 10••]. Several clinical causes of UAB/DU have been reported, including aging [5], bladder outlet obstruction (BOO) [11••], diabetes mellitus (DM) [12], central nervous system (CNS) disorders (e.g., spinal cord injury (SCI), multiple sclerosis, cerebrovascular accident (CVA), traumatic brain injury, Parkinson's disease) [13], and peripheral nervous system disorders (pelvic nerve injury, e.g., pelvic surgery, pelvic fracture, spinal stenosis, and herpes zoster) [14, 15]. DU is intuitively and easily linked to the underlying mechanism of detrusor/ myogenic failure; however, it is not exactly correct. The pathophysiology and/or bladder changes in most clinical causes of DU includes not only myogenic failure and efferent nervous dysfunction but also afferent nervous dysfunction, whose role as a potential contributory factor in DU is increasingly recognized [16].

The pathophysiology of chronic urinary retention may involve neurogenic, myogenic, and bladder outlet pathologies [17]. Recent studies have also revealed that urothelial dysfunction of the urinary bladder may be associated with impaired bladder sensation as well as impaired detrusor contractility [18]. Furthermore, urethral mucosal dysfunction and smooth muscle hyperactivity of the bladder neck and the urethra might also play important roles in the inhibition of micturition. More research is needed into the unexplored pathophysiology of DU and UAB.

Prevalence of UAB

UAB is a common urological problem in elderly patients presenting with urinary retention and lower urinary tract symptoms (LUTS). DU has been found in nearly two-thirds of incontinent institutionalized elderly people [19]. The incidence and prevalence of UAB are highly dependent on the definition and the availability of diagnostic tests. In a retrospective study, 40.2% of men and 13.3% of women undergoing a urodynamic study for LUTS were classified as having DU [20]. In the urodynamic evaluation of patients with non-neurogenic LUTS, DU was found in 9–48% of men and 12–45% of older women [10••]. A urodynamic pressure flow study revealed 41% of elderly men with symptoms of difficult bladder emptying had an obstructive high-pressure low flow pattern, 28.2% had an underactive detrusor contractility pattern, 20.5% had a mixed obstructive and underactive detrusor type, whereas 10.3% had a normal pattern [21]. The prevalence of BOO voiding difficulty and DU in female urology patients who visited several urology clinics in nine hospitals was 87.2% and 12.8%, respectively [13]. Gotoh et al. found impaired detrusor contraction in 81.9% and BOO in 14.8% of women with impaired bladder emptying [22].

UAB usually occurs in patients with SCI (central neuropathy) or post-pelvic surgery (peripheral neuropathy). Sakakibara et al. found the underlying diseases of women with urinary retention included multiple system atrophy, multiple sclerosis, cervical/thoracic tumors, and lumbar spondylosis [23]. UAB is also common in older patients, in those with general weakness and medical diseases such as DM, debilitating disease, and cancer in the terminal stages, and after major surgery [24]. Aging and urinary tract infection (UTI) are two independent factors contributing to impaired voiding function and DM bladder dysfunction [25]. A large proportion of patients with diabetic cystopathy were found to have electrophysiologic evidence of neuropathy, which could moderately predict the presence of cystopathy [26]. Patients with DU showed impaired emptying function, decreased sensation on cystometry and intravesical current perception threshold testing [27].

UAB and DHIC were also common (15% and 1%, respectively) in patients with recently ischemic stroke [28]. In one study, UAB was observed in 41% of patients presenting with urinary incontinence or LUTS following radical prostatectomy [14]. UAB may be chronic or temporary. In clinical practice, we have observed patients with BOO and normal detrusor contractility who developed transient UAB after transurethral resection of the prostate or immediately after a minor stroke. These patients may regain spontaneous voiding within 1 to 3 months [29•]. There must have some underlying pathogenesis for the development of transient UAB, such as detrusor muscle failure or neurological inhibition, which interferes with the integration of musculo-mucosal mechanoreceptors, mucosal mechanoreceptors and chemoreceptors [30]. In a recent investigation of video urodynamic characteristics in 1329 men with LUTS refractory to conventional treatment, DU was noted in 165 (12.4%), poor relaxation of external sphincter in 525 (39.5%) and BOO in 501 (37.7%). The bladder sensation of filling and fullness in patients with DU were significantly reduced compared with that in patients with BOO [31•]. The incidence of DU in 1333 female patients with LUTS was 11.4% and DHIC was noted in 4.3%. The medical comorbidity in 118 women presenting with chronic urinary retention or a large PVR included DM (43, 30.7%), hypertension (52, 37.1%), coronary arterial disease (17, 12.1%),

chronic obstructive pulmonary disease (3, 2.1%), and chronic kidney disease (25, 17.9%) [32].

Pathophysiology of UAB

UAB may result from different etiologies such as neurogenic lesion, myogenic failure, bladder outlet obstruction, or psychological inhibition. These factors contribute alone or in combination to attribute to the pathogenesis of UAB [33]. The clinical causes of UAB include aging, BOO, DM, neurological disorders, spinal cord lesions, pelvic plexus injury, and infectious neurogenic diseases [15]. The lesion causing UAB could be a damage to bladder afferent pathways, efferent pathways, lumbosacral cord, or detrusor myogenic failure [34]. There is a need for longitudinal investigating patient characteristics of UAB and to search for risk factors, develop screening tools, as well as to establish an animal model for translational research [35].

In addition to the overt neuropathy such as SCI, CVA, Parkinson's disease, UAB in patients with chronic urinary retention may be caused by latent neuropathy [10••, 36]. DU patients had a high percentage of neurological deficits in electrophysiologic studies. Re-innervation and reduced recruitment of the external urethral sphincter indicated that the lower urinary tract experienced an incomplete or inadequate recovery from potential neurological insults. Decreased amplitude in pudendal nerve conduction velocity also suggested the presence of internal pudendal neuropathy.

The disease spectrum of diabetic cystopathy, also known as diabetic bladder dysfunction, ranges from sensory dysfunctions to impaired bladder emptying, even DU [13]. Its pathophysiology is also thought to be multifactorial, including urothelial dysfunction, neuronal impairment, changes in detrusor physiology and structure, and systemic inflammation [37]. Diabetic cystopathy can occur silently in the early or late course of DM. DM induces a decrease in detrusor contractility and increases oxidative stress factors, resulting in urothelial dysfunction or causing alteration of the pathophysiology of detrusor muscle cells, resulting in impaired bladder sensation or impaired detrusor contractility [38].

In BOO, the bladder undergoes morphologic and physiologic changes of the urothelium, suburothelium, and detrusor muscle [39]. Chronic bladder ischemia and repeated ischemia/reperfusion cycles causing excessive oxidative stress is responsible for the development of DU [40]. In DU caused by BOO, afferent nervous dysfunction with urothelial dysfunction and altered expressions of sensory proteins [11••], increased inflammation, and denervation of the detrusor muscle [14] are possible mechanisms leading to impaired bladder emptying. Detrusor contractility may be reduced in patients with chronic urinary retention or a large PVR due to benign prostatic hyperplasia (BPH) with BOO [41]. However, it is difficult to differentiate idiopathic UAB from chronic urinary retention secondary to BOO. Patients with chronic BOO might also have low detrusor pressure and a large PVR.

In adult male patients with LUTS, detrusor contraction power parameters, the bladder contractility index and the maximum work (W_{max}) continuously increase with an increasing grade of BOO [42]. The ultrastructural changes seen on electromicroscopic examination of detrusor biopsies from DU bladders revealed approximately four times more disruptive cells than in controls, which might interrupt the electrical transmission between muscle cells and result in low detrusor contractility on stimulation [43]. Whether UAB is a progressive change from DHIC remains unknown, but the impairment of detrusor contractility with and without altered bladder sensation might be the causes of UAB and DHIC in aging patients, respectively [3, 44].

Normal afferent nerves convey the bladder sensations of filling, urgency, and nociception via C-fibers within the urothelium and suburothelium or A-delta fibers within the detrusor muscles. The sensory activation of the micturition reflex is essential for normal detrusor contractility on stimulation [6]. In patients with acute or chronic sensory afferent nerve lesions (such as herpes zoster infection or syphilis-induced tabes dorsalis), detrusor contractility is greatly impaired and urinary retention may ensue.

The inhibitory effects of detrusor contraction by the striated urethral sphincter and the bladder neck smooth muscle via alpha-adrenergic activity may also play a role in the development of UAB. Furthermore, normal perception of bladder fullness and an urge sensation are the fundamental basis for a normal micturition process. Patients with severe cortical degenerative disease may lack of bladder perception and be unable to initiate voiding. Aging can cause structural and functional changes in the bladder afferent nerves and detrusor power, and reflex activity might also be impaired [5]. In addition, chronic BOO, and latent cortical degeneration might also occur in elderly patients, especially when they experience severe illness or major surgery, which might result in UAB.

Molecular Characteristics of UAB

It is possible that bladder urothelial dysfunction, sensory nerve dysfunction, and detrusor myogenic dysfunction, as well as impaired CNS control, are involved, in part or totally, in the development of UAB. Understanding the pathophysiology of UAB in individual patients is the mainstay of appropriate management. Any pathophysiology for UAB must have underlying molecular characteristics, and investigating these molecular abnormalities provides therapeutic targets for correction of UAB and resumption of spontaneous urination. Different clinical causes and factors of UAB may produce

different profiles in the molecular characterization of the bladder.

The urothelium is not only a barrier to urine solutes but also expresses various receptors and ion channels which are responsible for mechanical or thermal changes in the bladder, such as receptors to bradykinin, trkA, p75, purine (P2X and P2Y), noradrenaline (alpha, beta adrenaline), and acetylcholine (muscarinic or nicotinic) [45–53]. The urothelium also expresses several vanilloid receptors, called transient receptor potential channels (TRPV1, TRPV 2, TRPV4, TRPM8, TRPA1), suggesting urothelial cells also exert a sensory function in bladder filling and noxious stimuli [54–58]. Stimulation of these sensory receptors by mechanical trauma, hydrostatic pressure changes, and chronic inflammation can release chemicals such as adenosine triphosphate (ATP), prostaglandins (PGs), nerve growth factors (NGF), acetylcholine (Ach), and nitric oxide (NO) which may have excitatory or inhibitory effects on the afferent nerves or detrusor contractility [59–63].

The urothelium might influence the contractile state of detrusor smooth muscles, both through modifying its contractility and the extent of spontaneous activity [18]. In one study, the ratio of ATP/NO, representing sensory transmission in the bladder, was high in a bladder model of OAB and low in a bladder model of UAB. ATP release had a positive correlation while NO release had a negative correlation with the bladder contraction frequency. The urinary ATP/NO ratio may be a clinically relevant biomarker which characterizes the extent of bladder dysfunction [63]. In the urothelium of men with DU and BPH, Cho et al. found that the mean level of endothelial NO was not changed, but ATP in the DU men was significantly lower than in the no DU group, and, in all patients, ATP positively correlated with the bladder contractility index and with detrusor pressure on maximal flow rate, suggesting ATP is closely associated with detrusor function [64••].

Aging and UAB

Aging can affect detrusor contractility in men and women [65]. In the aging bladder, afferent nervous dysfunction, efferent nervous dysfunction, and detrusor failure/dysfunction are the observed changes in DU, and all may contribute to its development [3]. Not only the failure of activity but also the inability of activation are the causes of aging-related DU.

In a study of women with age, postmenopausal age significantly affects detrusor force value [66]. However, age-related changes in voiding function might not be a result of impaired detrusor contractility or increased outflow obstruction, and intrinsic causes must be suspected [67]. Aged mice demonstrated voiding and storage dysfunctions resembling to DHIC, which were more pronounced in males. The decrease of mRNA expressions of M3 muscarinic receptors in aged males and β2-adrenoceptors in aged females were found [68•].

In addition, bladder ischemia and repeated ischemia/reperfusion during a micturition cycle may also produce oxidative stress, leading to denervation and further tissue damage in the bladder wall [40]. This ischemic effect on the bladder wall might be the cause of transient urinary retention in patients after major surgery or acute illness. In a rat model of iliac artery atherosclerosis and bladder ischemia, prolonged ischemia mediates the progression of OAB to dysfunctional patterns similar to DU [69]. Downregulation of M3 and upregulation of M1 were also detected at 16-week ischemia. Neural structural damage and marked neurodegeneration were found after 8 and 16 weeks of ischemia. In the elderly with systemic atherosclerosis and BOO, chronic bladder ischemia might result in a progressive change of detrusor contractility through these pathophysiology [40].

Testosterone level declines with aging in men. Reduced androgen levels may directly contribute to LUTS and bladder dysfunction. In a rat model study, intraluminal acetylcholine (Ach) release following bladder distension was significantly reduced following castration, while ATP release was unaffected. In contrast, stretch-induced ATP release from urothelial cells was significantly enhanced in low testosterone conditions, while ACh release was unaltered. Testosterone replacement to physiological levels prevented these changes, suggesting androgen deficiency may alter bladder function in men [70].

Myogenic Failure and Detrusor Hypocontractility in UAB

Human detrusor smooth muscle fibers are arranged longitudinal-circular-longitudinal (or oblique) from innermost to outermost layers within integral contraction during voiding phase to emptying bladder efficiently. Impairment in the integral contraction of detrusor smooth muscle can lead to DU. Aging is one of the major causes of myogenic failure. In human elderly subjects, decreased axonal content of the detrusor smooth muscle [71], and increased collagen deposition [72] are the main aging-related morphologic changes of the bladder. In human aging-related patients with impaired contractility, widespread degeneration of muscle cells and axons, superimposed on the dense band pattern, is demonstrated as the main structural change. [73] A selective age-related decrease in mRNA for M3, but not M2 muscarinic receptor in human detrusor is reported, and it may diminish the potential sensitivity of micromotion activity to cholinergic neurotransmitters corresponding with the decreased detrusor contractility with aging. [74] Similarly, in aged rats with weak contractile responses to carbachol and electrical stimulation, lower M3 muscarinic receptor mRNA expression and higher collagen deposition are observed and considered as the key factors for UAB [75].

Recent studies revealed that interstitial cells (ICs) are widely distributed in the genitourinary system and that they may be involved in spontaneous muscle activity. ICs act as electrical pacemaker for organ contractions and modulate smooth muscle activity in the urinary bladder. Hyperexcitation of ICs may induce detrusor overactivity, on the contrary, a decrease of IC numbers or activity might result in UAB [76]. The human bladder contains a network of KIT-positive interstitial cells of Cajal (ICC) in the lamina propria, which make frequent connections with a cholinergic nerve plexus. Detrusor ICCs are spindle-shaped, branched cells tracking the smooth muscle bundles, closely associated with smooth muscle cells and vesicular acetylcholine transferase nerves. These KIT-positive detrusor ICCs are believed to control bladder contractility [77]. Currently, there is no evidence that dysfunction of ICCs in human bladder wall is associated with the development of UAB; however, reduction of ICC in patients with DU has been noted.

Efferent Nervous Dysfunction and UAB

Normal voluntary control of lower urinary tract requires the complex interactions between autonomic (sympathetic and parasympathetic) and somatic efferent pathways [78]. Peripheral denervation may cause bladder efferent nervous dysfunction. Autonomic neuropathy in DM [79], cyclic ischemia and reperfusion injury with oxidative stress in BOO [79], and chronic bladder ischemia caused by arterial occlusive disease [69, 80] have been reported to factor in the pathophysiology of peripheral denervation of the urinary bladder and consequent DU.

Detrusor contraction is predominantly controlled by parasympathetic fibers releasing Ach and ATP. The smooth muscles also develop spontaneous contractions that determine the tone of the musculature. The cellular signaling pathways evoke contraction due to neurotransmitter release; there could be an interaction between smooth muscle and ICCs, which might play a role in regulating muscle contractility [81]. Sympathetic innervation inhibits detrusor contractions during bladder storage phase, and low doses of adrenergic agonists are capable of relaxing the bladder smooth muscle. β-3 adrenoceptor (AR) agonist has been widely used to treat OAB and highlights the potential role of sympathetic activity on UAB [82]. Using antibodies to tyrosine hydroxylase (TH) and vesicular monoamine transporter (vmat), TH, and vmat nerves are abundant surrounding blood vessels [83]. A population of vmat-immunoreactive (IR) cells was found within the network of ICs that surround the detrusor muscle bundles. Double staining with antibodies to β_1AR and vmat suggests that the majority of vmat-IR ICs shows β_1AR-IR indicative of an autocrine signaling system. There might exist a non-neuronal β-adrenergic system operating in the bladder wall possibly linked to one component of motor activity, microcontractions, and bladder sensation.

We also found that a higher expression of β-3 adrenoreceptor detected in patients with chronic urinary retention and DU [84••]. Since the activation of β-3 adrenoreceptors in the urothelium and suburothelium facilitates bladder storage through the inhibitory action of bladder afferent signaling, higher β-3 adrenoreceptor expression could account for the clinical presentation of hyposensitivity during urine storage in patients with DU [85].

In addition, the gap junction protein connexin 43 (Cx43) is also important in the transportation of normal electrical signals during detrusor contraction. An animal study had shown that immunostaining for smooth muscle Cx43, and its protein level were decreased by 28% compared with young rats. Age-related DU might be caused by the downregulation of gap junctional intercellular communication in the bladder [86]. Interstitial cells are the major site for the gap junction protein connexin 43 (Cx43) and allow propagation of electrical and calcium signals across a functional syncytium [87]. Currently, ICCs are believed to transmit signals from the urothelium to detrusor. Impaired function of ICCs might cause impaired detrusor contractility through impaired bladder urothelial sensory input. The number of ICCs and the density of Cx43 were found to increase in OAB [88]. Whether the density of Cx43 is decreased in the bladders of patients with UAB has not been elucidated. The density of ICCs in UAB bladders has also not been reported.

Afferent Nervous Dysfunction and Bladder Sensation and DU

Urothelium-afferent nerve interactions can influence and activate reflex bladder contractions [89]. In urinary bladder, urothelium is not only a barrier but also a sensor and transducer of the sensory signaling. [90] In DU human subjects, urothelial dysfunction with lower expression of E-cadherin and increased suburothelial inflammation are recently reported [83]. In addition, altered sensory protein expressions in bladder mucosa including lower expressions of both M2 and M3 muscarinic receptors, P2X3 purinergic receptors, and endothelial nitric oxide synthase, but a higher expression of β-3 adrenoreceptor are detected. The observed urothelial dysfunction and downregulated sensory protein expressions indicates that impaired urothelial signaling and sensory transduction pathways might advance the development of DU.

BOO is also a common cause of DU [11••]. In the study investigating the bladder mucosa of BOO patients, DU subgroup had higher expression of β-3 adrenoreceptors and lower expression of inducible nitric oxide synthase than in controls [11••]. In addition, DU subgroup in BOO had more severe urothelial dysfunction (lower E-cadherin expression) than detrusor overactivity subgroup. It suggested that DU in

BOO might be a more severe or decompensated status and support the hypothesis of detrusor overactivity progression to DU in BOO.

In mice model, aging is associated with a weakened ability to respond to the continuous bladder filling with cyclic voiding [91]. Aging bladder is associated with degenerative axonal changes [73] and impaired afferent outflow relative to bladder volume causing degradation of bladder sensations and then UAB [3]. In the study of aged rats, the densities of innervation by fibers immunoreactive for the neuropeptides including pituitary adenylate cyclase-activating polypeptide, calcitonin gene-related peptide, and substance P were reduced in urinary bladder [92]. It also supported that afferent limb of voiding reflexes might be perturbed in the aging bladder. The roles of peripheral and/or central sensory mechanism are highlighted and contribute to aging-related bladder dysfunction.

Urodynamic study in neurologically normal patients revealed diminished central sensitivity to volume afferent activity contributes to DU in non-obstructed, non-neurogenic symptomatic patients [93]. In comparison, the bladder sensation of urodynamic study among patients with DU, DHIC, hypersensitive bladder and DO, bladder contractility index, and voiding efficiency were significantly lower in DU and DHIC groups and higher in hypersensitive bladder and DO groups than normal tracing group. Reduced bladder sensation was noted in DU and negatively associated with detrusor contractility [94].

Previous studies have demonstrated age-related changes in detrusor function and urothelial transmitter release. In aged mice, increased voiding frequency and enhanced low threshold afferent nerve activity were observed, altered ATP and acetylcholine bioavailability, increased purinergic receptor sensitivity, and raised P2X3 receptor expression in the urothelium, suggesting that aging results in aberrant urothelial function, increased afferent mechanosensitivity, increased smooth muscle contractility, and changes in gene and protein expression (including P2X3) [95].

A recent study suggests TRPV4 senses bladder urothelial cultured cell stretching, which is converted to ATP signals in the micturition reflex pathway during the storage phase [96]. Downregulation of TRPV4 might lead to a decreased sensation of bladder fullness and DU. Recent research also revealed that intravesical activation of TRPV4 improves bladder dysfunction after bilateral pelvic nerve injury in rats by increasing afferent signaling, suggesting TRPV4 can be targeted to improve bladder function in animals that have an iatrogenic injury to the nerves innervating the bladder [97•].

UAB and OAB seem to be completely contrary terminology. The pathophysiology of OAB involves both motor and sensory bladder pathways, upregulation of bladder afferent signaling through the purinergic, muscarinic, and vanilloid receptors pathways have been reported [63, 98, 99]. In contrast, the afferent pathways in DU might be deficient either in peripheral or central sensory innervation or signal processing [16, 63]. An intact bladder afferent mechanism is important in the activation of the micturition reflex. Increase or decrease of the sensory signaling might result in OAB and UAB, respectively.

Our previous study has demonstrated that urothelial dysfunction, suburothelial inflammation, and urothelial cell apoptosis are increased, and urothelial sensory protein expressions are decreased in DU bladders. These phenomena might be responsible for the pathophysiology of DU [84••]. Impaired bladder afferent transmission with subsequent impaired detrusor contraction might be an important cause for the development of DU, and the altered afferent pathways might involve both the urothelium and the suburothelium [5, 100].

Urothelial Dysfunction in UAB

An intact bladder mucosa has been associated with an increase in spontaneous contractile activity in whole bladder preparations [101]. The urothelium exerts an excitatory effect on the underlying muscle while suburothelial tissue causes an inhibitory effect. It was proposed that mucosal M3 receptors induce the release of a contractile agonist or suppress the release of an agent which inhibits detrusor contractility [102]. A group of ICCs which have a contractile phenotype and contain smooth muscle actin has been found between the bladder mucosa and detrusor [103].

We have investigated urothelial dysfunction in patients with DU and healthy controls. In patients with DU, junction protein E-cadherin was significantly lower, and suburothelial inflammation determined by the mast cell count and urothelial cell apoptosis were significantly higher than in controls. However, there was no significant difference in barrier protein zonula occludens-1 expression between DU and controls. These results indicate that chronic inflammation and urothelial dysfunction are present in DU bladders. These immunohistochemistry findings can only explain that urothelial dysfunction is evident in patients with DU. We need further molecular studies of functional receptors such as TRPV4 and P2X3 to explore the possible pathomechanisms of UAB. TRPV4 is a nonselective cation channel involved in different sensory functions and was recently implicated in bladder mechanosensation. Immunoprecipitation experiments established a molecular connection of TRPV4 to the adherence junctions of the bladder mucosa [104]. The lower expression of E-cadherin may be associated with decreased bladder sensation during mucosal stretching.

Urothelium-afferent nerve interactions can influence reflex bladder contractions [88]. The activation of β-3 adrenoreceptors in the urothelium and suburothelium facilitates bladder storage and increases bladder capacity through the inhibitory action of bladder afferent signaling

[85]. In our recent study investigating patients with BOO, the DU subgroup had significantly higher expression of β-3 adrenoreceptors and lower expression of iNOS than controls did [11••]. In another study, patients with DU had lower expressions of M2 and M3 muscarinic receptors, P2X3 receptors, and eNOS in addition to a non-significantly lower expression of iNOS and a higher expression of β-3 adrenoreceptor than in controls [84••]. These results highlight the function of decreased bladder urothelial-afferent signaling (affected by lower muscarinic and purinergic receptor expressions and higher β-3 adrenoreceptor expression) in the pathophysiology of DU. Additionally, these signal changes could account for the clinical presentation of hyposensitivity during urine storage in patients with DU. The positive correlation between the expressions of M2 muscarinic receptors and P2X3 receptors further supports the close interaction of bladder afferent signaling in bladders with DU.

A new hypothesis that chronic untreated or treatment refractory OAB may progress to DHIC and finally UAB through the repeated cycles of ischemia and reperfusion injury has been proposed [40, 100]. Urothelial dysfunction (decreased E-cadherin expression) and increased suburothelial inflammation and apoptosis were observed not only in patients with OAB [104] but also in the patients with DU [84••]. The expressions of eNOS and iNOS increased in a bladder inflammation/cystitis rat model, suggesting their roles in inflammation [105, 106]. However, patients with DU and chronic urinary retention had lower expressions of eNOS and iNOS, suggesting DU represents a late phase of inflammatory consequence.

Diabetic cystopathy may also cause DU [15]. Chronic DM can cause urothelial dysfunction, neurotransmission deficiency, and detrusor myopathy, and finally result in DU [107]. In the early stage of diabetic cystopathy in rats, increased density of M3 muscarinic receptors is thought to alter the afferent function and causes DO [37, 108••]. In our study, more severe suburothelial inflammation and greater expression of M3 muscarinic receptors were noted in diabetic patients with DU, compared with non-diabetic DU patients [108••]. These findings suggest the effect of DM on bladder function might mainly from sensory nerve alteration. The exact pathogenesis of diabetic cystopathy needs time-sequential evaluation of the urothelial dysfunction and sensory protein expressions.

Potential Urinary Biomarkers for Recoverability of UAB

Clinically, DU patients might regain spontaneous voiding after bladder resting, bladder outlet surgery such as transurethral resection of the prostate, or urethral sphincter botulinum toxin A injection within 1 to 3 months [29•]. Some unknown underlying pathogenesis for transient DU might interfere the integration of musculo-mucosal mechanoreceptors, mucosal mechanoreceptors, and chemoreceptors [15, 30]. Previous studies have shown that urinary NGF, BDNF, and PGE2 levels are increased in OAB patients. These urinary proteins might serve as prognostic biomarkers of the prognostic biomarkers for treatment outcome [109–111]. Our recent study has revealed that baseline urinary PGE2, and BDNF levels, but not NGF level, were significantly higher in DU patients who had recovery of bladder contractility after treatment, but these urinary proteins remained in low levels in patients without bladder function recovery [108••].

NGF is the fundamental protein for development and maintenance of the sympathetic and sensory nervous systems. In several disease status, NGF secretion increases, which help stimulate division, regeneration, and differentiation of the sympathetic and sensory neurons [112]. Therefore, the increased secretion of urinary NGF level is not only observed in DO but also in DHIC or DU, in which nerve regeneration is needed [113–115]. In OAB and urodynamic DO, the levels of urinary NGF and BDNF have been found to elevate [116, 117]. Increased level of urinary BDNF in DU patients with bladder function recovery suggests a process of nerve regeneration is undergoing.

Patients with DU and bladder function recovery had significantly higher urinary PGE2 level than patients without recovery and DO, suggesting the factors contributing to detrusor contractility are not completely lost in these bladders. The highly secreted PGE2 in DU bladders might reflect a compensatory response to certain bladder pathological conditions causing temporary low detrusor contractility. Through the increase of PGE2 secretion from the urothelium or detrusor patients with DU may regain detrusor contractility gradually. In addition, ATP release had a positive correlation while NO release had a negative correlation with the bladder contraction frequency. The urinary ATP/NO ratio may be a clinically relevant biomarker which characterizes the extent of bladder dysfunction [118].

Like OAB, UAB is also a dynamic bladder condition that symptoms may change with time. The bladder function of UAB has a great variety, ranging from acontractile with chronic urinary retention to impaired contractility with low voiding efficiency. The underlying pathophysiology for different grade of UAB might be attributable to different kind or combination of underlying pathophysiology, such as urothelial dysfunction, neuropathy, detrusor myopathy, and bladder outlet resistance in individual patient. Each pathophysiology might have its own characteristic molecule biomarkers in urine. Therefore, it might be possible if we can combine a group of urinary proteins and define the different underlying etiologies in patients with UAB, the results might provide prognostic treatment outcome of DU [119].

Conclusions

UAB is a common urological problem in elderly patients presenting with urinary retention and lower urinary tract symptoms. Patients with UAB usually void incompletely with abdominal straining and have considerable post-void residual urine. The bladder sensation may be normal or reduced in sensing a first sensation or urge sensation. The pathophysiology of UAB may involve urotheliogenic, neurogenic, myogenic, and bladder outlet pathologies. Aging, bladder ischemia, low testosterone level, chronic inflammation, increased oxidative stress, decreased M2, M3 muscarinic receptor density, increased urothelial beta-3 adrenoceptors, alteration of TRPV4 and P2X3 receptors, and defective ICCs and gap junction protein Cx43 have been investigated to contribute to UAB. The urinary ATP/NO ratio may be a clinically relevant biomarker which characterizes the extent of bladder dysfunction. In addition, using urine biomarkers to measure neuronal regeneration activity, such as BDNF and PGE2, might provide predictive value for a reversible UAB after treatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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