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REVIEW

Urinary Biomarkers of Detrusor Underactivity

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Abstract

Purpose of Review Detrusor underactivity (DU) is a urodynamic diagnosis, often related with the multifactorial symptom complex designated as underactive bladder (UAB), resulting in prolonged and/or incomplete bladder emptying, and many times with a high postvoid residual. DU is a largely under-researched topic and constitutes a multifactorial condition, with several underlying pathophysiological mechanisms, which can be categorized as idiopathic, neurogenic, myogenic, or functional. The main etiological factors of DU are aging, diabetes mellitus, neurogenic disorders, and bladder outlet obstruction (BOO). Biomarkers constitute objectively measurable characteristics that can be evaluated as indicators of physiological and pathogenic processes and might be used as diagnostic, prognostic, or predictive tools in clinical care. Herein, we review up-to-date knowledge of urinary biomarkers of DU.

Recent Findings Several urinary biomarkers, including neurotrophins (NGF and BDNF), markers of oxidative stress, prostaglandins, inflammatory cytokines, ATP/NO, and miRNA, have recently been studied in relation to DU, providing potential insights into the pathophysiology and possible therapeutic targets for this condition.

Summary In DU, biomarkers could allow for early DU diagnosis and monitoring, also granting a larger potential for therapies to halt or revert pathologic changes, such as afferent neurogenic dysfunction, neuroinflammation, denervation and fibrosis of detrusor muscle, and myogenic failure.

Keywords Detrusor underactivity · Underactive bladder · Urinary biomarkers

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Introduction

Detrusor underactivity (DU) is defined by the ICS as a urodynamic diagnosis, normally associated with relevant symptoms and signs, characterized by low detrusor pressure or short detrusor contraction in combination with a low urinary flow rate, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span. A high postvoid residual may also be present [1].

DU pathophysiology is still under research. Several comorbidities seem to contribute such as aging, diabetes mellitus, and bladder outlet obstruction as well as various pathologic pathways such as ischemia reperfusion injury or oxidative stress [2].

DU is reported to afflict 15–40% of patients with LUTS and its incidence increases through life [3]. These patients typically present with LUTS; nevertheless, no specific clinical sign has been reported. Therefore, ascertaining DU diagnosis or even suspecting may be difficult among other more common pathologies.

In face of this clinically challenging scenario, biomarkers could be the cornerstone in the evaluation of bladder function, pointing the physician towards a non-invasive diagnosis of DU, precluding the appearance of LUTS, irreversible bladder dysfunction, and consequent urinary retention.

Biomarkers are molecules that can be accurately measured to indicate a normal biological process, a pathological condition, or a response to a therapeutic intervention. Their goal is to describe the presence and severity of a pathological process or to act as a surrogate endpoint to measure therapeutic results [4].

Urinary biomarkers seem especially appealing in the case of bladder dysfunction such as DU, since urine is easily obtained in a non-invasive process. Furthermore, urine is in close contact with the urothelium which is a key player in bladder dysfunction and some molecules involved in pathologic processes could be eluted. Finally, DU is commonly diagnosed only after complaints of LUTS, which might be already late, and some pathologic changes may already be irreparable. Biomarkers could allow for earlier DU identification, granting a larger potential for therapies to revert pathologic changes. Nevertheless, very few urinary biomarkers have been studied so far, and even fewer have been tested in DU.

Therefore, our goal was to review and summarize recent evidence regarding urinary biomarkers of DU.

Neurotrophins (Nerve Growth Factor/ Brain-Derived Neurotrophic Factor)

Neurotrophins are a group of molecules involved in the proliferation and survival of different neuronal populations, such as the sympathetic and sensory neurons of the lower urinary tract. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are two neurotrophins secreted by the urothelium which have drawn attention and been increasingly studied in urinary dysfunction by their potential role in neuronal plasticity of circuits controlling micturition [5].

NGF was one of the first growth factors discovered earning Rita Levi-Montalcini and Stanley Cohen the Nobel Prize in 1956 [6]. This molecule, secreted by the urothelium, that regulates the subpopulation of peptidergic bladder sensory afferents, has been implicated in the pathophysiology of several conditions associated with bladder dysfunction. Antunes-Lopes et al. found persistently low urinary levels of NGF and BDNF in adults without LUTS. These levels did not show a circadian pattern of variation and remained constant at 3 months [7]. In contrast, idiopathic overactive bladder (OAB) patients appear to have higher tecidular and urinary NGF and BDNF levels, the same being true for patients with OAB secondary to neurologic lesions. Wang et al. and Antunes-Lopes et al. reported that urinary BDNF and NGF levels corrected for creatinine were elevated in OAB patients but not in controls. Moreover, they showed that patients with urgency urinary incontinence (UUI) tend to have higher urinary levels of neurotrophins than OAB dry patients [7, 8]. In the experimental model, NGF-directed antibodies injected in the spinal cord of mice with medullary lesions improved hyperactivity and even detrusor-sphincter dyssynergia [9, 10]. Furthermore, urinary levels of neurotrophins decreased following successful management of OAB [7].

Nirmal et al. accessed NGF levels in streptozotocin-induced diabetic rats with hyposensitive underactive bladder and found significantly elevated NGF urinary levels after the animals acquired UAB phenotype, compared to when they were healthy. Furthermore, this group also reported lower bladder tecidular NGF levels, sustaining the thesis that inflammation and apoptosis may lead to loss of NGF receptors in the bladder leading to higher NGF urinary expulsion, despite lower tissue levels [11••]. Reports have suggested that gene therapy with NGF in the bladder might recover bladder underactivity and that reactive oxygen species (ROS) scavengers might improve bladder function and raise NGF tissue levels, although urinary levels are not reported in these papers [9].

Chen et al. studied urinary NGF and BNDF levels in 106 patients with urodynamically proven DU, detrusor overactivity (DO), and detrusor hyperactivity with inadequate contractility (DHIC). They found urinary NGF and BDNF levels to be significantly higher in the DU and DHIC when compared to volunteers with normal urodynamic tracing. This study also compared urinary BDNF levels in patients with DU after surgical treatment of bladder outlet obstruction (BOO) with those without surgical treatment. The authors reported significantly higher urinary levels of BDNF in patients who recovered from bladder dysfunction compared to healthy controls. Meanwhile, when the same comparison was made for NGF, no significant differences were found [12••].

NGF and BDNF are therefore putative urinary markers of DU and might eventually signal which patients could benefit from BOO treatment. These findings might be explained by the necessity for nerve regeneration in these patients, activating molecular pathways that lead to the production of BDNF and NGF. Therefore, their levels could serve as surrogate markers of neuronal regeneration potential in each patient.

Nonetheless, their value might be hampered by their limited specificity as they are elevated in other bladder dysfunctions sharing common pathophysiologic grounds such as inflammation and oxidative stress.

Oxidative Stress/Reactive Oxygen Species (ROS)

ROS are pleiotropic signaling agents implicated in multiple pathologic processes as they contribute to molecular damage, termed oxidative stress. They are produced in ischemia and inflammation [13].

8-Hidroxi-2-deoxiguanosine (8-OHdG) is a product of DNA oxidation and is one of the most used oxidative stress markers. Lin et al. reported on 8-OHdG urinary levels in rats with BOO, showing lower levels of this compound after BOO treatment [14]. As BOO is one of the causes of underactive detrusor, ROS markers might also be helpful in DU. In fact, ICI-RS in 2019 stated that researching urinary markers of bladder oxidative stress would be a key milestone in understanding lower urinary tract dysfunction mechanisms and the contribution of oxidative stress and pelvic ischemia [15].

Powell and colleagues studied the development of DU in Ossabaw pigs with metabolic syndrome and found higher thiobarbituric acid reactive substances, a marker of oxidative stress, after DU phenotype development when compared with baseline assessment. DU development was also associated with increased fibrosis in histologic analysis and higher urinary IL-17 levels, which is a marker of fibrosis [16••].

Jiang et al. when analyzing multiple putative biomarkers of DU in urine samples found significantly higher 8-OHdG, 8-isoprostan (an oxidative stress marker) urinary levels in DU patients when compared with healthy controls, and significantly lower urine total antioxidant capacity. This group also reports a multivariate analysis confirming 8-OHdG as a urinary marker of DU [17].

More recently, some challenging lines of thinking are trying to establish a parallel between the pathophysiology of heart failure (HF) and DU. Oxidative stress in a known key player in HF and might therefore also play a fundamental role in DU. In respect to this theory, drugs with an antifibrotic and antioxidant effect such as SGLT2 inhibitors might have a therapeutic benefit in DU, although this is yet to be explored [18].

Prostaglandins

Prostaglandins are produced from arachidonic acid released from cellular membranes via COX 1 and 2 enzymes. These are central molecules in many signaling cascades controlling several key functions as inflammation, hormone secretion, or muscle contraction. There are several subtypes of prostaglandin, according to tissue and species in focus [19, 20]. Prostaglandins are implicated in bladder function and can be produced in the mucosa but also on the detrusor layer [21, 22]. Several papers have reported higher prostaglandin levels in DO, inflammation, and DO secondary to neurologic lesions [23, 24]. Prostaglandins have also been found to enhance detrusor contractions triggered by ATP or acetylcholine [25].

Kim et al. published a paper in 2005, reporting lower urinary prostaglandin E2 (PGE2) levels in OAB patients with DU when compared with those without DU [26]. Nirmal et al. supported these findings when studying rats with streptozotocin-induced hyposensitive underactive bladder, as they found lower urinary PGE2 levels after acquiring DU phenotype, when compared to baseline. This paper also reports an upregulation of tissue prostanoid receptors in the bladder, probably to optimize contractile function in the setting of lower PGE2 [11••]. Nevertheless, in the abovementioned study by Chen et al., contradictory results were reported as urinary PGE2 levels were found to be higher in DU when compared to normal controls. Furthermore, when analyzing DU patients who recovered bladder function after BOO treatment, PGE2 levels were significantly higher than in controls, but were similar to the latter in those who did not recover [12••]. A recent study by Jiang et al. also found significantly higher PGE2 urinary levels in DU patients when compared with healthy controls [17].

As a matter of fact, PGE2 appears to play a role in detrusor underactivity pathophysiology and may serve as a biomarker, possibly with the ability to predict recovery after BOO treatment. Nevertheless, further studies are needed to cement its role.

Inflammatory Cytokines

Inflammation seems to be one of the pathophysiologic pathways involved in bladder dysfunction. Several works have demonstrated a pro-inflammatory state in OAB [27].

In 2017, Jiang and Kuo published a paper describing urothelial dysfunction and increased suburothelial inflammation in DU, using immunohistochemical analysis of bladder biopsies [28]. This group recently published another paper on this issue focusing on the quantification of urinary inflammatory cytokines and found significantly elevated levels of TNF-α, IL-1β, IL-5, IL-6, IL8, IL10, IL17A, and CXCL 10 in DU patients when compared with controls [17].

Therefore, this might indicate inflammation as a common pathologic pathway for OAB and underactive bladder, eventually backing the theory that these two entities represent just different points on the same pathologic spectrum of bladder dysfunction.

ATP/NO

Bladder urothelium is an active structure with neuronal-like properties sensitive to stimuli which lead both to the activation of afferent pathways and to the release of neurotransmitters from the urothelium. Furthermore, detrusor contraction is a complex process for which some of these molecules contribute. ATP has been reported to be released from urothelial cells and by its action on purinergic receptor to contribute to detrusor contraction. It has also been implicated as a marker of several benign bladder pathologies. Urothelium appears to produce and release more ATP in cases of interstitial cystitis, overactive bladder, infection/inflammation, and BOO compensated phase. For example, Silva-Ramos et al. found higher urinary ATP levels in women with OAB with detrusor hyperactivity when compared with healthy controls. Furthermore, in this report, urinary ATP levels correlated inversely with mean voided volumes [29].

Nitric oxide (NO) is an inhibitory neurotransmitter also released from the urothelium, but results in detrusor relaxation and reduced frequency of contraction. NO levels have been reported to be decreased in DO [30]. Vale et al. submitted a group of female rats to partial BOO (pBOO) and another group to a sham procedure and measured urinary ATP, comparing those who developed DU with those that did not from each group. Their study reports that ATP levels were significantly lower in DU submitted to pBOO when compared with sham and non-DU submitted to pBOO rats [31••].

A study by Munoz and colleagues found lower ATP and higher NO levels in the urine of rats with DU. This group also reported on ATP/NO ratio, representing bladder sensory transmission finding higher ratios in DO rats and lower in DU [32••]. Krishnan et al. studied urinary ATP levels in patients with DU and found significantly lower levels when compared to healthy controls. This study also analyzed urinary NO levels, finding significantly higher levels in DU cases when compared to controls. They calculated NO/ATP ratio and concluded it has excellent discrimination between DU and healthy controls (area under the ROC curve 0.91) [33••].

Nevertheless, ATP has some disadvantages as a biomarker because its levels are altered by several pathologies, some with a considerable incidence such as infection/inflammation. Furthermore, as a marker of lower urinary tract pathology, it should not be produced anywhere else in the urinary tract. Nonetheless, studies have shown urothelium of the kidney and ureter also release ATP. However, when released from this topography, it has a quick half-life of about 3 min compared with 30 min when released from the bladder due to the action of ATPases. Therefore, although upper urinary tract may have some interference, urinary ATP levels are mainly dependent on lower urinary tract release [34].

miRNA

miRNAs are small non-coding RNAs, about 22 nucleotides in length, that play a crucial role in post-transcriptional gene regulation. They interact with the 3′ UTR of target mRNAs to suppress expression. MiRNAs are involved in various biological processes, including cell proliferation, differentiation, apoptosis, and metabolism.

As they have a central role in controlling biological processes, O'Brien et al. hypothesized that miRNAs might also play a role in BOO-induced bladder dysfunction. They studied their expression in bladder biopsies and compared expression profiles between types of dysfunction, one of which was DU [35].

They identified specific mRNA and miRNA signatures that were significantly altered in the DU group compared to controls with normal bladder function. Notably, BMP7 and miR-199a-3p emerged as characteristic biomarkers of the underactive (DU) group. Additionally, pathway analysis unveiled important signaling cascades related to cellular growth, proliferation, development, and cytokine signaling, and they were shared among different BOO patient groups, including the DU group.

To the best of our knowledge, no similar analysis has been performed in urine samples [36•].

Conclusion

Detrusor underactivity is an under-researched complex and multifactorial condition only diagnosed by invasive urodynamics. There is a need to develop screening tools to assess and monitor the longitudinal change in bladder function in DU patients. Urinary biomarkers of DU could provide diagnostic and prognostic value for the bladder function recovery. Moreover, they could be helpful to elucidate different pathophysiological mechanisms of DU, paving the way for the emergence of novel pharmacological therapies to prevent or revert this disease.

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Declarations

Conflict of Interest João Oliveira, Gabriel Costa, Ana Charrua, Luís Vale, João Silva, Tiago Antunes-Lopes 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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