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Review Article

Urine biomarker could be a useful tool for differential diagnosis of a lower urinary tract dysfunction

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Abstract

A precision diagnosis of lower urinary tract dysfunctions (LUTD) such as bladder outlet obstruction, detrusor overactivity (DO), interstitial cystitis/bladder pain syndrome (IC/BPS), dysfunctional voiding (DV), or detrusor underactivity (DU) needs invasive videourodynamic study. Exploring non-invasive tools to help screening LUTD is necessary for clinicians in their daily practice. This article reviews recently clinical studies of using urinary inflammatory proteins and oxidative stress biomarkers in the identification of specific LUTD among men and women with lower urinary tract symptoms (LUTS). Some important findings have been reported: (1) Using urine chemokines CXCL-1 and interleukin-8 (IL-8), we may discriminate overactive bladder (OAB) symptoms in women between DO and urinary tract infection. (2) Urinary levels of oxidative stress biomarkers such as 8-hydroxydeoxyguanosine (8-OHdG) and 8-isoprostane have a potential being used as a tool to identify women with mixed DO and stress urinary incontinence. (3) Urine levels of total antioxidant capacity (TAC), and prostaglandin E2 (PGE2) are positively correlated with voiding detrusor pressure in patients with DU. (4) Urine levels of brain-derived neurotrophic factor (BDNF) and PGE2 were significantly higher in the DU patients with detrusor function recovery. (5) Women with DV had higher urinary levels of tumor necrosis factor-alpha (TNF-α) and 8-OHdG, and urinary IL-2 level was significantly lower. (6) Urine level of 8-isoprostane was higher in the patients with idiopathic DO and neurogenic DO. (7) Higher urine cytokine levels of monocyte chemoattractant protein-1 (MCP-1), regulated on activation, normal T-cell expressed and secreted (RANTES), CXCL-10, IL-7, and eotaxin-1 in patients with IC/BPS than controls. (8) The urine levels of IL-8, CXCL-10, BDNF, IL-6, and RANTES were significantly higher in patients with Hunner's IC than non-Hunner's IC. (9) Male patients with IC/BPS had a significantly higher level of eotaxin, MCP-1, TNF-α, 8-OHdG, and TAC. Combining a higher eotaxin and a higher TNF-α can provide a satisfactory diagnostic value in discriminating IC/BPS from other LUTD in men. These studies provide evidence that measurement of cluster of urine biomarkers could be used as a diagnostic tool to differentiate different LUTD in patients with similar LUTS.

Keywords: *Bladder outlet obstruction, Inflammation, Lower urinary tract symptoms, Overactive bladder, Painful bladder syndrome*

Introduction

Lower urinary tract symptoms (LUTS) involve symptoms from bladder and bladder outlet dysfunction. The composition of LUTS is complicated which include bladder storage and voiding symptoms and each symptom might result from a different underlying pathophysiology [1]. In clinical practice, a diagnosis of lower urinary tract dysfunction (LUTD) cannot be accurately made by the sum of LUTS such as International Prostate Symptom Score for bladder outlet obstruction (BOO), Overactive Bladder Symptom Score for detrusor overactivity (DO), or Interstitial Cystitis Symptom Index for interstitial cystitis/bladder pain syndrome (IC/BPS). In addition to the symptom scores, objective diagnostic tools and measurements such as the uroflowmetry parameters, voiding volume, flow pattern,

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post-void residual volume, bladder and prostate ultrasound, cystoscopy, and urodynamic study are necessary to precisely identify specific pathophysiology of lower urinary tract [2]. The bladder dysfunction includes hypersensitive bladder (HSB), DO, detrusor underactivity (DU), and low bladder compliance. The bladder outlet dysfunction includes bladder neck dysfunction, prostatic obstruction, poor relaxation of the urethral sphincter (PRES), dysfunctional voiding (DV), intrinsic sphincter deficiency (ISD), or urethral stricture. The LUTDs might also involve a combination of bladder and bladder outlet dysfunctions [3]. Therefore, an accurate diagnosis of LUTD in male or female patients is not easy without several sequential diagnostic procedures including videourodynamic study (VUDS) [3,4].

Although VUDS can provide a precision diagnosis of LUTD, the results of VUDS might not reflect the true pathophysiology underlying the clinical symptoms and urodynamic findings. In addition, the need of invasive transurethral catheterization and irradiation exposure has limited its wide application in screening patients with LUTS. Recent studies have revealed that urine levels of inflammatory proteins and oxidative stress biomarkers could be used for the discrimination of different LUTD [4,5]. Using a cluster of urinary biomarkers, the LUTD can be step by step divided into different subtypes [6,7]. This article reviews recently development of using urinary biomarkers in differential diagnosis of different LUTDs.

Urinary biomarkers in urinary tract infection and inflammation

Over 1500 proteins have been found in urine, which may increase or decrease in different urinary tract conditions such as urinary tract infection (UTI), inflammation, or reflecting systemic conditions [8,9]. Chemokines are molecule signature of infected cells as well as recruited inflammatory cells [10]. Previous studies have demonstrated that increased urine interleukin-8 (IL-8) level represents UTI [11], whereas monocyte chemoattractant protein-1 (MCP-1) is associated with OAB [12]. Using MILLIPLEX MAP Human Cytokine/Chemokine Immunoassay to measure urinary chemokines, we previously had found significant elevation of CXCL-1, CXCL-8 (IL-8), and CXCL-10 together with reduced levels for a receptor antagonist of IL-1A (sIL-1RA) were seen in UTI relative to OAB and asymptomatic controls. After antibiotics treatment, reduction was seen in all CXC chemokines with a significant reduction for CXCL-10 [13]. Using urine chemokines CXCL-1 and IL-8, we may discriminate women with frequency urgency symptoms between UTI and OAB.

The pathophysiology of LUTD usually involves chronic inflammation, urothelial dysfunction, tissue, and neurogenic modulation. These functional and morphological changes in LUTD could lead to different urinary protein expressions. Neurogenic inflammation is an important pathophysiology in the etiologic cascade of BOO, OAB, and IC/BPS [14]. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are the mostly studied biomarkers from the aspect of neurogenic inflammation [15]. In patients with OAB, IC/BPS, and BOO, the inflammatory process results in chronic inflammation in detrusor smooth muscles could produce cytokines and chemokines, therefore, the urinary levels of these inflammatory cytokines will elevate, especially in IC/BPS and BOO [16]. The common chemokines and cytokines that will elevated in LUTD include MCP-1, CXCL-10, regulated on activation, normal T-cell expressed and secreted (RANTES). MCP-1, CXCL-10, and RANTES are upregulated and involved in the chemokine signaling in peripheral neuroinflammatory responses. They were thought to play a central role in maintaining the afferent hypersensitivity and neuropathic pain state [17]. The other chemokines include eotaxin, macrophage inflammatory protein-1β (CCL4, MIP-1β), and IL-8, all play important roles in the pathophysiology of eosinophilic inflammatory diseases [18], chemoattractant of natural killer cells, monocytes, and many different immune cells [19], and regulation of angiogenesis by controlling the proliferation of endothelial cells [20], respectively. Detection of the urinary cytokine and chemokine levels may evaluate of different inflammatory conditions in the LUTDs [21].

Concerning the oxidative stress in LUTD, reactive oxygen species affect the release of pro-inflammatory cytokines, including IL-1β, tumor necrosis factor-alpha (TNF-α), and interferon-β, leading to related immune responses [22]. The chronic bladder ischemia induced by atherosclerosis, previous research had found significantly higher urine 8-hydroxydeoxyguanosine (8-OHdG) levels and higher pro-inflammatory cytokines (TNF-α, IL-6, and IL-8) in the studied bladder tissue than controls [23]. F2-isoprostatne is considered to be a reliable indicator or oxidative stress, which is detectable in the tissues and body fluids [24,25]. In the partial BOO model of rats, F2-isoprostane levels in bladder tissue could reflect the oxidative stress progression [26]. The total antioxidant capacity (TAC) is thought to be a useful biomarker to assess the antioxidant potential of body fluids such as urine [27,28]. Urine TAC levels can be affected by several body conditions, including infection, renal function impairment, systemic diseases, nutrition status, and lifestyle factors [28]. However, the interplay between oxidative stress and anti-oxidative stress is complex [22]. Therefore, the relationship between the oxidative stress biomarker and TAC in urine might not be consistent.

Detrusor overactivity and detrusor underactivity

OAB is a clinical diagnosis with symptoms of urgency, frequency, with or without urgency urinary incontinence (UUI). The OAB is an umbrella term which may include idiopathic, myogenic, neurogenic, urotheliogenic, or urethrogenic DO [29]. Patients with OAB can be divided into OAB dry and OAB wet, nearly all patients with OAB wet have urodynamic DO, but not all patients with OAB dry have DO. Patients with OAB have been found to have increased urinary inflammatory biomarkers, NGF, BDNF, and adenosine triphosphate [21,30]. Women with stress urinary incontinence (SUI) might have pure ISD or mixed with DO (mixed UI). In a recent study on women with genuine SUI and mixed UI, the urine levels of oxidative stress biomarkers such as 8-OHdG and 8-isprostane

can be used to identify women who had mixed UI [31]. Using the decision tree analysis, we select patients with a voided volume <384 mL, and urine level of 8-OHdG ≥35 ng/mL and urine 8-isoprostane level ≥37 pg/mL, an accuracy of 81.7% can be achieved in distinguishing women with mixed UI. The results of this study suggest that urinary oxidative stress biomarkers have a potential to be used as a tool to identify urodynamic DO in women with SUI.

DU is a condition that bladder inadequately contracts, which could be an end stage of bladder dysfunction resulting from other pathological mechanisms or neurodegeneration, and is often observed in the elderly patients with diabetes mellitus, neurogenic lesion, or after chronic BOO [32-34]. Bladder hypoxia, chronic ischemia, and BOO would contribute to altered sensory proteins and urothelial dysfunction [35]. With chronic inflammation, increased oxidative stress, and mitochondrial dysfunction, the patients with long-term untreated DO might also develop into DU with or without DO [36,37]. In a recent study, we found the urinary levels of TAC, and prostaglandin E2 (PGE2) are significantly correlated with detrusor voiding pressure, whereas in patients with DU and DO, the urinary levels of 8-OHdG, PGE2, IL-6, IL-10, and MIP-1α levels were positively correlated with maximal urinary flow rate, while urine IL-5, IL-10, and MIP-1α were negatively correlated with the first sensation of bladder filling [38]. The results of this study highlight that DU is a condition mixed with chronic ischemia, inflammation, and neuropathy that interfere the normal bladder sensation and contractility.

PGE2 is believed to have contribution to the pathophysiology of spontaneous detrusor contractility [39]. In patients with combined DO and DU the urinary level of PGE2 was decreased [40]. Using urine PGE2 level, we might predict the recovery of detrusor contractility [5]. Patients with BOO-induced DO or OAB, the urinary neurotrophin levels such as NGF and BDNF are elevated, and decreased after successful medical treatment [41]. The urine levels of oxidative stress biomarkers 8-OHdG, F2-isoprostane, and malondialdehyde have been demonstrated to increase in human BOO [24], and the oxidative stress will reverse after relief of BOO [42]. A previous study on the recovery of detrusor contractility in patients with urodynamic DU also revealed that the urinary BDNF and PGE2 levels were significantly higher in patients with DU having recovery of detrusor function compared with controls, but was not elevated in the DU patients without recovery [43]. These urine protein levels could be used in detecting patients with DU with or without a chance to have catheter removal.

Female bladder dysfunction and bladder outlet dysfunctions

LUTS in women might result from different subtypes of dysfunctions in the bladder or bladder outlet. The bladder dysfunction could be due to neuropathic, musculogenic, inflammatory, and urotheliogenic pathophysiology, whereas the bladder outlet dysfunctions might originate from bladder neck dysfunction, urethral sphincter dysfunction, or poor pelvic floor relaxation [44,45]. The LUTSs in these LUTDs are widely overlapping and might not provide accurate diagnosis without invasive diagnostic procedures.

LUTS include bladder storage symptoms and voiding symptoms. The bladder symptoms might originate from bladder hypersensitivity, bladder overactivity, or DU. These bladder sensory and motor disorders usually result in the symptoms of frequency, urgency, and UUI; some patients might also have difficulty in urinating and increased PVR.

The pathophysiology of OAB and HSB is multifactorial; there is an association between OAB and HSB due to afferent nerve hyperactivity. OAB usually can be easily treated by antimuscarinic agent or beta-3 adrenoceptor agonists. For the OAB refractory to conventional medication, the possible pathophysiology includes the latent neurogenic bladder, BOO, urethral incompetence related OAB, aging process or disease-related urothelial dysfunction, chronic ischemia of urinary bladder, chronic inflammation of the urinary bladder, central nervous system (CNS) sensitization, and autonomic dysfunction [29]. The urothelium and afferent nerves of the bladder wall express transient receptor potential vanilloid receptor 1 (TRPV1) and purinergic receptor P2X3 [46,47]. These sensory receptors are responsible for the bladder sensation and bladder reflex volume through urothelial stretch and noxious stimuli in the afferent pathways [48]. The increased expressions of sensory receptors and functional proteins in the urothelium are highly associated with chronic bladder inflammation, such as in diseases of interstitial cystitis/bladder pain syndrome (IC/BPS), DO, or BOO [49,50]. The true pathophysiology of this pathophysiology cannot be identified without bladder wall biopsy and immunohistochemistry staining in patients with clinical OAB. Because LUTS is usually not reliable in the differential diagnosis of OAB subtypes, urinary biomarker levels provide objective evidence to discriminate patients with idiopathic DO (IDO), neurogenic DO (NDO), DV, and HSB. A recent study identified VUDS confirmed different subtypes of OAB in women using urine biomarkers [51]. The results of one previous study showed that patients with different OAB subtypes have varied urine levels of inflammatory proteins and oxidative stress biomarkers. By analysis of the difference in urine biomarker levels, the urine levels of biomarkers might be used to differential diagnosis of bladder-centered OAB (IDO, NDO, and DV) and the HSB or normal bladder in women with urgency and frequency symptoms [Table 1].

Previous studies have shown a significant increase of urinary levels of inflammatory cytokines were noted in women with UTI and IC/BPS [13,52]. The urinary levels of inflammatory proteins and oxidative stress biomarkers are significantly associated with early bladder sensation and small bladder volume [51]. Among the OAB subgroups, we found patients with DV had a lower urine level of IL-2, vascular endothelial growth factor (VEGF), NGF, 8-isoprostane, and TAC, whereas patients with IDO had a higher urine level of VEGF and 8-isoprostane. Patients with NDO had a significantly higher 8-isoprostane level. Patients with HSB had similar urine levels of biomarkers as the urinary biomarkers

Table 1: The urinary levels of inflammation relate, neurogenic, and oxidative stress biomarkers in patients with different diagnosis of frequency urgency syndrome and controls [51]

	1 IDO (*n*=31)	2 NDO (*n*=8)	3 DV (*n*=45)	4 HSB (*n*=29)	5 control (*n*=34)	*P*	*Post hoc* analysis
IL-1b	0.74±0.9	1.28±2.06	1.16±1.4	0.71±0.63	0.56±0.26	0.192	
IL-2	0.74±0.19	0.71±0.16	0.28±0.22	0.64±0.14	0.79±0.19	<0.001	1245 versus 3, 135 versus 4, 34 versus 5
IL-6	2.05±2.62	1.9±1	2.14±5.16	1.53±1.71	1.22±1.29	0.588	
IL-8	29.3±58.8	61.3±114	31.0±63.9	48.3±97.7	13.6±22.8	0.451	
TNF-α	0.87±0.4	0.76±0.15	1.21±0.33	0.92±0.56	0.79±0.31	<0.001	1245 versus 3
VEGF	14.6±5.96	10.6±6.45	5.56±4.91	8.44±7.84	11.21±5.3	<0.001	1245 versus 3, 345 versus 1, 13 versus 4, 13 versus 5
NGF	0.26±0.07	0.27±0.06	0.21±0.05	0.22±0.07	0.27±0.07	0.007	125 versus 3, 15 versus 4
BDNF	0.6±0.22	0.68±0.23	0.63±0.15	0.74±0.77	0.57±0.14	0.629	
PGE2	262±175	134±68.7	218±187	283±259	171±107	0.047	
8-isoprostane	32.5±29.8	51.4±42.6	12.9±14.7	22.8±17.3	17.5±15.5	0.011	1 versus 3
TAC	1558±13,597	1472±1583	604±420	388±279	1107±1017	0.003	1 versus 34, 4 versus 5
8-OHdG	26±17.7	16.9±11.1	32.4±19.4	18.4±16.6	17.7±13.6	0.001	245 versus 3

IDO: Idiopathic detrusor overactivity, NDO: Neurogenic DO, DV: Dysfunctional voiding, HSB: Hypersensitive bladder, IL: Interleukin, TNF-α: Tumor necrosis factor-α, VEGF: Vascular endothelial growth factor, NGF: Nerve growth factor, BDNF: Brain-derived neurotrophic factor, PGE_2: Prostaglandin E2, TAC: Total antioxidant capacity, 8-OHdG: 8-hydroxydeoxyguanosine

in the controls, but lower levels of NGF and TAC. Urine PGE2 level was relatively higher in patients with IDO, DV, and HSB. These results revealed that patients with IDO and NDO had increased urine levels of oxidative stress biomarker 8-isoprostane, while higher urine levels of TNF-α and 8-OHdG were noted in patients with DV. However, patients with HSB did not show increased level of oxidative stress biomarkers, but had a higher urine PGE2 level. The other inflammatory proteins in urine did not have a difference in discriminating OAB subtypes.

Female dysfunctional voiding

DV is a LUTD that is frequently overlooked without the aid of videourodynamic study [53]. The pathophysiology of DV has not been fully elucidated. Patients usually have urodynamic DO and an overactive urethral sphincter activity during urination, resulting in a higher voiding detrusor pressure, lower maximal flow rate, and larger PVR than controls [54]. Some patients might also have chronic urinary retention. Elderly patients with DV have been found to develop CNS diseases in the long-term follow-up. The CNS diseases included cerebrovascular accident, Parkinson's disease, and dementia. Urodynamic DV might be the early neurological sign of these CNS diseases [55]. It has been estimated that about 17% of women with LUTS have videourodynamic proved DV [56]. The presence of BOO in women with DV, if not well treated, will lead to progressive bladder tissue remodeling, including excessive oxidative stress, chronic ischemia, and hypoxia-related inflammation [57]. Although urinary biomarkers have been associated with LUTS in numerous clinical studies, the lack of reproducibility of the accuracy results in a low clinical application of this diagnostic tool in the management of LUTD [58].

In a recent study, we have found that urine levels of oxidative stress biomarkers 8-OHdG, neurogenic protein BDNF, and inflammatory proteins IL-1β and IL-8 were significantly higher in patients with DV compared with the controls [59]. The urinary levels of 8-OHdG and IL-1β were positively associated with clinical symptoms of DV. Patients with a successful treatment outcome were found to have significantly lower pre-treatment urine levels of 8-isoprostane and TAC, in compared with those with an unsatisfactory outcome. These elevated levels of urinary biomarkers indicate that the bladder oxidative stress- and hypoxia-related inflammation might be involved in the pathophysiology of DV. These pathophysiologies are also linked to the clinical symptoms of frequency urgency and small bladder capacity [56,60].

In another clinical study, women with DV had higher urinary levels of 8-OHdG and TNF-α, while the urinary level of IL-2 was lower [7]. The DV patient with DO had significantly higher urine level of PGE2 than those without DO. These results further imply that the involvement of bladder ischemia and hypoxia-related inflammation in women with BOO is caused by DV, and the detrusor hyperactivity will also develop resulting in elevated urine PGE2 level and urodynamic DO. Analysis of urinary levels of 8-OHdG, TNF-α, IL-1β, and IL-8 might identify DV in women with LUTS and OAB and also has a prognostic role in female DV.

In the analysis of urinary biomarkers among female patients with different LUTDs, patients with DO and IC/BPS had higher urinary levels of 8-isoprostane and TAC [61]. The urinary 8-OHdG level was higher in patients with IC/BPS and DV, but not in patients with DO. The urine levels of inflammatory proteins IL-1β and TNF-α were significantly higher only in patients with DV, however, IL-2 level was significantly lower than that in other LUTD subgroups. By contrast, the urine level of VEGF was significantly higher in patients with DO and IC/BPS than in the DV and HSB. When we grouped patients with DO, IC/BPS, and DV as having bladder-centered LUTD, the urine levels of 8-isoprostane, TAC, 8-OHdG, VEGF, NGF, and PGE_2 were significantly higher in these patients, though IL-2 was significantly lower than in those with HSB and controls. By using the area under curve and cutoff value for each urine biomarker in discriminating LUTDs of DO, IC/BPS, and DV versus HSB and controls, only TAC (≥844.3 pg/mL) and 8-OHdG (≥24.13 pg/mL) had an area under curve of >0.70. However, other urine biomarkers did not reach a satisfactory

area under curve using the cutoff value analysis. Based on the analysis of the cutoff values of urinary biomarkers between different functional bladder disorders, a diagnostic algorithm of the identification of LUTD in women with LUTS was proposed [Figure 1].

Among the tested urine biomarkers, the oxidative stress biomarkers 8-isoprostane, 8-OHdG, or TAC is found to be useful in identifying the bladder-centered LUTD such as DO, IC/BPS, DV, and HSB [61]. With an elevated urine level of IL-1β and lower level of IL-2, and an elevated TNF-α level, most patients with DV can be identified by this cluster of urine biomarkers. Between patients with DO and IC/BPS, a higher urinary level of NGF can identify 58.3% of IC/BPS cases, whereas a lower level of NGF can identify 75.0% of DO cases.

Among the urine biomarkers, oxidative stress biomarkers are the most valuable noninvasive tool in discriminating patients with DO, IC/BPS, and DV from HSB and normal controls. Increased oxidative stress due to pelvic organ ischemia had been considered to play an important role in the pathogenesis of inflammatory-related LUTDs such as DO, OAB, and IC/BPS [36]. In animal model and human study, the bladder ischemia induced by atherosclerosis have been found to result in oxidative stress and chronic inflammation and urodynamic DO [23,62]. The urine levels of 8-OHdG and 8-isoprostane have been found to increase in patients with IC/BPS, OAB, and DV [59,63,64]. A significant decrease of blood perfusion during bladder filling and at a full bladder had been reported in patients with IC/BPS [65,66]. Increases in urinary levels of hypoxia-inducible factor-1α, VEGF, and immature vascularization in the bladder tissue have also been identified in patients with IC/BPS [67,68]. Based on these findings, it is likely that IC/BPS can be identified in patients who had elevated urine levels of oxidative stress biomarkers and VEGF. Since higher urine levels of 8-isoprostane, TAC, or 8-OHdG are found in patients with DO, IC/BPS, and DV but not in HSB and normal controls, it is possible to identify these bladder-centered dysfunctions by the analysis of elevated oxidative stress biomarkers urine levels.

Interstitial cystitis/bladder pain syndrome

IC/BPS is a bladder sensory disorder of undetermined etiology, which is characterized by urinary urgency, frequency, nocturia, and usually with pelvic pain, in the absence of bacterial UTI or identifiable pathology in the urinary tract [69]. Expressions of sensory proteins, inflammatory proteins, and pro-apoptotic proteins were increased in IC/BPS bladders, the expression levels of TRPV1, TRPV4, sigma-1, P38, tryptase, caspase-3, and BAD were significantly increased in the urothelium of IC/BPS patients compared with the controls. Inflammatory and pro-apoptotic protein expression levels in the urothelium were similar among the IC/BPS subgroups [70]. IC/BPS has different clinical phenotypes, including IC/BPS with Hunner's IC (HIC) and non-HIC (NHIC) [71]. In clinical presentation, IC/BPS also shows different clinical phenotypes, including urinary, psychosocial, organ specific, infection, neurological/systemic,

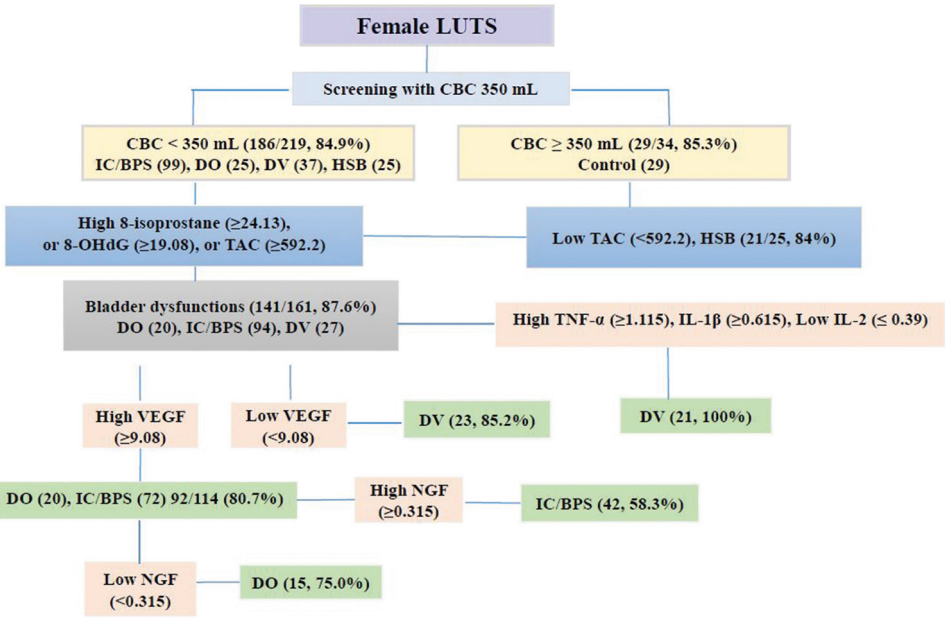

Figure 1: Diagnostic algorithm for female lower urinary tract dysfunctions (LUTDs). A small cystometric bladder capacity was used to exclude normal patients without LUTD. A lower total antioxidant capacity (TAC) can exclude 84% of patients with hypersensitive bladder (HSB). Among patients with detrusor overactivity (DO), interstitial cystitis/bladder pain syndrome (IC/BPS), and dysfunctional voiding (DV), a higher urine level of 8-isoprostane, 8-hydroxydeoxyguanosine (8-OHdG), or TAC were used to confirm 87.6% of patients with these bladder dysfunctions. A higher vascular endothelial growth factor (VEGF) was present in 80.7% of patients with DO and IC/BPS, whereas a low VEGF level confirmed 85.2% of patients with DV. Finally, and a higher urine level of nerve growth factor could be used to discriminate 58.3% of patients with IC/BPS and 75.0% of DO. Among patients with bladder dysfunctions, an elevated interleukin-1 beta and elevated tumor necrosis factor-alpha confirmed 100% of patients with DV. The unit of urinary biomarkers is pg/mL. LUTS: Lower urinary tract symptoms, CBC: Cystometric bladder capacity, IC/BPS: Interstitial cystitis/bladder pain syndrome, DO: Detrusor overactivity, DV: Dysfunctional voiding, HSB: Hypersensitive bladder, 8-OHdG: 8-hydroxydeoxyguanosine, TAC: Total antioxidant capacity, TNF-α: Tumor necrosis factor-alpha, IL-1: Interleukin-1, VEGF: Vascular endothelial growth factor, NGF: Nerve growth factor

and tenderness (UPOINT system) [72]. Patients with NHIC can be classified into different phenotypes according to different maximal bladder capacity and grade of glomerulations during cystoscopic hydrodistention [73]. The clinical phenotypes can also predict treatment outcome in patients with IC/BPS [71,73].

Compared with the controls, patients with IC/BPS were found to have several elevated urine levels of cytokines, and the cytokine levels also differed between the ESSIC IC/BPS subtypes 1 and 2. The significant urine cytokine levels include RANTES, MIP-1β, and IL-8 (with a high sensitivity); and MCP-1, CXCL-10, and eotaxin (with a high specificity) [74]. The urine levels of MCP-1, CXCL-10, eotaxin, and RANTES were all positively correlated with the glomerulation grades and negatively correlated with maximal bladder capacity. After multivariate analysis, the urine cytokines MCP-1, RANTES, CXCL-10, IL-7, and eotaxin-1 remained statistically significant in differentiating IC/BPS and controls.

The accurate differential diagnosis between patients with IC/BPS and OAB is not easy simply by the clinical symptoms. The cardinal symptom of IC/BPS is bladder pain, whereas there is urgency or UUI in OAB. However, patients with OAB might also complain of bladder pain when the bladder is full, while patients with IC/BPS may not experience bladder pain because they used to empty their bladders before the full bladder causing pain. Therefore, developing a non-invasive diagnostic algorithm between OAB and IC/BPS is essential to avoid over diagnosis and cystoscopic examination under anesthesia. Among the urinary cytokines, MIP-1β was reported to have the highest sensitivity for identifying patients with dysfunctional bladder from the controls. The cytokines which were found to have high diagnostic values in distinguishing IC/BPS from OAB included IL-10, RANTES, eotaxin, CXCL-10, IL-12p70, NGF, IL-6, IL-17A, MCP-1, and IL-1RA [75]. We may use a higher urine level of MIP-1β to select patients with IC/BPS and OAB, and then followed by confirmation tests of eotaxin, CXCL-10, and RANTES for a diagnosis of IC/BPS. A diagnostic rate of 81.6% can be obtained [Figure 2].

IC/BPS has been well accepted to include HIC and NHIC subtypes. These two subtypes have distinct pathophysiology, clinical symptoms, treatment modalities, and outcome [76,77]. Cystoscopy without anesthesia usually can find a characteristic erythematous patch with radiating vessels and friable central lesion in HIC [78]. Previous study using urinary biomarkers to discriminate IC/BPS revealed that the urine levels of inflammatory proteins MCP-1, eotaxin, MIP-1β, TNF-α, and PGE2 were significantly higher in patients with IC/BPS than controls. The urine levels of IL-8, CXCL-10, BDNF, IL-6, and RANTES were also found significantly higher in patients with HIC than NHIC [79]. Because patients with HIC usually have a higher grade of bladder inflammation than that of NHIC, a higher urinary level of cluster of urinary cytokines and chemokines could prompt urologists to make a diagnosis of HIC and give active management.

During cystoscopic hydrodistention for patients with IC/BPS, the MBC and grade of glomerulations differ in patients with NHIC. In analysis of urinary biomarkers, significantly higher urine levels of IL-8, CXCL-10, BDNF, eotaxin, and RANTES had been reported in patients with HIC than in NHIC or the controls. Significantly higher urine levels of MCP-1, eotaxin, TNF-α, and PGE2 were also found in patients with NHIC than in the controls [52]. The elevated urine levels of CXCL-10, MCP-1, eotaxin, IL-6, MIP-1β, RANTES, TNF-α, and PGE2 were significantly and negatively correlated with MBC in patients with NHIC. Moreover, the elevated urine levels of CXCL-10, MCP-1, IL-6, RANTES, and PGE2 were positively correlated with the grade of glomerulation during

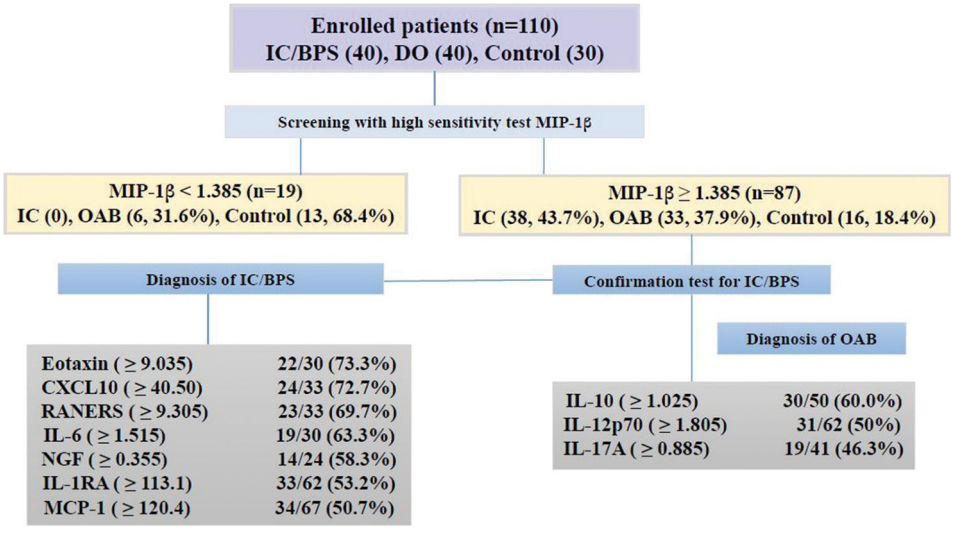

Figure 2: Diagnostic algorithm for diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS). Using a higher urine level of monocyte chemotactic protein-1β to select patients with IC/BPS and overactive bladder, and followed by the confirmation tests of eotaxin, CXCL-10, and regulated on activation, normal T cell expressed and secreted for IC/BPS. A diagnostic rate of 81.6% of IC/BPS can be obtained [75]. Unit: pg/mL. IC/BPS: Interstitial cystitis/bladder pain syndrome, DO: Detrusor overactivity, MIP-1β: Macrophage inflammatory protein-1β, IC: Interstitial cystitis, OAB: Overactive bladder, RANTES: Regulated on activation, normal T cell expressed and secreted, IL-6: Interleukin-6, NGF: Nerve growth factor, MCP-1: Monocyte chemoattractant protein-1

cystoscopy. The results suggested that increases of bladder inflammation are associated the decrease of MBC and increase of glomerulation grade in patients with IC/BPS. However, the symptom indexes ICSI and ICPI were significantly correlated with urine levels of CXCL-10, BDNF, eotaxin, and IL-6; but the VAS pain score was only correlated with urinary levels of BDNF, IL-6, and PGE2. Based on these findings, the bladder inflammation in IC/BPS might involve several different pathways that produce different cytokines and chemokines through different inflammatory cells and neurological activations.

Among the urinary biomarkers, TNF-α was shown to have a high sensitivity and specificity for the diagnosis of IC/BPS. Compared with the controls, a high urinary level of TNF-α was also noted in all subgroups of NHIC based on the subgroups with different MBC and glomerulation grades after cystoscopic hydrodistention. TNF-α is a proinflammatory cytokine, which can induce chronic tissue inflammation resulting in tissue damage [80]. The bladder tissue TNF-α level in patients with HIC has been found to significantly increase. The mast cell activation in IC/BPS can excessively release TNF-α and elicit inflammatory response in the bladder tissue, leading to an increase in urinary level of TNF-α [81]. A recent study had found that a small MBC in cystoscopic hydrodistention was significantly associated with higher urine levels of inflammatory proteins in patients with IC/BPS than the controls [52]. Higher urine levels of MCP-1 and PGE2 were only found in patients with a small MBC, while higher urinary levels of eotaxin and IL-6 were only observed in patients with NHIC with glomerulation >1 and MBC of ≤760 mL. These findings of urinary biomarkers also suggest that a small MBC during cystoscopic hydrodistention might be the hallmark of NHIC with severe bladder inflammation.

When we analyzed the urine levels of biomarker among patients with IC/BPS and different histopathological findings, we did not find urinary biomarkers had a significant correlation with specific bladder histopathological findings, such as eosinophil infiltration, plasma cell infiltration, lamina propria hemorrhage, suburothelial granulation, and nerve hyperplasia in the bladder specimens [82]. However, a significant association between elevated urinary biomarker levels and lower MBC, higher glomerulation grade, higher VAS score, and increased bladder sensation was noted. Patients with NHIC and having an MBC of ≤ 760 mL had significantly higher urine levels of CXCL-10, MCP-1, eotaxin, IL-6, MIP-1β, RANTES, PGE2, 8-isoprostane, and TAC. These findings suggest that the bladder inflammation grade in NHIC is not apparent in the bladder urothelial biopsy specimens, but severe inflammation might originate from the submucosal inflammation which limit the distension of the bladder during cystoscopic hydrodistention. A small MBC might indicate a bladder-centered IC/BPS rather than the grade of glomerulation.

Male lower urinary tract dysfunctions

Male LUTS include symptoms of bladder storage and emptying, which could be a result of bladder and bladder outlet dysfunctions. Although men with voiding predominant LUTS are usually diagnosed as having clinical benign prostatic hyperplasia (BPH), half of the patients with LUTS are actually resulted from different LUTD such as DO, DU, HSB, BND, DV, poor urethral sphincter relaxation, or IC/BPS [3,83-85]. Behind these LUTD, the pathophysiology of chronic bladder ischemia, BOO-induced bladder fibrosis, increased sensory hyperactivity, and neurogenic inflammation might produce different urinary proteins and biomarkers that lead to different functional and morphological modulations [24,86-90]. Therefore, it seems rational to measure the urinary biomarkers in discriminating different LUTD such as IC/BPS, DO, BOO, DO, HSB, and PRES in men with LUTS.

After analysis of the urodynamic parameters and urinary biomarker levels, the bladder volume of bladder sensation and cystometric bladder capacity (CBC) are smaller in male LUTD groups than in the control. Using receiver operation curve analysis, a CBC of more than 408.5 mL could identify male patients without evident bladder or bladder outlet dysfunction (including normal urodynamic tracing and PRES). Among the male patients with LUTD, patients with IC/BPS were found to have significantly higher urine levels of eotaxin, MCP-1, TNF-α, 8-OHdG, and TAC; and a significantly lower level of CXCL-10 [91]. The other urinary biomarker levels were not found significantly different among LUTD subgroups. After combining two or more urinary biomarkers which may have a more than 70% sensitivity, specificity, PPV, and NPV in discriminating IC/BPS from all LUTD subgroups, we found a combination of eotaxin (≥2.290 pg/mL) and TNF-α (≥1.165 pg/mL) could provide a satisfactory diagnostic value to identify patients with IC/BPS among men with LUTD. Based on these findings, it is feasible to use a small CBC of 408.5ml as the first screening tool to separate men with normal urodynamic findings and men with PRES. For male patients with IC/BPS, BOO, DO, and HSB, combination of urinary eotaxin (≥2.290 pg/mL) or TNF-α (≥1.165 pg/mL) could identify most male IC/BPS patients from the other LUTD subgroups. The sensitivity and specificity for IC/BPS is 91.7% and 92.0%, respectively; and a PPV is 78.6%, NPV 97.2% were noted**.** The urine biomarker MCP-1 and oxidative stress biomarkers 8-OHdG and TAC, although were significantly higher in patients with IC/BPS than those in normal and PRES subgroup, did not provide a diagnostic value to discriminating patients with IC/BPS from BOO, DO, or HSB subgroups.

Table 2 shows the significant increases in urine levels of biomarkers in patients with LUTD subgroups and control groups. Although the reproducibility of single urine biomarker for diagnosis of LUTD is not evident yet, with a cluster of urine biomarkers followed by step-by-step analysis, the majority of LUTD could be identified using this non-invasive diagnostic tool.

Conclusion

Urinary inflammatory proteins, neurogenic proteins, and oxidative stress biomarkers are significantly elevated in patients with LUTD. The urinary biomarker has its role in the pathophysiology of LUTS, and can be used as a screening test for LUTD. The measurement of urine biomarkers could

Table 2: Significant increases of urinary biomarkers in patients with lower urinary tract dysfunctions and control groups

LUTD versus control	Significant increase of urinary biomarkers	References
OAB versus normal	MCP-1, CD40, MIP-1β, IL-12p70/p40, IL-5, EGF, growth-related oncogene GRO-α, NGF, BDNF, ATP, 8-OHdG, 8-isoprostane	[21,30,31]
DU versus normal	TAC, PGE2, 8-OHdG, EGF, IL-5, IL-8, IL-10	[38]
IDO versus normal	VEGF, 8-isoprostane	[51]
MUI versus SUI	8-OHdG, 8-isoprostane	[31]
NDO versus normal	8-isoprostane	[51]
DV versus normal	8-OHdG, BDNF, IL-1β, IL-8, TNF-α	[7,59]
IC/BPS versus normal	RANTES, MIP-1β, IL-8, MCP-1, CXCL10, eotaxin	[74]
	MCP-1, eotaxin, MIP-1β, TNF-α, and PGE2	[79]
	8-OHdG, 8-isoprostane, and TAC	[61,63]
HIC versus NHIC	IL-8, CXCL10, BDNF, IL-6, RANTES	[79]
IC/BPS versus OAB	IL-10, RANTES, eotaxin, CXCL10, IL-12p70, NGF, IL-6, IL-17A, MCP-1, and IL-1RA	[75]
Male IC versus LUTD	Eotaxin, MCP-1, TNF-α, 8-OHdG, TAC	[91]

OAB: Overactive bladder, DU: Detrusor underactivity, IDO: Idiopathic detrusor overactivity, MUI: Mixed urinary incontinence, SUI: Stress urinary incontinence, NDO: Neurogenic detrusor overactivity, DV: Dysfunctional voiding, IC/BPS: Interstitial cystitis/bladder pain syndrome, HIC: Hunner's IC, NHIC: Non-Hunner's IC, LUTD: Lower urinary tract dysfunction, MCP-1: Monocyte chemotactic protein-1, MIP-1β: Macrophage inflammatory protein, IL: Interleukin, EGF: Epidermal growth factor, GRO-α: Growth-related oncogene-α, NGF: Nerve growth factor, BDNF: Brain derived neurotrophic factor, ATP: Adenosine triphosphate, 8-OHdG: 8-hydroxydeoxyguanosine, TAC: Total antioxidant capacity, PGE2: Prostaglandin E2, VEGF: Vascular endothelial growth factor, TNF-α: Tumor necrosis factor-α, RANTES: Regulated on activation, normal T cell expressed and secreted

provide evidence for differential diagnosis of the LUTDs with similar clinical symptoms such as hypersensitive bladder, overactive bladder, DO, DV, mixed urinary incontinence, BOO, and interstitial cystitis/bladder pain syndrome.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

Dr. Yuan-Hong Jiang and Hann-Chorng Kuo, the editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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