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New frontiers in molecular and imaging research on evaluation and diagnosis of bladder outlet obstruction in women

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Abstract

Purpose—Diagnosis of bladder outlet obstruction (BOO) often presents a challenge in female patients. Traditional diagnostic elements such as symptom history and urodynamic data are rarely clear cut in women. Therefore, we sought to review the current literature on diagnosis of female BOO, focusing on new frontiers in the realm of molecular markers and imaging modalities.

Recent Findings—In addition to fluoroscopy in the setting of videourodynamics, ultrasound and MRI can augment the diagnosis and aid in therapeutic planning in certain etiologies of female BOO. Furthermore, multiple potential biomarkers (i.e. nerve growth factor, prostaglandins, ATP) that have been studied in correlation to BOO in animal models as well as human subjects hold promise for diagnostic applications.

Summary—These novel techniques may augment standard clinical and urodynamic evaluation of BOO in females. Future directions include further studies of each of these biomarkers in female patients with BOO compared to normal controls to test their feasibility as potential screening tools.

Keywords

Bladder Outlet Obstruction; Diagnosis; Women; Biomarker; Urinary Nerve Growth Factor

Introduction and Background

Bladder outlet obstruction (BOO) in women represents a diagnostic challenge in urologic practice. Clinically, there is much overlap in storage and voiding symptoms in women with various etiologies of lower urinary tract dysfunction (1). Furthermore, objective parameters

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Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

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may also be unreliable in diagnosis of female BOO. The International Continence Society's (ICS) definition of BOO is characterized by "a reduced urine flow rate and/or presence of a raised post void residual and an increased detrusor pressure." (2) However, there are no universally accepted diagnostic criteria for BOO in females.

In men, benign prostatic hyperplasia (BPH) is the most prevalent cause of BOO, with multiple standardized nomograms existing to aid in diagnosis. In contrast, the etiology of BOO in females is substantially more variable compared to males. Causes of female BOO can be subdivided into anatomic and functional subgroups. Anatomic causes include urethral distortion caused by pelvic organ prolapse (POP), iatrogenic BOO most commonly caused by anti-incontinence procedures such as slings, intrinsic etiologies such as strictures and fibrosis, or urethral diverticula. Functional bladder outlet obstruction in women can result from primary bladder neck obstruction (failure of bladder neck relaxation), neurogenic detrusor external sphincter dyssynergia, non-neurogenic dysfunctional voiding (abnormal contraction of periurethral muscle), and Fowler's syndrome (failure of urethral relaxation) (3).

In this topic review, we discuss current literature on the diagnosis and management of female BOO, with a specific focus on basic science and translational research in the realm of imaging and biomarkers. These novel techniques may augment standard clinical and urodynamic evaluation.

Physiology of Voiding

Successful and complete voiding depends on the coordinated activity of the two functional and anatomical units of the lower urinary tract: the bladder and the outlet (bladder neck, urethra, and urethral sphincter). The complex and sophisticated neural control of the lower urinary tract in humans is regulated by central and peripheral nervous system pathways. Neural input from bladder receptors ascends to the periaqueductal gray, which then distributes these signals to regions of the forebrain. The various forebrain circuits then act on the pontine micturition center (PMC) to modulate the micturition reflex. Excitation of the PMC activates descending pathways to cause urethral relaxation and subsequently detrusor contraction (4).

In the setting of BOO, associated with a pathologic increase in outlet resistance, the detrusor muscle generates a more forceful contraction to produce flow across the outlet. This typically results in higher detrusor pressure during voiding in combination with a low flow rate. Over time, BOO can result in functional and anatomical changes in the detrusor (hypertrophy, detrusor overactivity, trabeculation, and bladder diverticulum) as well as alterations in neural networks (5). Neuroplasticity of the bladder afferent and efferent neurons (6), may contribute to the development of lower urinary tract symptoms (LUTS) in the setting of BOO.

Urodynamics

Pressure-Flow Studies

The widely used urodynamic nomograms for BOO in males are not applicable to females since normal detrusor pressure is often significantly lower in women (7). In addition to variations in voiding dynamics, differences in urethral anatomy may allow women to void via pelvic floor relaxation with a lower detrusor pressure, or to augment their voiding with abdominal straining (8).

There have been several urodynamic/flow definitions proposed for female BOO. In 1998, Chassagne et al. proposed pressure flow criteria values of $Q_{max} < 15 \text{ ml/s}$ and $P_{det}Q_{max} > 20 \text{ cm H}_2\text{O}$ (9). New cut-off values have been proposed at least twice prior to 2005: to $Q_{max} < 11 \text{ ml/s}$ and $P_{det}Q_{max} > 21 \text{ cm H}_2\text{O}$ by Lemack and Zimmern in 2000 (10) and then to $Q_{max} < 12 \text{ ml/s}$ and $P_{det}Q_{max} > 25 \text{ cm H}_2\text{O}$ by the same institution in 2004 (11). Using videourodynamics (VUDS), Nitti et al defined BOO as fluoroscopic evidence of obstruction between the bladder neck and urethra in combination with less stringent pressure flow criteria (i.e. the presence of sustained detrusor contraction of any magnitude, usually with reduced flow) (12). Based on uninstrumented pressure flow studies, Blaivas and Groutz developed a nomogram, which categorizes the degree of obstruction as none, mild, moderate, or severe in women (7). Nitti et al. performed analysis of the 5 aforementioned diagnostic criteria, applying them to 91 female patients (8). They concluded that the VUDS criteria had the highest concordance with suspicion of clinical obstruction, followed by the 1998 ($Q_{max} < 15 \text{ ml/s}$ and $P_{det}Q_{max} > 20 \text{ cm H}_2\text{O}$) and 2000 ($Q_{max} < 11 \text{ ml/s}$ and $P_{det}Q_{max} > 21 \text{ cm H}_2\text{O}$) criteria. The 2004 cut points ($Q_{max} < 12 \text{ ml/s}$ and $P_{det}Q_{max} > 25 \text{ cm H}_2\text{O}$) tended to underestimate BOO while the Blaivas-Groutz nomogram tended to overestimate it. Since then, there have been 8 additional papers examining different pressure-flow criteria, summarized in a recent review by Meier and Padmanabhan (3).

In short, there have been numerous proposed urodynamic/pressure flow diagnostic criteria for female BOO without definite consensus. In 2014, the International Consultation on Incontinence-Research Society (ICI-RS) stated that pressure-flow studies alone are not sufficient for future nomograms for women. ICI-RS made recommendations to acquire normative age-matched data in women to define “normal” and “pathological” parameters, relate bladder contractility to degree of obstruction, and develop contractility nomograms for women (13). These recommendations and shortcomings suggest a more objective and less invasive tool to diagnose and assess therapeutic outcome in BOO in females is necessary. As described in the following sections, potentially specific imaging and molecular biomarkers may augment the diagnosis and definition of BOO in women.

Imaging

Electromyography

“Pseudomyotonia,” or the presence of complex repetitive discharges (CRDs) and decelerating bursts (DBs), on striated external urethral sphincter electromyography (EMG) was originally found to be associated with failure of urethral relaxation by Fowler et al. (14). However, the presence of CRDs and DBs do not absolutely correlate with the diagnosis of

BOO, as these phenomenon were not uncommon in women with no retentive symptoms or in patients who underwent anti-incontinence procedures (15). A recent study also showed CRDs and DBs were present in a high proportion (53%) of asymptomatic women, were shown to change during the menstrual cycle in individual women, and occurred most commonly in the luteal phase (16).

Ultrasonography

Ultrasound may be a useful tool in female patients with various etiologies of BOO such as iatrogenic (caused by slings) or primary bladder neck obstruction. Specifically, ultrasound represents a useful imaging modality for evaluating midurethral slings, as it is noninvasive and readily available in the outpatient setting. Usually a transperineal (trans labial) approach is used: a 3.5–5 MHz transducer in the midsagittal plane allows visualization of the pubic symphysis, urethra, bladder neck, and bladder. Synthetic midurethral slings with polypropylene mesh appear to be hyperechoic with a honeycomb appearance on ultrasound and their location and movement has been evaluated by this imaging technology (17). (18). On dynamic assessment with 2D and 3D ultrasound, characteristics associated with better outcomes after sling placement included: concordance of urethral movement with sling, midurethral location, and deformability of sling (19).

In a study of 100 patients with previous TVT, perineal ultrasound findings in 8 patients with BOO included: 1) sling identified more proximal than midurethra (i.e. toward proximal urethra/bladder neck and above the posterior edge of the pubic bone), and 2) reduction of distance of mesh from pubic symphysis, associated with urethral kinking (20). A prospective observational study women with early postoperative voiding dysfunction after TVT sling placement used ultrasound to measure the distance between the sling and longitudinal smooth muscle (LSM) layer of the urethra (21). Criteria for TVT mobilization was $LSM < 3$ mm and post void residual > 100 ml, resulting in restoration of normal voiding in 96.7% of patients. In another study, two-dimensional transperineal ultrasound findings were found to correlate with urodynamic parameters such as high-pressure voiding, and thus bladder outlet obstruction (22). The detrusor pressure at the maximum flow rate was significantly higher in women whose sling had a C-shaped appearance (tight and curved on sagittal view, with the curve abutting the urethra) both at rest and with Valsalva (17, 22). Beyond assessment of the urethra, ultrasound can be used to identify changes in the bladder due to longstanding obstruction, such as detrusor thickness which has been found to correlate with severity of BOO in men with BPH (23). In addition to being a diagnostic modality to assess sling outcomes, ultrasound can also be used to aid in management of sling complications (i.e. preoperatively or intraoperatively in mesh excision)(24).

Ultrasound has also been studied in the setting of primary bladder neck obstruction. In patients with suspected PBNO on video-urodynamics, transvaginal ultrasound (TVUS) was performed at rest (basal) and during voiding (25). TVUS findings in these patients were characterized by a closed bladder neck during both rest and voiding. Typically, PBNO can be diagnosed on videourodynamics, characterized by relative high-pressure, low-flow voiding without opening of the bladder neck, despite relaxation of the striated sphincter. On fluoroscopy this appears as closed (no funneling) of the bladder neck without any evidence

of distal obstruction (26). As mentioned previously, there is no consensus on diagnostic urodynamic cutoffs; thus, ultrasound evaluation may help confirm the diagnosis of BOO in more complicated settings.

Magnetic resonance (Imaging)

Magnetic resonance imaging (MRI) represents a useful imaging modality for detailing pelvic anatomy, and can identify intrinsic and extrinsic causes of BOO. For example, structural MRI plays a vital role in the diagnosis of urethral diverticula as well as serves as a tool for surgical planning. On T2-weighted imaging, urethral diverticula are characterized by high signal intensity (27). In preoperative planning of urethral diverticulectomy, MRI is helpful in identifying the size, circumferential extent around the urethra, and location of ostia.

Structural MRI can also be used to identify external sources of compression on the urethra. There are case reports of MRI used to diagnose various leiomyomas (bladder, broad ligament, periurethral) (28–32) and one report of urethral venous thrombus (33).

Functional Magnetic resonance Imaging (fMRI)

Beyond the bladder and outlet, MRI can also play a role in evaluating the brain and spinal centers involved in neural control of voiding. Specifically, functional MRI (fMRI) studies have identified several cortical brain areas involved in the regulation of micturition (34). Our institution performed a pilot study of brain activity evaluated by fMRI during simultaneous urodynamic testing in 10 healthy female subjects and identified activation of a brain network consisting of regions for motor control, executive function and emotion processing at “initiating of micturition” (35). These functional imaging protocols can be applied to subjects with various urologic pathologies to better elucidate differences in neural control compared to normal subjects. For example, an fMRI study in 6 women with Fowler’s syndrome revealed widespread negative (deactivation) responses to bladder filling (36). This finding is consistent with the proposed pathophysiology of overactive urethra, which in turn inhibits bladder afferent signals to the periaqueductal grey resulting in impaired bladder sensation and ability to void. In the same subjects, treatment with sacral neuromodulation reduced deactivation responses in these supraspinal areas by blocking inhibition by urethral afferent signals.

Biomarkers

There have been a number of potential biomarkers studied in the literature, as summarized in Table 1.

Nerve Growth Factor (NGF)

Nerve growth factor (NGF) is produced by bladder smooth muscle cells, urothelial cells, and sensory afferent neurons. Increased urinary NGF levels are associated with bladder inflammation associated with chemical irritation, detrusor overactivity, and BOO (37). The role of NGF in the neurotrophic effects associated with obstruction was first identified by Steers et al. in 1991 (38). Liu and Kuo demonstrated that urinary NGF was shown to be

elevated in male patients with BOO plus overactive bladder (OAB) symptoms compared with normal controls and was shown to decrease with long-term medical management (39). Expression of NGF has been demonstrated to be modulated by intervention. In BOO-induced rats, expression of NGF in the urothelium was significantly increased and subsequently normalized after detrusor injection of botulinum toxin A (40). Similarly, administration of silodosin, an alpha (1A)-adrenoreceptor antagonist, resulted in decreased NGF expression in a rat model of BOO (41).

In 2015, our institution performed a prospective study on urinary NGF levels in 10 women with anatomic BOO vs 10 female controls (42). Cause of BOO was pelvic organ prolapse (POP) in 6 patients and prior anti-incontinence procedure in 5 patients; one patient had both etiologies. The urinary NGF/Cr levels in the patients with BOO (mean [SE] 20.8 [4.31] pg/mg) were significantly higher ($P = 0.0001$) than the levels in the control group (5.6 [0.65] pg/mg). Also, urinary NGF level showed a weak positive correlation ($r^2 = 0.16$) with UDI-6 symptom score. Nine patients underwent surgical intervention (i.e. prolapse repair, sling excision), and one patient was managed conservatively with clean intermittent catheterization (CIC). After treatment, the mean urinary NGF/Cr level significantly decreased to 6.50 (0.57) pg/mg ($P = 0.01$), and this decrease had a weakly positive correlation with symptom improvement, measured by the UDI-6 questionnaire. Thus, urinary NGF shows promise as a biomarker for women with suspected anatomic BOO and can also be followed after treatment of BOO.

Prostaglandin E2 (PGE2)

Prostaglandins stimulate the micturition reflex by decreasing thresholds necessary to trigger detrusor contraction via capsaicin-sensitive afferent nerves (43). PGE2 was shown to significantly increase in female patients with OAB, and was specifically related to changes in bladder capacity in this population (43). PGE2 is released from the bladder in response to distention and has also been implicated in detrusor overactivity associated with BOO (44). One study demonstrated higher levels of PGE2 in the bladders of pediatric males with lower urinary tract obstruction due to urethral stricture when compared with other pediatric male urology patients without BOO (49.1 ± 37.4 vs. 21.5 ± 10.1 pg/mL, $P = 0.0475$) (45).

Adenosine Triphosphate (ATP)

ATP is released by the urothelium in response to bladder distension, and may play a major sensory role on pelvic afferent nerve fibers (46). In a rat model, partial bladder outlet obstruction induced increased urothelial ATP release (47). In a prospective trial studying 79 male patients with BOO due to BPH and 22 asymptomatic controls, urinary ATP was significantly elevated in the BOO group, suggesting it could be used as a highly sensitive non-invasive biomarker of BOO (48). This potential biomarker has not yet been studied in female patients, and may represent a topic for future research.

Oxidative stress markers

Partial bladder obstruction (PBOO) causes an increase in tissue and systemic oxidative stress markers and cytokines. There have been a few basic science studies identifying both systemic and bladder biomarkers associated with oxidative stress. In a rabbit model of

PBOO, there was a significant increase of oxidative stress biomarkers 8-OHdG in urine and of MDA in plasma, and there was a significant decrease in total oxidant capacity (TAC) in plasma (49).

In a rat model of PBOO, plasma myeloid-derived suppressor cells (MDSCs), interferon-gamma, interleukin-10, and aldosterone were shown to increase during obstruction and returned to normal after reversal (50). Therefore, oxidative stress markers such as MDSCs may be potential prognostic markers associated with bladder obstruction. Similarly, F2-isoprostane measured in bladder tissue was shown to be a marker of oxidative stress in a chronic injury mouse model of PBOO (51).

Detrusor Muscle Biopsy

Previous ultrastructural studies in men with BOO have shown that the detrusor muscle develops features of myohypertrophy (52). In a recent abstract, Wang et al. demonstrated that this phenomenon also occurs in female BOO (53). In this study, 13 patients (7 female, 4 male) and 2 normal female controls underwent detrusor muscle biopsy. The female BOO muscle specimens had features of myohypertrophy (muscle fascicle derangement, collagenosis, myocyte irregularity), although less severe than their male counterparts. The severity of myohypertrophy correlated with severity and duration of obstruction. The female controls did not exhibit these ultrastructural changes.

Novel Targets

The *NLRP3 Inflammasome* has been identified as a sensor of cellular damage in the urothelium, part of inflammatory reaction in response to BOO. In a rat model of BOO, administration of a NLRP3 inhibitor (glyburide) was shown to block inflammasome activation, reduce hypertrophy, and prevent inflammation (54). This may represent a pathway that can be targeted with treatment of symptoms induced by BOO, related to the inflammatory response and development of OAB symptoms.

Piezo1 is a mechanically activated ion channel that may play a role in sensation of bladder distension. In a rat model of pBOO, Piezo1 expression increased significantly in the detrusor layer as well as suburothelial layer, as compared to predominant distribution in the urothelium in sham rats (55). Therefore, inhibition of Piezo1 may represent another therapeutic target in treatment of storage dysfunction in BOO.

In an animal model, BOO was also found to induce upregulation of *nicotinic acetylcholine receptors* in parasympathetic bladder pelvic ganglion neurons (56). This suggests a neural effect of BOO, contributing to the development of detrusor overactivity.

Conclusions

With regard to biomarkers, the above studies suggest correlation of these measurable markers with BOO, not necessarily causal effect. As a future direction, the development of a “point of care” panel or chip to screen for these markers would ideally aid in diagnosis of BOO, as well as be used to follow response to therapy. This would require study of these markers in normal voiders versus female patients with BOO, before and after intervention.

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Table 1**Biomarkers-Subjects and Potential Uses**

Biomarker	Subjects	Potential Uses
Nerve growth factor (NGF) ↑	Females Males Animal model	Diagnosis Response to therapy <i>Refs: 31, 32, 33, 34, 35</i>
Prostaglandin E2 ↑	Males (children)	Diagnosis <i>Refs: 36, 37, 38</i>
Adenosine triphosphate (ATP) ↑	Males Animal model	Diagnosis, Response to therapy <i>Refs: 39, 40, 41</i>
Oxidative stress markers <ul style="list-style-type: none"> • 8-OHdG, MDA ↑ • Total antioxidant capacity ↓ • Plasma myeloid-derived suppressor cells (MDSC) ↑ • F2-isoprostane ↑ 	Animal model	Diagnosis Response to therapy Prognostic marker <i>Refs: 42, 43, 44</i>
Detrusor muscle biopsy	Males Females	Diagnosis <i>Refs: 45, 46</i>
NLRP3 inflammasome ↑	Animal model	Therapeutic target <i>Ref: 47</i>
Piezol ↑	Animal model	Therapeutic target <i>Refs: 48</i>
Nicotinic acetylcholine receptor ↑	Animal model	Diagnosis <i>Ref: 49</i>