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REVIEW

Systematic review of urinary biomarkers of female bladder outlet obstruction (fBOO)

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Summary ***Objective: Diagnosis of bladder outlet obstruction (BOO) in females is often challenging, not only because of the overlap in storage and voiding symptoms in women with various etiologies of lower urinary tract (LUT) dysfunction but also due to the lack of standardized urodynamic criteria to define the condition. There is an unmet need of biologic markers to evaluate BOO in females as an adjunct to other clinical criteria. We sought to elucidate the role of urinary biomarkers in female BOO.***
Material and methods: We performed a systematic review of studies involving urinary biomarkers in female BOO.
The search was performed in PubMed. A total of 58 papers were retrieved and 2 were included for final analysis.
Results: Currently, there are no validated biologic markers for female BOO available. Having a biomarker that can be obtained through a urine sample will be an invaluable tool to evaluate and counsel patients with LUT symptoms and possible BOO. The use of NGF as an indicator of BOO in female patients seems to be promising: NGF levels are elevated in women with BOO when compared with normal controls.
Conclusions: We found that NGF levels may be applied as a useful biomarker in the diagnosis and evaluation of female patients with BOO symptoms. It will not completely replace other clinical diagnostic tools such as formal urodynamic testing but play a role as a supplement to it. Nevertheless, further studies should be conducted to establish NGF levels as a female BOO biomarker and a routine testing modality.

KEY WORDS: Urinary biomarkers; Bladder outlet obstruction; Female; Female bladder outlet obstruction.

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INTRODUCTION

Diagnosis of *bladder outlet obstruction* (BOO) in females is often challenging, not only because of the overlap in storage and voiding symptoms in women with various etiologies of lower urinary tract dysfunction but also due to the lack of standardized urodynamic criteria to define the condition (1).

The *International Continence Society* (ICS) defines BOO as "*generic term for obstruction during voiding. It is a reduced urine flow rate and/or presence of a raised PVR and an increased detrusor pressure. It is usually diagnosed by studying the synchronous values of urine flow rate and detrusor pressure and any PVR measurements. A urethral stricture or obstruction due to higher degrees of uterovaginal prolapse or obstructed voiding after stress incontinence procedures are amongst possible causes*" (2). Although the prevalence of female BOO has not yet been thoroughly studied, it is estimated to be between 2.7 and 23% (3).

ICS defines dysfunctional voiding as "*an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the peri-urethral striated or levator muscles during voiding in neurologically normal women. This type of voiding may also be the result of an acontractile detrusor (abdominal voiding) with electromyography (EMG) or video-urodynamics required to distinguish between the two entities*" (2).

Benign prostatic hyperplasia (BPH) represents the most common cause of BOO in males, being supported by several nomograms that aid in the diagnosis. In contrast, the etiology of BOO in women is diverse, being subdivided into anatomical and functional. Whereas anatomic causes consist mainly of anatomical conditions leading to obstruction of the bladder outlet [*pelvic organ prolapse* (POP), post-anti-incontinence procedures, strictures, fibrosis or urethral diverticula], functional BOO results from the inability to achieve a proper relaxation of the urethral sphincter during bladder emptying [primary bladder neck obstruction, neurogenic detrusor external sphincter, dyssynergia, non-neurogenic dysfunctional voiding (abnormal contraction of periurethral muscle), and Fowler's syndrome (failure of urethral relaxation)] (4).

Most BOO validated questionnaires were developed for prostate pathology and mention prostate specific wording in them. Therefore, in addition to a lack of standardized, widely accepted and accurate nomograms, urodynamic criteria and validated questionnaires and quality of life surveys to evaluate female BOO, there is an unmet need of biologic markers to this aim. Having an easy to obtain, accurate urine biomarker will be valuable when evaluating and counselling patients with lower urinary tract symptoms (5). Accordingly, we conducted a systematic review of studies assessing the role of urinary biomarkers in female BOO.

MATERIALS AND METHODS

Systematic literature review

We performed a systematic review of studies utilizing urinary biomarkers of female bladder outlet obstruction fol-

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lowing the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines. Comprehensive search strategies were used to identify all relevant studies investigating the use of urinary biomarkers in female bladder outlet obstruction. The search was performed in MEDLINE using search *Medical Subject Headings* (MESH) terms "*bladder outlet obstruction*", "*female*", "*women*", "*urine marker*", "*urine biomarker*", "*biomarker*", "*marker*", "*urine*", until the end of 2021 using the string [(bladder outlet obstruction) AND (women) AND (urine marker)] OR [(bladder outlet obstruction) AND (female) AND (urine biomarker)] OR [(bladder outlet obstruction) AND (female) AND (urinary marker)] OR [(bladder outlet obstruction) AND (biomarker) AND (female)] OR [(bladder outlet obstruction) AND (marker) AND (female)]. Only English-language publications were considered. Studies including BOO in males only were excluded. Commentaries were excluded. Basic research studies were excluded and only studies in humans were included. We did not find multiple reports on the same patient cohort.

Study review methodology

Two authors (A.B.S. and L.A.M.) reviewed and selected studies independently; ; disagreements were resolved by discussion and consensus. Titles and abstracts were used to screen for initial study inclusion. Full texts of studies thought to meet or possibly meet the study inclusion were then reviewed. The same reviewers extracted relevant data independently using standardized data collection forms. Data retrieved from the reports include publication details (year of publication and authors), methodological components, and trial characteristics (sample size and outcomes measures).
The association between urinary biomarkers and BOO in females was recorded.

Risk of bias assessment

A formal exclusion of studies due to *risk of bias* (RoB) assessment was not carried out as none of the existing RoB scales were felt to be appropriate for this systematic review.

Data synthesis

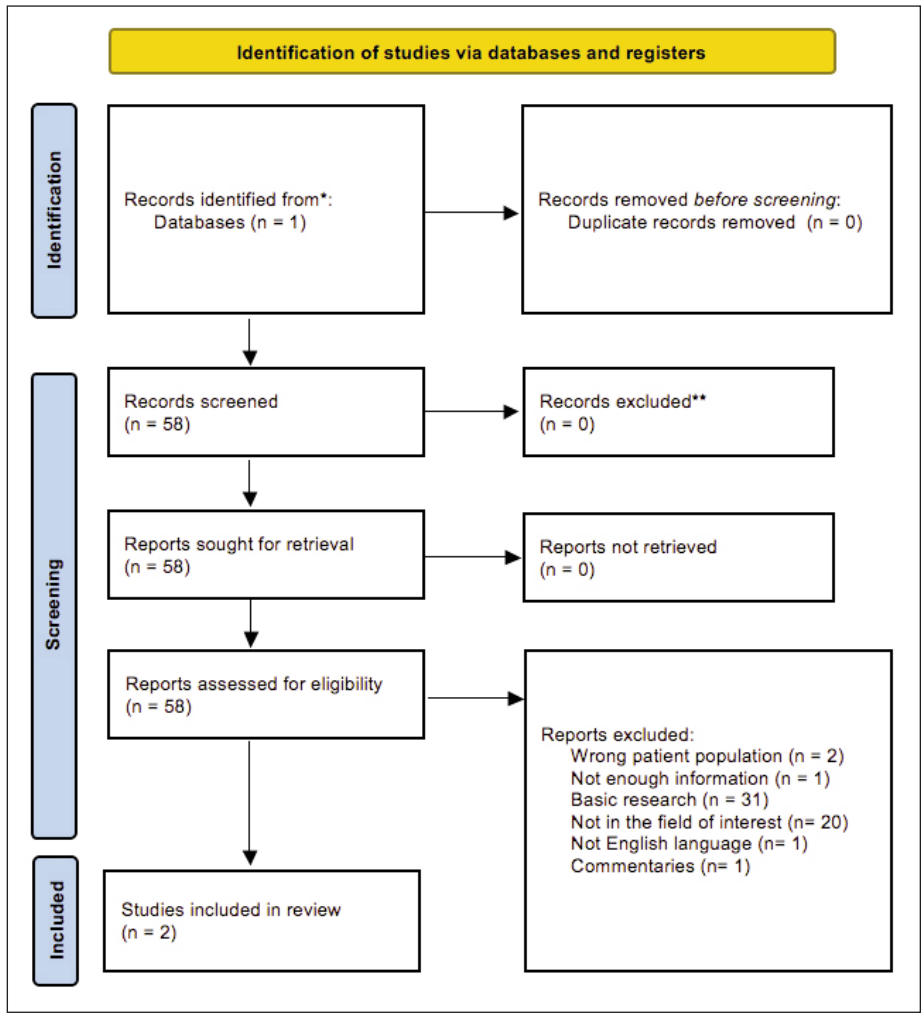
Data synthesis was made after a thorough search through current literature on the diagnosis and management of female BOO, with a specific focus on translational research in the field of urinary biomarker. Several potential urine biomarkers of female BOO have been studied in a basic research setting, *Nerve Growth Factor* (NGF) currently representing the most widely accepted one as it represents the only investigated in humans and, specifically, in females.
Data was stratified by the physiology of voiding and BOO, the basic knowledge on urinary NGF production and role and the relationship between NGF and BOO in female patients.

Results

Literature search results

In total, 58 citations were retrieved from the MEDLINE database. After removing duplicates and screening of titles and abstracts, 56 citations were excluded from further analysis. Figure 1 shows the PRISMA flow diagram of the study.
A total of 2 studies were included in the systematic review, one consisting of a nonrandomized comparative study of urinary NGF levels between female patients deemed to have BOO and their asymptomatic counterparts (5) and the other being a narrative review of the literature on evaluation and diagnosis of BOO in women (1).

Figure 1.
PRISMA flow diagram of the study.



Physiology of voiding and BOO

In the setting of BOO, a pathologic increase in outlet resistance is recorded, conducting to a more forceful contraction of the detrusor muscle to generate urine flow across the outlet. This dysfunction results in functional and anatomical changes in the detrusor as well as in the neural networks involved in the process (1).

Whereas BOO in males is mainly due to *benign prostatic hyperplasia* (BPH), the causes are more varied in females, being subdivided into anatomic and functional. Among anatomic causes, urethral distortion secondary to *pelvic organ prolapse* (POP), iatrogenic BOO caused by anti-incontinence procedures, intrinsic etiologies (strictures, fibrosis, urethral diverticula), should be considered. Functional BOO results 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 (1, 5).

Basic knowledge on NGF production and role

Multiple biomarkers have been studied as potential indicators of BOO in females. NGF is produced by bladder smooth muscle cells, urothelial cells, and sensory afferent neurons. The role of NGF in the neurotrophic effects associated with obstruction was first described in 1991 by *Steers et al.* (6).

Under normal conditions, NGF levels in the urine are low. Increased urinary NGF levels are associated with bladder inflammation secondary to chemical irritation, detrusor overactivity, and BOO. It has been hypothesized that, through mechanical stretching, NGF expression in the bladder wall may increase leading to a reduced sensory threshold resulting in urgency or a reduced threshold for mediating detrusor hyperactivity.

Liu and Kuo demonstrated that urinary NGF is elevated in male patients with BOO plus *overactive bladder* (OAB) symptoms compared with normal controls. Studies support the role of NGF in bladder overactivity, irritative voiding symptoms and afferent pathways plasticity. The increased concentration of NGF can reduce the threshold or increase excitability in the afferent fibers leading to increased bladder sensation or overactivity. Expression of NGF is modulated by intervention, being reduced after medical or surgical treatment of the obstruction (1, 5).

Relationship between NGF and BOO in female patients

A prospective study conducted in 2015 assessed the urinary NGF levels in 10 women with anatomic BOO and compared those to 10 asymptomatic female controls. All females referred for evaluation and management of BOO from POP or previous incontinence surgery were screened for enrollment. BOO was caused by POP in 6 patients, post-incontinence procedure in 5 patients and both etiologies in 1 patient. The urinary ratio between NGF and creatinine (Cr) levels in the patients with BOO (mean 20.8 pg/mg) were significantly higher ($p = 0.0001$) than the levels in the control group (5.6 pg/mg). A weak positive correlation between urinary NGF level and the symptoms severity (evaluated by the Urinary Distress Inventory-6 symptom score) was reported. A significant decrease in mean urinary NGF/Cr to 6.50pg/mg ($p = 0.01$) was recorded after treatment of the conditions responsible for the anatomic BOO (prolapse repair, sling excision). Furthermore, the decreases in NGF/Cr levels after treatment correlated with subjective improvement in the symptoms of patients as demonstrated by decreased UDI-6 survey scores and objective improvement as demonstrated by increased flow rates. Therefore, urinary NGF looks like a promising tool for women with suspected anatomic BOO as a diagnostic and an objective assessment of the therapeutic effects of surgical and medical interventions in women with BOO (1, 5).

Discussion

BOO in women is less understood than in men, as symptoms are scarce and misleading. Due to anatomical and physiological differences, the boundaries of normality are less well defined, and urodynamic diagnosis is often unsatisfactory and not universally accepted. Voiding dysfunction consists of a combination of BOO and *detrusor underactivity* (DU) in both sexes. BOO, as an increased outlet resistance to flow, cannot be separated from detrusor function: the balance between these two parameters will define a broader concept of voiding dysfunction. Increased urethral resistance in women is not as common as in men, but far from rare. In a retrospective study that included 1142 women, 192 (19%) were diagnosed with BOO. Functional sphincteric obstruction was diagnosed in 70 women (36%). The most common anatomical cause of BOO was previous anti-incontinence surgery, followed by urethral stricture, diagnosed in 21% and 20% of patients, respectively. The most common presenting symptoms were storage phase symptoms of daytime and night-time urinary frequency. Hence, BOO should be suspected in women with refractory LUTS, especially those presenting with urinary frequency (7).

Female voiding dysfunction has often a presentation similar to other conditions, lacking specific symptoms or signs. It was found in 23% of patients with OAB. BOO is more frequent than DU and should be suspected in patients with higher night-time frequency, presence of detrusor overactivity and a high post-void residual. Instead, DU should be suspected in patients with a smaller voided volume (8).

Several combinations of nomograms were tested to increase the accuracy of diagnosing BOO and *detrusor underactivity* (DU) among women with LUTS (9). Evidence on tests used to diagnose female bladder outlet obstruction was recently reviewed. The available evidence on diagnostic tests for female bladder outlet obstruction is limited and heterogeneous. The most common test used was found to be pressure-flow studies with or without fluoroscopy, which remains the current standard for diagnosing bladder outlet obstruction in women (10). Yet, as these methodologies frequently find blurred boundaries, are expensive, not widely available, and invasive, alternative or clarifying tests are needed.

Currently, no biologic markers for BOO to use as an adjunct to the evaluation and monitoring of lower urinary tract symptoms in women in parallel with nomograms, urodynamics, validated questionnaires, or quality-of-life surveys are available. Having a biomarker that can be eas-

ily obtained through a urine sample will be an invaluable tool to evaluate and counsel patients with lower urinary tract symptoms and possible BOO (5).
The prospective study included in the review demonstrates that the use of NGF as an indicator of BOO in female patients is adequate. Women with BOO presented elevated urinary NGF/Cr levels when compared with normal controls and these levels significantly decreased with appropriate surgical treatment. Nevertheless, the low number of patients included in this study represents its main limitation. The results are consistent and significant but further information regarding the diagnostic and appraisal potential of the urine biomarker are still missing (5).
Even though clinical studies in males and basic research studies were not included in the systematic review, several other parameters have been the object of investigation in these settings, namely urinary molecules.
Prior to being studied in females, urinary NGF has been proved to be elevated in men with BOO and to decrease in association with reduction of the prostate volume and relief of BOO making it a potential tool not only to diagnose but also to monitor the improvement of BOO in patients with BPH (5, 11).

Prostaglandin E2
The micturition reflex is stimulated by prostaglandins, which decrease the necessary threshold to trigger detrusor contraction through capsaicin-sensitive afferent nerves (12). Prostaglandins, such as *prostaglandin E2* (PGE2), show increased levels in conditions such as OAB, *detrusor overactivity* (DO) and BOO (13, 14).

ATP
Urothelial cells release ATP into the urine in response to bladder stretch. It may play a major sensory role on pelvic afferent nerve fibers (15). A rat model demonstrated an increase in urothelial ATP release due to partial BOO induction (16). In males with BOO due to BPH, there seems to be a higher release of ATP into the urine. The results suggest that urinary ATP may be a high-sensitive non-invasive biomarker of BOO with additional potential discriminative value of detrusor function when comparing BPH patients with low urinary flow rates. Furthermore, ATP levels may represent a surrogate marker for the degree of obstruction (17, 18).

mRNA and miRNA
BOO is responsible for significant organ remodeling which conducts to lower urinary tract symptoms and accompanying urodynamic changes in bladder function. BOO patients have mRNA and miRNA expression profiles correlated with urodynamic findings. The molecular changes in BOO might indicate an increasing involvement of miRNAs in the control of bladder function from the overactive to underactive/acontractile states. Thus, mRNA and miRNA might represent markers of detrusor competence (19, 20).

Oxidative stress markers
Partial BOO leads to an increase in tissue and systemic oxidative stress markers and cytokines in basic research models. A rise in 8-hydroxydeoxyguanosine (8-OHdG) in urine and *malondialdehyde* (MDA) in plasma of rabbits was documented along with a limited total oxidant capacity in plasma (21); a rise in the number of plasma-*myeloid-derived suppressor cells* (MDSCs), interferon-gamma, interleukin-10 and aldosterone was observed in a rat model (22); elevated levels of F2-isoprostane were noted in a chronic injury mouse model of partial BOO (23).

Detrusor muscle biopsy
Although the focus of this review is on urinary biomarkers of female BOO, there is emerging evidence on muscular hypertrophy as an indicator of this condition, as revealed by pathological analysis of detrusor specimens. Firstly, myohypertrophy was shown to be present in men with BOO (24). Afterwards, *Wang et al.*, proved this phenomenon to be present in female BOO and to be related to the degree and duration of obstruction with the female controls not displaying this sort of ultrastructural changes (25, 26).

Novel biomarkers
Future developments may involve further studies on NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, a sensor of cellular damage in the urothelium (27), piezo1, a mechanically activated ion channel present in the detrusor muscle and suburothelial layer implicated in sensation of bladder stretch (28), nicotinic acetylcholine receptors in parasympathetic bladder pelvic ganglion neurons, which expression has been shown to be increased due to its upregulation in BOO (29).
The study is not without limitations. It reflects the lack of information on the topic and the unmet need of translational studies in the field of urinary biomarkers of BOO in female patients. While the evidence on the use of NGF as a biomarker of female BOO grows, many questions on its validity remain including its specificity, sensitivity, cost- and time-effectiveness.

Conclusions
Even though these results indicate that NGF levels may be applied as a useful biomarker in female patients with BOO symptoms, research on biomarkers of BOO is lacking and further investigation is needed.
The use of NGF as a biomarker will not completely replace other clinical diagnostic tools such as formal urodynamic testing although it will probably be considered as a supplement to it. Nevertheless, further studies should be conducted in order to establish NGF levels as a female BOO biomarker and a routine testing modality.
Furthermore, this systematic review underlines the unmet need of urinary biomarkers of female BOO.

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