Review Article

# Female underactive bladder – Current status and management

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## ABSTRACT

Underactive bladder (UAB) is defined by the International Continence Society as a symptom complex characterized by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms. Until recently, the topic has received little attention in the literature probably due to a lack of consistent definitions and diagnostic criteria. We performed a literature review to identify articles related to the diagnosis and management of UAB, specifically in female patients. UAB is a common clinical entity, occurring in up to 45% of females depending on definitions used. Prevalence increases significantly in elderly women and women who live in long-term care facilities. The exact etiology and pathophysiology for developing UAB is unknown, though it is likely a multifactorial process with contributory neurogenic, cardiovascular, and idiopathic causes. There are currently no validated questionnaires for diagnosing or monitoring treatment for patients with UAB. Management options for females with UAB remain limited, with clean intermittent catheterization, the most commonly used. No pharmacotherapies have consistently been proven to be beneficial. Neuromodulation has had the most promising results in terms of symptom improvement, with newer technologies such as stem-cell therapy and gene therapy requiring more evidence before widespread use. Although UAB has received increased recognition and has been a focus of research in recent years, there remains a lack of diagnostic and therapeutic tools. Future research goals should include the development of targeted therapeutic interventions based on pathophysiologic mechanisms and validated diagnostic questionnaires.

## INTRODUCTION

There are two methods of categorizing bladder dysfunction due to underactivity. According to the International Continence Society (ICS), underactive bladder (UAB) syndrome is "characterized by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms."[1] Diagnosis of UAB is made based on clinical symptoms and can have a highly variable presentation. This differs from detrusor underactivity (DU), which is a diagnosis based on urodynamic studies (UDSs). DU is defined by ICS as a bladder contraction of reduced strength and/or duration resulting in prolonged or incomplete emptying of the bladder, and acontractile detrusor is specified when there is no contraction. While UAB and DU certainly coexist in many patients, the focus of this review will be the UAB in female patients.

Until recently, this topic has received little attention in the literature probably due to a lack of consistent definitions and diagnostic criteria.[2] In men, UAB has traditionally been difficult to study because of the difficulty in distinguishing UAB from bladder outlet obstruction (BOO) without the usage of pressure flow studies.[3] However, it has been proposed that by studying the presence of DU and UAB in women, in whom BOO is rarely diagnosed, it might be possible to isolate the clinical symptomatology specific to

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UAB and continue to refine its clinical definition.[3] DU is a common entity occurring in up to 13.3% of elderly women with lower urinary tract symptoms (LUTS) with the prevalence of clinically diagnosed UAB certainly exceeding that number.[4] In recent years, UAB has been recognized as contributing significantly to LUTS in the elderly and interest in the topic has grown.[5,6] In this review, we will focus on the definition, epidemiology, and etiology of female UAB. We will also discuss further advances in the diagnosis and management of female UAB that have come about from new understandings of the disease process.

## DEFINITIONS

Chapple *et al.* proposed a working definition of UAB to correspond to the urodynamic finding of DU as "a symptom complex suggestive of detrusor underactivity and is usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream."[7] In 2017, the Congress on UAB endorsed and refined this definition, more specifically defining UAB as "a symptom complex suggestive of DU and is usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, slow stream, palpable bladder, always straining to void, enuresis, and/or stress incontinence."[8]

Only recently has the ICS given a consensus definition for UAB, which will likely act as a guiding definition for clinical and research purposes. As stated earlier, UAB is "characterized by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms."[1] The important distinction of both the Congress on UAB and ICS definitions is that UAB is a symptom syndrome. Presentation and etiology can and will be highly variable between patients. However, the establishment of a consensus definition will encourage clinicians to consider UAB as a differential diagnosis in patients presenting with lower urinary tract voiding symptoms.

## EPIDEMIOLOGY

UAB as an entity remains difficult to study in part because its corresponding urodynamic correlate remains loosely defined, leading to significant variability in diagnostic criteria across research studies. Because of the variability in definition, reported prevalence also varies significantly. It is believed to range from 12% to 45% of females with increased prevalence with age.[2,4] Resnick *et al.* looked specifically at a population of women with incontinence in a long-term care facility. Overall, 38% of these women had impaired detrusor function, with DU in 8% of patients and involuntary detrusor contractions with incomplete emptying in 30%.[9] In a follow-up study, nearly one-quarter of women with DU on UDS had been misdiagnosed with stress urinary incontinence.[10]

In the ambulatory setting, DU is less common than in the long-term care facility setting. Of 206 consecutive women seen in the urogynecology practice, 62% of women self-reported voiding difficulties and 19.4% of women had demonstrable evidence of DU as characterized by incomplete emptying.[11] Interestingly, only 68% of women with incomplete emptying on UDS reported voiding symptoms. It is not clear if the disease processes that lead to DU affect a patient's symptomatology and perception of UAB or incomplete emptying. If so, this may explain why 32% of patients in this study have incomplete emptying on UDS consistent with DU and do not perceive symptoms of UAB.

Overall trends suggest that DU and UAB are more common in elderly women and more common in women residing in a long-term care facility. Several studies have demonstrated similar prevalence rates for DU in the ambulatory setting of around 12%–19.4%.[4,11-13] As would be expected, voiding symptoms consistent with UAB are slightly higher. A population-wide study in Detroit surveyed 291 women with 20% reporting difficulty with emptying their bladder.[14]

## ETIOLOGY AND PATHOPHYSIOLOGY

There is a controversy as to the exact etiology and pathophysiology underlying UAB. In a broad sense, impaired bladder emptying characteristic of UAB can arise from damage or malfunction of peripheral afferent, efferent, or central nervous system pathways, and detrusor myopathy.[3] Impaired afferent or sensory signaling, which is common with aging and diabetic cystopathy, can impair the micturition reflex leading to impaired emptying.[2] Impaired efferent or motor signaling due to peripheral nerve malfunction or injury can lead directly to impaired contractility. Neural signaling through central nervous system pathways, particularly from the pontine micturition center through the lumbosacral cord, is essential for generating adequate detrusor contractions. Disruptions of the central neural pathways can arise from many pathologic processes including spinal cord injuries, spinal stenosis, and malignancy or vascular insults. Detrusor myopathy is characterized by unfavorable smooth muscle remodeling and myogenic failure. It may result from neuropathy or it may be idiopathic. Some factors that may lead to detrusor myopathy include BOO, aging, denervation, ischemia, or inflammation. UAB often coexists with overactive bladder, though the disease processes appear distinct.[3]

Idiopathic causes, cardiovascular insults, and neurogenic causes may all underlie eventual development of UAB through the previously described pathophysiologic pathways.[15,16] A recent retrospective study of 1726 patients

believed to suffer from UAB found that based on patient history, 11.5% of patients would fall into the idiopathic subclass, with neurogenic causes accounting for 84.6% and myogenic causes 2.6%.[5] However, a 2016 retrospective study of 4 years of patients with UAB at one institution was unsuccessful in finding a correlation between clinical and urodynamic variables and etiologies of UAB.[6] A lack of distinct differentiation between etiological groups supports the idea that UAB more typically presents in a multifactorial fashion, or through converging pathways, rather than through clearly distinct underlying pathophysiological pathways.

## DIAGNOSIS

Patients with UAB often present in a similar fashion to patients with general LUTS. As such, the initial evaluation should be similar. All patients should undergo a history and physical examination, with specific attention paid to bowel habits, prior abdominal or pelvic surgeries, prior traumas, medications, neurologic history, physical examination, and pelvic floor examination. We recommend as first-line tests urinalysis and postvoid residual (PVR). Given low incidence of BOO in women, uroflowmetry can be particularly useful to identify patients with low flow. Although a specific cutoff for maximum flow rate characteristic of UAB has not been defined, there are typical findings. Uroflowmetry typically shows a slow take-off with low maximum flow rate, prolonged voiding time, and multiple intervals.[1]

There do not currently exist any validated patient symptom score scales for use in the diagnosis of UAB.[17] For the purposes of setting patient inclusion criteria, researchers have used urodynamic evidence of DU to identify patients likely presenting with UAB symptomology.[6,18]

In a retrospective qualitative study of 29 males and 15 females previously shown to have DU by urodynamic testing, Uren *et al*. performed structured interviews to establish a patient-centered perspective of DU symptoms.[17] Patients reported a wide variety of LUTS and associated impact on quality of life. Over half of the patients reported storage symptoms (nocturia, frequency, and urgency) and voiding symptoms (slow stream, hesitancy, and straining). Incomplete emptying and postvoid dribbling were also common. This study provided key insight into the experience of patients with UAB and confirmed DU. However, the lack of a comparative group without DU limits the ability to identify symptoms and complaints unique to the subgroup of patients with LUTS symptoms secondary to DU. There remains a need to develop a patient-reported outcome measure for the assessment of UAB with the goal of avoiding invasive testing.

In another retrospective study, Gammie *et al*. reviewed the pressure flow and symptom endorsement data of 1788 patients presenting at a single center over a 28-year period and compared the results of patients found to have normal flow, DU, and BOO to isolate the symptoms most related to UAB and DU.[18] The goal was to identify the characteristics specific to patients with DU. Women with DU were found to have a higher occurrence of decreased and/or interrupted urinary stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, absent and/or decreased sensation, enuresis, and impaired mobility compared with women with normal PFS.

Jeong *et al*. performed a similar retrospective review of 547 Korean women older than 65 years who had undergone UDS in the outpatient setting for LUTS.[4] About 13.3% of women were classified as having DU. Women with DU were significantly older than women without DU, and the prevalence of DU increases with age. In contrast to Gammie *et al*., clinical urinary symptoms, including storage symptoms, voiding symptoms, postmicturition symptoms, and stress urinary incontinence, were identical between the two groups. Despite the contradiction between the two studies, both papers support the need to identify a validated assessment questionnaire for UAB.

The necessity of urodynamic pressure-flow studies for specifying DU in patients with suspected UAB has not been proven. In men, differentiating BOO from DU can be difficult, which often makes UDS necessary to perform. However, the incidence of BOO in women with LUTS is very low, which may obviate the need for urodynamic testing.[4,19] Given the lack of a noninvasive diagnostic algorithm for UAB, urodynamic testing is often performed, which may demonstrate DU. Diagnosis of DU requires a contraction of reduced strength and/or duration resulting in prolonged or incomplete bladder emptying. Additional UDS findings of DU may include delayed start of bladder contraction and delayed urine flow despite desire to void. The detrusor trace may demonstrate a wandering pattern. Patients often rely on abdominal straining to enhance urine flow.[1]

While the rate of isolated BOO in women is low, there may be a subset of women who have a combination of DU and BOO. Wang *et al*. identified DU in 19.9% of women with LUTS, with 4.0% of those women having demonstrable BOO.[20] In women for whom there is uncertainty as to the etiology of LUTS or who are unresponsive to first-line therapies, urodynamics may be beneficial to identify a subset of patients with combined DU and BOO. In particular, video urodynamics may allow for the identification of anatomic obstruction, which in many cases can be surgically addressed.[21]

## MANAGEMENT

There are currently no proven therapeutic options to treat UAB; however, many behavioral modifications and

medication therapies have been proposed. There are two goals for the management of patients with UAB: symptomatic/risk management and therapeutic management. The options available for symptomatic management include behavior modification therapy, pelvic floor physiotherapy and biofeedback, and catheterization.

Behavior modification therapy is useful for patients with impaired bladder sensation who may not sense bladder distension. Timed voiding and double voiding should be encouraged to avoid overdistension and assist with incomplete emptying. This may have the added benefit of reducing frequency and/or incontinence in these patients. Voiding diaries can be important for identifying patients who chronically over-hydrate and can worsen the symptoms of UAB. These patients may benefit from a fluid restriction program. Patients can also perform Crede maneuver using manual pressure on the abdomen to apply pressure to the bladder to further promote bladder emptying. However, this technique should be avoided in patients with BOO as it may lead to vesicoureteral reflux and is cautioned in women as it may lead to increased UTIs due to stop-start voiding.[22]

Pelvic floor physiotherapy and biofeedback have not been directly studied in the female UAB population. Ladi-Seyedian *et al*. performed a randomized trial in two groups of children with nonneuropathic UAB looking at the benefits of animated biofeedback.[23] Both groups received behavioral modification therapy and education, while one group also received pelvic floor physiotherapy and biofeedback training with the assistance of animated imaging. The group that received pelvic physiotherapy demonstrated significantly improved bladder contractility with improved sensation of bladder fullness. While the results are promising, they have not been extended to the adult population in which the etiology of UAB may differ.

In UAB patients with incomplete emptying and high PVR volumes, clean intermittent catheterization (CIC) should be considered. CIC reduces many risks of incomplete emptying, including urinary tract infections, upper tract deterioration, and overflow incontinence. CIC is an adequate management strategy for many patients, but it is not known to be therapeutic. It is the most commonly used management strategy for UAB.[24]

## PHARMACOTHERAPY

Many therapeutic management options have been proposed. In theory, therapeutic interventions for UAB should have a basis in the pathophysiologic mechanisms of UAB.

The human bladder has five types of muscarinic receptors, with M2 the most prevalent and M3 the most important for detrusor contraction. In theory, muscarinic agonists and anticholinesterase inhibitors can increase the concentration of acetylcholine at the muscarinic receptor allowing for a strong bladder contraction. One of the more commonly prescribed medications for UAB is bethanechol, which is a nonselective muscarinic agonist.[25] Other parasympathomimetics that have been studied in the literature include carbachol and distigmine.[26,27] Results of multiple randomized controlled trials looking at the benefit of parasympathomimetics in patients with UAB have been mixed.[25] There has been no definitive evidence proving benefit. In addition, the side effect profile of parasympathomimetics is significant, including GI upset, blurred vision, bronchospasm, and bradycardia. For this reason, bethanechol and other parasympathomimetics are not recommended to treat UAB.

There has been an argument made to the potential benefit of alpha-adrenergic antagonists, such as tamsulosin, which function by decreasing sympathetic tone at the bladder neck and decreasing urethral muscle tone. This decreases the pressure against which the bladder needs to empty, which in turn may allow increased bladder emptying and improved UAB symptoms.[28] Yamanishi *et al*. studied the combined use of alpha-blockers and parasympathomimetics in women with UAB.[29] They found that the combined therapy was superior to either monotherapy in regard to improvement in voiding parameters and subjective symptoms. In the same study, alpha blockers were superior to parasympathomimetics alone. Of note, the International Prostate Symptom Score (IPSS) was used to assess voiding symptoms in men and women in this study. While the use of IPSS has not been validated for this purpose, there likely remains benefit in tracking progression of symptoms over time and response to treatment.

Prostaglandin E2 (PGE2) has been used to treat DU in humans.[30,31] Prostaglandins are known to be important in the modulation of bladder function.[32,33] The intravesical instillation of prostaglandins to promote earlier return of bladder activity has been studied in patients with postoperative urinary retention and DU.[34-36] Overall, results have been mixed, and intravesical prostaglandins are not recommended at this time. In addition, results are difficult to generalize to the general female UAB population given the different pathophysiologies. However, there are currently promising animal studies looking at a novel selective PGE2 and PGE3 receptor agonist in a rat lumbar spinal canal stenosis model for UAB/DU.[37] The prostaglandin selective agonist resulted in improved voiding parameters with decreased PVR due to increased bladder contractility and urethral muscle relaxation. While the results have not been extended to humans yet, the drug is promising.

## FUTURE DIRECTIONS IN PHARMACOTHERAPY

To our knowledge, no other medical therapies have been reported in humans for the treatment of female UAB.

Clearly, there remains a need to identify new drug therapies for the treatment of UAB. Chai and Kudze nicely theorize potential areas for investigation in their review paper by breaking down the voiding process from central nervous system to peripheral nervous system to the lower urinary tract at a macroscopic and microscopic level.[38] Theoretical targets of therapy at the motor or efferent system level that are discussed include ATP regulation, potassium channels, and excitation-contraction coupling through intracellular calcium concentrations. Three different mechanisms for modulating the bladder sensory or afferent system are discussed. In theory, by increasing bladder sensation, the downstream motor or efferent system can be amplified. The potential therapeutic targets discussed include bladder sensory-related neurotransmitters, suburothelial myofibroblasts that function as pacemaker cells within the lamina propria and communicate with afferent nerve fibers, and urothelial cells that are also part of the urothelial-afferent system.

## NEUROMODULATION

Sacral neuromodulation is an FDA approved therapy for patients with UAB as a means of improving voluntary voiding. In patients with neurogenic UAB, neuromodulation has been proposed as a mechanism through which a patient's malfunctioning neural system can be altered to allow adequate voiding. In theory, sacral neuromodulation may have the benefit of increasing detrusor contractility while decreasing outflow resistance. A number of trials have been published with overall promising results, demonstrating that sacral neuromodulation appears to decrease PVR volumes and/or the number of self-catheterization episodes per day.[39] It appears that the results of sacral neuromodulation with an implanted device are durable with >80% of patients demonstrating >50% improvement in symptoms after 5 years.[40] Measurable outcomes, such as increased detrusor contractility or decreased outflow resistance, have not been studied as closely.

Future studies for neuromodulation may focus on the central nervous system and closed-loop feedback neuromodulation. Mouse models have shown that stimulation of specific loci in the brain can induce increased voiding frequency.[41] Theoretically, transcranial stimulation in humans could target similar specific loci to increase voiding frequency. It is unknown if this technique could increase bladder contractility as well.

Closed-loop feedback neuromodulation allows for monitoring of bladder filling through sensory pathways and bladder stimulation through motor pathways. The process is automated and does not require patient input, as such bladder stimulation is induced when a full bladder is detected. The concept has been demonstrated in a rat model with improved voiding parameters after intervention.[42]

## STEM-CELL THERAPY

Stem-cell therapy has been proposed as a mechanism of therapy for patients with UAB caused by detrusor cell malfunction. Stem cells are pluri- or multipotent cells capable of regenerating and differentiating into more specialized cells. Stem cells in recent years become an increasingly popular area of research due to their potential use in the treatment of various diseases. The bladder is known to contain multipotent progenitor cells that can regenerate the urothelium and detrusor after injury.[43,44] It is unknown if these progenitor cells can be utilized to regenerate malfunctioning detrusor cells in patients with UAB and DU.

Animal studies have demonstrated that the injection of mesenchymal stem cells, which are derived from the bone marrow, can prevent the development of DU after ischemia.[45,46] Other studies have looked at the use of autologous muscle-derived cells (ADMCs). Animal models demonstrated the development of myofibroblasts and myotubes after injection of ADMCs.[47] A single case of ADMC injection into a 79-year-old man with UAB has been reported.[48] At 3 months, the patient achieved improved voiding and pressure parameters on UDS with decreased bladder volume and decreased CIC frequency. To our knowledge, ADMC injection into a female UAB patient has not been attempted or described.

## GENE THERAPY

Gene therapy is the delivery of genetic material into a patient's cells to treat disease. In the realm of female UAB, gene therapy remains experimental. Nerve growth factor (NGF) levels have been demonstrated to be decreased in neurogenic-type DU.[49] Therefore, the gene of choice for therapy of neurogenic DU is NGF. The NGF gene is introduced into sensory ganglia cells of the bladder using herpes simplex virus. Rats with DU transfected with the NGF gene demonstrate decreased bladder capacity and PVR.

## SURGICAL THERAPY

Various surgical therapies for reducing outflow resistance in patients with UAB and DU have been studied. OnabotulinumtoxinA (Botox) injections to the urethral sphincter have been used in patients with both neurogenic and nonneurogenic DU.[50] The benefits of Botox appear to be twofold. First, Botox can paralyze the striated urethral sphincter, which in turn can decrease urethral resistance. Second, Botox injections may eliminate the inhibitory effect of urethral afferent nerves on detrusor activity. Urethral sphincter Botox injections have been demonstrated to reduce voiding pressures, reduce PVR volumes, and increase detrusor contractility.[51,52]

Transurethral incision of the bladder neck (TUI-BN) has been reported as a surgical management strategy for women with DU who have failed medical therapy. Jhang *et al.* reported a case series of 31 women with DU who underwent TUI-BN.[21] They found that PVR decreased by 56.3% and 20 out of 27 patients no longer required CIC. Of note, three patients developed transient incontinence, and one developed a vesicovaginal fistula.

Myoplasty has been used with success in patients with acontractile bladder.[53] Myoplasty describes the process of transferring autologous latissimus dorsi muscle flaps from the axilla to the bladder. The muscle flap is draped over the bladder. Because the neural bundle of the flap is anastomosed to the 12$^{th}$ intercostal nerve, patients can voluntarily control the muscular flap. Long-term results have demonstrated that 17 out of 24 patients gained voluntary control of voiding with low PVRs and no need for CIC. The procedure has not been performed in women with UAB, so it is unclear what the functional and symptomatic effects of myoplasty would be on this patient population.

## CONCLUSION

UAB is a symptom complex characterized by a "slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms." UAB is a common, though underdiagnosed, clinical entity that has only recently been given formal recognition and definition by the ICS. Most studies of UAB have focused on patients with UAB and DU secondary to long-standing BOO, which is much less common in female patients. However, we know that UAB and DU are common in elderly women and women residing in long-term care facilities. There are currently no validated patient symptom-based tools to aid the diagnosis and management of UAB. Management strategies have not been directly studied in the female UAB patient population, though various therapies for DU have been studied with mixed results. Future research goals should include the development of targeted therapeutic interventions based on pathophysiologic mechanisms.

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